

Merck Neuroscience podcast —transcript

Paige Lacatena:

Hi everyone. Thanks so much for joining us. My name is Paige Lacatena and I'm a member of our business development and licensing team. I'm joined today by neurologist Joe Herring, psychiatrist Yuki Mukai, and neurologist Ari Merola. Today we're going to talk about Merck's neuroscience pipeline. As we get started, I guess one of the first questions is, how are the new technologies and advancements in disease biology informing on how we develop new medicines at our company?

Joe Herring:

There have been a lot of advancements in the technologies that we use for drug discovery and execution of our trials, and particularly in the clinical trial space. We have much better tools now for target engagement through non-invasive imaging, the use of PET to establish target engagement. And then in clinical trials, a lot of biomarkers, both imaging and CSF and now plasma-based biomarkers. We have a lot of tools in the toolkit for conducting neuroscience research and neuroscience trials.

Yuki Mukai:

Historically in neuroscience, one of the biggest challenges was to get past the blood-brain barrier. And as Joe mentioned now our discovery groups and our Phase 1 groups have PET imaging and other ways to confirm and establish the fact that we are in the brain, we are engaging the target. And that also helps us in dose selection as well as we move forward into development. As we come up with some thresholds of targets of how much we want to engage the target, we can also build a profile of both efficacy and tolerability to really inform phase three dosing as we move forward.

Ari Merola:

And I think another important point is that we also have different tools, different strategic therapeutic tools, such as monoclonal antibodies. Now it's becoming a tool that can be used also for neurodegenerative disorders, targeting very specific epitopes that could not be reached in other ways. And this is definitely something we are excited about.

Paige:

So maybe building on your comment, Ari, about new research areas specific to neuroscience, are there specific approaches that you all have most interest in or are keen to see our company focus on?

Ari:

Some approaches might be more tailored for disease modification, like for instance monoclonal antibodies, because they have the possibility of cleaning misfolded proteins or toxic elements. Other approaches may be more effective for inhibiting a specific function or enhancing different functions.

There is a new class of small molecules that doesn't directly target a receptor in an excitatory or inhibitory way, but those are called allosteric modulators, so the ability to modulate the activity of a receptor. And that's huge, because compared to classic agonist or antagonist, we now have the ability of having greater target selectivity, lower risk of developing no tolerance and the lower risk of toxicity.

Paige:

Thinking a little bit more about biomarkers and patient selection, different approaches for us in terms of identifying the appropriate patient for our clinical trials — what are some key ways that we're thinking about that?

Joe:

I mean, it's an exciting time, I think, for actually knowing what patient to study, versus in the past. So yeah, it's exciting times in the Alzheimer's space, and more and more is being learned about other spaces, like Parkinson's and pain. I mean, there are other ways to now find patients that have the disorder we hope to treat.

That's going to be a key part going forward of our work, is using both imaging biomarkers as well as now progress in plasma biomarkers, which are a lot easier obviously to implement, to help us screen patients and identify patients.

Ari:

The biomarkers are huge, not only because we can identify the right timing for intervention, but also because we can make sure that we are treating the actual disease that we are thinking about. I want to think that when it comes to Parkinson or Alzheimer's, we are talking about definitions that are 200 years old. And the clinical definition, why it still makes sense in defining the overall symptoms, is not very accurate when it comes to precision medicine targeting. And so, we need to make sure that we are actually treating patients who have the Alzheimer's pathology. And this big noise that was big a confounder in previous trials is now being cleaned out by the

use of biomarkers that tell us exactly who is the patient that has that specific pathology.

Yuki:

I think for psychiatric illnesses, the lack of biomarkers is still a big challenge. I think there's a lot of innovation coming out right now, especially with wearables in digital biomarkers, that people are exploring the potential of having other types of biomarkers. It may not be your traditional blood-based or PET, but there could be other ways to capture and also hone in on a specific patient population that could have some objective ways to say, okay, well if you have a wearable and let's say you're doing a bipolar study, well if their sleep duration is less, that's convincing evidence right there that you have the right types of patients, instead of just relying on self-report or caregiver reports. So I think in psychiatric illnesses there's definitely room for progress there, but there are some creative ways that people are managing to confirm the appropriate patient and really refine the patient selection that way.

Paige:

So we've kind of been dancing around a lot of the key focus areas, but how are we approaching these diseases at this point? Thinking of the neurodegenerative diseases, thinking of the psychiatric disorders, as well as pain.

Joe:

We as a company have really grown in our ability to explore new biologic mechanisms, including antibodies and potentially gene therapies. Those are always on our radar, and so some of our programs are aligned around that idea. You know, other approaches would include vaccines, for example.

I would say one area maybe that we haven't emphasized very much is on the small nucleotide inhibitors, the ASOs (antisense oligonucleotides). That's something that at least in neuroscience, we haven't really seriously considered, whereas some others have. But otherwise I'd say the field is wide open for us.

Yuki:

Another aspect that's unique to our company is that we have a large history of being in all these diverse spaces, and so we're able to use the lessons learned from another therapeutic area. One of the biggest challenges when you treat patients with schizophrenia is the compliance and adherence. There's a lot available out there that are these traditional, what's called long-acting injectables. But what we're also

exploring within our company is other ways to deliver longer-acting formulations of something that's effective, and using our experience through things that were developed for other therapeutic areas — or example, the implantables with birth control, or things that slow the gastric emptying and so forth — borrow that technology and apply it to ours to see if it makes sense to apply it to the compound and the needs of that specific illness.

