JOURNAL OF PROTEOMICS XX (2014) XXX–XXX

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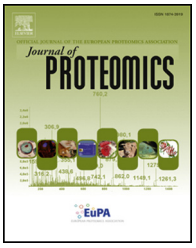

Review

Six decades searching for meaning in the proteome☆

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ARTICLE INFO

Keywords:
Proteomics
HPI
SISCAPA
MRM
MALDI
Biomarker
Plasma

ABSTRACT

This review describes one thread in a fabric of developments leading to the present state of proteomics, stretching over 60 years and ending with a prediction for 2024. While composed largely of personal reminiscences, the story offers some instructive success and failures, and appears to be nearing the long-sought goal of deep insights into real biology. This article is part of a Special Issue entitled: 20 years of Proteomics.

Contents

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http://dx.doi.org/10.1016/j.jprot.2014.03.005
1874-3919/

1. Introduction

September 2014 is an interesting point from which to look back at the history of what has been called proteomics, and I am grateful to the organizers of the 10th Siena meeting for the suggestion to do so — especially given that it will be 20 years since the first of these seminal conferences. I have been lucky enough to be present for all of them and in the process fallen in love with the city and its many treasures, along with the amazing, unique and wonderful circle of enthusiasts who organize and attend every other year. In the following I will look at the last 20 years of proteomics embedded in a personal reminiscence covering a larger swath of time — the five decades from 1964 to 2014, plus a peak 10 years into the future.

Today we are in a period of real optimism regarding the part of proteomics that interests me most — proteins as diagnostic biomarkers. This is a huge improvement on the recent history of the biomarker field, in which enormous effort was expended with disappointing results. While genomics made major strides and produced significant clinical results, particularly in cancer (a genetic disease), proteomics did not produce any bona fide (i.e., clinically approved) biomarkers. Of course genomics is meant to be straightforward — DNA is digital, and so progress in this field probably follows something very much like Moore's Law. Protein science is by comparison very messy, technically much more difficult, and represents an altogether deeper layer of biology. Despite this excuse, it was a frustrating time. At the end of the day, however, protein biomarkers, together with some metabolites, represent the best tools we have for objectively tracking changes in wellness and the emergence, classification and control of most diseases (personalized medicine). Persistence in addressing the challenges is therefore justified.

By my reckoning, something like proteomics has actually existed for most of my life. Here are a few decade-sized snapshots, including one that has not yet occurred.

2. 1964: molecular anatomy

In 1964, when I was 15 years old, my father (Norman G. Anderson, who has attended several of the Siena meetings and, at 95, is still contributing important ideas to science) was formulating what he called the Molecular Anatomy (MAN) Program at Oak Ridge National Lab. In summarizing the idea, he wrote in Science [1]:

> Molecular anatomy is concerned with the description, at the molecular level, of the structure and organization of cells and tissues. It is the logical extension of microscopic anatomy, and it will ultimately be the basis of the molecular pathology of human cells.

Looking back, of course the tools available at the time were not really up to the task: centrifugation, disc gel electrophoresis, Edman peptide sequencing (DNA sequencing was not yet possible), polyclonal antibodies and large-bore chromatography were not capable of dealing effectively with really large collections of molecules (and no one had a good idea how large those collections actually were). Neither the separative power available nor the analytical sensitivity was sufficient. Nevertheless the idea that we should enumerate all the building blocks of living things, as we had systematically explored all the isotopes in the periodic table of the elements (using preparative mass spectrometry at Oak Ridge), was correct and made sense as a large-scale scientific objective. Pursuit of the goal did lead to the development of a number of important pieces of technology including zonal ultracentrifuges [1], high speed parallel biochemical analyzers [2], and the first liquid chromatography systems operating at "high" pressures (5000 psi). I spent a lot of time in my father's lab at Oak Ridge (some of it trying to "borrow" components for rocket fuel), and became accustomed to the idea that developing new tools can be fun, and that these open up new vistas in biology.

3. 1974: 2-D gels

In 1974, Pat O'Farrell and Joachim Klose were preparing to publish the initial descriptions of 2-D electrophoresis [3,4] — the revolutionary method that first sparked widespread belief in the idea that we could look at many proteins at once. I went to visit Pat in Boulder Colorado where he had just finished his PhD, and he described the difficulty of getting his "mere method" published. One look at the gel picture (of the *Escherichia coli* proteome) in the finally-accepted JBC paper had made me a believer. I almost gave up on the technique after the first month of completely blank gels — "luckily" it turned out that my brand new bottle of Coomassie Blue from Fisher Scientific contained a completely unrelated blue dye with no affinity for proteins (Fisher apologized and said they would put the right compound in future bottles). Re-staining with real Coomassie Blue showed lots of spots, and pretty picture addiction set in. In 1975 I started working with my father to improve 2-D technology and we built a group at Argonne National Laboratory to bring some real engineering resources to bear on the problem (resulting in the original Iso-Dalt 2-D system [5]). Our first significant paper using the method described the 2-D pattern of human blood plasma [6], and in it we identified all the major spots by immunoprecipitating each protein with a specific antibody from the collection generated by the Behring Institute in Marburg, Germany for diagnostic purposes. The plasma 2-D pattern (still the most beautiful) summarizes an enormous amount of useful information about the most useful diagnostic sample. Slowly the technology matured, the stains got more sensitive [7], and image analysis systems began to deliver meaningful measurements of protein amounts (though the tiny computing power available then would make these approaches seem ridiculous now).

In parallel, a different protein survey approach, based on selecting monoclonal antibodies recognizing some expressed epitope, was beginning to emerge from Kohler and Milstein's work at the MRC lab in Cambridge [8], where I had gone to do a PhD in protein crystallography with Max Perutz. There I met Terry Pearson, a close friend and collaborator ever since, who made the first ever commercial monoclonal at about this time

Please cite this article as: Anderson L, Six decades searching for meaning in the proteome, J Prot (2014), http://dx.doi.org/10.1016/j.jprot.2014.03.005