

BUILDING THE CASE FOR A PD DRUG TARGET

Brian Fiske, associate director of research programs at The Michael J. Fox Foundation, discusses the role of the Foundation's Target Validation program in advancing promising ideas through the early stages of drug development.

A transcript of the interview follows. To listen to a podcast version, visit http://www.michaeljfox.org/newsEvents_podcasts.cfm

Opening Narration: Welcome to our continuing series of reports about new developments in Parkinson's disease research. You often hear about exciting discoveries in science, like a new Parkinson's gene or an enzyme that seems to be involved in the disease. But what happens next? How does that discovery become a therapy? The first step is to make sure that what you're looking at – the target – is really part of the disease.

BF: So target validation at its basic is really about demonstrating whether or not a particular biological component of our body, what we often call a target, has actually any link to Parkinson's disease.

Narration: That's Brian Fiske, associate director of research programs at The Michael J. Fox Foundation. One of the Foundation's Edmond J. Safra Core Programs for PD Research is called Target Validation and it's one of the first steps on the path from discovery to pharmacy when researchers begin to demonstrate that a particular target has potential to become a therapy. And that's important because it helps get scientists interested in the target, including industry drug developers.

BF: It takes millions of dollars for them to ultimately, if not billions of dollars, to take a drug from an original sort of idea all the way to approving it and getting into patient's medicine cabinets. So, you know, we kind of have to build a case for them to feel that a target is worth going after. The problem is it's not always sexy science. And so for many investigators who live in the sort of basic science world, for them the incentives are to do great science, discover great things, publish great papers and then move on to the next discovery. For industry, it's about developing the drugs that you can test in humans. But there's this sort of middle ground that doesn't get funded very well. So for the Foundation it became very important very early on for us to look at that particular bottleneck and say okay, can we take some of those ideas, can we pick the sort of best targets that are coming out of those basic discovery labs, and start moving them down that pipeline.

Narration: And that's exactly what the Foundation's target validation program aims to do. Recent awardees are looking at all kinds of potential drug targets, including genes and proteins associated with Parkinson's. One investigator, Andrea Giuffrida at UT Health Science Center at San Antonio, is looking at a protein target that might help alleviate the involuntary movements

known as dyskinesias. He's working on a way to activate this particular protein using a drug that's already approved for the treatment of diabetes.

BF: What's even great about this is the drug he is using is a drug called rosiglitazone which is an FDA-approved drug. So if he can actually demonstrate that this has benefit for dyskinesias in the preclinical models the path to maybe getting that tested in humans is much shorter and much quicker because it's already approved and safe.

Narration: Proteins are common targets in Parkinson's research because they play all kinds of important roles in the cell. But when there's a problem and proteins lose their shape they can become toxic, leading to cell death. Part of what may be at work in Parkinson's is a problem where a particular protein, known as alpha-synuclein, comes unfolded and accumulates in the cell. Claudio Hetz at the University of Chile, is looking at a target that's involved in our cell's natural response to this exact problem.

BF: So when proteins are produced in our cells they fold in special ways and there's a whole system in our cells whose goal and role is to make sure that that folding process happens correctly. When it doesn't, there's another system in place that responds to that misfolding of those proteins to try to protect the cell. And so he's found a target called XBP-1 that is very much involved in regulating that whole unfolded protein response.

Narration: The aim is to turn up the cell's protective response and in turn provide some protection against Parkinson's disease. For more information about the Foundation's target validation awards, visit www.michaeljfox.org.