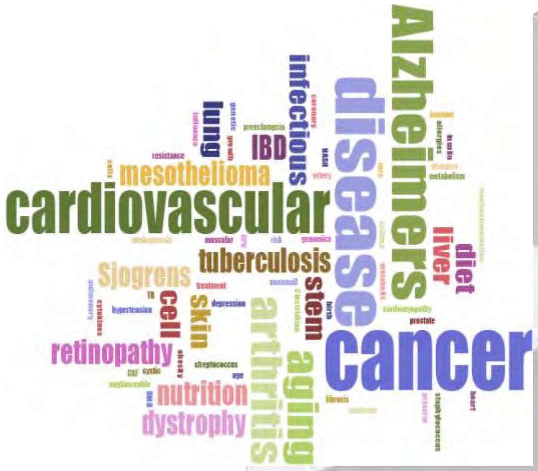
Annotated SomaLogic and Third-party Publications

This partial list of peer-reviewed publications includes those describing applications of SomaLogic technology (Section I, below) as well as basic research on the technology itself (Section II, starting on p.193). Links to the articles are provided and if access requires a subscription.

Note: Many of the studies refer to measuring different numbers of proteins in the SomaScan® Assay, which reflects the growth of the SomaScan® Platform.



I. SomaScan® Assay/SOMAmer® Reagent Applications Basic, preclinical and clinical

Latest updates

Carrasco-Zanini, J *et al.* (2022) "Proteomic signatures for identification of impaired glucose tolerance." *Nat Med* **28**(11): 2293-2300. **(Subscription required)**

https://www.doi.org/10.1038/s41591-022-02055-z

Isolated impaired glucose tolerance (iIGT) is a type of prediabetes that cannot be detected by current screening methods, so many people who are at high risk for developing type 2 diabetes are missed. In this study, researchers at the University of Cambridge, UK and the Berlin Institute of Health at Charité, Germany used the SomaScan Assay to measure the levels of nearly 5,000 proteins in blood samples from more than 11,000 participants in the Fenland Study. Study participants had undergone oral glucose tolerance testing, a cumbersome procedure that is the current gold standard for detecting iIGT. The authors created a machine learning algorithm that was able to extract three key protein biomarkers of iIGT. When combined with standard screening methods, the three-protein signature improved identification of individuals with iIGT in the Fenland study. The researchers confirmed their findings in the independent Whitehall II study. The team also discovered that fasting status did not significantly change the reliability of the three-protein signature, which would simplify clinical implementation. These results suggest a way to improve diabetes screening to enable preventative interventions in a currently overlooked population.

Pierson, SK *et al.* (2022) "CXCL13 is a predictive biomarker in idiopathic multicentric Castleman disease." *Nat Commun* **13**(1): 7236.

https://www.doi.org/10.1038/s41467-022-34873-7

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Idiopathic multicentric Castleman disease (iMCD) is a rare and potentially fatal disorder. For some patients, iMCD disease flares are driven by the proinflammatory protein interleukin-6 (IL-6), but treatment with siltuximab, an antibody that blocks IL-6, is not effective in all patients. In this study, a team led by researchers at University of Pennsylvania used the SomaScan Assay to search for proteins that could distinguish siltuximab responders from non-responders. They compared the levels of 1,178 proteins in serum from iMCD patients, patients with related diseases and healthy controls and identified CXCL13 as one of the most significantly increased proteins in two independent iMCD cohorts. They then examined protein levels pre- and post-treatment with siltuximab and found that siltuximab responders showed an early and significant decrease in CXCL13 serum levels. These results suggest that CXCL13 is a predictive biomarker of response to siltuximab in iMCD.

Zaghlool, SB *et al.* (2022) "Metabolic and proteomic signatures of type 2 diabetes subtypes in an Arab population." *Nat Commun* **13**(1): 7121.

https://www.doi.org/10.1038/s41467-022-34754-z

A previous data-driven cluster analysis of Scandinavian individuals with type 2 diabetes (T2D) identified four T2D subtypes: severe insulin deficient, severe insulin resistant, mild obesity-related, and mild age-related diabetes. In this article, researchers at Weill Cornell Medicine-Qatar applied the same approach to individuals with T2D from the Qatar Biobank and showed that the subtypes translated to an Arab population. They used proteomic and metabolomic data to identify subtype-specific signatures that have the potential to reveal biological drivers of disease progression and targeted therapeutic approaches.

Liu, X *et al.* (2022) "Plasma proteomic signature of decline in gait speed and grip strength." *Aging Cell*: e13736.

https://www.doi.org/10.1111/acel.13736

Slowing the physical decline that comes with age will help each person maintain the highest possible quality of life throughout their lifespan. In the first study of its kind, a team led by researchers at Stanford University School of Medicine examined the relationships between plasma proteins and changes in gait speed and grip strength, two standard measures of physical fitness. They used the SomaScan Assay to measure the levels of 1,154 plasma proteins in nearly 4,000 middle- to older-aged adults and identified 14 and 18 proteins that associated with declines in gait speed and grip strength, respectively. These novel proteins merit further exploration as possible targets for therapies that slow age-related functional decline.

Ge, Y-J *et al.* (2022) "Prioritization of drug targets for neurodegenerative diseases by integrating genetic and proteomic data from brain and blood." *Biol Psychiatry*, *epub ahead of print.*

https://www.doi.org/https://doi.org/10.1016/j.biopsych.2022.11.002

In this study, researchers in China integrated proteomic and genomic data to identify potential drug targets for Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), frontotemporal

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dementia, and Lewy body dementia. They leveraged protein quantitative trait loci (pQTLs) previously identified from post-mortem brain samples using mass spectrometry and pQTLs previously identified from blood samples using the SomaScan Assay. Mendelian randomization analysis identified 22 proteins that had possible causal associations with neurodegenerative diseases and that warrant further investigation as drug target candidates.

Lin, X *et al.* (2022) "Novel plasma and brain proteins that are implicated in multiple sclerosis." *Brain*, *epub ahead of print.* **(Subscription required)**

https://www.doi.org/10.1093/brain/awac420

In this study, researchers in Australia identified novel blood and brain proteins implicated in genetic susceptibility to multiple sclerosis (MS). They integrated data from previous plasma proteomic, brain proteomic and MS genome wide association studies and identified 39 novel proteins associated with MS risk. Based on corresponding genes for the 39 proteins, they identified 23 genes associated with MS disability progression. These results prioritize targets for future investigations of MS disease mechanisms and therapeutics.

Allam, V *et al.* (2022) "Macrophage migration inhibitory factor promotes glucocorticoid resistance of neutrophilic inflammation in a murine model of severe asthma." *Thorax, epub ahead of print*. **(Subscription required)**

https://www.doi.org/10.1136/thorax-2021-218555

Approximately half of asthma patients have non-eosinophilic disease, in which the dominant immune cells found in the airways are neutrophils. Severe neutrophilic asthma does not respond to current therapies such as corticosteroids. Macrophage migration inhibitory factor (MIF) is a protein that promotes neutrophil recruitment to the lung and inhibits glucocorticoid activity. This study, led by researchers in Australia, used the SomaScan Assay to measure protein levels in sputum from 120 individuals in a European study of severe asthma and found that increased MIF levels correlated with increased neutrophilic inflammation and number of asthma attacks. Treatment with an inhibitor of MIF significantly decreased neutrophilic inflammation and increased responsiveness to glucocorticoids in a mouse model of severe asthma. These data suggest that MIF represents a promising therapeutic target for treating glucocorticoid-resistant neutrophilic inflammation in severe asthma.

Gallego-Fabrega, C *et al.* (2022) "Biological Age Acceleration Is Lower in Women With Ischemic Stroke Compared to Men." *Stroke* 53(7): 2320-2330. **(Subscription required)**

https://www.doi.org/10.1161/STROKEAHA.121.037419

Women are less likely than men to suffer a stroke when they are younger, although this difference between sexes disappears in older age. A variety of age-related diseases are linked to differences in DNA methylation (DNAm), which can be used to predict biological age. Epigenetic age acceleration (EAA) refers to the difference between a person's chronological age and their age predicted from DNAm. In this study, researchers in Spain evaluated EAA in female and male

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stroke patients to determine if accelerated biological aging explains sex-related differences in age of stroke. Women had lower EAA than men, meaning that their biological age was younger than their chronological age at the time they suffered a stroke. SomaScan Assay data on 1,305 proteins were available for 26 samples and showed 42 proteins whose blood levels correlated with EAA. These results point to biological processes associated with accelerated aging that deserve further investigation.

Tarawneh, R *et al.* (2022) "Vascular endothelial-cadherin as a marker of endothelial injury in preclinical Alzheimer disease." *Ann Clin Transl Neurol.*, *epub ahead of print.*

https://www.doi.org/10.1002/acn3.51685

Dysfunction of the endothelium, the layer of cells that line blood vessels and organ cavities, is seen in the brains of people with Alzheimer's disease (AD). In this study, researchers at the University of New Mexico and Washington University, St. Louis established vascular endothelial cadherin (VEC) as a marker of endothelial injury in preclinical AD. VEC is a protein produced by endothelial cells and regulates their function. The researchers used the SomaScan Assay to measure the levels of VEC in cerebrospinal fluid (CSF) collected from 700 cognitively normal individuals, including those in the earliest stages of AD, before symptom onset. They found that CSF VEC levels were increased in preclinical AD and correlated with cognitive outcomes as well as CSF AD biomarkers of amyloid, tau and neurodegeneration. These results highlight the importance of endothelial injury in development of AD and as a possible therapeutic target to delay symptoms and disease progression.

Dammer, EB *et al.* (2022) "Multi-platform proteomic analysis of Alzheimer's disease cerebrospinal fluid and plasma reveals network biomarkers associated with proteostasis and the matrisome." *Alzheimers Res Ther* **14**(1): 174.

https://www.doi.org/10.1186/s13195-022-01113-5

In this study, researchers at Emory University School of Medicine used three different proteomic platforms — the SomaScan Assay, the Olink proximity extension assay and tandem mass tag-based mass spectrometry — to analyze cerebrospinal fluid (CSF) and plasma from 18 patients with Alzheimer's disease (AD) and 18 controls. Correlation of overlapping protein measurements across platforms in CSF and plasma was good, with more variability in plasma. They observed that medium to low abundance proteins were decreased in AD plasma compared to CSF, although it is unclear why. Surprisingly, many proteins altered in AD CSF were altered in the opposite direction in plasma, including known members of AD protein networks in brain. This study illustrated the value of multi-platform proteomic analysis for discovery of AD biomarkers.

Belkadi, A *et al.* (2022) "Identification of PCSK9-like human gene knockouts using metabolomics, proteomics, and whole-genome sequencing in a consanguineous population." *Cell Genomics*: 100218.

https://www.doi.org/https://doi.org/10.1016/j.xgen.2022.100218

Marriages between men and women who are related is common in Middle Eastern countries and increases likelihood of identifying individuals with the same mutation in both copies of a given gene. Linking these natural human gene knockouts to

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favorable health outcomes can lead to the discovery of candidate therapeutic targets. This study, led by researchers at Weill Cornell Medicine-Qatar, examined genomic, proteomic and metabolomic data from 3,000 individuals from the Qatar Biobank and identified natural gene knockouts that were associated with large changes in blood protein or metabolite levels. They found that the chance of identifying these types of genetic variants was 168 times higher than in a non-consanguineous population and can be leveraged for discovery of new targets for drug discovery.

Vorn, R *et al.* (2022) "Are EPB41 and alpha-synuclein diagnostic biomarkers of sport-related concussion? Findings from the NCAA and Department of Defense CARE Consortium." *J Sport Health Sci., epub ahead of print.*

https://www.doi.org/10.1016/j.jshs.2022.11.007

Previous studies aimed at identifying diagnostic markers of sports-related concussion (SRC) have focused on a small number of pre-determined proteins believed to be biologically important. In this study, a team led by researchers at Johns Hopkins School of Nursing and Medicine and the National Institutes of Health performed a more expansive search for novel SRC-related biomarkers. They used the SomaScan Assay to measure the levels of 1,305 proteins in blood collected within 48 hours of injury from 140 concussed and 21 non-concussed athletes and identified significant differences in 338 plasma proteins. A combination of two proteins (plasma erythrocyte membrane protein band 4.1 and alpha-synuclein) were the best at diagnosing concussion 7 to 48 hours post-injury. These results reveal proteins that may lead to more accurate methods for diagnosing concussion and to a better understanding of the body’s responses to injury.

Njunge, JM *et al.* (2022) "The Childhood Acute Illness and Nutrition (CHAIN) network nested case-cohort study protocol: a multi-omics approach to understanding mortality among children in sub-Saharan Africa and South Asia." *Gates Open Res* **6**: 77.

https://www.doi.org/10.12688/gatesopenres.13635.2

The Childhood Acute Illness and Nutrition (CHAIN) global research network is focused on improving survival of acutely ill and undernourished children. This CHAIN study protocol will use a multi-omic approach that includes SomaScan plasma proteomic measurements to identify biological factors associated with mortality in samples collected from hospitalized and non-hospitalized children in sub-Saharan Africa and South Asia.

Birkenbihl, C *et al.* (2021) "ANMerge: A Comprehensive and Accessible Alzheimer's Disease Patient-Level Dataset." *J Alzheimers Dis* **79**(1): 423-431.

https://www.doi.org/10.3233/JAD-200948

AddNeuroMed is a European consortium that was developed to find biomarkers for Alzheimer’s disease (AD). AddNeuroMed collected longitudinal patient data including clinical assessments, brain imaging, genotyping, transcriptomic profiling, and blood plasma proteomics. Some of these data were made public in 2015 but were difficult to us since they were incomplete and poorly organized. In this article, AddNeuroMed researchers presented ANMerge, a new version of data collected from

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1,702 participants. ANMerge is a rich AD data source that includes SomaScan Assay measurements on 1,001 distinct plasma proteins at baseline and one year into the study.

Berry, J *et al.* (2021) "Radicava/Edaravone Findings in Biomarkers From Amyotrophic Lateral Sclerosis (REFINE-ALS): Protocol and Study Design." *Neurol Clin Pract* **11**(4): e472-e479.

https://www.doi.org/10.1212/CPJ.0000000000000968

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease with no cure. Edaravone (Radicava) is an FDA-approved ALS therapy that was shown to slow physical decline. This article describes the protocol for REFINE-ALS, a prospective, observational, longitudinal, multicenter study designed to identify epigenetic and proteomic biomarkers of Edaravone effects in ALS.

Bridel, C *et al.* (2018) "No Plasmatic Proteomic Signature at Clinical Disease Onset Associated With 11 Year Clinical, Cognitive and MRI Outcomes in Relapsing-Remitting Multiple Sclerosis Patients." *Front Mol Neurosci* 11: 371.

https://www.doi.org/10.3389/fnmol.2018.00371

This study led by researchers at VU University Medical Center investigated whether plasma proteins could predict outcomes in patients with relapsing-remitting multiple sclerosis (RRMS). They used the SomaScan Assay to measure the levels of 1,310 proteins in plasma collected from 67 RRMS patients within 3 months of diagnosis but did not find a protein signature associated with clinical, cognitive or MRI outcomes, or with white matter lesion volume 11 years after diagnosis. This could be because the cohort used for the study had a relatively mild disease course, without dramatic differences in outcomes. In addition, cerebrospinal fluid might be than plasma for identifying prognostic protein markers of RRMS.

Silkoff, PE *et al.* (2018) "Toll-like receptor 3 blockade in rhinovirus-induced experimental asthma exacerbations: A randomized controlled study." *J Allergy Clin Immunol* **141**(4): 1220-1230.

https://www.doi.org/10.1016/j.jaci.2017.06.027

Asthma attacks are often triggered by respiratory viruses such as human rhinovirus (HRV). This article describes a clinical trial sponsored by Janssen Research and Development that investigated the safety and efficacy of an antibody that blocks Toll-like receptor 3, an inflammatory protein triggered by HRV. Healthy subjects and asthma patients received antibody or placebo before being inoculated with HRV. Participants were monitored for respiratory symptoms, lung function, and nasal viral load. The study also included biomarker assessments of nasal lavage fluid, blood and sputum using the SomaScan Assay. While the antibody did not attenuate the effects of HRV in asthmatic patients, it did suppress cold symptoms in healthy volunteers.

Welton, JL *et al.* (2017) "Cerebrospinal fluid extracellular vesicle enrichment for protein biomarker discovery in neurological disease; multiple sclerosis." *J Extracell Vesicles* **6**(1): 1369805.

https://www.doi.org/10.1080/20013078.2017.1369805

This article describes a pilot study conducted by researchers at Cardiff University School of Medicine in the UK examining extracellular vesicles isolated from cerebrospinal fluid (CSF-EVs) for biomarker discovery. They used a novel method to isolate CSF-EVs from four patients with relapsing remitting multiple sclerosis (RRMS) and three controls. They then used the SomaScan Assay to compare the levels of 1,128 proteins in CSF-EVs and CSF. Overall, 348 and 580 proteins were identified in CSF-EVs and CSF, respectively, of which 50 were significantly and exclusively enriched in RRMS CSF-EVs. This proof-of-concept study demonstrates how proteomic analysis of CSF-EVs could identify biomarkers and potential therapeutic targets for neurological diseases.

Lourdusamy, A *et al.* (2012) "Identification of cis-regulatory variation influencing protein abundance levels in human plasma." *Hum Mol Genet* **21**(16): 3719-3726.

https://www.doi.org/10.1093/hmg/dds186

In this article, a team led by researchers at Kings College London report the first large-scale genetic association study of plasma proteins. They used the SomaScan Assay to measure the levels of 813 proteins in plasma from 96 elderly Europeans and tested their association with 776,864 genetic variants located near the gene encoding the relevant protein. They identified 2,106 protein quantitative trait loci (pQTL) for 60 proteins. Of the 60 genes encoding protein, 20 had previously been associated with different diseases including Alzheimer’s disease.

Older entries

Kivimaki, M *et al.* (2022) "Comment on "A proteomic surrogate for cardiovascular outcomes that is sensitive to multiple mechanisms of change in risk"." *Sci Transl Med* **14**(665): eabq4810.

https://www.doi.org/10.1126/scitranslmed.abq4810

—and—

Williams, SA *et al.* (2022) "Response to comment on "A proteomic surrogate for cardiovascular outcomes that is sensitive to multiple mechanisms of change in risk"." *Sci Transl Med* **14**(665): eadd1355.

https://www.doi.org/10.1126/scitranslmed.add1355

These two articles comment on a previous SomaLogic-led publication describing a 27-protein signature that accurately predicted four-year cardiovascular disease (CVD) outcomes in high-risk individuals (see ref: Williams, SA *et al.* (2022) *Sci Transl Med* **14**(639): eabj9625. https://www.science.org/stoken/author-tokens/ST-476/full).

Kivimaki *et al.* report a replication analysis of the 27-protein model in an independent primary prevention study. Although the model performed well at predicting a first cardiovascular event in participants with no CVD at baseline, its screening performance for 10-year CVD risk was not superior to established measures such as the ASCVD risk score.

In their response, Williams and Ganz emphasize that the protein test was not designed to screen for primary events in healthy people without known drivers of risk and that the prognostic performance of the model was optimized for 4 years rather than 10 years. Unlike the ASCVD risk score, which is based on immutable factors such as sex, age and race, the protein model responds to change in risk with interventions and could be used in drug development to monitor changes in cardiovascular risk for new therapies. The protein model could also be used for clinical decision-making in health care, where an individualized risk assessment could improve the cost-effective allocation of drugs.

Hyland, PL *et al.* (2022) "Evaluating the Utility of Proteomics for the Identification of Circulating Pharmacodynamic Biomarkers of IFNbeta-1a biologics." *Clin Pharmacol Ther.*, *epub ahead of print.*

https://www.doi.org/10.1002/cpt.2778

Regulatory approval of a biosimilar requires demonstrating equivalence to an approved biologic product through comparative clinical studies that are time-consuming and expensive. Proteomics has the potential to accelerate biosimilar development by identifying protein signatures that reflect drug exposure and the body's response. In the first study of its kind, researchers at the U.S. Food and Drug Administration (FDA) used the SomaScan Assay to identify longitudinal pharmacodynamic (PD) biomarkers of interferon-beta 1a (IFNβ-1a) biologics that are approved treatments for multiple sclerosis. They compared the levels of more than 7,000 plasma proteins in 36 healthy participants given either placebo or therapeutic doses of IFNβ-1a or pegylated-IFNβ-1a (pegIFNβ-1a). They identified significant differences in 41 and 44 unique proteins for IFNβ-1a and pegIFNβ-1a, respectively, with 31 proteins in common. The common proteins responded similarly to IFNβ-1a and pegIFNβ-1a but differed in peak response time. These results expand the list of potential candidate plasma PD biomarkers for IFNβ-1a biologics and demonstrate a general strategy for identifying novel PD biomarker signatures that may streamline biosimilar development programs.

Steffen, BT *et al.* (2022) "Proteomic analysis of diabetes genetic risk scores identifies complement C2 and neuropilin-2 as predictors of type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) Study." *Diabetologia*, *epub ahead of print.*

https://www.doi.org/10.1007/s00125-022-05801-7

Previous studies have shown that genetics influences an individual's risk of developing type 2 diabetes (T2D), and genetic risk scores (GRS) have been generated to predict four T2D characteristics: beta cell dysfunction, insulin resistance, lipodystrophy and body mass index/lipid abnormalities. Researchers at the University of Minnesota used the SomaScan Assay to measure the levels of 4,870 proteins in a discovery sample of 7,241 White participants in the Atherosclerosis Risk in Communities Study (ARIC) cohort and a replication sample of 1,674 Black ARIC participants. They identified 22 plasma proteins associated with T2D-related GRS, of which 18 were associated with T2D and 10 were associated with T2D development over 24 years of follow up. Mendelian randomization analysis suggested that higher levels of the protein neuropilin-2 may protect against T2D, while high levels of the protein complement C2 may cause T2D. The identified proteins may represent targets for interventions that prevent, slow or reverse T2D progression.

Lindbohm, JV *et al.* (2022) "Immune system-wide Mendelian randomization and triangulation analyses support autoimmunity as a modifiable component in dementia-causing diseases." *Nat Aging* 2(10): 956-972.

https://www.doi.org/10.1038/s43587-022-00293-x

The blood brain barrier (BBB) plays a critical role in protecting the brain from harmful substances circulating in the body. Systemic inflammation can break down the BBB and is believed to contribute to neurodegenerative diseases. To identify causal risk factors for dementia-causing diseases, a team led by researchers at the Broad Institute of the Massachusetts Institute of Technology and Harvard University, University College London and University of Helsinki, Finland performed a Mendelian randomization (MR) analysis of 1,827 immune system- and BBB-related biomarkers measured previously in four different cohorts. They identified 127 unique biomarkers, including 42 circulating proteins, that associated with Alzheimer's and Parkinson's disease, vascular dementia, frontotemporal dementia or cognitive performance and identified several potential new drug targets. They identified 64 drugs target 18 of the 127 biomarkers that could be repurposed for treatment of dementia-causing diseases.

Candia, J *et al.* (2022) "Assessment of variability in the plasma 7k SomaScan proteomics assay." *Sci Rep* **12**(1): 17147.

https://www.doi.org/10.1038/s41598-022-22116-0

In this study, researchers at the National Institutes of Health (NIH) conducted an extensive technical assessment of the 7K SomaScan Assay and found the assay's extensive proteome coverage, sensitivity and consistently low variability to be particular strengths. As part of the study, the NIH researchers performed proteomic profiling on a total of 2,050 samples, including 1,806 human donor plasma samples distributed across 22 plates. The research team found high sensitivity, with only seven human proteins in their samples that were below the estimated limit of detection. The NIH research team emphasized the opportunities offered by the SomaScan Platform for biomarker discovery and the elucidation of biological pathways in response to disease or treatment, uncovering the complex connections between genome and proteome, and its potential as a companion diagnostic and tool for patient stratification.

Serban, KA *et al.* (2022) "Unique and shared systemic biomarkers for emphysema in Alpha-1 Antitrypsin deficiency and chronic obstructive pulmonary disease." *eBioMedicine* **84**.

https://www.doi.org/10.1016/j.ebiom.2022.104262

Alpha-1 Antitrypsin deficiency (AATD) is a genetic condition in which the level of the protein AAT is reduced. AAT protects the lungs from damage, so individuals with AATD are at higher risk of chronic obstructive pulmonary disease (COPD). However, blood levels of AAT do not correlate with COPD onset or progression, so other biomarkers are needed to risk

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stratify AATD individuals. This study, led by researchers at National Jewish Health and the University of Colorado, used the SomaScan Assay to measure the levels of 4,776 unique proteins in plasma or serum from 5,924 participants in four different AATD and COPD cohorts. They identified unique and shared plasma proteins in AATD and COPD and created a protein score that predicted emphysema in AATD and COPD subjects. The protein score could address the current need for a non-invasive test that is both diagnostic and prognostic of early emphysema in individuals with AATD.

Thareja, G *et al.* (2022) "Differences and commonalities in the genetic architecture of protein quantitative trait loci in European and Arab populations." *Hum Mol Genet.*, *epub ahead of print.*

https://www.doi.org/10.1093/hmg/ddac243

Polygenic scores (PGS) can be used to estimate an individual's lifetime genetic risk of disease. Most PGS are derived from genome wide association (GWAS) studies of Caucasian populations, so it is unclear how accurately they predict risk for individuals of different ethnicities. In this article, a team led by researchers at Weill Cornell Medicine-Qatar describe the first large-scale GWAS with proteomics in an Arab population. They used the SomaScan Assay to measure the levels of 1,301 plasma proteins in 2,935 participants of the Qatar Biobank. Combined with data on more than 10 million genetic variants, they identified 2,685 protein qualitative trait loci (pQTLs) and replicated the majority (up to 89%) in two previous European population studies. They compared the performance of a protein PGS derived from a Caucasian population in a European and an Arab cohort and found that it performed approximately 20% better in Europeans when compared to Arabs. These results shed new light on genetic variability between ethnicities and the generalizability of PGS.

Butler-Laporte, G *et al.* (2022) "The dynamic changes and sex differences of 147 immune-related proteins during acute COVID-19 in 580 individuals." *Clin Proteomics* **19**(1): 34.

https://www.doi.org/10.1186/s12014-022-09371-z

In this study, a team led by researchers at McGill University examined protein changes during acute COVID-19. They used the SomaScan Assay to measure the levels of 147 immune-related proteins in blood from 580 individuals at three large hospital-based centers in Canada and the United States. Samples were collected within 14 days of symptom onset, and 69 proteins showed significant differences in individuals who later died or needed respiratory support. Six proteins showed sex differences, of which three were also associated with severe COVID-19. These results provide greater insight into the COVID-19 immune response and how severe illness develops in men compared to women.

Cullell, N *et al.* (2022) "Altered methylation pattern in EXOC4 is associated with stroke outcome: an epigenome-wide association study." *Clin Epigenetics* **14**(1): 124.

https://www.doi.org/10.1186/s13148-022-01340-5

Heritable factors such as epigenetic DNA methylation could play a role in neurological changes that happen after suffering a stroke. This study led by researchers in Barcelona, Spain examined the association between DNA methylation and stroke severity and found a methylation site in the EXOC4 gene that was linked to worse stroke outcomes. They integrated

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SomaScan Assay measurements of 1,305 plasma proteins in 46 subjects and found 79 proteins that were associated with EXOC4 methylation. Many of the proteins are involved in regulating natural killer (NK) cells, which are key immune cells that infiltrate ischemic stroke lesions in the brain. These results reveal a potential epigenetic risk factor in stroke recovery.

Moin, ASM *et al.* (2022) "The severity and duration of Hypoglycemia affect platelet-derived protein responses in Caucasians." *Cardiovasc Diabetol* **21**(1): 202.

https://www.doi.org/10.1186/s12933-022-01639-w

People with type 2 diabetes (T2D) are at higher risk of cardiovascular disease. Low blood sugar episodes can hyperactivate platelets, which could contribute to atherosclerosis, deep vein thrombosis, stroke and heart attack. In this study, researchers at Royal College of Surgeons in Ireland, Bahrain and Hull York Medical School in the UK used the SomaScan Assay to compare the effects of mild prolonged hypoglycemia with severe transient hypoglycemia on 13 platelet-related proteins (PRP) in patients with T2D and nondiabetic controls. Hypoglycemia induced significant protein changes in both groups that continued up to 24 hours, and the changes differed depending on the severity and length of hypoglycemia. The researchers concluded that any amount of hypoglycemia may led to PRP changes that increase the likelihood of cardiovascular events.

Cai, Y *et al.* (2022) "Association of mTORC1-dependent circulating protein levels with cataract formation: a mendelian randomization study." *BMC Genomics* **23**(1): 719.

https://www.doi.org/10.1186/s12864-022-08925-7

The multiprotein complex, mTORC1 (mechanistic target of rapamycin complex 1), plays an important role in regulating cell growth. In the first study of its kind, researchers in China used Mendelian randomization to assess the causal role of mTORC1-dependent plasma protein levels in cataract development. They leveraged data from a published SomaScan study (see Sun, BB *et al.* (2018) *Nature* **558**: 73-79 https://www.ncbi.nlm.nih.gov/pubmed/29875488) to identify the protein EIF4EBP, a downstream target of mTORC1, as a high-risk factor for cataracts. This finding suggests a possible mechanism for cataract development and a target for their prevention and treatment.

Mofrad, RB *et al.* (2022) "Plasma proteome profiling identifies changes associated to AD but not to FTD." *Acta Neuropathol Commun* **10**(1): 148.

https://www.doi.org/10.1186/s40478-022-01458-w

Frontotemporal dementia (FTD) is a group of disorders caused by shrinkage of the frontal and temporal lobes of the brain. Symptoms typically start between 40 and 65 years of age. There are currently no biomarkers that can differentiate FTD from Alzheimer’s disease (AD) or diagnose pathological subtypes of FTD in living patients. This study led by researchers at VU University Medical Center Amsterdam in the Netherlands used the SomaScan Assay to measure the levels of 1,303 proteins in more than 260 plasma samples from FTD or AD subjects and non-demented individuals with subjective cognitive decline. The researchers developed a panel of 12 proteins that could discriminate FTD from AD with very high accuracy. They also examined proteins in post-mortem brain samples but were unable to develop a tissue or blood protein panel capable of distinguishing FTD from controls or FTD subtypes. These results may point to the heterogeneity of FTD and the need for larger studies with well-characterized cohorts.

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Sproull, M *et al.* (2022) "Prediction of Total-Body and Partial-Body Exposures to Radiation Using Plasma Proteomic Expression Profiles." *Radiat Res* **198**(6): 573-581.

https://www.doi.org/10.1667/RADE-22-00074.1

Better management of patients with radiation injury requires more accurate methods for assessing the severity of radiation exposure. In this article, researchers at the National Cancer Institute in the U.S. and Nagoya City University in Japan describe a proof-of-concept study to identify protein markers of total-body irradiation (TBI) and organ-specific irradiation. The researchers gave mice either a single total-body or brain-, lung- or gut-specific X-ray dose and then used the SomaScan Assay to measure the levels of 1,310 proteins in serial blood samples collected post-irradiation (1, 3 and 7 days for TBI, lung and brain; 3, 7 and 14 days for gut). The SomaScan data were used to construct three protein models that predicted radiation exposure: Model 1 was developed by comparing all irradiated samples to sham-irradiated controls; model 2 compared TBI, pooled partial irradiation and controls; and model 3 compared each organ-specific irradiation to controls. The overall predictive accuracies were 89%, 78% and 55%, respectively. All three models had difficulty distinguishing partial-irradiation from controls. This study illustrates the utility and challenges of developing proteomic algorithms for biodosimetry.

Ngo, D *et al.* (2020) "Circulating testican-2 is a podocyte-derived marker of kidney health." *Proc Natl Acad Sci U S A* **117**(40): 25026-25035.

https://www.doi.org/10.1073/pnas.2009606117

—and—

Wen, D *et al.* (2022) "Testican-2 is Associated with Reduced Risk of Incident ESKD." *J Am Soc Nephrol.*, *epub ahead of print*.

https://www.doi.org/10.1681/ASN.2022020216

In Ngo, D *et al*., researchers at Beth Israel Deaconess Medical Center and Massachusetts General Hospital, used the SomaScan Assay to examine the associations between circulating proteins and estimated glomerular filtration rate (eGFR), a measure of kidney function. They compared levels of 1,305 proteins in renal arterial and venous samples from 22 individuals. While most proteins decreased from artery to vein, indicating clearance by the kidneys, testican-2 increased. The researchers leveraged SomaScan data from two large community-based cohorts to show that higher plasma levels of testican-2 were associated with higher eGFR, lower rate of eGFR decline and lower risk of chronic kidney disease (CKD) in individuals with relatively normal kidney function.

In a follow-on study from Wen, D *et al*., researchers at Massachusetts General Hospital, Johns Hopkins Bloomberg School of Public Health and the CKD Biomarkers Consortium examined the association between testican-2 and progression of CKD, including development of end stage kidney disease (ESKD). They leveraged SomaScan measurements of testican-2 from three cohorts that included more than 8,000 individuals, many with CKD. They found that higher levels of plasma testican-2 associated with reduced risk of ESKD.

Taken together, these findings suggest that testican-2 could be a biomarker of kidney function and could be playing an active role in supporting kidney health.

Sveinbjornsson, G *et al.* (2022) "Multiomics study of nonalcoholic fatty liver disease." *Nat Genet.* **54**: 1652–1663

https://www.doi.org/10.1038/s41588-022-01199-5

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the world, but diagnosing and staging NAFLD remains challenging. NAFLD begins with buildup of fat in the liver (NAFL) and can progress to nonalcoholic steatohepatitis (NASH), which is characterized by chronic inflammation and liver damage. Individuals with NAFLD/NASH are at higher risk of developing cirrhosis and hepatocellular carcinoma. In this study, researchers at deCODE genetics, a subsidiary of Amgen, performed a genome-wide association study of NAFL, cirrhosis and hepatocellular carcinoma and integrated the findings with RNA expression and proteomic data. They designed models that included plasma proteins that could discriminate between NAFL and cirrhosis better than a model trained on liver enzymes and genetic risk scores (GRSs). The authors state, "Levels of plasma proteins have the potential to serve as a noninvasive tool for use in the diagnosis and monitoring of disease, whereas GRSs are associated with a lifetime risk of disease."

Nawaz, MS *et al.* (2022) "Thirty novel sequence variants impacting human intracranial volume." *Brain Commun* **4**(6): fcac271.

https://www.doi.org/10.1093/braincomms/fcac271

The volume of the cranial cavity (intracranial volume, ICV) is genetically linked to cognitive function and several neurological disorders. In this article, researchers at deCODE genetics/Amgen, University of Iceland and Landspitali University Hospital in Reykjavik describe a meta-analysis of three ICV genome-wide association studies. This was the largest study of its kind to date, with a total of 79,174 participants. They found 64 ICV-associated sequence variants, of which 30 were novel. Leveraging previously published transcriptomic and SomaScan proteomic data, they uncovered 12 genes that likely mediate the effect of the genetic variants. They observed that Parkinson's disease cases have greater ICV than controls, attention deficit hyperactivity disorder (ADHD) cases have smaller ICV than controls, and certain genetic variants increase risk of Parkinson's disease or decrease risk of ADHD. These findings demonstrate how multiomics can provide insight into complex biological relationships between ICV and brain dysfunction.

Omenn, GS *et al.* (2022) "The 2022 Report on the Human Proteome from the HUPO Human Proteome Project." *J Proteome Res.*, *epub ahead of print.*

https://www.doi.org/10.1021/acs.jproteome.2c00498

This report presents highlights from the HUPO Human Proteome Project, whose goals are to identify predicted proteins coded by the human genome and make proteomics an integral part of human health and disease studies.

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Zhou, L *et al.* (2022) "Integrated proteomic and metabolomic modules identified as biomarkers of mortality in the Atherosclerosis Risk in Communities study and the African American Study of Kidney Disease and Hypertension." *Hum Genomics* **16**(1): 53.

https://www.doi.org/10.1186/s40246-022-00425-9

The proteome and the metabolome are central to human health and disease, as proteins play critical roles in physiological processes and metabolites are often intermediates or end products in these processes. In this article, researchers at Johns Hopkins Bloomberg School of Public Health describe an integrated analysis of metabolomic data and SomaScan proteomic data in 4,027 participants in the Atherosclerosis Risk in Communities (ARIC) study, a general population cohort of older adults. They identified 224 modules of correlated proteins and metabolites, including 60 that were associated with mortality. Four of the mortality-related modules also associated in the African American Study of Kidney Disease and Hypertension (AASK), a chronic kidney disease cohort. The key proteins and metabolites in the four modules were all related to diabetes, insulin secretion, cardiovascular disease and kidney function. This study provides insight into how proteins and metabolites together contribute to mortality and established disease risk factors.

Butler, AE *et al.* (2022) "Components of the Complement Cascade Differ in Polycystic Ovary Syndrome." *Int J Mol Sci* **23**(20): 12232.

https://www.doi.org/10.3390/ijms232012232

Increased levels of proteins involved in the complement system (a part of the immune response) are seen in women with polycystic ovary syndrome (PCOS). In this study, researchers at Royal College of Surgeons in Ireland Bahrain and Hull York Medical School in the UK used the SomaScan Assay to perform a comprehensive assessment of complement proteins in blood samples collected from women with PCOS and age-matched controls. They found elevated levels of certain proteins as well as their inhibitors in the women with PCOS, which could be due to higher body mass index (BMI), hyperandrogenemia and insulin resistance.

Than, NG *et al.* (2022) "Molecular subclasses of preeclampsia characterized by a longitudinal maternal proteomics study: distinct biomarkers, disease pathways and options for prevention." *J Perinat Med*.

https://www.doi.org/10.1515/jpm-2022-0433

Preeclampsia is a potentially dangerous pregnancy complication for both mother and fetus. Currently, preeclampsia is classified into two major forms (early-onset and late-onset) based on gestational age at diagnosis rather than root causes of symptoms. In a previous study, researchers at the National Institutes of Health conducted a mass spectrometry-based investigation of maternal blood proteins that revealed four distinct patient clusters in preeclampsia. To gain further insight into the biological differences between disease subtypes, the investigators examined longitudinal blood samples collected from women with early-onset or late-onset preeclampsia and controls. They used the SomaScan Assay to compare the levels of 1,125 proteins and found that different blood proteins changed significant during pregnancy for the four preeclampsia subtypes. These findings may lead to improved biological markers of preeclampsia for screening, diagnosis and treatment.

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Ghaemi, MS *et al.* (2021) "Proteomic signatures predict preeclampsia in individual cohorts but not across cohorts - implications for clinical biomarker studies." *J Matern Fetal Neonatal Med*: 1-8.

https://www.doi.org/10.1080/14767058.2021.1888915

Preeclampsia (PE) is a potentially life-threatening disorder of pregnancy that varies widely in its clinical presentation, severity and outcomes. In this study, researchers at Stanford University School of Medicine examined the generalizability of protein models to predict preeclampsia. They used the SomaScan Assay to measure the levels of 1,305 proteins in blood samples from two cohorts of pregnant women. One cohort consisted of 18 women who developed PE and 18 women with uncomplicated pregnancies, and the second cohort consisted of 76 women with PE and 90 women with uncomplicated pregnancies. The protein models derived in each cohort failed validation in the other cohort. In contrast, protein models that predicted gestational age validated across cohorts. The authors believe that this may be because the proteomic signatures derived in individual cohorts may be capturing different PE subtypes represented within the cohorts. These results highlight the importance of using patient populations that are large enough to capture different drivers of pathophysiological processes to identify general signatures for heterogeneous disorders.

Stelzer, IA *et al.* (2021) "Integrated trajectories of the maternal metabolome, proteome, and immunome predict labor onset." *Sci Transl Med* **13**(592).

https://www.doi.org/10.1126/scitranslmed.abd9898

More accurate methods for predicting the timing of labor and day of delivery in pregnancy would help reduce complications for mother and baby. In this study, researchers Stanford University School of Medicine measured more than 7,000 plasma analytes and immune cell responses in serial blood samples collected during the last 100 days of pregnancy from 63 women who went into labor spontaneously. Plasma concentrations of 3,529 metabolites and 1,317 proteins were measured using mass spectrometry and the SomaScan Assay, respectively; mass cytometry was used to measure immune cell functions. Coordinated changes in the maternal metabolome, proteome, and immunome marked a biological shift two to four weeks before delivery. The researchers derived a multiomic model that predicted time to labor with high accuracy. These results lay the groundwork for developing a blood test to predict preterm and postterm pregnancy risk.

Tarca, AL *et al.* (2019) "The prediction of early preeclampsia: Results from a longitudinal proteomics study." *PLoS One* **14**(6): e0217273.

https://www.doi.org/10.1371/journal.pone.0217273

Tarca, AL *et al.* (2021) "Crowdsourcing assessment of maternal blood multi-omics for predicting gestational age and preterm birth." *Cell Rep Med* **2**(6): 100323.

https://www.doi.org/10.1016/j.xcrm.2021.100323

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Tarca, AL *et al.* (2022) "Human Plasma Proteome During Normal Pregnancy." *J. Proteome Res.* **21**(11): 2687–2702.

https://www.doi.org/10.1021/acs.jproteome.2c00391

Three studies led by researchers at the National Institutes of Health and Wayne State University School of Medicine used the SomaScan Assay to identify protein markers of normal pregnancies and pregnancies with complications. Their findings illustrate the potential of maternal plasma protein changes to identify women at risk of pregnancy complications with a single blood test.

In their 2019 article, Tarca *et al.* reported a longitudinal study of 90 women with normal pregnancies and 33 women with early preeclampsia (diagnosed prior to 34 weeks of gestation). They used the SomaScan Assay to measure the levels of 1,125 proteins in two to six maternal plasma samples collected throughout pregnancy from each woman. Proteomic profiles of early preeclampsia cases were also compared to those of late preeclampsia cases from a previous study. They developed protein models that could distinguish early and late preeclampsia and identified changes in maternal plasma proteins that have the potential to improve prediction of early preeclampsia and to distinguish between the early and late phenotypes.

Preterm birth (PTB) is the leading cause of newborn deaths but remains challenging to predict. In their 2021 article, Tarca reported a longitudinal whole-blood transcriptomic and SomaScan plasma proteomic study of 216 women with either normal pregnancy, spontaneous preterm birth or preeclampsia. They found that whole blood transcriptomic data could predict gestational age in both normal and complicated pregnancies as well as delivery date in normal pregnancies and PTB. Models built from plasma proteomic data predict spontaneous preterm delivery with higher accuracy and earlier in pregnancy than transcriptomic models.

Earlier versions of the SomaScan Assay have been used to identify maternal proteins that change during pregnancy and complications, and in their 2022 publication, Tarca et al. applied the latest version of the SomaScan Assay, which measures 7,288 proteins, to blood samples from 91 women during a normal pregnancy. Three to seven plasma samples were collected from the first trimester up to two days before the onset of labor, and the researchers found changes in 953 proteins that were correlated with gestational age (GA). Protein-based models that predicted GA and time from sampling to term delivery compared favorably with transcriptomic models. These results suggest that the plasma proteome may provide a non-invasive way to monitor health and predict complications in obstetrics.

Ghaemi, MS *et al.* (2019) "Multiomics modeling of the immunome, transcriptome, microbiome, proteome and metabolome adaptations during human pregnancy." *Bioinformatics* **35**(1): 95-103.

https://www.doi.org/10.1093/bioinformatics/bty537

In this study, researchers at Stanford University School of Medicine collected immunomic, transcriptomic, microbiomic, proteomic and metabolomic data on 51 samples from 17 women over the course of a normal pregnancy. Predictive modeling was used to evaluate the ability of each dataset to predict gestational age at the time of sampling. The datasets were combined into a single multiomic model that had significantly increased predictive power. The model revealed novel interactions between different biological processes that govern healthy pregnancies.

Roh, JD *et al.* (2022) "Plasma Proteomics of COVID-19-Associated Cardiovascular Complications: Implications for Pathophysiology and Therapeutics." *JACC Basic Transl Sci* **7**(5): 425-441.

https://www.doi.org/10.1016/j.jacbts.2022.01.013

Heart complications are seen in many COVID-19 patients, even those without pre-existing heart conditions. To gain greater insight into why cardiovascular complications often accompany COVID-19, a team led by researchers at Massachusetts General Hospital and Harvard Medical School used the SomaScan Assay to compare the levels of 4,996 proteins in plasma samples from 80 individuals that included healthy controls without COVID-19, moderate COVID-19 patients with or without cardiac complications, and severe COVID-19 patients with or without cardiac complications. They found that the senescence-associated secretory phenotype (SASP), a marker of aging, may play a key role in COVID-19 disease severity and cardiac involvement. In addition, increased activin/TGFβ signaling, which has been implicated in heart failure, and decreased levels of the antithrombotic protein ADAMTS13 were strongly associated with myocardial stress and injury in COVID-19 patients. They validated their findings in a second cohort of 305 COVID-19 patients as well as an animal model of COVID-19. All three of the biological processes identified can be targeted by existing FDA-approved drugs, which warrants further investigation.

Pietzner, M *et al.* (2022) “*ELF5* is a potential respiratory epithelial cell-specific risk gene for severe COVID-19.” *Nat Commun* **13**: 4484.

https://doi.org/10.1038/s41467-022-31999-6

There is accumulating evidence that a person’s genetics can predispose them to severe COVID-19. To gain insight into which genes are responsible and how they mediate their effects, a team led by researchers at Berlin Institute of Health at Charité in Germany and the University of Cambridge in the UK combined data from the COVID-19 Host Genetics Initiative with published plasma proteomic data. They identified eight possible causal proteins, including ELF5, a transcription factor that is highly expressed in the lungs. COVID-19 patients who carry a variant of the ELF5 gene had a four-fold higher risk of severe disease. They also found that people with high blood levels of G-CSF, a growth factor for blood cells, were less likely to develop severe COVID-19. A recent clinical trial showed that COVID-19 patients treated with synthetic G-CSF showed fewer severe symptoms, such as respiratory distress or sepsis. The results of this study illustrate how integrating proteomic data with genomic data can help identify putative causal factors in disease and potential treatment options.

Wu, X *et al.* (2022) "Serum proteomic profiling of rheumatoid arthritis-interstitial lung disease with a comparison to idiopathic pulmonary fibrosis." *Thorax* **77**: 1041-1044.

https://www.doi.org/10.1136/thorax-2021-217822

Pulmonary disease is commonly seen in patients with rheumatoid arthritis (RA) and many develop interstitial lung disease (ILD). ILD is characterized by lung inflammation and scarring that often goes undetected until the advanced stages, which may explain why most rheumatoid arthritis with interstitial lung disease (RA-ILD) patients die within three to five years of

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diagnosis. To identify predictive markers of ILD development or progression, a team led by researchers at Brigham and Women’s Hospital and Harvard Medical School conducted the first proteomic analysis of RA-ILD. They used the SomaScan Assay to measure the levels of 1,321 serum proteins from 159 patients that included RA, ILD, RA-ILD and healthy controls. They identified protein signatures of the presence and severity of RA-ILD that merit further study as non-invasive diagnostic tools.

Kobayashi, H *et al.* (2022) "Neuroblastoma suppressor of tumorigenicity 1 is a circulating protein associated with progression to end-stage kidney disease in diabetes." *Sci Transl Med* **14**(657): eabj2109. **(Subscription required)**

https://www.doi.org/10.1126/scitranslmed.abj2109

The transforming growth factor (TGF-β) family of proteins control an immense number of cellular processes that ensure proper functioning of the body. Disruption of TGF-β signaling pathways has been implicated in many human diseases, including development of diabetic kidney disease (DKD) and its progression to end-stage kidney disease (ESKD). In this study, a team led by scientists at the Joslin Diabetes Center and Harvard Medical School used the SomaScan Assay to measure the plasma levels of 25 TGF-β signaling proteins in four different cohorts with a total of 754 Caucasian or Pima Indian individuals with DKD. They found that the protein neuroblastoma suppressor of tumorigenicity 1 (NBL1) was the most strongly associated with development of ESKD during 10-year follow-up in all cohorts. Circulating NBL1 may play a role in progressive kidney decline and warrants further investigation as both a therapeutic target for reno-protective drugs and a prognostic biomarker for those at high risk of ESKD.

Pala, E *et al.* (2022) "Blood-biomarkers and devices for atrial fibrillation screening: Lessons learned from the AFRICAT (Atrial Fibrillation Research In CATalonia) study." *PLoS One* **17**(8): e0273571.

https://www.doi.org/10.1371/journal.pone.0273571

Atrial fibrillation (AF) is an irregular heartbeat that can in lead to blood clots, stroke and other heart complications. AF is often asymptomatic and goes undiagnosed. To identify biomarkers of AF that might be useful for screening, researchers in Spain used the SomaScan Assay to measure the levels of 1,305 proteins in plasma from 26 older adults with hypertension and diabetes, half with AF and half without. They identified 41 proteins that were significantly different in the individuals with AF. Two proteins, TIMP-2 and ST-2 were promising candidates that merit further investigation for possible use in AF screening.

Xie, Z *et al.* (2022) "Markers of endothelial glycocalyx dysfunction in Clarkson disease." *J Transl Med* **20**(1): 380.

https://www.doi.org/10.1186/s12967-022-03587-1

Idiopathic systemic capillary leak syndrome (ISCLS), also known as Clarkson’s disease, is a rare condition in which massive amounts of plasma leaks out of tiny blood vessels into the surrounding tissue. ISCLS episodes can cause dangerously low blood pressure and blood thickening as well as nerve, muscle and organ damage. ISCLS leakage could be caused by damage to the endothelial glycocalyx (eGCX) layer that coats the inner surfaces of blood vessels. In this study, a team led by researchers at the National Institutes of Health analyzed eGCX-related markers in blood from patients with ISCLS during acute disease flares and convalescence. Serum levels of eGCX-related factors measured using ELISA were elevated at baseline and during ISCLS flares. SomaScan proteomic analysis revealed increased levels of eGCX-related proteins in acute ISCLS compared to remission plasma, but the abundance of cell damage markers did not differ in acute and baseline plasma. These results suggest that eGCX dysfunction, but not blood vessel injury, may contribute to clinical symptoms of acute ISCLS.

Paranjpe, MD *et al.* (2022) "Neurocognitive trajectory and proteomic signature of inherited risk for Alzheimer's disease." *PLoS Genet* **18**(9): e1010294.

https://www.doi.org/10.1371/journal.pgen.1010294

This article from team led by researchers at the Broad Institute of MIT and Harvard describes a genetic predictor for Alzheimer’s disease (AD). To develop the polygenic risk score, the researchers used data from a genome wide association study involving 21,982 AD cases and 41,944 unaffected controls that analyzed over 7 million common DNA variants. They then used the SomaScan Assay to measure the levels of 3,231 proteins in the blood of 636 middle-aged individuals with high or low risk scores and found proteins whose levels were changed in individuals with a high genetic risk of developing AD. In addition to the well-known apolipoprotein E biomarker, their analysis uncovered 27 additional proteins, several of which have known roles related to AD pathogenesis. This study suggests a polygenic risk score that could be used to identify high-risk individuals before the onset of cognitive decline and identify new circulating protein markers of AD.

Abdelhamid, SS *et al.* (2022) “Multi-Omic Admission-Based Prognostic Biomarkers Identified by Machine Learning Algorithms Predict Patient Recovery and 30-Day Survival in Trauma Patients.” Metabolites **12**(9): 774.

https://doi.org/10.3390/metabo12090774

In this study, researchers at University of Pittsburgh applied machine learning algorithms to a database of over 8,500 proteomic, metabolomic, and lipidomic measurements of severely injured trauma patients to identify blood-based biomarkers that could predict death and slow recovery. A combination of five proteins derived from SomaScan measurements was best at discriminating patients who recovered quickly from those who died or spent longer than seven days in the intensive care unit. A combination of twenty-six markers (11 metabolites, 9 lipids and 6 proteins) was the best at predicting 30-day survival. These results suggest that a blood test delivered upon hospital admission could aid clinical decision making for trauma patients.

Appiah, D *et al.* (2022) "Long-term changes in plasma proteomic profiles in premenopausal and postmenopausal Black and White women: the Atherosclerosis Risk in Communities study." *Menopause* **29**(10): 1150-1160*.* **(Subscription required)**

https://doi.org/10.1097/gme.0000000000002031

Menopause is associated with several chronic conditions such as osteoporosis, breast and endometrial cancers and cardiovascular disease. To begin to understand why, a team led by researchers at Texas Tech University Health Sciences

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Center used SomaScan data on 4,697 plasma proteins from women enrolled in the Atherosclerosis Risk in Communities (ARIC) study. At baseline, 38 proteins differed significantly between premenopausal and postmenopausal women, with 29 of the proteins also showing different changes between groups as the premenopausal women reached menopause. These proteins warrant further study to help understand disease risk and development for women after menopause.

Casanova, R *et al.* (2022) "Is an MRI-derived anatomical measure of dementia risk also a measure of brain aging?" *Geroscience, epub ahead of print.* **(Subscription required)**

https://www.doi.org/10.1007/s11357-022-00650-z

In a previous study, researchers at Wake Forest School of Medicine developed an MRI-based measure of dementia risk called the Alzheimer's Disease Pattern Similarity (AD-PS) score. In this study, they found that the AD-PS score was associated with three indicators of biological aging: all-cause death, age-related proteins previously identified by the SomaScan Assay and a deficit accumulation index based on 38 health conditions. Their results suggest that the AD-PS score could be used to measure brain aging.

Javaheri, A et al. (2022) "Proteomic Analysis of Effects of Spironolactone in Heart Failure With Preserved Ejection Fraction." *Circ Heart Fail.* **15**(9): e009693. **(Subscription required)**

https://www.ahajournals.org/doi/10.1161/CIRCHEARTFAILURE.121.009693

TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial) was a multicenter clinical trial designed to evaluate the drug spironolactone in patients with HFpEF (heart failure with preserved ejection fraction). HFpEF, which happens when the heart pumps normally but the left ventricle is too stiff to fill properly, affects approximately half of heart failure patients. Initial results from TOPCAT showed no significant improvement in HFpEF patients treated with spironolactone vs. placebo. However, a post-hoc analysis did show significant improvements with spironolactone, but only in patients enrolled from centers in North and South America. This article from researchers at the University of Pennsylvania School of Medicine, Washington University School of Medicine and Bristol Myers Squibb reports for the first time, a comprehensive proteomic analysis of the effect of spironolactone therapy in TOPCAT participants from the Americas. The researchers used the SomaScan Assay to measure the levels of 4928 unique proteins in plasma samples from 164 plasma samples and identified seven proteins that were significantly impacted by spironolactone treatment. The seven proteins are involved in multiple biological processes, which illustrates the broad effects of spironolactone in HFpEF and provides greater insight into its mechanism of action as well as unintended effects.

Lu, T et al. (2022) "Circulating Proteins Influencing Psychiatric Disease: A Mendelian Randomization Study." *Biol Psychiatry, epub ahead of print.* **(Subscription required)**

https://doi.org/10.1016/j.biopsych.2022.08.015

New approaches for treating psychiatric disorders is urgently needed. In this study, researchers at Jewish General Hospital and McGill University in Montreal, Canada searched for circulating proteins associated with increased risk of ten complex

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psychiatric disorders: attention deficit hyperactivity disorder (ADHD), anorexia nervosa, anxiety disorders, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), schizophrenia and Tourette Syndrome. They used an analytical technique called Mendelian randomization to analyze genetic variants associated with 1,611 circulating proteins (i.e., protein quantitative trait loci, pQTLs) that had been identified in six large-scale proteomic studies (four that used the SomaScan Assay and two that used antibody-based assays). They found 413 protein-to-disease associations for seven of the psychiatric disorders, which may guide development of new preventative or therapeutic drugs.

Katz, DH et al. (2022) "Proteomic profiling platforms head to head: Leveraging genetics and clinical traits to compare aptamer- and antibody-based methods." *Sci Adv* **8**:eabm5164.

https://www.science.org/doi/10.1126/sciadv.abm5164?cookieSet=1

This study led by researchers at Beth Israel Deaconess Medical Center and Harvard Medical School compared the SomaScan and Olink Explore proteomic platforms across four performance metrics: precision, accuracy, analytic breadth, and phenotypic associations. The researchers assessed findings from two older versions of the SomaScan Assay (measuring approximately 1.3K or 5K proteins) and an older version of the Olink Explore (measuring approximately 1.5K proteins) in 568 adults from the Jackson Heart Study and 219 participants in the HERITAGE Family Study. The SomaScan Assay showed significantly better reproducibility than Olink, with smaller intra- and inter-assay variation, which means that the SomaScan Assay requires far fewer samples to detect meaningful biological differences. The SomaScan Assay also outperformed Olink in the variety of proteins analyzed. Although Olink's assay showed more protein associations with eight clinical traits, it did not explain more variance in each trait. The researchers did not have mass spectrometry data (the gold standard) to characterize protein target binding, so instead used genetic variation (i.e., protein quantitative trait loci, pQTLs) to infer specificity. A higher percentage of Olink proteins had cis-pQTLs, including many proteins with low correlation with the SomaScan Assay. The authors concluded that the SomaScan Assay had greater precision and analytic breadth across the proteome, while the Olink Explore had more reliable protein target specificity and phenotypic associations.

Shi, X *et al.* (2022) "The associations between plasma soluble Trem1 and neurological diseases: a Mendelian randomization study." *J Neuroinflammation* **19**(1): 218.

https://www.doi.org/10.1186/s12974-022-02582-z

Trem1, a protein that amplifies the inflammatory response, is associated with the development of neurological diseases. In this study, researchers in China examined causal relationships between the levels of Trem1 in plasma and the risk of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, cerebrovascular diseases and migraine. They performed a Mendelian randomization (MR) analysis using genetic variants from seven genome wide association studies and plasma Trem1 from a published SomaScan study (see Sun, BB *et al.* (2018) *Nature* **558**: 73-79 https://www.ncbi.nlm.nih.gov/pubmed/29875488).Their findings suggest that plasma Trem1 may be important in the development of both Alzheimer's disease and epilepsy.

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Moin, ASM et al. (2022) “Inflammatory Markers in Non-Obese Women with Polycystic Ovary Syndrome Are Not Elevated and Show No Correlation with Vitamin D Metabolites.” *Nutrients* **14**(17):3540.

https://doi.org/10.3390/nu14173540

Chronic low-grade inflammation and vitamin D deficiency are often seen in women with polycystic ovary syndrome (PCOS). In this study, researchers at Royal College of Surgeons in Ireland Bahrain used the SomaScan Assay to measure the levels of 24 inflammatory proteins and 12 matrix metalloproteinases (proteins modulated by the inflammatory process) in non-obese, non-insulin resistant women with PCOS. Compared to controls, there were no significant differences seen in any of the inflammatory proteins or in vitamin D metabolites, which suggest that these features may be obesity-driven rather than PCOS-driven.

Wu, J *et al.* (2022) "High Dimensional Multi-omics Reveals Unique Characteristics of Early Plasma Administration in Polytrauma Patients with TBI." *Ann Surg* **276**(4): 673-683.

https://www.doi.org/10.1097/SLA.0000000000005610

The Prehospital Air Medical Plasma (PAMPer) Trial found that thawed plasma (TP) given prior to hospital admission significantly increased survival rates of trauma patients with traumatic brain injury (TBI). A previous multi-omic study had shown unique circulating biomarkers in TBI patients who received early TP (see Wu, J *et al.* (2021) *Cell Rep Med* **2**: 100478. https://doi.org/10.1016/j.xcrm.2021.100478). This follow-on study led by researchers at University of Pittsburgh School of Medicine, University of Pittsburgh and Pittsburgh Trauma Research Center involved a deeper analysis to find the factors that explain why early TP specifically benefits severely injured TBI patients. They used the SomaScan Assay to measure the levels of 7,211 proteins in plasma from 149 trauma patients (87 survivors and 62 non-survivors). They combined the proteomic data with metabolomic and lipidomic data from the same patients and identified 16 proteins and 41 lipids that explained the survival benefit of pre-hospital TP to TBI patients. Many of the proteins are involved in blood clotting, and the investigators postulate that improved coagulation may prevent intracranial bleeding, where even small amounts of blood can be life-threatening.

Luther, J *et al.* (2022) "The circulating proteomic signature of alcohol-associated liver disease." *JCI Insight* **7**(14): e159775.

https://www.doi.org/10.1172/jci.insight.159775

Alcohol-associated liver disease (ALD) is liver damage caused by alcohol abuse and is a leading cause of liver disease and alcohol-related deaths. To identify new biomarkers of ALD, researchers at Massachusetts General Hospital used the SomaScan Assay to measure the levels of 1,305 plasma proteins in patients with mild to severe ALD and healthy controls. Roughly half of the proteins differed significantly between disease stages, and many had no previous links to ALD. Nine of the top 10 proteins associated with severe ALD were also elevated in heavy drinkers who had normal liver test results. This suggests that these proteins may be indicators of subclinical ALD, with potential as therapeutic targets and biomarkers for disease progression.

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Surapaneni, A *et al.* (2022) "Identification of 969 protein quantitative trait loci in an African American population with kidney disease attributed to hypertension." *Kidney Int* **102**(5): 1167-1177.

https://www.doi.org/10.1016/j.kint.2022.07.005

Connecting proteins to genetic variants linked to disease can help identify causal factors and targets for new or existing drugs. This article from researchers at Johns Hopkins University Bloomberg School of Public Health and New York University Grossman School of Medicines reports genetic determinants of the serum proteome in 466 African Americans with chronic kidney disease attributed to hypertension. The investigators used the SomaScan Assay to measure the levels of 7,596 plasma proteins in serum samples collected at baseline from participants in the African American Study of Kidney Disease and Hypertension (AASK) study. They identified more than 400 new protein quantitative trait loci (pQTLs) and confirmed previous pQTLs discovered in largely European-ancestry populations. These data are a valuable resource that can be used to find proteins that cause disease, to inform drug development and to understand racial differences in disease risk.

Shu, X *et al.* (2022) "Associations between circulating proteins and risk of breast cancer by intrinsic subtypes: a Mendelian randomisation analysis." *Br J Cancer* **127**(8): 1507-1514. **(Subscription required)**

https://www.doi.org/10.1038/s41416-022-01923-2

Breast cancer is a disease that can vary between individuals and even between tumors within the same individual, but this heterogeneity is not usually considered in determining breast cancer risk factors. This study led by researchers at Memorial Sloan Kettering Cancer Center evaluated the associations between 1,890 circulating proteins and breast cancer risk within five different molecular subtypes. They combined data from a genetic association study of breast cancer subtypes and a proteogenomic study that used the SomaScan Assay to identify protein quantitative trait loci (pQTLs) in 3,301 healthy individuals (see Sun, BB *et al.* (2018) *Nature* **558**: 73-79. https://www.ncbi.nlm.nih.gov/pubmed/29875488). They identified 98 proteins that were significantly associated with risk of one or more of the breast cancer subtypes. Three proteins (ICAM, PLA2R1 and TXNDC12) varied substantially in their risk of different cancer subtypes (i.e., higher levels of the protein increased risk for one subtype but decreased risk for another). These results illustrate the importance of accounting for cancer subtype when searching for new biomarkers and drug targets.

Degnes, ML *et al.* (2022) "Placenta-derived proteins across gestation in healthy pregnancies-a novel approach to assess placental function?" *BMC Med* **20**(1): 227.

https://www.doi.org/10.1186/s12916-022-02415-z

A healthy pregnancy requires a healthy placenta, but this is difficult to gauge due to the inaccessibility of the placenta and the lack of universally accepted biomarkers of placental function. In this article, a team led by researchers in Norway used the SomaScan Assay to measure the levels of nearly 5,000 proteins in blood samples collected from veins and arteries going in and out of the placenta for 75 healthy pregnancies. They identified 256 proteins secreted by the placenta and 101 taken up by the placenta. They also analyzed blood collected from 70 mothers at three different time points during their pregnancies and identified five placental-derived proteins that were tightly linked to gestational age. A “placental proteomic clock” could be used to diagnose and monitor placenta-related complications during pregnancy.

Sasamoto, N *et al.* (2022) "Circulating proteomic profiles associated with endometriosis in adolescents and young adults." *Hum Reprod* **37**(9): 2042-2053. **(Subscription required)**

https://www.doi.org/10.1093/humrep/deac146

Endometriosis is a condition in which the tissue that lines the uterus grows outside of the uterus. Although many women with endometriosis experience painful symptoms as teenagers, very little is known about endometriosis in adolescence. In this article, Researchers at Brigham and Women's Hospital, Beth Israel Deaconess and Harvard Medical School report the first study to examine circulating proteins in young women with and without endometriosis. They used the SomaScan Assay to compare the levels of 1,305 plasma proteins in 142 confirmed endometriosis cases and 74 controls. They identified 63 proteins associated with endometriosis, many of which are involved in cell migration and angiogenesis. These results provide valuable information on the early disease course of endometriosis.

Austin, TR *et al.* (2022) "Proteomics and Population Biology in the Cardiovascular Health Study (CHS): design of a study with mentored access and active data sharing." *Eur J Epidemiol* **37**(7): 755-765.

https://www.doi.org/10.1007/s10654-022-00888-z

This article describes collection of SomaScan Assay data measuring 4,979 proteins in plasma from 3,188 participants of the Cardiovascular Health Study (CHS), a cohort designed to evaluate risk factors for coronary heart disease and stroke in older adults. The data will be shared across seven CHS working groups evaluating associations between levels of circulating proteins and various health outcomes. The goals are to understand of the causes of heart disease and other conditions in older adults and identify targets for drug development.

Gudicha, DW *et al.* (2022) "The amniotic fluid proteome predicts imminent preterm delivery in asymptomatic women with a short cervix." *Sci Rep* **12**(1): 11781.

https://www.doi.org/10.1038/s41598-022-15392-3

Women with shortened cervixes are more likely to have preterm babies, increasing the likelihood of infant health complications and death. This study led by researchers at the National Institutes of Health and Wayne State University School of Medicine identified amniotic fluid (AF) proteins that could predict imminent delivery in mothers with a short cervix. They used the SomaScan Assay to measure the levels of 1,310 proteins in AF obtained from women with a short cervix at 16-21 weeks of gestation and found 17 proteins that were significantly different in those who delivered within two weeks of the amniocentesis. Many of the proteins are associated with immune function and inflammatory processes. The combination

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of AF protein abundances and quantitative cervical length improved prediction of the timing of delivery compared to cervical length alone and could have implications for managing higher risk pregnancies.

Vorn, R et al. (2022) “Proteomic Profiling of Plasma Biomarkers Associated With Return to Sport Following Concussion: Findings From the NCAA and Department of Defense CARE Consortium.” *Front Neurol* **13**: 901238.

https://doi.org/10.3389/fneur.2022.901238

Determining when an athlete can safely return to sport (RTS) after suffering a sports-related concussion (SRC) is challenging due to a lack of objective measures for assessing neurological recovery. In this article, a team led by researchers at Johns Hopkins University investigated whether profiling plasma proteins could identify biomarkers of SRC recuperation. They used the SomaScan Assay to measure the levels of 1,305 proteins in plasma samples from 140 concussed athletes enrolled in the NCAA–Department of Defense Concussion Assessment, Research and Education (CARE) Consortium. A single blood was collected from each participant within 48 hours of the SRC. The researchers identified 87 plasma proteins that were significantly different between athletes who were asymptomatic within 14 days post-concussion and those whose symptoms took longer to resolve. The proteins point to biological processes involved in neurological recovery and could aid clinicians in RTS decision-making.

Cederberg, KLJ et al. (2022) “Proteomic Biomarkers of the Apnea Hypopnea Index and Obstructive Sleep Apnea: Insights into the Pathophysiology of Presence, Severity, and Treatment Response.” *Int J Mol Sci. 23*(14): 7983.

https://doi.org/10.3390/ijms23147983

Obstructive sleep apnea (OSA) is a common disorder caused by airway blockage that pauses breathing and causes fragmented, nonrestorative sleep. OSA is associated with increased risk of high blood pressure, heart failure, arrythmia and stroke. In a previous study, researchers at Stanford University used the SomaScan Assay to identify serum proteins predictive of moderate to severe OSA and found 3 proteins that were responsive to positive airway pressure (PAP) treatment (see Ambati, A *et al.* (2020) *Sleep* **43**(11). https://pubmed.ncbi.nlm.nih.gov/32369590/). In this study, the investigators extended and validated their previous results, using the SomaScan Assay to measure more proteins (~5,000) on a larger group of participants (~1,400) in the Stanford Technology Analytics and Genomics in Sleep study. They identified 84 proteins that were associated with the apnea–hypopnea index, a measure of airway obstructions that occur during sleep. Forty-four of the 84 proteins (52%) were new as they were not in the older version of the SomaScan Assay used in the previous study. Eight proteins were robust predictors of the presence and severity of OSA and could be potential markers of treatment response. Some of the key proteins play roles in blood vessel wall function and coagulation which might explain the connection between OSA and cardiovascular disease.

