SomaLogic

Annotated SomaLogic and Third-party Publications

This partial list of peer-reviewed publications includes manuscripts describing applications of the technology (below) as well as basic research on the technology itself (starting on p. 24).

Note: Links are provided to the actual manuscript if it is Open Access, or to the PubMed entry if article access requires a subscription to that journal (as noted in each entry below).

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

Rossios, C *et al.* (2017) "Sputum transcriptomics reveal up-regulation of IL-1 receptor family members in severe asthma." *J Allergy Clin Immunol*, *in press.* **(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.

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Wang, T *et al.* (2017) "GDF15 is a heart-derived hormone that regulates body growth." *EMBO Mol Med, in press.*
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.

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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, in press.*
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.

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Howson, JMM *et al.* (2017) "Fifteen new risk loci for coronary artery disease highlight arterial-wall-specific mechanisms." *Nat Genet*, *in press.* **(Subscription required)**
https://www.ncbi.nlm.nih.gov/pubmed/28530674

An international team of scientists led by researchers at the University of Cambridge, the University of Pennsylvania and Stanford University conducted a large-scale study of genetic variants associated with coronary artery disease (CAD). They analyzed results from over 250,000 CAD patients and controls and identified 15 new regions of the genome that had not been previously linked to CAD. These regions contain genes that are involved in cellular adhesion, atherosclerosis, white blood cell migration, inflammation and smooth muscle cell differentiation.

To identify the disease pathways and biological functions controlled by these regions, the researchers conducted protein profiling of 3,301 blood samples using the SOMAscan assay. One DNA variant correlated with expression of apoliproprotein L1, a major component of high density lipoprotein (HDL) particles. Another DNA variant correlated with levels of protein C, which helps maintain the permeability of blood vessel walls. These and previous results point to both traditional (cholesterol) and novel (arterial wall) mechanisms that lead to CAD susceptibility.

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Tasaki, S *et al.* (2017) "Multiomic disease signatures converge to cytotoxic CD8 T cells in primary Sjogren's syndrome." *Ann Rheum Dis*, *in press.*
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.

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DeBoer, EM *et al.* (2017) "Proteomic profiling identifies novel circulating markers associated with bronchiectasis in cystic fibrosis." *Proteomics Clin Appl*, *in press.* **(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.

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Oller Moreno, S *et al.* (2017) "The differential plasma proteome of obese and overweight individuals undergoing a nutritional weight loss and maintenance intervention." *Proteomics Clin Appl*, *in press.* **(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.

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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.

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Saleheen, D *et al.* (2017) "Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity." *Nature* **544**(7649): 235-239. **(Subscription required)**
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 ~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.

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Asai, A *et al.* (2017) "Paracrine signals regulate human liver organoid maturation from induced pluripotent stem cells." *Development* **144**(6): 1056-1064.
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 (≥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.

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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.

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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.

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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.

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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.

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Escolano, JM *et al.* (2017) "Selection of aptamers to *Neisseria meningitidis* and *Streptococcus pneumoniae* surface specific proteins and affinity assay using thin film AlN resonators." *Sensors and Actuators B: Chemical* **246**: 591-596. **(Subscription required)**
http://www.sciencedirect.com/science/article/pii/S0925400517303258

Bacterial meningitis is a frightening illness—victims can die within a few hours and survivors can be left with severe afflictions such as brain damage or hearing loss. Different kinds of bacteria can cause meningitis, of which *Neisseria 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.

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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, D_3 & E and four carotenoids were measured for 36 overweight or obese males after overnight fasting and after eating a high fat shake. A proteomic analysis using the SOMAscan assay was conducted in parallel, and changes in protein levels were correlated with changes in micronutrient levels. The correlation analysis after the nutritional challenge was particularly interesting as it suggested that certain micronutrients (α-carotene, a vitamin A precursor; and γ-tocopherol, a form of vitamin E) are especially important for helping the body respond to oxidative and inflammatory stresses. This approach will be useful for quantifying the effects of diet on health.

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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.

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Sasayama, D *et al.* (2017) "Genome-wide quantitative trait loci mapping of the human cerebrospinal fluid proteome." *Hum Mol Genet* **26**(1): 44-51. **(Subscription required)**
https://academic.oup.com/hmg/article-abstract/26/1/44/2595397/Genome-wide-quantitative-trait-loci-mapping-of-the?redirectedFrom=fulltext

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.

