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Optogenetics, Or, Making Blind Mice See The Light

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(And other interesting things you can do with algae)

Last week, researchers formally announced in ***Molecular Therapy*** that they had at last found a way to make blind mice see — a true glimmer of hope for the 15+ million worldwide who lose their site to genetic or age-related macular degeneration and retinitis pigmentation. The work comes from a collaboration of labs out of California, Florida and MIT — and it all starts with, yes, algae.

Now here's how it works:

1) Certain types of algae possess proteins called *channelrhodopsins* that respond to light by firing up activity in the cells that host them. The genes for these proteins can be pulled out, cleaned up and inserted into completely different types of cells like neurons and retinas where they'll act in exactly the same way: light goes on, cell goes on.

2) In this study, the researchers isolated a gene for *channelrhodopsin-2* (ChR2) and piggybacked it — by way of viral vehicle — into the degenerated retinas of mice bred for adult blindness.

3) Once in, the genes slipped into the remaining layer of retinal cells and transformed them into working, light-sensitive substitutes for photoreceptors, which is the type of cell typically lost in adult onset blindness.

10 weeks later, treated mice were successfully swimming through illuminated water mazes almost as well as their naturally sighted cousins and far, far better than their untreated, blind counterparts. To be sure, it's doubtful they're seeing 20/20 color vision — a substitute photoreceptor still isn't the real thing — and in fact, this early on, researchers can't know exactly how well the mice see, only that they do.

But the fact remains: *they can see*.

This alone is mind-boggling, but in fact, it's only the latest breakthrough in the field of optogenetics, a study in which cells and neurons can be quite literally flipped on or off with a flash of light thanks to the embedded genes within. The field was co-invented in 2004 by the MIT Media Lab's **Ed Boyden**, then a Ph.D. candidate at Stanford University, in collaboration with Georg Nagel at the University of Wurzburg and Karl Deisseroth, then also of Stanford. Since then, it has leapt from a single lab bench to over 1,000 research groups across the world; potential applications extend far beyond blindness to encompass Parkinson's, PTSD, addiction, mood disorders, and neuron-by-neuron mapping of the entire brain from the inside out. Late last year, *Nature Methods* awarded it the Method of the Year.

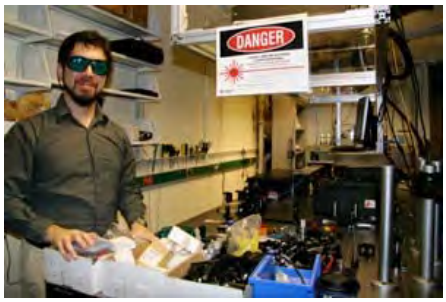

Photo courtesy of Ed Boyden

These days, though, blindness research comprises only a small portion of Boyden's projects. A methods man at heart, his primary focus is on perfecting his technology and finding better ways to understand exactly how the brain itself actually works.

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On the eve of this latest report, I stopped by the Media Lab to speak with this man who, late one August night in 2004, all but revolutionized the field of neuroscience. Here's what he had to say:

So this field has absolutely exploded since you kicked it off in 2005. What's next on the horizon?

Well, so there are three main things that are important right now. One, of course, is to make more powerful tools — though eventually, those will get as far as they can. Another one of the big things that we're still working on is mining genomes throughout the tree of life to find new genes that are higher performance, faster, with better light sensitivity, with higher magnitudes of currents, respond to different colors, and so on. For example, last year we had the first paper to report multi-color silencing [*Editor's Note: By implanting a* different *gene in a cell, yellow light will cause it to turn off*]. There are definitely still new things to come up with, but that said, we're also always looking for more *technologies* to come up with as well. In my lab, only about a third of the group works on the molecular perturbation sort of stuff.

And what are the other two thirds working on?

Well, one of the big issues we're working on is: how do we confront the complexity of the entire brain? So we've started to devise structures that allow us to perturb and record from sites throughout the brain. One of ideas we like to use to frame this whole endeavor is what we like to call *brain coprocessors*, basically using very fine probes to record data from throughout the brain, mine that data for information on the computations that are occurring in the brain, that can then be used to test theories of the brain. We also have an army grant to collaborate with Ki Goosens [at the MIT McGovern Institute], for which we're going to try to figure out whether there are any sites in the brain where you can erase PTSD.

So you started out an electrical engineer and a physicist working on quantum computing. Now you're in the middle of the brain and the co-founder of an entire field of neuroscience. What happened?

All through my undergrad work [at MIT] and when I started grad school [at Stanford], I was doing this quantum computer, and I really had two themes. One is, how do you control complex systems, and the second is how do we get at the essence of computation. For example, I wrote a control system for an autonomous submarine so that it could navigate underwater – actually, we won the Navy's first international autonomous underwater vehicle competition with that – then I also wrote an animation for video games based on the laws of physics. So I'm very obsessed with controlling things, because that's really what gives you a deep understanding of how things work — and it allows you to make stuff: you can *make* this submarine move underwater, or *make* this animation move realistically, and so on.

So I was really into control theory and controlling physical systems, and it all came to a head around the fall of 1998 when Motorola gave my undergraduate and masters lab $5 million. My then-PI said, okay, I'll pay for anybody to go wherever you want for a month to learn something new. I went to Bell Labs, which at the time, was *the* place to go, and it was fantastic. I was only there for a matter of weeks literally, but I came out with three novel things and it was just like, *wow*. In contrast to physics where we often just felt like we were checking Einstein for the 800th time and he was still correct for the most part.

From there, I went to Stanford to study in Dick Tsein's group – he was also an electrical engineer who switched into biology, and it was in his lab that I and Karl Deisseroth, the co-inventor who was also a student there, started doing the very first studies.

But why even head into the brain in the first place?

I'm interested in the brain for two reasons, one is a philosophical question: How do we think?

The second is pragmatic: The disease burden of the brain is huge, yet a lot of people have given up on figuring out how to treat them. ***The Wall Street Journal*** had an article a few weeks ago pointing out how the pharmaceutical companies — GlaxoSmithKline, AstraZeneca, and so on — have more or less given up on the vast majority of brain disorders, and that's kind of worrisome. I mean, something like a billion people worldwide have some kind of brain disorder, and if you look at the disorder, most of them have very little treatment at all and for the ones that do have treatment, it's not a cure if it usually has side effects. So how I think of it is: If the pharma industry is giving up on these, then that means that we have a duty to go after them and start working on them.

What was the transition like, from tidy engineering to messy biology?

I spent a full year just sort of getting used to that. There was a lot of floundering around.

Actually, I just came up with this analogy that I think finally captures it: I was listening to *This American Life* the other day, and poker was the theme for that week. In the opening spiel, they talked about this poker player who won a lot of money by breaking all the rules accidentally and at the end of it, he notes that the thing he hates about poker is that you can play all of your cards optimally, and you still might lose because of chance. I feel like neurotechnology is the same way. In some ways, it's the highest form of gambling because you can have just an amazing technology, and then some weird thing about the brain will come back and bite you and it won't work. There is a lot to wrestle with at this level.

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