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Hedou, J *et al.* (2022) "Proteomic Biomarkers of Kleine-Levin Syndrome." *Sleep* ***45****(9).*

https://www.doi.org/10.1093/sleep/zsac097

Kleine–Levin syndrome (KLS) is a rare disorder where patients, usually teenage boys, have episodes of excessive sleeping, as much as 20 hours a day. The cause of KLS is not known and it may last for more than a decade, but then usually disappears. In this study, an international team led by researchers at Stanford University used the SomaScan Assay to measure the levels of more than 1,000 proteins in cerebrospinal fluid (CSF) and serum from KLS patients and controls. They identified 28 proteins in CSF and 141 proteins in serum that were differentially expressed in KLS. These results provide insight into the biological processes dysregulated in KLS and protein signatures that could serve as possible diagnostic markers.

Nikpay, M *et al.* (2022) *"*Genome-wide screening identifies DNA methylation sites that regulate the blood proteome." *Epigenomics* **14**(13): 837–848. **(Subscription required)**

https://doi.org/10.2217/epi-2022-0119

Methylation is a DNA modification that affects gene expression and that can play an important role in health and disease. In this study, researchers at the University of Ottawa Heart Institute and Plastenor Technologies Company in Canada identified DNA methylation sites that impact the levels of circulating proteins. They integrated published data on genetic variants that affect DNA methylation with data on genetic variants that affect plasma protein levels (see Sun, BB *et al.* (2018) *Nature* **558**: 73-79. https://www.ncbi.nlm.nih.gov/pubmed/29875488) and identified 165 methylation sites that regulate 138 proteins. Most of the associations were located on different chromosomes. These findings can be used to investigate the molecular underpinnings diseases and potential targets for therapeutic interventions.

Timsina, J *et al.* (2022) "Comparative Analysis of Alzheimer's Disease Cerebrospinal Fluid Biomarkers Measurement by Multiplex SOMAscan Platform and Immunoassay-Based Approach."
J Alzheimers Dis. **89**(1): 193-207.

https://www.doi.org/10.3233/JAD-220399

This study led by researchers at Washington University School of Medicine compared the aptamer-based SomaScan Assay to antibody-based assays for five cerebrospinal fluid (CSF) proteins associated with Alzheimer's disease (AD) and neurodegeneration: neurofilament light chain protein (NfL), neurogranin, visinin like protein 1 (VILIP-1), soluble triggering receptor expressed on myeloid cells 2 (sTREM2) and synaptosomal-associated protein 25 (SNAP-25). The proteins were measured in CSF samples from four different cohorts that included patients diagnosed with AD or other types of neurodegenerative diseases as well as cognitively normal controls. Good inter-assay agreement was seen for all the proteins except SNAP-25, which will require follow-up investigation.

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Banu, K *et al.* (2022) “Prospects for the application of aptamer based assay platforms in pathogen detection.” *Biocybern Biomed Eng.* **42**(3): 934-949. **(Subscription required)**

https://doi.org/10.1016/j.bbe.2022.07.005

Aptamers bind to a wide range of target molecules and provide significant advantages over antibodies, such as stability at different temperatures and pH, ease of synthesis, longer shelf life and low batch-to-batch variability. This review provides an overview of aptamer-based technologies, including SOMAmer reagents and the SomaScan Platform, that could be used to detect pathogenic organisms.

Fernandez, N et al. (2022) “High dimensional immune profiling of smoldering multiple myeloma distinguishes distinct tumor microenvironments.” *Clin Lymphoma Myeloma Leuk* **22**(11): 853-862. **(Subscription required)**

https://doi.org/10.1016/j.clml.2022.07.001

Smoldering multiple myeloma (SMM) is a precancerous condition that can progress into multiple myeloma (MM), a cancer that develops in white blood cells found in bone marrow. Currently, there is no accurate way to predict which people with SMM are at high risk of developing MM. In this article, researchers at the Icahn School of Medicine at Mt. Sinai analyzed bone marrow samples from 72 individuals with SMM using a variety of techniques, including mass cytometry, T cell receptor sequencing and proteomics. They identified three groups of SMM individuals with differences in bone marrow microenvironments that may help determine those who progress to MM.

Luo, P *et al.* (2022) "Exploring the genetic relationship between deep vein thrombosis and plasma protein: a new research idea." *Expert Rev Hematol* **15**(9): 867-873. **(Subscription required)**

https://www.doi.org/10.1080/17474086.2022.2104707

The goal of this study was to analyze genetic correlations between plasma proteins and deep venous thrombosis (DVT). Researchers at Xi’an Jiaotong University and Sichuan University in China combined genome wide association study (GWAS) data of DVT with GWAS data of 3,283 plasma proteins from a published SomaScan study (see Sun, BB *et al.* (2018) *Nature* **558**: 73-79. https://www.ncbi.nlm.nih.gov/pubmed/29875488). They identified eight proteins connected to DVT, including Chromogranin-A as a possible causal factor.

Feng, R *et al.* (2022) "Genome- and transcriptome-wide association studies show that pulmonary embolism is associated with bone-forming proteins." *Expert Rev Hematol* **15**(10): 951-958. **(Subscription required)**

https://www.doi.org/10.1080/17474086.2022.2103534

A pulmonary embolism (PE) is a potentially life-threatening blood clot that blocks blood flow to the lung. In this article, researchers in China used published genomic, transcriptomic and proteomic data to identify five plasma proteins associated with PE. They also found that PE was highly correlated with bone morphogenic proteins. These results provide new insights into the pathogenesis of PE and possible biomarkers to allow identification of at-risk patients.

Delannoy-Bruno, O *et al.* (2022) "An approach for evaluating the effects of dietary fiber polysaccharides on the human gut microbiome and plasma proteome." *Proc Natl Acad Sci U S A* **119**(20): e2123411119.

https://www.doi.org/10.1073/pnas.2123411119

Two pilot studies led by scientists at Washington University examined the impact of different fiber supplements on the gut microbiome and the plasma proteome of overweight and obese individuals. During the 10-week trial, participants ate a normal diet supplemented with fiber-enriched snacks. The researchers used DNA sequencing to quantify genes encoding carbohydrate-active enzymes in the fecal microbiome, mass spectrometry to analyze carbohydrate structures in feces, and the SomaScan Assay to measure the levels of 1,305 proteins in plasma. This approach could be used to design dietary supplements that improve nutritional and health status.

Harbaum, L *et al.* (2022) "Mining the Plasma Proteome for Insights into the Molecular Pathology of Pulmonary Arterial Hypertension." *Am J Respir Crit Care Med* **205**(12): 1449-1460. **(Subscription required)**

https://www.doi.org/10.1164/rccm.202109-2106OC

Pulmonary arterial hypertension (PAH) is a rare type of high blood pressure in the arteries that lead to the lungs. This article from a team led by researchers at Imperial College London in the UK describes the first comprehensive integration of proteomic and genomic data in patients with PAH. They used the SomaScan Assay to measure the levels of 4,152 plasma proteins in 357 patients with idiopathic or heritable PAH, 103 healthy volunteers and 23 relatives of PAH patients. They identified 208 plasma proteins that were different between patients and controls, 49 of which were associated with transplant-free survival. Integrating genetic data on PAH-related DNA variants implicated two proteins, netrin-4 and thrombospondin-2, as likely causal factors. Their results suggest that suppressing netrin-4 levels or raising thrombospondin-2 levels could benefit PAH patients.

Wesenhagen, KEJ *et al.* (2022) "Effects of age, amyloid, sex, and APOE epsilon4 on the CSF proteome in normal cognition." *Alzheimers Dement (Amst)* **14**(1): e12286.

https://www.doi.org/10.1002/dad2.12286

This study led by researchers at Vrije Universiteit Amsterdam examined protein changes in cerebrospinal fluid (CSF) associated with increased Alzheimer's disease risk. They used mass spectrometry and the SomaScan Assay to measure the levels of 1,149 proteins in CSF from 277 adults without dementia. They identified 252 proteins that increased with age independent of amyloid status, and 21 proteins that decreased with age exclusively in people with abnormal amyloid levels. These results point to proteins that could serve as early markers of Alzheimer's disease and possible therapeutic targets.

Moore, HB *et al.* (2022) “Proteomics of Coagulopathy Following Injury Reveals Limitations of Using Laboratory Assessment to Define Trauma-Induced Coagulopathy to Predict Massive Transfusion.” *Ann Surg* **3**(2): e167.

https://www.doi.org/10.1097/AS9.0000000000000167

Severe trauma can induce coagulopathy, a potentially fatal condition that can cause uncontrolled bleeding requiring massive transfusion (MT). Trauma-induced coagulopathy (TIC) is currently diagnosed by testing the efficiency of blood clotting with methods such as prothrombin time (INR) or thrombelastography (TEG). This study led by researchers at University of Pittsburgh, University of Michigan Medical School and University of Colorado, Denver used the SomaScan Assay to see if protein changes associated with MT were the same as protein changes seen in TIC diagnosed by INR, TEG or a trauma surgeon. They used the SomaScan Assay to measure the levels of 1,305 proteins in blood samples from eight level I trauma centers and identified 578 proteins that were significantly different among MT patients and non-MT patients. Overall, only 27% of the proteins associated with MT were captured by TIC diagnosed using INR, TEG, or clinical judgement. These results indicate that proteomic analysis may be a more effective way to identify patients at risk for massive bleeding than existing methods.

Kobayashi, H *et al.* (2022) "Results of untargeted analysis using the SOMAscan proteomics platform indicates novel associations of circulating proteins with risk of progression to kidney failure in diabetes." *Kidney Int* **102**(2): 370-381.

https://www.doi.org/10.1016/j.kint.2022.04.022

In this study, a team led by researchers at Joslin Diabetes Center and Harvard Medical School searched for new biological markers of end-stage kidney disease (ESKD) in people with diabetes. They used the SomaScan Assay to measure the levels of 1,129 proteins in blood samples from four different cohorts encompassing 754 individuals with type 1 and type 2 diabetes and early and late diabetic kidney disease. Thirty percent of the individuals developed kidney failure within 10 years. The researchers identified eleven previously unreported circulating proteins associated with ESKD risk in diabetes. Interestingly, six of the proteins have roles in neuron development, which could point to causal mechanisms involved in disease development.

Matsuno, H *et al.* (2022) "Association between vascular endothelial growth factor-mediated blood-brain barrier dysfunction and stress-induced depression." *Mol Psychiatry* **27**(9): 3822-3832. **(Subscription required)**

https://www.doi.org/10.1038/s41380-022-01618-3

Stress is a strong risk factor for major depressive disorder (MDD), and there is evidence that this could be due to stress-induced permeability of the blood brain barrier (BBB). In this study, scientists in Japan investigated changes in BBB permeability in patients with MDD and in a mouse model of chronic stress. Vascular endothelial growth factor (VEGF) is a protein known to increase vascular permeability and served as a surrogate marker for BBB permeability. They found

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increased plasma levels of VEGF (measured by the SomaScan Assay) and CSF levels (measured by immunoassay) in patients with MDD. Inhibition of a receptor for VEGF suppressed BBB permeability and depressive-like behavior in mice, suggesting a possible therapeutic strategy for MDD.

Nocera, AL *et al.* (2022) "Cystatin SN is a Potent Upstream Initiator of Epithelial Derived Type 2 Inflammation in Chronic Rhinosinusitis." *J Allergy Clin Immunol* **150**(4): 872-881. **(Subscription required)**

https://www.doi.org/10.1016/j.jaci.2022.04.034

Chronic rhinosinusitis with nasal polyps (CRSwNP) is long-lasting sinus inflammation that often persists even after treatment with corticosteroids or surgical polyp removal. In a previous study, researchers at Harvard Medical School found that cystatins, a large family of proteins with diverse biological activities, are overproduced in CRSwNP (see Mueller, SK *et al.* (2019) *Int Forum Allergy Rhinol* **9**(2): 177-186 https://www.ncbi.nlm.nih.gov/pubmed/30485711**).** The goal of this study was to determine whether cystatins are a cause or consequence of inflammation in CRSwNP. The researchers used the SomaScan Assay to measure the levels of 1,305 proteins in nasal tissue and isolated exosomes from CRSwNP patients and found that high levels of cystatins SN and SA correlated with disease severity. Administering cystatin SN intranasally to healthy mice caused sinus inflammation. These data suggest that cystatin SN is a potent driver of inflammation and could be a therapeutic target for CRSwNP.

Vasbinder, A *et al.* (2022) "Assay-related differences in SuPAR levels: implications for measurement and data interpretation." *J Nephrol.*, *epub ahead of print.*

https://www.doi.org/10.1007/s40620-022-01344-7

Soluble urokinase plasminogen activator receptor (suPAR) is a protein implicated in kidney and cardiovascular disease. Researchers at the University of Michigan Frankel Cardiovascular Center compared plasma suPAR measurements collected using different assays (SomaScan, Olink and ELISA) and found significant variation. Circulating suPAR exists in different forms that originate from splice variants, proteolytic processing and glycosylation, which could account for some of the discrepancies between assays.

Loza, MJ *et al.* (2022) "Serological Biomarkers of Progression towards Diagnosis of Rheumatoid Arthritis in Active Component Military Personnel." *Arthritis Rheumatol.*, *epub ahead of print.* **(Subscription required)**

https://www.doi.org/10.1002/art.42260

Rheumatoid arthritis (RA) is an autoimmmune disease in which the immune system attacks its own tissue causing joint pain, swelling and damage. Early intervention can reduce disease progression, but RA is difficult to diagnose in its early stages because its symptoms resemble those of many diseases. The goal of this study led by researchers at Janssen Research and Development was to identify a set of serum biomarkers that could predict risk of developing RA. Serial blood samples were obtained from active US military personnel with RA, reactive arthritis or healthy controls and split into two phases.

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Phase 1 was analyzed using the SomaScan Assay to build predictive models for RA diagnosis and phase 2 was analyzed using Olink assay panels for model confirmation. They identified a group of serum proteins that could predict RA within six months of diagnosis. Although this time frame is quite short, the model could be used to screen military personnel prior to deployment to avoid placing those at imminent RA risk in a situation that could jeopardize the mission.

Bomba, L *et al.* (2022) "Whole-exome sequencing identifies rare genetic variants associated with human plasma metabolites." *Am J Hum Genet* **109**(6): 1038-1054.

https://www.doi.org/10.1016/j.ajhg.2022.04.009

In this study, a team led by researchers at Wellcome Sanger Institute in the UK measured 995 metabolites in plasma from nearly 4,000 healthy individuals. They identified 40 gene-metabolite associations and then investigated whether any of the genes were also associated with 3,622 plasma proteins measured by the SomaScan Assay in the same cohort. Overall, 66% of the associations implicated targets of approved drugs or bioactive compounds. The findings illustrate the value of metabolomics and proteomics in understanding genetic risk factors of disease.

Komarova, N *et al.* (2022) “Aptamers Targeting Cardiac Biomarkers as an Analytical Tool for the Diagnostics of Cardiovascular Diseases: A Review.” *Biomedicines* **10**(5): 1085.

https://doi.org/10.3390/biomedicines10051085

Aptamers are attractive alternatives to antibodies for analytical applications due to their low-cost synthesis, low batch-to-batch variability, ease of labeling, high specificity and high selectivity. This review evaluated existing aptamers to the most common cardiovascular biomarkers for use in routine clinical diagnostics.

Engelke, R *et al.* (2022) "Proteomic Analysis of Plasma Markers in Patients Maintained on Antipsychotics: Comparison to Patients Off Antipsychotics and Normal Controls." *Front Psychiatry* **13**: 809071.

https://www.doi.org/10.3389/fpsyt.2022.809071

Schizophrenia (SZ) or bipolar disorder (BD) are common psychiatric illnesses that share many symptoms, so correct diagnosis can be difficult. To search for more reliable biomarkers of SZ and BD, researchers at Weill Cornell Medicine in Qatar used the SomaScan Assay to measure the levels of 1,301 plasma proteins from medicated and unmedicated SZ and BD patients compared to healthy controls. They identified two proteins that accurately predicted SZ. Protein-based BD prediction was much less accurate, which may reflect different disease subtypes. Patients treated with antipsychotics showed more normal levels of several neurological proteins compared to patients who had been off drugs for at least six months. These results point to blood proteins that could inform diagnosis and management of SZ and BD.

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He, B *et al.* (2022) "Clinical applications of plasma proteomics and peptidomics: Towards precision medicine." *Proteomics Clin Appl* **16**(6): e2100097. **(Subscription required)**

https://www.doi.org/10.1002/prca.202100097

This review summarizes recent advances in plasma proteomics with a focus on applications in COVID-19 and cancer research.

Kindt, ASD *et al.* (2022) "Validation of disease-specific biomarkers for the early detection of bronchopulmonary dysplasia." *Pediatr Res*., *epub ahead of print.*

https://www.doi.org/10.1038/s41390-022-02093-w

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease that typically affects premature babies who need supplemental oxygen. There are currently no biological markers of BPD — it is usually diagnosed 28 days after birth if the baby still requires breathing assistance. A previous study led by scientists at Helmholtz Zentrum München in Germany used the SomaScan Assay to identify three proteins whose levels at birth and after 28 days predicted BPD development (see Forster, K *et al.* (2018) *Am J Respir Crit Care Med* **197**(8): 1076-1080 https://www.ncbi.nlm.nih.gov/pubmed/29053024). In this study, the researchers evaluated the performance of these potential BPD clinical biomarkers in a larger cohort. They found that a model combining the three proteins with gestational age successfully predicted BPD and all disease grades (mild, moderate and severe) in the first week of life. The model was also able to distinguish BPD from other neonatal and adult lung diseases These results pave the way for a phase 3 clinical trial to integrate the protein biomarkers into routine practice.

Haslam, DE *et al.* (2022) "Stability and reproducibility of proteomic profiles in epidemiological studies: Comparing the Olink and SOMAscan platforms." *Proteomics* **22**(13-14): e2100170. **(Subscription required)**

https://www.doi.org/10.1002/pmic.202100170

Variations in sample collection, processing and storage can affect proteomic biomarker discovery. In this study, a team led by researchers at Harvard Medical School and Brigham and Women's Hospital assessed the impact of preanalytical blood sample collection factors on protein levels measured by the SomaScan and Olink platforms (6,596 and 972 unique proteins, respectively). Overall, both platforms displayed excellent stability and reproducibility for blinded replicates and samples collected from the same person a year apart. Delays in sample processing post-blood draw impacted measurements of certain protein classes such as kinases. Correlations between proteins measured with the SomaScan and Olink platforms were highly variable, but this could be because different binding reagents recognize different epitopes or protein forms.

Shadrina, AS *et al.* (2022) "Mendelian randomization analysis of plasma levels of CD209 and MICB proteins and the risk of varicose veins of lower extremities." *PLoS One* 17(5): e0268725.

https://www.doi.org/10.1371/journal.pone.0268725

This study led by scientists in Russia used published genome-wide association study data and SomaScan proteomic data to investigate the relationship between plasma levels of two proteins and varicose veins. They confirmed that increased levels of one of the proteins, CD209, was associated with increased risk of varicose veins. This warrants further investigation to understand the role of CD209 in varicose vein development and progression.

Oskarsson, GR *et al.* (2022) "Genetic architecture of band neutrophil fraction in Iceland." *Commun Biol* **5**(1): 525.

https://www.doi.org/10.1038/s42003-022-03462-1

In this article, scientists at deCODE genetics looked for genetic variants that affect the shape of nuclei in white blood cells. Abnormalities in nuclear morphology are seen during infection and in certain diseases such as Pelger-Huët anomaly. They identified 13 variants linked to increased numbers of immature neutrophils and tested association of the variants with protein levels measured using the SomaScan Assay. Five of the variants were near the gene encoding a protein called Lamin B receptor (LBR), which suggests that LBR is the primary genetic determinant of nuclei shape in neutrophils.

Ostling, J *et al.* (2022) “A novel non-invasive method allowing for discovery of pathologically relevant proteins from small airways.” *Clin Proteomics* **19**(1): 20.

https://doi.org/10.1186/s12014-022-09348-y

Particles in Exhaled Air (PExA) is a new method of sampling the small airways of the lungs without an invasive bronchoscopy. In the first study of its kind, a team led by researchers at University of Gothenburg in Sweden conducted a proteomic analysis of PExA samples. They used the SomaScan Assay to measure the levels of over 1,000 proteins in the air particles and identified 207 proteins in up to 80% of the samples. Compared to healthy controls, nine proteins were significantly different in patients with asthma and high lung clearance index (a measure of airways disease). These results suggest that proteomic analysis of PExA samples could provide a noninvasive route to identifying biomarkers and drug targets for respiratory diseases.

Kuiper JJW *et al.* (2022) “A serum protein network early predicts the need for systemic immunomodulatory therapy in non-infectious uveitis.” *Ophthalmol Sci* **2**(3): 100175.

https://doi.org/10.1016/j.xops.2022.100175

Non-infectious uveitis is inflammation inside the eye that can lead to vision loss or blindness. Corticosteroids are often the primary treatment but can cause damaging side effects when used long term. Immunomodulatory therapy (IMT) is an alternative to corticosteroids but is typically reserved for severe, chronic cases of uveits. Objective biomarkers to assess

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disease severity and the need for IMT are currently lacking. In this study, researchers at University of Utrecht in the Netherlands, AstraZeneca and the National Institutes of Health examined whether blood proteins could identify uveitis patients who need IMT. They used the SomaScan Assay to measure the levels of 1,305 proteins in serum from 54 treatment-free uveitis patients and 26 healthy controls. They identified a cluster of 85 proteins whose concentrations were low in healthy controls but varied in patients with uveitis. Patients with high levels of the protein cluster at disease onset needed IMT at follow-up. The cluster was enriched with neutrophil-associated proteins, and the researchers found that neutrophil levels were highly predictive for IMT, which could be a simple way to stratify patients for treatment.

Zhang, Y *et al.* (2022) "CCL17 acts as a novel therapeutic target in pathological cardiac hypertrophy and heart failure." *J Exp Med* **219**(8): e20200418.

https://www.doi.org/10.1084/jem.20200418

This study led by researchers in China identified the protein CCL17 as a new biomarker of heart failure (HF). Aging is a major risk factor for heart failure, and the researchers used previously published SomaScan proteomic data as well as data from a HF patient study to establish that increased circulating levels of the protein CCL17 is associated with aging and deterioration of heart function. Subsequent experiments in mice showed that decreased CCL17 levels improved heart function and that CCL17-blocking agents reduce inflammation and could be a new strategy for treating HF.

Williams, SA *et al.* (2022) "A proteomic surrogate for cardiovascular outcomes that is sensitive to multiple mechanisms of change in risk." *Sci Transl Med* **14**(639): eabj9625.

https://www.science.org/stoken/author-tokens/ST-476/full

In one of the largest proteomic studies ever conducted, scientists at SomaLogic used the SomaScan Platform to create and validate a 27-protein model covering 10 different biologic mechanisms that accurately predicts the 4-year likelihood of myocardial infarction, heart failure, stroke or death. The 27-protein model outperformed current clinical models. The protein model was also reliably sensitive to longitudinal changes in risks from multiple mechanisms, including lifestyle changes and various classes of drugs – meeting a key requirement for a useful surrogate endpoint. No single known cardiovascular biomarker can currently predict heart disease in this manner. Surrogate endpoints are often used in clinical trials when outcomes, like a stroke, take a long time to study.

To develop and validate the model, the SomaLogic scientists used the SomaScan Assay to measure levels of approximately 5,000 proteins in more than 32,130 archived blood samples, deriving more than 160 million protein measurements. The samples represented 22,849 participants across 9 clinical studies. Using machine learning, the researchers developed the 27-protein model, which outperformed traditional and enhanced clinical models based on age, sex, race, total cholesterol, HDL cholesterol, blood pressure, diabetes and smoking.

The model performed consistently well across ethnicities, races, age ranges, geographic regions and in the presence of other comorbidities. The protein model was also sensitive to elevated cardiovascular risks from diseases and conditions where epidemiologic evidence showed elevated event rates that traditional risk factors failed to detect. Adding clinical risk factors to the protein model had little or no added value, demonstrating that the 27 proteins fully captured the underlying biology associated with clinical risk factors and provided additional independent information.

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A proteomic surrogate endpoint for cardiovascular events could be used for assessing clinical safety for many new drug mechanisms in different therapeutic areas, as well as accelerating the development of new cardiovascular drugs. In clinical settings, it could be used to identify individuals at highest risk to whom expensive therapies or therapies with potential side effects could be allocated.

Zhang, J *et al.* (2022) “Plasma proteome analyses in individuals of European and African ancestry identify cis-pQTLs and models for proteome-wide association studies” *Nat Genet* **54**(5): 593-602.

https://doi.org/10.1038/s41588-022-01051-w

Linking disease-associated DNA variants to differences in protein abundances is a powerful way to pinpoint molecular causes of diseases and possible protein targets for treating those diseases. This article describes a proteogenomic mapping study that is believed to be the first to include two large and ancestrally distinct population cohorts. A team led by investigators at Johns Hopkins Bloomberg School of Public Health used the SomaScan Assay to measure the levels of 4,657 plasma proteins in more than 7,000 European-American (EA) and nearly 2,000 African-American (AA) individuals from the Atherosclerosis Risk in Communities (ARIC) cohort. Combining SomaScan proteomic data with genomic data identified thousands of cis-protein quantitative trait loci (cis-pQTLs) for both groups. Using the EA dataset, they identified several proteins linked to the risk of gout and their findings suggest that anakinra, an existing rheumatoid arthritis drug, could be used to treat gout flares. Comparing results across ancestries revealed that 10% of the cis-pQTLs identified in the EA population were nonexistent or rare in the AA population, while about a third of the cis-pQTLs detected in the AA population were nonexistent or rare in the EA population. These data will improve understanding of how African ancestry may contribute to differences in health risks and disease rates.

Liu, S *et al.* (2022) "Translation of aptamers toward clinical diagnosis and commercialization." *Biosens Bioelectron* **208**: 114168. **(Subscription required)**

https://www.doi.org/10.1016/j.bios.2022.114168

As protein-binding reagents, aptamers have significant advantages over antibodies, including ease of manufacturing, small size, high stability and low immunogenicity. This review focuses on applications and challenges of developing aptamer-based diagnostics for preclinical research and clinical trials.

Osawa, Y *et al.* (2022) "Plasma growth and differentiation factor 15 predict longitudinal changes in bone parameters in women, but not in men." *J Gerontol A Biol Sci Med Sci* **77**(10): 1951-1958.

https://www.doi.org/10.1093/gerona/glac079

Bone density naturally decreases with age and increases the risk of fractures and disability. Currently, there are no biomarkers that can predict development of osteoporosis. A previous study of aging showed that higher plasma levels of the protein growth differentiation factor 15 (GDF-15) predicted mobility disability over a nine-year follow-up period. In this study, a team led by researchers at the National Institutes of Health found that plasma GDF-15 levels measured using the

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SomaScan Assay predicted accelerated loss of bone integrity in older women but not in older men (aged 65 or older). Identification of biological factors associated with osteoporosis and the risk of developing osteoporosis could lead to better diagnostic measures and new treatments.

Hardy-Sosa, A *et al.* (2022) "Diagnostic Accuracy of Blood-Based Biomarker Panels: A Systematic Review." *Front Aging Neurosci* **14**: 683689.

https://www.doi.org/10.3389/fnagi.2022.683689

This review highlights studies that focus on developing blood-based protein panels for Alzheimer's disease diagnosis, prognosis and screening. Panels of blood proteins appear to be more accurate than individual biomarkers and could be developed into inexpensive and minimally invasive tests for predicting Alzheimer's disease in low- and middle-income countries.

Aid, M *et al.* (2022) "Ad26.COV2.S prevents upregulation of SARS-CoV-2 induced pathways of inflammation and thrombosis in hamsters and rhesus macaques." *PLoS Pathog* **18**(4): e1009990.

https://www.doi.org/10.1371/journal.ppat.1009990

In this article, a team led by researchers at Beth Israel Deaconess Medical Center describe how vaccination offered protection in two animal models of COVID-19. They compared transcriptomic profiles of hamster lung tissues and SomaScan proteomic profiles of rhesus macaques blood serum in vaccinated and unvaccinated animals challenged with SARS-CoV-2. In both hamsters and macaques, vaccination attenuated excessive inflammatory and thrombotic responses, two hallmarks of severe COVID-19. These animal studies provide mechanistic insights into how immunization prevents the development of serious disease.

Dillon, ST *et al.* (2022) "Patterns and Persistence of Perioperative Plasma and Cerebrospinal Fluid Neuroinflammatory Protein Biomarkers After Elective Orthopedic Surgery Using SOMAscan." *Anesth Analg*., *epub ahead of print.* **(Subscription required)**

https://www.doi.org/10.1213/ANE.0000000000005991

Older adults who undergo surgery with anesthesia are at increased risk of postoperative neurological problems such as confusion, delirium or cognitive impairment. This study, led by researchers at Beth Israel Deaconess Medical Center and Harvard Medical School, used the SomaScan Assay to measure the levels of 1,305 proteins in plasma and CSF samples taken from older patients (over 65 years) undergoing hip and knee replacement surgery with spinal anesthesia. In plasma, they found that changes in proteins induced immediately after surgery mostly returned to baseline after one month. In CSF, they found that protein changes that persisted one month after surgery more closely resembled plasma protein changes immediately after surgery than one month later. Many of the CSF proteins identified are involved in neuronal function and neuroinflammation. The investigators identified 15 proteins that warrant further investigation as possible markers of long-term neuroinflammation.

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Nguyen, KA *et al.* (2022) "Epidermal growth factor receptor signaling in precancerous keratinocytes promotes neighboring head and neck cancer squamous cell carcinoma cancer stem cell-like properties and phosphoinositide 3-kinase inhibitor insensitivity." *Mol Carcinog* **61**(7): 664-676.

https://www.doi.org/10.1002/mc.23409

Head and neck squamous cell carcinoma (HNSCC) is one of the most common cancers worldwide. Consuming alcohol or tobacco can cause precancerous cells to form in areas adjacent to a tumor, increasing the likelihood of tumor progression or relapse. Activation of phosphoinositide 3-kinase (PI3K) signaling appears to play an important role in development of HNSCC, so there's considerable interest in PI3K inhibitors as potential treatments. To better understand how the tumor microenvironment affects PI3K inhibitor effectiveness, researchers at University of Colorado Anschutz Medical Campus and the VA Eastern Colorado Health Care System used the SomaScan Assay to measure the levels of more than 1,300 proteins in media from HNSCC cells cocultured with precancerous keratinocytes. They found that the precancerous cells secreted proteins that activated two oncogenic proteins, epidermal growth factor receptor (EGFR) and fibroblast growth factor receptor (FGFR). Inhibition of EGFR but not FGFR blunted resistance to a PI3K inhibitor. These results show how precancerous cells near a tumor can stimulate cancer proliferation and increase resistance to treatments. They also suggest that combination therapies may overcome resistance seen when using targeted drugs such as PI3K or EGFR inhibitors.

Hoppe, JE *et al.* (2022) "Effects of ivacaftor on systemic inflammation and the plasma proteome in people with CF and G551D." *J Cyst Fibros* **21**(6): 950-958. **(Subscription required)**

https://www.doi.org/10.1016/j.jcf.2022.03.012

Ivacaftor is a medication used to treat cystic fibrosis (CF) in people with specific mutations in the cystic fibrosis transmembrane conductance regulator. Ivacaftor improves lung function but its effects on inflammation, a key driver of CF-related lung damage and disease progression, are less clear. A new study led by researchers at the University of Colorado Anschutz Medical Campus used both traditional immunoassays and the SomaScan Assay to analyze proteins in blood samples from CF patients at baseline and at one and six months after administering ivacaftor. Ivacaftor treatment led to reductions in the levels of four inflammatory and proinflammatory proteins. The SomaScan Assay identified additional changes in nine proteins involved in lipid digestion, mobilization and transport and extracellular matrix organization, which may provide insights into the effects of ivacaftor on organs other than the lungs.

Jiang, W et al. (2022) "Analytical Considerations of Large-Scale Aptamer-Based Datasets for Translational Applications." *Cancers (Basel)* **14**(9): 2227.

https://doi.org/10.3390/cancers14092227

Aptamer-based proteomic technologies such as the SomaScan Assay allow researchers to measure thousands of proteins simultaneously in biological samples such as blood and urine with high precision and accuracy. This review addresses considerations for analyzing these large complex datasets and translating the findings into the clinic.

Nandakumar, M *et al.* (2022) "Severe iatrogenic hypoglycaemia modulates the fibroblast growth factor protein response." *Diabetes Obes Metab* **24**(8): 1483-1497.

https://www.doi.org/10.1111/dom.14716

Fibroblast growth factors (FGFs) are proteins that play important roles in regulating metabolism and whose levels are altered in diseases such as type 2 diabetes (T2D). In this article, a team led by researchers at Royal College of Surgeons in Ireland - Bahrain describe a pilot study using the SomaScan Assay to examine the effect of hypoglycemia on the levels of FGF proteins. Inducing hypoglycemia caused significant changes in the levels of seven FGF proteins in patients with T2D compared to age-matched controls. Five of the proteins are known to be associated with diabetes, but two have no known association with diabetes. These results suggest that changes in FGF proteins may lead to complications from hypoglycemia in those with T2D.

Dayon, L *et al.* (2022) "Proteomics of Human Biological Fluids for Biomarker Discoveries: Technical Advances and Recent Applications." *Expert Rev Proteomics*, **19**(2): 131-151.
(Subscription required)

https://www.doi.org/10.1080/14789450.2022.2070477

This review highlights proteomic technologies, including the SomaScan Assay, for biomarker discovery in biological fluids.

Wu, BS *et al.* (2022) "Identifying causal genes for stroke via integrating the proteome and transcriptome from brain and blood." *J Transl Med* **20**(1): 181.

https://www.doi.org/10.1186/s12967-022-03377-9

In this study, researchers at Qingdao University and Shanghai Medical College of Fudan University in China aimed to identify causal genes for stroke by integrating genomic, proteomic and transcriptomic data from blood and brain. They identified seven genes (two in brain and five in blood) with causal relationships to stroke, which could serve as potential targets for treatments.

Honey, S *et al.* (2022) "Acceptability and experience of a personalised proteomic risk intervention for type 2 diabetes in primary care: qualitative interview study with patients and healthcare providers." *Prim Health Care Res Dev* **23**: e24.

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https://www.doi.org/10.1017/S1463423621000591

This article from researchers at the University of Leeds in the UK reports patient and provider feedback from a pilot study of SomaSignal tests administered in primary care settings in Leeds between May 2019 and March 2020. SomaSignal tests for diabetes risk, heart disease risk, kidney function, liver fat, body fat percentage, lean body mass, tobacco smoke exposure and alcohol use were given to patients at increased risk of type 2 diabetes. Seventeen patients and four healthcare providers were interviewed for the article, and they reported overall positive experiences. Several participants improved specific behaviors after receiving their SomaSignal test results. This study illustrates the feasibility of integrating SomaScan technology into primary care and suggests that personalized proteomic health information may increase willingness of patients to change lifestyle behaviors.

Shuken, SR *et al.* (2022) “Limited proteolysis–mass spectrometry reveals aging-associated changes in cerebrospinal fluid protein abundances and structures.” *Nat Aging* **2**: 379-388. (**Subscription Required)**

https://doi.org/10.1038/s43587-022-00196-x

In this study, researchers at Stanford University and Stanford University School of Medicine used limited proteolysis–mass spectrometry to screen for aging-associated changes in cerebrospinal fluid (CSF) proteins from mice. They identified six proteins that underwent structural changes with aging. To investigate potential relevance of these proteins in humans, they analyzed SomaScan Assay data from 114 CSF samples taken from adults. They found that abundances of the six proteins associated with measures of brain health such as hippocampal volume, memory, dementia, neurological function or biomarkers of Alzheimer’s disease. These proteins could serve as potential biomarkers or therapeutic targets for neurodegeneration.

Edfors, F *et al.* (2022) "Proteomics in thrombosis research." *Res Pract Thromb Haemost* **6**(3): e12706.

https://www.doi.org/10.1002/rth2.12706

This review provides perspectives on affinity-based and mass spectrometry-based proteomic technologies and their applications in the field of venous thromboembolism.

Rhodes, CJ *et al.* (2022) "Harnessing Big Data to Advance Treatment and Understanding of Pulmonary Hypertension." *Circ Res* **130**(9): 1423-1444.

https://www.doi.org/10.1161/CIRCRESAHA.121.319969

This review summarizes big data sets in pulmonary hypertension and approaches for analyzing them to better understand pathogenesis, disease subtypes and treatment response.

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Curci, D *et al.* (2022) ”Proteome-Wide Analysis using SOMAscan Identifies and Validates Epidermal Growth Factor as a Disease Marker of Collagenous Gastritis.” *Gastro Hep Advances* **1**(5):689-702.

https://doi.org/10.1016/j.gastha.2022.04.016

Collagenous gastritis (CG) is an extremely rare gastrointestinal disease that affects both adults and children and can cause anemia and abdominal pain. A new study led by researchers at Beth Israel Deaconess Medical Center and Harvard Medical School used the SomaScan Assay to measure the levels of 1,305 proteins in serum from nine pediatric CG patients. They found 63 proteins that were significantly different in CG patients compared to those with non-collagenous gastritis or no gastritis. Many of the CG-related proteins are linked to fibrotic or inflammatory processes. Fifteen of the proteins were sufficient to accurately separate CG patients from controls. Using immunoassays, they confirmed that epidermal growth factor was significantly decreased in CG patients. This is the first study to identify blood proteins associated with pediatric CG, providing new biological insights and possible therapeutic targets.

Rashid, A *et al.* (2022) "Proteomics of lung tissue reveals differences in inflammation and alveolar-capillary barrier response between atelectasis and aerated regions." *Sci Rep* **12**(1): 7065.

https://www.doi.org/10.1038/s41598-022-11045-7

Atelectasis, the complete or partial collapse of a lung, is a common complication after major surgery and in critically ill patients. There is continued debate over whether atelectasis contributes to lung damage and if ventilation strategies to minimize atelectasis improve outcomes. To better understand the early-stage impact of atelectasis, an international team led by researchers at Massachusetts General Hospital used the SomaScan Assay to compare the levels of 1,305 proteins in lung tissue from sheep after eight-hour atelectasis and normal aeration. They also examined the effect of systemic inflammation with lipopolysaccharide (LPS) infusion. The observed protein changes showed a reduced immune response in atelectasis, which switched to an enhanced response upon addition of LPS. Their proteomic analysis also revealed that atelectasis affected proteins involved in gas exchange in the lung independent of LPS. The results provide insight into how atelectasis may contribute lung injury and possible therapeutic targets.

Axelsson, GT *et al.* (2022) "The Proteomic Profile of Interstitial Lung Abnormalities." *Am J Respir Crit Care Med* **206**(3): 337-346. **(Subscription required)**

https://www.doi.org/10.1164/rccm.202110-2296OC

Interstitial Lung Abnormalities (ILA) are common incidental findings from chest CT scans that progress to pulmonary fibrosis in more than fifty percent of individuals. To identify protein markers of ILA and ILA progression, a team led by researchers at the University of Iceland and the Icelandic Heart Association conducted the first large-scale assessment of ILA-associated blood proteins. SomaScan data from more than 4,700 proteins measured in more than 5,200 serum samples from the AGES-Reykjavik study were used for biomarker discovery and then replicated in nearly 4,900 plasma samples from the Genetic Epidemiology of COPD study. Several proteins were identified as potential markers of early fibrotic lung disease, suggesting that blood proteins could be used to improve detection of ILA and ILA progression.

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Saevarsdottir, S *et al.* (2022) "Multiomics analysis of rheumatoid arthritis yields sequence variants that have large effects on risk of the seropositive subset." *Ann Rheum Dis* **81**(8): 1085-1095.

https://pubmed.ncbi.nlm.nih.gov/35470158/

There are two main types of rheumatoid arthritis (RA), seropositive and seronegative. People with the more common seropositive RA have high levels of antibodies that can attack healthy joints and tissues. Those with seronegative RA don't have antibodies but do have RA symptoms. In the largest genome-wide association study (GWAS) to date, a team led by researchers at deCODE genetics, an Amgen subsidiary, used a combination of genomic, transcriptomic and SomaScan proteomic data to search for candidate causal genes in RA and both seropositive and seronegative RA subsets. They identified 37 sequence variants (25 for RA overall, 33 for seropositive RA and 2 for seronegative RA), including 15 that are novel. These results reveal causal genes and biological mechanisms involved in RA and its subtypes as well as possible targets for therapeutic intervention.

Muruve, DA et al. (2022) "Serum Protein Signatures Using Aptamer-Based Proteomics for Minimal Change Disease and Membranous Nephropathy." *Kidney Int Rep* **7**(7): 1539-1556.

https://doi.org/10.1016/j.ekir.2022.04.006

Membranous nephropathy (MN) and minimal change disease (MCD) are two kidney diseases are often indistinguishable based on clinical features, which hampers decision making and patient care. This article from researchers at Institut national de la santé et de la recherche médicale (Inserm), Beth Israel Deaconess Medical Center and Harvard Medical School, describe an exploratory biomarker discovery study using the SomaScan Assay to measure the levels of 1,305 proteins in serum from patients with MCD or MN. The high dynamic range of the SomaScan Assay overcomes one of the challenges of mass spectrometry-based proteomics, which is that high-abundance proteins in blood or urine often mask important, low-abundance proteins. The researchers successfully identified unique serum protein signatures and key biological pathways that differentiated MCD, MN and healthy controls. These results pave the way for development of non-invasive diagnostic markers that can provide better patient stratification and management of MCD and MN.

Manichaikul, A *et al.* (2022) "Lymphocyte activation gene-3-associated protein networks are associated with HDL-cholesterol and mortality in the Trans-omics for Precision Medicine program." *Commun Biol* **5**(1): 362.

https://www.doi.org/10.1038/s42003-022-03304-0

Although high-density lipoprotein cholesterol (HDL-C) is often referred to as "good cholesterol," some studies suggest that very high levels of HDL-C increases heart disease risk. Deficiency of the protein lymphocyte activation gene-3 (LAG3) is associated with increased HDL cholesterol and increased heart attack risk. This study led by researchers at the University of Connecticut Health used available genomic and SomaScan proteomic data from the Multi-Ethnic Study of Atherosclerosis (MESA) and Framingham Heart Study (FHS) to identify a common noncoding variant within the LAG3 gene that is significantly associated with LAG3 plasma levels. They also identified a protein network that is associated with LAG3, HDL-

C, and all-cause mortality which may provide greater insight into the relationship between HDL-C and cardiovascular disease.

Sacco, K *et al.* (2022) "Immunopathological signatures in multisystem inflammatory syndrome in children and pediatric COVID-19." *Nat Med*. **28**(5): 1050-1062.

https://www.doi.org/10.1038/s41591-022-01724-3

Although most children infected with SARS-CoV-2 have mild symptoms and recover, some later develop a potentially fatal condition called multisystem inflammatory syndrome in children (MIS-C). In this study, a team led by researchers at the National Institutes of Health conducted SomaScan proteomics, single-cell expression and immune repertoire analysis of blood samples collected over time from children with COVID-19 and/or MIS-C and healthy controls. They identified distinct differences in the host immune responses to pediatric COVID-19 and MIS-C that might help better characterize these disorders and guide treatment.

Corey, KE *et al.* (2022) "ADAMTSL2 protein and a soluble biomarker signature identify at-risk non-alcoholic steatohepatitis and fibrosis in adults with NAFLD." *J Hepatol* **76**(1): 25-33.

https://www.doi.org/10.1016/j.jhep.2021.09.026

Non-alcoholic fatty liver disease (NAFLD) is the most common form of liver disease in the world and continues to rise alongside obesity. Some with NAFLD will progress to non-alcoholic steatohepatitis (NASH), characterized by liver inflammation and scarring. Identifying fibrosis in those with NAFLD is critical for predicting those at risk of NASH but requires a liver biopsy. In this study, researchers at Massachusetts General Hospital, Harvard Medical School, Novartis Institutes of BioMedical Research, Beth Israel Deaconess Hospital and Vanderbilt University School of Medicine used the SomaScan Assay to measure the levels of 4,783 blood proteins in 316 adults with NAFLD. They found that both an 8-protein panel and the ADAMTSL2 protein alone were better at staging liver fibrosis than standard-of-care fibrosis scores. These results may provide a more accurate, minimally invasive way to identify at-risk NASH patients.

Bjornsdottir, G *et al.* (2022) "Rare SLC13A1 variants associate with intervertebral disc disorder highlighting role of sulfate in disc pathology." *Nat Commun* **13**(1): 634.

https://www.doi.org/10.1038/s41467-022-28167-1

In this article, a team led by researchers at deCODE genetics, a subsidiary of Amgen, report results from the largest genetic study of back pain to date. They conducted a meta-analysis of genome wide association studies (GWAS) linking genetic variants to diagnosed dorsalgia and intervertebral disc disorder. They linked genetic variants associated with back pain to plasma protein levels using previously collected SomaScan proteomic data, which flagged genes involved in cartilage and bone biology, as well as neurological and inflammatory processes. They also identified proteins that could potentially serve as targets for treating or preventing back pain.

Chen, G *et al.* (2022) "Identification of Distinct Inflammatory Programs and Biomarkers in Systemic Juvenile Idiopathic Arthritis and Related Lung Disease by Serum Proteome Analysis." *Arthritis Rheumatol* **74**(7): 1271-1283.

https://www.doi.org/10.1002/art.42099

Systemic Juvenile Idiopathic Arthritis (sJIA) is a rare and serious autoinflammatory disorder seen in children that affects all parts of the body. Patients with sJIA can develop additional complications such as lung disease (sJIA-LD) and macrophage activation syndrome (MAS), an episodic, life-threatening, hyper-inflammatory state. To better understand the relationships between sJIA, sJIA-LD and MAS, a team led by researchers at UPMC Children's Hospital & University of Pittsburgh Medical Center, the Children's Hospital of Philadelphia and Stanford University School of Medicine used the SomaScan Assay to compare 1,271 protein analytes in serum from healthy controls and patients with sJIA, sJIA-LD, MAS and other related diseases. The protein profiles of sJIA and MAS overlapped substantially and included known sJIA biomarkers as well as novel proteins. The researchers identified a distinct sJIA-LD protein signature. These results point to possible treatment targets for sJIA, MAS and sJIA-LD and proteins that could aid in early detection and monitoring of sJIA-LD.

Galbraith, MD *et al.* (2022) "Specialized interferon action in COVID-19." *Proc Natl Acad Sci U S A* **119**(11).

https://www.doi.org/10.1073/pnas.2116730119

Interferons (IFNs) are proteins that play critical roles in the host response to viral infections. IFNs have been reported to have both protective and harmful effects in COVID-19. This article from researchers at the University of Colorado Anschutz Medical Campus describes a multi-omic analysis of 12 different IFNs in hospitalized COVID-19 patients. They used previously collected data from the COVIDome Project (see Sullivan, KD *et al.* (2021) *Cell Rep* **36**(7): 109527. https://www.doi.org/10.1016/j.celrep.2021.109527), which included SomaScan and mass spectrometry plasma proteomics. There were clear differences among the IFNs throughout the disease course. Understanding the fine balance between IFNs required for defending the body and minimizing damage from COVID-19 has important implications for therapeutic interventions.

Stacey, D *et al.* (2022) "Elucidating mechanisms of genetic cross-disease associations at the PROCR vascular disease locus." *Nat Commun* **13**(1): 1222.

https://www.doi.org/10.1038/s41467-022-28729-3

Genome-wide association studies (GWAS) have identified many cases where a single genetic variant is associated with more than one disease. One such pleiotropic variant is PROCR-p.S219G which is associated with a lower risk of coronary artery disease (CAD) but a higher risk of venous thromboembolism (VTE). A team led by researchers at the University of Cambridge mined publicly available genomic, proteomic and health record data to explore the underlying biology affected by the PROCR-p.S219G variant. They identified protein C as a likely causal factor linking PROCR-219Gly to CAD through anti-

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inflammatory mechanisms and to VTE through pro-thrombotic mechanisms. These results have potential implications for development of drugs that target the protein C pathway.

Skuladottir, AT *et al.* (2022) "A genome-wide meta-analysis identifies 50 genetic loci associated with carpal tunnel syndrome" *Nat Commun* **13**: 1598.

https://doi.org/10.1038/s41467-022-29133-7

In this article, a team led by researchers at deCODE genetics, an Amgen subsidiary, describe a genome-wide association study of carpal tunnel syndrome (CTS). They identified 53 sequence variants at 50 loci that associated with CTS , which they then linked to RNA expression data and SomaScan proteomic data to highlight potential causal genes. Their results suggest that proteins in the extracellular matrix play a key role in CTS by putting pressure on the median nerve in the wrist.

Lopez-Silva, C *et al.* (2022) "Comparison of Aptamer-Based and Antibody-Based Assays for Protein Quantification in Chronic Kidney Disease." *Clin J Am Soc Nephrol* **17**(3): 350-360.

https://www.doi.org/10.2215/CJN.11700921

In this study, researchers at Johns Hopkins University School of Medicine compared measurements of nine proteins associated with chronic kidney disease progression between the SomaScan Assay and traditional immunoassays in the African American Study of Kidney Disease and Hypertension (AASK). They found strong correlations between methods for four of the proteins, but less so for the other five proteins, which could be due to biological or structural factors that affect aptamer binding to their targets.

Gadd, DA *et al.* (2022) "Epigenetic scores for the circulating proteome as tools for disease prediction." *Elife* **11**.

https://www.doi.org/10.7554/eLife.71802

DNA methylation is a common epigenetic modification that can turn genes on or off, without changing the DNA sequence. Certain DNA methylation signatures have been associated with disease risk. In this study, a team led by researchers at University of Edinburgh leveraged existing proteomic data to connect DNA methylation to protein levels and various common diseases, including diabetes, stroke, Alzheimer’s dementia and cancer. They generated epigenetic scores for 953 plasma proteins that predicted disease likelihood up to 14 years prior to diagnosis. Combining epigenetic data with proteomic data could improve risk stratification and age-related disease prevention.

Vanarsa, K *et al.* (2022) "Aptamer-based screen of Neuropsychiatric Lupus cerebrospinal fluid reveals potential biomarkers that overlap with the choroid plexus transcriptome." *Arthritis Rheumatol* **74**(7): 1223-1234.

https://www.doi.org/10.1002/art.42080

Neuropsychiatric SLE (NPSLE) is a subtype of lupus that affects the brain, spinal cord or peripheral nervous system. There are no reliable biomarkers of NPSLE, so diagnosis requires ruling out all other causes of observed neurologic or psychiatric symptoms. In the first study of its kind, an international team led by researchers at the University of Houston used the SomaScan Assay to compare the levels of 1,129 proteins in cerebrospinal fluid (CSF) from patients with NPSLE and patients with other neurological diseases. Four proteins, Lipocalin-2, M-CSF, IgM and complement C3, emerged as promising CSF biomarkers of NPSLE with diagnostic potential.

Ferrannini, E *et al.* (2022) "Differential Proteomics of Cardiovascular Risk and Coronary Artery Disease in Humans." *Front Cardiovasc Med* **8**: 790289.

https://www.doi.org/10.3389/fcvm.2021.790289

Coronary artery disease (CAD) happens when arteries become blocked, slowing blood flow to the heart that can lead to heart attack, stroke or death. Traditional risk factors such as high cholesterol, hypertension, diabetes, smoking and family history are not very accurate at predicting CAD risk. In this study, a team led by researchers at Consiglio Nazionale Delle Ricerche (CNR) Institute of Clinical Physiology in Italy used the SomaScan Assay to measure the levels of approximately 5,000 proteins in plasma from four different types of individuals: those with or without CAD (as assessed by computed tomography angiography) and with or without risk factors. They identified a 12-protein panel that was able to discriminate the four groups. Two proteins, myosin regulatory light chain 2 (MYO) and C-C motif chemokine-22 were associated with the absence of CAD despite multiple risk factors and could play a role in protecting against CAD. Two other proteins, shisa-3 homolog and platelet-activating factor acetyl hydrolase, were associated with the presence of CAD despite low risk factors. These findings could provide greater insight into the biology that contributes to CAD and new treatment targets.

Mookherjee, N *et al.* (2022) "Defining the effects of traffic-related air pollution on the human plasma proteome using an aptamer proteomic array: A dose-dependent increase in atherosclerosis-related proteins." *Environ Res* **209**: 112803. **(Subscription required)**

https://www.doi.org/10.1016/j.envres.2022.112803

Traffic-related air pollution is a major contributor to respiratory and cardiovascular disease and a risk factor for cognitive and neurodegenerative disease. In this study, researchers at the University of Manitoba and the University of British Columbia in Canada used the SomaScan Assay to measure changes in 1,307 plasma proteins in never-smokers after exposure to diesel exhaust. They saw increased levels of six proteins associated with atherosclerosis in response to diesel exhaust, which provides biological insight into how air pollution could lead to cardiovascular disease.

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Schreiner, C *et al.* (2022) "Placental proteins with predicted roles in fetal development decrease in premature infants." *Pediatr Res* **92**(5): 1316-1324. **(Subscription required)**

https://www.doi.org/10.1038/s41390-022-01942-y

Preterm birth complications are the leading cause of death among children under the age of five. Emerging evidence from animal studies suggest that various factors secreted from the placenta are critical for proper organ development in the fetus. In this study, researchers at the University of Colorado Anschutz Medical Campus used the SomaScan Assay to characterize umbilical vein, umbilical artery and neonatal blood collected from 25 preterm infants. They found 434 proteins that were increased in umbilical venous compared to arterial blood, suggesting that the placenta releases these proteins into fetal circulation. Many of the proteins are involved in lung and brain development. When born prematurely, the infants are deprived of these proteins, which could contribute to pre-term-related mortality.

Essone, PN *et al.* (2022) "Creatine kinase-(MB) and hepcidin as candidate biomarkers for early diagnosis of pulmonary tuberculosis: a proof-of-concept study in Lambarene, Gabon." *Infection* **50**(4): 897-905.

https://www.doi.org/10.1007/s15010-022-01760-8

A rapid, point-of-care test to diagnose active tuberculosis (TB) does not yet exist. A previous study used the SomaScan Assay to analyze blood samples from approximately 6,000 TB-infected people and identified 361 proteins whose levels were significantly different in those who developed TB disease within 2 years compared to those who did not. In this study, scientists at Centre de Recherches Médicales de Lambaréné, Gabon aimed to evaluate four of the previously identified proteins. Serum levels of two of the proteins, creatine kinase-MB and hepcidin, were different between confirmed TB cases and non-TB cases, which shows promise for rapid diagnosis of TB.

Povero, D *et al.* (2022) "Protein and miRNA profile of circulating extracellular vesicles in patients with primary sclerosing cholangitis." *Sci Rep* **12**(1): 3027.

https://www.doi.org/10.1038/s41598-022-06809-0

Primary sclerosing cholangitis (PSC) is rare, progressive disease of the bile ducts that can lead to liver damage requiring transplantation. There are no effective treatments or biomarkers for diagnosis or prognosis of PSC. It’s known that during PSC progression, the cells that line the bile ducts release extracellular vesicles (EVs) into the blood. In this study, a team led by researchers at University of California, San Diego used the SomaScan Assay to analyze 1,345 unique proteins in EVs isolated from people with PSC and healthy controls. They found that the levels of 282 proteins were significantly different in PSC patients and compared to control subjects. The inflammatory protein IL-13Ra1 was the most significantly increased protein in PSC-derived EVs and correlated with the severity of liver fibrosis. They also examined miRNAs in EVs and identified several new PSC-associated miRNAs. These proteins and miRNAs may lead to the development of more accurate methods for diagnosing PSC and predicting its progression.

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Moin, ASM *et al.* (2022) "Diagnostic and Prognostic Protein Biomarkers of beta-Cell Function in Type 2 Diabetes and Their Modulation with Glucose Normalization." *Metabolites* **12**(3).

https://www.doi.org/10.3390/metabo12030196

Beta cells in the pancreas produce insulin to control blood sugar levels. Chronic high blood sugar in Type 2 diabetes (T2D) causes progressive loss of beta cell function but current methods for measuring functional beta-cell decline are inaccurate. A previous study using the SomaScan Assay had identified a 43-protein panel that predicted beta-cell decline in non-diabetic adults who later developed impaired glucose tolerance. In this study, researchers at Royal College of Surgeons in Ireland, Bahrain and Hull York Medical School, UK found that 9 of the 43 proteins could distinguish patients with T2D from healthy controls and may prove useful for assessing beta-cell dysfunction in T2D.

Ding, Z *et al.* (2022) "Proteomics technologies for cancer liquid biopsies." *Mol Cancer* **21**(1): 53.

https://www.doi.org/10.1186/s12943-022-01526-8

This review describes high-plex proteomic technologies and their application to cancer liquid biopsies.

Cummins, TD *et al.* (2022) "Advances in proteomic profiling of pediatric kidney diseases." *Pediatr Nephrol* **37**(10): 2255-2265*.* **(Subscription required)**

https://www.doi.org/10.1007/s00467-022-05497-2

This review highlights applications of proteomics to pediatric kidney diseases.

Steffen, BT *et al.* (2022) "Proteomic Profiling Identifies Novel Proteins for Genetic Risk of Severe COVID-19: the Atherosclerosis Risk in Communities Study." *Hum Mol Genet* **31**(14): 2452-2461. **(Subscription required)**

https://www.doi.org/10.1093/hmg/ddac024

In this study, a team led by researchers at the University of Minnesota looked for protein differences related to six genetic variants associated with greater risk of severe COVID-19. They used the SomaScan Assay to measure the levels of 4,870 plasma proteins from 8,914 Black and White participants in the Atherosclerosis Risk in Communities Study. They found 84 proteins, including many involved in the immune response, that were significantly associated with two of the variants. Seven of the proteins predicted greater risk of other hospitalized respiratory infections over a 20-year follow up. Further examination of these proteins in COVID-19 patients who carry these genetic variants would provide insight into their role in COVID-19 respiratory disease.

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Ghanbari, F *et al.* (2022) "Connecting Genomics and Proteomics to Identify Protein Biomarkers for Adult and Youth-Onset Type 2 Diabetes: A Two-Sample Mendelian Randomization Study" *Diabetes* **71**(6): 1324-1337.

https://www.doi.org/10.2337/db21-1046

Identifying markers of youth-onset type 2 diabetes (T2D) is important for childhood screening and intervention. This article from researchers at University of Montreal and McGill University in Canada used published proteogenomic data to look for connections between circulating proteins and T2D risk in both adults and children. They identified 22 proteins that were causally linked to adult T2D and 11 proteins that associated with youth-onset T2D, which represent promising drug targets.

Sobolev, VV *et al.* (2022) "Proteomic Studies of Psoriasis" *Biomedicines* **10**(3): 619.

https://doi.org/10.3390/biomedicines10030619

This review discusses proteomic studies of psoriasis to elucidate disease mechanisms and monitor the effects of treatments.

Pala, E *et al.* (2022) "Proteins and pathways in atrial fibrillation and atrial cardiomyopathy underlying cryptogenic stroke." *Int J Cardiol Heart Vasc* **39**: 100977.

https://www.doi.org/10.1016/j.ijcha.2022.100977

Atrial fibrillation is an abnormal heart rhythm that is a preventable cause of recurrent stroke. Unfortunately, atrial fibrillation is often asymptomatic and therefore goes untreated. In this study, researchers in Spain used the SomaScan Assay to measure the levels of 1,310 blood proteins in 20 stroke patients with or without atrial fibrillation. They identified multiple proteins and pathways that may have a role in the development of atrial fibrillation that could help in its detection post-stroke.

Schubert, R *et al.* (2022) "Protein prediction for trait mapping in diverse populations." *PLoS One* **17**(2): e0264341.

https://www.doi.org/10.1371/journal.pone.0264341

Combining genomic with proteomic data can help identify causal factors in disease. However, the vast majority of proteogenomic studies have been conducted on samples of European ancestry, and the findings do not always transfer to other ethnic groups. In this article, a team led by scientists at Loyola University Chicago trained protein prediction models using genetic data and SomaScan Assay measurements of 1,305 plasma proteins in 971 individuals of African American, Chinese, European and Hispanic/Latino descent. They compared results within each population and across all populations and assessed model performance in an independent cohort. They found the most discoveries and reliable replications using ancestry-matched data. These results illustrate the importance and need for more genomic and proteomic data on diverse populations to inform potential differences in ethnic groups that affect health outcomes.

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Echouffo-Tcheugui, JB *et al.* (2022) "Diabetes, GDF-15 and incident heart failure: the atherosclerosis risk in communities study." *Diabetologia* **65:** 955–963. **(Subscription required)**

https://www.doi.org/10.1007/s00125-022-05678-6

The protein growth differentiation factor 15 (GDF-15) is produced by cells in response to stress, and elevated levels of GDF-15 are associated with both heart failure (HF) and diabetes. To gain insight into whether GDF-15 is prognostic of HF in those with or without diabetes, a team led by researchers at Johns Hopkins University School of Medicine used the SomaScan Assay to measure the levels of GDF-15 in participants of the Atherosclerosis Risk in Communities (ARIC) study. Plasma samples were collected from 10,750 people without HF, 2,429 of whom developed HF during two decades of follow up. They found that GDF-15 levels were independently associated with HF risk and that the association was more pronounced in those with diabetes. People with high GDF-15 levels and diabetes had a two-fold higher risk of HF than people with low GDF-15 and without diabetes. These results suggest that GDF-15 could help improve risk stratification for HF, particularly amongst those who also have diabetes, so that high-risk individuals can be targeted for more aggressive preventative strategies.

Lindbohm, JV *et al.* (2022) "Plasma proteins, cognitive decline, and 20-year risk of dementia in the Whitehall II and Atherosclerosis Risk in Communities studies." *Alzheimers Dement* **18**(4): 612-624.

https://doi.org/10.1002/alz.12419

Alzheimer's disease research has largely focused on amyloid beta and tau proteins but treatments targeting these proteins have not been successful in preventing or slowing the onset of dementia. In this article, an international team led by researchers at the University of Helsinki used the SomaScan Assay to examine the levels of 4,953 plasma proteins in samples from two cohorts with a total of 13,657 participants, some of whom developed dementia 20 years later. Fifteen non-amyloid/non-tau–related proteins were associated with increased risk of cognitive decline and dementia, and six of the proteins are targets of approved medications for other conditions. This study identified several plasma proteins in dementia-free people that may play a role in the early stages of neurodegeneration when dementia may be preventable.

Rhodes, CJ *et al.* (2022) "Using the Plasma Proteome for Risk Stratifying Patients with Pulmonary Arterial Hypertension." *Am J Respir Crit Care Med* **205**(9): 1102-1111.

https://www.doi.org/10.1164/rccm.202105-1118OC

Pulmonary arterial hypertension (PAH) is a rare, progressive disorder defined by high blood pressure in the arteries that go from the heart to the lungs. Although PAH is incurable, there are treatments that can improve symptoms and regular risk assessment is recommended to guide treatment strategies. Most PAH risk calculators include measurement of blood levels of brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), which have limited accuracy in predicting PAH outcomes. This article describes the most comprehensive study of plasma proteins in PAH patients to date from a team led by researchers at Imperial College London, UK. They used the SomaScan Assay to compare the levels of 4,152 proteins in plasma from patients with pulmonary arterial hypertension (PAH) and healthy age- and sex-matched controls. They identified

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new proteins associated with PAH prognosis and derived a six-protein risk score that can stratify PAH patients independent of established markers such as NT-proBNP. This six-protein panel may provide a more accurate method for assessing PAH risk and allow for more informed treatment decisions.

Gudjonsson, A *et al.* (2022) "A genome-wide association study of serum proteins reveals shared loci with common diseases." *Nat Commun* **13**(1): 480.

https://www.doi.org/10.1038/s41467-021-27850-z

—and—

Emilsson, V *et al.* (2022) "Coding and regulatory variants are associated with serum protein levels and disease." *Nat Commun* **13**(1): 481.

https://www.doi.org/10.1038/s41467-022-28081-6

Large genomic studies have reported thousands of genetic variants associated with disease risk, but identifying causal factors remains challenging. This is because most of risk variants lie in non-coding regions of the genome, which make it difficult to discern functional consequences. In addition, most common disorders are mediated through complex biological networks rather than a single gene. Combining genomic data with SomaScan proteomic data can provide a deeper understanding of disease biology, revealing potential drug targets and clinical biomarkers. In back-to-back articles published in *Nature Communications*, researchers at the Icelandic Heart Association, the National Institute on Aging and Novartis describe two proteogenomic studies of the Ages Reykjavik cohort, an Icelandic study of aging.

Gudjonsson *et al.* performed what is believed to be the largest genome-wide association study of serum protein levels to date. They mapped 7.5 million genetic variants to 4,782 serum proteins measured using the SomaScan Assay in samples from 5,328 Icelanders. They identified 4,035 protein quantitative trait loci (pQTLs) to 2,091 unique proteins, including 1,415 cis-pQTLs. A cis-pQTL is a sequence variant located near the gene that encodes the measured protein. They identified numerous associations between serum proteins and genetic risk factors for disease.

Emilsson *et al.* conducted a similar mapping of 54,469 low-frequency and common variants within protein-encoding genes using SomaScan Assay measurements of 4,782 serum proteins in samples from 5,343 Icelanders. They identified 5,451 pQTLs and linked 60% of them to disease-related traits. These results demonstrate how proteins can bridge the gap between genes and causal factors in a wide range of diseases.

Osawa, Y *et al.* (2022) "Proteins in the pathway from high red blood cell width distribution to all-cause mortality." *EBioMedicine* **76**: 103816.

https://www.doi.org/10.1016/j.ebiom.2022.103816

Red cell distribution width (RDW) is a measure of the variation in the volume and size of a person's red blood cells. High RDW is a risk factor for various diseases and mortality, although it is unclear why. In this article, a team led by researchers at the National Institutes of Health describe a study using the SomaScan Assay to measure the levels of 1,301 plasma proteins in baseline and 9-year follow-up samples from the InCHIANTI cohort, a study of older adults living in the Chianti region of Italy. They found 11 proteins that associated with baseline RDW and all-cause death within 15 years, and 2 proteins that associated with changes in RDW and all-cause death within 6 years. The protein insulin-like growth factor binding protein 2 (IGFBP2) measured at a single time point and over time mediated the association between RDW and mortality. The proteins identified in the study warrant further investigation to better understand how they contribute to premature death.

Levine, JA *et al.* (2022) "Effects of colchicine on lipolysis and adipose tissue inflammation in adults with obesity and metabolic syndrome." *Obesity (Silver Spring)* **30**(2): 358-368.

https://www.doi.org/10.1002/oby.23341

The goal of this study was to investigate whether colchicine, a well-studied anti-inflammatory drug used to treat gout, reduces obesity-induced chronic inflammation. Researchers at the National Institutes of Health and Johns Hopkins School of Medicine conducted a secondary analysis of a pilot clinical trial of colchicine in adults with obesity and metabolic syndrome (see Demidowich, AP *et al.* (2020) *Int J Obes (Lond)* **44**(8): 1793-1799 https://pubmed.ncbi.nlm.nih.gov/32461554/) They found that colchicine improved regulation of lipolysis and reduced systemic inflammation, which suggests that colchicine could have metabolic benefits.

Bagaria, J *et al.* (2022) "Genetics of Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) and Role of Sacsin in Neurodegeneration." *Int J Mol Sci* **23**(1): 552.

https://www.doi.org/10.3390/ijms23010552

This review discusses mutations in the gene encoding the protein sacsin, and their associations with Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS) and other neurodegenerative diseases.

Aljohani, MM *et al.* (2022) "Aptamers: Potential Diagnostic and Therapeutic Agents for Blood Diseases." *Molecules* **27**(2): 383.

https://www.doi.org/10.3390/molecules27020383

Aptamers have emerged as promising alternatives to antibodies due to their high specificity, ease of synthesis, stability and low immunogenicity. This review discusses applications of aptamers in the diagnosis and treatment of blood diseases.

