“Scanning” into the Future: The Promise of SOMAScan Technology for Kidney Disease

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Biomarker-related research has been prevalent in nephrology for the past 15 years, particularly as related to work in the setting of acute kidney injury (AKI) and chronic kidney disease (CKD). Most publications on biomarkers for AKI and CKD have used a prespecified “biased approach” for targeted assays (enzyme-linked immunosorbent assays or variants). A search of PubMed for “Biomarkers and AKI” yields >1900 nonreview articles, and a search for “biomarkers and CKD” yields >2800 references. One can argue about the yield of prespecified biased approaches to biomarker work in kidney disease. Although progress has been made, there is still significant work to be done to understand the pathophysiology of the complex syndromes of AKI and CKD. There is also a lack of Food and Drug Administration–qualified biomarkers for use as drug development tools for humans in this space (the only qualified biomarker in any type of kidney disease is total kidney volume for polycystic kidney disease).

The unbiased “-omic” approach contrasts the biased, targeted marker approach. Interrogation of the genome, transcriptome, proteome, and metabolome is ever present in various fields and disciplines, and is improving the understanding of complex disease. Experts have opined that the proteome has the potential to best grasp the changing trajectories of health and disease over time because it represents the final common output of the genome, expression, and epigenetic phenomena, such as posttranslational modifications due to environmental effects. The human proteome consists of approximately 20,000 proteins. However, a search of PubMed for “proteomics and AKI” yields only 75 articles, and a search for “proteomics and CKD” yields only 105 articles. In contrast, a search for “proteomics and cardiovascular” yields 3173 articles.

Thus, in the ideal world, the ability to profile the proteome of humans would be most advantageous. The problem has been that enzyme-linked immunosorbent assays and nuclear magnetic resonance, as well as mass spectrometry are not ideal for high throughput due to inherent limitations. The key to achieving that goal has been finding better protein-capture agents. This has been achieved in recent years via the use of aptamers. This new platform, called slow off-rate modified aptamers (SOMAmers), are deoxy-nucleotides with unique intramolecular motifs that bind to the respective protein targets in native conformations. Although initiation iterations of the platform measured 800 to 1300 proteins, the latest version of the platform allows for measurement of >4600 proteins from a small amount of biological samples (50 μl). Quality is not sacrificed for quantity; there are low limits of detection (300 fM median), with a wide dynamic range (7 logs from approximately 30 fM to 1 μM), with a low percentage of the coefficient of variation for most proteins (<5%).

The key factor that allows for the ability to measure so many proteins on 1 plate is the kinetic manipulations that deal with the problem of nonspecific aptamer-protein binding. Finally, although cross-reactivity and interference could be a theoretic problem, the chemical nature of SOMAmers (charged phosphodiester backbone) discourages SOMAmer–SOMAmer binding.

How can this type of high-throughput technology help understand severe AKI that requires dialysis, as was done in the study by Yu et al.? In the post hoc study of the VA ATN (Veteran’s Affairs Acute Renal Failure Trial Network) trial by Yu et al., the investigators found that 54 of the >1000 proteins that were measured via the SOMAscan analysis were differentially expressed by at least 1.2 fold in day 1 samples among AKI patients on dialysis who died compared with
COMMENTARY

analyses revealed that proteins associated with systemic inflammation increased coagulation and increased endothelial cell injury. The investigators went on to analyze the relationships among 5 of the proteins (fibroblast growth factor [FGF23], tissue plasminogen activator [tPA], matrix metalloproteinase-8, soluble urokinase plasminogen activator receptor, and interleukin-6 [IL-6]) and mortality after adjustment for age, sex, congestive heart failure, sequential organ failure assessment [SOFA] score, and diabetic status, and found that the biomarkers were independently associated with day 8 mortality. FGF23, tPA, and IL-6 measured on day 8 were associated with mortality by day 28. What can we conclude or take away from these findings? Are these the markers that will innovate our understanding of AKI-D, will be used for future prediction models, and will change care? It is a nice start, but still numerous steps are needed before we can conclude that these are the definitive markers to be assessed in this setting. First, the cohort was extremely small. Second, only 5 of the 54 proteins that were significantly different in those who survived versus those who died were extensively analyzed. Third, although these markers were independently associated, the baseline model was quite sparse, with adjustment only for age, sex, congestive heart failure, SOFA score, and diabetic status. Several other key covariates were missing, which might have confounded the relationship between the biomarkers and outcomes, including more chronic health conditions (chronic hypoxemia, cardiovascular disease, malignancy, immunosuppressive therapy), variables at the start of renal replacement therapy (heart rate, mean arterial pressure, urine volume), and several other key physiological values and laboratory values (pH, partial pressure of oxygen, serum bicarbonate, phosphate, albumin, total bilirubin, international normalized ratio, platelet count). When this much more comprehensive set of variables was used for prediction of mortality in the same parent cohort (the VA-ATN study), the area under the curve was 0.85 for mortality. The use of SOFA as a covariate in this analysis is a straw-man, because the analysis on the full cohort found that all of the scoring systems, including APACHE (Acute Physiologic Assessment and Chronic Health Evaluation) II, SOFA, and Cleveland Clinic Foundation, showed relatively poor discrimination, reflected by areas under the receiver-operating curves of 0.68 (0.64–0.71), 0.69 (0.66–0.73), and 0.65 (0.62–0.69), respectively. These limitations notwithstanding, it is warmly welcomed that this type of technology is finally being applied to cohorts in the nephrology setting. There have been tomes of work that have been trying to further the understanding of several diseases and syndromes, including AKI and CKD. How will this type of high-throughput, proteomic-based technology advance the field of nephrology? Clearly, there are numerous options, including subtyping and risk stratifying patients with AKI and CKD, as well as assessing response to therapy with novel agents (Table 1). The nephrology community can learn and see the potential of the assay because it has shown usefulness in other fields, including cardiovascular risk prediction in the Heart and Soul and HUNT3 (Helseundersøkelsen i Nord-Trøndelag) cohorts and risk assessment from randomization to intervention to torcetrapib in the ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events) trial.

