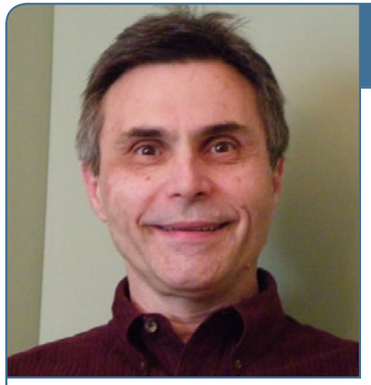
THE FUTURE OF BLOOD BIOMARKERS



THOMAS MISKO, Lead Scientist & Senior Scientific Director, Translational Neuroscience, **Abbvie Neuroscience Development**

Thomas Misko has had over 25 years of experience in pharmaceutical R&D. His expertise includes both small molecules and biologics and spans from early Discovery to Phase 2 POC. After receiving his Bachelor of Science degree in Biological Sciences from Indiana University, he received his doctorate in Biochemistry from Johns Hopkins University. As a postdoctoral fellow (Stanford) in the laboratory of Dr. Eric Shooter, he purified and cloned the low affinity NGFR (p75). Joining Searle-Monsanto (St. Louis), he contributed to/led several projects to discover/develop potential therapeutics for Inflammation and Neuroinflammation. During his tenure in St. Louis (Pharmacia, Pfizer), Tom co-discovered the activation of cyclooxygenase by NO and led a group that developed sensitive assays to monitor iNOS (inducible nitric oxide synthase) activity in vivo and in vitro by quantifying nitrites/nitrates as well as nitrated proteins. These assays were instrumental in the discovery and clinical development of selective inhibitors for iNOS through enabling the monitoring of target engagement in the clinic. Tom's collaborations with academia (e.g., Drs. Anne Cross, David Holtzman, L.S. Lohmander) helped to characterize the role of iNOS in diseases such as MS, AD and arthritis (RA, OA) in which free radical-mediated injury appears to contribute to disease pathology. His work in neuroscience, inflammation and neuroinflammation has resulted in over 60 peer-reviewed publications. As a Scientific Director in Translational Medicine at Takeda, Tom led teams monitoring biomarkers in CSF and in plasma to assess target engagement and coverage for potential disease-modifying and symptomatic therapies in schizophrenia, epilepsy and AD. Dr. Misko is currently a Senior Scientific Director in Translational Neuroscience at AbbVie where he has devoted his efforts to advancing AbbVie's growing portfolio in Neurology focused on disease-modifying therapeutics and neurorestorative therapies in MS, AD, Stroke and PD.

Could you tell us more about your use of blood biomarkers?

They fall into a couple of categories. One is looking at neurodegeneration markers like neurofilament light in plasma, because the reason for looking at plasma and serum is that you can take more time points, you can define a patient's trajectory much more easily than trying to get CSF. Patients often don't even want to give you one CSF, let alone two. The other approach is using and developing exosomal cargoes to monitor the disease, which basically translates into cells that are alive that will secrete small membrane vessels that have either good proteins or bad proteins in them. You can monitor the disease state by measuring them, isolating them, and measuring their cargoes in the periphery.

What would you say are the key benefits of using blood biomarkers?

You're able to define an individual patient's trajectory, because everyone is at a different stage of disease – even though we'd like to try to place everyone into a certain phase, everyone progresses at different rates. If you have a treatment, you can better understand how that treatment's affecting that individual as opposed to trying to clump everyone together. You might not end up understanding the response very well, because you might have seven that responded, and three that didn't. The three that didn't balance out the seven that did, so you end up with nothing.

Am I correct in saying that you're in the clinical stage in some of your work?

As a translational neuroscientist, what I do is I bridge between discovery and clinical, and I am in the clinical group. The objective is to identify biomarkers where you can monitor targets in the clinic. Either you've defined that you've now engaged the target by changing something that the target drives or like with things like NFL or neurofilament light, ensure that you're getting disease modification.

What are the main challenges that you face in the biomarker development?

It's getting clinically well-characterized samples. There are a few companies that can deliver them, like Precision Medicine in San Diego. Being able to get longitudinal samples is not always that easy. There are some companies that can get those for you. However, once again, you might not have some of the cognitive readouts from the individual patient, they might go to the patient at home like Sanguine does. If you don't know what their cognitive status is, it's a little hard to understand how the biomarker changes that you're looking at relate to their cognitive deficit.

How are recent innovations and new technologies benefiting the identification of biomarkers?

The availability of the digital ELISAs for proteins and immunoassays have been fantastic. Being able to measure different micro-RNAs and RNA species in the blood and cells. That's become more easily done than it used to be in the past. We're at a stage where, after 30 years of many failures, even though there was great science, we still haven't found anything for Alzheimer's; we're at the point where we are going to shoot up quickly, and we'll be able to identify treatments more easily.

Would you say that's the next steps for your company's work in this field?

It's to gain acceptance for different markers and that's really building the data set. That's the other challenge - you can't use certain markers as decision making markers. You have to build enough data to know that it really works and it's not just an aberration or a very small group of the population. That's where collecting the data, and being able to analyze it, is so important.

Are you partnering with any other companies to further the development of blood biomarkers?

Not at this point. I work with some people at Quanterix that do the digital ELISA. We're looking into some other approaches. I've talked to Abcam, and I'm interested in some of their approaches, but we're not closely linked with anyone at this point.

What are the top three takeaways from your presentation?

That plasma markers are real, that you can monitor CNS by looking at them. That each patient should be looked at as an individual case instead of looking at the bucket and saying they all need to cluster together, which they're not going to do.