Palstrom, NB *et al.* (2022) "Recent Developments in Clinical Plasma Proteomics-Applied to Cardiovascular Research." *Biomedicines* **10**(1): 162.

https://www.doi.org/10.3390/biomedicines10010162

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This review describes proteomic technologies for analyzing circulating proteins and their use in discovery of new biomarkers of cardiovascular diseases.

Rashid, MU *et al.* (2022) "Influenza A virus uses PSMA2 for downregulation of NRF2-mediated oxidative stress response." *J Virol*: jvi0199021.

https://www.doi.org/10.1128/jvi.01990-21

Proteasome subunit alpha type-2 (PSMA2) is a host protein whose levels increase when cells are infected by influenza A virus (IAV). In this article, researchers at the University of Manitoba in Canada studied the effect of PSMA2 knockdown in cultured lung cells infected with IAV and found that PSMA2 is critical for virus maturation. They used the SomaScan Assay to measure the levels of 1,307 proteins in cell lysates from IAV-infected cells and found that PSMA2 causes changes in protein responses that help IAV evade the host immune response. These results could aid in development of effective antiviral drugs.

Roy, R *et al.* (2022) "Acute serum protein and cytokine response of single dose of prednisone in adult volunteers." *Steroids* **178**: 108953. (**Subscription required**)

https://www.doi.org/10.1016/j.steroids.2021.108953

Corticosteroids such as cortisone and prednisone are commonly prescribed anti-inflammatory drugs whose long-term use can cause side effects such as weight gain, insulin resistance and osteoporosis. In this study, researchers at Binghamton University-SUNY, National Institutes of Health and Children's National Medical Center analyzed blood samples from healthy young adult volunteers taken before and 2, 3, 4 and 6 hours after a low dose of prednisone. They measured serum levels of 9 steroidal hormones using mass spectrometry, 10 inflammatory markers using ELISA, and 1,305 proteins using the SomaScan Assay. Broad suppression of adrenal gland hormones were observed within 3 hours, and decreased levels of inflammatory serum proteins were seen after 6 hours. These results may clarify the positive and negative effects of corticosteroids on the body.

Bhatti, G *et al.* (2022) "The amniotic fluid proteome changes with gestational age in normal pregnancy: a cross-sectional study." *Sci Rep* **12**(1): 601.

https://www.doi.org/10.1038/s41598-021-04050-9

Amniotic fluid (AF) surrounds the unborn baby and provides nutrient exchange between mother and fetus. In the first study of its kind to date, researchers at Wayne State University and the National Institutes of Health used the SomaScan Assay to profile changes in AF during normal pregnancies. They compared the levels of 1,310 proteins in AF samples collected from women at midtrimester (16-24 weeks of gestation) and at term (37-42 weeks of gestation) and found significant changes in nearly 25% of the proteins measured. These results could aid future studies to identify protein biomarkers of obstetrical diseases.

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Sproull, M *et al.* (2022) "Comparison of Proteomic Expression Profiles after Radiation Exposure across Four Different Species." *Radiat Res* **197**(4): 315-323.

https://www.doi.org/10.1667/RADE-21-00182.1

In this article, researchers at the National Cancer Institute, SRI International and the Armed Forces Radiobiology Research Institute describe a pilot study using the SomaScan Assay to characterize changes in 1,310 proteins in plasma samples after total-body irradiation in four different species. They characterized panels of radiation responsive proteins in mice, Sinclair minipigs, Rhesus monkeys and humans, and identified HIST1H1C as new protein marker of radiation exposure across species. These results may aid development of new biodosimeters for radiation exposure and new clinical biomarkers of radiation injury.

Todd, JL *et al.* (2022) "Association of Circulating Proteins with Death or Lung Transplant in Patients with Idiopathic Pulmonary Fibrosis in the IPF-PRO Registry Cohort." *Lung* **200**(1): 11-18.

https://www.doi.org/10.1007/s00408-021-00505-y

Idiopathic Pulmonary Fibrosis (IPF) is a progressive, ultimately fatal lung disease with no cure. The disease course is highly variable, with some patients experiencing long periods of stability and others declining quickly. In this article, a team led by researchers at Duke University Medical Center leveraged previously collected SomaScan proteomic data from 300 patients with IPF to determine the association of 1,305 plasma proteins with IPF outcomes. They identified a set of 47 unique proteins and 4 clinical measures that predicted the likelihood of respiratory death or lung transplant. These data may improve risk stratifications for patients with IPF.

Hinckley, JD *et al.* (2022) "An Approach to Biomarker Discovery of Cannabis Use Utilizing Proteomic, Metabolomic, and Lipidomic Analyses." *Cannabis Cannabinoid Res* **7**(1): 65-77. (**Subscription required**)

https://www.doi.org/10.1089/can.2020.0002

Although cannabis is increasingly used for medicinal purposes, relatively little is known about its biological effects on the body. This article from researchers at the University of Colorado School of Medicine describes a pilot study that used a multi-omics approach to examine differences in proteins, metabolites and lipid between cannabis users and nonusers. They measured the levels of 1,310 proteins using the SomaScan Assay: 314 metabolites and 34 lipids in 12 sets of twins, 4 with the same cannabis use and 8 with different cannabis use. They identified 13 proteins, 3 metabolites and 2 lipids associated with cannabis use, including many involved in immune system processes. These results begin to shed light on the biological effects of cannabis on the body.

Katz, DH *et al.* (2022) "Whole Genome Sequence Analysis of the Plasma Proteome in Black Adults Provides Novel Insights Into Cardiovascular Disease." *Circulation* **145**(5): 357-370.

https://www.doi.org/10.1161/CIRCULATIONAHA.121.055117

Combining genomics with proteomics can help identify causal factors in disease and new drug targets. However, most proteogenomic studies have focused almost entirely on people of Caucasian ancestry. In the largest study of its kind, team led by researchers at Beth Israel Deaconess Medical Center linked genomic sequence data on 28.1 million DNA variants to SomaScan proteomic data on 1,301 circulating proteins in 1852 Black adults from the Jackson Heart Study. They identified 569 protein quantitative trait loci (pQTLs) between 479 proteins and 438 unique genetic regions, including 114 pQTLs (20%) that were novel. Many of the pQTLs are important in cardiovascular biology and suggest new disease mechanisms linked to African ancestry.

Yazdanpanah, N *et al.* (2022) "Clinically Relevant Circulating Protein Biomarkers for Type 1 Diabetes: Evidence From a Two-Sample Mendelian Randomization Study." *Diabetes Care* **45**(1): 169-177.

https://www.doi.org/10.2337/dc21-1049

There are very few biomarkers available to predict who is at risk of developing type 1 diabetes. In this article, researchers at University of Montreal and McGill University in Canada evaluated causal effects of 1,611 plasma proteins from five proteogenomic studies on type 1 diabetes risk among 9,684 type 1 diabetics and 15,743 controls. They identified three proteins that associated with type 1 diabetes risk, which could be promising targets for drug development or screening tools for early prediction.

Mc Ardle, A *et al.* (2022) "Identification and Evaluation of Serum Protein Biomarkers That Differentiate Psoriatic Arthritis From Rheumatoid Arthritis." *Arthritis Rheumatol* **74**(1): 81-91.

https://www.doi.org/10.1002/art.41899

Psoriatic Arthritis (PsA) is a form of inflammatory arthritis that leads to joint damage, deformity and disability. Early diagnosis and management are critical but there is no diagnostic test for PsA, and early-stage PsA is difficult to distinguish from rheumatoid arthritis (RA). To identify putative protein biomarkers of PsA, a team led by researchers from University College Dublin in Ireland analyzed serum from patients with PsA or RA using either mass spectrometry, the SomaScan Assay or antibody assays. Applying machine learning techniques to the protein data from the three platforms, they produced a protein biomarker panel that could distinguish early PsA patients from those with RA. These results warrant further investigation in larger cohorts with other arthritis-related conditions but could improve diagnosis and clinical decision making for PsA patients.

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Yamaguchi, Y *et al.* (2022) "The Plasma Proteome Fingerprint Associated with Circulating Carotenoids and Retinol in Older Adults." *J Nutr* **152**(1): 40-48.

https://www.doi.org/10.1093/jn/nxab340

Carotenoids are naturally occurring pigments found in leafy vegetables and fruits that are believed to boost the immune system and protect against disease. In this article, a team led by researchers at Johns Hopkins University School of Medicine used the SomaScan Assay to measure the levels of 1,301 proteins in plasma from 728 older adults living in the Chianti region of Italy and identified circulating proteins that associated with elevated levels of circulating carotenoids. These proteins play roles in energy metabolism, inflammation, oxidative stress and longevity. These results provide insight into the biological processes that underly the beneficial effects of carotenoids on health.

Vasunilashorn, SM *et al.* (2022) "Proteome-Wide Analysis Using SOMAscan Identifies and Validates Chitinase-3-Like Protein 1 as a Risk and Disease Marker of Delirium Among Older Adults Undergoing Major Elective Surgery." *J Gerontol A Biol Sci Med Sci* **77**(3): 484-493.

https://www.doi.org/10.1093/gerona/glaa326

Delirium affects approximately one quarter of older adults undergoing major elective surgery, leading to longer hospitalizations and poorer outcomes. In this study, a team led by researchers at Beth Israel Deaconess Medical Center and Harvard Medical School used the SomaScan Assay to measure the levels of 1,305 plasma proteins pre- and post-surgery in 18 patients who experienced delirium compared to 18 controls. They identified chitinase-3-like-protein-1(CHI3L1) as a potential risk marker for post-operative delirium. Elevated blood levels of CHI3L1 have been associated with aging, mortality, inflammatory conditions and Alzheimer’s disease. These findings could lead to a cost-effective way to predict, diagnose and manage delirium in older adults undergoing surgery.

Rahman, ML *et al.* (2022) "Proteomic analysis of serum in workers exposed to diesel engine exhaust." *Environ Mol Mutagen* **63**(1): 18-28.

https://www.doi.org/10.1002/em.22469

Diesel engine exhaust (DEE) is carcinogenic to humans, although it is unclear how DEE exposure causes cancer. In this article, an international team led by scientists at the National Cancer Institute and Qingdao University used the SomaScan Assay to measure the levels of 1,317 targeted proteins in serum from 19 diesel-exposed workers and 19 unexposed controls in China. They identified 22 serum proteins that were associated with DEE exposure, many of which play a role in inflammation and immune regulation. These results provide insight into the biological mechanisms underpinning DEE-induced carcinogenicity.

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Chelliah, SS *et al.* (2022) "Identification of blood-based biomarkers for diagnosis and prognosis of Parkinson's disease: A systematic review of proteomics studies." *Ageing Res Rev* **73**: 101514. (**Subscription required**)

https://www.doi.org/10.1016/j.arr.2021.101514

In this article, scientists at Monash University in Malaysia conducted a systematic review and meta-analysis of proteomic studies of Parkinson's disease (PD). Apolipoprotein A-I was associated with PD pathogenesis in multiple cohorts using multiple proteomic platforms and was identified as a potential biomarker of early diagnosis and prognosis of PD.

Gropler, MRF *et al.* (2022) "Pediatric and adult dilated cardiomyopathy are distinguished by distinct biomarker profiles." *Pediatr Res* **92**(1): 206-215*.* (**Subscription required**)

https://www.doi.org/10.1038/s41390-021-01698-x

Dilated cardiomyopathy (DCM) is a rare condition in which the heart chambers become enlarged, affecting the heart's ability to pump blood. DCM can lead to heart failure in both children and adults, but despite similar clinical characteristics, there is emerging evidence that pediatric and adult DCM are two different diseases. In this proof-of-concept study, a team led by researchers at the University of Colorado Anschutz Medical Center used the SomaScan Assay to measure the levels of 1,310 proteins in 39 healthy children, 39 children with DCM and 40 adults with DCM. They found significant protein differences between the three groups, providing further support that the biology underlying pediatric and adult DCM is distinct. There were also significant protein differences among the children with DCM, suggesting that there are multiple disease subtypes within pediatric DCM.

Delannoy-Bruno, O *et al.* (2021) "Evaluating microbiome-directed fibre snacks in gnotobiotic mice and humans." *Nature* **595**(7865): 91-95.

https://pubmed.ncbi.nlm.nih.gov/34163075/

High fiber diets are associated with better health, including lower risks of cardiovascular disease, diabetes and obesity. In this study, researchers at Washington University School of Medicine analyzed gut microbiome and SomaScan proteomic data from overweight or obese participants fed a typical Western diet (high fat and low fiber) supplemented with one of three fiber-containing snacks. Fiber-specific changes in the participants' microbiomes were linked to changes in plasma proteins associated with energy metabolism, immune responses, blood coagulation and blood vessel function, as well as bone and nerve cell biology. This study illustrates how proteomics can be used to monitor the effects of dietary supplements and assess whether they lead to long-term improvements in health.

Chen, RY *et al.* (2021) "A Microbiota-Directed Food Intervention for Undernourished Children." *N Engl J Med* **384**(16): 1517-1528.

https://www.doi.org/10.1056/NEJMoa2023294

This article from researchers at Washington University Medical school describes a clinical trial of the effects of a microbiome-boosting diet on malnourished children in Bangladesh. In a previous pilot study, the investigators developed a microbiota-directed complementary food (MDCF) formulation that improved the microbiomes and plasma proteomic profiles of Bangladeshi children (see Gehrig, JL *et al.* (2019) *Science* **365**(6449); https://www.doi.org/10.1126/science.aau4732). This three-month clinical trial compared the effects of MDCF against an existing supplementary food (RUSF) in 118 Bangladeshi children between the ages of 12 and 18 months. The children given MDCF showed superior weight gains, even though it contained 20% fewer calories, and the growth rates were sustained a month after the children stopped receiving MDCF. Analysis of stool samples showed higher levels of 21 beneficial bacterial strains in the children who received MDCF. The researchers used the SomaScan Assay to measure the levels of 4,977 proteins in plasma samples collected at baseline, one month and three months. After three months, the children who received MDCF showed larger increases in proteins involved in bone growth and neural development and larger decreases in proinflammatory proteins than children who received RUSF. These protein changes provide insight into how gut microbes influence metabolism, immunity and overall development.

Chen, RY *et al.* (2021) “Duodenal Microbiota in Stunted Undernourished Children with Enteropathy.” *N Engl J Med* **383**(4): 321-333.

https://doi.org/10.1056%2FNEJMoa1916004

Environmental enteric dysfunction (EED) is a poorly understood inflammatory disease of the small intestine that is linked to childhood malnutrition and impaired growth. To study the role of gut microbiota in EED and stunted development, researchers at Washington University School of Medicine conducted a 3-month nutritional intervention in 525 children aged 12 to 18 months from an urban slum in Bangladesh. They confirmed EED in 80 of the children who failed to gain weight or show any growth and then examined duodenal tissue, plasma and fecal samples from these children. The children shared the same types of gut bacteria and transferring the bacteria into germ-free mice induced intestinal inflammation. In addition, SomaScan analysis of 4077 proteins in plasma and 2619 proteins in duodenal biopsy samples showed decreased levels of growth-potentiating and bone-forming proteins. Understanding the biological mechanisms by which the gut microbiome contributes to EED could lead to new therapies to address stunted growth and malnutrition.

Ferkingstad, E *et al.* (2021) "Large-scale integration of the plasma proteome with genetics and disease." *Nat Genet* **53**(12): 1712-1721. (**Subscription required**)

https://www.doi.org/10.1038/s41588-021-00978-w

In the largest proteogenomic study ever performed, scientists at deCODE genetics used the SomaScan Assay to measure the levels of 4,719 unique blood proteins in 35,559 Icelanders and mapped them to 27 million genetic sequence variants. This was also the largest proteomic study published to date with 170 million protein measurements. The researchers identified 18,084 associations between DNA variants and levels of proteins (protein quantitative trait loci, pQTL). Overall, 93% of the pQTLs were novel and 94% of the proteins measured using the SomaScan Assay showed an associated pQTL. Plasma levels of 4,719 proteins were tested for genetic associations with 373 diseases and traits, producing 257,490 of these associations. The study also identified 938 genes encoding potential protein drug targets for various diseases. These

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results demonstrate how combining proteomic measurements with genetic data on disease can inform understanding of causal factors in human diseases and assist in drug discovery efforts.

Pietzner, M *et al.* (2021) "Synergistic insights into human health from aptamer- and antibody-based proteomic profiling." *Nat Commun* **12**(1): 6822.

https://www.doi.org/10.1038/s41467-021-27164-0

In this article, a team led by researchers at the University of Cambridge & Berlin Institute of Health at Charité describe the largest, systematic assessment of two different affinity-based proteomic platform technologies to date. They measured the levels of 4,775 unique proteins using the SomaScan Assay from 12,345 plasma samples and 1,069 proteins across 12 Olink Target 96-plex panels from 485 samples. The researchers compared protein quantitative trait loci (pQTL) discovery between the SomaScan Assay and Olink panels for a subset of 871 proteins that overlapped between the two platforms. The majority of pQTLs (64%) were shared across both platforms, demonstrating that when constrained to examining the same proteins in the same samples, the aptamer-based SomaScan Assay performed as well as the antibody-based Olink assay. The shape-based recognition of SOMAmer reagents used in the SomaScan Assay allowed the discovery of multiple unique protein-phenotype links affected by the form rather than the abundance of protein, which can provide greater insight into disease mechanisms and the development of treatment strategies.

Dreyfuss, JM *et al.* (2021) "High-throughput mediation analysis of human proteome and metabolome identifies mediators of post-bariatric surgical diabetes control." *Nat Commun* **12**(1): 6951.

https://www.doi.org/10.1038/s41467-021-27289-2

Roux-en-Y gastric bypass (RYGB) surgery is a proven treatment for long-term weight loss and type 2 diabetes (T2D) remission. Interestingly, beneficial effects can be seen within days after surgery, well before significant weight loss has occurred. In this article, a team led by researchers at Harvard Medical School and the Joslin Diabetes Center developed a new statistical method to analyze metabolomic and SomaScan proteomic data collected up to 3 years from 38 obese T2D patients who either underwent RYGB or non-surgical diabetes and weight management. They identified growth hormone receptor (GHR) as a mediator of post-RYGB improvements in diabetes control, which suggests that GHR could be a target for non-surgical treatments for T2D.

De Miguel, Z *et al.* (2021) "Exercise plasma boosts memory and dampens brain inflammation via clusterin." *Nature* **600**(7889): 494-499. (**Subscription required**)

https://www.doi.org/10.1038/s41586-021-04183-x

Physical activity can improve brain health, although it is unclear how. A team led by researchers at Stanford University School of Medicine have shown that blood from exercising mice when infused into sedentary mice improved memory and reduced brain inflammation. Clusterin, a protein involved in clearing cellular debris, was largely responsible for the observed benefits. To determine if these results translate to humans, the researchers used the SomaScan Assay to measure the levels of clusterin in 20 people with mild cognitive impairment before and 6 months after a physical exercise intervention. They found that blood levels of clusterin were significantly higher in those who exercised. These results provide a clearer understanding of how exercise benefits the brain and suggest possible therapeutic strategies for improving cognitive health.

Helms, L *et al.* (2021) "Cross-validation of SARS-CoV-2 responses in kidney organoids and clinical populations." *JCI Insight* **6**(24): e154882.

https://www.doi.org/10.1172/jci.insight.154882

Although infection with SARS-CoV-2 often causes respiratory illness, many patients develop kidney injury or disease. Using a kidney cell organoid model, a team led by researchers at the University of Washington School of Medicine found that SARS-CoV-2 can infect and damage kidney cells. They used the SomaScan Assay to compare the levels of 4,984 proteins in urine from patients with and without COVID-19 and found increased levels of nine proteins in COVID-19 patients. RNA transcripts of eight of the nine proteins were increased in kidney organoids infected with SARS-CoV-2 compared to mock-infected controls. This study illustrates how kidney organoids can be a powerful model system for studying the effects of COVID-19 on the kidney and developing therapeutic treatments.

Norby, FL *et al.* (2021) "Proteomics and Risk of Atrial Fibrillation in Older Adults (From the Atherosclerosis Risk in Communities [ARIC] Study)." *Am J Cardiol* **161**: 42-50.

https://www.doi.org/10.1016/j.amjcard.2021.08.064

Atrial fibrillation (AF) is an irregular heartbeat that increases risk of stroke, heart failure and other cardiovascular diseases. To identify protein markers of AF development, a team led by researchers at Cedars-Sinai Health System used the SomaScan Assay to measure the levels of 4,877 plasma proteins in 4,668 participants in the Atherosclerosis Risk in Communities (ARIC) study. ARIC is a long-running study of heart health, and the blood samples were from Black and White adults in their 70s, of whom 585 later developed AF. The researchers identified 17 proteins that were significantly associated with AF risk and replicated nearly half of the proteins in samples collected earlier in midlife. They identified both new and established protein markers of AF that offer new insights into the biological changes that precede AF and that could serve as possible targets for therapeutic interventions.

Li, H *et al.* (2021) "Comprehensive aptamer-based screen of 1317 proteins uncovers improved stool protein markers of colorectal cancer." *J Gastroenterol* **56**(7): 659-672. (**Subscription required**)

https://www.doi.org/10.1007/s00535-021-01795-y

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States. With early detection, CRC is highly treatable, but approximately one third of screen-eligible individuals in the United States are not screened. Colonoscopy is the most accurate CRC screening test but is somewhat invasive and can miss precancerous lesions. Fecal

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occult blood testing (FOBT), which measures hemoglobin in stool samples, is non-invasive, but not very accurate. In this study, a team led by researchers at the University of Houston used the SomaScan Assay to compare the levels of 1,317 protein in stool samples from patients with colorectal cancer (CRC), patients with benign adenomas and healthy controls. Ninety-two proteins were significantly different in CRC patients relative to healthy controls. Of these, the top 16 proteins were subsequently validated by ELISA. Four of the proteins outperformed stool hemoglobin and represent promising stool biomarkers for improving non-invasive methods for CRC screening.

Govender, MA *et al.* (2021) “The Use of ‘Omics for Diagnosing and Predicting Progression of Chronic Kidney Disease: A Scoping Review.” *Front Genet* **12**: 682929.

https://doi.org/10.3389/fgene.2021.682929

This review is a synthesis of the current literature on the use of different ‘omic platforms (genomics, proteomics, metabolomic, transcriptomics and epigenomics) to identify biomarkers for chronic kidney disease (CKD) that could be used to detect early-stage CKD, predict disease progression, and understand biological drivers of CKD.

Yousri, NA *et al.* (2021) "Proteome-wide associations with short- and long-term weight loss and regain after Roux-en-Y gastric bypass surgery." *Obesity (Silver Spring)* **30**(1): 129-141.

https://www.doi.org/10.1002/oby.23303

For obese people, gastric bypass surgery can produce not only substantial long-term weight loss, but also health benefits such as improved cardiovascular health, lower blood pressure and remission of type 2 diabetes. To better understand the protein changes induced by bariatric surgery, a team led by researchers at Weill Cornell Medicine in Qatar used the SomaScan Assay to compare short term (2-year) and long term (12-year) differences in 1,297 proteins in 234 individuals who had gastric bypass surgery and 144 obese individuals who did not. Most of the short-term changes in proteins were maintained at 12 years and were associated with changes in body mass index. These results suggest protein targets for non-surgical weight loss interventions.

Ghodsian, N *et al.* (2021) "Blood Levels of the SMOC1 Hepatokine Are Not Causally Linked with Type 2 Diabetes: A Bidirectional Mendelian Randomization Study." *Nutrients* **13**(12): 4208.

https://www.doi.org/10.3390/nu13124208

Sparc-related modular calcium-binding protein 1 (SMOC1) is a liver-secreted protein that has been shown to regulate metabolism and blood sugar levels in mice. SMOC1 injections in mice significantly improved glycemic control and features of nonalcoholic fatty liver disease (NAFLD), suggesting SMOC1 as a potential therapeutic target for type 2 diabetes (T2D). In this study, researchers at Centre de Recherche de l’Institut Universitaire de Cardiologie et de Pneumologie de Québec in Canada examined published human genetic and SomaScan proteomic data on SMOC1 but found no evidence of causal associations of blood SMOC1 levels with T2D, NAFLD, and glycemic traits in humans.

Matias-Garcia, P *et al.* (2021) "Plasma Proteomics of Renal Function: A Trans-ethnic Meta-analysis and Mendelian Randomization Study." *J Am Soc Nephrol* 32(7): 1747-1763.

https://www.doi.org/10.1681/ASN.2020071070

Previous plasma proteomic studies of kidney function have revealed several protein markers associated with chronic kidney disease (CKD) but these studies have been limited to European populations and have not investigated causality. In this study, a team led by researchers at Helmholtz Zentrum München in Germany performed a cross-sectional study using SomaScan Assay data to search for associations between 1,095 plasma proteins and renal function in four independent cohorts with European and mixed ancestries (KORA, INTERVAL, HUNT, QMDiab). They identified 57 plasma proteins that were associated transethnically with estimated glomerular filtration rate (eGFR), including one novel protein, contactin-4. Twenty-three of the 57 proteins were also associated with CKD. Applying an analytical method called bidirectional Mendelian randomization to publicly available genomic-wide association study (GWAS) data, they identified one protein (testican-2) with a causal effect on eGFR and another three proteins (MIA, cystatin M and carbonic anhydrase) with potential causal effects on eGFR. These results warrant further investigation of these proteins as potential biomarkers of kidney disease progression.

O'Neil, LJ *et al.* (2021) "Proteomic Approaches to Defining Remission and the Risk of Relapse in Rheumatoid Arthritis." *Front Immunol* **12**: 729681.

https://www.doi.org/10.3389/fimmu.2021.729681

Rheumatoid arthritis (RA) is an autoimmune disease characterized by painful, stiff and swollen joints. Although there is no cure, with aggressive treatment RA can go into remission and some patients sustain remission even after tapering or stopping medication. In this article, researchers at the University of Manitoba in Canada and Friedrich-Alexander University in Germany used the SomaScan Assay to measure the levels of 1,307 proteins in serum taken from 130 RA patients in stable remission, prior to their participation in a study of therapy withdrawal. The researchers used supervised machine learning to identify protein signatures that predicted ongoing RA stability after therapy withdrawal and that may be useful for identifying those at highest risk of future disease flare.

Daniels, JR *et al.* (2021) "Discovery of Novel Proteomic Biomarkers for the Prediction of Kidney Recovery from Dialysis-Dependent AKI Patients." *Kidney360* **2**(11): 1716-1727.

https://www.doi.org/10.34067/kid.0002642021

Acute kidney injury (when the kidneys suddenly stop working) is a common complication seen among patients in intensive care units. To identify proteins that predict kidney recovery in patients with acute kidney injury requiring dialysis (AKI-D), a team led by researchers at the US Food and Drug Administration used the SomaScan Assay to measure the levels of 1,305 proteins in serum samples collected on day 8 of dialysis from 72 patients with AKI-D. They found significant differences in 119 proteins between the people who recovered kidney function and to those who remained on dialysis by day 28. These results suggest new predictive markers and potential biological mechanisms of kidney recovery after AKI-D.

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Nounu, A *et al.* (2021) "A Combined Proteomics and Mendelian Randomization Approach to Investigate the Effects of Aspirin-Targeted Proteins on Colorectal Cancer." *Cancer Epidemiol Biomarkers Prev* **30**(3): 564-575.

https://www.doi.org/10.1158/1055-9965.EPI-20-1176

There is considerable evidence that using aspirin decreases risk of colorectal cancer (CRC). To gain insight into aspirin's mechanism of action, an international team led by researchers at University of Bristol in the UK studied its effects on proteins in colorectal adenoma cells. They cultured the cells with aspirin for 24 hours and used mass spectrometry to identify 120 proteins in the cell lysates that were affected by aspirin treatment. They then used protein quantitative trait loci (pQTLs) that were previously identified using the SomaScan Assay and expression quantitative loci (eQTLs) to link four of the aspirin-regulated proteins to cancer incidence. Aspirin treatment decreased the expression of the four proteins in colorectal adenoma cells, which could help explain how aspirin prevents CRC.

Moin, ASM *et al.* (2021) "Heat Shock-Related Protein Responses and Inflammatory Protein Changes Are Associated with Mild Prolonged Hypoglycemia." *Cells* **10**: 3109.

https://doi.org/10.3390/cells10113109

—and—

Moin, ASM *et al.* (2021) "Hypoglycemia-induced changes in complement pathways in type 2 diabetes." *Atherosclerosis Plus* **46**: 35-45*.*

https://doi.org/10.1016/j.athplu.2021.11.002

Variability in blood sugar levels is associated with complications in patients with type 2 diabetes (T2D). In two pilot studies, researchers at Royal College of Surgeons of Ireland in Bahrain used the SomaScan Assay to investigate how hypoglycemia affects blood proteins. In an article entitled, "Heat Shock-Related Protein Responses and Inflammatory Protein Changes are Associated with Mild Prolonged Hypoglycemia," the authors describe differences in baseline levels of heat shock proteins (HSP) between patients with T2D and controls. HSP are produced by the body in response to stress. They found more differences in HSP after they induced mild hypoglycemia as well as changes in inflammatory proteins which could be driving the HSP response.

In an article entitled, "Hypoglycemia-induced changes in complement pathways in type 2 diabetes," the authors found increased baseline levels of two proteins in the complement system in people with T2D compared to controls. The complement system is part of the body's defense against pathogens, and more differences in complement proteins were seen after inducing hypoglycemia. In T2D, the protein changes appear to be driven by inflammatory proteins, which could contribute to a cardiovascular event.

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Wu, J *et al.* (2021) “Multi-omic analysis in injured humans: Patterns align with outcomes and treatment responses.” *Cell Rep Med* **2**: 100478.

https://doi.org/10.1016/j.xcrm.2021.100478

To explore how the human body responds to severe injury, a team led by researchers at the University of Pittsburgh analyzed plasma multi-omic data (clinical, cytokine, endotheliopathy biomarker, lipidomic, metabolomic, and proteomic) from trauma patients taken at different time points after injury. Immediately post-trauma, they saw a massive release of 1,061 biomolecules into circulation together with a massive loss of 892 biomolecules from circulation. The patterns of circulating molecules delineated two major patient clusters, and only one of the clusters benefitted from prehospital administration of thawed plasma. Analysis of the multi-omic data at 72 hours revealed major differences in circulating biomolecules between patients who recovered within a week and those who did not. These results identify potential drivers of recovery from severe trauma.

Suzuki, M *et al.* (2021) "Large-scale plasma proteomics can reveal distinct endotypes in chronic obstructive pulmonary disease and severe asthma." *Clin Transl Allergy* **11**(10): e12091.

https://www.doi.org/10.1002/clt2.12091

This review describes how integrating data from genomics, transcriptomics, proteomics, metabolomics, integromics, microbiomics, and systems biology can aid discovery of aging biomarkers, mechanisms of aging and identification of novel antiaging therapeutic targets.

Osborn, J *et al.* (2021) "Serum Proteomics Uncovers Biomarkers of Clinical Portal Hypertension in Children With Biliary Atresia." *Hepatol Commun* **6**(5): 995-1004.

https://www.doi.org/10.1002/hep4.1878

Biliary atresia (BA) is a rare condition in infants where the bile ducts are blocked. BA can lead to portal hypertension (PHT, elevated pressure in the major vein that leads into the liver) and subsequent liver damage. Measuring portal pressures is an invasive procedure that is not typically done in children, so PHT diagnosis usually happens after complications of PHT have already developed. Researchers at Cincinnati Children's Hospital Medical Center used the SomaScan Assay to compare serum levels of 1,305 proteins in children with BA with without PHT and validated five proteins that could accurately discriminate children with PHT. These novel proteins showed superior performance compared to previously described PHT markers and could play potential roles in PHT pathology.

Fenyves, BG *et al.* (2021) "Plasma P-selectin is an early marker of thromboembolism in COVID-19." *Am J Hematol* **96**(12): E468-E471.

https://www.doi.org/10.1002/ajh.26372

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Patients with COVID-19 are at increased risk of developing dangerous blood clots (venous thromboembolic events, VTE). To better understand why, researchers at Massachusetts General Hospital and Harvard Medical School leveraged published plasma proteomic data (see Filbin, MR et al. (2021) *Cell Rep Med* 2(5): 100287 https://www.doi.org/10.1016/j.xcrm.2021.100287) to examine the connection between 31 coagulation proteins and the occurrence of VTE in COVID-19 patients. They found that elevated levels of the protein P-selectin could predict the likelihood of developing VTE, independent of COVID-19 severity. Their results suggest that P-selectin could be used to identify COVID-19 patients who would benefit from anti-coagulation therapies when they are admitted to the hospital.

Wu, L et al. (2021) “Integrated Multi-Omics for Novel Aging Biomarkers and Antiaging Targets.” *Biomolecules* **12**: 39.

https://doi.org/10.3390/biom12010039

This review describes how integrating data from genomics, transcriptomics, proteomics, metabolomics, integromics, microbiomics, and systems biology can aid discovery of aging biomarkers, mechanisms of aging and identification of novel antiaging therapeutic targets.

Pietzner, M *et al.* (2021) "Mapping the proteo-genomic convergence of human diseases." *Science* **374**(6569): eabj1541.

https://www.doi.org/10.1126/science.abj1541

In one of the largest proteogenomic studies of its kind, an international research team led by scientists at the University of Cambridge used the SomaScan Assay to generate data on thousands of proteins in human blood. They then combined this information with genetic data to reveal a network of gene-protein connections that drive human diseases that span a variety of medical specialties and organ systems.

This genome-proteome-wide association study measured 10.2 million genetic variants and 4,775 distinct proteins in 10,708 individuals. Among the key findings of the study was the identification of 10,674 genetic variant-protein associations, or pQTLs, for 3,892 distinct proteins. By connecting disease-related genomic variations to specific encoded proteins that are affected by these variations, the team was able to identify 1,859 connections between protein-encoded genes and diseases. The results revealed an interconnectedness of many seemingly diverse diseases and point to candidate drug targets, opportunities for drug repurposing and potential treatment strategies to avoid adverse events.

Roberts, JA *et al.* (2021) "A brain proteomic signature of incipient Alzheimer's disease in young APOE epsilon4 carriers identifies novel drug targets." *Sci Adv* **7**(46): eabi8178.

https://www.doi.org/10.1126/sciadv.abi8178

APOE e4 is a genetic risk factor for developing Alzheimer’s disease (AD). Brain imaging studies of APOE e4 carriers have shown amyloid accumulation early in adulthood, well before the onset of cognitive decline. To gain a better understanding of

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the biological processes that lead to AD, a team led by researchers at the National Institute on Aging used the SomaScan Assay to compare brain protein levels in post-mortem samples from elderly AD patients vs. age-matched cognitively normal controls and from young APOE e4 carriers vs. noncarriers. They identified 25 proteins that overlapped between AD adults and APOE e4 carriers, and many of the proteins are targets of FDA-approved or experimental drugs for other diseases. An experimental drug for liver cancer and dasatinib, a drug approved for chronic myeloid leukemia, acted on the AD-related proteins in cell culture-based assays, suggesting they could be potential preventative therapies.

Pierson, SK *et al.* (2021) "Discovery and validation of a novel subgroup and therapeutic target in idiopathic multicentric Castleman disease." *Blood Adv* **5**(17): 3445-3456.

https://www.doi.org/10.1182/bloodadvances.2020004016

Idiopathic multicentric Castleman disease (iMCD) is a rare, potentially life-threatening disorder that affects the lymph system. Siltuximab, an antibody that neutralizes the IL-6, is the only iMCD treatment approved by the US Food and Drug Administration but siltuximab only works in approximately one third of iMCD patients. Few options exist for siltuximab nonresponders, and no validated tests are available to predict likelihood of response. In the largest study of its kind, a team led by researchers at the University of Pennsylvania used the SomaScan Assay to measure the levels of 1,305 proteins in serum from 88 iMCD patients, 60 patients with a related disease and 42 healthy controls. They identified a set of seven proteins that predicted iMCD patients with superior response to siltuximab and identified potential protein drug targets for siltuximab nonresponders.

Sivakumar, P *et al.* (2021) "Integrated plasma proteomics and lung transcriptomics reveal novel biomarkers in idiopathic pulmonary fibrosis." *Respir Res* **22**(1): 273.

https://www.doi.org/10.1186/s12931-021-01860-3

Idiopathic pulmonary fibrosis (IPF) is progressive lung disease that requires transplantation for survival. In a previous study, researchers at Bristol-Myers Squibb and the University of Pennsylvania conducted an RNA analysis of lung tissue from patients with transplant-stage IPF compared with acute lung injury (ALI) and healthy controls that revealed a gene expression signature unique to end-stage IPF. This study used the SomaScan Assay to profile blood proteins in the same patients. They identified 34 tissue and circulating biomarkers that could be useful for assessing IFP prognosis and treatment response.

Snider, JM *et al.* (2021) "Group IIA secreted phospholipase A2 is associated with the pathobiology leading to COVID-19 mortality." *J Clin Invest* **131**(19): e149236.

https://www.doi.org/10.1172/JCI149236

In this article, a team led by researchers at the University of Arizona found higher plasma levels of the protein secreted phospholipase A2 Group IIA (sPLA2-IIA) in COVID-19 patients who died compared to those who survived. Elevated sPLA2-

IIA levels were also associated with severe COVID-19 symptoms such as organ dysfunction and hypoxia. This study suggests that sPLA2-IIA could be a therapeutic target to reduce COVID-19 mortality.

Zimmermann, T *et al.* (2021) "Influence of renin-angiotensin-aldosterone system inhibitors on plasma levels of angiotensin-converting enzyme 2." *ESC Heart Fail* **8**(2): 1717-1721.

https://www.doi.org/10.1002/ehf2.13249

Angiotensin-converting enzyme 2 (ACE2) is a protein that acts as the entry receptor for SARS-CoV-2. There is some concern that ACE inhibitors and angiotensin receptor blockers (ARB), medications used to treat patients with cardiovascular disease, could increase levels of ACE2, thereby increasing the risk of COVID-19. In this study, researchers at University of Basel and University of Zurich in Switzerland used the SomaScan Assay to measure the levels of ACE2 in 4008 patients with established cardiovascular disease, 31% on ACE inhibitors and 31% on ARB. This large study found no association between treatment with ACE inhibitors or ARB and circulating plasma concentrations of ACE2.

Shi, L *et al.* (2021) "Identification of plasma proteins relating to brain neurodegeneration and vascular pathology in cognitively normal individuals." *Alzheimers Dement (Amst)* **13**(1): e12240.

https://www.doi.org/10.1002/dad2.12240

Blood-based biomarkers could serve as a simple and potentially cost-effective method for the early detection, classification, and monitoring of Alzheimer's disease (AD). In this study, a team of researchers in Scotland used the SomaScan Assay to measure the levels of 5,032 proteins in plasma from 1061 cognitively healthy individuals (728 women and 433 men). Nearly 90% of the study participants had magnetic resonance imaging of hippocampal volume (a measure of neurodegeneration) and white matter hyperintensities (a measure of vascular damage). There is increasing evidence that the biological mechanisms that lead to AD are different in women compared to men, and SomaScan analysis revealed four proteins that mediated sex-related differences in brain neurodegeneration and one protein that mediated sex-related differences in vascular damage. These results suggest that blood proteins could be used to predict brain changes in the very early stages of Alzheimer's and point to candidate protein targets for preventing AD in women vs. men.

Sproull, M *et al.* (2021) "Proteomic Biomarker Analysis of Serum from Japanese Field Mice (Apodemus Speciosus) Collected within the Fukushima Difficult-to-return Zone." *Health Phys* 121(6): 564-573.

https://www.doi.org/10.1097/HP.0000000000001467

The environmental impact of the radiation released from the 2011 Fukushima Daiichi nuclear power plant accident continues to be a source of ongoing concern. In this study, researchers from the National Cancer Institute, Colorado State University, Fukushima University and Japan International Atomic Energy Agency examined the effects of chronic radiation exposure on Japanese field mice. They used the SomaScan Assay to compare the levels of 1,310 serum proteins in mice from the Fukushima difficult-to-return zone and mice from the town of Soma, located approximately 28 miles north. They identified

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significant differences in the Fukushima mice highlighting protein involved in injury, respiratory, renal, urological, and gastrointestinal disease, and cancer that could serve as novel biomarkers of radiation exposure.

Deutsch, EW *et al.* (2021) "Advances and Utility of the Human Plasma Proteome." *J Proteome Res* **20**(12): 5241-526.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9469506/

This review summarizes recent technological advances, disease applications, and challenges in using plasma proteomics to deliver precision medicine.

Correa Rojo, A *et al.* (2021) "Towards Building a Quantitative Proteomics Toolbox in Precision Medicine: A Mini-Review." *Front Physiol* **12**: 723510.

https://www.doi.org/10.3389/fphys.2021.723510

This review discusses recent innovations in high-throughput, multiplex proteomic technologies and their use in clinical diagnostics, drug discovery and patient stratification.

Yu, Z *et al.* (2021) "Polygenic Risk Scores for Kidney Function and Their Associations with Circulating Proteome, and Incident Kidney Diseases." *J Am Soc Nephrol* **32**(12): 3161-3173.

https://www.doi.org/10.1681/ASN.2020111599

In this study, a team led by researchers at the Broad Institute developed a genome-wide polygenic risk score (PRS) of estimated glomerular filtration rate (eGFR), a measure of kidney function. They then tested the relationship between the PRS, incident kidney disease and circulating proteins measured using the SomaScan Assay in 8,866 adult participants in the Atherosclerosis Risk in Communities (ARIC) study. The PRS was significantly associated with risk of chronic kidney disease, end stage kidney disease, kidney failure, and acute kidney injury, and with 132 circulating plasma proteins at both midlife and older age. These results demonstrate that the PRS can identify individuals at higher genetic risk of kidney disease, well before eGFR decline, who might benefit from early intervention.

Esefeld, M *et al.* (2021) “The proteomic signature of recombinant Growth Hormone in recreational athletes.” *J Endocrine Soc* **5**(12): bvab156.

https://doi.org/10.1210/jendso/bvab156

In this study, a team led by researchers from Weill Cornell Medicine-Qatar and the World Anti-Doping Agency (WADA) investigated the effects of the performance-enhancing drug, human growth hormone (hGH), on blood proteins. Thirty-five

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recreational athletes were randomized into four groups, receiving either placebo, very low, low or high doses of hGH daily over a period of three weeks. Serum samples were collected at several time points, starting four weeks prior to treatment, during treatment, and six weeks post-treatment. The levels of 1,305 protein were measured using the SomaScan Assay. They identified 66 proteins that significantly associated with recombinant hGH administration and dosage, including both well known and unknown hGH-related proteins that could serve as potential markers of hGH doping. Network analysis revealed changes in specific biological pathways, primarily related to the immune system and glucose metabolism, which could indicate new risks associated with hGH misuse.

Slieker, RC *et al.* (2021) "Distinct Molecular Signatures of Clinical Clusters in People With Type 2 Diabetes: An IMI-RHAPSODY Study." *Diabetes* **70**(11): 2683-2693.

https://www.doi.org/10.2337/db20-1281

Type 2 diabetes (T2D) is a complex, heterogeneous disease with varying clinical characteristics and disease progression. In this article, a team led by researchers at Leiden University Medical Center in the Netherlands and University of Dundee in the UK compared the genomic, metabolomic, lipidomic and SomaScan proteomic features of five T2D subtypes identified in a recent study. The molecular signatures were markedly different, providing new insights into the biological drivers of each of the T2D subtypes.

Singh, K *et al.* (2021) "Ultrasensitive detection of blood biomarkers of Alzheimer's and Parkinson's diseases: a systematic review." *Biomark Med* **15**(17): 1693-1708.

https://www.doi.org/10.2217/bmm-2021-0219

This article describes a systematic review of 42 studies and meta-analysis of 23 studies of blood biomarkers for Alzheimer's and Parkinson's diseases and highlights three proteins (Nfl, T-tau and P-tau181) for their potential in diagnosing Alzheimer's disease.

Butler, AE *et al.* (2021) "Vitamin D association with the renin angiotensin system in polycystic ovary syndrome." *J Steroid Biochem Mol Biol* **214**: 105965. (**Subscription required**)

https://www.doi.org/10.1016/j.jsbmb.2021.105965

Vitamin D deficiency is common in women with polycystic ovary syndrome (PCOS), leading to renin-angiotensin system (RAS) overactivation, a known risk factor in developing cardiovascular disease. In this study, researchers from Royal College of Surgeons in Ireland Bahrain and Hull York Medical School in the UK used the SomaScan Assay to measure plasma levels of three RAS proteins (Angiotensin-converting enzyme 2 (ACE2), renin and angiotensinogen) in women with and without PCOS. They found RAS activation in vitamin D-deficient PCOS women compared to non-PCOS controls. In addition, decreased plasma ACE2 levels were seen in vitamin D deficient non-PCOS controls, which may predispose them to increased cardiovascular risk and susceptibility to infectious agents such as COVID-19.

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Park, YH *et al.* (2021) "Dysregulated expression levels of APH1B in peripheral blood are associated with brain atrophy and amyloid-beta deposition in Alzheimer's disease." *Alzheimers Res Ther* **13**(1): 183.

https://www.doi.org/10.1186/s13195-021-00919-z

In this article, a team led by researchers at Indiana University School of Medicine used blood transcriptomic data from two independent Alzheimer’s disease (AD) cohorts to investigate the effects of AD-associated genetic variants on gene expression levels. They identified seven AD target genes and associated them with neuroimaging biomarkers and plasma protein levels measured using the SomaScan Assay. Among the seven genes, APH1B expression levels were increased in the blood of AD patients and associated with brain atrophy and amyloid-beta deposition. These results warrant further investigation into the possible role of APH1B in AD development.

Bowker, N *et al.* (2021) "Genetically Predicted Glucose-Dependent Insulinotropic Polypeptide (GIP) Levels and Cardiovascular Disease Risk Are Driven by Distinct Causal Variants in the GIPR Region." *Diabetes* **70**(11): 2706-2719.

https://www.doi.org/10.2337/db21-0103

Glucose-Dependent Insulinotropic Polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are hormones produced by the gut that stimulate insulin production. Dual agonists of the receptors for GIP and GLP-1 (GIPR and GLP1R, respectively) are under development as treatments for type 2 diabetes and obesity. There is some genetic evidence that higher GIP levels increase the risk of coronary artery disease (CAD), raising potential safety concerns for GIPR agonists. In this study, researchers at the University of Cambridge, Eli Lilly and the Berlin Institute of Health and Charité combined genome-wide association data with SomaScan proteomic measurements of 12,084 participants of the Fenland study and found that higher fasting GIP levels mediated by DNA variants of GIPR are not associated with CAD risk. These results suggest that GIPR agonist treatments for diabetes or obesity would not have adverse effects on cardiovascular health.

Kivimaki, M *et al.* (2021) "Cognitive stimulation in the workplace, plasma proteins, and risk of dementia: three analyses of population cohort studies." *BMJ* **374**: n1804.

https://www.doi.org/10.1136/bmj.n1804

In the largest study of its kind to date, a team led by researchers at University College London found that people with mentally stimulating jobs have a lower risk of dementia in old age than those with non-stimulating jobs. Data were obtained from seven cohort studies examining 107,896 people followed for 13-30 years. For 13,656 participants from two of the studies, the researchers used the SomaScan Assay to examine the relationship between plasma protein levels and dementia risk. Lower levels of three proteins (SLIT2, AMD, and CHSTC) were associated with both mental stimulation at work and decreased risk of dementia. These three proteins play roles in preventing brain cells from forming new connections, which could provide clues to biological processes that underlie dementia risk.

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Yang, C *et al.* (2021) "Genomic atlas of the proteome from brain, CSF and plasma prioritizes proteins implicated in neurological disorders." *Nat Neurosci* **24**(9): 1302-1312.

https://www.doi.org/10.1038/s41593-021-00886-6

In this study, researchers at Washington University School of Medicine in St. Louis identified new protein targets as well as existing drugs that could potentially be repurposed for treating Alzheimer’s disease. The researchers used the SomaScan Assay to measure the levels of 1,305 proteins in cerebral spinal fluid (CSF), brain tissue and plasma from people with and without Alzheimer’s disease. They then linked the SomaScan proteomic data to genetic data from genome-wide association studies (GWAS) to identify 274, 127 and 32 protein quantitative trait loci (pQTLs) for cerebrospinal fluid, plasma and brain, respectively. More than 70% of the brain pQTLs were shared with plasma and CSF, which suggests that both blood and CSF reflect what is happening in the brain. The researchers used a method called Mendelian randomization to identify proteins linked to increased risk of Alzheimer’s disease, Parkinson’s disease, frontotemporal dementia, amyotrophic lateral sclerosis and stroke. They then searched for existing drugs that target these proteins and identified 25 drugs that could potentially be repurposed for treating neurological diseases.

Sayed, N. *et al.* (2021) An inflammatory aging clock (iAge) based on deep learning tracks multimorbidity, immunosenescence, frailty and cardiovascular aging. *Nat Aging* **1**: 598-615.

https://doi.org/10.1038/s43587-021-00082-y

Constant, low-grade inflammation throughout the body is believed to play a critical role in how we age, but currently there are no ways to measure systemic inflammation. In this article, an international team, led by researchers at Stanford, generated an inflammatory clock (iAge) that reflects a person’s age based on their inflammatory status. The researchers applied AI methods to blood immunological data from 1,001 healthy individuals aged 8 to 96 years and found that a set of approximately 50 immune proteins were sufficient to generate an iAge score that tracked with calendar age and the likelihood of having multiple age-related diseases. iAge was also able to predict frailty seven years in advance. Using SomaScan data collected on exceptionally long-lived individuals, the researchers found that the iAge of centenarians averaged 40 years younger than their calendar age. The strongest contributor to iAge was the protein CXCL9, which is linked to cardiac and vascular aging. Reducing CXCL9 levels in human and mouse cells restored function. These results suggest that iAge could be used as a metric for gauging healthy versus unhealthy aging, predicting health problems in advance and identifying possible protein targets for intervention.

Mills, RJ *et al.* (2021) "BET inhibition blocks inflammation-induced cardiac dysfunction and SARS-CoV-2 infection." *Cell* **184**(8): 2167-2182 e2122.

https://www.doi.org/10.1016/j.cell.2021.03.026

Using pre-clinical inflammatory models of COVID-19, a team led by researchers at QIMR Berghofer Medical Research Institute in Australia found that treatment with bromodomain and extraterminal (BET) inhibitors prevented heart dysfunction. Elevated levels of LGALS3BP, a known protein marker of COVID-19 severity, was identified as a key mediator of a “cardiac cytokine storm” in SARS-CoV-2-infected mice. Analysis of SomaScan data collected in a phase IIb clinical trial of the BET inhibitor apabetalone, showed reduced levels of LGALS3BP in patients with cardiovascular disease. These data suggest that BET inhibitors may be promising candidates to prevent COVID-19-mediated heart damage.

Goudswaard, LJ *et al.* (2021) "Effects of adiposity on the human plasma proteome: observational and Mendelian randomisation estimates." *Int J Obes (Lond)* **45**: 2221-2229.

https://www.doi.org/10.1038/s41366-021-00896-1

The goal of this study from a team of UK scientists was to understand the effect of obesity on circulating proteins. They used previously collected SomaScan data from 2,737 participants in a UK cohort of blood donors to estimate the effects of body mass index (BMI) on 4,034 (3,622 unique) plasma proteins. BMI associated with 1,576 proteins and was strongest for proteins involved in regulating appetite, sex hormones and inflammation. These proteins could serve as potential drug targets for prevention of cardiovascular disease, diabetes, cancer and other obesity-related diseases.

Jimenez-Balado, J *et al.* (2021) "New candidate blood biomarkers potentially associated with white matter hyperintensities progression." *Sci Rep* **11**(1): 14324.

https://www.doi.org/10.1038/s41598-021-93498-w

White matter hyperintensities (WMH) are bright regions frequently seen in brain imaging, and their spread is associated with increased risk of stroke or dementia. Currently, changes in WMH can only be detected by conducting magnetic resonance imaging (MRI) over time, which is costly. In this pilot study, researchers at the Universitat Autonoma de Barcelona in Spain used the SomaScan Assay to see if blood proteins are associated with WMH progression. They measured the levels of 1,305 proteins in plasma samples from 24 patients, 12 who showed WMH progression over 4 years follow up as well as 12 controls. They identified 41 proteins that were significantly different in baseline samples from those with WMH progression. Three of the proteins (MMP9, MET, and ASAH2) have known connections to cerebrovascular or neurological diseases and were selected for replication in 80 patients with WMH progression and 80 controls. Patients with WMH progression showed a steeper decline in MET levels between baseline and follow up visits and higher MMP9 and ASAH2 levels at the follow-up visit. Future studies in larger studies are needed, but these results suggest that MMP9, ME and ASAH2 are associated with WMH progression and could be potential drug targets for therapeutic intervention.

Filbin, MR et al. (2021) "Longitudinal proteomic analysis of severe COVID-19 reveals survival-associated signatures, tissue-specific cell death, and cell-cell interactions." *Cell Rep Med* 2(5): 100287.

https://www.doi.org/10.1016/j.xcrm.2021.100287

In this article, a team led by researchers at Massachusetts General Hospital and Harvard Medical School describe a comprehensive proteomic study of the host response to SARS-CoV-2 infection. The researchers analyzed plasma using both SomaScan and Olink proteomic assays from 384 people (306 confirmed COVID-19 patients and 78 symptomatic controls) admitted to the emergency department with severe respiratory distress. They also analyzed samples from COVID-

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19 patients still hospitalized on day 3 and day 7 and identified unique protein signatures associated with COVID-19 disease, severity, aging, tissue destruction and cellular death that they mapped to specific cell types. The results provide insight into underlying disease mechanisms and potential targets for treating COVID-19.

Hernandez Cordero, AI *et al.* (2021) "Multi-omics highlights ABO plasma protein as a causal risk factor for COVID-19." *Hum Genet* **140**(6): 969-979.

https://www.doi.org/10.1007/s00439-021-02264-5

This article describes the first study to demonstrate a causal association between COVID-19 and the protein that is determines a person’s ABO blood group. An international team, led by researchers at the University of British Columbia, used genomic, transcriptomic and SomaScan proteomic data to identify candidate genes that may be involved in COVID-19 pathogenesis. They showed that increased ABO plasma levels were associated with an increased risk of COVID-19 susceptibility and severity.

Moin, ASM *et al.* (2021) "Type 2 Diabetes Coagulopathy Proteins May Conflict With Biomarkers Reflective of COVID-19 Severity." *Front Endocrinol (Lausanne)* **12**: 658304.

https://www.doi.org/10.3389/fendo.2021.658304

—*and*—

Moin, ASM *et al.* (2021) "Soluble Neuropilin-1 Response to Hypoglycemia in Type 2 Diabetes: Increased Risk or Protection in SARS-CoV-2 Infection?" *Front Endocrinol (Lausanne)* **12**: 665134.

https://www.doi.org/10.3389/fendo.2021.665134

Two publications from researchers at Hamad Bin Khalifa University, Qatar, Hull York Medical School, UK, and Royal College of Surgeons in Ireland, Bahrain describe using the SomaScan Assay to measure the levels of potential COVID-19 protein biomarkers in people with Type 2 diabetes (T2D) compared to controls.

The protein neuropilin-1 (NRP1) may help SARS-CoV-2 infect host cells. In an article entitled "Type 2 Diabetes Coagulopathy Proteins May Conflict with Biomarkers Reflective of COVID-19 Severity," the authors found that lower-than-normal blood sugar levels led to higher levels of circulating NRP1 in people with T2D, which could place them at higher risk of SARS-CoV-2 infection.

People with T2D are more likely to have serious complications from COVID-19. In an article entitled “Type 2 Diabetes Coagulopathy Proteins May Conflict with Biomarkers Reflective of COVID-19 Severity" the authors found that 7 of 34 putative protein biomarkers of COVID-19 severity were significantly different in people with T2D and that the protein levels changed under low blood sugar conditions. These results suggest that changes in these proteins may not reflect worse COVID-19 outcomes in people with T2D.

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Barros, TT *et al.* (2021) “DNA Damage, n-3 Long-Chain PUFA Levels and Proteomic Profile in Brazilian Children and Adolescents.” *Nutrients* **2021**, *13*, 2483.

https://doi.org/10.3390/nu13082483

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega 3 fatty acids found in oily fish that have been shown to reduce the risk of heart disease or stroke. In a previous study, researchers at University of Sao Paulo in Brazil and Nestle Research in Switzerland found that higher blood levels of EPA and DHA correlated with lower amounts of DNA damage in healthy Brazilian children. In this study, the researchers used the SomaScan Assay to measure the levels of 1,129 proteins in the children and found that those with more DNA damage and lower levels of EPA and DHA also had higher levels of inflammatory proteins. These results point to a possible mechanism by which essential nutrients protect against development of future age-related diseases.

Kokelj, S *et al.* (2021) "Smoking induces sex-specific changes in the small airway proteome." *Respir Res* **22**(1): 234.

https://www.doi.org/10.1186/s12931-021-01825-6

Smoking is the leading cause of chronic obstructive pulmonary disease (COPD), although the biological mechanisms by which smoking contributes to inflammation and tissue damage are not completely understood. In this study, investigators at University of Gothenburg, PExA AB, AstraZeneca, Uppsala University and Linnaeus University in Sweden explored the effects of smoking on the small airway proteome. Exhaled particles were collected from 107 people (38 current smokers, 47 former smokers and 22 healthy non-smokers) and analyzed using the SomaScan Assay. In all, 203 proteins were detected in at least half of the samples. Clear differences were seen in the small airway protein profiles of current smokers compared to those who had never smoked, whereas the protein profiles of former smokers was similar to that of non-smokers. Women smokers are more likely to develop COPD than men, and the researchers found significant differences between men and women smokers, particularly in the levels of proteins related to the complement system. The complement system is part of the immune response and is believed to be an important driver of COPD inflammation. These results suggest that SomaScan analysis of the small airway proteome is a promising platform for discovering protein markers for early detection of COPD and identification of novel COPD drug targets.

Sullivan, KD *et al.* (2021) "The COVIDome Explorer researcher portal." *Cell Rep* **36**(7): 109527.

https://www.doi.org/10.1016/j.celrep.2021.109527

In this article, researchers at the University of Colorado Anschutz Medical Campus describe a multi-omics study of COVID-19 patients. They analyzed the whole blood transcriptome, SomaScan and mass spec plasma proteomics, cytokine profiling, plasma and red blood cell metabolomics, immune cell phenotyping, demographics and clinical data of 73 hospitalized COVID-19 patients compared to 32 COVID-19 negative controls. They used this “COVIDome” data set to identify diverse pathophysiological processes associated with C-reactive protein, a marker of poor COVID-19 prognosis. They also created an online portal where the data can be accessed by others to accelerate COVID-19 research.

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Liu, RX *et al.* (2021) "Comparison of proteomic methods in evaluating biomarker-AKI associations in cardiac surgery patients." *Transl Res* **238**: 49-62.

https://www.doi.org/10.1016/j.trsl.2021.07.005

In this article, researchers from Johns Hopkins University School of Medicine, Boston University Schools of Medicine and Public Health, University of California, San Francisco and the National Institutes of Health compared biomarker-disease associations identified using the SomaScan Assay and antibody-based assays in a study of acute kidney injury (AKI). There was a broad range of correlations between SomaScan and antibody-based assays for a set of 34 proteins that could be compared between platforms. Higher inter-platform correlations were seen for more abundant proteins. Importantly, all proteins significantly associated with AKI as measured by the SomaScan Assay were also significantly associated with AKI as measured by immunoassay.

Ogundele, M *et al.* (2021) "Validation of Chemokine Biomarkers in Duchenne Muscular Dystrophy." *Life (Basel)* **11**(8): 827.

https://www.doi.org/10.3390/life11080827

Duchenne muscular dystrophy (DMD) is a genetic disorder that leads to progressive muscle degeneration. In this study, researchers at Binghamton University SUNY used ELISA assays to validate three proteins previously identified by the SomaScan Assay as being elevated in the serum of DMD patients compared to healthy, age-matched controls. One of the proteins, CCL2, was significantly increased in the serum of a DMD mouse model and in the muscle tissue of DMD patients. These results warrant further investigation of CCL2 as a potential biomarker of DMD disease activity and as a potential therapeutic target.

Rhee, J *et al.* (2021) "Serum Proteomics of Older Patients Undergoing Major Cardiac Surgery: Identification of Biomarkers Associated With Postoperative Delirium." *Front Aging Neurosci* **13**: 699763.

https://www.doi.org/10.3389/fnagi.2021.699763

Postoperative delirium (POD) is commonly seen in older adults following heart surgery and can lead to longer hospital stays and recovery times. To gain a greater understanding of the biological processes underlying POD, researchers at Massachusetts General Hospital, Harvard Medical School and Beth Israel Deaconess Medical Center used the SomaScan Assay to measure the levels of serum proteins in samples from older adults collected before and after heart bypass surgery. Several inflammatory proteins were significantly increased in eight patients with POD compared to eight without POD, including IL-6, which has previously been associated with POD, and TIMP-1 which had not. These putative protein biomarkers could enable ways to identify patients at risk for POD, predict its severity and identify possible treatments.

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Abdel-Aziz, M. I., et al. (2021). "Association of endopeptidases, involved in SARS-CoV-2 infection, with microbial aggravation in sputum of severe asthma." *Allergy* **76**(6): 1917-1921.
https://doi.org/10.1111/all.14731

Asthma is a chronic respiratory disease with varying degrees of airway inflammation that could affect COVID-19 severity. In this study, a team led by researchers at Imperial College London examined transcriptomics, SomaScan proteomics, and genomics data collected on 120 sputum samples from severe asthmatics (smoking and non-smoking), mild-moderate asthmatics, and healthy controls. They found that levels of host enzymes involved in SARS-CoV-2 infection may be affected by higher levels of bacteria in the airways of severe asthmatics. These findings suggest that stratifying asthma patients is needed to assess risk of SARS-CoV-2 infection.

AlGhatrif, M *et al.* (2021) "Age-associated difference in circulating ACE2, the gateway for SARS-COV-2, in humans: results from the InCHIANTI study." *Geroscience* **43**(2): 619-627.

https://www.doi.org/10.1007/s11357-020-00314-w

The SARS-CoV-2 virus uses the protein angiotensin-converting enzyme 2 (ACE2) to infect cells, and higher levels of ACE2 have been implicated in worse COVID-19 outcomes. This study from researchers at the National Institutes of Health was the first to examine age-associated differences in circulating ACE2 levels. They used the SomaScan Assay to measure the levels of ACE2 in plasma from 967 older adults living in the Chianti region of Italy and found lower levels of ACE2 in people over the age of 60. They did not find any correlations with ACE2 levels and hypertension or diabetes but did find higher ACE2 levels in individuals with peripheral artery disease. Further study in larger cohorts is needed to confirm the associations of ACE2 with chronic conditions and COVID-19 severity.

Anisul, M et al. (2021) "A proteome-wide genetic investigation identifies several SARS-CoV-2-exploited host targets of clinical relevance." Elife **10**.

https://www.doi.org/10.7554/eLife.69719

In this study, a team led by researchers at the Wellcome Sanger Institute in the UK leveraged publicly available genomic and SomaScan proteomic datasets to identify host proteins that may contribute to the risk of severe COVID-19. Other studies have implicated the ABO blood type protein in COVID-19 susceptibility and severity. This study showed that ABO is associated with higher plasma concentrations of the protein CD209 and that CD209 directly interacts with the SARS-CoV-2 spike protein. These results suggest that CD209 could serve as an entry point for viral infection, which could explain the relationship between blood type and COVID-19 risk. Combining genomic and proteomic data, the researchers provide a list of potential protein drug targets for COVID-19 that warrant further investigation.

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Thanasupawat, T *et al.* (2021) "Slow Off-Rate Modified Aptamer (SOMAmer) Proteomic Analysis of Patient-Derived Malignant Glioma Identifies Distinct Cellular Proteomes." *Int J Mol Sci* **22**(17).

https://www.doi.org/10.3390/ijms22179566

Malignant gliomas represent nearly 80% of primary brain tumors. In this study, researchers at the University of Manitoba used the SomaScan Assay to measure the levels of 1,307 proteins in 89 patient-derived malignant glioma cells: anaplastic astrocytoma (AS), glioblastoma multiforme (GBM) and oligodendroglioma (ODG). The protein profiles of AS and GBM were similar and clearly distinct from ODG cells. The GBM samples clustered into four different protein profiles that may reflect different tumor subtypes. These results illustrate how protein signatures identified using the SomaScan Assay could be used to stratify cancer patients and identify potential drug targets for treating different types of brain tumors.

Walker, KA *et al.* (2021) “Large-scale plasma proteomic analysis identifies proteins and pathways associated with dementia risk.” *Nat Aging* **1**: 473–489. (**Subscription required**)

https://doi.org/10.1038/s43587-021-00064-0

In this article, a team led by researchers from Johns Hopkins Bloomberg School of Public Health describe protein changes that can be detected in the blood of individuals before the onset of dementia. In the most comprehensive analysis of its kind to date, the researchers used the SomaScan Assay to measure the levels of approximately 5,000 proteins in more than 4,000 plasma samples from a large biracial cohort of older adults in the United States. They examined samples taken in midlife (average age 60) and late in life (average age 75), comparing the blood proteomes of those who later developed dementia to those who did not. In samples collected late in life, the researchers found that the levels of 38 proteins differed significantly in those who developed dementia within 5 years of the blood draw. Of the 38 proteins, 16 predicted dementia risk in the samples collected in midlife, almost 20 years earlier. Two of the 38 dementia-associated proteins showed causal links to Alzheimer’s disease, and at least 10 of the proteins are targets of existing drugs. These results suggest that abnormal blood levels of certain proteins could predict future dementia well in advance of the onset of symptoms. Some of the identified proteins could also serve as possible targets for interventions that might slow or prevent cognitive decline.

Robbins, JM *et al.* (2021) "Human plasma proteomic profiles indicative of cardiorespiratory fitness." *Nat Metab* **3**(6): 786-797.

https://pubmed.ncbi.nlm.nih.gov/34045743/

Although exercise is generally considered beneficial for health, the way each person responds to exercise can vary widely. To help understand why, a team led by researchers at Beth Israel Deaconess Medical Center used the SomaScan Assay to measure the levels of approximately 5,000 plasma proteins in over 650 sedentary adults before and after 20 weeks of an endurance exercise program. They identified 147 proteins whose plasma levels were associated with maximal oxygen uptake (VO_2max), the gold standard measure of cardiorespiratory fitness. They also identified 102 proteins that associated with an individual’s change in VO_2max after completion of the exercise program. Interestingly, they found minimal overlap between the two sets of proteins. They then derived a protein score that improved the ability to predict an individual’s response to exercise compared to a clinical trait model that included age, sex, race and body mass index. Lastly, they found

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that key proteins associated with fitness were also associated with death in a separate cohort. These results improve our understanding of the biological processes important for cardiovascular fitness and could lead to tailored exercise programs for improving health.

Arthur L, *et al.* (2021) “Cellular and plasma proteomic determinants of COVID-19 and non-COVID-19 pulmonary diseases relative to healthy aging.” *Nat Aging* **1**: 535–549.

https://doi.org/10.1038/s43587-021-00067-x

Older people are much more likely to have severe symptoms from COVID-19. To better understand the body’s response to COVID-19, it’s important to account for age-related changes in the immune system. In this article, researchers at Washington University School of Medicine used clinical blood testing, immune cell cytometry and SomaScan Assay profiling of approximately 4,700 proteins to examine differences between people with COVID-19 or other respiratory illnesses (aged 25-80 years old) and healthy age-matched controls. They were able to disentangle COVID-19-specific changes from effects of other infections and of aging.

Elhadad, MA *et al.* (2021) "Metabolic syndrome and the plasma proteome: from association to causation." *Cardiovasc Diabetol* **20**(1): 111.

https://www.doi.org/10.1186/s12933-021-01299-2

Metabolic syndrome (MetS) is a set of risk factors including high blood pressure, high blood sugar, abnormal cholesterol levels and high abdominal fat that significantly increase the risk of type 2 diabetes and cardiovascular diseases. To better understand the biological basis of MetS. a team led by researchers at Helmholtz Zentrum München, German Research Center for Environmental Health used the SomaScan Assay to measure the levels of 1095 plasma proteins in 998 participants in the German KORA study cohort. They identified 116 MetS-associated proteins in the KORA study, of which 53 proteins were replicated in an independent Norwegian HUNT3 cohort. Thirty of the proteins had not been previously linked to MetS. The researchers also identified 14 proteins associated with developing MetS and 3 proteins that may cause MetS. These results highlight protein candidates that could potentially serve as targets for MetS prevention and therapy.