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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.

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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.

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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.

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Rice, LM *et al.* (2017) "A proteome-derived longitudinal pharmacodynamic biomarker for diffuse systemic sclerosis skin." *J Invest Dermatol* **137**(1): 62-70. **(Subscription required)**
http://www.jidonline.org/article/S0022-202X(16)32372-7/abstract

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.

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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 LBTI as well as the likelihood of progressing to active TB, which is a major limitation of currently available tests.

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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.

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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. The goal of this new study is to see whether the SOMAscan panel or fibulin-3 (a potential plasma biomarker of MPM) levels could provide clinically useful diagnostic and prognostic information. A non-invasive test that could distinguish MPM from confounding pleural malignancies would offer a major clinical advance over current approaches.

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Lynch, AM *et al.* (2016) "The relationship of novel plasma proteins in the early neonatal period with retinopathy of prematurity." *Invest Ophthalmol Vis Sci* **57**(11): 5076-5082.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5053115/pdf/i1552-5783-57-11-5076.pdf

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.

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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 Dohar, Qatar (site of one of the first installations of the SOMAscan assay outside of SomaLogic), compared SOMAscan with mass spectrometry (MS) and RNA sequencing (RNA-seq) in analyzing proteins from both human embryonic and mesenchymal stem cells. In addition to validating SOMAscan results with other, more traditional approaches, their research underscores SOMAscan’s “deep reach” into the proteome to identify the “rarer” proteins that may be the most critical biomarkers for a range of diseases and conditions of interest.

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Ashley, SL *et al.* (2016) "Six-SOMAmer index relating to immune, protease and angiogenic functions predicts progression in IPF." *PLoS One* **11**(8): e0159878.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0159878

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.

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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.
http://www.tandfonline.com/doi/full/10.3402/jev.v5.31209

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.

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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. **(Subscription required)**
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.”

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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.

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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. **(Subscription required)**
https://www.ncbi.nlm.nih.gov/pubmed/27444931

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Ngo, D *et al.* (2016) "Aptamer-Based Proteomic Profiling Reveals Novel Candidate Biomarkers and Pathways in Cardiovascular Disease." *Circulation* **134**(4): 270-285. **(Subscription required)**
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.*, below), 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.”

Access to an electronic version of the Circulation paper and the accompanying editorial is available on request.

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Sabatine, MS (2016) "Using aptamer-based technology to probe the plasma proteome for cardiovascular disease prediction." *JAMA* **315**(23): 2525-2526. **(Subscription required)**
https://www.ncbi.nlm.nih.gov/pubmed/27327798

-and-

Ganz, P *et al.* (2016) "Development and validation of a protein-based risk score for cardiovascular outcomes among patients with stable coronary heart disease." *JAMA* **315**(23): 2532-2541. **(Subscription required)**

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. A diagnostic test based on these results is under development for release later this year.

Access to an electronic version of the JAMA paper and the accompanying editorial is available on request.

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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.

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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. **(Subscription required)**
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.

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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.
http://www.nmd-journal.com/article/S0960-8966(15)30161-9/abstract

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.

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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.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4868006/pdf/13075_2016_Article_1006.pdf

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.

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Marion, T *et al.* (2016) "Respiratory mucosal proteome quantification in human influenza infections." *PLoS One* **11**(4): e0153674.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0153674

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.

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Drolet, DW *et al.* (2016) "Fit for the eye: Aptamers in ocular disorders." *Nucleic Acid Ther* **26**(3): 127-146.
http://online.liebertpub.com/doi/pdf/10.1089/nat.2015.0573

The first FDA-approved aptamer-based drug, Macugen, was developed for the treatment of the "wet form" of the eye disorder age-related macular degeneration (AMD). Two additional aptamer-based drugs for AMD are in late-stage clinical development. This review article covers not only the history of

the AMD-directed aptamers, but also discusses the many other potential therapeutic opportunities for aptamers (including SOMAmer reagents) in ophthalmological indications with significant unmet medical need.

