Broad Proteomics and Health Management

Larry Gold

COLS
Colorado Longitudinal Study

My History with Proteomics

I started to do broad, unbiased proteomics in 1969….I ran about 500,000 samples on Laemmli SDS gels over twenty years (~ 70 proteins resolved, quantitation is difficult, CVs are high)

Pat O'Farrell invented 2D gels in my lab (as a guest in my lab!), leading to his magnificent 1975 paper….(roughly 2,000 proteins resolved, quantitation is difficult, CVs are high)

Craig Tuerk and I invented** (along with Jack Szostak and Andy Ellington) SELEX and aptamers, and then SomaLogic made SOMAmers (better than aptamers), and then SomaLogic published SomaScan about a decade ago (today SomaScan quantifies about 11,000 human proteins, quantitation is spectacular – CVs are under 5%)

As many of you know, I stopped working at SomaLogic a few months ago

I Have Always Cared about Health

I think protein profiling is the molecular weapon to follow health for populations and intervene appropriately

For the last thirty years I have been driven by questions of scale: I have wanted protein profiling to be a tool used by the entire world, everyone and everywhere…COLS has been a large part of that effort

SomaLogic was formed to reach that scale; for more than twenty years I wanted to see **U**rine-Based **P**roteomics **I**nsights through **S**oma**S**can (the best backronym ever!)

Between O-Link and SomaLogic probably a million samples have been analyzed so far: we will need billions of people per year, analyzed longitudinally and frequently

We have a long way to go to make clinical proteomics ubiquitous

Just a Bit More about COLS

- As we were trying to get samples from biobanks for SomaLogic, we made a rather depressing observation…
  - There were large biobanks that had single collection times - many of these included longitudinal surveys and medical records but narrow specimen sets
  - There were smaller longitudinal biobanks (usually created by MDs with a specific disease focus) whose samples were first collected when people were diagnosed with a serious condition rather than prior to their diagnosis -
- COLS was designed to collect vast numbers of samples prior to any diagnosis, allowing control samples to exist for individuals who became ill later…
- The idea was LONGITUDINAL SCIENCE rather than only cross-sectional sample sets

This Talk is from My Post-SomaLogic Life

I had some free time…

Outline for the talk…(very few slides)

Will aptamers/SOMAmers provide specific binding SPECIFICTY comparable to what antibodies do in ELISA formats (Nebojsa Janjic's remarkable work)

The value of *longitudinal* clinical proteomics for understanding complexity

The COGS demands – what fraction of the healthcare budget could be used?

Cleaning in Place: Personalized medicine will use personalized devices – privacy will be retained

It could happen!

Why Are There No Green Dogs?
A story about evolution…

please read "Before the Big Bang…"

See a remarkable high resolution view (from the Lichtman lab) of the human temporal cortex – Science, May 10, 2024

Here is the Value Statement for Broad use of Clinical Proteomics…

…from my abstract…

What will it take for the clinical community to embrace broad proteomics with the same fervor as has the basic research community? Could we anticipate that proteomics, done frequently over time, will become a health management tool used for large fractions of global populations? The required pieces toward that end will require that diagnoses are better with proteomics and that health outcomes are improved. **The costs for healthcare systems must be small relative to those improvements.**

We Understood All of this Ten Years Ago…

- **DTC-and-Me: Patient, Provider, Proteins and Regulators**
  - **Fintan R. Steele and Larry Gold**
  - *J. Pers. Med.* **2014**, *4*, 79-87
- As far as Fintan and I can tell, no one ever read this paper…
- What follows is a "Good Idea whose Time Has Come"

  We will all get to watch what happens…
- Conceptually this paper is also a value statement for clinical proteomics!