Eiriksdottir, T *et al.* (2021) "Predicting the probability of death using proteomics." *Commun Biol* **4**(1): 758.

https://www.doi.org/10.1038/s42003-021-02289-6

Researchers at deCODE Genetics/Amgen used the SomaScan Assay to develop a protein predictor of death from all causes. They measured the levels of 4,684 plasma proteins in 22,913 Icelanders between the ages of 18 and 101 years old. During of a follow up period of approximately 14 years, 7,061 participants died. In a group of 60–80 years old participants, the protein model could identify a high-risk group with an 88 percent probability of dying within 10 years and a 67 percent probability of dying within 5 years. The protein model could also identify a low-risk group with a 1 percent probability of dying within 10 years. The protein-based models outperformed a predictor based on traditional risk factors such as diabetes,

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cancer, smoking, age, blood pressure, cholesterol levels, and body mass index. In an independent dataset, they found that high risk of death correlated with measures of health and frailty such as poor performance on an exercise test. The results show that measuring the plasma proteome in a single blood draw can be used to assess general health and estimate the risk of death, which could be useful for evaluating the effects of treatments in clinical trials.

Styrkarsdottir, U *et al.* (2021) "The CRTAC1 protein in plasma associates with osteoarthritis and predicts progression to joint replacements: a large-scale proteomics scan in Iceland." *Arthritis Rheumatol* **73**(11): 2025-2034.

https://www.doi.org/10.1002/art.41793

Osteoarthritis, sometimes called “wear and tear” arthritis, is a degenerative joint disease that affects hundreds of millions of people worldwide. In this article, researchers at deCODE Genetics describe the largest biomarker study of osteoarthritis to date. The researchers used the SomaScan Assay to measure the levels of 4,792 proteins in plasma from 37,278 Icelanders, of whom 12,178 had osteoarthritis and 2,524 had undergone joint replacement. They identified 45 proteins that associated with knee arthritis, 7 with hip arthritis and 44 with hand arthritis. They identified a novel biomarker, Cartilage Acidic Protein 1 (CRTAC1) that associated with all three osteoarthritis subtypes and progression to joint replacement. CRTAC1 was specific to osteoarthritis, with no association to other joint diseases such as gout, rheumatoid arthritis or psoriatic arthritis. These results warrant further investigation of CRTAC1 as a biomarker for diagnosing osteoarthritis and monitoring disease progression, which could help development of effective therapies for this common disease.

Gurinovich, A *et al.* (2021) "Effect of longevity genetic variants on the molecular aging rate." *Geroscience* **43**(3): 1237-1251.

https://www.doi.org/10.1007/s11357-021-00376-4

Many centenarians and their children manage to escape common age-related diseases and live long and healthy lives. To better understand the genetic and modifiable factors that contribute to healthy aging, a team led by researchers at Tufts Medical Center conducted a genome-wide association study of 1,320 centenarians from the New England Centenarian Study and 2,899 unrelated controls whose parents died young. A set of 56 genetic variants with the most significant links to extreme longevity were then correlated with 4,131 serum proteins measured in a subset of 224 study participants using the SomaScan Assay. The investigators replicated a protein signature associated with the apolipoprotein E (APOE) gene and identified three new protein signatures of longevity. The results show how integrating genetics and proteomics could help identify therapeutic targets for healthy aging.

Luo, Y *et al.* (2021) "SOMAscan Proteomics Identifies Serum Biomarkers Associated With Liver Fibrosis in Patients With NASH." *Hepatol Commun* **5**(5): 760-773.

https://www.doi.org/10.1002/hep4.1670

Nonalcoholic steatohepatitis (NASH) is a progressive condition in which fat builds up in the liver causing inflammation and damage. NASH is a silent disease, with few symptoms. The presence and extent of fibrosis is important for assessing NASH prognosis but requires a liver biopsy, which is invasive and costly. In this article, researchers at Bristol Myers Squibb and Virginia Commonwealth University used the SomaScan Assay to measure the levels of 1,305 proteins in serum from 113 NASH patients with varying stages of fibrosis. They applied machine learning techniques to create and validate a 12-protein model that could differentiate advanced from early fibrosis. The results warrant further evaluation of the model as a minimally invasive tool for diagnosing advanced fibrosis in patients with NASH.

Han, K *et al.* (2021) "Identification and Validation of Nutrient State-Dependent Serum Protein Mediators of Human CD4(+) T Cell Responsiveness." *Nutrients* **13**(5).

https://www.doi.org/10.3390/nu13051492

The Western diet of overeating has been linked to chronic low-grade inflammation that is thought to underlie various diseases. Fasting regimens have been shown to reduce inflammation although it is unclear why. To help understand the biological effects of restricting dietary intake, researchers at the National Institutes of Health conducted a pilot study using the SomaScan Assay to evaluate changes in serum protein levels in response to intermittent fasting. They measured the levels of 1,305 proteins in serum samples collected from healthy participants after an overnight fast, after eating a 500-calorie meal and 24-hour fast, and 3 hours after eating another 500-calorie meal. The data revealed a large number of proteins whose levels were significantly different between fasting and refed states. Many of the proteins identified are important for activating helper T cells, which modulate the immune response.

Tsim, S *et al.* (2021) "Serum Proteomics and Plasma Fibulin-3 in Differentiation of Mesothelioma from Asbestos-Exposed Controls and Patients with Other Pleural Diseases." *J Thorac Oncol*. **16**(10): 1705-1717.

https://www.doi.org/10.1016/j.jtho.2021.05.018

Malignant pleural mesothelioma (MPM) is a highly aggressive cancer associated with asbestos exposure that is difficult to diagnose. In this article, researchers in the UK and at SomaLogic describe a prospective multi-center study to assess whether two previously discovered MPM biomarkers the protein Fibulin-3 and a SomaScan-derived 13-protein signature could differentiate MPM from asbestos-exposed controls (AECs) or other patients with suspected pleural cancers. Although neither Fibulin-3 nor the SomaScan Assay proved useful in distinguishing MPM from suspected MPM, the SOMAscan Assay was able to distinguish MPM from AECs and could prove useful as a potential future screening test for MPM in people exposed to asbestos.

Sproull, M *et al.* (2021) "Novel Murine Biomarkers of Radiation Exposure Using an Aptamer-Based Proteomic Technology." *Front Pharmacol* **12**: 633131.

https://www.doi.org/10.3389/fphar.2021.633131

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The goal of this study was to identify plasma protein markers of radiation exposure. Researchers at the National Cancer Institute gave mice increasing doses of X-rays or sham radiation and then used the SomaScan Assay to measure the levels of 1,310 proteins in plasma collected 1, 3 and 7 days after exposure. The researchers were able to identify a novel panel of radiation-responsive proteins useful for predicting whether an animal had been exposed to radiation and what dose they had received.

Md Dom, ZI *et al.* (2021) "Effect of TNFalpha stimulation on expression of kidney risk inflammatory proteins in human umbilical vein endothelial cells cultured in hyperglycemia." *Sci Rep* **11**(1): 11133.

https://www.doi.org/10.1038/s41598-021-90496-w

The inflammatory protein TNFα is believed to be a key factor in the development and progression of diabetic kidney disease. In a previous study, investigators at the Joslin Diabetes Center and Harvard Medical School used a custom 194-protein version of the SomaScan Assay to identify a kidney risk inflammatory signature (KRIS) — a set of 17 circulating proteins strongly associated with 10-year risk of end-stage kidney disease (ESKD) in diabetes (see Niewczas, MA *et al.* (2019) *Nat Med* **25**(5): 805-813 https://www.ncbi.nlm.nih.gov/pubmed/31011203). Among the KRIS proteins identified were two receptors that bind TNFα. In this study, the researchers used a cell model to investigate the effect of TNFα on KRIS proteins. They exposed human umbilical vein endothelial cells to TNFα under high glucose conditions and measured the levels of 1,305 proteins within and outside of the cells using the SomaScan Assay. Although KRIS proteins were not significantly affected by TNFα, the researchers saw increases in a distinct set of 53 proteins that were not associated with progression to ESKD in diabetes in the previous study. These results suggest the elevated levels of TNFα do not regulate circulating levels of KRIS proteins and provide a more detailed picture of protein variations associated with the inflammatory response.

Gui, H *et al.* (2021) "Plasma Proteomic Profile Predicts Survival in Heart Failure with Reduced Ejection Fraction." *Circ Genom Precis Med* **14**(3): e003140.

https://www.doi.org/10.1161/CIRCGEN.120.003140

One of the challenges of managing patients with heart failure (HF) is the difficulty in predicting disease progression. In the largest study of its kind to date, a team led by researchers at the Henry Ford Hospital used the SomaScan Assay to measure the levels of 4,453 plasma proteins in 1,017 patients with HF with reduced ejection fraction (HFrEF). They derived and validated an eight-protein risk score for survival in HFrEF patients that improved risk stratification above current standards. While some of the key proteins have been implicated in HF, many are novel and deserve further investigation for their roles in HF progression and as potential therapeutic targets.

Katz, DH *et al.* (2021) "Multiomic Profiling in Black and White Populations Reveals Novel Candidate Pathways in Left Ventricular Hypertrophy and Incident Heart Failure Specific to Black Adults." *Circ Genom Precis Med* **14**(3): e003191.

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https://www.doi.org/10.1161/CIRCGEN.120.003191

Increased left ventricular (LV) mass is associated with heart failure (HF) and both conditions disproportionately affect Black individuals. To better understand why, a team led by researchers at Beth Israel Deaconess Medical Center conducted the largest proteomic profiling study of a Black population and compared the results to those from a white cohort. They used the SomaScan Assay to measure the levels of 1,305 plasma proteins from 1,772 Black participants in the Jackson Heart Study with LV mass. They identified 110 proteins associated with LV mass and 13 proteins associated with hospitalization for HF. Established biomarkers such as cystatin C and N-terminal pro-BNP showed consistent associations in Black and white individuals, but two proteins were significantly different between the two groups. LKHA4, a protein implicated in vascular inflammation, showed the strongest association with LV mass but not HF, and this association was unique to the Black population. Fractalkine, a protein implicated in atherosclerosis, was associated with incident HF but not LV mass, and this association was notably stronger in the Black population. These results reveal novel biological pathways that may contribute to increased risk of HF in Black individuals.

Mikhaylov, D *et al.* (2021) "Proteomic signatures of inflammatory skin diseases: a focus on atopic dermatitis." *Expert Rev Proteomics* **18**(5): 345-361.

https://www.doi.org/10.1080/14789450.2021.1935247

Atopic dermatitis (eczema, AD) is a chronic inflammatory skin condition. This review discusses key studies that used proteomic technologies to find new biomarkers of AD and to help define AD subtypes.

Zhou, S *et al.* (2021) "A Neanderthal OAS1 isoform protects individuals of European ancestry against COVID-19 susceptibility and severity." *Nat Med* **27**(4): 659-667.

https://www.doi.org/10.1038/s41591-021-01281-1

In this study, an international team of researchers used large-scale proteomic data to link genetic variants to COVID-19 outcomes. The researchers found that higher plasma levels of the protein OAS1 were associated with reduced COVID-19 death or ventilation. They then used the SomaScan Assay to validate this observation in a group of 399 COVID-19-positive individuals and 105 controls. These results suggest that therapies that increase OAS1 levels may protect against adverse COVID-19 outcomes.

Ramaswamy, A *et al.* (2021) "Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children." *Immunity* **54**(5): 1083-1095 e1087.

https://www.doi.org/10.1016/j.immuni.2021.04.003

Multisystem inflammatory syndrome in children (MIS-C) is a life-threatening, delayed inflammatory response that can happen 4-6 weeks after SARS-CoV-2 infection. MIS-C usually occurs in children who were previously healthy with no risk factors for severe COVID-19 disease. In this article, a team led by researchers at Yale University School of Medicine used single cell

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RNA sequencing, flow cytometry, antigen receptor repertoire analysis and SomaScan serum proteomics to compare samples from 23 MIS-C patients to healthy pediatric and adult controls. The researchers defined characteristics of MIS-C that correlated with disease severity and that could potentially be used to identify patients at risk of MIS-C for early intervention.

Matsuda, K *et al.* (2021) "A replication-competent adenovirus-vectored influenza vaccine induces durable systemic and mucosal immunity." *J Clin Invest* **131**(5): e140794.

https://www.doi.org/10.1172/JCI140794

Replicating vector vaccines produce new viral particles in the cells they infect. This can increase the amount of available antigen and lead to production of more robust neutralizing antibodies to the virus. In this study, researchers at the NIH, Icahn School of Medicine at Mount Sinai and Emergent Biosolutions examined the host response to a replicating adenoviral vaccine for influenza. They examined cell and antibody responses, virus shedding, adenovirus-related symptoms and induction of mucosal immunity, and found that the vaccine induced a durable immune response. They used the SomaScan Assay to measure serum levels of specific proteins after immunization. While the vaccine induced detectable levels of proinflammatory proteins, the levels were not extremely high overall or significantly higher in those who experienced vaccine-related symptoms. These results show that replicating adenoviral vectors are a promising platform for inducing immunity to influenza and potentially other viruses.

Zaghlool, SB *et al.* (2021) "Revealing the role of the human blood plasma proteome in obesity using genetic drivers." *Nat Commun* **12**(1): 1279.

https://www.doi.org/10.1038/s41467-021-21542-4

In this study, a team led by researchers at Beth Israel Deaconess Medical Center found that SARS-CoV-2 infection causes lung disease in rhesus macaques that is similar to COVID-19 in humans. They monitored differences in infected macaques compared to controls, conducting RNA profiling on bronchoalveolar lavage fluid and peripheral blood samples, as well as SomaScan proteomic profiling on serum samples collected over time. Their analysis suggests that SARS-CoV-2 infection activates proteins involved in inflammation and immune defense, which cause massive influxes of white blood cells that trigger blood clot formation and damage to the inner lining of blood vessels. These results improve our understanding of SARS-CoV-2 pathogenesis and suggest protein targets for treating COVID-19 in humans.

Gaziano, L *et al.* (2021) "Actionable druggable genome-wide Mendelian randomization identifies repurposing opportunities for COVID-19." *Nat Med* **27**(4): 668-676.

https://www.doi.org/10.1038/s41591-021-01310-z

A team led by researchers from the VA Boston Healthcare System and the University of Cambridge combined genetic, transcriptomic and proteomic data to identify drugs that could be repurposed for early management of COVID-19. The used transcriptomic cis-eQTL data from 49 tissues obtained from the Genotype-Tissue Expression (GTEx) project and cis-pQTL

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data for 67 plasma proteins measured using the SomaScan Assay on Fenland and INTERVAL cohorts to identify genetic variants that affect plasma levels of 1,263 proteins that are therapeutic targets of approved or clinical-stage drugs. Combining genetic data from 7,554 hospitalized COVID-19 patients and over a million controls with the transcriptomic eQTL data, they identified three proteins that colocalized with COVID-19 hospitalization and represent drug targets for COVID-19 disease management.

Ozen, A *et al.* (2021) "Broadly effective metabolic and immune recovery with C5 inhibition in CHAPLE disease." *Nat Immunol* **22**(2): 128-139.

https://www.doi.org/10.1038/s41590-020-00830-z

CHAPLE (CD55 deficiency with hyperactivation of complement, angiopathic thrombosis and protein-losing enteropathy) disease is a rare hereditary immune disorder caused by a lack of the protein CD55. CD55 blocks the activity of complement, a part of the immune system that plays a critical role in inflammation and defense against infections. CHAPLE disease is associated with severe gastrointestinal symptoms that cause a metabolic starvation state and deep vein blood clots that can be life-threatening. Previous studies reported improvements in three family members with CHAPLE disease using eculizumab, a therapeutic antibody approved to treat another rare condition called paroxysmal nocturnal hemoglobinuria. In this study, a team led by researchers at the National Institutes of Health used eculizumab to treat 16 patients with CHAPLE disease and demonstrated that it was broadly effective in restoring normal immunity and metabolism but that the effects of the drug were temporary. The researchers used the SomaScan Assay to measure the levels of 1,305 serum proteins in 8 CHAPLE patients and healthy age-matched controls. At baseline, 94 proteins were significantly different in those with CHAPLE disease and after eculizumab treatment, their protein profiles shifted closer to those of the controls. Treatment was also associated with increases in certain serum proteins that were normal in untreated disease, which may point to proteins that contribute to the therapeutic effects of eculizumab.

Larson, A *et al.* (2021) “Plasma Proteomic Profiling in Hypertrophic Cardiomyopathy Patients before and after Surgical Myectomy Reveals Post-Procedural Reduction in Systemic Inflammation.” *Int J Mol Sci.* 2021, **22**(5): 2474

https://doi.org/10.3390/ijms22052474

Hypertrophic cardiomyopathy (HCM) is a genetic disease in which the heart muscle becomes abnormally thick. Approximately 70% of HCM patients have left ventricular outflow tract (LVOT) obstruction, a life-threatening complication. Currently, diagnosis of LVOT obstruction requires imaging or invasive testing. To identify potential biological markers of LVOT obstruction, researchers at Tufts Medical Center and Beth Israel Deaconess Medical Center conducted the first plasma proteomics study of patients with obstructive HCM, before and after surgical myectomy. They used the SomaScan Assay to compare the levels of 1,305 proteins in plasma samples from 12 HCM patients with LVOT obstruction approximately 1 month before and 3 months after surgery and found 25 proteins that could distinguish preoperative and postoperative states. They found significant differences in proteins involved in inflammation, fibrosis and angiogenesis that likely reflect improvement in heart inflammation and physiological function after surgery.

Hanff, TC *et al.* (2021) "Quantitative Proteomic Analysis of Diabetes Mellitus in Heart Failure with Preserved Ejection Fraction." *JACC Basic Transl Sci* **6**(2): 89-99.

https://www.doi.org/10.1016/j.jacbts.2020.11.011

Diabetes mellitus (DM) affects approximately 45% of people with heart failure with preserved ejection fraction (HFpEF) and is associated with higher rates of cardiovascular death and hospitalization. In this study, researchers from the University of Pennsylvania Perelman School of Medicine, Bristol-Myers Squibb, Washington University School of Medicine, Ghent University in Belgium and SomaLogic used the SomaScan Assay to measure the levels of 4,776 unique proteins in plasma samples from 2 independent cohorts of HFpEF patients with and without DM. They identified 10 proteins related to lipid metabolism, inflammation, and oxidative stress that were significantly different in the HFpEF patients with DM. Apolipoprotein M (ApoM), a protein with anti-inflammatory, anti-oxidant and anti-atherogenic effects, was significantly reduced in the patients with DM and associated with worse outcomes. These results suggest that ApoM could be a useful prognostic marker for patients with HFpEF and DM and that increasing ApoM levels could be an effective treatment.

Galbraith, MD *et al.* (2021) "Seroconversion stages COVID19 into distinct pathophysiological states." *Elife* 10: e65508.

https://www.doi.org/10.7554/eLife.65508

In this article, researchers at the University of Colorado Anschutz Medical Campus performed multi-omics analyses of blood from hospitalized COVID-19 patients compared to COVID-19 negative controls. They measured antibodies against SARS-CoV-2, conducted plasma proteomics using the SomaScan Assay and mass spectrometry, and analyzed immune cell types by mass cytometry. They identified hundreds of proteins and dozens of immune cell types that significantly correlated with seroconversion (when antibodies to the virus become present in blood). Their results suggest that seroconversion status could be used to stratify COVID-19 patients for therapeutic intervention and to inform analysis of clinical trial results.

Moaddel, R *et al.* (2021) "Proteomics in aging research: A roadmap to clinical, translational research." *Aging Cell* **20**(4): e13325.

https://www.doi.org/10.1111/acel.13325

In this review, researchers at the National Institutes of Health, the Buck Institute for Research on Aging, Johns Hopkins University School of Medicine and University of Bologna report on a detailed literature search for proteomic studies performed using multiple platforms, including the SomaScan Assay. They identified 232 plasma proteins that were significantly associated with age across studies. The proteins identified were enriched in biological processes known to be important in aging. Further investigation of these proteins is expected to reveal new mechanisms underlying healthy aging and age-related diseases.

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Hewitson, L *et al.* (2021) "Blood biomarker discovery for autism spectrum disorder: A proteomic analysis." *PLoS One* **16**(2): e0246581.

https://www.doi.org/10.1371/journal.pone.0246581

Autism spectrum disorder (ASD) refers to a broad range of neurodevelopmental disorders characterized by problems with social skills and communication as well as repetitive behaviors and interests. Early diagnosis and intervention are critical for ASD, but existing diagnostic and screening tools are based on behavioral criteria and are subjective and difficult to assess in younger children. To help identify biological markers of ASD, researchers at the Johnson Center for Child Health and Development, the University of Texas at Dallas and UT Southwestern Medical Center used the SomaScan Assay to compare the levels of 1,125 proteins in serum from 76 boys with ASD and 78 typically developing boys (aged 18 months to 8 years). The levels of 86 proteins were decreased and 52 proteins were increased in boys with ASD. Three computational methods were combined to identify a panel of nine proteins with high predictive power for ASD. The nine proteins were significantly correlated with ASD severity, and many have been linked previously to ASD. This set of nine proteins has the potential to be a new blood-based diagnostic of ASD in boys and could provide further insight into the biological processes associated with ASD.

Moin, ASM *et al.* (2021) "Metabolic consequences of obesity on the hypercoagulable state of polycystic ovary syndrome." *Sci Rep* **11**(1): 5320.

https://www.doi.org/10.1038/s41598-021-84586-y

—and—

Moin, ASM *et al.* (2021) “Vitamin D Association with Macrophage-Derived Cytokines in Polycystic Ovary Syndrome: An Enhanced Risk of COVID-19 Infection?” Front Endocrinol (Lausanne) **12**: 638621.

https://doi.org/10.3389/fendo.2021.638621

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that affects women during their childbearing years and can lead to infertility, diabetes and heart disease. Two publications from researchers at Hamad Bin Khalifa University, Qatar, Hull York Medical School, UK, and Royal College of Surgeons in Ireland, Bahrain used the SomaScan Assay to measure protein levels in women with PCOS compared to normal controls.

Women with PCOS have an increased tendency to develop blood clots, and in an article entitled “Metabolic consequences of obesity on the hypercoagulable state of polycystic ovary syndrome," the authors established that pro-coagulation proteins were elevated in women with PCOS. However, the protein changes were dependent on increased body mass index, inflammation and insulin resistance, rather than being intrinsic to PCOS.

In an article entitled, “Vitamin D Association with Macrophage-Derived Cytokines in Polycystic Ovary Syndrome: An Enhanced Risk of COVID-19 Infection?” the researchers found that inflammatory proteins associated with acute respiratory distress syndrome in COVID-19 were increased in women with PCOS. The women with PCOS also had lower vitamin D levels, a known risk factor for severe COVID-19. The protein changes and vitamin D deficiency were dependent on

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increased body mass index, which suggests that obese women with PCOS and vitamin D deficiency may be at greater risk of more severe COVID-19 infection.

Skuladottir, AT *et al.* (2021) "A meta-analysis uncovers the first sequence variant conferring risk of Bell's palsy." *Sci Rep* **11**(1): 4188.

https://www.doi.org/10.1038/s41598-021-82736-w

Bell's palsy is an unexplained weakening or paralysis of facial muscles that cause one side of the face to droop. A team led by scientists at deCODE Genetics/Amgen conducted the first meta-analysis of genome-wide association studies (GWAS) results from four cohorts and identified the first sequence variant conferring risk of Bell's palsy. They used transcriptomic and SomaScan proteomic data but were unable to pinpoint a gene associated with the variant. The variant also confers risk of intervertebral disc disorders and may point to a common pathogenesis.

Ziemba, M *et al.* (2021) "Biomarker-focused multi-drug combination therapy and repurposing trial in mdx mice." *PLoS One* **16**(2): e0246507.

https://www.doi.org/10.1371/journal.pone.0246507

Duchenne muscular dystrophy (DMD) is a progressive muscle wasting disease with no cure. In this study, researchers at the State University of New York at Binghamton, AGADA Biosciences in Canada, Mount Sinai Hospital and Children's National Medical Center used the SomaScan Assay to search for blood proteins that reflect drug response in an *mdx* mouse model of DMD. Four drugs (prednisolone, vamorolone, rituximab, and β-aminoisobutyric acid) were used singly and in combination to treat *mdx* mice for four weeks. The levels of 1,310 proteins were measured in serum collected at the end of treatment using the SomaScan Assay. The researchers found data concordance between different treatment groups where a single drug was held in common, and some overlap with human pharmacodynamic biomarkers for the same drug. These results suggest that a proteomic approach could provide objective outcome measures for testing and optimizing multi-drug approaches to DMD.

Huang, J *et al.* (2021) "Advances in Aptamer-Based Biomarker Discovery." *Front Cell Dev Biol* **9**: 659760.

https://www.doi.org/10.3389/fcell.2021.659760

This review highlights the SomaScan Assay for discovery of predictive, diagnostic or prognostic biomarkers in various diseases.

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Shi, L *et al.* (2021) "Replication study of plasma proteins relating to Alzheimer's pathology." *Alzheimers Dement* **17**(9): 1452-1464.

https://www.doi.org/10.1002/alz.12322

The "ATN" framework for classifying Alzheimer's disease (AD) is based on three biomarkers: amyloid pathology (A), tau pathology (T), and neurodegeneration (N) that are challenging to measure. In the largest study of its kind, a European team led by researchers at the University of Oxford in the UK examined whether measuring blood proteins could serve as a less invasive and potentially cost-effective option for the detection, classification and monitoring of AD. Plasma samples from 972 people (191 with AD, 409 with mild cognitive impairment, and 372 cognitively normal controls) were analyzed using both the SomaScan Assay (4,001 proteins) and targeted panels (25 proteins). The SomaScan Assay data revealed changes in individual proteins as well as networks of proteins relating to the ATN framework in poorly understood preclinical stages of AD. The researchers also found that different plasma proteins correlated with different common measures of neurodegeneration such as brain atrophy or cerebrospinal fluid markers. The study suggests that blood proteins can be used to predict and diagnose AD. The proteins identified may help elucidate the pathogenesis of AD and could potentially be used to prescreen individuals for clinical trials.

Moin, ASM *et al.* (2021) "Platelet Protein-Related Abnormalities in Response to Acute Hypoglycemia in Type 2 Diabetes." *Front Endocrinol (Lausanne)* **12**: 651009.

https://www.doi.org/10.3389/fendo.2021.651009

People with type 2 diabetes (T2D) have platelet hyperactivation that places them at higher risk for blood clots. Coagulation abnormalities can often lead to severe COVID-19 outcomes. In this study, researchers at Hamad Bin Khalifa University, Qatar, Hull York Medical School, UK, and Royal College of Surgeons in Ireland, Bahrain used the SomaScan Assay to determine levels of a panel of platelet-related proteins in plasma from 33 T2D patients compared to controls. Prothrombotic platelet proteins were elevated in T2D versus controls and remained unchanged after normal blood sugar levels were established using a glucose clamp. This hypercoagulability in T2D patients could be exacerbated by COVID-19 infection, placing them at higher risk of COVID-19-related organ failure or death.

Renwick, J *et al.* (2021) "Early Interleukin-22 and Neutrophil Proteins Are Correlated to Future Lung Damage in Children with Cystic Fibrosis." *Front Pediatr* **9**: 640184.

https://www.doi.org/10.3389/fped.2021.640184

Cystic fibrosis (CF) is a hereditary disease characterized by chronic lung infections that lead to permanent lung damage. Neutrophils, a type of white blood cell, dominate the inflammatory response in CF and are associated with airway-clogging mucus and lung injury. In this pilot study, researchers at Trinity College Dublin and Tallaght University Hospital in Ireland aimed to identify proteins in bronchoalveolar lavage (BAL) fluid in infants that correlate with CF severity in later childhood. They used the SomaScan Assay to measure the levels of 1,305 proteins in BAL from 14 children aged 1-5 years with CF. After age 6 years, high resolution computed tomography (HRCT) was performed on the children and a validated scoring system was used to assess CF progression. The researchers identified 18 proteins that correlated significantly with HRCT scores of CF severity, including many proteins produced by neutrophils. These proteins warrant further investigation as putative predictive biomarkers for severe disease progression and as possible targets for early therapeutic interventions in CF.

Germain, A *et al.* (2021) "In-Depth Analysis of the Plasma Proteome in ME/CFS Exposes Disrupted Ephrin-Eph and Immune System Signaling." *Proteomes* **9**(1).

https://www.doi.org/10.3390/proteomes9010006

Myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) is a disabling illness characterized by profound exhaustion that lasts for more than six months and does not improve with rest. There is no known cause, diagnostic test or cure for ME/CFS. In this article, researchers at Cornell University created the largest proteomics dataset of ME/CFS to date, using the SomaScan Assay to compare the levels of 4,790 unique blood proteins in 20 women with ME/CFS and 20 age-matched, healthy controls. Between the two groups, they saw significant differences in the levels of 19 proteins involved in cellular structure, the immune system and cell–cell communication. These results illustrate the promise of plasma proteomics for diagnosing and understanding the biological basis of ME/CFS.

Xu, X *et al.* (2021) "Inhibition of the Complement Alternative Pathway by Chemically Modified DNA Aptamers That Bind with Picomolar Affinity to Factor B." *J Immunol* 206(4): 861-873.

https://www.ncbi.nlm.nih.gov/pubmed/33419768

The complement system plays a critical role in the body's defense against invading pathogens, but its activation can trigger inflammation that leads to tissue damage and disease. This spurred interest in finding inhibitors of proteins that modulate complement activity. In this paper, researchers at Kansas State University and SomaLogic report the creation and structural characterization of two SOMAmer reagents that bind tightly to factor B, a central enzyme in the complement system. Crystal structures of each SOMAmer reagent bound to factor B show how they block binding to the protein C3b, which prevents complement activation. The potent inhibition displayed by SOMAmer reagents along with their enhanced pharmacological profile and low-cost synthesis compared to antibodies suggest that they could be useful for treating complement-related diseases.

Ngo, LH *et al.* (2021) "Plasma protein expression profiles, cardiovascular disease, and religious struggles among South Asians in the MASALA study." *Sci Rep* **11**(1): 961.

https://www.ncbi.nlm.nih.gov/pubmed/33441605

Religious faith helps some people cope with stressful life events but exacerbates stress for those who struggle with feeling punished or abandoned by God. Stress is an important risk factor for cardiovascular disease (CVD), and this article describes the first study to explore whether strong religious and spiritual beliefs affect blood proteins associated with CVD risk in US South Asians, a group with disproportionately high incidence of CVD. Researchers at Massachusetts General Hospital, Beth Israel Deaconess Medical Center and the University of California, San Francisco used the SomaScan Assay

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to measure the levels of 1,305 proteins in blood collected from 100 people participating in both the Mediators of Atherosclerosis in South Asians Living in America (MASALA) Study and the Study on Stress, Spirituality and Health (SSSH). They identified three proteins that significantly associated with risk of a future CVD event, and two of the proteins were significantly modified by reported levels of religious or spiritual struggles. The results illustrated how religiosity and spirituality can affect biological processes that could reduce CVD risk. The researchers plan to follow up this pilot study with a larger validation study that includes more diverse participants from SSSH.

Sharma, R *et al.* (2021) "Circulating markers of NADH-reductive stress correlate with mitochondrial disease severity." *J Clin Invest* 131(2): e136055.

https://www.ncbi.nlm.nih.gov/pubmed/33463549

MELAS (Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes) is a rare disorder caused by mutations in the DNA of mitochondria, often called the powerhouses of cells. MELAS affects the nervous system and muscles causing headaches, vomiting, hearing loss, seizures and stroke-like episodes that typically begin in childhood and progress unpredictably. There are no proven treatments for MELAS and disease management is hampered by a lack of markers for monitoring its progression. In this article, a team led by researchers at Massachusetts General Hospital used metabolomics and SomaScan proteomic measurements to identify and validate a set of 20 metabolites and proteins that distinguish MELAS patients from controls. Many of the biomarkers correlated with disease severity could be helpful for monitoring MELAS progression and for developing new treatment strategies for mitochondrial disorders.

Sebastiani, P *et al.* (2021) "Protein signatures of centenarians and their offspring suggest centenarians age slower than other humans." *Aging Cell*: e13290.

https://www.ncbi.nlm.nih.gov/pubmed/33512769

The goal of this study by researchers at Tufts Medical Center, Boston University, Boston University School of Medicine, Novartis, the National Institute on Aging, Herbert Wertheim College of Medicine and Regeneron Pharmaceuticals was to determine whether specific changes in blood proteins are linked to longevity and healthy aging. They used the SomaScan Assay to measure the levels of 4116 unique proteins in serum samples collected from 77 centenarians, 82 centenarians' offspring and 65 unrelated controls who were age-matched to the offspring but did not have a family history of longevity. They found 1312 proteins that differed significantly in the centenarians and found two different protein signatures that predict longer survival in centenarians and in younger people. By comparing the centenarian signature with two independent proteomic studies of aging, they identified two serum protein signatures of extreme old age. The data suggest that centenarians may age more slowly than other people and point to potential protein targets for treating age-related diseases.

O'Neil, LJ *et al.* (2021) "Association of a Serum Protein Signature with Rheumatoid Arthritis Development." *Arthritis Rheumatol* **73**(1): 78-88.

https://www.doi.org/10.1002/art.41483

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This article describes a protein signature that can accurately identify individuals at highest risk of developing rheumatoid arthritis (RA) years before disease onset. In RA, the body's immune system attacks healthy tissue causing pain and disability. Antibodies that target a person's own proteins have been detected in blood before clinical symptoms manifest, but the presence of self-antibodies does not guarantee that an individual will develop RA. In this study, researchers at the University of Manitoba and Health Sciences Centre and the University of Pennsylvania Perelman School of Medicine used the SomaScan Assay to measure the levels of 1,307 proteins in serum samples from a group of native North Americans at risk of RA (some with self-antibodies and some without), including 17 individuals who eventually progressed to RA. For the 17 progressors, they were able to analyze samples over time and monitor serum protein changes before and after the appearance of clinical symptoms. Comparing the preclinical serum proteome of progressors to those of non-progressors, they defined a protein signature that could distinguish those who developed RA, regardless of whether their blood contained self-antibodies. They also identified proteins that could be involved in development of RA well in advance of diagnosis and that might serve as targets for early therapeutic intervention.

Fong, TG *et al.* (2021) "Identification of plasma proteome signatures associated with surgery using SOMAscan." *Ann Surg* **273**(4): 732-742.

https://www.ncbi.nlm.nih.gov/pubmed/30946084

The goal of this study was to determine if changes in circulating proteins could predict poor outcomes after surgery. Harvard Medical School researchers used the SomaScan Assay to measure the levels of 1,305 proteins in plasma collected from 36 patients who were over 70 years old and undergoing major, noncardiac surgery. They found 110 proteins whose levels were significantly different before and after surgery. Three of these proteins, chitinase-3-like protein 1 (CHI3L1), C-reactive protein (CRP), and interleukin-6 (IL-6), increased post-surgery and correlated with a greater likelihood of the patient being discharged to a rehabilitation center rather than to their home. Elevated levels of CHI3L1 and IL-6 also associated with more postoperative complications and longer hospital stays. IL-6 and CRP promote inflammation and had been detected previously in a study of post-surgery delirium. However CHI3L1, which is produced in neurodegenerative diseases such as Alzheimer's and is associated with neuroinflammation, was only found by the SomaScan Assay. The group speculated that this was because the levels of CHI3L1 were too low to be detected by other proteomic methods. Further study of the other proteins identified by the SomaScan analysis could advance understanding of how the body responds to surgical stress, improve risk prediction of surgical procedures and speed patient recovery.

Suhre, K *et al.* (2021) "Genetics meets proteomics: perspectives for large population-based studies." *Nat Rev Genet* **22**(1): 19-37. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/32860016

This review focuses on technologies, including the SomaScan Platform, that can profile circulating blood proteins at scale. The authors discuss how applying large-scale proteomic data to genome-wide association studies can improve understanding of the disease pathology and help identify new biomarkers and drug targets.

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Richardson, TG *et al.* (2021) "Evaluating the effects of cardiometabolic exposures on circulating proteins which may contribute to severe SARS-CoV-2." *EBioMedicine* **64**: 103228.

https://www.ncbi.nlm.nih.gov/pubmed/33548839

It is unclear why some individuals with COVID-19 develop severe symptoms, while others have mild symptoms or are asymptomatic. In this study, researchers at University of Bristol and University of Oxford in the United Kingdom used genetic variation to estimate the effects of 10 cardiometabolic risk factors (e.g. cholesterol, body mass, smoking and blood pressure) on the levels of 97 circulating proteins that may influence COVID-19 severity. The 97 proteins were identified in a previous study using the SomaScan Assay (see Pietzner, M *et al.* (2020) *Nat Commun* 11(1): 6397; https://www.ncbi.nlm.nih.gov/pubmed/33328453). The new findings highlight several proteins and biological processes that are altered by modifiable lifestyle factors that affect disease risk.

Emilsson, V *et al.* (2021) "Serum levels of ACE2 are higher in patients with obesity and diabetes." *Obes Sci Pract* **7**(2): 239-243.

https://www.doi.org/10.1002/osp4.472

In this study, researchers from the Icelandic Heart Association, the National Institute on Aging and the Novartis Institutes for Biomedical Research analyzed SomaScan data from the Age, Gene/Environment Susceptibility Reykjavik Study and found that serum levels of the SARS-CoV-2 receptor ACE2 were significantly elevated in people with conditions associated with poor COVID-19 outcomes—smoking, high blood pressure, Type 2 diabetes, obesity, coronary heart disease, kidney disease or chronic obstructive pulmonary disease (COPD). These results suggest that measuring blood levels ACE2 could help predict COVID-19 severity.

Morani, F *et al.* (2020) "Functional Network Profiles in ARSACS Disclosed by Aptamer-Based Proteomic Technology." *Front Neurol* **11**: 603774.

https://www.doi.org/10.3389/fneur.2020.603774

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a rare neurodegenerative condition caused by mutations in the SACS gene that encodes the protein sacsin. In this study, a team led by researchers at the IRCCS Stella Maris Foundation in Italy used the SomaScan Assay to compare the levels of 1,300 proteins in cell lysates from three ARSACS patients vs. three healthy controls and wild-type vs. SACS knockout neuroblastoma cells. They found significant differences in proteins involved in neuroinflammation, synaptogenesis, and engulfment of cells. They also identified several proteins encoded by genes already known to be mutated in other forms of neurodegeneration. Understanding the underlying biological processes in ARSACS could offer new diagnostic markers and as well as new therapeutic targets.

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Aid, M *et al.* (2020) "Vascular Disease and Thrombosis in SARS-CoV-2-Infected Rhesus Macaques." *Cell* **183**(5): 1354-1366.e13.

https://www.ncbi.nlm.nih.gov/pubmed/33065030

In this study, a team led by researchers at Beth Israel Deaconess Medical Center found that SARS-CoV-2 infection causes lung disease in rhesus macaques that is similar to COVID-19 in humans. They monitored differences in infected macaques compared to controls, conducting RNA profiling on bronchoalveolar lavage fluid and peripheral blood samples, as well as SomaScan proteomic profiling on serum samples collected over time. Their analysis suggests that SARS-CoV-2 infection activates proteins involved in inflammation and immune defense, which cause massive influxes of white blood cells that trigger blood clot formation and damage to the inner lining of blood vessels. These results improve our understanding of SARS-CoV-2 pathogenesis and suggest protein targets for treating COVID-19 in humans.

Adamo, L *et al.* (2020) "Proteomic Signatures of Heart Failure in Relation to Left Ventricular Ejection Fraction." *J Am Coll Cardiol* **76**(17): 1982-1994.

https://www.ncbi.nlm.nih.gov/pubmed/33092734

Left ventricular ejection fraction (LVEF) is a method for assessing how well the heart pumps out blood. Although LVEF is currently the most accurate clinical measure for diagnosing, treating and monitoring heart failure (HF), there is growing evidence of its limitations. In this article, researchers at Washington University School of Medicine explored whether measuring blood proteins could more accurately characterize disease in HF patients. They used the SomaScan Assay to measure the levels of proteins in blood from 172 patients within three LVEF categories: HFrEF (LVEF<40%), HFmrEF (LVEF 40-50%), and HFpEF (LVEF >50%). They found that they were able to distinguish patients within the three groups as well as patients whose heart problems were caused by narrowed coronary arteries. These finding suggest that using protein profiling combined with conventional LVEF measurement may provide a better way of stratifying and providing personalized care for HF patients.

Pietzner, M *et al.* (2020) "Genetic architecture of host proteins involved in SARS-CoV-2 infection." *Nat Commun* 11(1): 6397.

https://www.ncbi.nlm.nih.gov/pubmed/33328453

In this article, an international consortium led by researchers at the Medical Research Council in the UK working with SomaLogic describe the largest and most systematic genetic investigation of host proteins involved with SARS-CoV-2 infection or COVID-19 severity or mortality. They integrated large-scale genomic data with plasma proteomic data from more than 10,000 individuals and identified 220 DNA variants that influence the levels of 97 out of 179 investigated host proteins. These 179 proteins were identified with the aid of the SomaScan Assay. Among the 97 proteins, 38 are targets of existing drugs that could potentially be used to treat the virus. The researchers also established for the first time, a link between proteins related to excessive blood clotting and genetic risk of COVID-19 respiratory failure that is related to specific blood types. Anticoagulation treatment has already been shown to improve prognosis of patients with severe COVID-19.

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The study results are being shared through an open-access platform to accelerate drug discovery and repurposing efforts to prevent, treat or reduce severe COVID-19 outcomes. In addition to helping prioritize drug targets and gaining deeper insights into the pathophysiology of COVID-19, the results may help medical researchers identify patients at risk of developing severe disease, so they can get the help they need earlier. The data will allow other groups to stratify populations, by blood type for example, to more quickly identify effective interventions.

Govaere, O *et al.* (2020) "Transcriptomic profiling across the nonalcoholic fatty liver disease spectrum reveals gene signatures for steatohepatitis and fibrosis." *Sci Transl Med* **12**(572):eaba4448.

https://www.ncbi.nlm.nih.gov/pubmed/33268509

Nonalcoholic fatty liver disease (NAFLD) is a condition in which fat builds up in the liver and can cause inflammation, scarring and fibrosis. NAFLD affects approximately 25% of adults worldwide and is becoming more prevalent with the continued rise in global obesity. In this article, a team led by researchers at Newcastle University report a comprehensive RNA analysis of a large cohort of European patients with varying degrees of NAFLD severity. They found gene expression signatures that associated with early stages of disease and its progression to cirrhosis. They used the SomaScan Assay on more than 300 NAFLD serum samples to confirm that circulating concentrations of the proteins AKR1B10 and GDF15 were strongly associated with disease activity and extent of fibrosis. The results provide insights into potential biological drivers of NAFLD. This information could also be used to help diagnose and stratify patients for treatment or enrollment in clinical trials without the need for an invasive liver biopsy.

Sathyan, S *et al.* (2020) "Plasma proteomic profile of age, health span, and all-cause mortality in older adults." *Aging Cell*: e13250.

https://www.ncbi.nlm.nih.gov/pubmed/33089916

Chronological age refers to the number of years a person has lived, whereas biological age refers to how well a person’s mind and body function. Biological age is a better way to assess health but is difficult to measure accurately since it’s influenced by a variety of factors such as diet, exercise, stress and chronic conditions. In this article, researchers at the Albert Einstein College of Medicine in New York used the SomaScan Platform to characterize the proteomic signature of aging. They measured the levels of over 4200 plasma proteins in 1025 older Ashkenazi Jewish adults and identified 754 proteins that associated with chronological age. Interestingly, many of these proteins have also been linked to age-related conditions such as diabetes, heart attack, stroke, hypertension, cognition and frailty. The researchers constructed a protein-based age model that was better at predicting death than either chronological age or frailty. Approximately half of the people in the study had at least one parent who lived to age 95 or older and their protein profiles reflected younger biological age than individuals with no family history of longevity. These results suggest plasma proteins that could be targeted to delay the onset of age-related diseases and maximize healthy lifespan.

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Jankowski, W *et al.* (2020) "Modified aptamers as reagents to characterize recombinant human erythropoietin products." *Sci Rep* **10**(1): 18593.

https://www.ncbi.nlm.nih.gov/pubmed/33122796

To gain approval from the US Food and Drug Administration (FDA), protein-based biosimilar candidates must demonstrate that they are similar to an approved reference product in structure, function, safety and efficacy. Distinguishing subtle differences between two nearly identical proteins is extremely difficult and better analytical methods are needed to improve both the efficiency of biosimilar development and detection of unlicensed products. In this study, researchers at the FDA Center for Biologic Evaluation and Research and SomaLogic tested whether SOMAmer reagents could identify structural differences in recombinant human erythropoietin (rHuEPO), a protein used illicitly as a performance enhancing drug. The researchers generated four SOMAmer reagents that bound to different places on the surface of rHuEPO. They then compared binding of the SOMAmers to an FDA-licensed rHuEPO reference product, three US-licensed rHuEPO biosimilars and eight rHuEPO products that are not approved in the US or European Union. They were able to detect significant differences between the approved biosimilars and the non-licensed rHuEPO products, which suggests that SOMAmers could be used to screen for substandard or counterfeit drug products.

Schaffer, M *et al.* (2020) "Activity of ibrutinib plus R-CHOP in diffuse large B-cell lymphoma: Response, pharmacodynamic, and biomarker analyses of a phase 1b study." *Cancer Treat Res Commun* **25**: 100235.

https://www.ncbi.nlm.nih.gov/pubmed/33188997

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. DLBCL is an aggressive cancer, and although many patients initially respond well to standard chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), approximately 40% of patients relapse or develop refractory disease. There is some evidence that adding the drug ibrutinib to R-CHOP treatment may benefit younger patients with certain subtypes of DLBCL. In this article, researchers from Janssen R&D, Novartis Pharmaceuticals, Genmab US, Jazz Pharmaceuticals and Memorial Sloan Kettering Cancer Center describe a post-hoc analysis of data from a phase 1b clinical trial of ibrutinib combined with R-CHOP treatment in DLBCL subtypes. They used the SomaScan Assay to measure the levels of 1124 blood proteins and found distinct differences in the protein profiles of 16 patients who achieved complete remission compared to 3 patients who did not. The proteins identified may be indicators of more aggressive disease and poorer response to ibrutinib plus R-CHOP therapy.

Narasimhan, A *et al.* (2020) "Identification of Potential Serum Protein Biomarkers and Pathways for Pancreatic Cancer Cachexia Using an Aptamer-Based Discovery Platform." *Cancers (Basel)* **12**(12): 3787.

https://www.ncbi.nlm.nih.gov/pubmed/33334063

Close to one third of people with pancreatic cancer die from cachexia, a metabolic disorder that causes extreme weight loss and muscle wasting. Currently, there are no easy ways of detecting cachexia or monitoring its progression. Researchers at Indiana University School of Medicine used the SomaScan Assay to measure the levels of 1,310 plasma proteins in 30

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patients with pancreatic cancer compared to 11 controls. They identified both well-known and novel proteins that associated with cancer, cancer stage and cachexia. This study provides new insights into the biological underpinnings of pancreatic cancer and cachexia and shows that “liquid biopsies” could be a powerful method for monitoring cachexia and the effectiveness of interventions.

Ganz, P *et al.* (2020) "Proteomics for personalized cardiovascular risk assessment: in pursuit of the Holy Grail." *Eur Heart J* **41**(41): 4008-4010.

https://www.doi.org/10.1093/eurheartj/ehaa661

In this commentary, Ganz et al. describe progress in using proteomic technologies to assess cardiovascular risk.

Idemoto, K *et al.* (2020) "Platelet-derived growth factor BB: A potential diagnostic blood biomarker for differentiating bipolar disorder from major depressive disorder." *J Psychiatr Res* **134**: 48-56. **(Subscription required)**

https://doi.org/10.1016/j.jpsychires.2020.12.051

Bipolar disorder (BD) is frequently misdiagnosed as major depressive disorder (MDD) since they share similar symptoms. A previous SomaScan analysis of serum samples from patients with BD and MDD and healthy controls (HCs) suggested that the protein platelet-derived growth factor BB (PDGF-BB) could distinguish BD and MDD. In this article, investigators in Japan describe a multicenter study with a total of 549 participants (157 with BD, 144 with MDD, and 248 HCs) that used an immunoassay to measure serum PDGF-BB levels. The researchers found that PDGF-BB levels were significantly lower in those with MDD compared to those with BD, regardless of mood state, with no significant difference between the BD and HC groups. PDGBF-BB levels were also lower in BD patients treated with sodium valproate, a mood stabilizer medication. These findings suggest that serum PDGF-BB could be a protein biomarker for differentiating between BD and MDD.

Zampino, M *et al.* (2020) "A Plasma Proteomic Signature of Skeletal Muscle Mitochondrial Function." *Int J Mol Sci* **21**(24): 9540.

https://www.ncbi.nlm.nih.gov/pubmed/33333910

Mitochondria are the “powerhouses” within cells that convert oxygen and nutrients into energy. Mitochondrial dysfunction has been implicated in aging, muscle loss, weakness and several age-related diseases. In this study, researchers at the National Institute of Aging, the National Cancer Institute and Johns Hopkins University School of Medicine used the SomaScan Assay to measure the levels of approximately 1,300 proteins in blood collected from 165 adults. They identified 87 proteins that significantly associated with muscular mitochondrial oxidative capacity. These results could be used to develop a blood test to assess mitochondrial function.

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Corlin, L *et al.* (2020) "Proteomic Signatures of Lifestyle Risk Factors for Cardiovascular Disease: A Cross-Sectional Analysis of the Plasma Proteome in the Framingham Heart Study." *J Am Heart Assoc* **10**(1): e018020.

https://www.ncbi.nlm.nih.gov/pubmed/33372532

Lifestyle choices, such as smoking, drinking and lack of exercise, can increase a person's risk of a heart attack, although it's unclear why. In this study, researchers at Boston University, Beth Israel Deaconess Medical Center and the National Institutes of Health found that certain modifiable risk factors for cardiovascular disease have distinct effects on proteins circulating in the body. They used the SomaScan Assay to measure the levels of 1,305 proteins in plasma samples from 897 Framingham Heart Study participants and found specific sets of proteins that correlated with three different lifestyle behaviors—smoking, alcohol consumption and physical activity. These protein signatures point to possible biological processes through which lifestyle factors might affect the risk of chronic disease.

Oyama, Y *et al.* (2020) "Intense light as anticoagulant therapy in humans." *PLoS One* **15**(12): e0244792.

https://www.ncbi.nlm.nih.gov/pubmed/33382840

Studies in mice have shown that the light-regulated circadian rhythm protein PER2 reduces blood clots and is cardioprotective. In this study, researchers at the University of Colorado Anschutz Medical Campus found that deleting PER2 in specific bone marrow cells in mice caused their platelets to clot more and increased the amount of tissue damage after a heart attack. To study the effects of PER2 in humans, they collected blood samples before and after exposing 6 healthy volunteers to 30 minutes of intense light for 5 consecutive days. Five days of intense light therapy reduced the rate of blood clotting, and SomaScan analysis of over 1200 plasma proteins revealed that many proteins involved in coagulation processes were repressed. These results suggest that intense light could be used as a novel therapy to prevent or treat blood clotting.

Wang, TJ (2020) "The Evolution of the Cardiovascular Biomarker Study." *Circulation* **142**(15): 1422-1424.

https://www.ncbi.nlm.nih.gov/pubmed/33044857

—and—

Chan, MY *et al.* (2020) "Prioritizing Candidates of Post-Myocardial Infarction Heart Failure Using Plasma Proteomics and Single-Cell Transcriptomics." *Circulation* **142**(15): 1408-1421.

https://www.ncbi.nlm.nih.gov/pubmed/32885678

Heart attacks (a.k.a. myocardial infarctions, or MI) can affect the heart's ability to effectively pump blood, and often lead to heart failure. Unbiased screening tools have identified hundreds of proteins associated with heart failure following a heart attack, but since it's impossible to pursue experimental or clinical studies of each hit, very few have translated into

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biomarkers that are used in the clinic. In this article, researchers from Singapore, New Zealand and Malaysia described an approach for winnowing a large number of potential biomarkers down to a more manageable set for further study. The researchers used the SomaScan Assay to measure the levels of 1,305 proteins in plasma samples collected one month after an MI and identified circulating proteins associated with developing heart failure in two different patient cohorts. In parallel, they cross-referenced four human and mouse single-cell transcriptomic (RNA) data sets and identified genes that were differentially expressed in response to cardiac stress or injury. Combining methods narrowed the initial discovery list to 83 proteins (6 top candidates, 19 intermediate priority, and 58 lower priority). Two of the top six proteins, NT-proB natriuretic peptide and cardiac troponin are well-established biomarkers of post-MI heart failure and the other four are newly emerging biomarker candidates. Future studies should establish whether the identified proteins are potential drug targets or can help diagnose, prognose, or manage heart failure in patients post-MI. In an accompanying editorial, Dr. Thomas Wang from the University of Texas Southwestern Medical Center states that, “Although further work is clearly required, the present study shows how far the cardiovascular biomarker study has come.”

Lee, SJ *et al.* (2020) "Targeting myostatin/activin A protects against skeletal muscle and bone loss during spaceflight." *Proc Natl Acad Sci U S A* **117**(38): 23942-23951.

https://www.ncbi.nlm.nih.gov/pubmed/32900939

Loss of bone and muscle mass are major health challenges for astronauts during long missions in space. In this article, scientists from the Jackson Laboratory for Genomic Medicine, the University of Connecticut School of Medicine, the National Aeronautics and Space Administration, the Center for the Advancement of Science in Space, the Connecticut Children’s Center for Rare Bone Disorders and SomaLogic report that treatment with an inhibitor of myostatin/activin A (called ACVR2B/Fc) protected from muscle and bone loss in mice sent to the International Space Station. Myostatin and activin A are proteins that are important for regulating muscle and bone growth, respectively. Both Earth-bound and microgravity-exposed mice that were injected with ACVR2B/Fc showed dramatic increases in both muscle mass and bone density compared to untreated mice. The researchers used the SomaScan Assay to measure proteomic changes in the mice after their spaceflight and/or treatment with ACVR2B/Fc to identify biological pathways that influence muscle and bone mass and the overall effects of blocking those pathways. The findings have implications not only for astronauts in space, but potentially for earth-bound people who suffer from muscle atrophy and bone degeneration conditions.

Chirinos, JA *et al.* (2020) "Clinical and Proteomic Correlates of Plasma ACE2 (Angiotensin-Converting Enzyme 2) in Human Heart Failure." *Hypertension* **76**(5): 1526-1536.

https://www.ncbi.nlm.nih.gov/pubmed/32981365

Angiotensin-converting enzyme 2 (ACE2) is a protein that plays a critical role in heart failure, hypertension, and various other cardiovascular conditions. ACE2 is also an entry point for SARS-CoV-2, the coronavirus that causes COVID

-19 disease, to infect cells. In this study, researchers at the Hospital of the University of Pennsylvania, the University of Pennsylvania Perelman School of Medicine, the University of Arizona, Tucson, the University of Utah, Salt Lake City, the University of Ottawa, Canada and SomaLogic used the SomaScan Assay to identify associations between ACE2 and other circulating proteins as well as clinical factors in human heart failure. They measured the levels of over 4700 proteins in samples collected from 2200 patients with chronic heart failure and found that plasma ACE2 was not correlated with use of ACE inhibitors or angiotensin II receptor blockers, medications often prescribed for heart failure. Significant associations were found between ACE2 and over a thousand plasma proteins, including proteins that help cells absorb metabolites, hormones and viruses. Lower ACE2 levels correlated with clinical factors linked to severe COVID-19 disease, such as older age, male sex, and diabetes mellitus. Future studies will assess whether the proteins and biological processes identified are important targets for management of cardiovascular disease or SARS-CoV2 infection.

Moin, ASM *et al.* (2020) "Renin-Angiotensin System Overactivation in Polycystic Ovary Syndrome, a Risk for SARS-CoV-2 Infection?" *Metabol Open* **7**: 100052.

https://www.ncbi.nlm.nih.gov/pubmed/32838280

The renin–angiotensin system (RAS) plays a central role in regulating blood pressure and maintaining fluid and electrolyte balance. RAS overactivation is associated with obesity, type 2 diabetes and metabolic syndrome, conditions that are also characteristic of Polycystic Ovary Syndrome (PCOS), a common hormonal disorder that causes ovarian dysfunction. In this study, researchers at Hamad Bin Khalifa University, Qatar, Hull York Medical School, UK, and Royal College of Surgeons in Ireland, Bahrain examined whether RAS overactivity is also present in PCOS. They used the SomaScan Assay to determine the levels of the RAS-related proteins angiotensin-converting enzyme 2 (ACE2), renin, and angiotensinogen (AGT) in plasma collected from 146 women with PCOS and 97 age-matched controls. Compared to controls, renin levels were elevated and ACE2 and AGT levels were suppressed in the PCOS cohort, indicative of RAS overactivation. ACE2 provides an entry point for the SARS-CoV-2 coronavirus to infect cells and reduced ACE2 levels are associated with greater disease severity. These results suggest that women with PCOS may be at higher risk of severe outcomes for COVID-19.

Shi, L *et al.* (2020) "Dickkopf-1 Overexpression in vitro Nominates Candidate Blood Biomarkers Relating to Alzheimer's Disease Pathology." *J Alzheimers Dis* **77**(3): 1353-1368.

https://www.ncbi.nlm.nih.gov/pubmed/32831200

In 2018, the National Institute on Aging-Alzheimer's Association introduced a classification system for Alzheimer's disease (AD), called the "ATN framework," which is based on the presence or absence of three AD markers: amyloid, tau, and neurodegeneration. There is growing evidence that amyloid, tau, and neurodegeneration may be linked by Wnt signaling and that inhibition of Wnt signaling may trigger development of AD. The protein DKK1 is an inhibitor of Wnt signaling and elevated levels of DKK1 have been observed in the AD brain, suggesting that it could be driving AD. In this study, an international team led by researchers at the University of Oxford, UK used the SomaScan Assay to identify a 100-protein signature induced by DKK1 in human cells. They then conducted SomaScan analysis of plasma from two large independent cohorts containing people with AD, with mild cognitive impairment, and healthy controls and found that the derived protein signature associated with the ATN framework and AD clinical outcomes. The results of this study support a role for DKK1 in disease pathogenesis and demonstrate how a proteomic-based approach can identify biomarkers to help inform selection of participants for AD clinical trials and monitor trial outcomes.

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Soliman, GA *et al.* (2020) "Causal association between mTOR-dependent EIF-4E and EIF-4A circulating protein levels and type 2 diabetes: a Mendelian randomization study." *Sci Rep* **10**(1): 15737.

https://www.ncbi.nlm.nih.gov/pubmed/32978410

The protein complex called “mammalian target of rapamycin complex 1” (mTORC1) plays a key role in metabolism and has been linked to type 2 diabetes (T2D). To investigate whether mTORC1 plays a causal role in T2D, scientists at the City University of New York Graduate School of Public Health and Health Policy and the University of Hong Kong School of Public Health used an analytical method called Mendelian randomization to assess whether the risk of T2D varied with genetically predicted plasma levels of five proteins regulated by mTORC1 (EIF4EBP2, EIF-4E, EIF-4G, EIF-4A and RP-S6K). The study leveraged data taken from two previous genome wide association studies: one that linked genetic variants to diabetes and another that identified genetic variants strongly predictive of protein plasma levels measured using the SomaScan Assay. The results of this secondary analysis of publicly available data identified causal protective association of circulating levels EIF-4E and EIF-4A with T2D, which suggest that repurposing existing therapeutics that target EIF-4E and EIF-4A could help reduce T2D risk.

Lynch, AM *et al.* (2020) "Plasma Biomarkers of Reticular Pseudodrusen and the Risk of Progression to Advanced Age-Related Macular Degeneration." *Transl Vis Sci Technol* **9**(10): 12.

https://www.ncbi.nlm.nih.gov/pubmed/32974084

Age-related macular degeneration (AMD) is a progressive eye disease and one of the leading causes of blindness in people over 50 years old. Yellowish subretinal deposits called reticular pseudodrusen (RPD) are associated with increased risk of progression to advanced AMD. In this article, researchers at the University of Colorado School of Medicine, the University of Colorado School of Public Health and SomaLogic describe the first large-scale biomarker discovery study of intermediate-stage AMD using the SomaScan Assay. They used the SomaScan Assay to measure the levels of approximately 5000 proteins in plasma collected from 109 patients with intermediate AMD. They found only two proteins that differed in patients with and without RPD, but higher levels of several proteins were seen in those who converted from intermediate to advanced AMD. These results suggest that there are systemic factors that may impact AMD progression and that could represent possible novel protein targets for therapeutic intervention.

Tawalbeh, SM *et al.* (2020) "Serum protein biomarkers for juvenile dermatomyositis: a pilot study." *BMC Rheumatol* **4**: 52.

https://www.ncbi.nlm.nih.gov/pubmed/33015544

Juvenile Dermatomyositis (JDM) is a rare autoimmune disease that causes inflammation of muscle, skin and small blood vessels in children. Symptoms can range from mild rashes and muscle weakness to severe skin ulcers and difficulty swallowing. Early treatment can help prevent permanent disability, but effective methods for assessing JDM disease activity and response to therapies are needed. In this pilot study, researchers at the State University of New York at Binghamton and Northwestern’s Feinberg School of Medicine used the SomaScan Assay to identify blood-based protein markers of JDM disease. They measured the levels of 1,305 proteins in serum samples collected from eight JDM patients before start of

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treatment, while on therapy, and after tapering off therapy. Comparing JDM patients to age-matched healthy controls revealed 251 proteins that were significantly different, including some previously identified as JDM biomarkers, but many that were entirely new. Administering treatment caused changes in the levels of 82 of the JDM-associated proteins and of these, 12 returned to their original levels after treatment ended. These results identified a group of candidate protein biomarkers for determining JPM severity, prognosis and response to treatments.

Tawalbeh, S *et al.* (2020) "Comparison of Serum Pharmacodynamic Biomarkers in Prednisone-Versus Deflazacort-Treated Duchenne Muscular Dystrophy Boys." *J Pers Med* **10**(4): 164.

https://www.ncbi.nlm.nih.gov/pubmed/33053810

Duchenne muscular dystrophy (DMD) is a genetic disorder that causes progressive muscle weakness and wasting, primarily in young boys. While there is no cure, the glucocorticoids prednisone (Pred) and deflazacort (Dfz) can slow loss of motor function, but long-term steroid use can lead to other problems such as weight gain, growth stunting, osteoporosis and diabetes. This article from researchers at Binghamton University and Children’s National Hospital describes the first study to compare serum proteins in blood collected from DMD patients treated with either Pred or DFz. In a previous study, the researchers used the SomaScan Assay to identify 107 proteins that responded to glucocorticoid treatment in DMD (Hathout, Y *et al.* (2019) *Sci Rep* **9**(1): 12167. https://www.ncbi.nlm.nih.gov/pubmed/31434957). In this study, they conducted SomaScan analysis of 35 blood samples collected over 4-10 years from 8 Pred-treated and 7 Dfz-treated boys. Out of the 107 pharmacodynamic protein markers identified previously, 17 were differentially altered between the 2 drugs, including proteins associated with bone mineralization, growth stunting, and development of type 2 diabetes. Future studies in larger patient groups are needed to validate and test these proteins for use in clinical decision making and drug development

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Yang, J *et al.* (2020) "Impact of kidney function on the blood proteome and on protein cardiovascular risk biomarkers in patients with stable coronary heart disease." *J Am Heart Assoc* **9**(15): e016463.

https://www.ncbi.nlm.nih.gov/pubmed/32696702

People with chronic kidney disease (CKD) are often underdiagnosed and undertreated for cardiovascular disease despite being at significantly higher risk. To identify biomarkers that can more effectively predict cardiovascular risk in those with CKD, investigators at University of California, San Francisco, San Francisco Veterans Affairs Health Care System, SomaLogic, Hospital of the University of Pennsylvania and Zuckerberg San Francisco General Hospital assessed the effects of kidney function on circulating proteins in patients with stable coronary heart disease. Previously, they used the SomaScan Assay to measure the levels of 1054 plasma proteins in 938 participants of the Heart and Soul observational study and identified 196 proteins prognostic of secondary cardiovascular risk (see Ganz, P *et al.* (2016) *JAMA* 315(23): 2532-2541; https://doi.org/10.1001/jama.2016.5951). In this new study, they determined that only 87 of the 196 proteins were independent of kidney function. To discover new protein markers of cardiovascular risk in patients with CKD compared to those with normal kidney function, they divided the Heart and Soul participants according to estimated glomerular filtration rate into non-CKD and CKD groups. Of the 1054 proteins measured by SomaScan, 84 were prognostic of cardiovascular risk in non-CKD patients and 21 were prognostic of cardiovascular risk in CKD patients, including 8 that were unique to patients

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with impaired kidney function. Future studies will investigate whether these eight proteins are causal and might represent new therapeutic targets for reducing cardiovascular disease risk in those with CKD. This study illustrates how SomaScan data sets can be mined repeatedly to discover new protein patterns associated with different clinical indications.

Gudmundsdottir, V *et al.* (2020) "Circulating protein signatures and causal candidates for type 2 diabetes." *Diabetes* **69**(8): 1843-1853.

https://www.ncbi.nlm.nih.gov/pubmed/32385057

In this study, a team led by researchers at the University of Iceland and the Icelandic Heart Association used the SomaScan Assay to identify a set of blood proteins that may cause type 2 diabetes (T2D). Using a custom version of the SomaScan Assay, they measured the levels of 4,137 proteins in blood samples from 5,438 elderly Icelanders, including some with T2D (prevalent disease) and some who later developed T2D (incident disease). They identified 536 proteins associated with either prevalent or 5-year incident T2D and validated 33 proteins in a smaller independent study of T2D in people of Arab and Asian ethnicities. Applying a statistical method that uses genetic variants to assess causality revealed 15 proteins that may cause T2D. These results may provide insight into the biological processes that contribute to T2D development and help identify new therapeutic targets for treatment or prevention.

Guseh, JS *et al.* (2020) "An expanded repertoire of intensity-dependent exercise-responsive plasma proteins tied to loci of human disease risk." *Sci Rep* **10**(1): 10831.

https://www.ncbi.nlm.nih.gov/pubmed/32616758

In this article, scientists at Massachusetts General Hospital, Harvard Medical School and Harvard University describe the first comprehensive characterization of how proteins in the blood respond to exercise. They used the SomaScan Assay to measure the levels of 1,305 plasma proteins in 12 participants before and immediately after running five miles on a treadmill at moderate intensity (6 mph) and high intensity (maximal effort). Almost half of the proteins measured (623 in total) were affected: 159 by both types of exercise in an intensity-dependent manner, and 25 or 439 proteins uniquely by moderate or high intensity exercise, respectively. Moderate intensity exercise primarily affected proteins involved in bone growth and lipid metabolism, consistent with clinical observations that exercise can prevent osteoporosis and improve lipid profiles. Unexpectedly, high intensity exercise showed the largest effects on nervous system proteins. Relative to moderate intensity, high intensity exercise produced a 30% increase in the levels of brain-derived neurotrophic factor, a protein linked to improved mood and cognitive function. High intensity exercise also induced protein changes associated with increased risk of coronary artery disease, which could explain the connection between vigorous exercise and sudden cardiac death. The results of this study illustrate how blood proteins dynamically change in response to even short bouts of exercise and how monitoring an individual's proteins could be used to design workout regimens to optimize health benefits.

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Dong, L *et al.* (2020) "Aptamer based proteomic pilot study reveals a urine signature indicative of pediatric urinary tract infections." *PLoS One* **15**(7): e0235328.

https://www.ncbi.nlm.nih.gov/pubmed/32628701

A bacterial urine culture is the gold standard for diagnosing urinary tract infection (UTI) but is time consuming and expensive, so urine dipsticks are typically used for routine screening. Although quick and easy, dipsticks are not very accurate since they detect either nitrate (produced by bacteria) or leukocyte esterase (LE, produced by white blood cells), neither of which are specific to UTIs. In this pilot study, a group led by researchers at Indiana University used the SomaScan Assay to analyze urine samples from 32 children: 16 UTI culture/LE dipstick positive, 8 culture negative/dipstick positive, and 8 culture/dipstick negative. They identified eight proteins that were significantly increased in the confirmed UTI samples and that represent excellent biomarker candidates. Future studies will focus on developing a protein panel that can help clinicians identify true UTI positive patients at point of care.