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Murota, A *et al.* (2016) "Serum proteomic analysis identifies interleukin 16 as a biomarker for clinical response during early treatment of rheumatoid arthritis." *Cytokine* **78**: 87-93. **(Subscription required)** https://www.ncbi.nlm.nih.gov/pubmed/26700586

In this study, researchers from Keio University and Takeda Pharmaceutical Company used the SOMAscan assay to identify blood (serum)-based biomarkers of rheumatoid arthritis (RA) that could be correlated with disease progression and treatment efficacy. Comparing RA patients with non-RA volunteers, the researchers found that the serum levels of interleukin-16 (IL-16) are a better indicator than other measurement in current use, and thus IL-16 may be a more useful clinical biomarker of response to treatment. They also note that such studies have been difficult to impossible to perform prior to the availability of the "new, reliable and comprehensive" SOMAscan assay.

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Sattlecker, M *et al.* (2016) "Longitudinal protein changes in blood plasma associated with the rate of cognitive decline in Alzheimer's disease." *J Alzheimers Dis* **49**(4): 1105-1114. **(Subscription required)** https://www.ncbi.nlm.nih.gov/pubmed/26599049

One of the more powerful uses of the SOMAscan assay is in performing "longitudinal" proteomics (i.e., tracking the changes in protein levels over time). In this study, an international group of researchers looked for changes in the blood of patients who transitioned from mild cognitive impairment (MCI) to Alzheimer's disease 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.

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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. http://online.liebertpub.com/doi/pdf/10.1089/nat.2015.0567

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.

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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. **(Subscription required)**
https://www.ncbi.nlm.nih.gov/pubmed/26576488

Preterm birth is major global health problem, and babies born preterm (<37 week 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 preterm birth risk, with the goal of making successful early intervention possible.

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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.

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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.

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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.
http://www.nature.com/tp/journal/v5/n6/pdf/tp201578a.pdf

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.

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Hattori, K *et al.* (2015) "Increased cerebrospinal fluid fibrinogen in major depressive disorder." *Sci Rep* **5**: 11412.
http://www.readcube.com/articles/10.1038%2Fsrep11412

“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.

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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.
http://www.pnas.org/content/112/23/7153.full.pdf?with-ds=yes

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.

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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.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4175044/pdf/280_2014_Article_2539.pdf

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.

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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/pmc/articles/PMC4217074/pdf/mtna201449a.pdf

A comprehensive review of the development of SOMAmer reagents with an overview of the many applications for these breakthrough protein-binding molecules.

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Menni, C *et al.* (2015) "Circulating proteomic signatures of chronological age." *J Gerontol A Biol Sci Med Sci* **70**(7): 809-816.
http://biomedgerontology.oxfordjournals.org/content/70/7/809.full.pdf+html

An international team of researchers used the SOMAscan assay to begin to dissect the proteomic features of aging in plasma. Initial finding from 202 subjects were subsequently replicated in 677 additional subjects. The researchers found that 11 proteins of those measured are associated with chronological age. This initial study underlines the importance of the proteome in understanding molecular mechanisms involved in human health and aging.

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Mehan, MR *et al.* (2014) "Validation of a blood protein signature for non-small cell lung cancer." *Clin Proteomics* **11**(1): 32.
http://www.clinicalproteomicsjournal.com/content/pdf/1559-0275-11-32.pdf

Building on previous work (see Ostroff *et al.* 2010, below), an international group of researchers led by SomaLogic scientists validate 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.

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Baumstummler, A *et al.* (2014) "Specific capture and detection of *Staphylococcus aureus* with high-affinity modified aptamers to cell surface components." *Lett Appl Microbiol* **59**(4): 422-431.
http://onlinelibrary.wiley.com/doi/10.1111/lam.12295/epdf

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.

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Morine, MJ *et al.* (2014) "Genetic associations with micronutrient levels identified in immune and gastrointestinal networks." *Genes Nutr* **9**(4): 408.
http://link.springer.com/article/10.1007%2Fs12263-014-0408-4

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.

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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.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4026438/pdf/12263_2014_Article_403.pdf

Similar in approach to Morine *et al.* (above), 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.

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Sattlecker, M *et al.* (2014) "Alzheimer's disease biomarker discovery using SOMAscan multiplexed protein technology." *Alzheimers Dement* **10**(6): 724-734.
http://www.alzheimersanddementia.com/article/S1552-5260(14)00031-4/pdf

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.

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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).