Table 1. Existing and potential future use cases for aptamer-based assays in kidney disease

| Use case                                      | Outside nephrology (published) | Nephrology published |
|------------------------------------------------|---------------------------------|-----------------------|
| Diagnosing complex syndrome early             | Alzheimer’s Dz                  |                       |
|                                                | Lung cancer                     |                       |
|                                                | Type 2 DM                       |                       |
| Endophenotyping complex disease               | Alzheimer’s                     |                       |
|                                                |                                 |                       |
| Risk stratifying acute disease/syndrome       | Active TB                       | VA ATN trial          |
|                                                |                                 |                       |
| Risk stratifying for chronic disease complex  | CV outcomes in Heart and Soul   |                       |
|                                                | and HUNT3                       |                       |
|                                                |                                 |                       |
| Early pharmacodynamic signal of new agent     | Response to treatment for PBN   |                       |
|                                                | y before intervention           |                       |
|                                                | Early detection of harm in       |                       |
|                                                | response to torcetrapib         |                       |
| Mechanistic insights to complex disease       | Duchenne MD                     |                       |
|                                                |                                 |                       |
|                                                | GFR on proteome                 |                       |

1 Belongie KJ, Ferrannini E, Johnson K, et al. Identification of novel biomarkers to monitor beta-cell function and enable early detection of type 2 diabetes risk. PLoS One. 2017;12:e0182532.
2 Kiddle SJ, Stevens CJ, Mehta M, et al. Plasma protein biomarkers of Alzheimer’s disease endophenotypes in asymptomatic older twins: early cognitive decline and regional brain volumes. Transl Psychiatry. 2015;5:e584.
3 De Groote MA, Sterling DG, Hraha T, et al. Discovery and validation of a six-marker serum protein signature for the diagnosis of active pulmonary tuberculosis. J Clin Microbiol. 2017;55:3507–3571.
4 Sattelle M, Khondoker M, Protis P, et al. Longitudinal protein changes in blood plasma associated with the rate of cognitive decline in Alzheimer’s disease. J Alzheimers Dis. 2016;49:1105–1114.
5 Paramo S, Marchetti L, Lauria M, et al. Combined use of protein biomarkers and network analysis unveils deregulated regulatory circuits in Duchenne muscular dystrophy. PLoS One. 2018;13:e0194225.
6 Christensen AS, Ash JA, DeLisle RK, et al. The impact of the glomerular filtration rate on the human plasma proteome. Proteomics Clin Appl. 2018;12:e170587.
Proteomic basic technologies have seen quite an interest over recent years in nephrology because of the apparent usefulness of the CKD273 classifier, not only for prediction of CKD incidence and progression in large cohorts, but also as a prognostic enrichment marker in the PRIORITY (Proteomic Prediction and Renin Angiotensin Aldosterone System Inhibition Prevention of Early Diabetic Nephropathy in Type 2 Diabetic Patients With Normoalbuminuria) study, which is enrolling individuals with a high-risk CKD273 score to spironolactone versus standard therapy. These types of novel approaches should bring new opportunities for effective therapies in CKD, which have been hard to find in recent years.

What is to come for the future for SOMAscan? Before full-scale usage, more work needs to be done on the accuracy and variability of the assay. There are high risks for false negative and false positive results with the assay. Confirmation of aptamer measurements for the most promising markers identified with traditional antibody-based measurements will be necessary. Alternatively, liquid chromatography–mass spectrometry will need to be used to verify potential markers that do not have a specific antibody available. False discovery will need to be tempered, and pathway and clustering approaches can assist with reducing the number of dimensions and potential false positives in the data sets.

Regardless, much of this work can be done in parallel because multiple CKD cohorts are in the process of performing measurements of SOMAscan in the near future. As a part of the work being done by the CKD Biomarker Consortium (CKD Biocon 2), together with dozens of targeted markers that will be measured, there are major efforts via the unbiased approaches of both proteomics (with the SOMAscan assay) and metabolomics (through the Broad Institute and Metabolon) to understand pathways of CKD and find new markers that predict poor outcomes in these patients. It is an exciting era for nephrology; the years 2020 and beyond should be revolutionary.

DISCLOSURE
In the past 3 years, the author has served as a consultant for Janssen Pharmaceuticals for litigation related to SGLT2 inhibitor-associated AKI, and as a consultant to CHF Solutions and Quark Biopharma. The author is a co-founder and serves on the scientific advisory board of RenalytixAI.

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