Paige:

How do you view external collaborations and external partnerships in the neuroscience therapeutic area?

Ari:

In terms of partnership — a commercial partnership or scientific partnership — one of the benefits of working for a company so big and diversified and with so much opportunities like our company, is that there is always the opportunity to look for if someone else came up with a great idea that is worth it to be partnered with, developed further or even acquired. And this is something that we do on a constant basis.

Paige:

So maybe turning to immuno-oncology, how has the efforts within that space impacted our thinking in neuroimmunology? I know we've talked a lot about the different proteins that are misfolded, the different types of neuropsychiatric disorders, but really, I think, inflammation is taking a rising role in many different disorders within neuroscience. How are you thinking of the immunology realm within neuroscience?

Joe:

There's a long history of understanding that inflammation plays a role in neurodegenerative diseases, and if not is an inciting event, it's a bystander event that would warrant treatment and could have benefits to patients. I think, again, within our organization there's a huge amount of expertise obviously in immunology and oncology, and the learnings from those successful programs are really translating over into other therapeutic areas, including neuroscience, where we've been looking at targets of interest that are related to neuroinflammatory pathways. And the discovery team is working towards bringing candidates forward in that space. We're kind of there and just hoping to get some of these into the clinic so we can begin to study them in patients.

Ari:

I think it's a very complex and multilayered approach, because on one side the neuroimmunology can be viewed as a way to use antibodies as a way to deliver a treatment. So the immunology in this case becomes like a means to deliver a specific treatment, to engage a specific aspect. Instead of targeting a bacteria or a virus, we can use this antibody to target whatever we believe is going to be toxic or negative for the body.

We have to understand that inflammation is part of the disease itself. And so, we still don't know exactly who comes first, but at a certain point in the process the inflammation plays a role. And being able to modulate this inflammation becomes critical if we want to do something more than just cleaning some bad protein, but really modifying the way that the brain is reacting to certain toxic agents.

Paige:

So maybe speaking a little bit more about clinical trials in this space, it always seems to be that neuroscience requires many more patients than other therapeutic areas. I would love to hear your thoughts on that. From a psychiatric perspective, ensuring that you have the right patient and the number of patients, et cetera, how does that sort of play into a lot of the work that you do, Yuki?

Yuki:

For I think psychiatric illnesses, what's really challenging is that they're subjective rating scales. And so, patients are reporting how they're feeling in those symptoms and the rater is the one delivering the subjective assessment. There's two components where variability can be introduced: one by the rater and how they administer the question and how they rate the patient's response to that question, and the patient and how they interpret the question and how they respond to it. Because of that, psychiatric trials tend to have a certain variability that we need to build into that sample size calculation in order to really effectively detect that treatment signal.

Those are part of the reasons why we do have the sample sizes that we need, and we're just learning ways to refine it. And hopefully we'll be at a point where Alzheimer's is getting towards where you have established biomarkers for study entry, and perhaps even biomarkers as endpoints.

Ari:

There are a number of factors to consider when looking at the variability and the duration and the sample size of neuroscience trials. The first one and the most important is that we're dealing with the brain. The brain is way more complex than other organs, and we need to keep into account the fact that this is an ambitious target and therefore requires more effort. The second point is that the brain is not accessible to biopsies like other organs, so our understanding of the biology and the pathology behind the diseases unfortunately is lagging behind.

And the third important factor is that the brain is associated with a very important function, which is the mind. And therefore, every meaningful outcome has to be filtered through that. We cannot just see how much the weight of the brain is, but we have to see how this is functioning, how the subject perceives this change in functioning as meaningful. And this unfortunately comes with the job, but everybody who went into neuroscience knew that. Because this is the most ambitious challenge of all, and that's why it's probably the most exciting.

Joe:

It's sort of like the final frontier. You're going off into space to try to figure out how to do very difficult things. The double-edged sword is that we don't always have objective endpoints, and we have to wait a long time for things to happen. I think one of the great things about working in this company is the investment that's been made in this area. There's a true commitment to neuroscience, and I think that's why many of us have stayed as long as we have.

Ari:

Something I want to add is that the prevalence of these disorders, neurodegenerative disorders, is on the rise. We estimated that in 20, 30 years we're going to have two, three more times, four more times number of patients with Parkinson's and Alzheimer's than today. That's due to a number of factors: aging of the population, better treatment of other causes of death, but also there seems to be a higher predisposition to these disorders. We still don't know exactly why, but clearly this is a huge need.

Paige:

So what about the caregiver? We've talked a lot about the actual patient and the different disorders that we have a large interest in at our company, but what about the implications to the broader families of these patients or participants?

Yuki:

At least for psychiatric disorders, schizophrenia specifically but also with depression, I think, like you said, there's a lot of hope out there right now, because there's a lot of companies investing in neuroscience. So that's really exciting to not just the patients with schizophrenia, but if you think about the disorder and when it hits, this is something that hits young adults. You know, they're 18, 19 years old. And many of them never are able to be independent and in the workforce, so there's a lot of morbidity associated to it.

Ari:

There's no class of disorders like the neuropsychiatric disorders that have a greater impact on caregivers. Because clearly it touches very deeply many different aspects, and frequently caregivers are family members. And something that is becoming more and more clear is that these disorders, they have a genetics background. So, the caregivers are very motivated and they're also scared for themselves, because they share frequently common genetic background to that. And so, it's a very difficult place to be.