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Webber, J *et al.* (2014) "Proteomics analysis of cancer exosomes using a novel modified aptamer-based array (SOMAscan™) platform." *Mol Cell Proteomics* **13**(4): 1050-1064.
http://www.mcponline.org/content/13/4/1050.full.pdf+html

Exosomes (small vesicles secreted by most, if not all, cell types into the blood) could serve as a source of biomarkers for early detection of disease. In this study, researchers from Cardiff University and SomaLogic applied SOMAscan to a prostate cancer cell line, hoping to discover better biomarkers for early detection of the disease. The unbiased protein measurement resulted in the discovery of over 300 proteins previously unassociated with prostate cancer, and establishes the technology as "an effective proteomics platform for exosome-associated biomarker discovery in diverse clinical settings."

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Kiddle, SJ *et al.* (2014) "Candidate blood proteome markers of Alzheimer's disease onset and progression: a systematic review and replication study." *J Alzheimers Dis* **38**(3): 515-531.
http://content.iospress.com/download/journal-of-alzheimers-disease/jad130380?id=journal-of-alzheimers-disease%2Fjad130380

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.

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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).

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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.
http://embor.embopress.org/content/embor/14/12/1120.full.pdf

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.

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Loffredo, FS *et al.* (2013) "Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy." *Cell* **153**(4): 828-839.
http://ac.els-cdn.com/S009286741300456X/1-s2.0-S009286741300456X-main.pdf?_tid=f886b958-3165-11e5-909d-00000aacb35d&acdnat=1437675153_b2edc94375d8935136162c7cc44d6ecf

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.

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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.
http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0071703&representation=PDF

Epidermal growth factor receptor (EGFR) is a cell surface protein that is the target of the anticancer drugs cetuximab (Erbitux®) and panitumumab (Vectibix®). In this manuscript, scientists from Quest Diagnostics and SomaLogic describe the use of a SOMAmer that binds the extracellular domain of EGFR to determine the amount of drug-unbound EGFR in patients being treated with either drug. This assay could help determine drug efficacy and dosing for individual patients.

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De Groote, MA *et al.* (2013) "Elucidating novel serum biomarkers associated with pulmonary tuberculosis treatment." *PLoS One* **8**(4): e61002.
http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0061002&representation=PDF

This manuscript describes the first large-scale proteomic analysis employing SOMAscan in a study of active tuberculosis (TB). The international team of scientists identified multiple proteins that exhibit significant expression differences during the intensive phase of TB therapy, in particular discovering protein changes in conserved networks of biological processes and function (antimicrobial defense, tissue healing and remodeling, acute phase response, pattern recognition, protease/anti-proteases, complement and coagulation cascade, apoptosis, immunity and inflammation pathways). Some of these were known previously (providing validation for the work), but many novel proteins were also identified.

These newly identified proteins may provide new insights for understanding TB disease, its treatment and subsequent healing processes that occur in response to effective therapy.

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Ostroff, RM *et al.* (2012) "Early detection of malignant pleural mesothelioma in asbestos-exposed individuals with a noninvasive proteomics-based surveillance tool." *PLoS One* **7**(10): e46091. http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0046091&representation=PDF

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.

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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. http://ajp.amjpathol.org/article/S0002-9440(11)01014-5/abstract

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.

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Mehan, MR *et al.* (2012) "Protein signature of lung cancer tissues." *PLoS One* **7**(4): e35157. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0035157

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, below). 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.

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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.

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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. http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0015003&representation=PDF

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.

Gawande, BN *et al.* (2017) "Selection of DNA aptamers with two modified bases." *Proc Natl Acad Sci U S A* **114**(11): 2898-2903.
http://www.pnas.org/content/114/11/2898.long

SomaLogic scientists report on the generation and characterization of SOMAmers that contain two types of modified nucleotides. The current SomaLogic technology uses bases that have been modified with amino acid-like sidechains at the 5 position of deoxyuridine (dU). Now, for the first time, researchers have created SELEX libraries that also contain 5-position modified deoxycytosine (dC). Eighteen different DNA libraries were synthesized that contained zero, one or both modified bases. SELEX was conducted against proprotein convertase subtilisin/kexin type 9 (PCSK9), a human therapeutic target protein that helps regulate cholesterol. The aptamers with the highest affinity for PCSK9 contained two modifications. Similar results were observed with another target protein, prostate-specific membrane antigen (PSMA), a predictor for progression and prognosis of prostate cancer.

