PROFILES

Ricardo Dolmetsch: Regenerating the cells of autism

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The transformations that take place in **Ricardo Dolmetsch**'s laboratory are, by his own admission, freaky.

They begin innocently enough, with a few skin cells in a dish. But when bathed in a precisely mixed potion, those cells grow into little rosettes, which turn into tubes and change again to become miniature brains.

It's even stranger when, using a slightly different chemical concoction, he creates heart muscle. "You get these little balls of ventricular and atrial cells, and they beat — and they beat, and they beat," Dolmetsch says. "It feels a little like Edgar Allen Poe."

Thanks to these tell-tale hearts, Dolmetsch and his team at Stanford University have identified effective antiarrhythmic drugs for individuals with Timothy syndrome, a rare genetic disorder that causes slow heart rhythms, anxiety and autism.

The study, reported in *Nature* earlier this year[1], was the team's first demonstration of cell reprogramming in individuals with autism.

When Dolmetsch first began this line of work a few years ago, "people thought it was very far out," he says. "But we're now convinced this is a very viable approach to studying autism."

Dolmetsch speaks as though his lips are trying furiously to keep up with the ideas flipping through his mind. It would be easy to blame his diction on his South American upbringing, except that he seems to move through life at the same rapid clip. He worked as a waiter, a technician in an animal care facility, a photographer and a computer programmer for the World Health Organization, all before he turned 20. He then became a successful scientist, with a streak of high-profile publications. Five years ago, after his son received an autism diagnosis, he turned his attention to

the disorder.

So far, Dolmetsch, 40, has made reprogrammed cells — so-called induced pluripotent stem (iPS) cells — not only from people with Timothy syndrome, but from those with Phelan-McDermid syndrome, an autism-related disorder that is caused by a **deletion on chromosome 22**, and schizophrenia. His team is also working on a mouse model of Timothy syndrome and a **much-talked about mouse** carrying **autism-linked deletions** on chromosome 16.

Dolmetsch has his fingers in many pots, and freely admits that he is "slightly obsessive." When he's curious about a scientific topic, he delves into the scientific literature and learns as much about it as he can. He only sleeps a few hours a night, he says, and rises around 4 a.m. for his daily run.

Meddling and mischief:

Rich Lewis, Dolmetsch's graduate school advisor and longtime collaborator, attributes his former student's success to two seemingly conflicting characteristics. The first is Dolmetsch's zeal for new ideas. "It's a combustible creativity," says Lewis, professor of molecular and cellular physiology at Stanford.

At the same time, Dolmetsch is concerned about rigorously testing his hypotheses, Lewis says. "He's always thinking about, 'Is that logical? Does that really make sense? How good is the evidence for that?'" Lewis says. "He's got that skeptical approach, and somehow it doesn't get in the way of his creativity."

Dolmetsch graduated from his high school in Cali, Colombia, at age 16. He flew with his school's track team to the junior world championships in Athens, Greece, and didn't return for many years.

In the fall of 1986, after some eclectic work experiences in Europe and the U.S., Dolmetsch began attending college at Brown University in Providence, Rhode Island. Broke and carrying a load of student loans, he eventually landed a job as a research assistant in the tiny neuroscience lab of Constance Bowe.

As a child neurologist, Bowe had many clinical responsibilities and, as Dolmetsch recalls, didn't spend much time on research or lab management.

"So I ended up spending all my time cutting bits of nerve and making sections and trying to figure out how the electrophysiology things work," he says. "This was like heaven."

He was still prone to this kind of tinkering a year later, when he began working in Lewis' lab. Lewis recalls a time when he needed to switch a microscope lamp from AC power to DC power, but had little money left in the budget.

"I said, 'Ricardo, do you know electronics at all?' and he said, 'Oh yeah, sure.'" Lewis says. As it turned out, Dolmetsch didn't know enough. "When he plugged the thing in, it exploded — it shot metal up to the ceiling," Lewis says, laughing.

The anecdote says a lot about Dolmetsch's character, Lewis adds. "The desire to see how things work inside is a pretty powerful motivation, and so he doesn't have any hesitation to dive into something new. But then it's a matter of finding your way out again."

When Dolmetsch launched his own lab, in 2003, he was interested in the complicated ways that cells use calcium to communicate. He was already a rising star in his field, with six high-profile publications in as many years[2,3].

But he abruptly shifted focus in 2006, when his son was diagnosed with autism. He chose to study the related disorder Timothy syndrome, which begins with a glitch in a calcium channel.

Diving in:

Around the same time, research groups in Wisconsin and Japan were creating the first iPS cells. Their findings electrified biology because the cells have the potential to develop into any type of tissue, bypassing the political maelstrom surrounding embryonic stem cells.

The iPS approach is especially powerful for investigating how genetic variations carried by an individual express themselves at the cellular level. For psychiatric disease, for instance, "iPS cells are a window into looking at an actual neuron from an individual and seeing what's going on," says **Maria Karayiorgou**, professor of psychiatry at Columbia University, whose team is creating iPS neurons from individuals with schizophrenia.

Despite the cells' potential, Dolmetsch found it extremely difficult to get funded for his initial work on iPS cells. "Unfortunately, if you do something which is out of the box, [funders] are often all too critical," says **Joachim Hallmayer**, associate professor of psychiatry at Stanford, and one of Dolmetsch's collaborators.

Dolmetsch and Hallmayer's grant application on the Timothy syndrome project was rejected so many times that Hallmayer began to wonder if it was worth the effort.

But Dolmetsch, Hallmayer says, refused to give up.

In 2008, Dolmetsch's persistence paid off. He received a $2.5 million '**Pioneer Award**' from the National Institutes of Health, intended to support high-risk creative research.

Since then, Dolmetsch has been comparing iPS neurons made from individuals with various forms of autism, and controls. In unpublished work, his group has found several ways in which the

Timothy syndrome cell lines are different; for example, they have too many cells that produce norepinephrine, a neurotransmitter. Even more tantalizing: Exposing these neurons to certain kinds of compounds reverses the abnormality. One undisclosed drug is already approved by the U.S. Food and Drug Administration, he says.

Dolmetsch is known for doing carefully controlled experiments, which are much needed in the highly technical and fast-moving iPS field, notes Karayiorgou. "He's terrific. He's one of the key people who I'm glad is doing it," she says.

Dolmetsch is tackling some of biology's messiest and most bizarre experiments. And yet, he says, it's the calm precision of science that motivates him the most.

"There's a certain elegance, a certain **symmetrical wonderfulness** about science, and I love that," Dolmetsch says. "I want to do the kinds of studies that are like that: interesting and rigorous and — as much as they can be — clean."

References:

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