A Conversation with Ricardo Dolmetsch

INTERVIEWER: GARY STIX

Senior Editor, Scientific American

Ricardo Dolmetsch is the Global Head of Neuroscience at the Novartis Institutes for BioMedical Research and an Adjunct Professor of Neurobiology at the Stanford University School of Medicine.

Gary Stix: You've had an interesting career. What I'm interested in is why, after a successful career in academia that was continuing to progress, you decided to make the move to industry.

Dr. Dolmetsch: There were at least two things that motivated my change. The first was that I had become very interested in translational research. I have a son who has autism. I had become very interested in identifying mutations that lead to intellectual disability as well as autism, and I'd become very close to the families and I was getting a little frustrated that we weren't making much progress in terms of trying to come up with treatments. I thought that I needed to be in a place where I could do that. That was one reason.

The second reason was that I found that we probably didn't have the expertise required to pursue some of the scientific questions that I wanted. That was mostly because we were not really very well set up to try to do studies in humans the way I wanted to do them. So those are the two main motivations for moving.

Gary Stix: The development of new drugs in industry in the "neuro" space has been very challenging. There've been swings where there's suddenly enthusiasm, but then there are failures or it takes a really long time. You get these announcements periodically that drug companies are moving out of "neuro." It seems like you're getting more optimistic now. There are various areas of drug development, exploration, the preclinical models, and the actual moving to humans that make you more optimistic. I think that's why you were hired by Novartis. Can you talk about that?

Dr. Dolmetsch: I think one of the reasons why companies have moved out of neuroscience and why there was not a lot of enthusiasm was that despite the fact that there's a huge unmet medical need, people started to feel that we didn't have the right targets, we couldn't perhaps find the right populations, and that the trials were becoming enormously long and enormously expensive.

In order to move the needle, to change things, we have to come up with better ways of identifying targets. There has been a revolution in genetics that now allows us to

identify genetic variants that are associated with specific diseases, even complex diseases. This means that we now have targets that are validated in people. There's something broken in some patients that is giving them a disease. In principle, at least for a few people, we have something that is a reasonable target. It is not just a target that works in some animal model or that rhymes with an old target that we had. That's one good thing.

We are developing better preclinical models and that means that in addition to some of the mouse models—which we tend to not use for efficacy any longer, only for toxicology and distribution—we can also use human models. Essentially, we can make biopsies of people. We can't get a biopsy of somebody's brain, but we can take skin cells and make them into stem cells and then take those stem cells and make them into neurons or neuron organoids, and then use those as a tool to develop new medicines. We've been doing that quite extensively. We're optimistic about that because we think that it provides a more human drug development system that is not so different from what people have been doing in other areas, like in oncology.

The third thing that has changed is that we now have new modalities. I'm specifically enthusiastic about gene therapy because this has been on the horizon for a long time, but I think now we finally have the right kinds of vectors that allow us to put genes back into the nervous system in a sufficient number of neurons at the right part of the spinal cord and the brain. We now have some fantastic proofs of concept including the recent successes by AveXis—which is one of the Novartis companies—in gene therapy for spinal muscular atrophy that is really revolutionary. This is something that we never expected. This means that we can now deliver genes, we can deliver antibodies, we can deliver all kinds of things, and it's a one-shot treatment. That has the potential to be revolutionary, at least in neuroscience.

The final thing is that our approach to clinical trials is changing. Historically, we had these episodic pencil-and-paper tests. You'd show up to your neurologist or your psychiatrist, they would essentially give you a battery of tests. Because these were quite invasive and required a lot of expertise, you didn't do them very often. Even in the

best of cases you might do them once every 2 weeks or once a month, and you can imagine that all kinds of things could have happened, right? If you had to travel a long way, you didn't sleep well, or you had a cup of coffee, that kind of spoiled the measurement. So the signal-to-noise is very poor, which meant that you needed to have enormous populations. So the studies were really big, which made them really expensive. In addition to that, they required lots of really expensive qualified people.

We've been moving away from that toward less invasive ways of quantifying and measuring human behavior: phones that give you short tests for emotion or cognition; ways of measuring how you're getting from point A to point B and seeing how often you get lost, for Alzheimer's; ways of measuring eyeball movement and tracking of people's gaze to measure attention and measure social interactions. These things have two advantages. One, they're likely to be less prone to error because they are measuring you every day, and so therefore they can be averaged over time. They are probably less subject to placebo effects because it isn't as if you're saying, "Well, *I think* I felt better last week," or some caregiver is saying that, so they are somewhat more objective. But also they should be less expensive, because we need essentially fewer interactions with caregivers and less travel and they're less invasive. So those things are changing the panorama for the future.

