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EDITORIAL

Proteomics in CKD: The Young Man and the "See"

Hemingway's 1952 Pulitzer Prize-winning novella, *The Old Man and the Sea*,[1] described the physically rigorous but simple Cuban fishing method of yore used by protagonist Santiago during his 3-day ordeal with a giant marlin. In the end, Santiago is declared triumphant, despite the loss of the greatest "catch" of his life. The inspired dedication exemplified by Santiago has been mirrored by protein chemists for decades. These men of science clearly understood that analyzing, categorizing, and characterizing the end-product of a gene, the protein, were and would be critical to several disciplines, including medicine. However, for sometime, the alpha-to-omega relationship of gene-to-protein was reversed and all biological buzzwords began with "gene or genomic."

In "Revolution Postponed," Stephen S. Hall notes that the Human Genome Project had not yet attained those miracles of medicine,[2] so desperately awaited during the frenzied period marked by the sequencing of human DNA. Notwithstanding the numerous advances brought forth by the substantial efforts of many researchers during this epochal phase of fundamental biology, another field increasingly emerged and with less fanfare: proteomics, the study of the proteome. This portmanteau of *proteins* and *genome* represents the large-scale description of the complement of proteins expressed by a cell, organ, or organism, during a defined period or set of conditions. In the domain of nephrology, proteomics may reflect the unique protein signatures that appear in the plasma or urine during normal kidney health or during its derangement(s) by any one of various causes and conditions.

The proteome in human beings is much smaller in number than the putative number of genes, by approximately two orders of magnitude, as only 1.5% of the genome is transcribed and translated to proteins. We have witnessed this disparity in the past. Previously, we posited that our immunological system, to afford protection and competence, was of necessity and required to recognize approximately million antigens. Correspondingly, there was a requirement for production of the same number of different antibodies, thereby directing the bulk of metabolic activities to that end. Presently, we know better and acknowledge that sophisticated intracellular and molecular processing derivatizes many foreign antigens into simpler and more fundamental units for antigen presentation that are dealt with by far fewer antibodies. Essentially, nature evolved and adapted a modular approach, thereby providing itself efficiency and throughputness. As Einstein put it, nature made things simpler but not simple. The same is true of proteins, wherein a particular proteome as a module, give or take a few proteins, may satisfy a host of biological requirements. Conversely, the lack of vital components of a proteome may render an organism ill-equipped to handle a particular group or set of stressors.

Proteomics has advanced remarkably in the past decade and nearly every major university maintains a proteomics core laboratory. This field has been enhanced by the ultrafine specificity intrinsic to its methodology of separative analysis. Two-dimensional gel electrophoresis, combining resolution of proteins by charge and mass, identifies protein identities on the basis of their respective, unique, migratory patterns and helps determine the proteome.[3] This technique is highly synergized and automated by mass spectrometry (MS) and peptide mass fingerprinting, which is aided and abetted by powerful bioinformatical databases. MS, commonly used by analytical laboratories, characterizes the physical, chemical, and biological properties of many compounds and is available in a variety of forms, including time of flight, quadrupole mass filter, and orbitrap, among others. Another method, tandem MS sensitively and specifically determines individual sequence information at the peptide-level, comparing fragment ion profiles generated by colliding peptides in a nonreactive gas. Furthermore, peptidomic analysis may render insights into treatment efficacy: one peptidome may predict a positive response to a prescribed therapy, whereas another may

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differentiate an intermediate or null response.[4] Such differential responses may greatly precede any clinical measurement(s), and may be of extreme importance when a given treatment is potentially toxic.

In this year-end issue of *Advances in Chronic Kidney Disease*, we fix our diagnostic and therapeutic gaze toward 2011 and beyond. As such, we have enlisted the efforts and visions of 2 Guest Editors and proteomics experts, Dr. Jonathan Klein, M.D., Ph.D., University of Louisville School of Medicine, and Dr. John Arthur, M.D., Ph.D., Medical University of South Carolina. The Guest Editors have in turn chosen contributors who will provide the underpinnings of the array of opportunities that proteomics parlays in CKD, in terms of diagnostics and therapeutics. To this end, this compilation focuses primarily on expression and functional proteomics rather than structural proteomics.

Dr. Klein elucidates the nephropathic proteome of diabetes. Here, the fundamental realism of biomarkers will be understood and provide a prototype for Dr. Yamamoto's characterization of CKD as a series of enlarging proteomic databases. The unions and intersections of these bioinformatic repositories represent a nexus of knowledge for many disease states, not just renal ones. The acquisition speed of such knowledge occurs at breathtaking speed and is now at the end-user level. No supercomputer required! Dr. Mischak describes the urinary proteome of CKD, a novel form of urinalysis—indeed, a biomolecular biopsy of the kidney that begs for clinical correlation and begets directed therapy. Dr. Merchant expands on the uses of MS in kidney research and finally, Dr. Devarajan describes the use of targeted kidney biomarkers in CKD, today and in the future.

Therefore, and not too futuristically, applied proteomics provides disease detection at the asymptomatic disease phase and quantitative treatment timing and directionality, which is presently impossible to achieve by contemporary clinical and imaging technologies. In conclusion and on reflection, I recall the time when I was much younger and thinking that our future would be revealed as deoxyribonucleic acid was unwound and decoded, this aspiring nephrologist- and physiologist-to-be was presagingly, albeit clairvoyantly, informed by a wiser and more experienced mentor, "Young man, in the end, you'll see … it's in the proteins." And, it is.

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Editor

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