Kemp, PR *et al.* (2020) "Metabolic profiling shows pre-existing mitochondrial dysfunction contributes to muscle loss in a model of ICU-acquired weakness." *J Cachexia Sarcopenia Muscle* **11**(5): 1321-1335.

https://www.ncbi.nlm.nih.gov/pubmed/32677363

Some patients lose significant amounts of muscle after surgery, which can slow recovery and lengthen hospital stays. To determine whether there are biological factors that can predict significant muscle wasting, researchers at Imperial College London, Guy's and St. Thomas' NHS Foundation Trust, GlaxoSmithKline and Edgewise Therapeutics looked at circulating metabolites and proteins in relation to muscle loss in 20 older men undergoing elective aortic surgery. The scientists identified 104 blood metabolites that differed between wasting and non-wasting patients. Comparing the changes in metabolites with changes in inflammatory proteins measured using the SomaScan Assay suggested potential protein regulators of muscle wasting in response to surgery. These results provide insight into the variability of muscle loss seen in patients after surgery and may help identify new markers and therapeutic targets for prevention.

Dang, UJ *et al.* (2020) "Serum biomarkers associated with baseline clinical severity in young steroid-naive Duchenne muscular dystrophy boys." *Hum Mol Genet* **29**(15): 2481-2495.

https://www.ncbi.nlm.nih.gov/pubmed/32592467

Duchenne muscular dystrophy (DMD) is a rare genetic disorder caused by loss of the protein dystrophin that results in muscle weakness, deterioration and early death. DMD onset and progression varies widely, which makes it difficult to assess treatment efficacy in clinical trials. This article describes a new study that used previously collected SomaScan Assay data to identify blood serum proteins associated with DMD severity in untreated boys aged 4-6 years old. This age range is of particular interest for early therapeutic interventions. Researchers at SUNY, Binghamton, the University of Pittsburgh School of Medicine, and ReveraGen BioPharma identified two different but overlapping sets of 17 proteins that correlated with two clinical outcomes: time to stand from the floor (TTSTAND, a measure of strength) and the 6-minute walk test (6MWT, a measure of endurance). The proteins associated with TTSTAND were generally involved in cell growth and tissue repair, whereas proteins associated with 6MWT were primarily involved in muscle fibrosis. This study is the first to identify protein

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correlates of early age DMD severity in drug-naïve boys and may improve monitoring disease progression and response to experimental treatments.

Sathyan, S *et al.* (2020) "Plasma proteomic profile of frailty." *Aging Cell* **19**(9): e13193.

https://www.ncbi.nlm.nih.gov/pubmed/32762010

Frailty is associated with poorer health and loss of independence in older adults but doesn't have a standard clinical definition. This article describes the first large-scale study of proteins associated with frailty. Researchers at Albert Einstein College of Medicine used the SomaScan Assay to measure the levels of 4265 plasma proteins in 880 older adults in an Ashkenazi Jewish cohort. They identified 143 proteins that were significantly associated with an established cumulative frailty index. They identified many novel proteins and physiological processes linked to frailty that may be useful for establishing better biological markers and identifying potential drug targets to help mitigate future frailty.

Norman, KC *et al.* (2020) "Identification of a unique temporal signature in blood and BAL associated with IPF progression." *Sci Rep* **10**(1): 12049.

https://www.ncbi.nlm.nih.gov/pubmed/32694604

Idiopathic pulmonary fibrosis (IPF) is lung scarring that worsens over time, making it harder and harder to breathe. Prognosis is poor but the rate of decline varies, with some individuals losing lung function quickly and others remaining stable for several years. A protein signature that can differentiate IPF progressors from non-progressors has now been determined by researchers at University of Michigan, University of Michigan Medical School, Vanderbilt University Medical School and Weill Cornell School of Medicine. They measured 1,129 proteins in blood (using the SomaScan Assay) and 29 protein in bronchoalveolar lavage (using antibody-based assays) from a group of 59 IPF patients that included 34 classified as progressors based on their lung decline in 80 weeks of follow up. From baseline samples, they identified a signature of 51 blood and 3 lung proteins that separated progressors from non-progressors with high accuracy. Proteins that regulate the immune response were enriched in non-progressors. Analyzing SomaScan data from samples taken at baseline, week 48 and week 80 identified time-dependent protein changes in progressors that were absent in non-progressors. These results suggest potential prognostic signatures for IPF and describe a general strategy for distinguishing disease subtypes.

Glover, K *et al.* (2020) "ZIKV infection induces DNA damage response and alters the proteome of gastrointestinal cells." *Viruses* **12**(7): E771.

https://www.ncbi.nlm.nih.gov/pubmed/32708879

Zika virus infection can cause gastrointestinal symptoms such as nausea, abdominal pain, diarrhea, and vomiting. To better understand the source of these symptoms, investigators at the University of Manitoba and the Children's Hospital Research Institute of Manitoba in Canada monitored virus-induced protein changes in a colon-derived cell line. They used the SomaScan Assay to measure the levels of 1,305 human proteins at 12, 24 and 48 hours post-infection and identified 71

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proteins that changed in concentration significantly, including many already associated with various gastrointestinal diseases. Interestingly, some of the proteins they identified are known to be important for brain development, which may help explain the congenital defects seen in babies born to Zika-infected mothers. These proteins warrant further investigation as potential targets for anti-viral therapies.

Giudice, V *et al.* (2020) "Aptamers and antisense oligonucleotides for diagnosis and treatment of hematological diseases." *Int J Mol Sci* **21**(9): 3252*.*

https://www.ncbi.nlm.nih.gov/pubmed/32375354

In this review, researchers at the University of Salerno and Salerno University Hospital in Italy discuss current preclinical and clinical applications of aptamers and SOMAmers in leukemias, lymphomas, multiple myeloma, graph-versus-host disease, aplastic anemia and sickle disease.

Xing, J *et al.* (2020) "Evaluation of a novel blood microsampling device for clinical trial sample collection and protein biomarker analysis." *Bioanalysis* **12**(13): 919-935. (**Subscription required**)

https://www.ncbi.nlm.nih.gov/pubmed/32686955

Researchers at the Novartis Institutes for BioMedical Research used the SomaScan Assay to evaluate a device designed for blood sample collection at home. The Touch Activated Phlebotomy (TAP) device attaches to the upper arm and draws microsamples of peripheral blood, which is stored in the device for delivery to a lab. Peripheral blood is a combination of arterial and venous blood, so its protein composition is likely different from samples collected using standard venipuncture, which could affect test results. The researchers used the SomaScan Assay to measure the levels of 4120 plasma proteins in samples collected using phlebotomy or the TAP device from 16 healthy volunteers. Comparing venous to TAP samples, the researchers identified a subset of 1623 concordant proteins (~39%) that might feasibly be collected remotely using the TAP device and stored for up to 72 hours prior to processing.

Posavi, M *et al.* (2019) "Characterization of Parkinson's disease using blood-based biomarkers: A multicohort proteomic analysis." *PLoS Med* **16**(10): e1002931.

https://www.doi.org/10.1371/journal.pmed.1002931

Parkinson’s disease (PD) is a neurological disorder that causes loss of muscle control. There is increasing evidence that neurodegeneration begins decades before physical symptoms appear, which provides an opportunity for early diagnosis and possible therapeutic intervention. To discover new diagnostic and prognostic markers of PD, a team led by researchers at the Perelman School of Medicine at the University of Pennsylvania used the SomaScan Assay to measure the levels of more than 1,000 plasma proteins in 527 individuals with either PD, amyotrophic lateral sclerosis (ALS) or no neurological disease. They found that the levels of four proteins—bone sialoprotein, osteomodulin, aminoacylase-1, and growth hormone receptor—were consistently different in people with PD compared to people without PD. Growth hormone receptor predicted subsequent cognitive decline in those with PD. These results show how proteomic profiling of blood can provide insight into neurological disorders and possible therapeutic targets. This study also suggests that it may be possible to develop blood-based tests to help confirm PD diagnosis and predict disease progression.

Xie, Z *et al.* (2019) "Neutrophil activation in systemic capillary leak syndrome (Clarkson disease)." *J Cell Mol Med* **23**(8): 5119-5127.

https://www.doi.org/10.1111/jcmm.14381

Systemic capillary leak syndrome (SCLS, Clarkson disease) is a rare, potentially fatal disorder in which fluids suddenly leak out of capillaries into surrounding tissues. The cause of these sudden episodes is not known. In this article, a team led by researchers at the National Institutes of Health describe protein differences in plasma samples collected from nine patients in crisis and in remission. The levels of more than 600 of 1,300 proteins measured using the SomaScan were significantly increased during an SCLS episode. Many of the proteins are known to be released by neutrophils (a type of white blood cell). The researchers found that serum taken from patients during the acute phase of SCLS increased activation of neutrophils, and supernatants from activated neutrophils made blood vessels more permeable. These results suggest a potential disease mechanism of SCLS and possible protein targets for therapeutic interventions.

Begic, E *et al.* (2019) "SOMAscan-based proteomic measurements of plasma brain natriuretic peptide are decreased in mild cognitive impairment and in Alzheimer's dementia patients." *PLoS One* **14**(2): e0212261.

https://www.ncbi.nlm.nih.gov/pubmed/30763368

—and—

Begic, E *et al.* (2020) "Increased Levels of Coagulation Factor XI in Plasma Are Related to Alzheimer's Disease Diagnosis." *J Alzheimers Dis* **77**(1): 375-386. (**Subscription required**)

https://www.ncbi.nlm.nih.gov/pubmed/32804133

Two papers from the Causevic group at the Sarajevo School of Science and Technology in Bosnia used previously collected SomaScan data to identify blood proteins that may signal the development of Alzheimer's disease (AD). The datasets were obtained from the AddNeuroMed partnership for AD biomarker discovery and included over 600 patients diagnosed as either healthy, with probable AD, or with mild cognitive impairment (MCI). In the 2019 article, Begic *et al.* found that the levels of brain natriuretic peptide, a well-known indicator of heart failure, were lowest in MCI patients and highest in healthy controls. In the 2020 article, Begic *et al.* found that increased levels of coagulation factors IX and XI were significantly increased in patients with probable AD diagnosis and correlated with a decline in cognitive function. These findings warrant further investigation as they may provide new insight into the biological processes involved in dementia.

Stanley, S *et al.* (2020) "Comprehensive aptamer-based screening identifies a spectrum of urinary biomarkers of lupus nephritis across ethnicities." *Nat Commun* **11**(1): 2197.

https://pubmed.ncbi.nlm.nih.gov/32366845/

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Systemic lupus erythematosus (SLE) is a disease in which the body’s immune system attacks its own tissues and organs. Approximately 60% of people with SLE will develop inflammation of the kidneys, lupus nephritis (LN), a serious problem that can lead to kidney failure. Early detection and treatment can improve LN outcomes, but diagnosis typically requires a kidney biopsy, which is highly invasive and not easily repeated over time. To screen for urine-based biomarkers of LN, a team lead by researchers at the University of Houston used the SomaScan Assay to measure the levels of 1,129 proteins in urine samples from 23 people (7 with LN, 8 with inactive SLE and 8 healthy controls). Twelve proteins that were significantly elevated in patients with LN compared to SLE were successfully validated in an independent cohort using traditional antibody-based assays. These 12 proteins were then tested in two different cohorts containing African Americans, Caucasians and Asian patients (107 with LN, 127 with inactive SLE, 67 with active non-renal SLE and 74 healthy controls). Interestingly, the best urine protein markers for LN were different within each ethnic group. Racial differences are known to impact SLE symptoms and disease course, and these results may help explain why. A longitudinal study is needed to investigate how the proteins identified in this study affect LN progression, whether they can be used to predict renal flares, and if they can be used to develop a noninvasive method to diagnose and monitor LN (and if that method needs to be specific for different populations).

Chirinos, JA *et al.* (2020) "Reduced apolipoprotein M and adverse outcomes across the spectrum of human heart failure." *Circulation* **141**(18): 1463-1476.

https://pubmed.ncbi.nlm.nih.gov/32237898/

In this study, scientists from Washington University School of Medicine, University of Pennsylvania Perelman School of Medicine, Bristol-Myers Squibb, SomaLogic, Lund University in Sweden, Wake Forest School of Medicine, University of Arizona and Rigshospitalet in Denmark found that reduced levels of apolipoprotein M (apoM) are a risk factor for patients with heart failure. ApoM is a protein associated with high-density lipoprotein (HDL, also known as “good” cholesterol). The researchers used ELISA as well as the SomaScan Assay to measure the levels of apoM in blood samples from 2170 patients enrolled in a prospective study of heart failure. They found that patients with lower levels of apoM had worse outcomes (hospitalization, heart pump implantation, heart transplant or death) and confirmed their findings in two independent cohorts. They measured the levels of approximately 5000 proteins using the SomaScan Assay and found that lower levels of apoM associated with higher levels of proteins involved in inflammation and coagulation. Further studies are needed to understand the mechanisms by which apoM mediates cardioprotection and whether it is a target for treating heart failure.

Ferrannini, E *et al.* (2020) "Mechanisms of Sodium-Glucose Cotransporter 2 Inhibition: Insights From Large-Scale Proteomics." *Diabetes Care* **43**(9): 2183-2189.

https://www.ncbi.nlm.nih.gov/pubmed/32527800

Drugs that block the sodium-glucose cotransporter 2 (SGLT2) lower blood sugar levels by causing the kidneys to excrete glucose through the urine. Clinical trials of SGLT2 inhibitors in people with type 2 diabetes (T2D) have also shown protective effects against cardiovascular disease, although it is unclear why. In this study, researchers at the CNR Institute of Clinical Physiology in Pisa, Yonsei University College of Medicine in Seoul, University of Glasgow, University of California San Francisco and SomaLogic analyzed the effects of the SGLT2 inhibitor empagliflozin on circulating proteins. They used the

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SomaScan Assay to measure the levels of 3,713 proteins in 144 paired plasma samples taken from individuals with T2D before and after four weeks of empagliflozin treatment. Empagliflozin significantly altered the levels of 43 proteins, including those involved with heart muscle function, iron handling, and lipid and glucose metabolism. This exploratory study provides greater insight into the systemic effects of empagliflozin treatment and how SGLT2 inhibitors lower cardiovascular disease risk in people with T2D.

Ambati, A *et al.* (2020) "Proteomic biomarkers of sleep apnea." *Sleep* **43**(11).

https://pubmed.ncbi.nlm.nih.gov/32369590/

Obstructive sleep apnea (OSA) is a common sleep disorder in which the throat muscles relax, blocking the airway and repeatedly interrupting breathing. The sudden drops in oxygen cause blood pressure to rise and put greater strain on the heart, so people with OSA are not only sleep deprived but at greater risk of high blood pressure, heart disease, stroke and diabetes. The gold standard for diagnosing OSA is an overnight study done at a sleep lab, but this is costly and inconvenient for the patient. In this article, researchers at Stanford University, Weill Cornell Medicine Qatar and Washington University describe an exploratory proteomic study of OSA that used the SomaScan Assay to measure levels of 1,300 proteins in blood taken from 713 participants in the Stanford Sleep Cohort. They identified 65 serum proteins (predominately involved in immune system function and coagulation) that associated with OSA severity. A risk model trained on the protein data alone was able to predict moderate to severe apnea with similar performance to questionnaire-based methods. The researchers also examined protein profiles before and after continuous positive airway pressure (CPAP) therapy in a separate cohort of 16 people and found 3 proteins that were significantly changed by CPAP treatment. These results identified potential protein biomarkers of OSA that could aid diagnosis and provide new insights into the biological effects of sleep apnea.

Walker, ME *et al.* (2020) "Proteomic and metabolomic correlates of healthy dietary patterns: the Framingham Heart Study." *Nutrients* **12**(5): 1476.

https://pubmed.ncbi.nlm.nih.gov/32438708/

Poor diet kills more people worldwide than smoking and is a preventable risk factor for disease. To understand how diet affects body chemistry, a team led by researchers at Boston University measured 1373 proteins (using the SomaScan Assay) and 216 metabolites (using liquid chromatography/tandem mass spectrometry) in blood samples from the Framingham Offspring Study, a familial study of heart disease. They correlated proteins and metabolites with three indices of dietary quality: the Alternative Healthy Eating Index (AHEI), the Dietary Approaches to Stop Hypertension (DASH) diet; and a Mediterranean-style (MDS) diet. They found 103 proteins and 65 metabolites that associated with at least one dietary pattern and 5 proteins and 24 metabolites that associated with all three healthy dietary patterns. While both AHEI and DASH showed unique protein signatures, the protein correlations with MDS were not very strong. In general, the proteins that associated with healthy diets were involved in processes related to metabolism, cell proliferation, inflammation and the immune response. The results provide insight into how eating a healthy diet can improve metabolic health, lower the risk of chronic diseases and increase lifespan.

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Demidowich, AP *et al.* (2020) "Colchicine's effects on metabolic and inflammatory molecules in adults with obesity and metabolic syndrome: results from a pilot randomized controlled trial." *Int J Obes (Lond)* **44**(8): 1793-1799.

https://pubmed.ncbi.nlm.nih.gov/32461554/

Metabolic syndrome refers to a group of factors — including high blood pressure, high blood sugar, high triglycerides and abdominal fat — that increase risk of heart disease, diabetes and stroke. In a previous pilot study of obese adults with metabolic syndrome, researchers at the National Institutes of Health and the Johns Hopkins School of Medicine saw beneficial effects of treatment with colchicine, an anti-inflammatory medication used for gout. This article describes a secondary analysis that used the SomaScan Assay to measure the levels of 1,305 proteins in blood taken before and after three months of treatment with either colchicine or placebo. They identified 34 proteins that were significantly changed by colchicine, including many implicated in development of diabetes and cardiovascular disease. One of the proteins suppressed by colchicine was interleukin 6 (IL-6), a protein associated with severe symptoms in COVID-19. Additional studies in larger cohorts are needed to dissect the key biological processes behind colchicine's protective effects in adults with obesity and to investigate whether colchicine could be repurposed to suppress hyperactive inflammation in COVID-19 patients.

Harwardt, MIE *et al.* (2020) "Single-molecule super-resolution microscopy reveals heteromeric complexes of MET and EGFR upon ligand activation." *Int J Mol Sci* **21**(8):2803.

https://pubmed.ncbi.nlm.nih.gov/32316583/

Receptor tyrosine kinases (RTKs) are proteins that play diverse roles in cell communication, movement, growth and differentiation. RTKs are present on the surfaces of cells where they bind ligands such as growth factors, triggering interactions with adjacent receptors that lead to activation. The MET receptor and the epidermal growth factor receptor (EGFR) are two RTKs that are important drug targets in oncology. Inhibitors of the MET receptor or EGFR often shrink tumors initially, but then lose effectiveness because drug resistance develops. One theory behind drug resistance is that interactions between different kinds of RTKs activate processes that compensate for the receptor that's been blocked. In this article, researchers at Goethe University Frankfurt, Ludwig Maximilian University in Munich, Max Planck Institute of Biochemistry and SomaLogic report the first direct proof of ligand-induced cross-interactions between RTKs on living cells. They used single-molecule super-resolution microscopy (see Strauss, S *et al.* (2018) *Nat Methods* **15**(9): 685-688; https://pubmed.ncbi.nlm.nih.gov/30127504/) to visualize MET receptor and EGFR clusters at nanoscale resolution in two cancer cell lines. This method, which can be adapted to other cell lines and other receptors, could help predict whether drugs that target RTKs are likely to be successful cancer therapies.

Valsesia, A *et al.* (2020) "Integrative phenotyping of glycemic responders upon clinical weight loss using multi-omics." *Sci Rep* **10**(1): 9236.

https://pubmed.ncbi.nlm.nih.gov/32514005/

Low calorie diets can help obese people lose weight and lower their risk of cardiometabolic diseases, but they don't work for everyone. In a previous dietary intervention study, a team led by researchers at Nestlé Institute of Health Sciences were able to distinguish people who lost weight and improved blood sugar (glycemic) control following a low calorie diet from those who lost significantly less weight and showed no improvement in glycemic control by examining their circulating lipid profiles. To gain further insight into the differences between glycemic responders and non-responders, the researchers conducted metabolomic, proteomic and transcriptomic studies of the two groups. Samples were from 174 responders and 201 non-responders taken before and after an eight-week low calorie diet and after six months of weight maintenance. RNA sequencing of fat tissue showed reduced expression of genes involved in fat formation in responders relative to non-responders; metabolomics showed increased byproducts of fat metabolism in the blood; and proteomic analysis using the SomaScan Assay revealed differences in lipoproteins. A predictive model based on blood measurements taken before the diet outperformed clinical models in distinguishing non-responders. These findings could help clinicians gauge whether dietary interventions are likely to be effective for improving the health of obese individuals.

Ruffieux, H *et al.* (2020) "A fully joint Bayesian quantitative trait locus mapping of human protein abundance in plasma." *PLoS Comput Biol* **16**(6): e1007882.

https://pubmed.ncbi.nlm.nih.gov/32492067/

Protein quantitative trait locus (pQTL) studies aim to identify causal factors of disease by linking genetic variants to protein changes. Since a single gene variant usually induces small effects on many different proteins, deconvoluting relationships between thousands of genes and proteins simultaneously is extremely challenging, particularly for complex conditions such as obesity and cardiometabolic disease. In this article, a team led by researchers at Nestlé Research in Switzerland used their newly developed “LOCUS” method to perform a pQTL analysis of millions of gene variants and thousands of plasma proteins measured using the SomaScan Assay and mass spectrometry. They discovered 136 pQTLs in data from a clinical cohort of obese/overweight individuals and replicated over 80% of them in an independent cohort. LOCUS confirmed 93 pQTLs found in other much larger studies and revealed 20 new pQTLs that warrant further investigation. These results highlight the efficiency of LOCUS for finding gene variants that show weak effects but play potentially important roles in complex diseases.

Rashid, MU *et al.* (2020) "Zika virus dysregulates human Sertoli cell proteins involved in spermatogenesis with little effect on tight junctions." *PLoS Negl Trop Dis* **14**(6): e0008335.

https://pubmed.ncbi.nlm.nih.gov/32511241/

Zika virus can be passed from mother to fetus and cause severe birth defects. Although Zika virus is primarily spread by mosquitoes, it can also be transmitted sexually—the virus can survive for over a year in semen from infected men. In this article, researchers at the University of Manitoba in Canada monitored protein changes in testicular Sertoli cells following infection with Zika virus. They used the SomaScan Assay to measure the levels of 1,305 human proteins at three different time points up to five days post-infection. Zika virus did not kill the cells, but caused significant changes in 299 proteins, including many involved in sperm production. These studies are a first step in understanding how Zika virus can persist in latent reservoirs and how it might affect male fertility.

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George, MJ *et al.* (2020) "Novel insights into the effects of interleukin 6 antagonism in non-ST-segment-elevation myocardial infarction employing the SOMAscan proteomics platform." *J Am Heart Assoc* **9**(12): e015628.

https://pubmed.ncbi.nlm.nih.gov/32515246/

Interleukin 6 (IL-6) is an inflammatory protein that contributes to coronary artery disease (CAD) and is associated with poor outcomes following heart attacks (myocardial infarctions, MI). Drugs that block IL-6 are therefore of interest for treating cardiovascular disease. Tocilizumab is an IL-6 inhibitor currently used to treat rheumatoid arthritis. The first clinical trial of tocilizumab for treating cardiovascular disease showed that it reduced inflammation in patients with MI. In this follow-up study, a team led by researchers at University College London in the UK used the SomaScan Assay to identify other plasma proteins modulated by tocilizumab treatment in MI. They compared the levels of over 1000 proteins in plasma samples taken 48 hours after treatment with either tocilizumab or placebo and identified 5 proteins that could be contributing to tocilizumab's beneficial effects. These results expand our understanding of tocilizumab's mechanism of action and could lead to the identification of new drug targets for treating CAD and MI.

Fajgenbaum, DC *et al.* (2019) "Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease." *J Clin Invest* **129**(10): 4451-4463.

https://pubmed.ncbi.nlm.nih.gov/31408438/

Arenas, DJ *et al.* (2020) "Increased mTOR activation in idiopathic multicentric Castleman disease." *Blood* **135**(19): 1673-1684.

https://pubmed.ncbi.nlm.nih.gov/32206779/

Pai, RL *et al.* (2020) "Type I IFN response associated with mTOR activation in the TAFRO subtype of idiopathic multicentric Castleman disease." *JCI Insight* **5**(9): e135031.

https://pubmed.ncbi.nlm.nih.gov/32376796/

Idiopathic multicentric Castleman disease (iMCD) is a rare disease with a range of symptoms that can include enlarged lymph nodes, abnormal blood cell counts, systemic inflammation and life-threatening multi-organ failure. Since so little is known about iMCD, there are few treatment options and prognosis is poor—35% of diagnosed patients die within 5 years. The inflammatory protein interleukin 6 (IL-6) has been linked to disease flares in some cases, but the majority of iMCD patients do not respond to treatments that block IL-6.

The most severe cases of iMCD often belong to a clinical subtype with thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly (TAFRO) syndrome. Three publications from the Fajgenbaum group at the University of Pennsylvania Perelman School of Medicine describe studies that used a variety of techniques, including the SomaScan Assay, to better understand what drives iMCD-TAFRO and to identify new drug targets.

In Fajgenbaum *et al.,* the researchers analyzed blood and tissue samples from three iMCD-TAFRO patients who failed to respond to IL-6 blocking treatments and found increased activity of a key regulator of cell growth and proliferation called

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mTOR. Treatment with the mTOR inhibitor sirolimus, a drug used to prevent organ transplant rejection, led to long-lasting disease remission in all three patients. Arenas *et al.* describes a follow up study in a larger cohort of patients that confirmed hyperactivation of mTOR. These results support mTOR as a novel therapeutic target for iMCD-TAFRO, which is being investigated in a clinical trial of sirolimus.

In Pai *et al*., the researchers correlated increased mTOR activity in iMCD-TAFRO patients with type I interferons (IFN-I), proteins that regulate the immune response. This was seen in both responders and non-responders to IL-6 blocking treatments and suggests that IFN-I may drive widespread systemic inflammation in iMCD-TAFRO disease flares.

Raffield, LM *et al.* (2020) "Comparison of proteomic assessment methods in multiple cohort studies." *Proteomics*: e1900278.

https://pubmed.ncbi.nlm.nih.gov/32386347/

In this article, a team led by researchers at the University of North Carolina compared protein measurements obtained using the SomaScan Assay to those obtained using antibody-based assays. The data were taken from four different clinical studies that used older versions of the SomaScan Assay to measure either 1.1k or 1.3k proteins. Correlations between the SomaScan Assay and conventional immunoassays or the antibody-based Olink platform varied widely by protein. This could be due to differences in binding of either SOMAmer reagents or antibodies, most likely as a result of the availability of the targeted epitopes (three-dimensional structures) of the proteins analyzed, a phenomenon also seen comparing different antibodies to the same protein. The results provide information to help compare and integrate proteomics data across different platforms.

Ferrannini, G *et al.* (2020) "Coronary artery disease and type 2 diabetes: a proteomic study." *Diabetes Care* **43**(4): 843-851.

https://www.ncbi.nlm.nih.gov/pubmed/31988066

Approximately half of all diabetics die from coronary artery disease (CAD). Detecting CAD and understanding its risk factors is critical for improving treatments and prevention, especially in those with diabetes. In the first study of its kind, a team of researchers from Italy, Sweden and SomaLogic used the SomaScan Assay to identify blood proteins that were associated with type 2 diabetes (T2D) and CAD. They measured the levels of approximately 5000 proteins in plasma samples from 528 patients with no previous cardiovascular event (34% with CAD, 12% with T2D and 7% with both). They found 15 proteins that associated with both T2D and CAD, 3 that associated with T2D only and 2 that associated with CAD only. These proteins may play important roles in the development of T2D and/or CAD and warrant further investigation as possible disease markers and/or therapeutic targets.

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Zaghlool, SB *et al.* (2020) "Epigenetics meets proteomics in an epigenome-wide association study with circulating blood plasma protein traits." *Nat Commun* **11**(1): 15.

https://www.ncbi.nlm.nih.gov/pubmed/31900413

Epigenetics refers to modifications of DNA that can affect gene expression without changing the original DNA sequence. The most common epigenetic modification is DNA methylation, which is believed to play a role in the development and progression of many common diseases, at least in part by changing protein expression levels. This article describes the largest epigenome-wide association study with proteomics to date. A team led by researchers at Weill Cornell Medicine-Qatar looked for associations between 1123 protein levels measured using the SomaScan Assay and 470,837 DNA methylation sites. They identified 98 associations (pQTMs) using blood samples from 944 participants in a German population health study and replicated the results in a multi-ethnic group of 344 individuals. Many of the pQTMs involved the protein pappalysin-1, which has been linked to cardiovascular disease, type 2 diabetes and cancer. Another group of pQTMs involved NLRC5 methylation, an epigenetic hallmark of chronic inflammation. These results show how large-scale measurements of proteins could be used to help identify epigenetic contributions to disease.

Smith, MA *et al.* (2020) "Using the circulating proteome to assess type I interferon activity in systemic lupus erythematosus." *Sci Rep* **10**(1): 4462.

https://www.ncbi.nlm.nih.gov/pubmed/32157125

Type I interferons (IFN) are a large group of proteins that help defend the body against viruses. IFN are also key drivers of many autoimmune diseases, including systemic lupus erythematosus (SLE). To help identify proteins that are activated by IFN and contribute to SLE disease, scientists at AstraZeneca and the National Institutes of Health used the SomaScan Assay to measure the levels of 1,129 proteins in blood serum from 143 patients with mild to moderate SLE and 50 healthy controls. People with SLE produce large amounts of self-antibodies that interfere with SOMAmer reagents used in the assay, so a modified protocol was employed that used fish DNA to neutralize the self-antibodies in the blood samples.

The researchers identified a set of four proteins that were significantly different in SLE patients and optimally correlated with a previously validated 21-gene IFN signature. The 4-protein IFN signature was elevated in SLE patients and decreased following treatment with an antibody that neutralizes IFN. Interestingly, the researchers identified a new subgroup of SLE patients with high IFN protein signatures but low IFN gene signatures. Unlike the IFN gene signature, the IFN protein signature was relatively unaffected by changes in the cellular composition of blood, which suggests that the proteins may also be reporting on SLE-affected tissues. The IFN protein signature also correlated significantly with the IFN gene signature in patients with myositis, another autoimmune disease in which IFN plays an important role. Taken together, the results suggest that proteins controlled by IFN have the potential to detect unique tissue biology that is not accessible by measuring gene expression in blood. Since IFN are central regulators of the immune response, the new protein signature may provide insight into the biology of many different diseases that have an immune component, including cancer and chronic infections.

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Wolk, SK *et al.* (2020) "Modified nucleotides may have enhanced early RNA catalysis." *Proc Natl Acad Sci U S A*. **117**(15): 8236-8242.

https://www.ncbi.nlm.nih.gov/pubmed/32229566

RNA replicates itself without any help from DNA, proteins or other cellular components. RNA's ability to store genetic information and function as an enzyme has led to the hypothesis that the earliest life forms were RNA-based. Some objections to the "RNA World Hypothesis" are that RNA is inherently unstable and long sequences are needed to gain useful catalytic activity. This perspective from SomaLogic scientists speculates that RNA bases with chemical modifications (similar to those of SOMAmer reagents) could have existed on primordial Earth. As is seen in SOMAmer reagents, protein-like appendages could have stabilized short RNA sequences and helped the RNA fold up on itself to aid catalysis in the early evolution of life.

Osawa, Y *et al.* (2020) "Plasma proteomic signature of the risk of developing mobility disability: A 9-year follow-up." *Aging Cell* **19**(4): e13132.

https://www.ncbi.nlm.nih.gov/pubmed/32157804

Mobility declines with old age and those with severe disability are more prone to developing disease and having a poorer quality of life. In this article, scientists at the National Institutes of Health, Johns Hopkins University School of Medicine, the National Cancer Institute, Sanofi and Azienda Sanitaria di Firenze report the first comprehensive study of proteins associated with mobility disability. They used the SomaScan Assay to measure the levels of 1301 proteins in plasma taken from 660 men and women enrolled in an aging study of the Chianti region in Italy. At the start of the study, participants (aged 60-94 years old) were able to walk 400 meters at a fast pace, but over a nine-year follow up period, 292 participants became disabled. Plasma levels of 75 proteins predicted loss of mobility. After adjusting for various factors such as sex, age and walking speed, three proteins emerged as the most significant. Interestingly, none of the three had previously been associated with risk of mobility loss. The results warrant further investigation as they may help define new markers of mobility disability as well as biological targets for its prevention.

Apps, R *et al.* (2020) "Multi-modal immune phenotyping of maternal peripheral blood in normal human pregnancy." *JCI Insight* **5**(7): e134838.

https://www.ncbi.nlm.nih.gov/pubmed/32163376

Pregnancy alters the mother's immune system in complex ways that are poorly understood—increasing resistance to some infections and increasing susceptibility to others. This article from researchers at the National Institutes of Health and the National Cancer Institute reports changes in immune cells and in blood proteins that occur during the course of normal pregnancies. Four blood samples were taken from 33 mothers, three during gestation and one after delivery. White blood cell populations were characterized using flow cytometry and the levels of 1,305 serum proteins were measured using the SomaScan Assay. SomaScan analysis validated previous findings and identified a new set of seven proteins to predict gestational age. Gestational age could also be predicted from complete blood count tests and characterization of five major

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immune cell populations. These results improve our understanding of the changes in maternal immunity during normal pregnancy and may improve our understanding of changes that confer risk.

Shainker, SA *et al.* (2020) "Placenta accreta spectrum: biomarker discovery using plasma proteomics." *Am J Obstet Gynecol* **223**(3): 433 e431-433 e414.

https://www.ncbi.nlm.nih.gov/pubmed/32199927

Placenta accreta spectrum (PAS) is a potentially life-threatening pregnancy complication that occurs when the placenta grows too deeply into the wall of the uterus and is unable to detach at childbirth. Up to 50 percent of PAS cases go undiagnosed because imaging is imprecise and there are no reliable biomarkers for PAS. The goal of this exploratory study led by researchers at Beth Israel Deaconess Medical Center at Harvard Medical School was to see if specific blood proteins are associated with women with PAS. They used the SomaScan Assay to measure levels of 1,305 proteins in plasma samples taken prior to delivery from 16 women with PAS and ten controls. Proteins with known roles in inflammation, blood vessel formation and cellular invasion were significantly different between the two groups. Additional studies are needed to assess whether these potential protein biomarkers could improve diagnosis of PAS before birth.

Sher, AA *et al.* (2020) "Autophagy modulators profoundly alter the astrocyte cellular proteome." *Cells* **9**(4): 805.

https://www.ncbi.nlm.nih.gov/pubmed/32225060

Autophagy is normal bodily process that removes dysfunctional cells and recycle parts of them to make healthy new ones. Autophagy is dysregulated in various diseases including neurodegenerative disorders and cancer, which makes compounds that modulate autophagy attractive drug candidates. To examine the effects of autophagy modulators on human cells, researchers at the University of Manitoba in Canada used the SomaScan Assay to measure the levels of 1,305 proteins in astrocytes treated with either bafilomycinA1 (an autophagy activator) or rapamycin (an autophagy inhibitor). Comparing treated vs. untreated cells revealed significant differences in many proteins not previously associated with autophagy. Both bafilomycinA1 and rapamycin are known to impact the brain, and since astrocytes are abundant in the brain, the results of this study could provide information regarding possible side effects of autophagy modulators.

Celik, H *et al.* (2020) "Highly multiplexed proteomic assessment of human bone marrow in acute myeloid leukemia." *Blood Adv* **4**(2): 367-379.

https://www.ncbi.nlm.nih.gov/pubmed/31985806

Acute Myeloid leukemia (AML) is a type of cancer in which the bone marrow makes abnormal blood cells that proliferate and quickly crowd out their normal counterparts. With chemotherapy, most AML patients achieve complete remission, but many are at risk of relapse. To gain insight into how the bone marrow environment might allow cancerous cells to survive chemotherapy, scientists at the National Institutes of Health profiled bone marrow proteins using the SomaScan Assay. They measured the levels of 1,305 proteins in the liquid portion of bone marrow collected from 10 patients with AML and 10 age-and sex-matched healthy controls. They identified 168 proteins in bone marrow that were significantly different in people with AML. Some of the proteins had known associations to AML but many were completely new. They also performed SomaScan analysis of circulating blood taken from the same people and performed RNA sequencing of their bone marrow cells. Only 66 of the proteins overlapped between bone marrow and blood serum and only 45 of the proteins overlapped between bone marrow and RNA sequencing data, which highlights differences in the bone marrow microenvironment. This study is the first comprehensive profiling of proteins in bone marrow and could help elucidate the biological factors that drive AML disease.

Guerrero, CLH *et al.* (2020) "Proteomic profiling of HTLV-1 carriers and ATL patients reveals sTNFR2 as a novel diagnostic biomarker for acute ATL." *Blood Adv* **4**(6): 1062-1071.

https://www.ncbi.nlm.nih.gov/pubmed/32196559

Adult T-cell leukemia/lymphoma (ATL) is a rare, aggressive cancer that occurs in people infected with human T-lymphotropic virus type 1 (HTLV-1). Only about five percent of those with HTLV-1 develop ATL, but there is currently no way to distinguish those who will progress to disease. In this study, scientists in Japan used the SomaScan Assay to measure the levels of 1,305 proteins in plasma taken from 40 people with asymptomatic HTLV-1, 40 people with ATL and 5 people in remission. They identified 333 proteins that were significantly different between those with and without ATL and confirmed by ELISA that one protein, soluble tumor necrosis factor 2 (sTNFR2) was ten times higher in those with ATL than in HTLV-1 carriers and those in remission. Additional studies in larger patient groups is needed, but sTNFR2 could be a candidate biomarker for diagnosing ATL, assessing disease risk and monitoring treatment efficacy.

Arjaans, S *et al.* (2020) "Early angiogenic proteins associated with high risk for bronchopulmonary dysplasia and pulmonary hypertension in preterm infants." *Am J Physiol Lung Cell Mol Physiol* **318**(4): L644-L654.

https://www.ncbi.nlm.nih.gov/pubmed/31967847

Some premature babies may need respiratory support to stay alive, but this treatment increases their risk of developing bronchopulmonary dysplasia (BPD), a chronic lung disease. Up to a quarter of infants with BPD develop pulmonary hypertension (PH, high blood pressure in the arteries to the lungs), which raises death rates to close to fifty percent. To better understand the factors that contribute to BPD and PH, a team led by researchers at University of Groningen in the Netherlands and the University of Colorado Denver collected plasma samples from 102 preterm babies in the first week after birth and measured the levels of 1121 proteins using the SomaScan Assay. Of the 102 infants that were tested, 82 were later diagnosed with BPD and 13 were diagnosed with BPD and PH. Ninety-seven proteins were significantly different in the infants who developed severe BPD, including many involved in inflammation, cell development and new blood vessel formation. Changes in the levels of BMP10, a protein involved in vascular development, were strongly linked to both BPD and PH. These results identified candidate protein markers that could help assess risk of BPD and PH in newborns and lead to new preventative strategies.

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Kahal, H *et al.* (2020) "Effect of induced hypoglycemia on inflammation and oxidative stress in type 2 diabetes and control subjects." *Sci Rep* **10**(1): 4750.

https://www.ncbi.nlm.nih.gov/pubmed/32179763

People with type 2 diabetes (T2D) are two to four times more likely to die of cardiovascular disease (CVD) than those without. Controlling blood sugar is a key to managing T2D, but strict control measures appear to increase the number of CVD-related deaths in diabetics. To examine what happens when blood sugar levels become too low (hypoglycemia), a team led by researchers at Hull York Medical School in the UK and Hamad Bin Khalifa University in Qatar induced hypoglycemia in ten people with T2D and eight age-matched healthy controls and then analyzed endothelial function (a measure of arterial health) as well as biochemical markers using a combination of traditional methods and the SomaScan Assay. Inducing hypoglycemia for one hour did not affect endothelial function in either group but caused levels of inflammatory and oxidative stress markers (two factors associated with heart attacks and stroke) to rise in T2DM subjects 24 hours after the event. These results suggest that in people with T2D, low blood sugar may trigger inflammation and oxidative stress that persists long after blood glucose levels have returned to normal.

Tala, JA *et al.* (2020) "Protein biomarkers for incident deep venous thrombosis in critically ill adolescents: An exploratory study." *Pediatr Blood Cancer* **67**(4): e28159.

https://www.ncbi.nlm.nih.gov/pubmed/31904170

Deep vein thrombosis (DVT) is a potentially life-threatening condition caused by blood clots, usually in the leg. Adults considered at risk are often given blood thinners to help prevent DVT, but this prophylactic intervention does not appear to be effective in children. While DVT is uncommon in healthy children, it can occur during lengthy hospital stays, and currently there is no way to identify children who are at high risk of developing DVT. In this study, a team led by researchers at Yale-New Haven Children’s Hospital analyzed plasma samples from 59 adolescents (13-17 years old) who received cardiopulmonary support in intensive care units, 9 of whom developed DVT. They measured the levels of clotting factors and other proteins using a combination of traditional antibody-based assays and the SomaScan Assay and identified five proteins as potential high-risk markers of DVT. The researchers plan to validate their results in future studies that include children of all ages.

Leonard, A *et al.* (2020) "Atopic dermatitis endotypes based on allergen sensitization, reactivity to Staphylococcus aureus antigens, and underlying systemic inflammation." *J Allergy Clin Immunol Pract* **8**(1): 236-247 e233. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/31430591

Atopic dermatitis, the most common type of eczema, is a chronic skin condition in which itchy rashes periodically flare up. People with atopic dermatitis are more likely to develop allergies and some studies have suggested that those with allergies may have a different subtype of the disease that could benefit from more targeted treatments. In this article, researchers from MedImmune and the Icahn School of Medicine at Mount Sinai conducted allergy testing on blood samples taken from 76 people with moderate to severe atopic dermatitis compared to 39 healthy controls. In parallel, they measured the levels of 1,129 proteins in the blood samples using the SomaScan Assay and found that different proteins were increased in those

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with atopic dermatitis depending on the type of allergies they had (i.e. food, seasonal, perennial or mixed). These protein inflammatory signatures could be valuable for more precisely characterizing atopic dermatitis patients and determining the best therapies for them.

Shubin, NJ, *et al.* (2020) "Serum protein changes in pediatric sepsis patients identified with an aptamer-based multiplexed proteomic approach." *Crit Care Med* **48**(1): e48-e57. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/31714400

Sepsis occurs when the body's immune response overreacts to an infection, causing severe systemic inflammation that can be life-threatening. Diagnosing sepsis in children is particularly difficult since symptoms can be hard to detect or can mimic the original illness. This can have dire consequences as delaying treatment for even a few hours can cause organ failure or death. In this article, researchers at Seattle Children's Research Institute, Immunexpress, Seattle Children's Hospital and the University of Washington School of Medicine compared serum samples from 35 children with sepsis to 28 pediatric bypass surgery patients with infection-negative systemic inflammation. They used the SomaScan Assay to measure the levels of 1,305 proteins in each blood sample and found 76 proteins that correlated strongly with clinical measures of sepsis, many of which were new. The protein changes identified could become the basis for a single diagnostic test for pediatric sepsis.

King, JD *et al.* (2020) "Joint fluid proteome after anterior cruciate ligament rupture reflects an acute posttraumatic inflammatory and chondrodegenerative state." *Cartilage* **11**(3): 329-337.

https://www.ncbi.nlm.nih.gov/pubmed/30033738

Abrupt trauma to a joint (such as an acute ACL injury) can trigger osteoarthritis (OA). Early intervention with anti-inflammatory agents may slow or prevent cartilage deterioration, but this is difficult to gauge since decades can pass before the changes are detectable by radiation scans. The goal of this study led by a team from the University of Kentucky was to identify protein markers of post-traumatic OA. Synovial fluid was obtained from 6 patients approximately 6 and 14 days after they suffered an ACL injury, and the levels of 1,129 proteins were analyzed using the SomaScan Assay. Fifteen proteins significantly increased between the two time points, and five of the proteins had been previously associated with rheumatoid arthritis. These results suggest that OA-related processes start soon after injury. The work suggests that proteomic profiling could help monitor the efficacy of therapies and help identify new targets for intervention.

Semba, RD *et al.* (2020) "Elevated Plasma Growth and Differentiation Factor 15 Is Associated With Slower Gait Speed and Lower Physical Performance in Healthy Community-Dwelling Adults." *J Gerontol A Biol Sci Med Sci* **75**(1): 175-180.

https://www.doi.org/10.1093/gerona/glz071

In this study, Chinese researchers evaluated the potential effects of circulating proteins on the development of osteoporosis. They measured genetic differences and bone mass density (BMD) in 2286 American Caucasians and then calculated the

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aggregate influence of multiple genetic markers on 267 plasma proteins that had been previously identified in a SomaScan study that linked protein levels and genetic variants to disease (see Suhre, K *et al.* (2017) *Nat Commun* **8**: 14357; https://doi.org/10.1038/ncomms14357). They found genetic correlations between BMD and 41 blood proteins. Some of the proteins had been previously associated with osteoporosis but some were entirely new. These results may provide new insights into the biological causes of osteoporosis and possible new targets for therapeutic interventions.

Moin, ASM *et al.* (2020) “Pro-fibrotic M2 macrophage markers may increase the risk for COVID19 in type 2 diabetes with obesity.” *Metabolism* **112**: 154374

https://doi.org/10.1016/j.metabol.2020.154374

Obese diabetics are at higher risk of serious COVID-19 complications, such as acute respiratory distress syndrome (ARDS). Plasma lipopolysaccharide (LPS) is a key activator of macrophages that is elevated in obesity and activated macrophages produce proinflammatory proteins that drive ARDS. In this Letter to the Editor, researchers at Hamad Bin Khalifa University in Qatar, Hull York Medical School in the UK and Royal College of Surgeons in Ireland Bahrain describe a study using the SomaScan Assay to compare levels of proteins in plasma from 23 obese type 2 diabetics (OT2D) compared to nondiabetic controls. They found significantly higher levels of macrophage-derived proinflammatory proteins in OT2D, which could place them at higher risk of severe COVID-19.

Cuvelliez, M *et al.* (2019) "Circulating proteomic signature of early death in heart failure patients with reduced ejection fraction." *Sci Rep* **9**(1): 19202.

https://www.ncbi.nlm.nih.gov/pubmed/31844116

Heart failure is a condition in which the heart doesn’t pump efficiently and is a leading cause of death worldwide. Better methods are needed to identify high-risk patients who might benefit from invasive treatments. In this study, scientists at the University of Lille in France used the SomaScan Assay to measure the levels of 1,310 proteins in plasma samples taken from 168 patients hospitalized for systolic heart failure. Half the samples were from patients who died within three years of follow up and half were from patients who survived. They found 203 proteins that were significantly different between the two groups, and using statistical models, they identified six proteins that could predict early death. These findings warrant further investigation in larger independent cohorts but could help stratify heart failure patients and provide greater insight into the underlying biology of this complex disease.

Emilsson, V *et al.* (2019) "Predicting health and life span with the deep plasma proteome." *Nat Med* **25**(12): 1815-1816. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/31806904

—and—

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Williams, SA *et al.* (2019) "Plasma protein patterns as comprehensive indicators of health." *Nat Med* **25**(12): 1851-1857.

https://www.ncbi.nlm.nih.gov/pubmed/31792462

In this article, an international team led by researchers from the University of California San Francisco, University of Cambridge and SomaLogic describes how information about a person's current health status, modifiable behaviors and future risks of cardiometabolic disease can be discerned entirely from different patterns of proteins their blood. The results show how scanning the levels of thousands of plasma proteins simultaneously could capture enough information to deliver a one-stop, "liquid health check" for personalized detection, prevention and treatment of disease.

The work is a new milestone for large-scale protein scanning, with a total of approximately 85 million individual protein measurements and for the first time, evaluating proteins alone as the single source of medical information. Using the SomaScan Platform, the levels of approximately 5000 proteins were measured in each archived plasma sample from nearly 17,000 participants in 5 well-characterized patient groups. Applying sophisticated computer algorithms to the massive data set in rigorously pre-defined analyses revealed protein patterns that correlated with medical information provided with the blood sample, such as the results of a liver ultrasound, a treadmill test or whether the patient later suffered a heart attack or developed diabetes.

Out of 13 different health indicators examined, 11 protein-based models were developed that could successfully predict: presence/absence of liver fat; kidney function; percent body fat; visceral fat; lean body mass; cardiopulmonary fitness; average daily physical activity; alcohol consumption; cigarette smoking; diagnosis of diabetes in pre-diabetics within 10 years; and likelihood of heart attack, stroke, heart failure or cardiovascular death within 5 years in people without known heart disease. The accuracy of the protein-based models varied, but all were either better predictors than models based on traditional risk factors or would constitute more convenient alternatives to traditional testing.

In an accompanying editorial, Emilsson, Gudnason and Jennings note that, "Much remains to be elucidated, yet at this point it can be imagined that in the near future thousands of proteins will be routinely screened in a single drop of blood for an objective survey of health and for delivering early warning signs of future disease, thereby enabling an integrated plan for wellness checks and healthcare."

Gehrig, JL *et al.* (2019) "Effects of microbiota-directed foods in gnotobiotic animals and undernourished children." *Science* **365**(6449).

https://www.doi.org/10.1126/science.aau4732

There is increasing evidence that poorly developed gut microbiomes contribute to childhood malnutrition. In this article, researchers at Washington University School of Medicine show how foods designed to boost microbial communities can improve the health of malnourished children. They first characterized the gut microbiome of Bangladeshi children with severe acute malnutrition (SAM) and also used the SomaScan Assay to measure the levels of more than 1,300 proteins in their blood. They then colonized mice with the microbes found in the children's intestines and fed the mice different diets to find the best microbiota-directed complementary foods (MDCFs). They developed three MDCF formulations and conducted a randomized, controlled clinical trial on Bangladeshi children aged 12 to 18 months with moderate acute malnutrition. Twice a day for four weeks, the children were fed one of three MDCFs or a traditional rice- and lentil-based food. One MDCF induced a shift in the microbiome and in the levels of plasma proteins toward that of healthy children and away from that of children with SAM. These results suggest that targeting the microbiome is an effective strategy for improving the long-term health of malnourished children.

Lehallier, B *et al.* (2019) "Undulating changes in human plasma proteome profiles across the lifespan." *Nat Med* **25**(12): 1843-1850.

https://www.ncbi.nlm.nih.gov/pubmed/31806903

In this article, an international team led by scientists at Stanford University developed a “proteomic clock” that could provide information on how well a person is aging based on the proteins circulating in their blood. The researchers used the SomaScan Assay to measure the levels of 2,925 proteins in plasma samples from 4,263 adults (aged 18-95 years old) and identified 1379 proteins that changed significantly with age. Approximately two-thirds of the proteins were different between men and women, but the researchers were able to define a group of 373 proteins that could predict age regardless of sex, with high accuracy (93-97%). Interestingly, people predicted to be younger than their age from birth were also more mentally and physically fit than their peers. SomaScan analysis showed that people do not age in a linear fashion. Instead, the levels of most plasma proteins fluctuated over time, with three major waves of protein changes that peaked at ages 34, 60 and 78. Among the hundreds of different proteins that changed at ages 60 and 78 were many associated with cardiovascular disease, Down syndrome and Alzheimer’s disease. A better understanding of the age-related changes in blood proteins could lead to better tools for identifying the onset of age-related diseases and strategies for promoting healthy aging.

Hathout, Y *et al.* (2019) "Disease-specific and glucocorticoid-responsive serum biomarkers for Duchenne Muscular Dystrophy." *Sci Rep* **9**(1): 12167.

https://www.ncbi.nlm.nih.gov/pubmed/31434957

Previous studies have used the SomaScan Platform to identify circulating proteins associated with Duchenne Muscular Dystrophy (DMD), a hereditary, muscle-wasting disease. In this article, a team led by scientists at Binghamton University refined the list of protein biomarkers of DMD by examining the effects of two factors that can alter protein levels independent of disease state: patient age and glucocorticoid steroid use (a standard treatment for DMD). To assess the effect of steroid use, the researchers used the SomaScan Assay to compare the levels of 1,310 proteins in blood samples from 18 boys with DMD (ages 4–10) who had not been treated with steroids and 12 age-matched healthy controls. They identified 178 proteins that were significantly altered in DMD patients, of which approximately 45% overlapped with DMD biomarkers found previously using a different cohort. To assess the effect of age, the team analyzed blood samples collected over approximately one year from 12 steroid-free DMD patients. Of the 178 DMD-associated proteins, only 3 changed significantly over time, and the researchers speculated that their declining levels reflect early muscle damage. The researchers also analyzed blood samples from 10 DMD patients before and after steroid treatment and found that the levels of 107 proteins significantly changed. Of these, 27 proteins overlapped with those identified as DMD markers, and 17 of them tended to return to levels seen in healthy individuals. This suggests that these proteins could be used to monitor efficacy of steroid treatment in DMD patients.

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Graumann, J *et al.* (2019) "Multi-platform affinity proteomics identify proteins linked to metastasis and immune suppression in ovarian cancer plasma." *Front Oncol* **9**: 1150.

https://www.ncbi.nlm.nih.gov/pubmed/31737572

High-grade serous carcinoma (HGSC) is the most common and deadliest type of ovarian cancer. Survival rates are low because the majority of women are not diagnosed until their disease is at an advanced stage. In this article, investigators in Germany looked for differences in blood taken from 20 untreated stage III HGSC patients compared to 20 individuals with non-malignant gynecological conditions. Using the O-link proteomics technology, they identified 176 of 368 plasma proteins whose levels were increased in the HGSC patients and then validated their results using the SomaScan Assay and ELISA-based affinity assays. Further studies in larger, independent cohorts are needed to evaluate the clinical potential of the identified protein markers.

Aguado, BA *et al.* (2019) "Transcatheter aortic valve replacements alter circulating serum factors to mediate myofibroblast deactivation." *Sci Transl Med* **11**(509).

https://www.doi.org/10.1126/scitranslmed.aav3233

Aortic valve stenosis (AVS) is a progressive disease that occurs when the heart's aortic valve thickens and calcifies, limiting blood flow to the body. AVS can lead to heart failure and sudden cardiac death. Transcatheter aortic valve replacement (TAVR) is a minimally invasive procedure used to treat AVS. In this article, researchers at the University of Colorado used the SomaScan Assay to analyze serum samples taken from patients before TAVR and one month after TAVR. Post-TAVR, they found increased levels of dozens of proteins involved in the inflammatory response that impeded fibrosis in a cardiac cell model. These results suggest that TAVR alters the circulating proteome in a beneficial way that could help patients with advanced AVS to prevent further disease progression.

Xiong, H *et al.* (2019) "Cancer protein biomarker discovery based on nucleic acid aptamers." *Int J Biol Macromol* **132**: 190-202.

https://www.doi.org/10.1016/j.ijbiomac.2019.03.165

In this review, researchers in China discuss aptamer-based technologies and demonstrate their unique advantages in discovering cancer protein biomarkers.

Frottin, F *et al.* (2019) “The nucleolus functions as a phase-separated protein quality control compartment.” *Science* 365(6451): 342-347. **(Subscription required)**

https://doi.org/10.1126/science.aaw9157

In this article, researchers at Max Planck Institute for Biochemistry in Germany used fluorescent-tagged SOMAmer reagents for super-resolution imaging of the nucleolus, a structure found in the cell nucleus. They found that under heat stress,

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improperly folded proteins moved to the nucleolus, where they were kept in a liquid-like state that prevented potentially toxic, irreversible aggregation. These results revealed a new mechanism that protects cells from damage.

Coombs, KM *et al.* (2019) "Aptamer profiling of A549 cells infected with low-pathogenicity and high-pathogenicity influenza viruses." *Viruses* **11**(11): 1028.

https://www.ncbi.nlm.nih.gov/pubmed/31694171

Influenza A viruses are a constant threat to public health, causing both seasonal epidemics and global pandemics. Designing safe and effective drugs is difficult because type A flu viruses can mutate quickly and because they can infect animals (such as pigs, birds, bats and horses), evolve and then reemerge in humans. Viruses use the host's cells to replicate and spread, so identifying host factors that are affected by infection is important for developing anti-viral strategies. In this article, scientists at the University of Manitoba and the Public Health Agency of Canada examined the effects of influenza type A infection on the levels of 1,310 host proteins using the SomaScan Assay. They infected human lung cells with five different influenza type A viruses: three H1N1 strains (including the 2009 pandemic strain) and two avian strain (the H5N1 "Bird flu", and an H7N9 strain with low pathogenicity in birds, but high pathogenicity in humans). Compared to mock-infected cells, the levels of more than 500 proteins were changed significantly by one or more of the viruses, although no protein was changed significantly by all five. The two avian strains showed the largest effects, decreasing the levels of many proteins involved in important cell functions. These results warrant further investigation as they may help explain why the avian flu strains have such high pathogenicity in humans.

Almufleh, A *et al.* (2019) "Biomarker discovery in cardiac allograft vasculopathy using targeted aptamer proteomics." *Clin Transplant*: e13765. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/31815308

Cardiac allograft vasculopathy (CAV), also known as transplant coronary artery disease, happens when the blood vessels that feed the transplanted heart gradually narrow. CAV occurs in approximately one-third of patients within five years post-transplant and is the second most common cause of death after the first year. Diagnosing CAV is challenging because symptoms are often absent or variable, and coronary angiography, an invasive procedure recommended for monitoring CAV, has difficulty detecting early disease. The only long-term solution for advanced CAV is another heart transplant.

In this article, scientists at the University of Ottawa Heart Institute in Canada and King Saud University in Saudi Arabia used the SomaScan Assay to identify circulating markers of CAV. They measured the levels of over 1,300 proteins in serum taken from 31 transplant patients who underwent coronary angiography: 12 with mild to moderate CAV, 9 with severe CAV and 10 normal controls. They identified 14 proteins that were significantly altered in patients with CAV compared to controls, including 4 proteins that were significantly different in patients with mild to moderate CAV compared to those with advanced disease. With further validation, these proteins could lead to a less invasive diagnostic test for CAV and could provide insight into the causes of CAV as well as possible targets for therapeutic intervention.

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Kukova, LZ *et al.* (2019) "Comparison of urine and plasma biomarker concentrations measured by aptamer-based versus immunoassay methods in cardiac surgery patients." *J Appl Lab Med* **4**(3): 331-342.

https://www.ncbi.nlm.nih.gov/pubmed/31659071

In this article, researchers at Yale School of Medicine, Icahn School of Medicine at Mount Sinai, Johns Hopkins University School of Medicine and the University of California, San Francisco compared protein-measurement results obtained using the SomaScan Assay with those obtained using traditional antibody-based approaches. They used the SomaScan Assay to measure the levels of over 1,300 proteins in pre- and post-operative blood and urine samples from 54 patients with acute kidney injury following cardiac surgery. Many of the proteins identified by SomaScan analysis were not within the detectable range of traditional antibody-based assays, but those that could be compared showed moderate to strong correlations in plasma and weaker but promising correlations in urine. This was the first study to test the utility of the SomaScan Platform in urine, and although further validation in larger sample cohorts is needed, the results illustrate its potential for high-throughput discovery of new disease markers.

Shubin, AV *et al.* (2019) "Blood proteome profiling using aptamer-based technology for rejection biomarker discovery in transplantation." *Sci Data* **6**(1): 314.

https://www.ncbi.nlm.nih.gov/pubmed/31819064

This article describes a SomaScan Platform data set generated in a previous study of serum protein markers of face transplant rejection. See: Kollar, B *et al.* (2018) "Increased levels of circulating MMP3 correlate with severe rejection in face transplantation." *Sci Rep* **8**(1): 14915; https://www.ncbi.nlm.nih.gov/pubmed/30297859

Teumer, A *et al.* (2019) "Genome-wide association meta-analyses and fine-mapping elucidate pathways influencing albuminuria." *Nat Commun* **10**(1): 4130.

https://www.ncbi.nlm.nih.gov/pubmed/31511532

Elevated levels of protein in the urine is a sign of kidney failure and measuring urinary albumin to creatinine ratio (UACR) is a common test for diagnosing and monitoring kidney disease. Elevated UACR is also associated with increased risk of heart disease and death. Genetic factors are believed to play a role in high UACR levels, but thus far, genome wide association studies (GWAS) have been unable to identify causal genes. In this article, an international team of investigators described the acquisition of GWAS data from 564,257 multi-ethnic European participants and identification of 68 genetic locations that correlated with UACR, gene expression in different tissues and altered plasma protein levels measured using the SomaScan Assay. The findings suggest potential causal factors for UACR and possible drug targets for kidney and heart disease.

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Deterding, RR *et al.* (2019) "Pulmonary aptamer signatures in children's interstitial and diffuse lung disease." *Am J Respir Crit Care Med* **200**(12): 1496-1504.

https://www.ncbi.nlm.nih.gov/pubmed/31409098

Childhood interstitial lung disease (chILD) refers to a group of over 30 different rare lung disorders that can affect babies, children and teens. Since it covers such a wide range of conditions, a chILD diagnosis is often not precise enough to design the best treatment for a particular person. In this article, researchers at the University of Colorado School of Medicine used the SomaScan Assay to measure the levels of 1,129 proteins in 47 bronchoalveolar lavage fluid samples taken from chILD patients and controls. The protein profiles could distinguish between different lung conditions and may help distinguish their underlying causes. This information could be used to improve chILD diagnosis and to identify targets for therapeutic interventions.

Shi, L *et al.* (2019) "Discovery and validation of plasma proteomic biomarkers relating to brain amyloid burden by SomaScan Assay." *Alzheimers Dement* **15**(11): 1478-1488.

https://www.ncbi.nlm.nih.gov/pubmed/31495601

One of the hallmarks of Alzheimer's disease is clumps of the protein amyloid-β (amyloid plaques) that form and spread in the brain. Current methods for assessing plaque deposits (PET scan brain imaging and measuring amyloid-β levels in cerebrospinal fluid) are costly, time consuming and work poorly for those with no or mild symptoms of Alzheimer's disease. Accurately measuring amyloid plaques is critical for understanding if they drive Alzheimer's disease and if therapies that target them can slow cognitive decline.

In the largest study of its kind to date, an international team led by researchers at the University of Oxford in the UK used the SomaScan Assay to look for blood-based protein markers of brain amyloid plaques. The researchers measured the levels of 4,001 proteins in 881 plasma samples from participants in 11 different European studies of Alzheimer's disease. Participants included healthy controls, those with mild cognitive impairment and those with Alzheimer's disease, all of whom had measured amounts of amyloid in the brain. They identified 44 proteins that, when coupled with information about age and APOE (a known genetic risk factor for Alzheimer's disease), were able to predict amyloid deposition in the brain. The panel could potentially help with early detection and monitoring of Alzheimer's disease and be a more effective method to screen participants for clinical trials of drug candidates that target amyloid plaques.

Finkernagel, F *et al.* (2019) "Dual-platform affinity proteomics identifies links between the recurrence of ovarian carcinoma and proteins released into the tumor microenvironment." *Theranostics* **9**(22): 6601-6617.

https://www.ncbi.nlm.nih.gov/pubmed/31588238

High-grade serous carcinoma (HGSC) is the most common and most aggressive form of ovarian cancer. Although survival rates are low, approximately 20 percent of HGSC patients remain relapse-free for five years or longer. In this article, researchers in Germany used the SomaScan Assay to measure the levels of 1,305 proteins in peritoneal fluid (ascites) from HGSC patients. Ascites is rich in proteins that can affect tumor growth and spread, and the researchers found 779 proteins

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that associated with length of relapse-free survival. Proteins linked to worse outcomes included growth factors associated with metastasis, whereas proteins linked to favorable outcomes included factors that stimulate the immune response. They created two multi-protein signatures that could identify either short-term or long-term survivors and that could potentially improve patient stratification and personalized treatment options.

Sebastiani, P *et al.* (2019) "A serum protein signature of APOE genotypes in centenarians." *Aging Cell* **18**(6): e13023.

https://www.ncbi.nlm.nih.gov/pubmed/31385390

A gene called APOE is considered a risk factor for developing Alzheimer's disease later in life. There are three forms of APOE: APOE e4 is believed to increase Alzheimer's disease risk, APOE e3 is believed to have no effect, and APOE e2 is associated with longevity and believed to be protective against disease. In this study, researchers from Boston University, the Novartis Institutes for Biomedical Research and the National Institute on Aging used a custom version of the SomaScan Assay to measure the levels of 4785 proteins in blood samples from 222 participants in the New England Centenarian study, which included 55 carriers of APOE e2. They identified a set of 16 proteins that correlated with different forms of the APOE gene, 14 of which were novel. They were able to replicate their findings in three independent studies, and found that the blood-based protein signature was consistent with data obtained from post-mortem brain tissue. Seven of the identified proteins also correlated with cognitive function. The protein signature could potentially be used to diagnose, predict or develop treatments for cognitive decline.

Tsujikawa, LM *et al.* (2019) "Apabetalone (RVX-208) reduces vascular inflammation in vitro and in CVD patients by a BET-dependent epigenetic mechanism." *Clin Epigenetics* **11**(1): 102.

https://www.ncbi.nlm.nih.gov/pubmed/31300040

Apabetalone is a drug candidate that significantly reduced the number of deaths, heart attacks and strokes in phase 2 clinical trials of patients with cardiovascular disease. In this study, a team led by scientists at Resverlogix, Corp. used the SomaScan Assay to measure the levels of 1,305 proteins in plasma taken from clinical trial patients treated with either apabetalone or placebo for 26 weeks. Treatment with apabetalone significantly decreased the blood levels of proteins that promote inflammation and that are implicated in atherosclerotic plaque formation and instability. These results support further pre-clinical studies in mice and provide greater insight into apabetalone's mechanism of action: Inhibition of vascular inflammation is predicted to reduce adverse cardiovascular events in an ongoing phase 3 clinical trial of apabetalone.

Malekzadeh, A *et al.* (2019) "Plasma proteome in multiple sclerosis disease progression." *Ann Clin Transl Neurol* **6**(9): 1582-1594.

https://www.ncbi.nlm.nih.gov/pubmed/31364818

Multiple sclerosis (MS) is a chronic, degenerative disease that affects the central nervous system and disrupts communication between the brain and the body. The majority of people with MS experience periods of increased symptoms

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followed by periods of full or partial recovery (relapsing-remitting MS, RRMS), but within this group, some people progress slowly while others progress rapidly. There are also those who experience a steady decline from disease onset (primary progressive MS, PPMS). Currently, it is not possible to predict how MS will affect an individual, which makes it difficult to choose the best therapy.

This article describes the first study to evaluate large numbers of blood proteins in MS patients with different rates of disease progression. Researchers at Amsterdam University Medical Centre in the Netherlands and University Hospital Basel in Switzerland used the SomaScan Assay to measure the levels of 1,129 proteins in plasma taken from: RRMS patients who progressed slowly over four years, RRMS patients who progressed rapidly over four years, PPMS patients and healthy controls. They identified eight previously unsuspected proteins that correlated with brain imaging and clinical assessments of MS progression. These results need to be validated in cohorts with longer follow-up but could provide new ways of predicting disease course, monitoring progression and evaluating the efficacy of treatments.

Di Narzo, AF *et al.* (2019) "High-Throughput Identification of the Plasma Proteomic Signature of Inflammatory Bowel Disease." *J Crohns Colitis* **13**(4): 462-471.

https://www.doi.org/10.1093/ecco-jcc/jjy190

In this article, investigators at the Icahn School of Medicine at Mount Sinai, Janssen R&D, Sema4 and Tongji University in China describe the largest proteomics study to date on inflammatory bowel disease (IBD). They used the SomaScan Assay to measure the levels of plasma proteins in two different cohorts of patients with colitis (UC) and Crohn's disease (CD), two well-characterized IBD subtypes. The plasma protein profiles of UC and CD patients were similar to each other but significantly different from those of healthy controls. The plasma proteomic data showed little correlation with blood and intestine transcriptomic data, which suggests that the complementary information provided by proteomics will offer a more expansive view of IBD biology.

