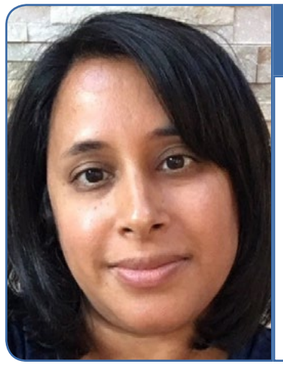
NEUROFILAMENT AND BIOMARKER RESEARCH



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Dr. Mehta is a Director in the department of Development Biomarkers and Bioanalytical Sciences at Biogen. She received her Bachelors in molecular biology and immunology from University of California, Berkeley in 1998 and earned her Ph.D. in biomedical sciences from Harvard University in 2005. She completed a postdoctoral fellowship at the Novartis Institutes for Biomedical Research and then joined Tolerx as a Scientist responsible for developing preclinical PK/PD studies and clinical biomarkers for immune-modulating drug programs. Dr. Mehta joined Biogen in 2011 where she currently supports clinical programs in the multiple sclerosis and neuroinflammatory disease areas. She has special interests in advancing and implementing industry-wide best practices for biomarker and bioanalytical strategies, clinical assay development, and "fit-for-purpose" assay validation.

Why is there so much excitement surrounding neurofilament?

I think the excitement stems from the fact that there are new methodological advances that make it possible to measure neurofilament in blood. What's interesting about that is you now have a window into what is happening in the Central Nervous System (CNS) and into the pathological processes of different neurological diseases. Now you have the ability to monitor this more frequently in patients, whereas collecting Cerebrospinal Fluid (CSF) is not something you could do routinely or repeatedly. That excitement has led to the ability to further understand some of the disease pathogenesis in emerging disease areas. People are trying to leverage this therapeutically in neuroscience and understand whether emerging treatments really have an impact in the CNS, without having direct access to the CNS.

How could this impact the field?

There are so many potential contexts of use for this biomarker and it is very dependent on the disease and what question you are trying to ask. There is a clear opportunity in drug development and how it can enable the drug development process and help internal decision making about your therapeutic approach. One also could potentially use neurofilament to monitor individual patients, however neurofilament is not a specific biomarker, it is present in many diseases and we would have to interpret the biomarker in the context of other data.

What are the recurrent challenges that you come across?

The biggest challenge is trying to take an emerging biomarker from the research setting, by understanding the most appropriate context of use and have the data to support that, so that you can have a clinically actionable biomarker. It takes many different people to be able to fill that gap with their clinical and statistical counterparts and biomarker expertise. They need to agree on what is the most appropriate use for that biomarker and how you then implement that; either through drug development or thinking about the clinical space, and how to use it to monitor patients and what sort of decisions you make based on that.

What is the next step for the research?

I think biomarker research is very iterative. You start somewhere, you learn and gain knowledge, and then you go back and refine your context of use. With that there probably comes again another iteration of new assay development and generating new data. Now with where the field is heading, we have a pretty high confidence of what we could potentially do with neurofilament, particularly in the multiple sclerosis space where there's been a lot of data generated, not just by Biogen, but across the leading academic centers and other companies. Now it's about taking it into the real world. We have done this in the clinical trial phase, but we next need to determine how to translate that into the real world of medicine.

In terms of developing assays for neurosciences, as opposed to other therapeutic areas, are there any particular challenges that come from that?

I think the biggest thing is the space, the compartmentalization of the CNS. Having access to the brain is not something that we easily have, so most of the biomarkers you typically see in neuroscience are imaging markers. But those imaging approaches, like MRI, tend not to be very specific and you have to take into account other clinical data to be able to interpret that image. The opportunity now is that with more sensitive technologies, we are able to see specific fluid biomarkers that traditionally you would only be able to measure in the CSF and we can now measure this in the blood using ultra-sensitive methods. Now that you can measure it, what do you do with that information? You have to go back to the clinical data to be able to understand what the potential implications of the biomarker are in that disease setting.

Are there many applications of genomic biomarkers in neuroscience currently?

There are quite a few applications of genomic biomarkers in neuroscience. This has a lot to do with if there are inherited mutations related to certain psychological diseases, for example with Amyotrophic lateral sclerosis (ALS) there are known familial mutations. You can think about using genomic biomarkers to include patients who may have a high risk of developing ALS, or to identify those patients who have a particular pathogenic process that you are interested in interrogating with your therapeutic approach. Because of that genetic component, you can very easily identify the right patients and validate your target. A lot of these approaches now are coming towards gene therapy using RNA modalities and so you are treating the specific, underlying genetic mutations.

A lot of companies are very excited about neurofilament and there is a lot of collaboration and competition within this. Are you partnering with other organisations to take it further?

I think the science is already "partnered", with a lot of collective engagement across companies and academic leaders in the field. They talk about what the recent data are and how that evolves our understanding of neurofilament. You will see the latest Multiple Sclerosis (MS) conferences went from a handful of posters and presentations on neurofilament to an entire symposium. So there's a lot of communication about the emerging science and potential opportunities for the biomarker. In terms of how you get it to the next level, Biogen is partnering with Siemens and developing a new assay that would have more of a worldwide footprint. Really the intention is to open that up to have access to individuals to be able to generate the right data sets, so that we have the understanding of how to use the biomarker in the real world setting.

Are there any particular technologies in neuroscience that are impacting the biomarker space at the moment?

I think the more ultrasensitive technologies now enable us to look at fentigram levels of markers that have leaked out of the CNS into the fluid peripheral compartment. Now that we are able to reliably measure these proteins of interest, that has opened the door a lot for neuroscience. We are now able to understand a lot more about disease pathogenesis, without having to have direct access to the CNS compartment. But it remains to be determined just how useful these things are in the clinical setting. It is an evolving space which is being driven by these new technologies.

What will the future of neuroscience research be over the next year?

It is really about bringing medicine and innovation to a large population of patients and being able to drive it to clinical practice. It is about being able to find those right biomarkers in the blood, as opposed to relying on the more expensive imaging techniques or having access to the CSF. I think that is really where the field needs to continue to evolve. There is not just neurofilament, there is also the emerging research on amyloid-beta where we may be able to measure Alzheimer's disease-relevant species in the blood. All of these new innovations are really important and have implications for patients with neurological diseases.

Could you tell me the top three takeaways from your presentation?

First, it starts with context of use, being driven by context of use and understanding what you want to do with the biomarker. The second thing is developing that knowledge base and that is not something that one company can do alone. People need to come together with their datasets and share and communicate, so we are all aligned on what that marker is really telling us. The third thing is that the assay development has to be running in parallel speed with the knowledge sharing and developing the context of use, because you may not have the right assay at the beginning. It gets you started and then you need to evolve that approach.