Illumina-SomaLogic Deal to bring together genomics and proteomics technology platforms

An interview with Phil Febbo, MD and Roy Smythe, MD

ILLUMINA, a global next-generation sequencing technology company, and SomaLogic, an innovator in aptamer-based proteomic platform technologies, announced a strategic collaboration to bring together genomics and proteomics to enable multi-omics research. The partnership joins Illumina's DNA sequencing and array-based technologies with SomaLogic's SOMAmer® reagents and its SomaScan® Platform to measure a profile of circulating proteins. As part of the agreement, Illumina will develop and deploy NGS-based protein identification and measurement tools into laboratories and facilitate the development and use of high-multiplex protein pattern recognition tests.

Through this worldwide commercial partnership, the two companies will develop next-generation sequencing (NGS)-based proteomics products and leverage their complementary expertise to build on their established customer and market bases.

We contacted Phil Febbo, MD, Chief Medical Officer at Illumina and Roy Smythe, MD, Chief Executive Officer at SomaLogic to address a few questions on the deal and its impact on a range of business and technical areas. Read their replies below.

Business/Commercial

Q. Both Illumina and SomaLogic have been in business for some time. Why is now a good time to execute this deal? What catalyzed the first overtures to spark the discussions?

PF: Our understanding of biology has developed rapidly over the past two decades. Whereas incredible insights have resulted from progress in sequencing technologies, there is a growing need to match genomic understanding with the complexity of protein expression and activity. Given progress

on the part of SomaLogic and Illumina, the time is appropriate for our companies to work together and provide a solution.

SomaLogic has over the years steadily been expanding the content (i.e., the number of protein targets that their SOMAmers can detect) of their SOMAmer panel to the point where it now exceeds thousands of targets that can be detected simultaneously. That has brought affinity-based protein detection into a new realm of proteomics where one can start envisioning detection of all proteins present in a given sample. SomaLogic technology has matured to a point where it can make a real difference in science and medicine.

Illumina, on the other hand has continued to push the envelope on increasing the number of reads per sequencing run and the speed with which these data points can be accessioned, all while driving the cost per data point down, thus creating the highest throughput, most economical, flexible and robust readout technology on the market.

Combining the high-target, high-multiplex SomaScan technology with the high throughput read out capability of Illumina's sequencing platforms will enable researchers to analyze thousands of proteins in tens to hundreds of samples simultaneously. This unprecedented highly multiplexed, high-throughput capability will change how proteomics studies will be carried out going forward.

The combination of the three critical attributes, (1) target content size to biologically describe the complexity and unique signature of a particular state such as healthy or disease; (2) sample throughput to enable large association studies to add statistical power to any biological state across a population or disease cohort; and (3) economics to design and fund large studies that have statistical power, are key to conducting large scale experiments.

RS: One of the main reasons for initiating this partnership is that the technology to identify, measure and interpret protein data has finally begun to approach that of genetic sequencing – in regard to both the scope and scale of what can be done. The scientific community has been saying for a few decades that proteomics was a discipline that was "just about to be important." What has been missing is the measurement of enough of the proteome to both better understand biologic networks on the life sciences tools side to assist with the development of new therapeutics, and to get enough of a "signal" from the proteome to create new diagnostics. Since proteins represent about 99% of all drug targets, and since biologic "life" (including disease and response to disease) is driven by proteins acting in innumerable ways on human physiology – the fact that measuring more of the proteome could be impactful in both of these contexts shouldn't be shocking.

SomaLogic has been working in the proteomics sector longer than any other commercial organization, and we have developed a proprietary front-end sample prep and protein identification tool using synthetic nucleic acid constructs called aptamers that is highly flexible and can power a number of different back-end approaches, including array, NGS, mass spectrometry and evolving chip-based systems.

The reasons we were interested in moving forward with NGS specifically – in addition to our existing robust array capabilities – include the following: (1) we had completed proof of concept experiments to demonstrate the ability to very effectively combine our reagents with NGS platforms, (2) we strongly believe that NGS will be one of the important ways that individuals identify and measure proteins, and later run high-plex proteomics diagnostics based in part with on the increasing installed base of these systems around the world and the familiarity of use, and (3) the genomics "market" (e.g. genomics labs around the world currently not as involved with proteomics) was ready to move more aggressively into this sector – to add phenotype data to genotype data in a more sophisticated way.

We decided two years ago that we wanted to focus our own internal efforts on the non-NGS approaches and diagnostics applications and wanted to find a partner for NGS, rather than attempt to develop this sector of the market alone. The reasons we were interested in working with Illumina should almost be self-evident. While the field is growing in both numbers and approaches, Illumina is the unquestioned leader in this space with the largest worldwide installed base, a highly effective commercial organization, and a respected research and development group who are constantly innovating and improving their various tools, solutions and services.