Daniels, JR *et al.* (2019) "Stability of the human plasma proteome to pre-analytical variability as assessed by an aptamer-based approach." *J Proteome Res* **18**(10): 3661-3670.
https://www.ncbi.nlm.nih.gov/pubmed/31442052

In this study, a team led by scientists from the US Food and Drug Administration used the SomaScan Assay to assess whether differences in sample handling can affect blood test results. They measured the levels of 1,305 proteins in blood from 16 healthy donors that was collected and stored in 6 different ways. The levels of as many as 200 proteins changed significantly depending on how the samples were processed and each procedure had its own characteristic protein signature. The results suggest that variability in sample handling needs to be taken into account when measuring specific proteins in clinical testing, something SomaLogic has studied in detail to offer helpful guidance to sample providers.

Grover, M *et al.* (2019) "Proteomics in gastroparesis: unique and overlapping protein signatures in diabetic and idiopathic gastroparesis." *Am J Physiol Gastrointest Liver Physiol* **317**(5): G716-G726.

https://www.ncbi.nlm.nih.gov/pubmed/31482734

Gastroparesis, sometimes called stomach paralysis or delayed gastric emptying, is a condition in which food stays too long in the stomach. It can cause nausea, vomiting, abdominal pain, bloating, heartburn, poor blood sugar control and malnutrition. Gastroparesis most often occurs in long-term diabetics but can also happen post-surgery or for other unknown reasons (idiopathic disease).

In this article, a team led by scientists at the Mayo Clinic used the SomaScan Assay to measure the levels of 1,305 proteins in gastric tissue samples taken from 9 diabetic gastroparesis patients, 7 idiopathic gastroparesis patients and 5 healthy controls. Nearly twice as many proteins were significantly different in those with idiopathic compared to diabetic gastroparesis (132 vs. 73 proteins), which suggests that different biological processes function in different disease types. The study also revealed novel proteins that warrant further investigation as potential drug targets and markers of gastroparesis.

Suhre, K *et al.* (2019) "Fine-mapping of the human blood plasma N-glycome onto its proteome." *Metabolites* **9**(7): 122.

https://www.ncbi.nlm.nih.gov/pubmed/31247951

Proteins in the body are frequently modified by attached sugar “chains” that can affect their form, function and stability. The attachment site on the protein, the types of sugars in the chain and how the sugars are connected to one other can all vary tremendously, which makes protein-linked sugars very difficult to study. One type, known as “N-linked” sugars (attached to the protein through a nitrogen atom), has been associated with a variety of conditions including autoimmune disorders, chronic inflammation, neurological diseases and cancer.

In the first study of its kind, an international team led by researchers at Weill Cornell Medicine College in Qatar mapped the N-linked sugars found in blood plasma to their associated proteins. They used the SomaScan Assay to measure the levels of 1,129 proteins in plasma and in parallel analyzed the N-linked sugars cleaved off of the proteins. Analyzing 344 blood samples taken from individuals of Arab, South-Asian, and Filipino descent, they correlated 1116 blood circulating proteins with 113 types of sugars and replicated their results in 46 blood samples taken from individuals of European descent. Some of the protein-sugar associations confirmed previous results and some were entirely new. These findings represent a first step in understanding the roles of protein-attached sugars in both normal and disease processes.

Shimada, YJ *et al.* (2019) "Application of proteomics profiling for biomarker discovery in hypertrophic cardiomyopathy." *J Cardiovasc Transl Res* **12**(6): 569-579.

https://www.ncbi.nlm.nih.gov/pubmed/31278493

Hypertrophic cardiomyopathy (HCM) is a common genetic disorder, in which the heart muscle thickens and makes it increasingly harder for the heart to pump blood. Many people with HCM have no symptoms and are unaware that they have

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it, which is why it is the most common cause of sudden cardiac death in people under 30. Even with the help of advanced imaging techniques, HCM can be challenging to distinguish from other conditions, so there is a need for more accurate, rapid, low cost diagnostics. In this pilot study, researchers at Harvard Medical School, Columbia University Medical Center and the Korea Institute of Oriental Medicine used the SomaScan Assay to measure the levels of 1,129 proteins in plasma taken from 15 patients with HCM compared to 22 healthy controls. The researchers used computer modeling to identify the 50 most discriminant proteins, many of which correlated with known markers of advanced HCM. These findings may lead to development of a simple blood test to improve diagnostic accuracy and help understand the different biological processes that can lead to HCM.

Niewczas, MA *et al.* (2019) "A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes." *Nat Med* **25**(5): 805-813.

https://www.ncbi.nlm.nih.gov/pubmed/31011203

Diabetes is the leading cause of kidney disease worldwide, and diabetic kidney disease (DKD) is the leading cause of end-stage renal disease (ESRD). Chronic inflammation is believed to contribute to the progression of DKD to ESRD, although it is unclear how. To better understand the link between inflammation and DKD outcomes, an international team led by researchers at the Joslin Diabetes Center and Harvard University used a custom version of the SomaScan Assay to measure the levels of 194 circulating inflammatory proteins in samples collected from a group of 219 patients with type 1 diabetes and impaired kidney function. They found significantly higher levels of 35 proteins in individuals who later developed ESRD and validated 17 of the identified proteins in a group of 162 patients with type 2 diabetes. Sixteen of the 17 validated proteins were then replicated in a cohort of Pima Indians with normal renal function at the time of sample collection, which suggests that these proteins represent a kidney risk inflammatory signature (KRIS). Unexpectedly, the researchers found that the high levels of KRIS proteins originated outside of the kidney, which implies that DKD progression involves inflammation occurring in other parts of the body. Since the KRIS proteins are elevated in patients with different types of diabetes, different levels of kidney function and different ethnicities, they may prove to be universal markers of DKD that could be used to identify new therapeutic targets, predict risk of ESRD progression and measure response to treatments.

Wells, QS *et al.* (2019) "Accelerating biomarker discovery through electronic health records, automated biobanking, and proteomics." *J Am Coll Cardiol* **73**(17): 2195-2205.

https://www.ncbi.nlm.nih.gov/pubmed/31047008

In this article, a team led by researchers at Vanderbilt University Medical Center describe an automated strategy for finding new blood-based markers of disease. Vanderbilt maintains a biobank containing discarded plasma samples that are linked to de-identified electronic health records. The researchers developed computer algorithms to mine the health records and identify patients with heart failure. They then selected 96 patients (split evenly between those with and without heart failure) and used the SomaScan Assay to measure the levels of 1,129 proteins in their archived plasma samples. Nine candidate biomarkers of heart failure were identified and two proteins, angiopoietin-2 and thrombospondin-2, were subsequently validated in three different patient groups. The researchers found significantly higher levels of angiopoietin-2 and thrombospondin-2 in patients with acute heart failure that decreased after heart transplantation or left ventricular assist device implantation. When measured in combination with B-type natriuretic peptide levels (a common measure of cardiac

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function), angiopoietin-2 and thrombospondin-2 improved acute heart failure diagnosis beyond the current clinical standard. These results demonstrated a strategy for rapid biomarker discovery and identified two new proteins that may prove useful for diagnosing or predicting risk of heart failure.

Gordin, D *et al.* (2019) "Characterization of glycolytic enzymes and pyruvate kinase M2 in type 1 and 2 diabetic nephropathy." *Diabetes Care* **42**(7): 1263-1273

https://www.ncbi.nlm.nih.gov/pubmed/31076418

The Joslin Diabetes Center at Harvard Medical School runs a study of individuals who have lived with type 1 diabetes for at least 50 years. One of the goals is to determine what factors prevent “50-year Medalists” from developing serious diabetes-related complications such as nerve, heart and kidney disease. Less than 10% of 50-year Medalists have kidney problems, and previously Joslin scientists found that preserved kidney function correlated with elevated levels of proteins involved in glucose and mitochondrial metabolism. This article reports similar findings in post-mortem tissue taken from shorter-term type 1 diabetics and type 2 diabetics. In addition, the researchers used the SomaScan Assay to compare the levels of 1,129 plasma proteins in 50-year Medalists with and without moderate kidney damage. They confirmed elevated blood levels of 6 of the 14 protective proteins identified previously in tissue and found significantly decreased levels of many established markers of kidney damage. The researchers speculate that the circulating proteins could be helping the 50-year Medalists resist damage to other organs and could be useful for developing treatments that slow progression of diabetes-related complications.

Penn-Nicholson, A *et al.* (2019) "Discovery and validation of a prognostic proteomic signature for tuberculosis progression: a prospective cohort study." *PLoS Med* **16**(4): e1002781.

https://www.ncbi.nlm.nih.gov/pubmed/30990820

One third of the world’s population have tuberculosis (TB) bacteria lying dormant in their bodies. However, only five to ten percent of those with latent TB will go on to develop active disease. Identifying those individuals is critical for controlling the spread of new infections and for focusing precious treatment resources. An international team led by scientists at the University of Cape Town used the SomaScan Assay to measure the levels of 3040 proteins in plasma collected from TB-infected South African adolescents. They identified 135 proteins that were significantly different between those who progressed to active TB compared to those who did not. The researchers successfully validated two different sets of proteins that could predict the subset who went on to develop active TB within a year. Although more work is needed to meet the threshold of performance criteria defined by the World Health Organization, the results suggest that a blood-based protein test for determining TB progression is possible.

Mahendra, A *et al.* (2019) "Beyond autoantibodies: Biologic roles of human autoreactive B cells in rheumatoid arthritis revealed by RNA-sequencing." *Arthritis Rheumatol* **71**(4): 529-541.

https://www.ncbi.nlm.nih.gov/pubmed/30407753

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B cells are white blood cells that normally protect the body by producing antibodies against foreign invaders such as bacteria and viruses. However, in autoimmune diseases such as rheumatoid arthritis (RA), B cells mistakenly produce autoantibodies that attack the body’s own tissue. Depleting B cells helps some RA sufferers, but the effect isn’t correlated with fewer autoantibodies in the blood. To better understand how B cells contribute to RA, a team led by researchers at the University of Houston conducted the first comprehensive RNA sequencing of B cells isolated from the blood of RA patients. They used the SomaScan Assay to confirm key differences in the levels of circulating proteins in RA patients compared to healthy controls and identified several proteins that are targets of current FDA-approved drugs. These results improve our understanding of the roles that B cells play in RA and suggest strategies for repurposing existing drugs to treat RA and other autoimmune diseases.

Huang, G *et al.* (2019) "Circulating biomarkers of testosterone's anabolic effects on fat-free mass." *J Clin Endocrinol Metab* **104**(9): 3768-3778.

https://www.ncbi.nlm.nih.gov/pubmed/31120518

Loss of muscle mass and strength (sarcopenia) places older adults at risk of falls, disability, hospitalization and death. With a rapidly aging population, this is a huge potential public health problem. Currently, there are no FDA-approved treatments for sarcopenia, although some research suggests that taking hormones such as testosterone can add lean muscle mass. This study from researchers at Brigham and Women’s Hospital, Eli Lilly and Nordic Bioscience used a combination of antibody-based assays and the SomaScan Assay to measure protein changes in blood samples from a previous clinical trial in which testosterone was given to healthy young men whose normal testosterone production was suppressed. The researchers discovered four new proteins that changed in response to testosterone and that correlated with increases in lean muscle. These protein markers could serve as valuable tools for evaluating drug candidates for treating sarcopenia and warrant validation in older adults.

Mulla, CM *et al.* (2019) "Plasma FGF-19 levels are increased in patients with post-bariatric hypoglycemia." *Obes Surg* **29**(7): 2092-2099.

https://www.ncbi.nlm.nih.gov/pubmed/30976983

Gastric bypass and other bariatric surgeries can be effective treatments for severe obesity, but sometimes lead to dangerously low blood sugar (hypoglycemia), which in turn can lead to fainting, seizures, brain damage and even death. To better understand how post-bariatric hypoglycemia occurs, a team led by Harvard Medical School researchers examined the proteins in blood taken from individuals with or without hypoglycemia after undergoing gastric bypass surgery. Blood samples collected after an overnight fast and at 30 and 120 minutes after a liquid meal were analyzed using the SomaScan Assay. Seventeen of the 1,129 measured proteins were significantly different at all three time points in the hypoglycemic individuals, and the protein that showed the largest increase was fibroblast growth factor 19 (FGF19), a hormone secreted by the intestine that helps regulate fat absorption by the small intestine. Increased FGF19 levels are associated with many of the beneficial effects of bariatric surgery, such as long-term weight loss and diabetes remission. However, further studies are needed to understand the complex roles of FGF19 in glucose regulation and energy metabolism.

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Helfand, BT *et al.* (2019) "A novel proteomics approach to identify serum and urinary biomarkers and pathways that associate with lower urinary tract symptoms in men and women: pilot results of the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) study." *Urology* **129**: 35-42.

https://www.ncbi.nlm.nih.gov/pubmed/30922973

Lower urinary tract symptoms (LUTS) refer broadly to problems with urination or urine storage. LUTS occur in both men and women and can be caused by any number of conditions, which makes them difficult to evaluate and treat. In this pilot study, a team led by researchers at NorthShore University Health System used the SomaScan Assay to analyze blood and urine from participants in the Symptoms of Lower Urinary Tract Dysfunction Research Network run by the National Institute of Diabetes and Digestive and Kidney Diseases. The levels of 1,305 proteins were measured in samples from eighteen men or women with LUTS and compared to twelve matched controls. The SomaScan results from serum were much more reproducible than those from urine, and many more significant protein changes were seen in men than in women. Interestingly, the LUTS-associated proteins in men were not the same as those in women, which implies that the underlying causes of LUTS differ between sexes. This proof-of-concept study suggests that with further investigation in larger-scale studies, the SomaScan Assay could be used to find new biomarkers, to better understand causal factors and to develop more targeted treatment strategies for LUTS.

Zahedi-Amiri, A *et al.* (2019) "Influenza A virus-triggered autophagy decreases the pluripotency of human-induced pluripotent stem cells." *Cell Death Dis* **10**(5): 337.

https://www.ncbi.nlm.nih.gov/pubmed/31000695

Is it true that women who catch the flu while pregnant are at higher risk of delivering babies with birth defects? To better understand how the influenza virus affects cells during fetal development, researchers at the University of Manitoba used the SomaScan Assay to measure the levels of 1,307 proteins in influenza-infected compared to mock-infected cells. They infected adult cell mimics of embryonic stem cells and found that influenza virus reduced their viability and pluripotency, the critical property that allows embryonic stem cells to mature into all the different cell types that make up an adult body. The evidence is suggestive, but further studies are needed to understand specific processes that are disrupted by influenza virus and any subsequent negative effects on embryo development.

Tin, A *et al.* (2019) "Reproducibility and variability of protein analytes measured using a multiplexed modified aptamer assay." *J Appl Lab Med* **4**(1): 30-39.

https://www.ncbi.nlm.nih.gov/pubmed/31639705

The goal of this study by a team led by researchers at the Johns Hopkins Bloomberg School of Public Health was to evaluate the SomaScan Assay for conducting large-scale proteomic studies over time. Using plasma samples collected at multiple time points from 42 participants in the Atherosclerosis Risk in Communities Study (ARIC) study, the authors characterized the reproducibility of the SomaScan Assay as well as protein level changes that occurred both in the short term (four to nine weeks) and in long term (approximately 20 years). Reproducibility (assessed by splitting the collected plasma samples into two vials and running them separately) was excellent, with 89% of 3,693 proteins having a coefficient of variation less than 10%. Only one protein showed significant short-term variability, whereas 866 proteins showed significant

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changes over the long term. The observed long-term changes correlated well with patient demographics (e.g., age, sex, and race) and kidney function (which clears small proteins from the blood and diminishes with age). The authors concluded that the SomaScan Assay is highly reproducible for use in clinical assessments of protein changes over time.

Roh, JD *et al.* (2019) "Activin type II receptor signaling in cardiac aging and heart failure." *Sci Transl Med* **11**(482): eaau8680.

https://www.ncbi.nlm.nih.gov/pubmed/30842316

More than 6 million Americans are living with heart failure and 900,000 new cases are diagnosed each year. Age is a key risk factor, although it is not known why. In this study, a team led by Massachusetts General Hospital researchers identified activin type II receptor (ActRII) as an important link between aging and heart failure. The investigators reanalyzed SomaScan Assay data collected previously from 899 participants in the Framingham Heart Study and found that the levels of the protein follistatin-like 3 (FSTL3, an indicator of ActRII activity) increased with aging. They ran the SomaScan Assay on blood samples from an independent cohort of 50 people and found that circulating levels of FSTL3 also increased with frailty and worsening heart failure. In a mouse model of heart aging, the levels of the ActRII ligand activin A were three times higher in aged mice compared to young mice. Increasing the levels of circulating activin A in young mice led to cardiac dysfunction, whereas inhibiting ActRII improved cardiac function. The investigators found that ActRII signaling caused breakdown of SERCA2a, a protein critical for regulating heart function. Several ActRII inhibitors are currently being tested in humans for other indications, and these results suggest that they could also be useful for treating heart failure.

Mysona, D *et al.* (2019) "A combined score of clinical factors and serum proteins can predict time to recurrence in high grade serous ovarian cancer." *Gynecol Oncol* **152**(3): 574-580.

https://www.ncbi.nlm.nih.gov/pubmed/30578005

Although a relatively “rare” disease, over 20,000 women in the U.S. are diagnosed with ovarian cancer each year. Early detection of ovarian cancer is difficult and although most patients respond well to treatment, the rate of recurrence is 70-95% for those who were diagnosed in later stages of the disease. This suggests that undetectable cancer lives on in most women declared in remission. In this study, researchers at the Medical College of Georgia used the SomaScan Assay to identify proteins that predicted ovarian cancer recurrence. They measured the levels of 1,129 proteins in blood samples collected from 35 ovarian cancer patients during remission and identified changes in 86 proteins associated with patient survival. Twenty-six of these proteins were selected for further study, confirmed using an antibody-based assay, and validated in an additional 36 patients. The researchers used a computer algorithm to create a risk score (based on two clinical factors and eight proteins) that could predict the time to recurrence among advanced-stage patients. The results of this work are promising, but need to be validated for predicting patient outcomes in remission.

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Hemnes, AR *et al.* (2019) "Human PAH is characterized by a pattern of lipid-related insulin resistance." *JCI Insight* **4**(1): e123611.

https://www.ncbi.nlm.nih.gov/pubmed/30626738

In pulmonary arterial hypertension (PAH), narrowing or blockage of the small arteries in the lungs forces the heart to pump harder and harder until it eventually weakens and fails. PAH is associated with insulin resistance (IR), a condition where the body doesn't use insulin effectively. Insulin is important for metabolizing both glucose and lipids, and patients with PAH are known to have altered triglyceride and cholesterol levels. To better understand the connection between IR and PAH, a team led by researchers from Vanderbilt University Medical Center analyzed the proteins, metabolites and lipids in blood taken from PAH patients and triglyceride-matched controls. They used the SomaScan Assay to measure the levels of 1,139 proteins in fasting plasma and were able to easily distinguish those with PAH due to differences in proteins associated with insulin or lipid metabolism. The metabolite and lipid analyses showed more lipid-related, rather than glucose-related abnormalities in the PAH patients. These results provide new insights into the metabolic dysfunction and the possible consequences of IR in PAH.

Lynch, AM *et al.* (2019) "Proteomic profiles in advanced age-related macular degeneration using an aptamer-based proteomic technology." *Transl Vis Sci Technol* **8**(1): 14.

https://www.ncbi.nlm.nih.gov/pubmed/30697465

Age-related macular degeneration (AMD) is a progressive eye disease that is the leading cause of vision loss in people over fifty. There are two advanced forms of AMD, neovascular (in which abnormal blood vessels grow under the retina and leak fluid) and geographic atrophy (GA, in which patches of retinal cells die off). Neovascular AMD is treatable, although the response to treatment is variable, whereas there are currently no treatments for GA. In this pilot study, researchers at the University of Colorado School of Medicine and SomaLogic compared the circulating proteins of AMD patients to those of age-matched controls. They used the SomaScan Assay to measure the levels of 4,001 proteins in plasma samples from 10 patients with neovascular AMD, 10 patients with GA, and 10 patients with cataracts but no AMD. They identified four proteins that were significantly different among the patients with AMD. Compared to controls, patients with neovascular AMD had higher levels of vinculin and lower levels of CD177, whereas patients with GA had higher levels of neuregulin-4 and lower levels of soluble intercellular adhesion molecule-1. The authors used computational tools to look for coordinated changes in proteins and found that different biological processes were associated with GA vs. neovascular AMD. These results, if validated in larger studies, could provide insight into the causes of AMD and lead to blood-based protein biomarkers for specific AMD diagnosis, progression and treatment response.

Ko, D *et al.* (2019) "Proteomics profiling and risk of new-onset atrial fibrillation: Framingham Heart Study." *J Am Heart Assoc* **8**(6): e010976.

https://www.ncbi.nlm.nih.gov/pubmed/30841775

Atrial fibrillation (AF) is a common cardiac arrhythmia that occurs when the chambers of the heart beat out of sync. Although some people report mild or no symptoms, if left untreated AF can increase the likelihood of blood clot formation and stroke.

As the global population continues to age, new cases of AF are predicted to rise dramatically, so improved methods of detection, prevention and treatment are needed. This study, led by a team of researchers at the Boston University School of Medicine, used the SomaScan Assay to look for protein markers of new-onset AF. They measured the levels of 1,373 proteins in blood samples obtained from 1,885 participants in the Framingham Heart Study (a long-term study of cardiovascular health and disease), 349 of whom later developed AF. They identified eight proteins that correlated with increased AF risk, none of which were coded by genetic variants identified in previous genome-wide association studies of AF. Two of the proteins, N-terminal pro-B-type natriuretic peptide and ADAMTS 13, remained significantly associated even after accounting for clinical risk factors of AF, such as smoking, weight, blood pressure, and diabetes. N-terminal pro-B-type natriuretic peptide is produced in response to changes in pressure inside the heart and has been previously linked to new-onset AF. ADAMTS 13 is involved in blood clotting and could help explain the increase in heart attacks and strokes seen in those with AF. Future studies are needed to replicate the findings and establish whether changes in the identified proteins could be used to predict the risk of developing AF.

Bodewes, ILA *et al.* (2019) "Fatigue in Sjögren's syndrome: a search for biomarkers and treatment targets." *Front Immunol* **10**: 312.

https://www.ncbi.nlm.nih.gov/pubmed/30863411

Primary Sjögren’s syndrome (pSS) is a disease in which the immune system attacks the salivary glands. In addition to dry mouth and dry eyes, one of the most common symptoms of pSS is debilitating fatigue. To gain insight into the causes of fatigue in pSS sufferers, researchers at Erasmus University Medical Center in the Netherlands used the SomaScan Assay to compare the levels of 1,300 proteins in blood samples taken from 63 pSS patients and 20 healthy controls. A total of 104 proteins were significantly different between the two groups, and 16 proteins were significantly different between fatigued and non-fatigued patients. When possible, the proteins identified by SomaScan were validated using conventional antibody-based techniques, which showed good correlations and reliability. Fatigued pSS patients showed increased levels of several proteins that promote inflammation as well as various proteins that function in the brain. Although proinflammatory processes have been suspected to play a role in fatigue, this is the first evidence of a link in pSS. The ‘fatigue signature’ proteins need to be validated in larger cohorts but could be very useful for identifying therapeutic targets and developing potential treatments for those with pSS.

Desai, VG *et al.* (2019) "Candidate early predictive plasma protein markers of doxorubicin-induced chronic cardiotoxicity in B6C3F1 mice." *Toxicol Appl Pharmacol* **363**: 164-173. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/30517846

Anthracyclines such as doxorubicin (DOX) are among the most effective drugs for treating a variety of cancers. However, they often lead to heart damage, which can occur even decades after chemotherapy has ended. In this preclinical study, a team led by researchers at the U.S. Food and Drug Administration used the SomaScan Assay to measure the levels of 1,129 proteins in mice treated with DOX compared to mice treated with saline. They identified 18 proteins whose levels were significantly different in DOX-treated mice during eight weeks of treatment. Further studies are needed to determine if changes in these candidate proteins could predict or detect the cardiotoxic effects of DOX in humans.

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Michelsen, TM *et al.* (2019) "The human placental proteome secreted into the maternal and fetal circulations in normal pregnancy based on 4-vessel sampling." *FASEB J* **33**(2): 2944-2956. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/30335547

The placenta is a critical organ that produces hormones, growth factors and other proteins that are secreted into the mother's or child's blood to ensure healthy pregnancy and normal development. In this article, a team led by researchers in Norway describe the use of a novel technique to obtain fetal and maternal blood samples going into and out of the placenta for 35 healthy women who had term pregnancies. They used the SomaScan Assay to compare differences in the levels of 1,310 blood proteins from maternal and fetal veins and arteries. Thirty-four proteins were significantly secreted by the placenta into the maternal blood and 341 proteins were significantly secreted by the placenta into the fetal blood. Using blood collected serially through pregnancy, they found that 8 of the 34 proteins secreted into the maternal circulation changed significantly across gestation. These results should help identify potential protein markers of normal fetal and maternal changes during pregnancy and provide greater insight the many functions of the human placenta.

Foulkes, AC *et al.* (2019) "A framework for multi-omic prediction of treatment response to biologic therapy for psoriasis." *J Invest Dermatol* **139**(1): 100-107.

https://www.ncbi.nlm.nih.gov/pubmed/30030151

In this article, a team led by British researchers looked at the effect of the drug etanercept on a small group of patients with psoriasis, a skin condition characterized by dry, scaly lesions. Participants were assessed before etanercept treatment, one week after and 12 weeks after using the Psoriasis Area and Severity Index (PASI) to gauge response. The researchers used the SomaScan Assay to measure the levels of proteins in patient blood samples and sequencing methods to measure RNA levels in blood and skin samples. Etanercept blocks the protein tumor necrosis factor (TNF), and the researchers found an association between drug response and TNF-regulated genes in blood and skin. The results from this pilot study suggest that blood-based biomarkers may be informative predictors of response to psoriasis treatments.

Wu, D *et al.* (2019) "Osteitis is associated with dysregulated pro-osteoblastic activity in patients with nasal polyps." *Laryngoscope* **129**(3): E102-E109. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/30537181

Nocera, AL *et al.* (2019) "Exosome swarms eliminate airway pathogens and provide passive epithelial immunoprotection through nitric oxide." *J Allergy Clin Immunol* **143**(4): 1525-1535 e1521. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/30442371

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Mueller, SK *et al.* (2019) "Noninvasive exosomal proteomic biosignatures, including cystatin SN, peroxiredoxin-5, and glycoprotein VI, accurately predict chronic rhinosinusitis with nasal polyps." *Int Forum Allergy Rhinol* **9**(2): 177-186. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/30485711

Three different studies led by Benjamin S. Bleier's group at Harvard Medical school used the SomaScan Assay to better understand the biology of the human nasal cavity.

Wu *et al.* measured the levels of proteins in nasal mucus taken from people who suffer from chronic rhinosinusitis with nasal polyps (CRSwNP). CRSwNP is a chronic nasal inflammation condition whose severity and resistance to treatment is often associated with bone inflammation (osteitis) in the sinus walls. Bone morphogenic proteins (BMPs) were significantly reduced in samples obtained from sites of osteitis in CRSwNP patients compared to healthy controls. These results suggest that BMPs, which help maintain healthy bones, may be driving osteitis and could be targets for therapeutic interventions in patients with CRSwNP.

Nocera *et al.* analyzed the proteins contained in exosomes (small sacs shed by cells) isolated from nasal mucus. They found that exposure to LPS (a molecule present in bacteria) doubled the numbers of exosomes that were produced as well as their associated antimicrobial proteins. These exosome 'swarms' may help protect us when we inhale pathogens such as bacteria.

Mueller *et al.* measured proteins in exosomes isolated from nasal mucus taken from CRSwNP patients. They found a unique protein signature that could provide a noninvasive method of detecting CRSwNP and also suggests new potential therapeutic targets for the disease.

Liang, X *et al.* (2019) "Assessing the genetic correlations between blood plasma proteins and osteoporosis: a polygenic risk score analysis." *Calcif Tissue Int* **104**(2): 171-181.

https://www.ncbi.nlm.nih.gov/pubmed/30306195

In this study, Chinese researchers evaluated the potential effects of circulating proteins on the development of osteoporosis. They measured genetic differences and bone mass density (BMD) in 2,286 American Caucasians and then calculated the aggregate influence of multiple genetic markers on 267 plasma proteins that had been previously identified in a SomaScan study that linked protein levels and genetic variants to disease (see Suhre, K *et al.* (2017) *Nat Commun* **8**: 14357; https://doi.org/10.1038/ncomms14357). They found genetic correlations between BMD and 41 blood proteins. Some of the proteins had been previously associated with osteoporosis but some were entirely new. These results may provide new insights into the biological causes of osteoporosis and possible new targets for therapeutic interventions.

Halama, A *et al.* (2019) "Metabolic and proteomic signatures of hypoglycaemia in type 2 diabetes." *Diabetes Obes Metab* **21**(4): 909-919.

https://www.ncbi.nlm.nih.gov/pubmed/30525282

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Hypoglycemic episodes – when blood sugar levels are too low – place diabetics at greater risk of developing complications such as heart arrhythmias and seizures. To better understand how the body responds to low blood sugar, an international team led by researchers at Weill Cornell Medicine Qatar looked at the effects of hypoglycemia on blood metabolites and proteins in a small group of type 2 diabetics (T2D) compared to healthy controls. Mass spectrometry was used to analyze 955 metabolites, and the SomaScan Assay was used to measure the levels of 1,125 proteins in blood samples collected sequentially: after an overnight fast, after returning blood glucose to normal levels for one hour, after inducing hypoglycemia for one hour, and after another overnight fast. Under hypoglycemic conditions, the metabolites that were altered in T2D were mostly involved in fatty acid metabolism. Since the heart uses fatty acids as an energy source under fasting conditions, this could help explain heart complications in T2D. The proteins that differed in T2D vs. controls were mostly involved in inflammation processes and included proteins that had been previously implicated in heart attacks. This study was the first to explore the biochemical consequences of an insulin-induced hypoglycemic event and suggests how low blood sugar could trigger cardiovascular events in diabetics.

Glover, KKM *et al.* (2019) "Vero cell proteomic changes induced by Zika virus infection." *Proteomics* **19**(4): e1800309.

https://www.ncbi.nlm.nih.gov/pubmed/30578658

—and—

Sher, AA *et al.* (2019) “Zika virus infection disrupts astrocytic proteins involved in synapse control and axon guidance.” *Front Microbiol* **10**: 596.

https://www.ncbi.nlm.nih.gov/pubmed/30984137

In 2016, following a series of outbreaks across the Americas, the World Health Organization declared Zika virus a long-term global health problem. Although Zika virus usually causes mild or no symptoms after infection, babies born to Zika virus-infected mothers are at increased risk of having severe neurological problems and brain defects. To better understand how Zika virus affects its host, the Coombs group at the University of Manitoba infected cells and then used the SomaScan Assay to monitor subsequent protein changes. Their results are reported in two different publications.

In Glover *et al.*, the researchers describe the use of African green monkey kidney (Vero) cells since Vero cells are easily infected by Zika virus and are commonly used to test antiviral drugs. They measured the levels of 1,322 proteins up to 48 hours after infection and identified 125 that changed significantly compared to mock-infected controls. Many of the proteins that increased are associated with the immune system’s first line of defense against pathogens.

In Sher *et al.*, the researchers document the use of more physiologically relevant human astrocyte (U251) cells. Astrocytes are one of the most abundant cell types in the central nervous system and serve as entry points for Zika virus infection of the brain. Viral infection of U251 cells caused significant changes in the levels of 170 proteins compared to mock-treated controls, most of these protein differences had not been seen previously in Vero cells. Computational analysis of the processes affected by the differentially produced proteins predicted impacts on brain development and neurotransmission. Further analysis of the similarities and differences in Vero and U251 cell responses to Zika virus infection is underway to help identify candidate protein targets for diagnostic development and therapeutic interventions.

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Xie, Z *et al.* (2018) "Adrenomedullin surges are linked to acute episodes of the systemic capillary leak syndrome (Clarkson disease)." *J Leukoc Biol* **103**(4): 749-759.

https://pubmed.ncbi.nlm.nih.gov/29360169/

Systemic capillary leak syndrome (SCLS), also known as Clarkson's disease, is a rare but potentially fatal disorder in which small blood vessels suddenly leak massive amounts of fluid into surrounding tissues (up to 70% of total plasma). This can cause very low blood pressure, blood thickening and edema that can damage limbs, nerves and organs. The causes of SCLS are unknown, and its rareness means that it is also frequently misdiagnosed. Since there is no cure, recognizing and managing the symptoms during disease episodes is the only treatment. In this study, a team led by researchers from the National Institutes of Health used the SomaScan Assay to measure the levels of over 1,300 proteins in nine matched pairs of plasma taken during SCLS flare and remission and identified 612 proteins that were more than two-fold changed and 81 proteins that were more than three-fold changed. Many of the proteins found to be elevated in SCLS flares are released by neutrophils, white blood cells that fight off infections. The researchers also found that the factors released by activated neutrophils increased permeability of cells that line blood vessels, which could explain the fluid leakage that occurs during SCLS episodes. The results of this study provide insight into disease mechanisms and offer potential protein biomarkers to improve SCLS diagnosis and treatment.

Hok, AHYS *et al.* (2019) "Guidelines for CSF Processing and Biobanking: Impact on the Identification and Development of Optimal CSF Protein Biomarkers." *Methods Mol Biol* **2044**: 27-50.

https://www.doi.org/10.1007/978-1-4939-9706-0_2

This protocol from researchers at VU University Medical Center in the Netherlands shows the impact of delayed storage and freeze/thaw conditions on cerebrospinal fluid samples measured using the SomaScan Assay.

Simats, A *et al.* (2019) "Application of an Aptamer-Based Proteomics Assay (SOMAscan) in Rat Cerebrospinal Fluid." *Methods Mol Biol* **2044**: 221-231. **(Subscription required)**

https://www.doi.org/10.1007/978-1-4939-9706-0_13

This protocol from researchers at Universitat Autònoma de Barcelona in Spain details the processing steps for analyzing cerebrospinal fluid (CSF) using the SomaScan Assay and its application to neurological biomarker discovery.

Lukjanenko, L *et al.* (2019) "Aging Disrupts Muscle Stem Cell Function by Impairing Matricellular WISP1 Secretion from Fibro-Adipogenic Progenitors." *Cell Stem Cell* **24**(3): 433-446 e437.

https://www.doi.org/10.1016/j.stem.2018.12.014

Aging affects the function of fibroadipogenic progenitors (FAPs), cells that help coordinate muscle repair following injury. In this article, a team led by researchers at Nestlé Research used a combination of transcriptomic and SomaScan proteomic

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profiling to show that aged mouse FAPs produce less of the protein WISP1. Restoring WISP1 levels rescued muscle regeneration, suggesting a potential therapy for rejuvenating aged muscles.

Masvekar, R *et al.* (2018) "Cerebrospinal fluid biomarkers link toxic astrogliosis and microglial activation to multiple sclerosis severity." *Mult Scler Relat Disord* **28**: 34-43.

https://www.ncbi.nlm.nih.gov/pubmed/30553167

Multiple sclerosis (MS) is a chronic disease in which the myelin sheath that surrounds and protects nerve fibers erodes, resulting in a wide range of neurological problems. Disease progression is largely unpredictable, but generally falls into one of three types: Relapsing-Remitting (RR-MS, characterized by flare-ups followed by periods of remission), primary progressive (PP-MS, characterized by steady worsening of symptoms) and secondary progressive (SP-MS, characterized by an initial period of RR-MS followed by more continuous decline). There are very few treatment options once MS reaches a progressive stage and developing new therapies is difficult without ways of seeing inside a living brain to identify which cells and which biological processes to target. In this study, a team led by researchers at the NIH first used the SomaScan Assay to identify proteins produced by different types of nerve cells. They then used the SomaScan Assay to see whether the levels of these proteins differed in cerebral spinal fluid taken from healthy patients and those with different types of MS. They found two protein clusters, produced by glial cells, whose levels were elevated in MS patients and correlated with clinical measures of disease severity. Although this is a promising finding, further studies are needed to see if therapies that inhibit the glial cell activation that produces these proteins could slow MS disease progression.

Mosley, JD *et al.* (2018) "Probing the virtual proteome to identify novel disease biomarkers." *Circulation* **138**(22): 2469-2481.

https://www.ncbi.nlm.nih.gov/pubmed/30571344

Thousands of proteins circulate throughout the body and facilitate information exchange between various cells, tissues and organs. Tapping into these protein communication networks is therefore an effective strategy for finding new disease biomarkers. However, measuring thousands of blood proteins can be costly and difficult to implement across tens of thousands of samples. In this study, a team led by researchers at Vanderbilt University Medical Center and Beth Israel Deaconess Medical Center conducted “virtual proteomic” screening by leveraging genetic variation and SomaScan Assay data from several hundred individuals to predict the levels of 268 blood proteins in >40,000 individuals. Using electronic health record data, they found 55 proteins that associated with 89 different clinically diagnosed conditions. The predicted levels of select proteins associated with cardiovascular disease were then validated directly using SomaScan Assay data from a different cohort, and two promising blood-based markers of atherosclerosis were identified. This study illustrates how computational prediction can overcome many of the challenges of direct sample testing and has the potential to accelerate discovery of new markers of disease.

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Dubin, RF *et al.* (2018) "Proteomic analysis of heart failure hospitalization among patients with chronic kidney disease: the Heart and Soul Study." *PLoS One* **13**(12): e0208042.

https://www.ncbi.nlm.nih.gov/pubmed/30557359

People with chronic kidney disease (CKD), even mild to moderate disease, are much more likely to die of heart failure than renal failure. Decreased kidney function also correlates with increased cardiovascular risk for patients without CKD, although it is unclear why. To gain insight into this association, investigators at the San Francisco Veterans Affairs Medical Center and the University of California, San Francisco analyzed circulating proteins in blood samples taken from patients with and without CKD, some of whom had been later hospitalized due to heart failure. The levels of 1068 unique proteins in plasma samples from 976 patients were measured using the SomaScan Assay. Four proteins were predictive of heart failure among those with CKD. One protein – called NOTCH1 – regulates new blood vessel formation and was associated with lower risk of heart failure only in CKD patients. These results suggest that the causes of cardiovascular disfunction differ between patients with and without CKD and if validated, could lead to more targeted therapies for patients with CKD.

Giudice, V *et al.* (2018) "Aptamer-based proteomics of serum and plasma in acquired aplastic anemia." *Exp Hematol* **68**: 38-50.

https://www.ncbi.nlm.nih.gov/pubmed/30312735

Acquired aplastic anemia (AA) is a rare disease in which the body's immune cells attack the bone marrow so it can't produce blood cells. In cases where a bone marrow transplant is not possible, immunosuppressive therapies (IST) are used, although it's unclear how they work. In this article, researchers from the National Institutes of Health used the SomaScan Assay to measure protein levels in blood serum and plasma taken from AA patients before and after IST and compared them to healthy controls. They identified 28 plasma and 19 serum proteins as candidate markers of AA responsiveness to IST, some of which may play roles in blood cell production and renewal. Although the functions of these proteins require further study, the work illustrates the power of the SomaScan Assay for large-scale screening of new biomarkers for disease and therapeutic response.

DeBoer, EM *et al.* (2018) "Novel application of aptamer proteomic analysis in cystic fibrosis bronchoalveolar lavage fluid." *Proteomics Clin Appl* **13**(3): e1800085. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/30431231

Cystic fibrosis (CF) is an inherited disease that causes thick mucus to accumulate in the lungs, which leads to persistent infections that damage the lungs. CF progression varies widely from person to person but involves periodic episodes with severe symptoms that require prompt and aggressive treatment. Better methods for predicting and responding to "lung attacks" would greatly help CF disease management. This article from a team led by researchers at the University of Colorado, Denver used the SomaScan Assay to measure the levels of 1,129 proteins in bronchoalveolar lavage fluid from children with CF compared to healthy controls. The CF protein signatures were easily distinguished from controls and could be further differentiated into two groups based on the type of inflammation and infection. These results demonstrate how unbiased protein analysis can be used to discern CF subtypes and lead to improved, more targeted disease management.

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Conklin, LS *et al.* (2018) "Serum biomarkers of glucocorticoid response and safety in anti-neutrophil cytoplasmic antibody-associated vasculitis and juvenile dermatomyositis." *Steroids* **140**: 159-166.

https://www.ncbi.nlm.nih.gov/pubmed/30352204

Juvenile dermatomyositis (JDM) and anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) are rare, chronic inflammatory diseases that are typically treated using steroid hormones called glucocorticoids. Long-term treatment with glucocorticoids can have serious effects on health, including bone fragility, muscle weakness, diabetes and hypertension. A previous study that had used the SomaScan Assay to assess the effects of glucocorticoids on patients with Duchenne muscular dystrophy (DMD), identified 11 protein markers of treatment efficacy and 7 protein markers of safety. This study led by researchers at ReveraGen Biopharma and the State University of New York at Binghamton evaluated whether these 18 proteins could also serve as biomarkers of glucocorticoid treatment in patients with JDM and AAV. Using serum samples that had been obtained from patients with active disease both before and after glucocorticoid treatment, the researchers validated 10 of 11 efficacy and 6 of 7 safety biomarker proteins for JDM and 8 of 11 efficacy and 5 of 7 safety biomarker proteins for AAV. These results suggest that measurement of these proteins may help assess new drug candidates as alternatives to glucocorticoids for treating JDM, AAV and potentially other inflammatory disorders.

Jung, YJ *et al.* (2018) "Clinical validation of a protein biomarker panel for non-small cell lung cancer." *J Korean Med Sci* **33**(53): e342.

https://www.ncbi.nlm.nih.gov/pubmed/30595683

Lung cancer is the most common cancer worldwide. Lung cancer screening is typically done using low-dose computerized tomography (LDCT). However, LDCT scans have difficulty discriminating between malignant and benign lung abnormalities, so it is unclear whether the benefits of LDCT outweigh the risks. In a previous study, Jung *et al.* used results from the SomaScan Assay to develop a seven-protein biomarker panel for lung cancer (see Jung, YJ *et al.* (2017) *Clin Lung Cancer* **18**(2): e99-e107; https://doi.org/10.1016/j.cllc.2016.09.012). In this article, the investigators validated the panel's performance using blood serum samples taken from 200 patients with Stage I-IV non-small cell lung cancer and 200 patients with benign lung nodules. The panel performed well at discriminating those with cancer from the controls and could potentially complement LDCT in lung cancer screening.

Santos-Parker, JR *et al.* (2018) "Habitual aerobic exercise and circulating proteomic patterns in healthy adults: relation to indicators of healthspan." *J Appl Physiol (1985)* **125**(5): 1646-1659.

https://www.ncbi.nlm.nih.gov/pubmed/30236049

In the first study of its kind, researchers at the University of Colorado, Boulder found that regular aerobic exercise is reflected in changes in the proteins that circulate in the blood. They used the SomaScan Assay to measure the levels of 1,129 proteins in the plasma of healthy sedentary men and women compared to those exercise regularly. They identified ten distinct protein patterns, nine of which associated with exercise status, sex, and/or age. Five of the exercise-influenced patterns also correlated with clinical health measures such as blood pressure, insulin resistance, aerobic capacity and blood

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vessel function. Exercise altered the levels of proteins involved in wound healing, cell death, as well as stress and immune responses. This pilot study illustrates how circulating proteins are modulated by exercise and could potentially be used as measures of healthy lifespan.

Conklin, LS *et al.* (2018) "Phase IIa trial in Duchenne muscular dystrophy shows vamorolone is a first-in-class dissociative steroidal anti-inflammatory drug." *Pharmacol Res* **136**: 140-150.

https://www.ncbi.nlm.nih.gov/pubmed/30219580

In this article, a team led by researchers at the University of Pittsburgh and ReveroGen Biopharma describes the first-in-patient study of vamorolone, a first-in-class steroidal drug for treatment of Duchenne muscular dystrophy (DMD). DMD is a rare muscle wasting disease that affects primarily young boys. The DMD standard of care is treatment with glucocorticoids, which help slow disease progression but have severe side effects. In a multiple-ascending dose study, vamorolone was safe and well-tolerated in boys with DMD. The SomaScan Assay was used to compare protein levels at baseline and after two weeks of daily vamorolone treatment at four different dose levels. Vamorolone treatment led to decreased serum creatine kinase, a marker of muscle disease activity as well as decreases in levels of inflammatory proteins. These results suggest that vamorolone has a beneficial effect and an anti-inflammatory mechanism of action.

Curran, AM *et al.* (2018) "A proteomic signature that reflects pancreatic beta-cell function." *PLoS One* **13**(8): e0202727.

https://www.ncbi.nlm.nih.gov/pubmed/30161145

Beta cells in the pancreas produce and secrete insulin to help ensure that blood sugar levels stay in the normal range. Decreased beta cell function is a precursor to type 2 diabetes. In this study, researchers at University College Dublin, University of Trento, and Nestlé Institute of Health Sciences used the SomaScan Assay to measure the levels of 1,129 protein in blood samples taken from 100 participants in an Irish study of metabolism. They identified 22 proteins that correlated with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and 17 proteins that correlated with Disposition Index, two common methods for assessing beta cell function. These results, which still need validation, suggest that a panel of proteins might enable early detection of beta cell dysfunction to allow interventions that slow or even halt progression of diabetes.

Kollar, B *et al.* (2018) "Increased levels of circulating MMP3 correlate with severe rejection in face transplantation." *Sci Rep* **8**(1): 14915.

https://www.ncbi.nlm.nih.gov/pubmed/30297859

Whereas solid organ transplantation has a rejection rate of 10-20%, face transplantation—which involves replacing some or all of a patient's face with one taken from a cadaver—has a rejection rate of >80% within the first year. Skin biopsy is the gold standard for assessing tissue rejection but puts the patient at further risk of infection, bleeding, or scarring. A less invasive method for routinely monitoring face transplant recipients is thus needed. In a pilot study, researchers from Brigham

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and Women’s hospital, Beth Israel Deaconess Medical Center and Harvard University used the SomaScan Assay to look for biomarkers that predict face transplant rejection. They measured the levels of 1,310 proteins in 24 serum samples taken from 6 patients at different times after their face transplant operation. Five of the samples were taken during rejection episodes that could be managed by immunosuppressive drugs (“non-severe”), 6 samples were from episodes that required more aggressive treatment (“severe”), and 13 samples were from “no-rejection” episodes. Five proteins—MMP3 (matrix metalloproteinase 3), ACY1 (aminoacylase-1), IL1R2 (interleukin-1 receptor type 2), SERPINA4 (kallistatin) and CPB2 (carboxypeptidase B2)—were significantly increased in the severe compared to non-severe or no-rejection samples. MMP3 levels alone were sufficient to diagnose severe rejection with 83.33% sensitivity and 100% specificity. If validated, these results could lead to a less-invasive way of identifying acute rejection as well as the best treatment strategy for face transplant patients.

Dudani, JS *et al.* (2018) "Classification of prostate cancer using a protease activity nanosensor library." *Proc Natl Acad Sci U S A* **115**(36): 8954-8959.

https://www.ncbi.nlm.nih.gov/pubmed/30126988

Prostate cancer is the most prevalent non-skin cancer and the second leading cause of cancer deaths in American men. Elevated blood levels of prostate specific antigen (PSA) is typically used to screen for prostate cancer, but there is some debate over its usefulness since PSA often flags noncancerous conditions or slow-growing tumors that do not require invasive biopsies or treatments. To find better disease markers, researchers at MIT, Brigham and Women’s Hospital, Harvard Medical School and the Broad Institute of MIT and Harvard used RNA data in The Cancer Genome Atlas and protein data from a SomaScan analysis to look for enzymes like PSA that are overproduced in prostate cancer vs. normal tissue. They identified 19 different prostate cancer-associated enzymes and developed a biosensor panel that could measure their activities in urine. The biosensor panel successfully classified more aggressive cancer types and outperformed PSA in a mouse model of the disease. This work lays the foundation for an improved test for diagnosis and prognosis of human prostate cancer.

Rice, LM *et al.* (2018) "Serum biomarker for diagnostic evaluation of pulmonary arterial hypertension in systemic sclerosis." *Arthritis Res Ther* **20**(1): 185.

https://www.ncbi.nlm.nih.gov/pubmed/30115106

Systemic scleroderma (SSc) is a rare disease of unknown origin characterized by hardening of the skin and abnormalities in small blood vessels. High blood pressure in the arteries that go from the heart to the lungs (pulmonary arterial hypertension, PAH) is the most common cause of death in SSc patients, with a 3-year survival rate of approximately 50%. Early detection of SSc-PAH is difficult since accurate diagnosis requires highly invasive heart catheterization. In this study, researchers at Boston University School of Medicine, Tufts University and University of Pittsburgh Medical Center used the SomaScan Assay to look for blood-born protein markers of SSc-PAH. They found 82 proteins (32 increased; 50 decreased) that differed significantly in serum samples taken from 13 SSc-PAH subjects compared to 16 SSc controls. The combination of two proteins (Follistatin-like 3 and Midkine) was able to distinguish SSc patients with PAH in two independent cohorts with high accuracy. This suggests that Follistatin-like 3 and Midkine could be helpful in diagnosing SSc-PAH and may be potential drug targets for early intervention.

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Altieri, A *et al.* (2018) "Cytokines IL-17, TNF and IFN-gamma alter the expression of antimicrobial peptides and proteins disparately: a targeted proteomics analysis using SomaScan technology." *Vaccines (Basel)* **6**(3): 51.

https://www.ncbi.nlm.nih.gov/pubmed/30087279

The body produces antimicrobial peptides and proteins (APPs) that can directly kill foreign pathogens and modulate the immune response. To better understand how APPs work in fighting lung infections, researchers at the University of Manitoba used the SomaScan Assay to measure the levels of 39 APPs produced by bronchial cells before and after being stimulated by either interleukin-17 (IL-17), tumor necrosis factor (TNF), or interferon-γ (IFN-γ); three proteins that enhance airway inflammation. TNF and IL-17 caused similar responses, but IFN-γ was quite distinct. These results suggest that the presence of different inflammatory proteins can affect APP production and infection control.

Mueller, SK *et al.* (2018) "Highly multiplexed proteomic analysis reveals significant tissue and exosomal coagulation pathway derangement in chronic rhinosinusitis with nasal polyps." *Int Forum Allergy Rhinol* **8**(12): 1438-1444. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/30091854

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a serious inflammatory condition with symptoms such as facial pain/pressure, loss of sense of smell/taste, runny nose, congestion, and post-nasal drip that last for months. Little is known about the causes and drivers of CRSwNP, so even after surgery, sufferers are rarely fully cured. Managing CRSwNP costs billions of dollars each year. In this article, researchers at Harvard Medical School, Friedrich-Alexander University Erlangen-Nürnberg, and Beth Israel Deaconess Medical Center describe how they used the SomaScan Assay to measure the levels of 1,305 proteins in nasal tissue and exosomes (small sacs secreted by cells) in nasal mucus. They found that proteins that promote blood clotting were significantly increased and proteins that prevent blood clots from becoming too large were significantly decreased in CRSwNP tissue compared to healthy controls. The inverse was seen in the CRSwNP nasal mucus exosome samples, although it is unclear why. The results confirm other observations that implicated coagulation-related proteins in CRSwNP. Twelve of the 23 coagulation-related proteins identified by the SomaScan Assay represent entirely new potential biomarkers for disease. The results provide insight into the pathology of CRSwNP that could lead to better treatments or a diagnostic based on proteomic analysis of exosomes that replaces invasive tissue biopsies.

Patel, V *et al.* (2018) "Aptamer-based search for correlates of plasma and serum water T2: implications for early metabolic dysregulation and metabolic syndrome." *Biomark Res* **6**: 28.

https://www.ncbi.nlm.nih.gov/pubmed/30237882

Metabolic syndrome is a set of inter-related conditions—high blood pressure, high blood sugar, high cholesterol, and excess abdominal fat—that increase the risk of developing heart disease and diabetes. In a previous study, researchers at University of North Texas Health Science Center and the Texas Tech University Health Sciences Center School of Medicine demonstrated that the motional properties of water in a plasma or serum sample (as measured by a spectroscopy parameter

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called “water T2”) can serve as a biomarker of metabolic disease. In this study, the researchers used the SomaScan Assay to measure the levels of 1,310 proteins and identified five new proteins that were predictive of water T2. Three of the proteins had been previously associated with cardiometabolic diseases, and two were entirely new. The results illustrate the value of the SomaScan Assay in unbiased biomarker discovery and provide new insights into the pathophysiology of metabolic syndrome.

Yao, C *et al.* (2018) "Genome-wide mapping of plasma protein QTLs identifies putatively causal genes and pathways for cardiovascular disease." *Nat Commun* **9**(1): 3268.

https://www.ncbi.nlm.nih.gov/pubmed/30111768

It is very difficult to establish whether proteins that are linked to a particular disease actually play causal roles. To bridge this knowledge gap, a team led by researchers at the NIH and the Framingham heart study examined whether circulating proteins known to have strong associations to cardiovascular disease (CVD) also have links to CVD-risk mutations. They identified over 16,000 gene variants that associated with 57 CVD-related proteins in Framingham heart study participants, and then used the SomaScan Assay to measure protein levels in blood samples from two independent cohorts to help validate the results. Eight of the proteins predicted new CVD events in Framingham heart study participants with long-term follow up. These results demonstrate that linking genetic variants to proteins can help identify putative causal roles in disease.

Han, Z *et al.* (2018) "Validation of a novel modified aptamer-based array proteomic platform in patients with end-stage renal disease." *Diagnostics (Basel)* **8**(4): 71.

https://www.ncbi.nlm.nih.gov/pubmed/30297602

This study from a team led by researchers at University of Tennessee Health Science used the SomaScan Assay to measure the levels of 1317 proteins in plasma samples from patients with end stage renal disease (ESRD). The results for three proteins associated with adverse outcomes in patients with ESRD were then validated using traditional antibody-based methods. Good but not perfect correlations were seen that suggest that the SomaScan has potential for identifying new prognostic indicators for ESRD.

Emilsson, V *et al.* (2018) "Co-regulatory networks of human serum proteins link genetics to disease." *Science* **361**(6404): 769-773.

https://www.ncbi.nlm.nih.gov/pubmed/30072576

In this article, researchers from Novartis and the Icelandic Heart Association demonstrated that communication between networks of proteins can explain the connections between genes and complex disorders, such as heart disease and diabetes. They began with an established Icelandic study of aging (AGES-Reykjavik), which initially focused on understanding the role of genetic variations in late-onset, age-related diseases. Participants in AGES-Reykjavik were over 65 and included both healthy adults and those diagnosed with various conditions of old age. However, linking individual gene

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variants to disease proved almost impossible since common chronic conditions of aging are not caused by defects in a single gene.

In the study, the research teams used a custom version of the SomaScan Assay to measure the levels of over 4,000 different human proteins in 5,457 blood samples from individuals in the AGES-Reykjavik study. Using advanced computational tools to mine approximately 27 million protein measurements, the researchers found that the examined proteins clustered into 27 different groups or “networks” composed of 20 to 921 proteins. Each network contained a few central players that were highly connected, and these “hub proteins” seemed to organize interactions and information flow within the network. When investigators incorporated genetic data on AGES participants, they found that the hub proteins were often regulated by genetic variations that had been previously linked to cardiovascular and metabolic diseases, but for which the biological underpinnings were unknown.

These findings show how the thousands of proteins detectable in the blood can facilitate communication between the various cells, tissues and organs of the body. Using the SomaScan Assay to “listen into” these communication networks may reveal new ways to detect, predict, monitor and even treat common age-related disorders.

Coca, SG (2018) ""Scanning" into the future: the promise of SomaScan technology for kidney disease." *Kidney Int Rep* **3**(5): 1020-1022.

https://www.ncbi.nlm.nih.gov/pubmed/30197965

—and—

Yu, LR *et al.* (2018) "Aptamer-based proteomics identifies mortality-associated serum biomarkers in dialysis-dependent AKI patients." *Kidney Int Rep* **3**(5): 1202-1213.

https://www.ncbi.nlm.nih.gov/pubmed/30197987

Acute kidney injury requiring dialysis (AKI-D) is a serious, often fatal, complication that happens in approximately 15% of hospitalized patients. To see if they could identify factors that could predict AKI-D survival, a team lead by researchers at the University of Virginia used an earlier version of the SomaScan Assay to measure the levels of 1,305 blood proteins taken from 207 AKI-D patients enrolled in a clinical trial sponsored by the VA and NIH. They found 33 serum proteins that were increased in those patients who died within the first 8 days compared to patients who survived the first 8 days. Many of these proteins were associated with inflammation, coagulation, and endothelial cell injury. Analysis of samples taken 8 days after study enrollment further corroborated that high levels of the proteins fibroblast growth factor 23, tissue plasminogen activator and interleukin-6 were associated with increased mortality between 8-28 days. These results may be helpful for understanding the pathophysiology of AKI-D, identifying potential drug targets and identifying which patients are at high risk of dying.

In the accompanying commentary, Steven Coca at the Icahn School of Medicine at Mt. Sinai suggests that the SomaScan Assay could advance the field of nephrology in many ways. “The nephrology community can learn and see the potential of the assay because it has shown usefulness in other fields, including cardiovascular risk prediction in the Heart and Soul and HUNT3 cohorts and risk assessment from randomization to intervention to torcetrapib in the ILLUMINATE trial.”

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Tasaki, S *et al.* (2018) "Multi-omics monitoring of drug response in rheumatoid arthritis in pursuit of molecular remission." *Nat Commun* **9**(1): 2755.

https://www.ncbi.nlm.nih.gov/pubmed/30013029

Rheumatoid arthritis (RA) is chronic inflammatory condition in which the body's defense system mistakenly attacks the joints, leading to painful swelling. If left untreated, bone and cartilage can become permanently damaged and disfigured. Early diagnosis and treatment with disease-modifying antirheumatic drugs (DMARDs) can help slow progression, but sustained drug-free remission of RA has not yet been achieved. To illuminate the biological processes that underlie RA disease activity, researchers at Takeda Pharmaceutical Company and Keio University of Medicine analyzed blood samples taken from RA patients before and after treatment with DMARDs. They measured the levels of 12,486 RNA transcripts, 1070 proteins (using the SomaScan Assay), and 26 cell types. The DMARDs methotrexate (MTX), infliximab (IFX) and tocilizumab (TCZ) caused the RA patients' blood profiles to become more like those of the healthy controls, with IFX and TCZ showed larger effects than MTX. After 24 weeks of treatment, there were still significant differences in the levels of 800 transcripts and 13 serum proteins, which could be largely explained by imbalances in the different types of white blood cells. Similar post-treatment disease signatures have been reported in inflammatory bowel disease and obesity, which suggests that all three conditions may have similar origins. This detailed biological information may help identify new markers for precise monitoring of disease progression and therapeutic efficacy in patients with RA.

Tanaka, T *et al.* (2018) "Plasma proteomic signature of age in healthy humans." *Aging Cell* **17**(5): e12799.

https://www.ncbi.nlm.nih.gov/pubmed/29992704

The goal of this study led by researchers from the NIH was to identify blood proteins that track with chronological age. They used the SomaScan Assay to measure the levels of 1301 proteins in plasma samples from 240 healthy men and women between 22-93 years old. They found 217 proteins that change significantly with age and created a proteomic signature for age based on 76 of the proteins. The signature needs to be tested on an independent cohort but would be useful for identifying the biological causes of aging and tracking the efficacy of interventions meant to slow aging.

Pierson, SK *et al.* (2018) "Plasma proteomics identifies a 'chemokine storm' in idiopathic multicentric Castleman disease." *Am J Hematol* **93**(7): 902-912.

https://www.ncbi.nlm.nih.gov/pubmed/29675946

Idiopathic multicentric Castleman disease (iMCD) is a rare, life-threatening disorder characterized by enlarged lymph nodes and a wide variety of severe symptoms. iMCD disease progression is believed to be driven by uncontrolled release of proinflammatory proteins, particularly interleukin 6 (IL-6), however most iMCD patients do not respond to IL-6-blocking treatments. To better understand the pathogenesis of iMCD, a team led by researchers at the University of Pennsylvania used the SomaScan Assay to measure the levels of 1,129 plasma proteins in six iMCD patients. They found that the protein profiles during disease flare and remission were quite distinct, and that chemokines—proteins that attract white blood cells to sites of infection—were more highly enriched during flares than interleukins or other proinflammatory proteins. Two of the

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patients belonged to a separate clinical subtype and could be distinguished from the others by their distinct protein profiles. Both patients failed to respond to anti-IL-6 therapies, which suggests that different disease mechanisms exist and that measuring plasma protein levels may aid diagnosis and direct treatment of iMCD subgroups.

Jalal, D *et al.* (2018) "Endothelial microparticles and systemic complement activation in patients with chronic kidney disease." *J Am Heart Assoc* **7**(14): e007818.

https://www.ncbi.nlm.nih.gov/pubmed/30006493

People with chronic kidney disease (CKD) are more likely to die of cardiovascular disease (CVD) than kidney failure. Traditional CVD risk factors such as high cholesterol, high blood pressure or diabetes do not explain the increased risk, and traditional CVD treatments do not improve survival rates for those with CKD. To better understand the link between kidney disfunction and cardiovascular risk, a team led by researchers at the University of Iowa school of medicine used the SomaScan Assay to analyze microparticles taken from CKD patients. Microparticles are little sacs shed from cells that line the blood vessels and the heart, and studies have shown that microparticles are more prevalent in people with kidney and heart disease. Compared to healthy controls, people with stage III/IV CKD have microparticles that contain significantly higher levels of the inflammation marker, factor D. The researchers showed that factor D-containing microparticles isolated from CKD patients could activate the alternative complement pathway, a part of the body's natural defense against infections; inhibiting factor D blocked activation. This study provides insight into the underlying causes of inflammation in CKD and may reveal new drug targets for preventing cardiovascular complications.

Ciampa, E *et al.* (2018) "Cerebrospinal fluid protein changes in preeclampsia." *Hypertension* **72**(1): 219-226.

https://www.ncbi.nlm.nih.gov/pubmed/29844151

Preeclampsia is a pregnancy disorder characterized by high blood pressure that, in severe cases, can lead to seizures and force preterm births. The exact cause of preeclampsia is unknown. To better understand why some women with preeclampsia are at risk of seizures, a team led by researchers from Beth Israel Deaconess Medical Center and Harvard Medical School analyzed the cerebrospinal fluid (CSF) of preeclampsia patients using the SomaScan Assay. They found 82 proteins whose expression levels were significantly different compared to pregnant controls. Many of the proteins have roles in processes such as neuronal survival, metabolism, inflammation, and vascular remodeling. Among the patients with preeclampsia who also reported neurological symptoms such as headaches or blurry vision, the SomaScan data revealed proteins previously associated with neuronal inflammation and increased seizure susceptibility. This work may help improve understanding of the biology behind the neurological complications of preeclampsia.

Sun, BB *et al.* (2018) "Genomic atlas of the human plasma proteome." *Nature* **558**: 73-79.

https://www.ncbi.nlm.nih.gov/pubmed/29875488

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Over the past decade, genome-wide association studies (GWAS) have identified thousands of DNA variants that are linked to complex traits and diseases but have not explained exactly why they are important. The vast majority of DNA differences flagged by GWAS lie in regions of the genome with no known function and have small effect sizes. This surprising finding makes establishing causal relationships or determining disease risk extremely difficult, even for conditions with a strong hereditary component such as obesity or cancer.

In the largest study of its kind to-date, an international team led by researchers from the University of Cambridge and Merck used the SomaScan Assay to measure the levels of 2,994 plasma proteins and compared those levels with 10.6 million DNA variants across 3,301 healthy individuals of European heritage. They identified 1,927 genetic variants that impact the levels of 1,478 plasma proteins, of which approximately 90% had not been previously reported. Many of the variants act in “trans” (i.e., they lie far from the gene whose activity is altered, typically on different chromosomes). *Trans* associations are particularly interesting because they can highlight biological connections that are difficult to predict otherwise.

The authors cross-referenced their findings with known disease-associated GWAS variants to identify proteins that might cause disease. Some disease-associated proteins are targets of existing drugs, which suggests possible therapeutics for new indications. Connecting protein perturbations to disease endpoints also allows identification of new drug targets and potential safety concerns for drugs under development. These results also suggest that monitoring protein levels over time may be sufficient for medical or health management.

Kim, CH *et al.* (2018) "Stability and reproducibility of proteomic profiles measured with an aptamer-based platform." *Sci Rep* **8**(1): 8382.

https://www.ncbi.nlm.nih.gov/pubmed/29849057

The goal of this study led by researchers at Harvard Medical School was to examine the stability and reproducibility of the SomaScan Assay on blood samples obtained under “less-than-ideal” conditions. They performed three different pilot studies: one that assessed SomaScan reproducibility using split sample sets, another that compared samples processed 0, 24 or 48 hours after collection, and a third that compared samples collected at baseline and a year later. The levels of 1,305 proteins were measured in blood plasma taken from 14 male and female locally recruited volunteers, from 16 female participants of the original Nurses’ Health Study (NHS) and from 40 female participants in the NHS II (NHS and NHS II were prospective studies that looked at risk factors for chronic disease). Overall, the SomaScan reproducibility was excellent with coefficients of variation <20% for 99% of proteins and <10% for 83% of proteins. Although the number of samples investigated was small, the results help demonstrate that the SomaScan Assay may be at least partially unaffected by the kinds of collection and processing conditions typically seen with archived blood samples from population-based studies.

Jin, P *et al.* (2018) "Plasma from some cancer patients inhibits adenoviral Ad5f35 vector transduction of dendritic cells." *Cytotherapy* **20**(5): 728-739.

https://www.ncbi.nlm.nih.gov/pubmed/29655599

Cancer immunotherapy involves isolating a person’s immune cells, training them to attack cancer cells, and then reintroducing them into the patient. The immune cells are usually cultured using the patient’s own serum or plasma (as opposed to serum pooled from healthy subjects) as it reduces the chances of exposure to an infectious disease.

Researchers from the NIH were manufacturing dendritic cells to produce a protein called HER2/neu and noted highly variable expression when they cultured cells in media containing the patient's own plasma. To try to understand the source of the inconsistencies, they used the SomaScan Assay to measure the levels of 1322 proteins in 8 plasma samples that resulted in low HER2/neu expression and 12 that resulted in high HER2/neu expression. SomaScan analysis revealed 29 proteins that were differentially expressed between the two groups, and the levels of 14 proteins were sufficient to predict which plasma samples gave high or low HER2/neu expression.

Spitali, P *et al.* (2018) "Tracking disease progression non-invasively in Duchenne and Becker muscular dystrophies." *J Cachexia Sarcopenia Muscle* **9**(4): 715-726.

https://www.ncbi.nlm.nih.gov/pubmed/29682908

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are muscle wasting diseases caused by mutations in the gene that produces the protein dystrophin. BMD symptoms are typically milder and worsen at a slower rate than DMD, but both diseases are fatal. Muscle biopsies are often used to assess disease progression and therapeutic efficacy but are costly and highly invasive. In this study, investigators in the Netherlands, the UK and Sweden used the SomaScan Assay to compare blood serum proteins in DMD patients, BMD patients and healthy controls. They identified 10 proteins that could discriminate between the three groups. The researchers also conducted a longitudinal analysis of DMD patients, measuring the levels of over 4,000 proteins in 14 patients for an average of 4 years, and identified 427 proteins that changed significantly as the disease progressed. These proteins warrant further investigation as candidate blood biomarkers for monitoring muscular changes in DMD patients using less invasive methods than tissue biopsies.

Hess, AL *et al.* (2018) "Analysis of circulating angiopoietin-like protein 3 and genetic variants in lipid metabolism and liver health: the DiOGenes study." *Genes Nutr* **13**: 7.

https://www.ncbi.nlm.nih.gov/pubmed/29619113

Approximately one quarter of U.S. adults have metabolic syndrome, a set of conditions (obesity, high blood pressure, high cholesterol/triglycerides, high blood sugar) that increases their risk of type 2 diabetes, stroke, heart attack, non-alcoholic fatty liver disease. Angiopoietin-like 3 (ANGPTL3) is a protein produced in the liver that may be involved with development of metabolic syndrome. This study led by Danish researchers used the SomaScan Assay to measure plasma levels of ANGPTL3 and other protein markers of liver health in participants of a European weight loss study. While they did not find a clear link between circulating levels of ANGPTL3 and lipid metabolism during weight loss, there did seem to be a link between ANGPTL3 and certain markers of liver function, and they identified two gene regions that associate with changes in ANGPTL3 during dietary intervention.