A Robust Literature Supports Clinical Proteomics

- Proteomic studies using either O-Link, SomaScan, or mass spec have shown repeatedly that diagnoses are available from simple “elevator” science (things go up or down over time, during disease trajectories)
- There might be a thousand reports of this kind, and there will be more
- I do not know of a single study in which protein biomarkers were not observed when two sets of samples differing only in disease status were compared
- **Proteomics already makes diagnostics possible**
- Leading to my favorite proteomics paper of all time (so far)… in Nature, Vol 624, December 7, 2023 – ***you just heard this story from the first author***

“Organ aging signatures in the plasma proteome track health and disease”

- Animal studies show aging varies between individuals as well as between organs within an individual, but whether this is true in humans and its effect on age-related diseases is unknown. We utilized levels of human blood plasma proteins originating from specific organs to measure organ-specific aging differences in living individuals. Using machine learning models, we analysed aging in 11 major organs and estimated organ age reproducibly in five independent cohorts encompassing 5,676 adults across the human lifespan. **We discovered nearly 20% of the population show strongly accelerated age in one organ and 1.7% are multi-organ agers.** Accelerated organ aging confers 20–50% higher mortality risk, and organ-specific diseases relate to faster aging of those organs. We find individuals with accelerated heart aging have a 250% increased heart failure risk and accelerated brain and vascular aging predict Alzheimer’s disease (AD) progression independently from and as strongly as plasma pTau-181, the current best blood-based biomarker for AD. Our models link vascular calcification, extracellular matrix alterations and synaptic protein shedding to early cognitive decline. We introduce a simple and interpretable method to study organ aging using plasma proteomics data, predicting diseases and aging effects.

- This paper *alone* argues that clinical proteomics has value for health management

Costs for Clinical Proteomics: What Might be Acceptable?

- The total annual health care budget in the world today is about $12T (that's a T)
- About 4% of that is spent on diagnostics (about $500B/year)
- To keep the math simple, let's assume we must do clinical proteomics on 5 billion people every year, so the proteomics cost has to be $100/person
- …and worst of all, we have no idea how often that proteomics analysis should be done (some disease trajectories are fast and might be helped by frequent proteomics during a short disease event -sepsis or viral infections – while some diseases progress more slowly)
- Most people imagine narrow analyte choices for clinical proteomics – I am not in that camp…*this would be a good topic for debate…*

EKGs Can be had as Easily and Regularly as one's Blood Pressure, Weight, or Pulse…

- **Introducing KardiaMobile® Card (an aside, but a metaphor)**
- The future of heart health is in your wallet.
- Less than $100 on Amazon
- Could clinical proteomics be done on a reusable device, driving costs down?
- I first proposed this to DARPA more than twenty years ago, and the time finally has come (UPISS – pee, quantify, wash, repeat)

Towards Maintenance-Free Biosensors for Hundreds of Bind/Release Cycles

Radislav A. Potyrailo,* Anthony J. Murray, Nandini Nagraj, Andrew D. Pris, Jeffrey M. Ashe, and Milos Todorovic from General Electric in Schenectady, New York, a lab I worked in during the summers of 1961 and 1962 (with Carl Woese as my friend and mentor) Angew. Chem. Int. Ed. 2015, 54, 2174 –2178

Abstract: A single aptamer bioreceptor layer was formed using a common streptavidin–biotin immobilization strategy and employed **for 100–365 bind/release cycles**. Chemically induced aptamer unfolding and release of its bound target was accomplished using alkaline solutions with high salt concen- trations or deionized (DI) water. The use of DI water scavenged from the ambient atmosphere represents a first step towards maintenance-free biosensors that do not require the storage of liquid reagents. The aptamer binding affinity was determined by surface plasmon resonance and found to be almost constant over 100–365 bind/release cycles with a variation of less than 5 % relative standard deviation. This reversible operation of biosensors based on immobilized aptamers without storage of liquid reagents introduces a conceptually new perspective in biosensing. Such new biosensing capability will be important for distributed sensor networks, sensors in resource-limited settings, and wearable sensor applications…**and reusable SomaScan (detection will be critical – fortunately Jas Cleveland invented a way to quantify binding that is compatible with multiple bind lease cycles)**

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A Thought

- Society believes that patients and citizens must control their own health data - genomic data are considered “risky” but…
- Longitudinal clinical proteomic data likely will become “risky” also…
  - Insurance policies
  - Employment issues
- If people own their reusable SomaScan arrays and get their longitudinal proteomic data privately (with analytics done securely), privacy fears could disappear
- This could turn important molecular data and prognostics into the equivalent of daily visits to your own scale…one’s own business!

Summary

- Clinical proteomics will arrive in the next decade – high quality data for a large fraction of the human proteome
- The equivalent of SomaScan could be available to a large fraction of the world's population
- The annual costs will be acceptable to health systems – under 4% of the world's total healthcare budget
- The positive impact on major and rare diseases should be substantial
- Thanks…