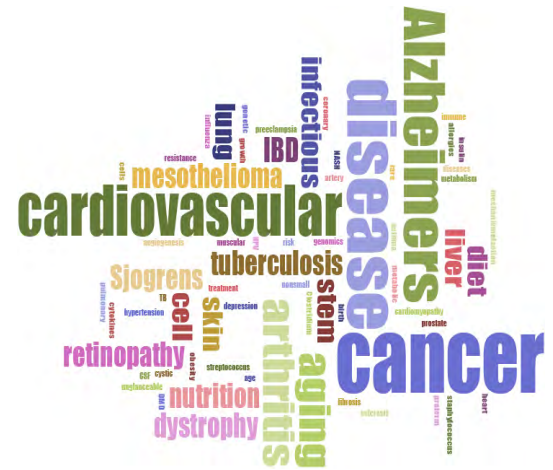


Annotated SomaLogic and Third-party Publications

This partial list of peer-reviewed publications includes manuscripts describing applications of the technology (Section I below) as well as basic research on the technology itself (starting on p. 66). Links to the articles are provided, and if article access requires a subscription, it is noted in each entry.



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



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.

(Subscription required)

<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.

(Subscription required)

<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 1129 proteins in their archived plasma samples. Nine candidate biomarkers of heart failure were identified and two proteins, angiotensin-2 and thrombospondin-2, were subsequently validated in three different patient groups. The researchers found significantly higher levels of angiotensin-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 function), angiotensin-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*, *epub ahead of print*. **(Subscription required)**

<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 1129 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.



Fong, TG *et al.* (2019) "Identification of plasma proteome signatures associated with surgery using SOMAscan." *Ann Surg.*, *epub ahead of print*. **(Subscription required)**

<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 1305 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.



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 5-10% 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. **(Subscription required)**

<https://www.ncbi.nlm.nih.gov/pubmed/30407753>

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.*, *epub ahead of print.* **(Subscription required)**

<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. **(Subscription required)**
<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 1129 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.



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 1129 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.



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, epub ahead of print.* **(Subscription required)**
<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 1305 proteins were measured in samples from 18 men or women with LUTS and compared to 12 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 1307 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., epub ahead of print.* **(Subscription required)**
<http://jalm.aaccjnls.org/content/early/2019/01/11/jalm.2018.027086>

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 3693 proteins having a coefficient of variation less than 10%. Only one protein showed significant short-term variability, whereas 866 proteins showed significant 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). **(Subscription required)**
<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. **(Subscription required)**
<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 1129 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.



Hemnes, AR *et al.* (2019) "Human PAH is characterized by a pattern of lipid-related insulin resistance." *JCI Insight* **4**(1).

<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 1139 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 4001 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 1373 proteins in blood samples obtained from 1885 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 1300 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.



Masvekar, R *et al.* (2018) "Cerebrospinal fluid biomarkers link toxic astroglia and microglial activation to multiple sclerosis severity." *Mult Scler Relat Disord* **28**: 34-43.
(Subscription required)
<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.



Glover, KKM *et al.* (2018) "Vero cell proteomic changes induced by Zika virus infection." *Proteomics* **19**(4): e1800309.
<https://www.ncbi.nlm.nih.gov/pubmed/30578658>

—and—



Sher *et al.* (2019) "Zika virus infection disrupts astrocytic proteins involved in synapse control and axon guidance." *Front Microbiol.*, *epub ahead of print.*
<https://doi.org/10.3389/fmicb.2019.00596>

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 1322 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.



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 1129 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.



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 1310 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. **(Subscription required)**
<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>



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 2286 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](#)). 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.



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.



Halama, A et al. (2018) "Metabolic and proteomic signatures of hypoglycemia in type 2 diabetes." *Diabetes Obes Metab.*, epub ahead of print. **(Subscription required)**

<https://www.ncbi.nlm.nih.gov/pubmed/30525282>

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 1125 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.



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 dysfunction 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. **(Subscription required)** <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*: 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 1129 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.



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.](#)) 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. **(Subscription required)**
<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 1129 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 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 1129 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 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 1310 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.



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).
<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 1305 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 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 1310 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).

<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. **(Subscription required)**
<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 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 1305 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."



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. **(Subscription required)**
<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 1129 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 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.



King, JD *et al.* (2018) "Joint fluid proteome after anterior cruciate ligament rupture reflects an acute posttraumatic inflammatory and chondrodegenerative state." *Cartilage, epub ahead of print.* **(Subscription required)**
<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 1129 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.



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 dysfunction 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.



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](#)). 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.



Sun, BB *et al.* (2018) "Genomic atlas of the human plasma proteome." *Nature* **558**: 73–79.

(Subscription required)

<https://www.nature.com/articles/s41586-018-0175-2>

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 1305 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 4000 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 angiotensin-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. Angiotensin-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>

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 1129 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.

<https://www.ncbi.nlm.nih.gov/pubmed/29506994>

—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.