Simats, A *et al.* (2018) "Characterization of the rat cerebrospinal fluid proteome following acute cerebral ischemia using an aptamer-based proteomic technology." *Sci Rep* **8**(1): 7899.

https://www.ncbi.nlm.nih.gov/pubmed/29784938

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The goal of this study from researchers at the Universitat Autònoma de Barcelona in Spain was to understand what happens to molecules in the brain immediately following a stroke. They used the SomaScan Assay to measure protein levels in the cerebrospinal fluid taken from rats before and 30 minutes after a surgically-induced stroke. After discounting any proteins found altered in sham surgical controls, they identified 716 proteins that were significantly changed, most of which were involved in inflammatory response and neuronal death processes. Five proteins that were among the top hits (CKB, CaMK2B, CaMK2D, CaMK2A and CMPK) were examined further in circulating blood samples taken from human patients before and <6 hours after suffering an ischemic stroke. The levels of CKB and CMPK were significantly higher in stroke patients than in controls and the levels of CaMK2B and CMPK were significantly higher in stroke patients who had worse functional outcomes. This SomaScan study in a rodent model successfully identified three proteins for further study as potential biomarkers of strokes in humans.

Depner CM *et al.* (2018) "Mistimed food intake and sleep alters 24-hour time-of-day patterns of the human plasma proteome." *Proc Natl Acad Sci U S A* **115**(23): E5390-E5399.

https://www.ncbi.nlm.nih.gov/pubmed/29784788

The body's internal workings are tuned to natural rhythms that rise and fall over the course of a day. When those timings are disrupted (e.g. jet lag, shift work), health problems can occur. To gain a better understanding of what happens when biological clocks are disrupted, a team lead by researchers at the University of Colorado Anschutz medical campus investigated how plasma proteins fluctuate over the course of a 24-hour day. They used the SomaScan Assay to measure the levels of 1,129 proteins in blood samples collected from six healthy male volunteers on a "circadian aligned" schedule (eat during the day and sleep at night) compared to a "circadian misaligned" schedule (sleep during the day and eat at night). The switch from a day to a night shift significantly changed the patterns and/or levels of 127 proteins, including many associated with the immune system function, energy metabolism and cancer. These findings may help explain why night shift workers are more prone to metabolic diseases and emphasizes the importance of timing when conducting diagnostic blood testing and administering medications.

Lam, MPY *et al.* (2018) "Harnessing the power of proteomics to assess drug safety and guide clinical trials." *Circulation* **137**(10): 1011-1014.

http://circ.ahajournals.org/content/137/10/1011?iss=10

—and—

Williams, SA *et al.* (2018) "Improving assessment of drug safety through proteomics: early detection and mechanistic characterization of the unforeseen harmful effects of torcetrapib." *Circulation* **137**(10): 999-1010.

http://circ.ahajournals.org/content/137/10/999.long

This article from Pfizer, the University of California, San Francisco, the Karolinska Institute and SomaLogic demonstrates how monitoring blood-based protein changes in response to experimental therapies could one day improve the efficiency and safety of drug development. Researchers used the SomaScan Assay to measure the levels of 1,129 proteins in samples from ILLUMINATE, Pfizer's phase 3 clinical trial of torcetrapib, a drug candidate for treating heart disease. Torcetrapib raises levels of 'good' cholesterol and lowers levels of 'bad' cholesterol and was expected to be a blockbuster drug that reduced the risk of serious cardiovascular events such as heart failure and stroke. Instead, an increase in deaths and heart problems was seen in trial subjects taking torcetrapib, and ILLUMINATE was abruptly terminated. This happened in 2006 after Pfizer had invested 15 years and nearly a billion dollars in torcetrapib development.

The new study used a previously validated nine-protein cardiovascular risk score (Ganz, P *et al.* (2016) *JAMA* 315(23): 2532-2541; https://doi.org/10.1001/jama.2016.5951) to successfully predict the harmful effects of torcetrapib after three months of treatment—much earlier than the point at which ILLUMINATE was stopped (approximately 18 months). The work also provides new insights into how torcetrapib acts in the body and possible clues to its toxicity. Analysis of the 200 proteins that changed significantly compared to matched controls revealed that torcetrapib had widespread and unanticipated effects on immunity and inflammation. In addition, changes in eight proteins were linked to synthesis or function of aldosterone, a steroid hormone involved in regulating blood pressure. These results help explain the hypertensive side effects seen early in torcetrapib's development.

Torcetrapib is a cholesteryl ester transferase (CETP) inhibitor, a drug class that is of considerable interest to the pharmaceutical industry. In addition to Pfizer, both Eli Lilly and Roche had CETP inhibitors that were dropped late in development due to lack of efficacy. However, Merck recently announced that their drug candidate anacetrapib successfully completed the longest CETP trial to date. This article shows how profiling proteins could provide early warning of off-target effects and help speed drug development. It also suggests that these same proteins can be used to monitor the ongoing effectiveness of drug treatment in individuals and populations. In their accompanying editorial, Lam and Ge state that "With continual development and lowering costs of proteomics technologies, future trials will likely be routinely embedded with longitudinal proteomics profiling to enhance participant safety and inform drug assessment."

McGarrah, RW *et al.* (2018) "Integrative omics: harnessing the proteome to maximize the potential of the genome." *Circulation* **137**(11): 1173-1175.

http://circ.ahajournals.org/content/137/11/1173.long

—and—

Benson, MD *et al.* (2018) "Genetic architecture of the cardiovascular risk proteome." *Circulation* **137**(11): 1158-1172.

http://circ.ahajournals.org/content/137/11/1158.long

Changes in protein levels reflect the functional consequences of gene variants and can help establish hereditary causes of disease. Previously, investigators at the Beth Israel Deaconess Medical Center used the SomaScan Assay to identify 156 plasma proteins that associated with clinical risk factors for developing cardiovascular disease (CVD)—age, sex, cholesterol, blood pressure, diabetes, and smoking (see Ngo, D *et al.* (2016) *Circulation* **134**(4): 270-285; https://doi.org/10.1161/CIRCULATIONAHA.116.021803). In this study, the researchers integrated genomic data into their SomaScan-based proteomic profiling and found a number of new connections between gene variants and circulating proteins that are important in CVD. One of the DNA-protein associations led to the discovery that the gene for protein phosphatase 1 (PPM1G) regulates the levels of apolipoprotein E, a cholesterol transporter. This is the first time that PPM1G has been linked to lipid metabolism. The authors have made their gene variant-protein association data publicly available, which should hasten the discovery of additional insights into CVD biology, potential biomarkers and putative drug targets. The accompanying editorial by McGarrah and Shah explains how proteomic information helps expand beyond the static 'snapshot' of CVD provided by genetic studies.

Jacob, J *et al.* (2018) "Application of large scale aptamer-based proteomic profiling to "planned" myocardial infarctions." *Circulation* **137**(12): 1270-1277.

https://www.ncbi.nlm.nih.gov/pubmed/29222138

In this study, researchers at the Novartis Institute for BioMedical Research, Beth Israel Deaconess Medical Center, and Brigham and Women's Hospital used the SomaScan Platform to measure the levels of approximately 5,000 proteins in blood samples taken from patients undergoing a "planned" heart attack, a medical procedure that can help reduce severely overgrown heart muscle (hypertrophic cardiomyopathy). They analyzed plasma taken before and at different time points after the procedure, looking for proteins whose levels changed significantly. Their results not only confirmed findings from a prior study that used an earlier, smaller version of the SomaScan Platform (see Ngo, D *et al.* (2016) *Circulation* **134**(4): 270-285; https://doi.org/10.1161/CIRCULATIONAHA.116.021803) but also identified nearly 150 new proteins, many of which had not been previously associated with heart damage. Twenty-nine of the proteins that were significantly increased within an hour after a planned heart attack were also elevated in patients who suffered "unplanned" heart attacks.

This article is the first published description of large-scale protein profiling at a level that has not previously been reported. The expanded SomaScan Assay platform provides opportunities for unbiased discovery of disease markers to improve diagnosis, predict future events, monitor responses to therapies and identify targets for drug development. Ongoing studies by these authors are applying this expanded SomaScan Platform to larger groups of patients.

Parolo, S *et al.* (2018) "Combined use of protein biomarkers and network analysis unveils deregulated regulatory circuits in Duchenne muscular dystrophy." *PLoS One* **13**(3): e0194225.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0194225

Duchenne muscular dystrophy (DMD) is a disease characterized by progressive muscular atrophy and death, usually by young adulthood. Although the genetic cause of DMD (mutations in the gene that produces the protein dystrophin) has been known since the mid-80s, it is still poorly understood how loss of dystrophin drives DMD progression. In this study, Italian researchers re-analyzed previously published SomaScan Assay data (see Hathout, Y et al. (2015) *Proc Natl Acad Sci U S A* **112**(23): 7153-7158; https://doi.org/10.1073/pnas.1507719112) to identify 52 proteins that were significantly different in the DMD patients, of which 27 had been identified in the previous study. The researchers found that only six of the proteins were needed to diagnose DMD with 100% accuracy. Using previously developed computational methods to see how proteins relate to one another, they identified several biological processes and functions that are dysregulated in DMD. In addition to demonstrating how rich SomaScan data are (and how they can be continuously mined for new insights), this study expands our molecular understanding of DMD, which is essential for developing effective treatments.

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Wang, X *et al.* (2018) "Chemotherapy-induced differential cell cycle arrest in B-cell lymphomas affects their sensitivity to Wee1 inhibition." *Haematologica* **103**(3): 466-476.

http://www.haematologica.org/content/103/3/466.long

A single cell divides to create two new genetically identical daughter cells in a controlled series of events called the "cell cycle." There are four stages to the cell cycle and progression from one stage to the next is governed by three checkpoints, where the process can arrest to ensure that problems such as DNA damage are fixed before being passed on to the daughter cells. If the damage isn't repaired the cell will die, so figuring out a way to bypass the checkpoints could be a strategy for killing tumor cells containing chemotherapy-induced DNA lesions.

The focused goal of this study conducted by investigators at the University of Colorado Anschutz Medical Campus was to understand how inhibition of a particular checkpoint protein called Wee1 affects the actions of the chemotherapeutic agents cytarabine (Ara-C) and doxorubicin (DOX) on B cell lymphomas. They used the SomaScan Assay to look at differences in protein levels between B cells that were left untreated or treated with Ara-C. Surprisingly, only 3 of the 1,310 proteins in the SomaScan Assay changed significantly, including 2 proteins (cyclin A2/B1) that are known to control progression through the cell cycle. Addition of a Wee1 checkpoint inhibitor promoted cell death, but only for cells arrested in particular stages of the cell cycle, and the stage of arrest could be shifted by adding DOX. Their results suggest that a combination of Ara-C, DOX and Wee1 inhibitor could be effective for treating specific types of B cell cancers.

Zhang, W *et al.* (2018) "Proteomic analysis reveals distinctive protein profiles involved in CD8(+) T cell-mediated murine autoimmune cholangitis." *Cell Mol Immunol* **15**(8): 756-767.

https://www.ncbi.nlm.nih.gov/pubmed/29375127

Primary biliary cholangitis (PBC) is an autoimmune disease in which the bile ducts of the liver are slowly destroyed. This destruction causes bile and other toxins to build up, leading to further damage and eventual liver failure. An international team led by investigators at the University of California, Davis have developed a mouse model of PBC, and in this study, they used the SomaScan Assay to look at blood proteins of the mice at different ages. They found significant differences in the serum protein profiles of diseased mice compared to healthy mice and identified a number of proteins that warrant further investigation for their potential importance in progression of human PBC.

Christensson, A *et al.* (2018) "The impact of the glomerular filtration rate on the human plasma proteome." *Proteomics Clin Appl* **12**(3): e1700067. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/29281176

Approximately 30 million adults in the US have chronic kidney disease (CKD), a devastating illness in which the kidneys gradually lose their ability to filter blood. The standard indicator of kidney decline is a diminished "glomerular filtration rate (GFR)," as assessed by the time it takes a kidney to clear a compound injected into the subject. However, GFR is costly and time-consuming to measure and is not very accurate at discerning mild kidney impairment. More sensitive methods are needed that enable early detection of CKD when therapeutic intervention is still possible.

The goal of this study from researchers at Skåne University Hospital and SomaLogic was to see whether blood proteins could provide and accurate picture of kidney function. They used the SomaScan Assay to measure the levels of 2893 proteins in plasma taken from 364 people with a wide range of GFRs. The protein that was most significantly negatively correlated with GFR (levels increased as GFR decreased) was the well-established kidney biomarker cystatin C. Many other proteins were negatively or positively correlated with GFR and warrant further investigation as potential biomarkers. Such proteins may also reveal the underlying biological mechanisms that lead to kidney failure and possible treatment strategies.

Wasiak, S *et al.* (2018) “Benefit of apabetalone on plasma proteins in renal disease.” *Kidney International Reports* **3**(3): 711-721.

https://www.sciencedirect.com/science/article/pii/S2468024917304576

Bromodomain and Extra-Terminal domain (BET) proteins, which help turn specific genes on and off, are important drug targets for a wide range of conditions including cancer, neurological disorders and obesity. Apabetalone, a BET inhibitor under development to treat cardiovascular disease (see Wasiak, S *et al.* (2017) *J Cardiovasc Transl Res,* **10**(4): 337-347; https://doi.org/10.1007/s12265-017-9755-z), can reduce renal inflammation in patients with severely impaired kidney function. To better understand the effects of apabetalone, a team led by investigators at Resverlogix Corp. compared the levels of circulating proteins in healthy patients and those with chronic kidney disease (CKD). Blood samples from eight people with CKD and eight matched controls were collected before and after taking apabetalone and analyzed using the SomaScan Assay. The levels of 169 proteins differed significantly in CKD patients compared to controls. Many of the identified proteins are well-established markers of kidney function but some are entirely new. Within 12 hours, a single dose of apabetalone significantly lowered the levels of proteins that contribute to inflammation, atherosclerosis and fibrosis. These results suggest that apabetalone may be useful for treating not just CKD, but multiple diseases in which the BET proteins play a role.

Zaghlool, SB *et al.* (2018) "Deep molecular phenotypes link complex disorders and physiological insult to CpG methylation." *Hum Mol Genet* **27**(6): 1106-1121.

https://www.ncbi.nlm.nih.gov/pubmed/29325019

Adding a methyl group to DNA is a way to change gene expression without altering the DNA sequence itself. The most common sites for DNA methylation are on cytosines that are followed by guanines (CpG). CpG methylation occurs during normal embryonic development and aging but may also be altered by environmental stress, lifestyle and disease. Previously, an international team led by researchers at the Weill Cornell Medical College in Qatar identified 20 CpG sites that associated with obesity-, diabetes- and smoking-related blood metabolites. In this study, the investigators used a multi-omics approach to replicate and expand upon their earlier findings. They conducted blood, urinary, and salivary metabolomics, lipidomics, glycomics and SomaScan proteomics analysis on 359 samples from a multi-ethnic cohort, and identified 138 associations between CpG sites and biomarkers of obesity, diabetes and smoking. Their preliminary results lead to new hypotheses for future studies to help understand the causal relationships between DNA methylation sites and disease phenotypes.

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Thrush, AB *et al.* (2018) "Diet-resistant obesity is characterized by a distinct plasma proteomic signature and impaired muscle fiber metabolism." *Int J Obes (Lond)* **42**(3): 353-362.

https://www.ncbi.nlm.nih.gov/pubmed/29151592

The goal of this study was to see if there are physiological differences between obese individuals who successfully lose weight on diets and those who don't. An international team led by scientists at the University of Ottawa compared the muscle tissue, cells and circulating proteins of 20 women classified as either obese diet sensitive (ODS) or obese diet resistant (ODR) based on their weight loss after six weeks of meal replacement. They found distinct metabolic differences between ODS and ODR women under both fasting conditions and after eating a high fat meal. SomaScan analysis identified a number of blood proteins whose levels differed significantly between the two groups, and that may help predict weight loss success.

Hussein, AI *et al.* (2018) "Serum proteomic assessment of the progression of fracture healing." *J Orthop Res* **36**(4): 1153-1163.

https://www.ncbi.nlm.nih.gov/pubmed/28971515

The goal of this study was to see whether changes in protein levels could be used to monitor bone regeneration. Currently, this assessment is done using radiology and physical examination, which are subjective and hard to detect reliably, particularly in the early stages of the healing process. Researchers at the Boston University School of Medicine used the SomaScan Assay to monitor blood protein levels in mice as they recovered from a bone fracture. They identified 692 proteins that changed significantly over a seven-week time course of healing, most of which are known to function in repair processes such as coagulation, immune response, bone and blood vessel formation. This study shows the potential of plasma proteins to predict normal bone healing and could lead to a minimally invasive diagnostic for human fracture care.

Vilar-Gomez, E *et al.* (2018) "Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers." *J Hepatol* **68**(2): 305-315. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/29154965

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of liver disease worldwide. Liver inflammation (NASH) and fibrosis are key determinants of NAFLD prognosis but require liver biopsy, which is not suitable for routine screening. This review discusses less invasive and more cost-effective methods, including the SomaScan Assay, for predicting NASH and advanced fibrosis in patients with NAFLD.

Oller Moreno, S *et al.* (2018) "The differential plasma proteome of obese and overweight individuals undergoing a nutritional weight loss and maintenance intervention." *Proteomics Clin Appl* **12**(1). **(Subscription required)** https://www.ncbi.nlm.nih.gov/pubmed/28371297

Obesity is a global problem that affects all people of all ages and incomes. Worldwide, obesity rates have more than doubled since 1980. Although weight gain is preventable, no country has successfully reduced obesity rates in over 30 years. Drug treatment for obesity has been only moderately successful, partly because the ability to lose weight and keep it off depends in part on each person’s physiology and metabolism. Thus, approaches that are tailored to an individual’s specific body chemistry are needed to help manage weight more effectively.

In this study, Nestlé researchers used mass spectrometry together with the SomaScan Assay to analyze samples from overweight or obese (but non-diabetic) individuals enrolled in a multi-center European dietary intervention study. Plasma proteins were measured before and after successful weight loss. Most of the proteins whose levels changed significantly are known, but the study also identified new proteins that if validated could serve as potential biomarkers for obesity and/or weight loss.

Oak, P *et al.* (2017) "Attenuated PDGF signaling drives alveolar and microvascular defects in neonatal chronic lung disease." *EMBO Mol Med* **9**(11): 1504-1520.

https://www.ncbi.nlm.nih.gov/pubmed/28923828

—and—

Forster, K *et al.* (2018) "Early identification of bronchopulmonary dysplasia using novel biomarkers by proteomic screening." *Am J Respir Crit Care Med* **197**(8): 1076-1080.

https://www.ncbi.nlm.nih.gov/pubmed/29053024

Ventilation with supplemental oxygen can be a life-saving treatment for preterm infants who have difficulty breathing on their own, but it puts some at risk of developing neonatal chronic lung disease, also known as bronchopulmonary dysplasia (BPD). Two different studies led by investigators in Germany used the SomaScan Assay to better understand the molecular underpinnings of BPD.

The paper from Oak *et al.* used the SomaScan Assay to look at plasma protein levels in preterm infants with gene variants linked to BPD. They found that impairment of platelet-derived growth factor (PDGF, a protein that regulates cell growth and division) leads to air sac and blood vessel defects seen in BPD. The researchers then found that treatment with supplemental PDGF improved lung function in a mouse model of the disease.

The paper by Förster *et al.* used the SomaScan Assay to discover and validate a set of 12 blood proteins whose levels were significantly different in preterm infants who developed BPD. These studies represent the first steps towards developing tools for early diagnosis and treatment of preterm infants at risk for BPD.

Wermuth, PJ *et al.* (2018) "Identification of novel systemic sclerosis biomarkers employing aptamer proteomic analysis." *Rheumatology (Oxford)* **57**(10): 1698-1706.

https://www.ncbi.nlm.nih.gov/pubmed/29140474

Systemic sclerosis (SSc) is a chronic autoimmune disorder characterized by overproduction of collagen that leads to hardening of the skin and internal organs. There is an unmet need for clinically validated, non-invasive biomarkers to diagnose and manage SSc. This review illustrates the potential of the SomaScan Platform to discover SSc biomarkers and to improve management of rheumatic diseases.

Rossios, C *et al.* (2018) "Sputum transcriptomics reveal up-regulation of IL-1 receptor family members in severe asthma." *J Allergy Clin Immunol* **141**(2): 560-570.

https://www.ncbi.nlm.nih.gov/pubmed/28528200

Most asthma can be managed using standard medications such as inhaled corticosteroids, but severe asthma often does not respond to traditional treatments. There are no universally accepted criteria to diagnose severe asthma, and the exact causes of airway inflammation likely vary between patients. This lack of understanding and ‘one size fits all’ approach impairs quality of care and, for many, the disease remains either poorly controlled or not controlled at all. In this study, scientists in the UK analyzed gene and protein expression in sputum samples from people with severe asthma (non-smokers and smokers), moderate asthma (non-smokers) or no asthma (non-smokers). SomaScan analysis revealed several inflammatory factors and immune system proteins that differed significantly in severe asthma patients compared to those with mild asthma or healthy controls. These results should help elucidate various mechanisms that cause disease pathogenesis and guide targeted therapies.

Norman, KC *et al.* (2018) "Proteomics: Clinical and research applications in respiratory diseases." *Respirology* **23**(11): 993-1003.

https://www.doi.org/10.1111/resp.13383

In this review, investigators at the University of Michigan and the University of Michigan Medical School discuss proteomic technologies, including the SomaScan Assay, as well as bioinformatic analysis of proteomic data. They also discuss proteomic applications in respiratory diseases such as asthma, lung cancer, idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease (COPD).

Aghaeepour, N *et al.* (2018) "A proteomic clock of human pregnancy." *Am J Obstet Gynecol* **218**(3): 347 e341-347 e314.

https://www.doi.org/10.1016/j.ajog.2017.12.208

Researchers at Stanford University used the SomaScan Assay to identify precisely timed changes in levels of blood proteins that occur over the course of pregnancy. They developed a “proteomic clock” using eight proteins that strongly predicted

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gestational age in full-term pregnancies. These results suggest that deviations from the normal protein profiles could help diagnose problems during pregnancy and potentially reveal their underlying causes.

O'Dwyer, DN *et al.* (2017) "The peripheral blood proteome signature of idiopathic pulmonary fibrosis is distinct from normal and is associated with novel immunological processes." *Sci Rep* **7**: 46560.

https://www.ncbi.nlm.nih.gov/pubmed/28440314

Idiopathic pulmonary fibrosis (IPF) is a fatal condition characterized by scar tissue that builds up in the lungs, making it harder and harder to breathe. The course of the disease is highly variable, and the cause is usually unknown, which makes it difficult to devise appropriate interventions. Previously, a team led by University of Michigan researchers used the SomaScan Assay to develop a six-protein panel that was able to predict IPF disease progression (Ashley, SL et al. (2016) *PLoS One* 11(8): e0159878; https://doi.org/10.1371/journal.pone.0159878). The goal of this new study was to see if circulating proteins could shed light on the disease biology of IPF. The researchers used the SomaScan Assay to compare protein levels in blood from IPF and healthy patients and identified 164 proteins that differed significantly between the two groups. The identified proteins play roles in the defense response, wound healing and protein phosphorylation, which should be helpful for finding new drug targets for treating IPF. Eight proteins were sufficient to distinguish IPF patients from normal controls, which could lead to a minimally invasive way to differentiate IPF from other chronic lung diseases.

Barbour, C *et al.* (2017) "Molecular-based diagnosis of multiple sclerosis and its progressive stage." *Ann Neurol* **82**(5): 795-812.

https://www.ncbi.nlm.nih.gov/pubmed/29059494

Neurological diseases such as multiple sclerosis (MS) are extremely hard to diagnose since there is no easy way to see inside the brain of a living person at a sufficient level of detail. Currently, there are no laboratory or physical tests that can definitively establish if a person has MS, and many common conditions (e.g., depression, migraine, fibromyalgia) resemble MS on brain scans and in clinical symptoms. Misdiagnosis of MS is a frequent problem (by some estimates >20% misdiagnosis rate) that puts many patients at unnecessary risk.

Scientists at the NIH have developed a protein-based diagnostic test for MS that greatly outperformed the current gold standard. They used the SomaScan Assay to measure the levels of 1128 proteins in the cerebral spinal fluid (CSF) of 225 people from 6 different groups: healthy donors, those with different types of MS (relapsing-remitting, primary or secondary progressive), and those with inflammatory or non-inflammatory neurological disorders that mimic MS (e.g., meningitis or epilepsy). The 500 proteins with the highest signals were used to generate a computer algorithm that could distinguish MS from non-MS patients in a separate patient cohort with 90.6% accuracy. A different CSF protein-based classifier was able to differentiate patients with progressive vs. relapsing-remitting forms of MS with 89.4% accuracy. They were unable to create a classifier that could distinguish between different types of progressive MS based on CSF protein levels, which suggests that primary and secondary progressive MS may be biologically equivalent. Taken together, these results may help improve MS diagnosis, monitoring disease progression and predicting treatment efficacy.

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Carayol, J *et al.* (2017) "Protein quantitative trait locus study in obesity during weight-loss identifies a leptin regulator." *Nat Commun* **8**(1): 2084.

https://www.ncbi.nlm.nih.gov/pubmed/29234017

Genome-wide association (GWAS) studies have identified many common gene variants in obese individuals but have not explained how that genetic variability contributes to obesity. To help understand the functional consequences of obesity-related gene differences, researchers from the Nestlé institute of Health Science, Quartz Bio, University of Toulouse, Maastricht University Medical Centre and University of Copenhagen used the SomaScan Assay to examine how gene variants affected the levels of 1,129 blood proteins in 494 obese individuals placed on an eight-week diet. They identified 192 proteins that associated with body mass index (BMI) prior to dietary intervention, a third of which were regulated by obesity-related gene variants. A particularly interesting finding was that lower levels of a protein called Fam46A led to higher levels of the protein leptin, a hormone produced by fat cells that helps control appetite. Very little is known about the biological function of Fam46A. This study is one of the first to demonstrate at a molecular level how gene variants can affect the levels of key proteins involved in weight management. These findings may also help researchers design tailored treatments for obesity and other complex metabolic conditions that have so far proven difficult to address.

Skarke, C *et al.* (2017) "A pilot characterization of the human chronobiome." *Sci Rep* **7**(1): 17141.

https://www.ncbi.nlm.nih.gov/pubmed/29215023

Each person has an internal “clock,” and various physiological traits (metabolism, blood pressure, body temperature, etc.) rise and fall based on unique daily rhythms. Previous studies have shown that most available drugs act on protein targets whose levels oscillate over the course of a day, so understanding a person’s “chronobiome” may help doctors not only give the right treatment but give it at the right time—a primary goal of precision medicine. In this pilot study, a team lead by researchers at the University of Pennsylvania Perelman School of Medicine tested the feasibility of detecting time-dependent signals in six healthy men over four months. Through the course of the study, the men reported what they ate and wore remote sensors as they went about their daily activities. Biological specimens collected over two 48-hour periods were analyzed using a “multi-omics” approach (microbiome, metabolome, transcriptome and SomaScan-measured proteome). Despite the small sample size, time-dependent patterns were visible, but more frequent sampling will be needed to confidently differentiate signal from noise—which the researchers hope to accomplish in upcoming studies.

Romero, R *et al.* (2017) "The maternal plasma proteome changes as a function of gestational age in normal pregnancy: a longitudinal study." *Am J Obstet Gynecol* **217**(1): 67.e1-67.e21.

https://www.ncbi.nlm.nih.gov/pubmed/28263753

The goal of this study led by researchers at Wayne State University School of Medicine was to characterize the maternal proteome to better understand the biological processes that are affected over the course of a normal pregnancy. Blood samples were collected at different times during the pregnancies of 43 mothers who delivered at term and analyzed using the SomaScan Assay. The levels of 1125 proteins were measured, 112 of which changed significantly as a function of

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gestational age. Nine of those proteins increased by more than five-fold over gestation, and are involved in processes such as growth regulation, embryogenesis, angiogenesis, immunoregulation and inflammation. This preliminary study helps establish a baseline for the early identification of deviations that signal an abnormal pregnancy, perhaps even early enough to prevent complications or mortality.

Spitsin, S *et al.* (2017) "Antiinflammatory effects of aprepitant coadministration with cART regimen containing ritonavir in HIV-infected adults." *JCI Insight* **2**(19): e95893.

https://www.ncbi.nlm.nih.gov/pubmed/28978797

HIV-infected individuals take antiretroviral therapies to help keep the virus at bay, but still suffer from systemic inflammation and immune dysfunction, which affects their quality of life and ability to survive. In this article, researchers at the Children's Hospital of Philadelphia Research Institute and the Perelman School of Medicine at the University of Pennsylvania describe a dose and time escalation clinical trial of the anti-inflammatory drug aprepitant on 12 HIV-positive patients. The goal was to see if co-administration of aprepitant with ritonavir (an antiretroviral medication) would safely reduce residual inflammation. The SomaScan Assay was used to assess the global effects of aprepitant and identified 176 plasma proteins whose levels changed after drug treatment. These included proteins involved in inflammation and immune regulation as well as blood, lipid and cholesterol metabolism, which warrant caution and further investigation.

Curran, AM *et al.* (2017) "Sexual dimorphism, age, and fat mass are key phenotypic drivers of proteomic signatures." *J Proteome Res* **16**(11): 4122-4133. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/28950061

An international team led by investigators at University College Dublin Institute of Food and Health and the Nestlé Institute of Health Sciences used the SomaScan Assay to see if a person's sex, age and body fat mass are reflected in their blood protein profile. In healthy individuals (94 men and 102 women), they identified proteins that were significantly different depending on sex (141 proteins), age (51 proteins) and fat mass (112 proteins), respectively, and validated their results in a separate cohort. This study illustrates the need to consider these factors when developing protein markers for use in diagnosis or treatment strategies for many different diseases and conditions.

Pannerec, A *et al.* (2017) "Vitamin B12 deficiency and impaired expression of amnionless during aging." *J Cachexia Sarcopenia Muscle* **9**(1): 41-52.

https://www.ncbi.nlm.nih.gov/pubmed/29159972

Scientists in Singapore and the Nestlé Institute of Health Sciences used the SomaScan Assay in a study of the connection between vitamin B12 deficiency and aging. The researchers measured levels of methylmalonic acid (MMA), an indicator of vitamin B12 deficiency, in blood samples from 238 participants in a Singapore aging study. MMA levels were significantly higher in elderly participants compared to young controls, and even higher in elderly participants who were classified as physically frail. They then analyze blood protein changes in a rat model of aging where the animals had been fed a controlled diet that contained the recommended amounts of vitamin B12. They found that age-related vitamin B12 deficiency correlates with high levels of the protein amnionless (AMN) in blood serum. AMN is involved in B12 absorption and transport, and these studies suggest that it could be used as a biomarker for early detection of vitamin B12 deficiency.

Coghlan, RF *et al.* (2017) "A degradation fragment of type X collagen is a real-time marker for bone growth velocity." *Sci Transl Med* **9**(419): eaan4669.

https://www.ncbi.nlm.nih.gov/pubmed/29212713

Bone growth is often used as a metric of healthy development, but bones grow slowly making it difficult to measure growth rates in real time. In this article, an international team led by scientists at the Shriners Hospitals for Children and the Oregon Health and Science University in Portland found that a protein fragment of type X collagen correlates with bone growth. Using a SOMAmer reagent that binds tightly to the fragment, they developed an assay to measure the protein in plasma, serum and dried blood spots. This assay may prove to be a useful tool to monitor fracture healing and treatment progress for growth disorders.

Sullivan, KD *et al.* (2017) "Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation." *Sci Rep* **7**(1): 14818.

https://www.ncbi.nlm.nih.gov/pubmed/29093484

Down syndrome, or Trisomy 21, is caused by having three copies of chromosome 21 instead of two. Although the genetics of Down syndrome have been known for 60 years, it is still unclear how having the extra chromosome leads to various Down syndrome traits, including changes in common disease susceptibilities (e.g., Down syndrome individuals are more likely to develop Alzheimer’s, leukemia and autoimmune disorders, but less likely to develop solid tumors and cardiovascular disease). Understanding the biology that underlies these differences could inform a wide range of medical conditions that affect not only Down syndrome individuals, but the entire population.

In the largest and most comprehensive study of its kind to date, investigators at the Crnic Institute for Down Syndrome, the Sie Center for Down Syndrome, the University of Colorado, and SomaLogic measured the levels of over 3500 proteins in the blood of 165 Down syndrome patients and compared them to 98 non-Down syndrome controls. They identified 299 proteins that differed significantly between the two groups. Surprisingly, most of these proteins are not encoded by genes located on chromosome 21 but are associated with immune system control. Down syndrome individuals appear to have something that resembles an autoinflammatory condition, with elevated levels of proteins that promote inflammation but deficiencies in proteins that help eliminate foreign pathogens. The findings provide a new framework for understanding the physiological mechanisms that drive the altered disease susceptibilities seen in individuals with Down syndrome, and suggest that individuals with Down syndrome could benefit from therapies that decrease or modulate immune responses.

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Candia, J *et al.* (2017) "Assessment of variability in the SomaScan Assay." *Sci Rep* **7**(1): 14248.

https://www.ncbi.nlm.nih.gov/pubmed/29079756

In this article, researchers at the NIH conducted a meta-analysis of SomaScan Assay performance in blood serum and plasma. They analyzed multiple runs that used an earlier version of the assay capable of measuring 1,305 different protein analytes, assessing different procedures for data processing as well as assay variability within and between runs. The paper is accompanied by an interactive web-based tool.

Scriba, TJ *et al.* (2017) "Sequential inflammatory processes define human progression from *M. tuberculosis* infection to tuberculosis disease." *PLoS Pathog* **13**(11): e1006687.

https://www.ncbi.nlm.nih.gov/pubmed/29145483

An estimated 1.7 billion people—one quarter of the world's population—are infected with the bacterium that causes tuberculosis (TB), but only approximately 10% develop active pulmonary disease. In this article, scientists from the South African TB Vaccine Initiative, the University of Cape Town, the Center for Infectious Disease Research and SomaLogic looked for changes in various molecules in blood that together could predict the risk of TB progression from latent to active disease. The time between the initial blood collection and TB diagnosis ranged from 1 to 894 days, so the investigators could construct a timeline of changes that occurred as the disease evolved.

The blood analyses revealed that TB progression associated with sequential modifications of immunological processes. Some of these processes, such as type I/II interferon signaling and complement cascade, were elevated as early as 18 months before TB diagnosis.

Understanding the biology of progression from infection to active pulmonary TB opens the door to blood-based tests that may determine those who are at risk of developing active disease and who need early treatment. These findings could also help development of better vaccines and host-directed therapies to battle the TB epidemic.

Habiel, DM *et al.* (2017) "Divergent roles for clusterin in lung injury and repair." *Sci Rep* **7**(1): 15444.

https://www.ncbi.nlm.nih.gov/pubmed/29133960

Idiopathic pulmonary fibrosis (IPF) is characterized by lung scarring that prevents sufferers from taking deep breaths. There is no cure and patients typically die of respiratory failure within a few years after diagnosis. In this article, an international team of researchers led by investigators at Cedars-Sinai Medical Center and MedImmune demonstrate that the protein clusterin plays an important role in IPF. clusterin is produced by cells in response to stress and exists in different forms located either inside or outside cells. Using a combination of gene expression, flow cytometry, histology and the SomaScan Assay, the researchers found significantly higher levels of clusterin inside lung cells but significantly lower levels circulating in the blood of IPF patients compared to either chronic obstructive pulmonary disease (COPD) or healthy controls. Studies in human cells and in mice exposed to a toxic agent demonstrated that clusterin has different effects on cell regeneration and

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lung repair depending on where it's located. These results suggest possible therapeutic strategies for IPF that warrant further investigation.

Lertudomphonwanit, C *et al.* (2017) "Large-scale proteomics identifies MMP-7 as a sentinel of epithelial injury and of biliary atresia." *Sci Transl Med* **9**(417): eaan8462.

https://www.ncbi.nlm.nih.gov/pubmed/29167395

Biliary atresia (BA) is a rare disease that occurs in infants where their bile ducts become blocked. Bile accumulates in the liver and causes damage that can lead to liver failure. Early diagnosis is critical for successful treatment, but BA is often difficult to distinguish from newborn jaundice. In this article, an international team led by researchers at Cincinnati Children's Hospital Medical Center used the SomaScan Assay to compare protein levels in blood serum taken from infants with BA, normal age-matched controls, and those with prolonged jaundice (longer than 2 weeks). The data revealed significantly higher levels of matrix metalloproteinase-7 (MMP-7) in infants with BA. MMP-7 combined with γ-glutamyltranspeptidase, a marker of decreased bile flow, predicted BA with 95% accuracy in two independent cohorts. Studies in mice point to a role for MMP-7 in disease pathogenesis since MMP-7 concentrations increased when bile duct injury was induced in mice and blocking MMP-7 function decreased tissue damage. Taken together, these results illustrate the potential of MMP-7 as a diagnostic biomarker of BA and perhaps even a new therapeutic target.

Russell, T *et al.* (2017) "Potential of high-affinity, Slow Off-Rate Modified Aptamer (SOMAmer) reagents for *Mycobacterium tuberculosis* proteins as tools for infection models and diagnostic applications." *J Clin Microbiol* **55**(10): 3072-3088*.*

https://www.ncbi.nlm.nih.gov/pubmed/28794178

—and—

De Groote, MA *et al.* (2017) "Discovery and validation of a six-marker serum protein signature for the diagnosis of active pulmonary tuberculosis." *J Clin Microbiol* **55**(10): 3057-3071*.*

https://www.ncbi.nlm.nih.gov/pubmed/28794177

Tuberculosis (TB) is one of the top 10 causes of deaths worldwide. Because TB is spread through the air by people with active lung infections, early detection and treatment is important for disease containment. Examining and culturing lung sputum is the standard method for diagnosing TB, but there is a need for more rapid tests with greater accuracy. The World Health Organization (WHO) has defined non-sputum, point-of-care diagnostics for active TB screening as a high priority.

In this pair of articles, SomaLogic researchers assessed the ability of the SomaScan Assay to diagnose active pulmonary TB from blood serum. Russell *et al.* describes the generation of SOMAmer reagents to specific TB bacterial proteins and incorporation of those SOMAmers into the SomaScan Assay. Although the SOMAmers bound tightly to their intended targets, the test could not distinguish between TB patients and non-TB controls, probably because the bacterial proteins are not at high enough concentrations in circulating blood.

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In contrast, De Groote *et al.* describe finding distinct differences in human host serum protein levels between TB and non-TB patients. Previous work produced a nine-protein model that predicted active TB with 80% sensitivity and 84% specificity (De Groote, MA *et al.* (2013) *PLoS One* 8(4): e61002; https://doi.org/10.1371/journal.pone.0061002). This study used an expanded version of the SomaScan Assay to measure the levels of over 4,000 human proteins in nearly 1,500 serum samples. The samples were from patients in seven different countries who were diagnosed with TB or had TB-like symptoms and who were either HIV negative or positive. While some of the proteins that distinguished TB from non-TB groups were the same as those identified previously, many were new. This prompted the investigators to create and validate a refined six-protein model with 90% sensitivity and 80% specificity. These results reached the performance criteria outlined by WHO for point-of-care TB screening and justify further diagnostic development.

Anderson, J *et al*. (2017) “Interleukin 1 receptor-like 1 protein (ST2) is a potential biomarker for cardiomyopathy in Duchenne muscular dystrophy.” *Pediatr Cardiol* **38**(8): 1606-1612.

https://www.ncbi.nlm.nih.gov/pubmed/28821969

Duchenne muscular dystrophy (DMD) is a rare genetic disorder that causes progressive loss of muscle function until an early death, usually from heart muscle failure. Early detection of heart disease is critical for prolonging the lives of DMD patients but is difficult since most DMD patients do not display typical symptoms. To try to identify biomarkers of DMD cardiac disease, this study from the Children’s Research Institute used the SomaScan Assay to measure the levels of 1125 proteins in blood serum from DMD patients with or without heart disease and compared them to those of healthy controls. Elevated levels of the inflammation protein ST2 were seen in DMD patients with cardiac dysfunction compared to DMD patients with normal cardiac function and controls. These results warrant further investigation to see if ST2 can be used to monitor heart disease progression in DMD patients and to enable early detection, which is essential for starting mitigation therapies.

Ali A *et al.* (2017) “Efficacy of individualised diets in patients with irritable bowel syndrome: a randomised controlled trial.” *BMJ Open Gastro* **4**(1): e000164.

http://bmjopengastro.bmj.com/content/4/1/e000164

Irritable bowel syndrome (IBS) is a chronic condition that affects the large intestine. Although IBS does not appear to harm the tissue, the symptoms can be painful, embarrassing or even disabling for sufferers. The exact cause of IBS is unknown and there is no cure, but a new study from investigators at Yale University provides evidence that avoiding foods that trigger inflammation can help alleviate IBS symptoms.

The researchers conducted a four-week dietary intervention on 58 adults with IBS. Each participant was tested for sensitivity to various foods, and then half were told to avoid foods that activated their white blood cells (intervention group), and the other half were told to avoid foods that did not activate their white blood cells (control group). IBS symptoms and quality of life were assessed prior to starting the diet, on the last day of the diet, and four weeks after ending the diet. All participants showed some improvement (likely a placebo effect), but those in the intervention group reported feeling significantly better than those in the control group. SomaScan analysis of blood from six people with the best responses showed reduced levels of elastase, an enzyme that degrades various proteins and may affect gut permeability. This finding may provide new insight into the mechanisms by which diet—and subsequent inflammation—contributes to IBS.

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Wagner, BD *et al.* (2017) "Proteomic profiles associated with early echocardiogram evidence of pulmonary vascular disease in preterm infants." *Am J Respir Crit Care Med* **197**(3): 394-397.

https://www.ncbi.nlm.nih.gov/pubmed/28650220

Many premature babies are diagnosed with pulmonary vascular disease (PVD), which is characterized by abnormal blood flow between the heart and lungs. In this study from the University of Colorado Denver, the SomaScan Assay was used to measure proteins in blood samples from 100 preterm infants, 44 of which had PVD. Researchers identified 18 proteins that a week after birth could distinguish babies who developed PVD from those who did not. Eight of these proteins had no previous association with PVD. Although preliminary, these results may provide insight into why some infants develop respiratory problems, and how these problems contribute to lung diseases in adulthood. The authors note that the SomaScan is particularly well-suited for neonatal studies since only a small amount of blood (50uL serum) is needed to measure >1000 proteins.

Wang, J *et al.* (2017) "Identification of unique proteomic signatures in allergic and non-allergic skin disease." *Clin Exp Allergy* **47**(11): 1456-1467*.*

https://www.ncbi.nlm.nih.gov/pubmed/28703865

Chronic inflammatory conditions such as psoriasis (PS), atopic dermatitis (eczema, AD) and contact dermatitis (CD) cause skin rashes that can be itchy, painful or embarrassing. Accurate diagnosis is needed for effective management but can be difficult without a skin biopsy. Investigators at MedImmune used the SomaScan Assay to measure the levels of 1,129 proteins in blood serum taken from 12 patients with PS, 20 with AD, 10 with CD, 10 with both AD and CD, and 10 healthy controls. Overall, 66 proteins were significantly increased and 64 proteins were significantly decreased in at least one of the diseases, and PS, AD and CD could be distinguished from one another based on their unique protein signatures. These data need further validation, but measuring the circulating proteome may lead to a less invasive method for diagnosing inflammatory skin conditions and provide insights into disease pathogenesis and targeted treatments for severe cases.

Aghaeepour, N *et al.* (2017) "An immune clock of human pregnancy." *Sci Immunol* **2**(15): eaan2946.

https://www.ncbi.nlm.nih.gov/pubmed/28864494

A successful pregnancy requires that the mother's immune system can still attack foreign invaders but leave the growing fetus alone. Researchers at Stanford University found that this trick requires a series of precisely timed immune adaptations throughout fetal development. They obtained blood samples collected at early, middle, late and post-pregnancy time points for 18 women who delivered at full-term and then analyzed them using mass cytometry (a technique that can determine which immune cells are present and how they respond to compounds that mimic bacteria and viruses). They fed these data into a computer algorithm to develop a model that predicts the immune system changes that occur over the course of a normal pregnancy, and then validated the resulting model on 10 additional women. Using the SomaScan Assay, they identified those proteins that likely have a critical role in modulating the function of certain types of white blood cells during

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pregnancy. The researchers next hope to compare blood samples from mothers who deliver too early to see if premature births can be predicted and prevented.

Giannitsis, E *et al.* (2017) "Aptamer-based proteomic profiling for prognostication in pulmonary arterial hypertension." *Lancet Respir Med* **5**(9): 671-672.

https://www.doi.org/10.1016/S2213-2600(17)30209-6

—and—

Rhodes, CJ *et al.* (2017) "Plasma proteome analysis in patients with pulmonary arterial hypertension: an observational cohort study." *Lancet Respir Med* **5**(9): 717-726.

https://www.ncbi.nlm.nih.gov/pubmed/28624389

In this multicenter study, researchers from the UK, France and Germany used the SomaScan Assay to measure the levels of 1,129 proteins in blood samples from patients with pulmonary arterial hypertension (PAH). PAH is a rare, incurable disease where the small arteries in the lung progressively narrow, and the heart is forced to pump harder and harder until it eventually fails. The investigators identified nine proteins that differentiated PAH survivors from non-survivors and used this protein panel to develop a risk score that predicted patient survival better than existing clinical tests. The protein-based risk score was then validated on two separate patient cohorts, including one that contained 43 paired plasma samples taken when PAH was first diagnosed and after treatment. Increased risk scores at follow-up correlated with poorer survival rates and outperformed established measures. These results suggest that the nine-protein risk score could be used to monitor PAH progression, assess treatment efficacy and stratify patients in clinical trials. Further investigation of the proteins that make up the panel may provide insights into the causes of PAH and possible therapeutic targets.

In an accompanying commentary, Giannitsis, Mueller-Hennessen and Katus state that, “The findings raise expectations that novel proteomics-based technologies will ultimately find their way into routine clinical practice because protein biomarkers can be helpful for early detection of disease, diagnosis, differential diagnosis, prognosis, and allow monitoring of disease and guidance of targeted therapy.”

Belongie, KJ *et al.* (2017) “Identification of novel biomarkers to monitor β-cell function and enable early detection of type 2 diabetes risk.” *PLoS One* **12**(8): e0182932.

https://www.ncbi.nlm.nih.gov/pubmed/28846711

Progression to type 2 diabetes is caused by a decline in function of pancreatic beta cells that produce and secrete insulin. Current methods for assessing beta cell function lack accuracy and reproducibility, so it is difficult to predict whether a person with higher than normal blood sugar levels will progress to diabetes. This is important since as of 2015, diabetes was the seventh leading cause of death in the US and an estimated 84.1 million American adults were pre-diabetic.

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In this article, an international team lead by investigators at Janssen Pharmaceuticals and the University of Glasgow conducted a retrospective study of blood samples from the RISC (Relationship between Insulin Sensitivity and Cardiovascular Disease) cohort, a well-characterized group of healthy, non-diabetic Europeans whose beta cell function and insulin sensitivity were tested at baseline and after three years. The researchers profiled plasma proteins and microRNAs in 40 RISC participants who showed the largest decline in beta cell function at follow up and compared them to 40 matched controls who showed no decline. The SomaScan Assay analysis showed several proteins whose levels were significantly different between the two groups. Some such as adiponectin, a hormone that regulates glucose, have known links to type 2 diabetes, but others were novel. Many of the proteins and RNAs were associated with a process that is important for pancreas formation during development. If validated, these results could provide better indicators of beta cell function and new prevention therapies for type 2 diabetes.

Erez, O *et al.* (2017) "The prediction of late-onset preeclampsia: Results from a longitudinal proteomics study." *PLoS One* **12**(7): e0181468.

https://www.ncbi.nlm.nih.gov/pubmed/28738067

Preeclampsia is a pregnancy condition characterized by maternal high blood pressure that can progress rapidly and result in serious or even fatal complications for mother and baby. A recent study found that in 2012, the medical costs of preeclampsia were $2.18 billion for the first year after delivery. To identify patients at risk of developing late-onset (after 34 weeks) preeclampsia, scientists at the NIH and Wayne State University used the SomaScan Assay to measure the levels of 1,125 proteins in plasma from women who had normal pregnancies and those who experienced late-onset preeclampsia. Over the course of gestation, 36 proteins differed significantly between the two groups. Of these, the best predictors were high levels of the immune protein matrix metalloproteinase 7 (MMP-7) early in pregnancy (8-16 weeks) and low levels of the placental growth factor (PIGF) later in pregnancy (after 22 weeks). In addition, decreased PIGF levels correlated with the more severe form of preeclampsia. These results suggest that monitoring protein levels during pregnancy can help identify mothers who will develop late-onset preeclampsia and those who are at greatest risk for complications. This information could help physicians manage and treat the disorder, improve the safety of mother and child and lower the associated health costs.

Fitzgibbons, TP *et al.* (2017) “Activation of inflammatory and pro-thrombotic pathways in acute stress cardiomyopathy” *Frontiers in Cardiovascular Medicine* **4**: 49.
https://www.ncbi.nlm.nih.gov/pubmed/28824923

Stress cardiomyopathy (SCM) is a temporary weakening of the heart that is triggered by intense emotional or physical stress (e.g., loss of a loved one, winning the lottery, asthma attack, etc.). Although it is not caused by clogged arteries, SCM symptoms mimic those of a heart attack (shortness of breath, chest pain), and patients are often subject to unnecessary heart catheterization. To identify markers of SCM, a group led by investigators at the University of Massachusetts medical school used the SomaScan Assay to measure the levels of 1,310 proteins in blood serum from patients with SCM, patients with acute myocardial infarction (AMI) and normal controls. They found that proteins involved in inflammation and coagulation were activated in SCM patients *vs.* normal controls. This finding was unexpected and may explain why SCM patients are at higher risk for future heart disease or heart failure. Four proteins were increased in SCM relative to AMI

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compared to normal controls. These results require further validation but may provide better, less invasive ways to distinguish SCM from heart attack patients.

Sun, HH *et al.* (2017) "Diagnosis and prognosis-review of biomarkers for mesothelioma." *Ann Transl Med* **5**(11): 244.

https://www.ncbi.nlm.nih.gov/pubmed/28706912

Malignant pleural mesothelioma (MPM) is an aggressive lung cancer caused by previous asbestos exposure, usually decades before the disease is detected. This review discusses the most recent and promising markers of MPM — including a panel of 13 proteins discovered using the SomaScan Platform (Ostroff, RM *et al.* (2012) *PLoS One* **7**(10): e46091; https://doi.org/10.1371/journal.pone.0046091) — and their potential for diagnosing and treating future MPM patients.

Wasiak, S *et al.* (2017) "Downregulation of the complement cascade in vitro, in mice and in patients with cardiovascular disease by the BET protein inhibitor apabetalone (RVX-208)." *J Cardiovasc Transl Res,* **10**(4): 337-347.

https://www.ncbi.nlm.nih.gov/pubmed/28567671

Apabetalone (RVX-208) is a first-in-class small molecule drug being developed by Resverlogix Corp. to treat cardiovascular disease (CVD). To better understand the biological pathways that are modulated by RVX-208, scientists at Resverlogix used the SomaScan Assay to measure blood proteins in plasma samples from patients with coronary artery disease who were given either placebo or RVX-208. They found that RVX-208 leads to a significant reduction in circulating levels of complement proteins and activators. The complement system is part of the body's innate immune response that promotes inflammation by helping antibodies and white blood cells kill microbes and clear damaged cells. Complement activity is tightly controlled since overstimulation is associated with chronic inflammation, susceptibility to infectious disease, metabolic syndrome and atherosclerosis. Reduced expression of complement proteins by RVX-208 did not appear to interfere with normal immune function as there was no increase in infections amongst those taking RVX-208. These results suggest that repressing the complement system may contribute to the decreased incidence of major adverse cardiac events seen in RVX-208 clinical trials and provide a general strategy for reducing CVD risk.

DeBoer, EM *et al.* (2017) "Proteomic profiling identifies novel circulating markers associated with bronchiectasis in cystic fibrosis." *Proteomics Clin Appl* **11**(9-10). **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/28452194

Bronchiectasis is a condition where the lung airways thicken and become damaged due to inflammation. It is a hallmark of cystic fibrosis (CF) and is linked to disease progression and mortality. Current techniques for monitoring bronchiectasis are CT scanning (which involves repeated radiation exposure) and bronchoalveolar lavage (which is invasive). Thus, finding noninvasive biomarkers of bronchiectasis is highly desirable. Researchers at the University of Colorado Medical School used the SomaScan Assay to measure plasma protein levels in 26 children with CF. Twenty-two proteins showed significant correlation with the severity of bronchiectasis and structural lung injury as deduced from CT scans. Several were novel proteins that has not been previously linked to CF or bronchiectasis and with further validation may be a less harmful way to assess structural lung damage in children with CF.

Wang, T *et al.* (2017) "GDF15 is a heart-derived hormone that regulates body growth." *EMBO Mol Med* **9**(8): 1150-1164.

https://www.ncbi.nlm.nih.gov/pubmed/28572090

Bodily organs communicate with each other by secreting hormones that help regulate metabolism and maintain whole body health. Little is known of heart-derived hormones, although heart disease is associated with Failure To Thrive (FTT), a condition where children do not grow normally. Researchers at the Children's Hospital of Philadelphia and the University of Pennsylvania of Perelman School of Medicine used the SomaScan Assay and RNA sequencing to identify plasma proteins whose levels were altered in a mouse model of human FTT. They identified growth differentiation factor 15 (GDF15) as a heart secreted factor that inhibits growth hormone signaling by the liver. They found elevated plasma concentrations of GDF15 in children with heart disease compared to age-matched healthy controls. Furthermore, those with heart disease and FTT had GDF15 levels that were 80% higher than those with heart disease and normal body weight.

Howson, JMM *et al.* (2017) "Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms." *Nat Genet* **49**(7): 1113-1119.

https://www.ncbi.nlm.nih.gov/pubmed/28530674

An international team of scientists led by researchers at the University of Cambridge, the University of Pennsylvania and Stanford University conducted a large-scale study of genetic variants associated with coronary artery disease (CAD). They analyzed results from over 250,000 CAD patients and controls and identified 15 new regions of the genome that had not been previously linked to CAD. These regions contain genes that are involved in cellular adhesion, atherosclerosis, white blood cell migration, inflammation and smooth muscle cell differentiation. To identify the disease pathways and biological functions controlled by these regions, the researchers conducted protein profiling of 3,301 blood samples using the SomaScan Assay. One DNA variant correlated with expression of apoliproprotein L1, a major component of high density lipoprotein (HDL) particles. Another DNA variant correlated with levels of protein C, which helps maintain the permeability of blood vessel walls. These and previous results point to both traditional (cholesterol) and novel (arterial wall) mechanisms that lead to CAD susceptibility.

Tasaki, S *et al.* (2017) "Multiomic disease signatures converge to cytotoxic CD8 T cells in primary Sjogren's syndrome." *Ann Rheum Dis* **76**(8): 1458-1466.

https://www.ncbi.nlm.nih.gov/pubmed/28522454

The goal of this research is to elucidate the pathology of Sjögren syndrome (SS), an autoimmune disease that attacks the tear and salivary glands. Previously, the researchers used the SomaScan Assay to profile serum proteins in samples from

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SS patients vs. healthy controls (Nishikawa, A et al. (2016) *Arthritis Res Ther* 18(1): 106; https://dx.doi.org/10.1186%2Fs13075-016-1006-1). In this study, they profiled RNA transcripts of the same blood samples and integrated the two data sets. Their ‘multiomic’ approach identified SS-associated pathways and linked them to different white blood cell types. These results should aid development of targeted therapies and biomarkers of disease progression.

Westwood, S *et al.* (2017) "The influence of insulin resistance on cerebrospinal fluid and plasma biomarkers of Alzheimer's pathology." *Alzheimers Res Ther* **9**(1): 31.

https://www.ncbi.nlm.nih.gov/pubmed/28441961

Insulin resistance (IR) is a pathological condition in which the body fails to respond to insulin. Previous research demonstrated that IR may contribute to mental decline and an increased risk of developing Alzheimer’s disease (AD). To better define the relationship between IR and AD, researchers at Oxford used the SomaScan Assay to measure protein levels in plasma and cerebrospinal fluid (CSF) from cognitively healthy men with IR compared to age-matched controls. They observed differential expression of 200 proteins in CSF and 487 proteins in plasma between the IR and non-IR groups. Twenty-five proteins were associated with both IR and AD and are potential markers of shared pathology. Although promising, further investigation is needed to identify common biological pathways affected by IR and AD.

Saleheen, D *et al.* (2017) "Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity." *Nature* **544**(7649): 235-239.

https://www.ncbi.nlm.nih.gov/pubmed/28406212

Human ‘knockouts’ are people who lack functional copies of a particular gene. In most populations where the parents are unrelated, natural knockouts are very rare. However, in Pakistan many people marry their first cousins, which increases the chances that children will inherit mutant copies of the same gene from both parents.

In this study, an international team led by researchers at the Broad Institute of Harvard and MIT sequenced the genes of 10,503 participants in the Pakistani Risk of Myocardial Infarction Study (PROMIS) and looked for loss of function mutations. The rate of inbreeding in PROMIS participants is 4-fold higher than in typical European or African American populations. They found 1,317 different genes that they predicted were inactivated, representing approximately 7% of known protein-coding genes.

To better understand the consequences of loss of function mutations in living people, the researchers measured more than 200 biochemical disease traits for 426 genes that were knocked out in two or more people. In addition, for 84 participants they analyzed blood levels of 1,310 proteins using the SomaScan Assay. A detailed analysis of human knockouts of apolipoprotein C3 (apoC3) found that they had almost no circulating apoC3 protein. ApoC3 impedes fat clearance and is a drug target for heart disease. Compared to those with a functional gene, the human apoC3 knockouts had lower fasting levels of triglycerides and increased levels of high density lipoprotein (HDL) cholesterol. People lacking apoC3 also had significantly lower levels of triglycerides in their blood after eating a fatty meal. This observation demonstrates that apoC3 protein can be removed from the body without harmful effects and suggests that inhibiting apoC3 protein may be an effective therapeutic strategy cardiovascular disease. This study serves as a proof-of-principle for future efforts to understand the biological consequences of systematically knocking out every gene in humans.

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Asai, A *et al.* (2017) "Paracrine signals regulate human liver organoid maturation from induced pluripotent stem cells." *Development* **144**(6): 1056-1064.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5358109/

Human induced pluripotent stem cells (iPSCs) can differentiate and self-organize into a liver “organoid” in a Petri dish. Investigators at Cincinnati Children’s Hospital Medical Center found that a three-dimensional architecture only forms when iPSC-derived liver cells (HE-iPSCs) are in direct contact with mesenchymal stem cells (MSCs) and human umbilical vein endothelial cells (HUVECs). However, maturation of HE-iPSCs from fetal to adult-like hepatocytes can be induced even when the cells are kept separate but allowed to exchange soluble factors. To identify these signaling molecules, the SomaScan Assay was used to analyze the supernatants of HE-iPSCs co-cultured with either MSCs, HUVECs or both. The levels of 228 proteins changed significantly (≥three-fold) when compared to HE-iPSCs cultured alone, and different proteins were secreted depending on the combination of cells that were present. These results will help further studies to dissect the mechanisms behind liver organogenesis and regeneration.

Trausch, JJ *et al.* (2017) "Development and characterization of an HPV Type-16 specific modified DNA aptamer for the improvement of potency assays." *Anal Chem* **89**(6): 3554-3561. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/28233502

Robust potency tests ensure that vaccines released to the public remain safe and effective. Most approved potency assays rely on antibody reagents, which have many drawbacks (e.g. time-consuming discovery process, limited shelf life, batch-to-batch variability, etc.). To get around these problems, researchers at Merck substituted an antibody with an aptamer in a human papilloma virus (HPV) potency assay. They worked with SomaLogic to create a custom SOMAmer reagent (named HPV-07) that binds tightly to HPV 16, a high-risk type for cervical cancer. HPV-07 was designed to bind selectively to HPV 16 in samples that contain many other HPV types. Competition experiments revealed that HPV-07 binds to the same epitope as a well-characterized HPV 16 antibody, and when used in an ELISA format, HPV-07 displayed high accuracy, precision and a wide linear range. The researchers then functionalized HPV-07 to develop a simple “mix and read” assay that was faster and cheaper to run than an ELISA. They note that the properties of SOMAmers could be exploited further to create a multiplexed assay that measures the potency of all antigens in a multivalent vaccine simultaneously.

Wood, GC *et al.* (2017) "A multi-component classifier for nonalcoholic fatty liver disease (NAFLD) based on genomic, proteomic, and phenomic data domains." *Sci Rep* **7**: 43238.

http://www.nature.com/articles/srep43238

Approximately 25% of Americans have non-alcoholic fatty liver disease (NAFLD), a disorder in which excess fat accumulates in the liver. NAFLD is often associated with obesity and can progress to more serious chronic conditions including liver inflammation, fibrosis and cirrhosis. Many people with NAFLD are asymptomatic, and commonly used tests of liver function lack the specificity and sensitivity to check for NAFLD. As obesity rates in the U.S. continue to rise, there is an urgent public health need for clinical biomarkers of NAFLD. In this study, researchers at the Geisinger Obesity Research Institute in

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Pennsylvania and National Jewish Health in Colorado used genomic, phenomic and proteomic data to develop an algorithm that predicts NAFLD in an extremely obese population. The data included a single nucleotide polymorphism in the PNPLA3 gene that is linked to NAFLD susceptibility, 16 clinical variables that had been shown previously to correlate with NAFLD, and 8 serum protein biomarkers of NAFLD identified by SomaScan Assay analysis. The results represent an important step toward developing a minimally invasive test for NAFLD diagnosis and prognosis.

Guiraud, S *et al.* (2017) "Identification of serum protein biomarkers for utrophin based DMD therapy." *Sci Rep* **7**: 43697.

http://www.nature.com/articles/srep43697

Duchenne muscular dystrophy (DMD) is a fatal degenerative muscle disorder that is caused by mutations in the gene that encodes "dystrophin," a critical muscle structure protein. Utrophin is a protein with high similarity to dystrophin (80% homology) that can compensate for loss of dystrophin function. Overexpression of utrophin prevents disease pathogenesis in a mouse model of DMD and is of great interest as a potential therapeutic strategy in humans. Researchers at the University of Oxford performed the SomaScan Assay on blood serum samples from wild type, dystrophin-null (*mdx*) and utrophin-overexpressing *mdx* (*Fiona*) mice. They identified 83 proteins that differed significantly in concentration (>two-fold) between *mdx* and wild type mice, 34 of which were fully restored to normal levels in *Fiona* mice. These proteins represent possible biomarkers that, if validated in humans, could be used to monitor disease progression and response to therapeutics.

Suhre, K *et al.* (2017) "Connecting genetic risk to disease end points through the human blood plasma proteome." *Nat Commun* **8**: 14357.

http://www.nature.com/articles/ncomms14357

Researchers at the Weill Cornell medical college in Qatar used the SomaScan Assay to investigate the impact of common gene variants on protein levels in human plasma. Using samples from a German cohort, they identified 539 single nucleotide polymorphism-protein associations and replicated over half of the results in an Arab and Asian cohort. The associations overlap with 57 genetic risk loci for 42 different disease endpoints. Interestingly, many of the proteins are modulated by variations that occur on different chromosomes. This study demonstrates how proteomics can help tie genomic observations to actual changes in physiology and pathology. The authors anticipate that further mining of their data will provide insights into disease-related biological pathways and therapeutic interventions.

Escolano, JM *et al.* (2017) "Selection of aptamers to *Neisseria meningitidis* and *Streptococcus pneumoniae* surface specific proteins and affinity assay using thin film AlN resonators." *Sensors and Actuators B: Chemical* **246**: 591-596. **(Subscription required)**

http://www.sciencedirect.com/science/article/pii/S0925400517303258

Bacterial meningitis is a frightening illness—victims can die within a few hours and survivors can be left with severe afflictions such as brain damage or hearing loss. Different kinds of bacteria can cause meningitis, of which *Neisseria*

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meningitidis and *Streptococcus pneumoniae* are the most common. Researchers in Madrid generated polyclonal SOMAmers to two bacterial surface-expressed proteins, PavA from *S. pneumoniae* and FHbp from *N. meningitidis* and demonstrated specific binding of the SOMAmers to their target proteins. This work represents an important first step towards creating a biosensor for rapid detection of bacterial meningitis.

van den Broek, TJ *et al.* (2017) "The impact of micronutrient status on health: correlation network analysis to understand the role of micronutrients in metabolic-inflammatory processes regulating homeostasis and phenotypic flexibility." *Genes Nutr* **12**: 5.

https://www.ncbi.nlm.nih.gov/pubmed/28194237

Health can be defined as the body's ability to adapt to environmental changes, such as infection, stress or exercise. Researchers in the Netherlands and Switzerland used this definition to study the roles of fat-soluble micronutrients in maintaining normal physiological processes. Plasma concentrations of vitamins A, D$_3$ & E and four carotenoids were measured for 36 overweight or obese males after overnight fasting and after eating a high fat shake. A proteomic analysis using the SomaScan Assay was conducted in parallel, and changes in protein levels were correlated with changes in micronutrient levels. The correlation analysis after the nutritional challenge was particularly interesting as it suggested that certain micronutrients (α-carotene, a vitamin A precursor; and γ-tocopherol, a form of vitamin E) are especially important for helping the body respond to oxidative and inflammatory stresses. This approach will be useful for quantifying the effects of diet on health.

Di Narzo, AF *et al.* (2017) "High-throughput characterization of blood serum proteomics of IBD patients with respect to aging and genetic factors." *PLoS Genet* **13**(1): e1006565.

https://doi.org/10.1371/journal.pgen.1006565

In this article, scientists at the Icahn School of Medicine at Mt. Sinai analyzed the blood serum of patients with inflammatory bowel disease (IBD)—ulcerative colitis and Crohn's disease (CD)—as well as healthy controls. They describe using the SomaScan Assay to identify serum proteins that correlate with CD and with aging. Within a CD cohort, they found 41 proteins that associated with previously identified gene loci, including a well-known IBD susceptibility locus. This study illustrates the value of the SomaScan Assay in interpreting genome-wide association study (GWAS) results and in gaining insight into the molecular events that cause IBD.

Sasayama, D *et al.* (2017) "Genome-wide quantitative trait loci mapping of the human cerebrospinal fluid proteome." *Hum Mol Genet* **26**(1): 44-51.

https://www.ncbi.nlm.nih.gov/pubmed/28031287

Measuring analytes in cerebrospinal fluid (CSF) can be useful for diagnosing diseases of the central nervous system. Researchers in Japan conducted a genome-wide study of single nucleotide polymorphisms (SNPs) in the CSF of 133 physically healthy individuals and used the SomaScan Assay to look for correlated changes in protein concentrations. They

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identified over 400 SNP-protein pairs, of which 28 had been shown previously to associate with specific traits or diseases. Interestingly, many of the protein associations appear to be unique to CSF (i.e., they had not been previously identified from blood). This suggests that gene variants differentially control protein levels in the central vs. peripheral nervous system. These results should aid future efforts to understand brain biochemistry and to discover new biomarkers for neurological diseases.

Jung, YJ *et al.* (2017) "Development of a protein biomarker panel to detect non-small-cell lung cancer in Korea." *Clin Lung Cancer* **18**(2): e99-e107. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/27836219

Lung cancer is the most common and most deadly cancer in the world. Early detection and treatment greatly improves chances of survival, but this can be difficult since people with early stage lung cancer are often asymptomatic. The only currently recommended screening test for lung cancer is a low-dose CT scan, which has a high false positive rate (23.3%). Investigators at the Ulsan College of Medicine in South Korea used results from the SomaScan Assay to construct a panel of seven protein biomarkers that could discriminate a Korean cohort with non-small cell lung cancer (NSLC) from negative controls. The ability of their protein panel to detect true positives was 75% overall and 61.9% for early stage (stages I & II) lung cancer. The seven-marker panel outperformed the common lung cancer marker Cyfra 21-1 in identifying NSLC at all four stages of disease, with an overall accuracy of 80.4% compared to 59.5%. The panel was also superior at distinguishing early stage NSLC from benign lung nodules. The results of this study could be useful for developing a better lung cancer diagnostic and a noninvasive test to evaluate lung nodules identified by CT screening for the Korean population.