Q. Can you comment on how you foresee positioning both genomics and proteomics to customers, especially those who may be focused on one and not the other?

PF: Offering both genomic and proteomic solutions to customers will facilitate the elucidation of biological connections between genetic information (genotype) and cellular function (phenotype). Proteomics is a natural complement of genomics, deepening researchers' understanding of biology and disease. While customers often choose between technologies to best understand the focus of their study, bringing both genomics and proteomics onto a single platform eliminates the need for choice and enables deeper understanding.

The product of this partnership will enable existing and future NGS customers to conduct high throughput multi-omic studies. New to NGS proteomics researchers will be able to interrogate proteins at higher multiplexity and higher throughput than has been possible to date and expand their investigations beyond proteins to correlate their findings back to, e.g., transcriptomic and genomic discoveries.

RS: The entire field of experimental biology, as well as medical practice will increasingly focus on combining both proteomics and genomics data. Human biology is highly networked – gene-gene, gene-protein and protein-protein interactions drive most of human biology and the things that are happening at the interface of normal human biology and disease. A number of the larger high-throughput genomics labs around the world are not heavily involved with proteomics research, and this collaboration should give them a powerful on-ramp to do so.

Q. Press releases[1,2] noted that "Illumina also plans to create combined workflows that provide genomic and proteomic information in the same analysis." What hurdles do you anticipate in combining the workflows?

PF: To benefit fully from having access to genomic and proteomic data, investigators need integrated analytic tools. As a critical part of the full end-to-end proteomics NGS solution that this partnership will deliver, are informatics toolsets and DRAGEN™ software. These toolsets will not just analyze the proteomic data but will also integrate that data with other -omic data types such as genomic and transcriptomic data. Multi-omic data integration requires pre-processing of each -omic data set that includes data quality control, normalization and scaling, and mapping to the relevant reference to ensure an equal contribution of each modality to the final integrated multi-omic data set.

Subsequent interpretation of multi-omic data is a significant challenge, including the validation of relationships between the different -omic data and between the multi-omic data and phenotypes, disease, biological insights, etc. While difficult, there is increasing evidence that the optimal management of some disease states will require information from the genome and proteome, and we are excited to provide solutions through this partnership.

RS: We have been seriously working on the bioinformatics of proteomics for more than a

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decade, and Illumina has been doing the same with genomics. We will be working together to combine our knowledge in this area, as well as the solutions we provide to the market separately. One of the areas where we believe SomaLogic can be particularly impactful to future customers on the platform will be as a development partner for high-plex proteomic diagnostic models and combined genomic-proteomic diagnostic models driven from data being generated by NGS. We have a great deal of experience in doing this work, have a large pipeline of our own diagnostic models we have already created and validated, and have developed a number of bespoke tools to facilitate this work for others.

Q. Will the offerings be research-use only or for the clinic? In either case, what are the plans to validate the combined platforms?

PF: The initial focus of the partnership is on launching a research product, but Illumina and SomaLogic are also setting up a path to the clinic with the eventual development of *in vitro* diagnostics as an important future consideration.

RS: While we are a life sciences tools company, we are keenly interested in providing the unique, first -in-class diagnostic models we have developed using machine learning and high-plex protein pattern recognition to clinicians and their patients. Our goal is to have the ability to leverage our front-end technology to run diagnostics on several platforms, with NGS being one of the most important, and we are excited to work with our colleagues at Illumina to develop these capabilities, as well as facilitate together the ability of others to develop and run their proteomics diagnostics leveraging this combined technology offering.

Q. How will SomaLogic-Illumina differentiate its offerings from existing genomic-proteomic platforms (in-house or purchased)?

PF: The most important areas of differentiation are high-multiplex, high sensitivity, and high specificity protein SomaScan technology, combined with high sensitivity, scale and speed of Illumina NGS technology, resulting in the highest multiplexed, highest throughput proteomics solution on market.

Combine that with Illumina's considerable background expertise in genomics, both in NGS technology and informatics toolsets, and you'll have a world-class genomic-proteomic platform.

RS: This is the first genomic-proteomic partnership to drive the ability to measure and identify this number of proteins at scale with market-leading technical specifications and high throughput. There is no other product like it on the market, or one that is contemplated like this in the near term. The experience that both groups have with the normalization, interpretation and analysis of both genomic and proteomic data is unparalleled, which should create real value for customers right out of the gate exclusive of technology capabilities.

Technology/Science

Q. What are the strategic plans to roll out the two companies' integrated genomics and proteomics databases? Will that integrated database offering precede any laboratory-based products?

