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Straight talk with… Ricardo Dolmetsch

Neuroscience, in recent years, has started to look like a graveyard for drug development, with many large pharmaceutical companies either eliminating their brain disorder programs or cutting back heavily on such research. Novartis seemed to have made exactly this kind of drastic change two years ago when the company announced plans to shutter its neuroscience operations at its global headquarters in Basel, Switzerland. But the company made it known then that its intention was to ultimately set up a new neuroscience division at the company's US base in Cambridge, Massachusetts.

The US site was initially picked to take advantage of the local academic strength in the field of psychiatric genetics. Now, it seems that Novartis is also looking to add stem cell technologies to the mix with the appointment in August of Ricardo Dolmetsch as the company's global head of neurosciences—the first new hire for the company's reincarnated division. As a professor at California's Stanford University School of Medicine for the past ten years, Dolmetsch made his name using induced pluripotent stem (iPS) cells to study a rare form of autism known as Timothy syndrome. **Elie Dolgin** met with Dolmetsch at the Novartis Institutes for BioMedical Research in the Technology Square area of Cambridge to discuss how he plans to succeed where so many others have failed.

While maintaining a lab at Stanford, you additionally joined the Allen Institute for Brain Science in Seattle in March 2012 as its Senior Director of Molecular Networks. Why change jobs again so soon?

If one's interested in developing new medicines and if you really want to treat patients, you want to be in a place where that's the whole mission of the institution. At the Allen Institute, they've done a lot of great things, but that's not their main mission. I just felt the opportunities were better here.

What's the focus of this new neuroscience unit?

We have two main focuses. One is on genetically defined orphan diseases for which we have a scientific rationale, we know something about the population and we think we can address a significant unmet medical need. Then we hope we will be able to expand those insights to a much larger population. That's approach [number] 1. Approach 2 is to take advantage of our understanding of circuits and the fact that we now know about some of the cells that modulate certain behaviors. We think that we can develop drugs that attack those circuits more intelligently because we know those circuits better.

Can you tell me which diseases will be top of the priority list?

I can tell you broadly that we're interested in neurodegeneration and we're interested in psychiatry, including autism and schizophrenia. We understand that those are not single diseases, so of course we'll go for different subtypes of those disorders.

Will you maintain your own lab at Novartis?

I hope to eventually have my own group. For now, I'm focusing all my energy on trying to recruit the smart people, ideally smarter than me, who are going to do all the great science. But I want to remain as involved as possible and eventually have my own postdocs. I think if you get very far away from the bench, then your capacity to make really good decisions goes down.

Tell me about the new team.

We're hiring about 30 people per year for three years, so ultimately it's going to be about 100 staff members total. We're looking for people who have expertise both in iPS cell and ES [embryonic stem] cell differentiation to different classes of neurons, and we're looking for people who have expertise in optogenetics. But we're also interested in people who have good ideas and are good neuronal biologists.

At a time when many big pharma companies are pulling out of neuroscience, Novartis is moving in the opposite direction. Why?

There's a huge unmet medical need, and if you really care about patients then you have to go where there is an unmet medical need. I think people thought, "Well, there are lower hanging fruit and easier opportunities in other disease areas," and some of that is true. But there have been developments in neuroscience that make things a little less risky and a little more plausible. We now understand some cells much better than we used to, and we can target them in more intelligent ways.

One of the first partnerships you have is with the Broad Institute's Stanley Center for Psychiatric Research. What will that entail?

We're essentially collaborating on trying to validate the hits that are emerging from large [genetic] screens for bipolar disorder, schizophrenia and autism. They are helping us identify targets, and we believe in this genetics-guided approach to drug discovery.

You've spoken openly about your son who has autism. How much did your family situation affect your decision to move into industry?

A lot. I actually started off being very interested in fundamental mechanisms of brain development and function. But I changed the direction of my lab [in 2007], in part because I was spending a lot of my time thinking about how we were going to treat our son. So, coming to Novartis is a continuation of that. It was really the combination of my family but also the fact that I thought it was a scientifically tractable problem to treat neurological and psychiatric diseases that really motivated me.