Qiao, Z *et al.* (2017) "Proteomic study of hepatocellular carcinoma using a novel modified aptamer-based array (SomaScan™) platform." *Biochim Biophys Acta* **1865**(4): 434-443. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/27663888

Hepatocellular carcinoma (HCC) is the most common form of liver cancer and its incidence is expected to continue to grow. Accurate diagnosis and prognosis would greatly improve HCC treatments and clinical outcomes. Towards this end, researchers in Japan used the SomaScan Assay to compare global protein levels within HCC tumor and non-tumor tissue, as well as cancerous tissues with different vascular invasion status. The levels of 68 proteins were tumor-dependent, and eight proteins were associated with vascular invasion. With further validation underway, these data may help elucidate disease mechanisms and lead to improved tools for screening and evaluating HCC therapies.

Zyba, SJ *et al.* (2017) "A moderate increase in dietary zinc reduces DNA strand breaks in leukocytes and alters plasma proteins without changing plasma zinc concentrations." *Am J Clin Nutr* **105**(2): 343-351.

http://ajcn.nutrition.org/content/105/2/343.long

Researchers at the Children's Hospital Oakland Research Institute used the SomaScan Assay to analyze serum from 18 men who were fed zinc-fortified rice, a type of dietary supplement given to people in developing countries. They found that a modest increase in dietary zinc leads to an increase in the concentrations of proteins that prevent DNA damage, inflammation and oxidative stress. These results could help explain the connection between zinc deficiencies and chronic diseases such as cancer, diabetes and atherosclerosis.

Rice, LM *et al.* (2017) "A proteome-derived longitudinal pharmacodynamic biomarker for diffuse systemic sclerosis skin." *J Invest Dermatol* **137**(1): 62-70.

https://www.ncbi.nlm.nih.gov/pubmed/27640094

Diffuse cutaneous systemic sclerosis (dcSSc) is an autoimmune disease that is characterized by excessive collagen deposition that causes hardening of the skin. The disease can spread to internal organs including the heart, lungs, and kidneys and cause organ failure and death. Testing for serum autoantibodies (i.e., antibodies that attack “self” tissues) can be helpful for diagnosis, but autoantibody concentrations do not necessarily correlate with dcSSc severity, so they cannot be used to monitor disease progression or therapeutic response. The goal of this study was to use the SomaScan Assay to identify longitudinal biomarkers of dcSSc. Proteomic analysis of sera from two independent cohorts found 181 proteins with altered levels between dcSSc patients and healthy controls. Eight of the hits were subsequently validated, including three new proteins that had not been previously associated with dcSSc. A combination of two proteins (ST2 and SPON1) robustly described longitudinal changes and could prove useful for monitoring changes in dcSSc patients over time.

De Groote, MA *et al.* (2017) "Highly multiplexed proteomic analysis of quantiferon supernatants to identify biomarkers of latent tuberculosis infection." *J Clin Microbiol* **55**(2): 391-402.

https://www.ncbi.nlm.nih.gov/pubmed/27852671

An estimated two billion people are infected with tuberculosis (TB) worldwide, although not everyone who harbors the TB bacterium will become sick. Eliminating the disease will require better methods to identify and treat those with latent TB infection (LTBI). In this pilot study, researchers from Denver Health and SomaLogic ran the SomaScan Assay on untreated and TB antigen-stimulated plasma samples from LTBI positive and negative individuals. They identified several new proteins that distinguished those infected with TB from uninfected controls. These findings could lead to more accurate tests for diagnosing LBTI as well as the likelihood of progressing to active TB, which is a major limitation of currently available tests.

Billing, AM *et al.* (2017) "Complementarity of SomaScan to LC-MS/MS and RNA-seq for quantitative profiling of human embryonic and mesenchymal stem cells." *J Proteomics* **150**: 86-97.

https://www.ncbi.nlm.nih.gov/pubmed/27613379

“Dynamic range” is perhaps the single most difficult challenge in measuring the proteome in any meaningful way. In other words, proteins are present in any given biological fluid across a large range of concentrations, greater than ten logs of relative abundance. This particular challenge is the one best addressed by the SomaScan Assay, as demonstrated in this article. A research team at Weill Cornell Medical College in Dohar, Qatar (site of one of the first installations of the SomaScan Assay outside of SomaLogic), compared SomaScan with mass spectrometry (MS) and RNA sequencing (RNA-seq) in analyzing proteins from both human embryonic and mesenchymal stem cells. In addition to validating SomaScan results with other, more traditional approaches, their research underscores SomaScan's "deep reach" into the proteome to identify the "rarer" proteins that may be the most critical biomarkers for a range of diseases and conditions of interest.

Gramolini, A *et al.* (2016) "Identifying low-abundance biomarkers: Aptamer-based proteomics potentially enables more sensitive detection in cardiovascular diseases." *Circulation* **134**(4): 286-289.

https://www.ncbi.nlm.nih.gov/pubmed/27444931

—and—

Ngo, D *et al.* (2016) "Aptamer-based proteomic profiling reveals novel candidate biomarkers and pathways in cardiovascular disease." *Circulation* **134**(4): 270-285.

https://www.ncbi.nlm.nih.gov/pubmed/27444932

Following closely on the publication of results from the use of SomaScan to identify even low-concentration protein changes that foretell the personalized risk of cardiovascular events (see Ganz P *et al.* (2016) *JAMA* **315**(23): 2532-2541; https://doi.org/10.1001/jama.2016.5951), this set of studies by researchers at Beth Israel Deaconess Medical Center and the Broad Institute of MIT and Harvard demonstrates the power of the SomaScan Assay for finding novel biomarkers of cardiovascular disease in response to a "planned" heart attack (part of a unique treatment protocol for patients undergoing septal ablation for hypertrophic cardiomyopathy). Not only were potential low-abundance biomarkers consistently recovered from patient samples, but the proteins identified by SomaScan were also validated by rigorous mass spectrometry analysis. The relevance of these to "unplanned" myocardial infarctions is being further investigated. As summarized in the accompanying editorial by Anthony Gramolini, Edward Lau and Peter Liu, "If these technologies continue to develop apace as expected, we can look forward to a bounty of new insights for patient care even from minute amounts of liquid biopsies."

Sabatine, MS (2016) "Using aptamer-based technology to probe the plasma proteome for cardiovascular disease prediction." *JAMA* **315**(23): 2525-2526. **(Subscription required.)**

https://www.ncbi.nlm.nih.gov/pubmed/27327798

—and—

Ganz, P *et al.* (2016) "Development and validation of a protein-based risk score for cardiovascular outcomes among patients with stable coronary heart disease." *JAMA* **315**(23): 2532-2541.

https://www.ncbi.nlm.nih.gov/pubmed/27327800

Every patient diagnosed with stable coronary heart disease is currently treated aggressively in order to help prevent any future cardiovascular events. However, not every such individual is at significant risk of such events, leading to expensive overtreatment and mental anguish. In this breakthrough study, researchers from UCSF and SomaLogic used SomaScan to discover and validate a group of nine blood proteins whose levels can reliably and accurately predict who is at high or low risk of future events. These proteins can also be used to track who is getting closer to an event, and who is benefitting from preventative interventions. The accompanying editorial by Dr. Marc Sabatine from Harvard puts these findings in the context of emerging personalized or precision medicine, as well as the possibility that several of the novel proteins uncovered could be future therapeutic targets.

Heier, CR *et al.* (2016) "Identification of pathway-specific serum biomarkers of response to glucocorticoid and infliximab treatment in children with inflammatory bowel disease." *Clin Transl Gastroenterol* **7**(9): e192.

https://www.ncbi.nlm.nih.gov/pubmed/27628422

Inflammatory bowel disease (IBD) is a chronic condition where the body's immune system attacks its own digestive tract. The goal of most IBD treatments is to achieve remission, however there is increasing evidence that alleviating the symptoms does not ultimately improve outcomes. Repeated colonoscopy can be used to monitor patients' response to IBD therapies, but the technique is costly, invasive and can be risky, particularly for children. In order to find pharmacodynamic biomarkers of IBD, researchers at the Children's National Health Center in Washington, D.C. ran the SomaScan Assay on pediatric serum samples obtained before and after treatment with a corticosteroid (prednisone) or a biologic (infliximab) anti-inflammatory drug. They identified 18 proteins and 3 miRNAs whose levels changed in a similar manner (either increased or decreased) for both drugs. Eight of the markers that decreased are associated with inflammation, whereas many that increased are associated with resolving inflammation and tissue damage. With further validation, these protein biomarkers could be used to track treatment, optimize dosing, and accelerate new drug development for IBD patients.

Tsim, S *et al.* (2016) "Diagnostic and Prognostic Biomarkers in the Rational Assessment of Mesothelioma (DIAPHRAGM) study: protocol of a prospective, multicentre, observational study." *BMJ Open* **6**(11): e013324.

https://www.ncbi.nlm.nih.gov/pubmed/27884852

This publication describes the protocol for a clinical trial to assess the performance of protein biomarkers for malignant pleural mesothelioma (MPM). MPM is a rare, aggressive, pulmonary cancer that is usually caused by asbestos exposure. Previously, scientists at SomaLogic used the SomaScan Assay to develop a panel of 13 proteins from serum that could detect MPM with 92% accuracy (Ostroff, RM *et al.* (2012) *PLoS One* **7**(10): e46091; https://doi.org/10.1371/journal.pone.0046091). The goal of this new study is to see whether the SomaScan panel or fibulin-3 (a potential plasma biomarker of MPM) levels could provide clinically useful diagnostic and prognostic information. A non-invasive test that could distinguish MPM from confounding pleural malignancies would offer a major clinical advance over current approaches.

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Lynch, AM *et al.* (2016) "The relationship of novel plasma proteins in the early neonatal period with retinopathy of prematurity." *Invest Ophthalmol Vis Sci* **57**(11): 5076-5082.

https://www.ncbi.nlm.nih.gov/pubmed/27679852

Retinopathy of prematurity (ROP) is an eye disease that affects smaller premature infants and is a leading cause of childhood blindness worldwide. Not all premature babies develop ROP and not all babies affected by ROP experience impaired vision later in life. However, the risk factors for developing clinically significant (high-grade) ROP are not known. Researchers at the University of Colorado School of Medicine ran the SomaScan Assay on blood samples obtained from pre-term infants in the first week of life, and found several proteins that appear to be associated with clinically significant ROP. Although preliminary, these proteins may be diagnostic of ROP severity, as well as potential targets for future therapeutics. The authors noted that the ability to measure low abundant proteins was an important advantage of using aptamer-based technologies for this study.

Ashley, SL *et al.* (2016) "Six-SOMAmer index relating to immune, protease and angiogenic functions predicts progression in IPF." *PLoS One* **11**(8): e0159878.

https://www.ncbi.nlm.nih.gov/pubmed/27490795

Idiopathic pulmonary fibrosis (IPF, the thickening of lung tissue—and thus compromise of breathing leading to death—for reasons unknown) is likely several different diseases at the molecular level, requiring different therapeutic approaches. Some people with IPF manage well over time; others rapidly progress and die. Being able to tell the difference in a non-invasive manner should lead to better treatment decisions and outcomes. A group of researchers from Medimmune and the University of Michigan applied the SomaScan Assay to blood samples from a group of IPF patients to identify potential biomarkers that distinguish long-term non-progressors from those who progressed quickly. A six-analyte index (signature) of proteins was identified, which not only suggests a better way to manage patients but also reveals some novel IPF biology to further explore.

Welton, JL *et al.* (2016) "Proteomics analysis of vesicles isolated from plasma and urine of prostate cancer patients using a multiplex, aptamer-based protein array." *J Extracell Vesicles* **5**: 31209.

https://www.ncbi.nlm.nih.gov/pubmed/27363484

Despite the high prevalence of prostate cancer, most men will die with the disease rather than of it. There is a huge unmet medical need to be able to tell the difference. The measurement of PSA (prostate-specific antigen) in the blood is a mixed success at best: Better biomarkers are needed. In this study, scientists at Cardiff University look at the protein profiles of “exosomes,” small vesicles shed by various cell types (including cancer), to determine if they can pick up prostate cancer-specific markers in the blood and urine of metastatic prostate cancer patients (and normal controls for comparison). Although a preliminary study, the researchers establish a proof of principle for this approach, and preliminary data that suggest its viability.

Wu, D *et al.* (2016) "Incorporation of Slow Off-Rate Modified Aptamers reagents in single molecule array assays for cytokine detection with ultrahigh sensitivity." *Anal Chem* **88**(17): 8385-8389.

https://www.ncbi.nlm.nih.gov/pubmed/27529794

Recent concerns about antibody consistency and quality in both clinical and bench research applications have many scientists looking for more reliable alternatives. In this article, researchers from Tufts University and SomaLogic demonstrate that SOMAmer reagents can be used in place of antibodies in ultrasensitive “single molecule array (Simoa) assays,” demonstrating their efficiency in measuring six different cytokine targets. The authors suggest that this combination “will greatly benefit both biomarker discovery and disease diagnostic fields.”

Hathout, Y *et al.* (2016) "Serum pharmacodynamic biomarkers for chronic corticosteroid treatment of children." *Sci Rep* **6**: 31727.

http://www.nature.com/articles/srep31727

Corticosteroids are used effectively across a large number of diseases and conditions in which inflammation plays at least a partial role. But regular, repeated use can bring along a host of side effects, many of which can be worse than the initial disease or condition. In one particular disease, Duchenne muscular dystrophy (DMD), corticosteroids are a current standard of care, but efficacy gives way to safety issues over time, varying by patient. In this article, a multicenter group of researchers use the SomaScan Assay to identify protein biomarkers of corticosteroid efficacy and side effects, with the goal of developing a diagnostic tool to optimize the use of these powerful treatments in DMD patients—and young patients with other diseases—over time.

Gupta, V *et al.* (2016) "An evaluation of an aptamer for use as an affinity reagent with MS: PCSK9 as an example protein." *Bioanalysis* **8**(15): 1557-1564. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/27397798

In this article, a research group at Merck Research Laboratories further demonstrates the extensive utility of individual SOMAmer reagents across multiple life science and clinical applications. They use a particular SOMAmer reagent, in this case one that binds the PCSK9 protein (a target of great interest in cardiovascular medicine), to enrich the protein from patient samples for subsequent analysis by mass spectrometry. The PCSK9 SOMAmer performed as well as—if not better than—PCSK9 antibodies, but provides significant advantages over those antibodies in terms of consistency, background, and stability.

Lukjanenko, L *et al.* (2016) "Loss of fibronectin from the aged stem cell niche affects the regenerative capacity of skeletal muscle in mice." *Nat Med* **22**(8): 897-905.

https://www.ncbi.nlm.nih.gov/pubmed/27376579

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Muscle has a remarkable ability to regenerate itself via dedicated muscle stem cells and their surrounding microenvironment of signaling and other molecules (the so-called stem cell “niche”). However, that ability decreases with age, for reasons that are still unknown. In this paper, an international research collaboration led by scientists from Nestle Institute of Health Sciences undertook a series of studies to determine the cause (and potential treatment) of aging muscle deterioration. Among those studies was a SomaScan Assay to determine what proteins might be altered in the aged muscle stem cell niche vs. younger muscle. They found that one protein in particular, fibronectin, was significantly decreased in the older muscle tissue, and addition of fibronectin could regain the regenerative capability in that muscle. They also demonstrate the structural mechanism by which fibronectin helps maintain muscle regeneration. While further studies are needed, this is an exciting insight into how to perhaps modulate one of the more devastating bodily effects of aging.

Petek, LM *et al.* (2016) "A cross sectional study of two independent cohorts identifies serum biomarkers for facioscapulohumeral muscular dystrophy (FSHD)." *Neuromuscul Disord* **26**(7): 405-413.

https://www.ncbi.nlm.nih.gov/pubmed/27185459

Facioscapulohumeral muscular dystrophy (FSHD), the third most common genetic disease of skeletal muscle, is usually first diagnosed, progressing towards increased disability, decreased quality of life, and death. Although there are potential treatments, the slow and often sporadic progression of FSHD makes it difficult, at best, to assess their efficacy. Thus, there is a great need for robust, reliable biomarkers. This preliminary study, using SomaScan, identified several biomarkers that appear to correlate with clinical severity, though further studies are needed.

Nishikawa, A *et al.* (2016) "Identification of definitive serum biomarkers associated with disease activity in primary Sjögren's syndrome." *Arthritis Res Ther* **18**(1): 106.

https://www.ncbi.nlm.nih.gov/pubmed/27180164

Sjögren’s syndrome (SS), an autoimmune disease in which immune cells target the body’s moisture producing cells, is the third most common rheumatic autoimmune disorder (after rheumatoid arthritis and systemic lupus erythematosus). Despite its prevalence, SS is not well understood, and treatment interventions have had mixed success at best. In an effort to identify markers of disease and potential new drug targets, Nishikawa *et al.* used SomaScan in samples from 88 patients with primary SS (i.e., patients without other rheumatic diseases noted). They identified 82 proteins associated with pSS, nine of which were associated with disease activity and five of these validated by traditional ELISA. Larger studies are underway to determine additional markers and to evaluate these markers as potential new therapeutic targets.

Marion, T *et al.* (2016) "Respiratory mucosal proteome quantification in human influenza infections." *PLoS One* **11**(4): e0153674.

https://www.ncbi.nlm.nih.gov/pubmed/27088501

Influenza virus seriously sickens three to five million people worldwide each year, causing an estimated 250,000 to 500,000 deaths annually. The degree of morbidity and mortality depends not only on the strain of virus, but also on the interaction of

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the virus with host factors of infected individuals. In one of the first studies of its kind, an international group of researchers used SomaScan to understand the intricate interplay of host and virus proteins by identifying protein changes in nasal secretions during infection and disease progression. Though preliminary, this study provides a large number of new insights and potential new research directions for addressing this common but deadly virus.

Hathout, Y *et al.* (2016) "Clinical utility of serum biomarkers in Duchenne muscular dystrophy." *Clin Proteomics* **13**: 9.

https://www.doi.org/10.1186/s12014-016-9109-x

In this review, investigators at the Center for Genetic Medicine, Children's National Healthy System in Washington, DC highlight advances in techniques such as the SomaScan Assay for developing minimally invasive blood biomarkers to assess disease progression and response to treatments in Duchenne muscular dystrophy.

Drolet, DW *et al.* (2016) "Fit for the eye: aptamers in ocular disorders." *Nucleic Acid Ther* **26**(3): 127-146.

http://online.liebertpub.com/doi/pdf/10.1089/nat.2015.0573

The first FDA-approved aptamer-based drug, Macugen, was developed for the treatment of the "wet form" of the eye disorder age-related macular degeneration (AMD). Two additional aptamer-based drugs for AMD are in late-stage clinical development. This review article covers not only the history of the AMD-directed aptamers, but also discusses the many other potential therapeutic opportunities for aptamers (including SOMAmer reagents) in ophthalmological indications with significant unmet medical need.

Murota, A *et al.* (2016) "Serum proteomic analysis identifies interleukin 16 as a biomarker for clinical response during early treatment of rheumatoid arthritis." *Cytokine* **78**: 87-93. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/26700586

In this study, researchers from Keio University and Takeda Pharmaceutical Company used the SomaScan Assay to identify blood (serum)-based biomarkers of rheumatoid arthritis (RA) that could be correlated with disease progression and treatment efficacy. Comparing RA patients with non-RA volunteers, the researchers found that the serum levels of interleukin-16 (IL-16) are a better indicator than other measurement in current use, and thus IL-16 may be a more useful clinical biomarker of response to treatment. They also note that such studies have been difficult to impossible to perform prior to the availability of the "new, reliable and comprehensive" SomaScan Assay.

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Sattlecker, M *et al.* (2016) "Longitudinal protein changes in blood plasma associated with the rate of cognitive decline in Alzheimer's disease." *J Alzheimers Dis* **49**(4): 1105-1114. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/26599049

One of the more powerful uses of the SomaScan Assay is in performing “longitudinal” proteomics (i.e., tracking the changes in protein levels over time). In this study, an international group of researchers looked for changes in the blood of patients who transitioned from mild cognitive impairment (MCI) to Alzheimer’s disease (AD) over the course of the year, comparing those changes to individuals with stable MCI, diagnosed AD, and controls (i.e., no MCI or AD). They found that the levels of proteins known to be involved in the complement pathway were significantly elevated in patients undergoing rapid transition from MCI to AD. These results reveal not only potential new biomarkers for testing the efficacy of investigational AD drugs, but also suggest new drug targets. Longer-term validation studies are underway.

Hirota, M *et al.* (2016) "Chemically modified interleukin-6 aptamer inhibits development of collagen-induced arthritis in cynomolgus monkeys." *Nucleic Acid Ther* **26**(1): 10-19.

https://www.ncbi.nlm.nih.gov/pubmed/26579954

In this manuscript, researchers from SomaLogic and Otsuka Pharmaceutical describe a series of studies that demonstrate that treatment with a novel SOMAmer reagent can significantly delay the onset and reduce the severity of rheumatoid arthritis (RA) in a cynomolgus monkey model of the disease. The SOMAmer molecule used in these studies, named SL1026, was initially selected for its ability to directly bind and block the signaling of the critical inflammatory protein interleukin-6 (IL-6), which is known to be involved in RA onset and progression. Because it is based on nucleic acids rather than amino acids, SL1026 offers certain advantages over antibody-based drugs such as tocilizumab, including the lack of an immune response to the drug itself, and a more consistent chemical rather than biological synthesis method.

Lynch, AM *et al.* (2016) "The relationship of circulating proteins in early pregnancy with preterm birth." *Am J Obstet Gynecol* **214**(4): 517 e511-518.

https://www.ncbi.nlm.nih.gov/pubmed/26576488

Preterm birth is major global health problem, and babies born preterm (<37 weeks gestation) have an elevated risk of a spectrum of medical problems. In this paper, researchers from the University of Colorado used the SomaScan Assay to identify a signature of protein biomarkers that could foretell pre-term birth risk, with the goal of making successful early intervention possible.

McArdle, A *et al.* (2016) "Developing clinically relevant biomarkers in inflammatory arthritis: A multiplatform approach for serum candidate protein discovery." *Proteomics Clin Appl* **10**(6): 691-698. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/26332844

Blood-based biomarkers that can distinguish between psoriatic arthritis (PsA) and rheumatoid arthritis (RA) are a significant medical need, particularly to guide treatment choice of available drugs. In this manuscript, the authors combine three proteomics approaches to identify such markers (LC-MS/MS, a Luminex immunoassay, and the SomaScan Assay), and compare the results. They found 42 (LC-MS/MS), 3 (Luminex), and 127 (SomaScan Assay) proteins respectively that distinguish between PsA and RA patients. Besides providing the largest number of reproducible protein findings, the SomaScan Assay covered a significantly broader range of the blood proteome compared to the other two approaches.

Voyle, N *et al.* (2015) "Blood protein markers of neocortical amyloid-beta burden: a candidate study using SOMAscan technology." *J Alzheimers Dis* **46**(4): 947-961.

https://www.doi.org/10.3233/JAD-150020

Amyloid beta (Aβ) plaques in the brain are a hallmark of Alzheimer's disease (AD), and studies have shown that plaques develop decades before clinical symptoms arise. In this study, researchers at Kings College London, Janssen R&D, CSIRO in Australia, GE Global Research and NHIR Maudsley Biomedical Research Centre in the UK investigated blood proteins previously linked to Aβ burden in the brain using the SOMAscan Assay and serum samples from an Australian study of aging. Two proteins, pancreatic polypeptide and IgM showed a significant association with Aβ assessed by brain imaging and warrant further investigation as potential blood-based makers of AD.

Olson, KA *et al.* (2015) "Association of growth differentiation factor 11/8, putative anti-ageing factor, with cardiovascular outcomes and overall mortality in humans: analysis of the Heart and Soul and HUNT3 cohorts." *Eur Heart J* **36**(48): 3426-3434.

https://www.ncbi.nlm.nih.gov/pubmed/26294790

This study is particularly notable for its demonstration that Growth Differentiation Factor-11/8 (GDF-11/8) may play a role in humans similar to that seen previously in mice (see Loffredo FS *et al.* 2013, below). The authors demonstrate that higher levels of GDF-11/8 are associated with a lower risk of cardiovascular events and death in patients with stable ischemic heart disease, suggesting that the molecular pathway represented by GDF-11/8 is a target for reducing cardiovascular risk associated with aging in humans.

Kiddle, SJ *et al.* (2015) "Plasma protein biomarkers of Alzheimer's disease endophenotypes in asymptomatic older twins: early cognitive decline and regional brain volumes." *Transl Psychiatry* **5**: e584.

https://www.ncbi.nlm.nih.gov/pubmed/26080319

Although there are no treatments known today that can delay or even prevent Alzheimer's disease (AD), having useful markers of very early onset (pre-symptomatic) is critical to testing new therapeutic interventions. Imaging approaches (e.g., MRI or PET) can detect early signs of Alzheimer's, though they are expensive and require high levels of expertise. In this study of asymptomatic older twins, the authors build on earlier work they have done by applying the SomaScan Assay to find

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early blood markers of AD, as well as looking at genetic contributions. They detected two proteins in particular, called “MAPKAPK5” and “MAP2K4,” which are under further evaluation now as potential biomarkers for clinical trials.

Hattori, K *et al.* (2015) "Increased cerebrospinal fluid fibrinogen in major depressive disorder." *Sci Rep* **5**: 11412.

https://www.ncbi.nlm.nih.gov/pubmed/26081315

“Major depressive disorder” (MDD), like many common diseases, is a blanket term for at least several different abnormalities at the level of protein and/or genetic differences. In this manuscript, researchers describe the use of the SomaScan Assay to look for differences among patients in the levels of the protein fibrinogen in cerebrospinal fluid (CSF), one of the many biological fluids amenable to such analysis. They detected a subset of MDD patients with increased fibrinogen in CSF, which was verified using traditional protein measurement tools. They also correlated the increased level of fibrinogen in the CSF with specific damage to the brain, particularly in the white matter.

Hathout, Y *et al.* (2015) "Large-scale serum protein biomarker discovery in Duchenne muscular dystrophy." *Proc Natl Acad Sci U S A* **112**(23): 7153-7158.

https://www.ncbi.nlm.nih.gov/pubmed/26039989

Although we have known the genetic cause of Duchenne muscular dystrophy since 1986, our knowledge of the actual biology of the disease and its progression is still incomplete. This lack of understanding seriously compromises our efforts to find effective new treatments, as well as new diagnostic tests that can help patients and their caregivers manage disease progression. This paper, the result of a focused collaboration between industry, advocacy and Duchenne patient advocates, describes the first truly large-scale, unbiased biomarker discovery in Duchenne patients vs. controls, using the SomaScan Assay. A total of 44 proteins were identified, 24 of which are up and 20 that are down in Duchenne patients as compared to controls. Some of these were expected (and confirmatory of previous studies), but others were not, and suggest new approaches for diagnosis, prognosis and novel therapeutic discovery for this devastating disease.

Menni, C *et al.* (2015) "Circulating proteomic signatures of chronological age." *J Gerontol A Biol Sci Med Sci* **70**(7): 809-816.

https://www.ncbi.nlm.nih.gov/pubmed/25123647

An international team of researchers used the SomaScan Assay to begin to dissect the proteomic features of aging in plasma. Initial finding from 202 subjects were subsequently replicated in 677 additional subjects. The researchers found that 11 proteins of those measured are associated with chronological age. This initial study underlines the importance of the proteome in understanding molecular mechanisms involved in human health and aging.

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Zhao, X *et al.* (2015) "A candidate plasma protein classifier to identify Alzheimer's disease." *J Alzheimers Dis* **43**(2): 549-563. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/25114072

Currently, there is no test that can definitively establish whether a person has Alzheimer's disease (AD), and an estimated 24% of cases are misdiagnosed. Cerebrospinal fluid (CSF) taps and brain scans are sometimes used to aid diagnosis but are too invasive or expensive to be used routinely. In this study, scientists at Merck Research Laboratories used the SomaScan Assay to measure the levels of 1,129 proteins in plasma collected from 50 individuals without dementia and compared them to 77 with probable AD. They created a five-protein classifier that could discriminate AD patients from controls, and that matched or outperformed the leading CSF diagnostic indicator. The classifier was also able to identify 29 out of 30 patients with mild cognitive impairment, which suggests that the five identified proteins are involved (either directly or indirectly) in the early stages of AD. These studies illustrate how plasma proteins could be used to develop less invasive methods to more accurately diagnose AD, to further our understanding of AD pathology and progression, and even improve patient stratification for clinical trials and speed development of new therapies.

Hathout, Y (2015) "Proteomic methods for biomarker discovery and validation. Are we there yet?" *Expert Rev Proteomics* **12**(4): 329-331.

https://www.doi.org/10.1586/14789450.2015.1064771

An editorial by Hathout at Children's National Medical Center describes how new proteomic methods such as the SomaScan Assay are becoming attractive tools to monitor disease progression, aid drug development programs and use as surrogate outcome measures in clinical trials.

Motzer, RJ *et al.* (2014) "Investigation of novel circulating proteins, germ line single-nucleotide polymorphisms, and molecular tumor markers as potential efficacy biomarkers of first-line sunitinib therapy for advanced renal cell carcinoma." *Cancer Chemother Pharmacol* **74**(4): 739-750.

https://www.ncbi.nlm.nih.gov/pubmed/25100134

The drug sunitinib (SUTENT®) is approved worldwide for treatment of renal cell carcinoma. However, no good biomarkers for selecting likely responders and monitoring treatment efficacy have yet been identified. In this study, a research team lead by Pfizer scientists employed SomaScan (and several other genomic and proteomic approaches) to discover such markers in a phase 2 clinical trial of sunitinib. Two particular protein biomarkers were identified that are now under further investigation for their predictive and prognostic value in clinical settings.

Rohloff, JC *et al.* (2014) "Nucleic acid ligands with protein-like side chains: Modified aptamers and their use as diagnostic and therapeutic agents." *Mol Ther Nucleic Acids* **3**: e201.

https://www.ncbi.nlm.nih.gov/pubmed/25291143

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A comprehensive review of the development of SOMAmer reagents with an overview of the many applications for these breakthrough protein-binding molecules.

Mehan, MR *et al.* (2014) "Validation of a blood protein signature for non-small cell lung cancer." *Clin Proteomics* **11**(1): 32.

https://www.ncbi.nlm.nih.gov/pubmed/25114662

Building on previous work (see Ostroff RM *et al.* (2010) *PLoS One* **5**(12): e15003; https://doi.org/10.1371/journal.pone.0015003), an international group of researchers led by SomaLogic scientists validated a protein signature for the detection of non-small cell lung cancer. This potential new test could be useful in particular, in follow up testing for patients diagnosed with a lung nodule using CT scanning, which has only a 4% positive rate for lung cancer detection. The work is also notable for the application of “Sample Mapping Vectors” (i.e., protein changes that are a result of blood handling rather than biological status) in validating this protein signature.

Baumstummler, A *et al.* (2014) "Specific capture and detection of *Staphylococcus aureus* with high-affinity modified aptamers to cell surface components." *Lett Appl Microbiol* **59**(4): 422-431.

https://www.ncbi.nlm.nih.gov/pubmed/24935714

This study by researchers from Merck Millipore and SomaLogic demonstrates the binding ability of SOMAmer reagents created against bacterial cell surface proteins (in this case, *S. aureus*), and their applicability to the sensitive detection of the pathogen in standard biodetection, biosurveillance and food safety applications.

Morine, MJ *et al.* (2014) "Genetic associations with micronutrient levels identified in immune and gastrointestinal networks." *Genes Nutr* **9**(4): 408.

https://www.ncbi.nlm.nih.gov/pubmed/24879315

This proof-of-concept study, published by researchers at Nestlé and their global collaborators, describes one of the first studies that aims to correlate metabolites, genetic variation, plasma proteomic changes, and environmental factors to begin to understand the “physiological processes for maintaining health.” SomaScan was used for longitudinal monitoring of protein changes over two years in 45 genetically unique individuals with 61 sets of metabolite, protein and diet variables.

Monteiro, JP *et al.* (2014) "Methylation potential associated with diet, genotype, protein, and metabolite levels in the Delta Obesity Vitamin Study." *Genes Nutr* **9**(3): 403.

https://www.ncbi.nlm.nih.gov/pubmed/24760553

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Similar in approach to Morine, MJ *et al.* (2014) *Genes Nutr* **9**(4): 408; https://doi.org/10.1007/s12263-014-0408-4, this study from a global research group led by Nestlé scientists attempted to measure and correlate dietary intakes, micronutrients, and plasma proteins to identify subgroups of individuals for targeted nutritional interventions. Among other results, it is clear that measuring multiple proteins to find patterns that correlate with metabolite levels through data mining revealed the association of certain metabolic pathways (e.g., hormonal responses, neuronal responses, etc.). Protein differences in sex, age, and weight (obesity) were also seen, but further validation is required.

Sattlecker, M *et al.* (2014) "Alzheimer's disease biomarker discovery using SomaScan multiplexed protein technology." *Alzheimers Dement* **10**(6): 724-734.

https://www.ncbi.nlm.nih.gov/pubmed/24768341

Biomarkers that can predict the onset of Alzheimer's disease (AD) before the appearance of clinical symptoms (i.e., the "predementia phase") are critically needed for the development of early intervention therapeutics. In this manuscript, a multinational team of researchers describes the application of SomaScan to the unbiased discovery of potential blood-based AD biomarkers associated with various aspects of the disease. A number of protein biomarkers (including both previously described and novel biomarkers) are shown to be predictive of the various aspects of the disease, and further evaluation is underway.

Nahid, P *et al.* (2014) "Aptamer-based proteomic signature of intensive phase treatment response in pulmonary tuberculosis." *Tuberculosis (Edinb)* **94**(3): 187-196.

https://www.ncbi.nlm.nih.gov/pubmed/24629635

The desperate need for new therapeutic agents for tuberculosis (TB) is compounded by the challenges of evaluating emerging new compounds early and effectively in clinical trials. This manuscript describes a SomaScan-based approach to finding blood-based protein biomarkers that could speed up clinical development of new therapeutics, as well as help with monitoring patients on these new treatment regimes. The researchers identified an initial five protein-marker "signature" that differentiated between treatment-responders and slow-responders, and was predictive of the current surrogate end point used in TB therapeutic trials (eight-week culture status).

Webber, J *et al.* (2014) "Proteomics analysis of cancer exosomes using a novel modified aptamer-based array (SomaScan™) platform." *Mol Cell Proteomics* **13**(4): 1050-1064.

http://www.mcponline.org/content/13/4/1050.full.pdf+html

Exosomes (small vesicles secreted by most, if not all, cell types into the blood) could serve as a source of biomarkers for early detection of disease. In this study, researchers from Cardiff University and SomaLogic applied SomaScan to a prostate cancer cell line, hoping to discover better biomarkers for early detection of the disease. The unbiased protein measurement resulted in the discovery of over 300 proteins previously unassociated with prostate cancer and establishes the technology as "an effective proteomics platform for exosome-associated biomarker discovery in diverse clinical settings."

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Kiddle, SJ *et al.* (2014) "Candidate blood proteome markers of Alzheimer's disease onset and progression: a systematic review and replication study." *J Alzheimers Dis* **38**(3): 515-531.

https://www.ncbi.nlm.nih.gov/pubmed/24121966

A total of 163 candidate blood-based protein biomarkers were previously described in the scientific literature for the potential diagnosis of Alzheimer’s disease (AD). By applying SomaScan (which includes SOMAmers to 94 of the 163 proteins previously described) to a large clinical sample set, researchers from King’s College London and SomaLogic found that 9 of the 94 candidates are reliably associated with AD-related phenotypes, and are now being validated as a biomarker signature for the disease (as a set of protein biomarkers). Biomarkers that could predict onset and progression of AD would have great utility clinically, as well as for clinical trials and especially in the selection of subjects for preventative trials.

Steele, FR *et al.* (2014) "DTC-and-me: patient, provider, proteins and regulators." *J Pers Med* **4**(1): 79-87.

https://www.doi.org/10.3390/jpm4010079

This commentary by SomaLogic describes how direct-to-consumer (DTC) tests based on proteomics could help provide a deeper, integrated form of personalized medicine.

Ochsner, UA *et al.* (2013) "Detection of *Clostridium difficile* toxins A, B and binary toxin with slow off-rate modified aptamers." *Diagn Microbiol Infect Dis* **76**(3): 278-285. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/23680240

Clostridium difficile (*C. diff*) is a rapidly growing infectious disease health threat worldwide. A simple and highly specific diagnostic test for *C. diff* would have great utility in both the developed and developing world. This manuscript describes the generation of specific SOMAmers to several *C. diff* proteins and, equally important, the straightforward incorporation of SOMAmers into methods and platforms that are most commonly used for antibody-based tests (i.e., solution binding, pull downs with beads, dot blots, and sandwich assays).

Xie, Y *et al.* (2013) "Interaction with both ZNRF3 and LGR4 is required for the signalling activity of R-spondin." *EMBO Rep* **14**(12): 1120-1126.

https://www.ncbi.nlm.nih.gov/pubmed/24165923

Proteins in the Wnt pathway are involved in the regulation of multiple cellular processes (proliferation, cell polarity and cell fate determination), and thus implicated in multiple cancers and other proliferative disorders. In an effort to further understand the pathway, researchers at Novartis and SomaLogic identified a SOMAmer that specifically neutralized the

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activity of RSPO1 (R-spondin), a critical modulator of the Wnt pathway, to determine its target and suggest new therapeutic approaches to cancer and tissue degeneration.

Loffredo, FS *et al.* (2013) "Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy." *Cell* **153**(4): 828-839.

https://www.ncbi.nlm.nih.gov/pubmed/23663781

In this manuscript, a team of researchers led by scientists from the Harvard Stem Cell Institute, describe the discovery of a circulating protein called growth differentiation factor 11 (GDF-11), that can reverse age-related cardiac hypertrophy in mice. After failing to find the factor using lipidomic, metabolomic, and other proteomic approaches, the Harvard team turned to the SomaScan Assay, finding several proteins (including GDF-11) whose levels of expression change with age. The researchers then demonstrated that treating older mice with a recombinant version of the GDF-11 protein can rapidly reverse age-related cardiac hypertrophy. Studies aimed at extending these observations to humans are underway. It is interesting to note that, although the proteins targeted by SomaScan are the human version, sufficient evolutionary conservation exists to make SomaScan a useful tool for at least some non-human species applications.

Park, NJ *et al.* (2013) "Measurement of cetuximab and panitumumab-unbound serum EGFR extracellular domain using an assay based on slow off-rate modified aptamer (SOMAmer) reagents." *PLoS One* **8**(8): e71703.

https://www.ncbi.nlm.nih.gov/pubmed/23990977

Epidermal growth factor receptor (EGFR) is a cell surface protein that is the target of the anticancer drugs cetuximab (Erbitux®) and panitumumab (Vectibix®). In this manuscript, scientists from Quest Diagnostics and SomaLogic describe the use of a SOMAmer that binds the extracellular domain of EGFR to determine the amount of drug-unbound EGFR in patients being treated with either drug. This assay could help determine drug efficacy and dosing for individual patients.

De Groote, MA *et al.* (2013) "Elucidating novel serum biomarkers associated with pulmonary tuberculosis treatment." *PLoS One* **8**(4): e61002.

https://www.ncbi.nlm.nih.gov/pubmed/23637781

This manuscript describes the first large-scale proteomic analysis employing SomaScan in a study of active tuberculosis (TB). The international team of scientists identified multiple proteins that exhibit significant expression differences during the intensive phase of TB therapy, in particular discovering protein changes in conserved networks of biological processes and function (antimicrobial defense, tissue healing and remodeling, acute phase response, pattern recognition, protease/anti-proteases, complement and coagulation cascade, apoptosis, immunity and inflammation pathways). Some of these were known previously (providing validation for the work), but many novel proteins were also identified. These newly identified proteins may provide new insights for understanding TB disease, its treatment and subsequent healing processes that occur in response to effective therapy.

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Ostroff, RM *et al.* (2012) "Early detection of malignant pleural mesothelioma in asbestos-exposed individuals with a noninvasive proteomics-based surveillance tool." *PLoS One* **7**(10): e46091.

https://www.ncbi.nlm.nih.gov/pubmed/23056237

This manuscript describes a set of multi-center case-control studies of serum from 117 malignant mesothelioma (MM) patients and 142 asbestos-exposed control individuals. Biomarker discovery, verification, and validation were performed using the SomaScan Assay. From 64 candidate protein biomarkers identified, the team of scientists from New York University and SomaLogic derived a 13-marker random forest classifier that demonstrated extremely high sensitivity and specificity (97%/92% in training and 90%/95% in blinded verification, and 90%/89% in a second blinded validation set). This result was far superior to that of mesothelin, the currently used biomarker for mesothelioma detection/diagnosis. The SOMAmer biomarker panel discovered and validated in these studies provides a solid foundation for surveillance and diagnosis of MM in those at highest risk for this disease.

Baird, GS *et al.* (2012) "Age-dependent changes in the cerebrospinal fluid proteome by slow off-rate modified aptamer array." *Am J Pathol* **180**(2): 446-456. https://www.ncbi.nlm.nih.gov/pubmed/22122984

This manuscript is the first published description of the use of SomaScan to perform unbiased protein discovery in cerebrospinal fluid (CSF), a biological matrix that may provide early detection and diagnosis for several central nervous system (CNS) degenerative diseases. Scientists from the University of Washington and SomaLogic examined the CSF proteome from 90 normal adults (ages 21–85). In addition to demonstrating the applicability of SomaScan to CSF, they discovered a set of protein changes that correlate with increasing age, a finding that may have relevance in diagnosing age-related CNS diseases.

Mehan, MR *et al.* (2012) "Protein signature of lung cancer tissues." *PLoS One* **7**(4): e35157.

https://www.ncbi.nlm.nih.gov/pubmed/22509397

In this first report of SomaScan applied to tissue samples, a team of scientists from SomaLogic and the University of Washington compared the protein expression signatures of non-small cell lung cancer (NSCLC) tissues with healthy adjacent and distant tissues from surgical resections. They found that 36 proteins exhibited the largest expression differences between matched tumor and non-tumor tissues (20 proteins increased and 16 decreased in tumor tissue). Thirteen of these proteins have not been previously described in NSCLC. These tissue biomarkers also overlap with a core set of proteins identified in a large serum-based NSCLC study with SomaScan (see Ostroff RM *et al.* (2010) *PLoS One* **5**(12): e15003; https://doi.org/10.1371/journal.pone.0015003). By using the SOMAmers to the proteins identified in the study as novel histochemical probes, the scientists demonstrated that differences in protein expression are greater in tissues than in serum (as expected). The combined results of this study and the serum study present the most extensive view to date of the complex changes in NSCLC protein expression and have important implications for development of new diagnostic and therapeutic approaches.

Gupta, S *et al.* (2011) "Rapid histochemistry using slow off-rate modified aptamers with anionic competition." *Appl Immunohistochem Mol Morphol* **19**(3): 273-278. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/21217521

This manuscript is the first description of the utility of individual SOMAmers as immunohistochemical imaging reagents, both for research and potentially clinical (e.g., intraoperative) settings. The unique specificity and dissociation kinetics of the two SOMAmers used—against epidermal growth factor receptor, EGFR, and human epidermal growth factor receptor 2, HER2—allowed the two closely related protein targets to be distinguished in frozen tissue sections. Further work is underway for various imaging applications of SOMAmers.

Ostroff, RM *et al.* (2010) "Unlocking biomarker discovery: large scale application of aptamer proteomic technology for early detection of lung cancer." *PLoS One* **5**(12): e15003.

https://www.ncbi.nlm.nih.gov/pubmed/21170350

This manuscript describes both the first large-scale application of SomaScan to a specific disease and the most complete clinical serum proteome analysis of non-small cell lung cancer (NSCLC) to date. Archived serum samples from 1326 individuals (including 291 diagnosed NSCLC patients and 1,035 heavy smoker controls) from four independent studies were analyzed with SomaScan. A 12-protein biomarker signature was found that discriminated NSCLC from controls with high specificity and sensitivity (91%/84% in training sets and 89%/83% in a separate verification set). This work, which forms the basis for a new diagnostic test in development by Quest Diagnostics, is being further extended and refined.

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M McKeague, et al. (2022) “The minimum aptamer publication standards (MAPS guidelines) for *de novo* aptamer selection.” *Aptamers* **6**: 10-18.

http://japtamers.co.uk/the-minimum-aptamer-publication-standards-maps-guidelines-for-de-novo-aptamer-selection/

Aptamers are short single-stranded DNA or RNA sequences that selectively bind to specific targets such as proteins, peptides and small molecules. This article, written on behalf of the International Society on Aptamers and the Aptamer Consortium, proposes guidelines for reporting work on new aptamers. Adopting minimum publication standards for aptamers could help avoid the irreproducibility that is often seen with antibodies.

Chan, KY *et al.* (2022) "Chemical modifications for a next generation of nucleic acid aptamers." *Chembiochem* **23**(15): e202200006. **(Subscription required)**

https://www.doi.org/10.1002/cbic.202200006

This review focuses on how modified aptamers, such as SOMAmer reagents, can be selected and evolved to expand the functional applications of aptamers.

Qian, S *et al.* (2022) "Aptamers from random sequence space: Accomplishments, gaps and future considerations." *Anal Chim Acta* **1196**: 339511. (**Subscription required**)

https://doi.org/10.1016/j.aca.2022.339511

This review summarizes accomplishments in the field of aptamers and describes lessons learned from nature that could be used to produce even better aptamers.

Ren, X *et al.* (2021) "Evolving A RIG-I Antagonist: A Modified DNA Aptamer Mimics Viral RNA." *J Mol Biol* **433**(21): 167227.

https://www.doi.org/10.1016/j.jmb.2021.167227

RIG-I is an important protein that recognizes when cells have been infected with an RNA virus (e.g., SARS-CoV-2, West Nile or influenza) and helps trigger an immune response. Hyperactivation of RIG-I has been linked to autoimmune diseases and COPD, so there is considerable interest in developing molecules that block RIG-I functions. In this study, scientists from Yale University and SomaLogic created a SOMAmer reagent that binds tightly to RIG-I and then solved the high-resolution crystal structure of the complex. This study illustrates a powerful, general strategy that could be used to create immunomodulatory drugs.

Elskens, JP *et al.* (2020) "Chemical Modification of Aptamers for Increased Binding Affinity in Diagnostic Applications: Current Status and Future Prospects." *Int J Mol Sci* **21**(12): 4522.

https://doi.org/10.3390/ijms21124522

Aptamers are short strands of DNA or RNA that bind tightly to their given targets, which can be proteins, carbohydrates, small molecules, bacteria or even cells. Aptamers are extremely versatile since they have selectivity similar to antibodies but can be engineered *in vitro* and synthesized chemically. In this review, Elskens *et al.* discuss methods for improving aptamer binding properties. They include an overview of SOMAmer reagents, which have amino acid-like side chains that help them bind tightly to protein targets and discuss how SOMAmer reagents have been used in diagnostic assays and biomarker discovery.

Datta, G *et al.* (2019) "Balanced event prediction through sampled survival analysis." *Systems Medicine* **2**(1): 28-38.

https://www.liebertpub.com/doi/full/10.1089/sysm.2018.0015

Many health studies monitor individuals to see how many of them develop disease during a specific time frame. Often the number of study participants who progress to disease is quite small compared to those who don't, and this skew in the data makes it difficult to build accurate models for predicting disease risk. In this article, SomaLogic scientists described a new strategy to address "class imbalanced" data sets that incorporated both sampling techniques (which are used to mitigate class imbalance) and survival analysis (which accounts for the time until an event of interest occurs). They tested their approach on a model that used SomaScan Assay proteomic data to predict heart attack risk within four years among patients with stable coronary heart disease. They used time-to-event data that were highly imbalanced. Combining sampling and survival analysis techniques produced models that performed better than three competing models and illustrated the effectiveness of their approach for predicting disease risk based on imbalanced data sets.

Alexaki, A *et al.* (2019) "Effects of codon optimization on coagulation factor IX translation and structure: Implications for protein and gene therapies." *Sci Rep* **9**(1): 15449.

https://www.ncbi.nlm.nih.gov/pubmed/31664102

Manufacturing large amounts of a therapeutic protein usually requires inserting a human gene into a foreign organism such as bacteria or yeast. All living cells decode the DNA sequence of a gene in the same way, by reading the bases in groups of three, called "codons." Each codon encodes one amino acid in the protein. Since there are 64 possible DNA triplets and only 20 amino acids, different codons sometimes encode the same amino acid (synonymous codons). The frequency of codon use varies depending on the organism, so 'codon optimization' — replacing a rare codon with a more common synonymous codon — is often done to increase protein yields. Since substituting a synonymous codon does not change the amino acid, it's been assumed that codon optimization does not affect the resulting protein. A new study led by researchers at the US Food and Drug Administration, suggests that this is not always the case. The group looked at the effect of codon optimization on human blood coagulation factor IX, an important therapeutic protein. They found that the codon-optimized protein differed in conformation from its wild type counterpart, based on SOMAmer binding, limited proteolysis and antibody inhibition of activity. These results have direct implications for codon optimization strategies used to produce recombinant proteins and gene therapies.

Ochsner, UA *et al.* (2019) "Targeting unique epitopes on highly similar proteins GDF-11 and GDF-8 with modified DNA aptamers." *Biochemistry* **58**(46): 4632-4640. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/31638376

Growth differentiation factor 11 and 8 (GDF-11 and GDF-8) are two proteins that are essentially identical in both amino acid sequence and in three-dimensional structure, but not in function. There have been reports that GDF-11 helps muscles regenerate and could act as an anti-aging factor, while GDF-8 may do the opposite. Confirming these results has been difficult since commercially available binding reagents have problems discriminating between such highly similar proteins. In this article, SomaLogic scientists describe a new strategy that successfully generated specific SOMAmer reagents that bound tightly to either GDF-11 or GDF-8 and not the other. The SOMAmer reagents described here could serve as useful tools for distinguishing the distinct biology of GDF-11 and GDF-8 and their roles in aging and underlines the exquisite specificity that can be realized by the SOMAmer technology for many different proteins.

Strauss, S *et al.* (2018) “Modified aptamers enable quantitative sub-10-nm cellular DNA-PAINT imaging.” *Nat Methods* **15**(9): 685-688

https://www.ncbi.nlm.nih.gov/pubmed/30127504

—and—

Moore, RP *et al.* (2018) "Improving probes for super-resolution." *Nat Methods* **15**(9): 659-660. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/30171240

The advent of “super-resolution microscopy” has allowed scientists to breach the diffraction limit and see inside cells at an unprecedented level of detail. To help orient the view, individual proteins within individual cells are commonly labeled with antibodies, which are then detected by fluorescent probes. However, antibodies are usually three or four times larger than their target proteins, so the position of the antibody rather than the protein of interest is what’s seen in the image.

In this *Nature Methods* paper, a team of scientists from Ludwig Maximilian University in Munich, Max Planck Institute of Biochemistry, the European Molecular Biology Laboratory (EMBL), and SomaLogic substituted SOMAmer reagents for antibodies as labeling reagents for the super-resolution microscopy technique known as “DNA Points Accumulation in Nanoscale Topography” (DNA-PAINT). SOMAmers — modified aptamers that bind tightly and specifically to protein targets — are approximately a tenth of the size of antibodies. Using SOMAmer reagents, the investigators were able to resolve the membrane receptor protein EGFR to less than 8 nm, an approximate two-fold improvement over labeling using conventional antibodies. They also demonstrated that SOMAmer reagents could provide quantitative information on the number of target proteins present, simultaneously label multiple cellular proteins, image proteins inside cells, and image proteins on living

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cells. This new use for SOMAmer reagents opens the door to viewing how biological structures are organized on a molecular scale and how they function in living tissue in real time.

Katilius E *et al.* (2018) "Sperm cell purification from mock forensic swabs using SOMAmer^{TM} affinity reagents." *Forensic Sci Int Genet* **35**: 9-13. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/29609058

Extracting sperm cells from forensic samples typically involves selectively dissolving away other contaminants, which is both time-consuming and labor-intensive. Attempts to simplify the method by using antibody-based affinity purification have not been effective because the recovery yields were too low.

In this proof-of-concept study, investigators from the Denver police department crime laboratory and SomaLogic demonstrate how SOMAmers can be used to selectively capture sperm from mock swab samples. The SOMAmer-based method was as effective as differential extractions for high sperm count samples, but less effective for low sperm count samples. This is possibly due to storage conditions or sample handling (i.e. repeated freeze/thaw, overdilution) that affect the ability of SOMAmers to bind to their native target proteins and could be resolved with further optimization.

Duo J *et al.* (2018) "Slow Off-Rate Modified Aptamer (SOMAmer) as a novel reagent in immunoassay development for accurate soluble glypican-3 quantification in clinical samples." *Anal Chem* **90**(8): 5162-5170.

https://www.ncbi.nlm.nih.gov/pubmed/29605994

The protein glypican-3 (GPC3) is expressed on the surface of cells and a soluble form is elevated in the blood of hepatocellular carcinoma (HCC) patients. Characterizing the circulating forms of GPC3 (e.g. whether the soluble protein is full-length, N- or C-terminal fragment) is critical for its validation as a diagnostic biomarker for HCC. However, the only antibodies that are available bind to the C-terminal region of GPC3. This study from scientists at Bristol Myers Squibb used a SOMAmer reagent that binds to the N-terminal region of GPC3 to develop an immunoassay to determine the relevant soluble GPC3 forms in clinical samples. This work is a clear example of how SOMAmer reagents can be used for immunoassay development to address questions that cannot be answered by traditional antibody reagents alone.

Gupta, S *et al.* (2017) "Pharmacokinetic properties of DNA aptamers with base modifications." *Nucleic Acid Ther* **27**(6): 345-353.

https://www.ncbi.nlm.nih.gov/pubmed/28961063

Rapid blood clearance currently limits the therapeutic uses of DNA aptamers. SOMAmers contain DNA bases with amino acid-like modifications that make them more resistant to breakdown by the body. The goal of this SomaLogic study was to understand how various modified groups in SOMAmers affect plasma clearance. Shorter aptamers (≤24 bases) with larger numbers of hydrophilic modifications had longer plasma residence times. These observations will help in future design of aptamers for therapeutic treatments.

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Ren, X *et al.* (2017) “Structural basis for IL-1α recognition by a modified DNA aptamer that specifically inhibits IL-1α signaling.” *Nat Commun* **8**(1): 810.

https://www.ncbi.nlm.nih.gov/pubmed/28993621

IL-1 alpha is an inflammatory protein involved in fever and sepsis and implicated in tumor formation and metastasis. Scientists at Yale University and SomaLogic created a SOMAmer (named SL1067) that binds tightly and specifically to IL-1 alpha, and then determined the crystal structure of the SOMAmer-protein complex. This is the first high resolution structure of IL-1 alpha and reveals the molecular details of its binding interactions with SL1067. It will be of great interest in developing new therapies that target IL-1 alpha. The researchers found that SL1067 inhibits IL-1 alpha activity by binding the same interface that IL-1 alpha uses to bind to its native receptor on cells. Thus, SL1067 represents a powerful tool for studying IL-1 alpha’s role in normal inflammatory responses and those that lead to disease.

Gawande, BN *et al.* (2017) "Selection of DNA aptamers with two modified bases." *Proc Natl Acad Sci U S A* **114**(11): 2898-2903.

http://www.pnas.org/content/114/11/2898.long

SomaLogic scientists report on the generation and characterization of SOMAmers that contain two types of modified nucleotides. The current SomaLogic technology uses bases that have been modified with amino acid-like sidechains at the 5 position of deoxyuridine (dU). Now, for the first time, researchers have created SELEX libraries that also contain 5-position modified deoxycytosine (dC). Eighteen different DNA libraries were synthesized that contained zero, one or both modified bases. SELEX was conducted against proprotein convertase subtilisin/kexin type 9 (PCSK9), a human therapeutic target protein that helps regulate cholesterol. The aptamers with the highest affinity for PCSK9 contained two modifications. Similar results were observed with another target protein, prostate-specific membrane antigen (PSMA), a predictor for progression and prognosis of prostate cancer.

The increased chemical diversity of SELEX libraries should expand the repertoire of protein targets. In addition to displaying tighter binding while maintaining high specificity, SOMAmers with two modified bases were significantly more resistant to degradation than those with a single modification. Doubly modified aptamers also showed greater epitope coverage, which should be useful for developing reagents for assays that require simultaneous binding to a given protein target.

Cotton, RJ *et al.* (2016) "readat: an R package for reading and working with SomaLogic ADAT files." *BMC Bioinformatics* **17**(1): 201.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4857291/

The SomaScan Assay measures over 1,300 proteins in small amounts of biological samples. Experimental data from the SomaScan Assay are provided in a proprietary “ADAT” file format that is difficult to import into non-SomaLogic software packages. To overcome this limitation, two researchers at Weill Cornell Medicine in Qatar have developed “readat,” a free, open source, R software package that allows users to import and analyze SomaLogic’s ADAT format files.

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Gelinas, AD *et al.* (2016) "Embracing proteins: structural themes in aptamer-protein complexes." *Curr Opin Struct Biol* **36**: 122-132.

https://www.ncbi.nlm.nih.gov/pubmed/26919170

Single stranded nucleic acids can fold into a wide variety of different shapes, many of which can recognize and bind other molecules. This review summarizes the different motifs that have been seen in structural studies of aptamer-protein complexes, including the expanded structural “vocabulary” made possible by modifying the nucleic acid bases (e.g., SOMAmer reagents).

Gold, L (2015) "SELEX: How it happened and where it will go." *J Mol Evol* **81**(5-6): 140-143.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4661202/

In this mini-review, SomaLogic Founder and Chairman Larry Gold describes the origins of SELEX and aptamers, the launch of SomaLogic and SOMAmer reagents, and anticipates what is coming next.

Eid, C *et al.* (2015) "Rapid Slow Off-Rate Modified Aptamer (SOMAmer)-based detection of c-reactive protein using isotachophoresis and an ionic spacer." *Anal Chem* **87**(13): 6736-6743. **(Subscription required)**

https://www.doi.org/10.1021/acs.analchem.5b00886

In this article, researchers at Stanford University and SomaLogic describe an on-chip electrophoretic assay for rapid protein detection using a SOMAmer reagent.

Carlson, M *et al.* (2015) "Improved preparation of 2 M triethylammonium bicarbonate." *Green Chem Lett Rev* **8**(3-4): 37-39.

http://www.tandfonline.com/doi/full/10.1080/17518253.2015.1091039

SomaLogic researchers describe a new method to generate a laboratory chemical used extensively in making SOMAmer reagents, resulting in a reduction of carbon dioxide waste emission by approximately 90% over current methods to generate the same chemical.

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Wolk, SK *et al.* (2015) "Influence of 5-N-carboxamide modifications on the thermodynamic stability of oligonucleotides." *Nucleic Acids Res* **43**(19): 9107-9122.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4627095/

The incorporation of DNA base modifications results in the high specificity for and broader range of protein types targeted by SOMAmer reagents. In this paper, the authors delve deeper into understanding the thermodynamic effects of these modifications on the stability of the SOMAmer oligonucleotides, both in their single-stranded and duplex forms. The results of these studies demonstrate that, depending on the type of modification, the addition can either destabilize or further stabilize the duplex forms, but in the single-stranded state (the usual use of SOMAmer reagents in biomarker discovery or other assays), the modifications significantly stabilized the oligonucleotide shapes as compared to unmodified single-stranded DNA.

Jarvis, TC *et al.* (2015) "Non-helical DNA triplex forms a unique aptamer scaffold for high affinity recognition of nerve growth factor." *Structure* **23**(7): 1293-1304.

https://www.ncbi.nlm.nih.gov/pubmed/26027732

The structural explanation for the tight binding of a unique SOMAmer reagent to its target (nerve growth factor, or NGF) is described in this paper, the third in a series of manuscripts defining the precise molecular structure of specific SOMAmer:protein pairs (see Gelinas *et al.* 2014 and Davies DR *et al.* 2012, below). Like the previous two descriptions, the structure of the NGF SOMAmer is unlike any previously described traditional aptamer configuration and underlines the critical role of the DNA base modifications used in generating SOMAmer reagents.

Rohloff, JC *et al.* (2015) "Practical synthesis of cytidine-5-carboxamide-modified nucleotide reagents." *Nucleosides Nucleotides Nucleic Acids* **34**(3): 180-198.

https://www.ncbi.nlm.nih.gov/pubmed/25710355

The exquisite specificity of SOMAmer reagents for their cognate proteins lies in their expanded chemical diversity over traditional aptamers via the protein-like modifications added to the chemical structure of some of the nucleotides that make up the SOMAmer sequence. This manuscript describes the further expansion of that chemical diversity through the successful efforts of SomaLogic scientists to add chemical modifications to cytidine (C). These modifications do not interfere with either solid-state synthesis or enzymatic synthesis of oligonucleotides containing such modified C bases. Modified C bases are already being incorporated into new SOMAmer discovery experiments.

Lollo, B *et al.* (2014) "Beyond antibodies: new affinity reagents to unlock the proteome." *Proteomics* **14**(6): 638-644.

https://www.doi.org/10.1002/pmic.201300187

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This viewpoint by SomaLogic compares protein binding using SOMAmer reagents to traditional aptamers and antibodies. They also describe the SomaScan Assay, which uses SOMAmers to measure proteins at scale and provide several examples in biomarker discovery.

Ochsner, UA *et al.* (2014) "Systematic selection of modified aptamer pairs for diagnostic sandwich assays." *Biotechniques* **56**(3): 125-128, 130, 132-133. https://www.ncbi.nlm.nih.gov/pubmed/24641476

This manuscript is the first published description (proof-of-concept) of the use of SOMAmers in a sandwich assay. In this paper, SOMAmer pairs were generated against both *Clostridium difficile* binary toxin and for a group of seven proteins previously shown to be promising biomarkers for cardiovascular risk. The ability to use SOMAmer pairs in diagnostic applications rather than traditional antibody pairs holds promise for accelerated development of rapid tests and/or specific diagnostic panels.

Gelinas, AD *et al.* (2014) "Crystal structure of interleukin-6 in complex with a modified nucleic acid ligand." *J Biol Chem* **289**(12): 8720-8734.

http://www.jbc.org/content/289/12/8720

– and –

Gupta, S *et al.* (2014) "Chemically modified DNA aptamers bind interleukin-6 with high affinity and inhibit signaling by blocking its interaction with interleukin-6 receptor." *J Biol Chem* **289**(12): 8706-8719.

http://www.jbc.org/content/289/12/8706

This pair of papers, published simultaneously in the *Journal of Biological Chemistry*, describes the development of new SOMAmer reagents that can block signaling by interleukin-6 (IL-6, a critical protein involved in inflammation and cancer), as well as the structural interaction of the IL-6 SOMAmer and its target protein. This work both confirms the unique protein-binding properties of SOMAmers and underlines their potential as a new class of therapeutic reagents. The work was done in collaboration with Otsuka Pharmaceuticals and Emerald Bio.

Brody, E *et al.* (2012) "Life's simple measures: unlocking the proteome." *J Mol Biol* **422**(5): 595-606. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/22721953

This review article describes both the SOMAmer/SomaScan technology and gives examples of its multiple applications in unbiased protein biomarker discovery. It also includes a description of the bioinformatics methods used to interpret the large datasets generated by SomaScan.

Davies, DR *et al.* (2012) "Unique motifs and hydrophobic interactions shape the binding of modified DNA ligands to protein targets." *Proc Natl Acad Sci U S A* **109**(49): 19971-19976.

https://www.ncbi.nlm.nih.gov/pubmed/23139410

This manuscript is the first demonstration of the unique molecular structure of a SOMAmer reagent bound to its specific protein target. The analyses reveal the molecular basis for the vast improvement in protein binding by SOMAmers as compared to traditional aptamers, emphasizing that SOMAmers represent an entirely new class of molecular "affinity reagents" with multiple useful applications in life sciences and medicine. This work was done as a collaboration between SomaLogic and Emerald Bio.

Gold, L *et al.* (2012) "Aptamers and the RNA world, past and present." *Cold Spring Harb Perspect Biol* **4**(3).

https://www.ncbi.nlm.nih.gov/pubmed/21441582

This review article clearly lays out the reasoning and the development of SOMAmers that would provide two simultaneous elements of specificity (e.g., the equivalent to a good antibody sandwich assay within a single SOMAmer reagent). Those two elements are (1) affinity for their target protein (i.e., pM or lower Kd), and (2) a kinetic component (slow off-rate, or remarkable slow dissociation rate constants). These two properties, along with the chemical basis for SOMAmers, overcome the specific technical challenges faced by other current proteomic technologies, and provide the basis for the steps comprising the SomaScan Assay.

Kraemer, S *et al.* (2011) "From SOMAmer-based biomarker discovery to diagnostic and clinical applications: a SOMAmer-based, streamlined multiplex proteomic assay." *PLoS One* **6**(10): e26332.

https://www.ncbi.nlm.nih.gov/pubmed/22022604

This manuscript demonstrates that the SomaScan Assay provides a seamless transition from SOMAmer-based biomarker discovery to routine protein measurements for diagnostic and research purposes. Furthermore, the assay can be semi-automated (here they developed a plate-based version) and can be performed with multiple "back end" readouts (qPCR, bead-based—e.g., Luminex, etc.), underlining the compatibility of this approach with current nucleic-acid based diagnostic technologies.

Brody, EN *et al.* (2010) "High-content affinity-based proteomics: unlocking protein biomarker discovery." *Expert Rev Mol Diagn* **10**(8): 1013-1022.

https://www.ncbi.nlm.nih.gov/pubmed/21080818

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This review article compares the SomaScan Assay directly to other current proteomic technologies (mass spectrometry and antibody-based), particularly in high-content protein biomarker discovery. It demonstrates how SomaScan overcomes the specific technical challenges faced by these other approaches, particularly the need for high content with high sensitivity and specificity to address the circulating proteome.

Vaught, JD *et al.* (2010) "Expanding the chemistry of DNA for *in vitro* selection." *J Am Chem Soc* **132**(12): 4141-4151. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/20201573

This manuscript describes the fundamental biochemical steps necessary to incorporate modified nucleotides into DNA-based aptamers (and thus the first published description of "SOMAmers," though the name was subsequently coined). The manuscript also describes the identification of a modified DNA aptamer with high affinity for the tumor necrosis factor receptor superfamily member 9 (TNFRSF9), a protein that had proven refractory to aptamer selection using traditional unmodified DNA aptamers.

Gold, L *et al.* (2010) "Aptamer-based multiplexed proteomic technology for biomarker discovery." *PLoS One* **5**(12): e15004.

https://www.ncbi.nlm.nih.gov/pubmed/21165148

This manuscript is the first published detailed description of the breakthrough SOMAmer-based SomaScan technology and demonstrates its power through application to samples from patients with chronic kidney disease, finding not only known markers of the disease but many previously unknown protein biomarkers. (Companion paper, Ostroff RM *et al.* 2010; https://doi.org/10.1371/journal.pone.0015003 — above in "SOMAmer/SomaScan Applications").

Zichi, D *et al.* (2008) "Proteomics and diagnostics: Let's get specific, again." *Curr Opin Chem Biol* **12**(1): 78-85. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/18275862

This manuscript describes the inherent specificity limitations of antibody-based arrays for large-scale biomarker discovery, and introduces the basic idea behind the SOMAmer reagent and its two elements of specificity (i.e., high affinity and slow dissociation rates).

Eaton, BE *et al.* (1995) "Let's get specific: the relationship between specificity and affinity." *Chem Biol* **2**(10): 633-638.

https://www.ncbi.nlm.nih.gov/pubmed/9383468

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This review article lays out a systematic argument for selecting molecules that bind with high specificity to a particular target by screening for molecules with high affinity to that target. It applies that understanding to the selection of traditional aptamers, suggesting the critical role aptamer-based reagents can play in diagnostic and therapeutic applications.

Jenison, RD *et al.* (1994) "High-resolution molecular discrimination by RNA." *Science* **263**(5152): 1425-1429.

https://www.ncbi.nlm.nih.gov/pubmed/7510417

— *and* —

Zimmermann, GR *et al.* (1997) "Interlocking structural motifs mediate molecular discrimination by a theophylline-binding RNA." *Nat Struct Biol* **4**(8): 644-649. **(Subscription required)**

https://www.ncbi.nlm.nih.gov/pubmed/9253414

These two manuscripts together describe (1) the isolation of an RNA-based aptamer that can bind theophylline with a 10,000-fold better affinity than it binds the closely related caffeine molecule (which differs from theophylline by only an extra methyl group) and (2) the structural basis of that affinity. These early studies of the incredible specificity that can be achieved with traditional aptamers are being even more fully realized with the work being done with SOMAmer reagents today.

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