PF: Another benefit of the partnership is to ensure that both genomic and proteomic output from Illumina sequencers can be seamlessly brought into Illumina Connected Analytics (ICA) for analysis. ICA will be the environment through which genomic and proteomic results can be analyzed with a growing number of knowledge bases to facilitate discovery.

RS: We haven't discussed integrating our current database into a combined asset for use in genomic-proteomic data analysis or use, but that discussion is planned. The opportunity to provide more comprehensive solutions for customers in regard to genomic-proteomic data interpretation and use is significant.

Q. Does the partnership have long-term plans to offer an even-more expanded multi-omic capability (e.g., genome, transcriptome, proteome) – assays, devices, instruments, and computational analysis package? Some or all of the above?

PF: Illumina has genomics, transcriptomics, and epigenetic solutions on the market today and this partnership will deliver a distributable, end-to-end proteomics solution using Illumina sequencers. SomaLogic and Illumina are excited that this partnership will enable investigators to analyze each critical step to the life of a single cell and organisms. There will, of course, continue to be innovations from both companies to ensure more comprehensive assays and even better integrative analysis.

RS: The incredible flexibility of our proteomics assay reagents, and the speed with which they can be developed will make it possible to expand into other areas as desired or where we believe there is an opportunity to create value. Everywhere an antibody is currently used in single cell, spatial or in situ proteomics, and even in more common pathology endeavors such as immunohistochemistry – our proprietary modified aptamer reagents can work as well.

Q. Are there plans to focus on specific therapeutic areas or diseases, e.g., cancers and beyond? Have these therapeutic areas or diseases been prioritized?

PF: Given the fundamental role that comprehensive DNA, RNA, and protein analysis has in facilitating new discoveries and insights, we expect broad adoption by researchers. Certainly, in the fields of oncology and other complex diseases, our partnership will enable investigators to embrace not only the power of large genomic studies based on DNA and RNA but to expand into comprehensive proteomic studies, but we have not prioritized specific therapeutic areas, diseases, or indications. The initial products are intended as discovery tools covering up to 10K proteins with implications across diseases and biological pathways.

RS: While the product we are developing with Illumina is designed initially to be a life sciences discovery tool capable of identifying and measuring a market-leading 10,000 proteins, we have developed and validated a number of proteomics diagnostic models at SomaLogic we are interested in providing on the Illumina NGS platform. A large subset of these products we have already developed are in the cardiovascular disease area, but there are several others as well, including a set of cancer tests currently in the near-term pipeline that are unique: these tests have the potential to determine the biologic risk of developing cancer before it actually develops.

Q. One anticipates the discovery of novel biomarkers from innovative assays. How will the two companies collaborate on creating, e.g., novel "genotype-proteotype" panels for specific biomarker discovery applications?

PF: Our primary focus is to get a comprehensive, optimally performing offering to customers as quickly as possible. As customers start understanding the benefit of combined genomic and proteomic analysis, we anticipate there will be a considerable number of opportunities for focused assays and our companies will work together to determine how to best complement the initial assay.

RS: We are interested in developing the array of products customers want, on as many platforms as they want to use. Once this initial product is launched, we will be listening carefully to what they would like to see as new products or extensions

of the base product and we are excited to work together with Illumina to meet those needs.

Q. Will a "grand strategy" be developed, say, to use genomics to narrow to a transcript profile to a proteome signature and resulting assays and results?

PF: At this stage, our focus is on empowering discovery and the generation of novel insights. What we have seen over the past decades is that investigators that adopt this breakthrough capability will apply it to disease settings and find novel ways to understand disease. With that understanding, there can then be clinical studies to determine if clinical tests that combine genomic and proteomic information can improve the management of patients. Our partnership will empower our customers with a complete tool set (i.e., end-to-end multi-omic assays, platforms and informatics toolsets and software) to start down this path.

RS: The industry will eventually be here, but it will take some time to learn how to integrate all this data (genomic, transcriptomic, proteomic and others) and to make important inferences from it. When you think about it, all data that can be collected from discovery experiments in research settings (or as we move forward from patients and those who wish to avoid being patients in clinical settings) should all be integrated and analyzed together in some way. We are well positioned with Illumina to help lead these efforts.

Q. Finally, how will this combined approach lead to more precise diagnostics to guide physicians in their choice of patient treatments – that is, not just more data but also more and better actionable information?

PF: The number of diseases where genomic or proteomic markers help improve care and outcomes for patients is rapidly growing. However, with this partnership and an enhanced ability to interrogate both genomics and proteomics simultaneously, investigators will better understand complex biological systems in health and disease. Different -omics layers can help fill the gaps in understanding the relationship between genotype and phenotype, between risk, causation, and disease manifestation. This is likely to lead to increased sensitivity and specificity of diagnostic tests, and improved outcome prediction, acceleration of drug discovery and biomarker discovery, and patient stratification in clinical trials.

