Pioneers in Proteomics

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In part five of our Pioneers in Proteomics series, Dr. Stanley Hefta discusses the challenges of identifying biomarkers amongst highly abundant proteins, the need to create standard practices between laboratories, and the promising future of proteomics.

Dr. Hefta is Executive Director of Proteomics in the Departments of Applied Genomics and Clinical Discovery at Bristol-Myers Squibb in Princeton, NJ. Prior to joining Bristol-Myers Squibb, Dr. Hefta was an Associate Professor at the Beckman Research Institute at the City of Hope Medical Center in Duarte, California. Dr. Hefta's research has included development of technologies for the micro analytical characterization of the proteome.

On the challenge of identifying clinically-relevant biomarkers

A biomarker that's used pre-clinically doesn't have to be as exact or validated as a biomarker that's used clinically. Pre-clinically you're doing a lot of hypothesis testing. You're putting out a question and you're attacking that question from a variety of angles. The biomarker itself, it can be many biomarkers, it doesn't have to be just one… the validity of that measurement isn't as exacting as it is in a clinical organization. In the clinical organization, if you're going to be basing your read out of drug efficacy, of toxicity, of prediction of response, on a biomarker, you have got to be dead on with that biomarker. It has to be totally validated, all the assays. Pre-clinically, it's not quite that stringent, because you're not basing your entire interpretation of the experiment just based on the read out of a biomarker.

On using mass spec to identify low abundance proteins

Your biomarker is only going to be present in certainly much less than one percent of the total amount of proteins that are in blood. And, being able to drill down that far into the dynamic range of proteins that exist in blood, is a major problem. It's something that we have not fully overcome yet.

You've got somewhere around eighty milligrams per ml of protein in plasma, human plasma. But, ninety-nine percent of that is accounted for by only twenty-two proteins. So, if your biomarker happens to be one of those twenty-two, you're in really good shape, right? But, if it's not…you have to get rid of those guys and have to be able to go way down in abundance to those low abundant proteins that are shed from cells that are signaling molecules and other things, which are functionally important in cancer. And, so you have to be able to look at the low abundant proteins to identify really the most important ones for cancer diagnosis.

I realized that in order to advance our ability to analyze very low abundant proteins, we needed to bring mass spectrometry into this field. The beauty of a mass spectrometer is the ability to look globally at what's in a sample.

On the importance of standards

As we try to share data more across from one university to another, or between one industrial lab and another, that's when the need for standards and standard processes and so forth, becomes more and more. The other thing to keep in mind is that we are not making measurements just on one protein anymore. It used to be that you would work very hard to purify a protein to homogeneity and then you would identify it, sequence it. Now we're looking at tens of thousands of proteins simultaneously. And, when you're making measurements of large numbers of things, if you have a standard deviation of too much, you've got a lot of false positives that you've got to go through. So as we both deal with the complexity of the problem and try to share data from one lab to another to another creating these federated databases and so forth, there's just inherently a need for bringing into that process standards and standard processes.

On the need for multi-disciplinary collaboration

I think that we're in a very exciting period for science today because of the integration of so many different technologies and disciplines. There's still a place for the individual laboratory manager working in his field to just work with one technology or one approach. But, genomics, proteomics is very large and you do have to bring in other communities. In my lab we have molecular, cellular biochemists. We have mass spectrometrists. We have statisticians. We have informatics folks to deal with information management. And, we reach out to disease biology groups for programs to work on. So, it is a very multi-disciplinary approach when you're talking about using proteomics or genomics when you're talking about discovering a biomarker and bringing it up through assay development and bringing it into the diagnostic fields. A very long term commitment. Multiple groups engaged in the process. There has to be, I think, an involvement between the academic centers, the industrial centers, the government centers, agencies, to drive this process forward.

On the sharing of information

Science is continuing, evolving and advancing, it's a product of the world. You never know where that discovery is going to come from. It may be from an academic lab. We were working on trying to identify some processes, biological processes that were behind a particular disease state. Not having a lot of luck at it and out of the blue came a discovery in an academic lab in Belgium, that unlocked the key and provided that little bit of data that helped us understand that process that we were trying to understand, and opened the door. So, you never know where that discovery is going to come from**.** But, it's through the sharing of information like that, and in this particular case it was a publication. In other cases it's a discussion in the hallway. Just a different way of looking at data or at biology that can provide that little bit of hint that sends you down a different path than what you were on before that leads ultimately then to the discovery of what you're looking for.

On the future of proteomics

In the future, I think we're going to have much greater throughput with protein chips, primarily, that will allow us to interrogate every protein in the body. In the future, we will have all the splice variants of proteins on chips or in some format that we can interrogate very quickly. In the future, we will have micro machines that will allow us to, with just a drop of blood, identify what's going in a particular patient. Those things will happen. There's no question about it. There's so much activity going on in all of these related areas. Nanotechnology, great advancements going on there to interrogate even further down in abundance of proteins. Once you marry nanotechnology with the protein chip, arrays, and so forth, you have then I think a very powerful platform for looking at protein levels and correlating those levels with disease and/or treatment efficacy, etc. And, then of course, as we've been talking about, there's just an explosion of data out there, being presented at meetings, being deposited into databases, that make it so easy nowadays. And, it will be even so much more easy in the future to compare your results with that of the external community. I think that the future is very bright for not only proteomics, but for genomics technologies also.

It's a process that we're going through. But, it's headed in a good direction.