We've also had a few successes recently that are making us enthusiastic. One particular success is in migraine, which is a disease area that had not moved in three decades. We now have, for the first time, a prevention. We're enthusiastic about that. Of course, it's not just Novartis. We have other competitors, but this can only be good for neuroscience and for the field and for patients. There are some follow-up therapies for migraine that will, I think, reduce suffering enormously. So, a little success goes a long way. Twenty years of abject failure discouraged everybody. The successes in migraine, the successes in multiple sclerosis (MS) ... multiple sclerosis went from being essentially a death sentence to being a chronic disease that is manageable.

Gary Stix: There's been a lot of drugs coming on the market for multiple sclerosis, but progressive multiple sclerosis has always been a challenge. You said you've got one drug for this, as well?

Dr. Dolmetsch: We were really surprised, because progressive multiple sclerosis is something that has turned out to be really difficult. Where many drugs have failed, Siponimod has effect in at least secondary progressive multiple sclerosis. We're cautiously optimistic that this may be the beginning of treatment for this aspect of MS, which affects many people. It's not a cure. It is not the be-all and end-all, but it is far better than what we have today.

Gary Stix: We don't have much time left, but just give me a précis on what exactly you're optimistic about with Dravet syndrome.

Dr. Dolmetsch: Dravet syndrome is caused by a mutation in $Na_v1.1$, which is a sodium channel that seems to play a

particularly important role in inhibitory neurons. As a consequence, it leads to intractable seizures, and it is a devastating disorder for these families. These children seize many times a day, and we don't have very many good treatments. The good news is that they have one copy of this ion channel left, so we've worked very hard on trying to develop drugs that will increase the activity of that ion channel. For a long time we thought this wasn't viable, because it turns out that there are many different kinds of sodium channels. They are all very similar, and some of them play an important role in the heart, others play important roles in excitatory neurons. So we had to get cell activity and we had to get something that would activate the ion channel.

I think we're finally in the right chemical space and we now have things that kind of work in vivo, so we're cautiously optimistic that we may be able to do something for these families that actually works on the actual molecule that is affected in the disease, the actual gene. There are other symptomatic treatments for Dravet that are now winding their way through the regulatory pipeline, but I would say that none of them actually address the root cause of the disease. We hope that it will not only address the seizures, but also the autism cognitive delay that is associated with the disease. And because it is so devastating and one of the most common causes of early-onset seizures, we think that there's a huge unmet medical need and we have the opportunity to maybe do something about it.

Gary Stix: What's driven you for a long time has been trying to find general treatments for autism. Dravet is one example, but it's a special form of it. Do you think you'll be able to get back to that or is that too big a challenge?

Dr. Dolmetsch: Well, autism is not a single disease. Autism is a collection of diseases that have common symptoms. I have taken two approaches to it. Approach number one is to take these rare disorders and then see whether, once we test them in those specific populations, we can expand it to a broader population. A significant fraction of kids with autism also have seizures. This might be a general antiseizure medication that we can use in children. Beyond just Dravet's, there have never been drugs that are developed specifically for seizures in kids. Most of them are developed for seizures in adult and then they're tested in children. The one exception is the recent trials with cannabidiol, but in general this could be a new class of antiepileptics that is compatible with normal development. That, in itself, will really be important because many kids with autism already have seizures and the seizures could well be a part of their developmental delay. That's approach number one.

Approach number two is to think about it symptomatically and think about approaches to improve social interactions. What do we really understand about the roles of serotonin and dopamine and these other neurotransmitters in driving social interactions? Are there any examples of anything that works? So we're working on that as well. That's a much slower process because our capacity to translate those things preclinically to the patient has not

been good. Our social assays in mice turn out not to be very reproducible, so if you want a symptomatic treatment, you're going to have to gamble in humans, and that's a bigger gamble. But we're taking both approaches.

Gary Stix: Do you still have the dream of returning to Colombia and setting up a center? I recently visited Colombia to interview Francisco Lopera and the Alzheimer's trial that's happening there.

Dr. Dolmetsch: Yeah, I'd love to do that one day. I'm superexcited about how the country has moved over the last couple of decades and how the health system has become much more developed, as well as the scientific infrastructure. I still think that it is very difficult to do some of the things that I'd like to do there. What I'd like to do is develop enough financial support and infrastructure so if I were to go back and set something up, I could do it in a way that was self-sustaining.

Cold Spring Harbor Symposia on Quantitative Biology

A Conversation with Ricardo Dolmetsch

Cold Spring Harb Symp Quant Biol 2018 83: 246-248 originally published online June 11, 2019
Access the most recent version at doi:[10.1101/sqb.2018.83.037515](https://doi.org/10.1101/sqb.2018.83.037515)

Creative Commons License

This article is distributed under the terms of the <http://creativecommons.org/licenses/by/4.0/>, which permits unrestricted reuse and redistribution provided that the original author and source are credited.

Email Alerting Service

Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article or [click here](#).

To subscribe to *Cold Spring Harbor Symposia on Quantitative Biology* go to:
<http://symposium.cshlp.org/subscriptions>