The increased chemical diversity of SELEX libraries should expand the repertoire of protein targets. In addition to displaying tighter binding while maintaining high specificity, SOMAmers with two modified bases were significantly more resistant to degradation than those with a single modification. Doubly modified aptamers also showed greater epitope coverage, which should be useful for developing reagents for assays that require simultaneous binding to a given protein target.

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Cotton, RJ *et al.* (2016) "readat: An R package for reading and working with SomaLogic ADAT files." *BMC Bioinformatics* **17**(1): 201.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4857291/

The SOMAscan assay measures over 1,300 proteins in small amounts of biological samples. Experimental data from the SOMAscan assay are provided in a proprietary “ADAT” file format that is difficult to import into non-SomaLogic software packages. To overcome this limitation, two researchers at Weill Cornell Medicine in Qatar have developed “readat,” a free, open source, R software package that allows users to import and analyze SomaLogic’s ADAT format files.

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Gelinas, AD *et al.* (2016) "Embracing proteins: structural themes in aptamer-protein complexes." *Curr Opin Struct Biol* **36**: 122-132.
http://www.sciencedirect.com/science/article/pii/S0959440X16000129

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).

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Gold, L (2015) "SELEX: How it happened and where it will go." *J Mol Evol* **81**(5-6): 140-143.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4661202/

In this 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.

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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 ~90% over current methods to generate the same chemical.

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Wolk, SK *et al.* (2015) "Influence of 5-N-carboxamide modifications on the thermodynamic stability of oligonucleotides." *Nucleic Acids Res* **43**(19): 9107-9122.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4627095/

The incorporation of DNA base modifications results in the high specificity for and broader range of protein types targeted by SOMAmer reagents. In this paper, the authors delve deeper into understanding the thermodynamic effects of these modifications on the stability of the SOMAmer oligonucleotides, both in their single-stranded and duplex forms. The results of these studies demonstrate that, depending on the type of modification, the addition can either destabilize or further stabilize the duplex forms, but in the single-stranded state (the usual use of SOMAmer reagents in biomarker discovery or other assays), the modifications significantly stabilized the oligonucleotide shapes as compared to unmodified single-stranded DNA.

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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.* 2015 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.

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Rohloff, JC *et al.* (2015) "Practical synthesis of cytidine-5-carboxamide-modified nucleotide reagents." *Nucleosides Nucleotides Nucleic Acids* **34**(3): 180-198.
http://www.tandfonline.com/doi/pdf/10.1080/15257770.2014.978011

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.

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Ochsner, UA *et al.* (2014) "Systematic selection of modified aptamer pairs for diagnostic sandwich assays." *Biotechniques* **56**(3): 125-128, 130, 132-123.
http://www.biotechniques.com/multimedia/archive/00231/BTN_A_000114134_O_231855a.pdf

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.

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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

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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*, describe 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.

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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.

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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.
http://www.pnas.org/content/109/49/19971.full.pdf+html

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.

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Gold, L *et al.* (2012) "Aptamers and the RNA world, past and present." *Cold Spring Harb Perspect Biol* **4**(3).
http://cshperspectives.cshlp.org/content/4/3/a003582.full.pdf+html

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.

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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.
http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0026332&representation=PDF

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.

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Brody, EN *et al.* (2010) "High-content affinity-based proteomics: unlocking protein biomarker discovery." *Expert Rev Mol Diagn* **10**(8): 1013-1022.
http://www.tandfonline.com/doi/full/10.1586/erm.10.89

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.

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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.

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Gold, L *et al.* (2010) "Aptamer-based multiplexed proteomic technology for biomarker discovery." *PLoS One* **5**(12): e15004.
http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0015004&representation=PDF

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").

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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).

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Eaton, BE *et al.* (1995) "Let's get specific: The relationship between specificity and affinity." *Chem Biol* **2**(10): 633-638.
http://ac.els-cdn.com/1074552195900233/1-s2.0-1074552195900233main.pdf?_tid=2d0444ae-3169-11e5-855b00000aacb35d&acdnat=1437676530_f6803454a6da15b1b8b669dc920c5086

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.

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Jenison, RD *et al.* (1994) "High-resolution molecular discrimination by RNA." *Science* **263**(5152): 1425-1429. **(Subscription required)**
https://www.ncbi.nlm.nih.gov/pubmed/7510417

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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.