Today, implementation of multi-omics is complex as different technologies are utilized to interrogate different analyte types, often with complex workflows, and standardization and correlation across different platforms poses a significant challenge.

The outcome of this partnership is a major step in the direction of simplifying the generation and the integration of multi-omic data sets.

RS: While we agree that using all available sources of -omic data will improve diagnostics in ways we likely can now only imagine, high-plex proteomics is already providing windows into body conditions, disease and disease trajectory which are either difficult to obtain from traditional diagnostics, or more or less impossible to obtain from them currently. We have developed test models for everything from determining someone's VO2max (level of aerobic fitness) to near-term risk of acute cardiovascular events using protein pattern recognition and machine learning, and an NGS platform actually allows us the opportunity to deploy them more quickly and more widely to meet patient and clinician needs.

Over time, it is likely that proteomics data combined with polygenic analyses will combine to create additional tests of predictive value, and proteomics phenotypes may help you understand when to act on dominant mutation diseases when identified (when does someone need an oophorectomy and mastectomy for BRCA1 mutations if that test result is obtained at a very young age, for example?), but proteomics itself, with high-plex measurement capabilities and high reproducibility will be impactful soon.

JPM: Thank you both for your insights. JoPM

References

1. Illumina, SomaLogic Ink Co-development Agreement for Proteomics Assays With Sequencing Readout; https://www.genomeweb.com/sequencing/illumina-somalogic-ink-codevelopment-agreement-proteomics-assays-sequencing-readout#.YfLGVerMLIU
2. Illumina Enters Co-Development Partnership with SomaLogic; https://www.illumina.com/company/news-center/press-releases/press-release-details.html?newsid=a15d9995-59d6-450c-b83f-4a76aada73de

Roy Smythe, MD

Roy Smythe, M.D., joined SomaLogic in November 2018 as Chief Executive Officer. During his career, Dr. Smythe has been an internationally recognized surgeon, biomedical scientist, academician, health system administrator and healthcare business entrepreneur.

While in medical school at Texas A&M, he was a Charles A. Dana Foundation Scholar at the University of Pennsylvania School of Medicine and the Wharton School of Business. Following medical school, he trained in general surgery, surgical oncology and thoracic surgery and completed a postdoctoral research fellowship in molecular therapeutics at the University of Pennsylvania. His medical and translational research career then began at the University of Texas MD Anderson Cancer Center, where he was the recipient of NIH and numerous other funding awards. He subsequently chaired the Department of Surgery at Baylor Scott & White Health System and the Texas A&M Health Science Center College of Medicine, where he was the Roney Endowed Chair, and later became the Medical Director of Innovation and Executive Vice President for Institute Development before moving into expanded roles in corporate healthcare.

Dr. Smythe came to SomaLogic from Royal Philips, where he served as Global Chief Medical Officer for Strategy and Partnerships. Before joining Philips, he served as Chief Medical Officer at Valence Health, a Chicago-based healthcare company. He held the same title previously at AVIA, a healthcare technology accelerator.

As a medical and scientific thought leader, Dr. Smythe is the author of more than 300 papers, abstracts and essays in academic, literary and humanities publications and a sought-after speaker.

Phil Febbo, MD

Phil Febbo, MD was appointed as Chief Medical Officer in March 2018. In this role, he is responsible for developing and executing the Company's medical strategy to drive genomic testing into healthcare practice. Dr. Febbo has a successful track record of translational research, clinical excellence, and for embedding molecular insights into clinical care.

Immediately before joining Illumina, Dr. Febbo served as CMO of Genomic Health. Prior to his five years at Genomic Health, Dr. Febbo was a Professor of Medicine and Urology at the University of California, San Francisco (UCSF), where his laboratory focused on using genomics to understand the biology and clinical behavior of prostate cancer, and his clinical practice focused on genitourinary oncology.

Before joining the faculty of UCSF as an associate professor in 2010, Dr. Febbo worked at Duke University Medical Center's Institute of Genome Sciences and Policy. He completed his internal medicine residency at the Brigham and Women's Hospital, and his fellowship in oncology at the Dana-Farber Cancer Institute. After which he was an Attending Physician in the Genitourinary Oncology Center at Dana-Farber, Instructor at Harvard Medical School, and a post-doctoral fellow in Dr. Todd Golub's laboratory at Dana-Farber, as well as the Whitehead Institute Center for Genomic Research of MIT (now the Broad Institute). Throughout his career, Dr. Febbo has served as a primary investigator for the Translational Research Program of The Alliance, an NCI-supported cooperative group, where his work focused on incorporating biomarkers into large clinical trials.

Dr. Febbo holds a Bachelor of Arts degree in Biology from Dartmouth College and an M.D. from UCSF.