<https://www.ncbi.nlm.nih.gov/pubmed/28974520>

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 1129 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.](#)) 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.

<https://www.ncbi.nlm.nih.gov/pubmed/29530892>

—and—





Benson, MD *et al.* (2018) "Genetic architecture of the cardiovascular risk proteome." *Circulation* **137**(11): 1158-1172.
<https://www.ncbi.nlm.nih.gov/pubmed/29258991>

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 (ref: [Ngo, D *et al.* \(2016\) *Circulation* **134**\(4\): 270-285.](#)). 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.



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.
<https://www.ncbi.nlm.nih.gov/pubmed/29529088>

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 (ref: [Hathout, Y *et al.* \(2015\) *Proc Natl Acad Sci U S A* **112**\(23\): 7153-7158.](#)) 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.



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.
<https://www.ncbi.nlm.nih.gov/pubmed/29217775>

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 1310 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. **(Subscription required)**
<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 an 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.ncbi.nlm.nih.gov/pubmed/29854980>

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 (ref: [Wasiak, S *et al.* \(2017\) *J Cardiovasc Transl Res*, **10**\(4\): 337-347.](#)), 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.



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, Al *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.

(Subscription required)

<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.



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.



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 1129 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 each individual's 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 led 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 e61-67 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 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.



Jacob, J *et al.* (2017) "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 (ref: [Ngo, D et al. \(2016\) *Circulation* 134\(4\): 270-285.](#)) 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.



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 SOMAscan 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.



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 1305 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 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.

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](#)). 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.
<https://www.ncbi.nlm.nih.gov/pubmed/29018540>

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.



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 (50µL 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 1129 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.



Aghaepour, N *et al.* (2017) "An immune clock of human pregnancy." *Sci Immunol* **2**(15): ean2946.

<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 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.



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.



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.

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 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](#))—and their potential for diagnosing and treating future MPM patients.



Rossios, C *et al.* (2017) "Sputum transcriptomics reveal up-regulation of IL-1 receptor family members in severe asthma." *J Allergy Clin Immunol* **141**(2): 560–570. **(Subscription required)**

<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.



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 apolipoprotein 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 SS patients vs. healthy controls ([Nishikawa, A *et al.* \(2016\) *Arthritis Res Ther* 18\(1\): 106](#)). 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 1310 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.



Asai, A *et al.* (2017) "Paracrine signals regulate human liver organoid maturation from induced pluripotent stem cells." *Development* **144**(6): 1056-1064.
<http://dev.biologists.org/content/144/6/1056.long>

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 (\geq 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 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 AIN 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 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://genesandnutrition.biomedcentral.com/articles/10.1186/s12263-017-0553-7>

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, D₃ & 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.
<http://journals.plos.org/plosgenetics/article?id=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 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)**
<http://www.sciencedirect.com/science/article/pii/S1525730416302388>

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)**
<http://www.sciencedirect.com/science/article/pii/S1570963916301935>

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.

<http://jcm.asm.org/content/55/2/391.long>

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 LTBI 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.

<http://www.sciencedirect.com/science/article/pii/S1874391916304006>

"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 Doha, 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.



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.

<http://www.nature.com/ctg/journal/v7/n9/pdf/ctg201649a.pdf>

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.

<http://bmjopen.bmj.com/content/6/11/e013324.long>

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](#)). 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.



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.



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](#)), 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. Access to an electronic version is available on request.)**
<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.



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>

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 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.



Drolet, DW *et al.* (2016) "Fit for the eye: aptamers in ocular disorders." *Nucleic Acid Ther* **26**(3): 127-146.

<https://www.ncbi.nlm.nih.gov/pubmed/26757406>

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.



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.



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 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.



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>

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.](#)), 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.



Baumstummeler, 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/24551850>

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>

Similar in approach to [Morine, MJ *et al.* \(2014\) *Genes Nutr* **9**\(4\): 408](#), 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.
<https://www.ncbi.nlm.nih.gov/pubmed/24505114>

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."



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.



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 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 (Erbix®) 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.



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.](#)). 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.

II. SOMAscan®/SOMAmer® Technology Publications



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 SOMAmers 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 SOMAmers, 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 SOMAmers 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 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™ 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.



Ren, X *et al.* (2017) "Structural basis for IL-1 α recognition by a modified DNA aptamer that specifically inhibits IL-1 α signaling." *Nat Commun* **8**(1): 810.

<https://www.nature.com/articles/s41467-017-00864-2>

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.

<https://www.ncbi.nlm.nih.gov/pubmed/28265062>

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/pubmed/27146037>

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.



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.
<https://www.ncbi.nlm.nih.gov/pubmed/26480964>

In this brief 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.



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.



Wolk, SK *et al.* (2015) "Influence of 5-N-carboxamide modifications on the thermodynamic stability of oligonucleotides." *Nucleic Acids Res* **43**(19): 9107-9122.
<https://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.



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>

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](#)—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>

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.