Dave Iverson: This is Dave Iverson, and welcome to Getting to a Cure: The Science Behind the Search, our continuing series of interviews that focus on the latest scientific developments in Parkinson's disease research. Autophagy is one of those scientific terms that's hard enough to pronounce, let alone understand. It refers to a natural process cells utilize to replenish themselves, getting rid of the old stuff and building the new.

Samantha Hutton: I like to think of autophagy as a cells recycling system where old, no longer needed, or damaged proteins are brought to a specific place of every cell, and that place is the lysosome. Once there, these proteins are broken down into building blocks, which can then be used to make new protein, so it's really the cells recycling department.

Dave Iverson: That concept of recycling seems so front and center right now in our larger understanding of Parkinson's disease, this ability for the cells to be able to get rid of the bad stuff, whether that's the protein alpha-synuclein or something else, somehow seems really important to furthering our understanding of what really goes amiss in Parkinson's. Do you share that sense, Samantha? Do you see this as being really central to furthering our understanding of Parkinson's?

Samantha Hutton: That's right, Dave, and actually it makes sense because you could imagine even in our own recycling centers in our towns and our homes. When you have too much garbage or too much recycling, it starts overflowing and, eventually, you can't contain it all, but you can imagine that a cell, there's a lot of different components, a lot of different things that are going on, energies being made, things are being broken down, and things are being built.

You can't have room for the new proteins and the new responsibilities that have to occur if you have so much accumulation of the garbage, the things that you no longer need, so it's really important for cells to have this constant breakdown and recycling so that they can continue to build new and do the functions that they really need to do to survive every day. This is particularly important for brain cells because brain cells are a nonrenewable resource. Skin cells slough off every day and new skin cells are created, but it's really important for brain cells because we really want to make sure that those cells are protected.

Dave Iverson: I want to ask you, Samantha, about how this links together with a number of other things that we've been hearing more about. For example, you've heard about the role that mitochondria play in Parkinson's. That's that energy-producing part of the cell and that something may go wrong with that, and that also has to do with this ability to recycle. Is in a sense, then, this idea of autophagy and recycling really a
Samantha Hutton: Yeah, that's a good point, Dave. Autophagy is thought to play a role in Parkinson's disease through something called mitophagy. As you mentioned, mitochondria are the powerhouses in all of our cells that generate energy, but even these mitochondria need to be broken down and replaced, especially when they become dysfunctional. Dysfunctional mitochondria do cause oxidative stress, which is known to be a problem in Parkinson's disease, so even entire organelles like mitochondria can be broken down inside the lysosomes, which is the cellular recycling compartment.

This process is called mitophagy, and mitophagy has been shown to be impaired in Parkinson's disease, and there are proteins that are specifically related to mitochondrial health and this mitophagy process, and mutations in those proteins have been linked to genetic forms of Parkinson's disease.

Dave Iverson: Where will this take us, Samantha, in terms of our overall goal which is, of course, to figure out a way to slow down or stop the progression of the disease. Can this understanding of autophagy lead to that? Will this somehow lead to a way to come up with a better fix that could slow down or stop the progression of Parkinson's?

Samantha Hutton: Yeah, that's a good question. I guess there's two things at play here. One is whether we can potentially measure autophagy as a potential way to distinguish people who have Parkinson's disease as a mile marker. There aren't currently easy ways to measure how autophagy is working in patients, in humans, but we are actually ... The Fox Foundation is currently supporting biomarker efforts aimed at measuring autophagy in human blood, and this might ultimately lead to a test that's easy to administer, which could tell us whether a person's cellular recycling system is working properly.

Dysfunctional autophagy has been demonstrated in cell and animal models of Parkinson's, but it is possible that it could be a human biomarker, and that work is under way, although very preliminary. In parallel to learning how to measure autophagy as a potential biomarker for Parkinson's disease, we are also funding research aimed at increasing the productivity of these cellular recycling systems, so drug compounds which could increase specific forms of autophagy are being tested in cells and animal systems, and these drugs could eventually be used to enhance autophagy, which would facilitate cellular recycling and, hopefully, prevent or eliminate the accumulation of proteins like alpha synuclein in the Parkinson's disease brain.

Dave Iverson: Let's take that a step further because we've known for some time now that those clumps of the alpha-synuclein protein are central to what seems to go amiss, to kill cells in Parkinson's disease, so it's one of the potential goals then to increase the cells' ability to get rid of those clumps through this recycling process? How might something like that actually work?
Samantha Hutton: Exactly. Researchers have shown that the alpha-synuclein protein is normally degraded by the autophagy system but, actually, mutant forms of alpha-synuclein which have been linked to genetic forms of Parkinson's disease can actually get stuck in this cellular recycling center, so this work has mainly been done in cell models and animal models of Parkinson's disease, but this could potentially explain why alpha-synuclein builds up in the brains of Parkinson's patients because it isn't actually being recycled properly.

This is an example of how the particular protein alpha-synuclein isn't properly degraded through the autophagy system, and it could explain why these alpha-synuclein protein clumps form in the brains of people with Parkinson's disease, so you could imagine if we had drugs that could ramp up this process or, specifically, help this process to be more efficient or effective than those drugs could help people with Parkinson's disease by facilitating better recycling in our cells so that the proteins in our cells, the proteins that clump up in Parkinson's disease brains wouldn't actually clump.

Dave Iverson: Are some of those drug candidates out there now being tested? Where are we as far as our development of some of these drugs that might ramp up the cells recycling ability?

Samantha Hutton: We're actually really early stage on this process, so these drug compounds are really being tested in test tubes right now in cellular systems and animal models. They're not at all ready for human consumption, but I think it represents an exciting avenue. You could imagine that you don't want the cell recycling things too quickly, so I think there's a balance, and you don't necessarily want the cell recycling everything at an accelerated pace, so I think we're really working on the specificity and really determining whether or not these drug compounds are effectively changing autophagy in cell systems.

Dave Iverson: Come back in a way to this theme we've been talking about. Do you have a sense these days that, with scientists and physicians for people who are living with Parkinson's disease, that we really are getting closer to our fundamental understanding of what goes wrong. I have the sense that we're really getting closer to putting this puzzle together to really understanding the disease in a way that we have not before, which is tremendously exciting. Do you share that sense, Samantha, and how does this particular avenue of interest, autophagy, further that understanding?

Samantha Hutton: Yeah, Dave, I think you're right. I think we're sort of hitting it from all angles so, from the autophagy standpoint, I think there's been a lot of really exciting basic science research in the last five or so years that has really helped us to understand what's going on with these pathways and how cells are responding to autophagy dysfunction as it relates to key proteins that are relevant for Parkinson's disease. We know that mutant alpha-synuclein and mutant forms of LRRK2, which are implicated in genetic forms of Parkinson's disease actually get stuck and are not
properly degraded through the autophagy system.

I think knowing that and then being able to translate that into a specific drug target is really an exciting time for this field. I think if we can find ways to modulate autophagy, armed with the knowledge that we’re getting about how the pathway works and then a better understanding of how alpha-synuclein works, how LRRK2 works, how mitophagy works. With all this information and being able to tie it together, I think we’re at a stage where we might be able to think about how we can start targeting these specific pathways like autophagy in relation to the specific proteins and really tying everything together in a meaningful way.

That was Dr. Samantha Hutton, senior associate director of Research Programs at The Michael J. Fox Foundation. To learn more about autophagy and all the latest news in Parkinson’s disease research, visit michaeljfox.org. I’m Dave Iverson.

This is Michael J. Fox. Thanks for listening to this podcast. Learn more about The Michael J. Fox Foundation’s work and how you can help speed a cure at michaeljfox.org.