

BRAIN SCIENCE PODCAST

With Ginger Campbell, MD

Episode #59

**Interview with Molecular Biologist, Dr. Guy Caldwell, from at the
University of Alabama¹**

Aired July 10, 2009

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INTRODUCTION

This is Episode 59 of the [Brain Science Podcast](#), and I'm your host, Dr. Ginger Campbell. Today's episode is an interview with [Dr. Guy Caldwell](#) from the [University of Alabama](#). Because today's interview is a little longer than usual, I need to make a few announcements before we get started.

If you live in the Atlanta area and you are listening to this before July 18, 2009, I want to remind you that I will be the guest speaker at the July meeting of Skeptics in the Pub. Check the Show Notes for the link.

I'm happy to announce that transcripts are now available for all of the episodes of the *Brain Science Podcast*. And from now on I anticipate that new episodes

¹ Dr. Caldwell is an Associate Professor in the Department of Biological Sciences at The University of Alabama. He also holds adjunct professorial appointments in the Depts. of Neurology and Neurobiology and the Center for Neurodegeneration and Experimental Therapeutics at the University of Alabama School of Medicine (UAB).

should have a transcript up within a couple of days, if not the same day that the episode is released. You will find these with the Show Notes.

For those of you who use Facebook, we've had a Brain Science Podcast group for a couple of years, but I have finally started a *Brain Science Podcast* fan page. I hope you will join, and also contribute content. The page went over 300 people on the first day. It already has more people than our [Discussion Forum](#) or Flickr Group, so I'm hoping that this can become a really active place for listeners to share content with each other, and also an easy way for me to send you updates.

It's been over a year since I started the website, sciencepodcasters.org, and I'm happy to report that we now have quite a few shows on that site. One of the charter podcasts on the site was [Brains Matter](#) from Australia. And I've mentioned this show, I think, in the past. At any rate, I was interviewed for [Episode 96 of Brains Matter](#), so you might want to check that out. There will, of course, be a link in the Show Notes.

Before I tell you a little bit about today's guest I want to say something about how I choose the content for each episode. Obviously neuroscience is such a huge area that even if I put out an episode every day I would barely scratch the surface. Also, while I try to aim the show at a very general audience, I know from your emails that you have very diverse backgrounds. Some of you actually know more about neuroscience than I do.

So what I try to do is vary the shows between those that I hope will appeal to almost everyone, and those that are more technical. Last month's episode was sort of in between, since it included some philosophy of mind. This month is one of our more technical episodes. But don't be intimidated by the topic. I think there is something here for everyone.

One other thing. I want to thank Ken Cater, President of the [Parkinson Association of Alabama](#), for inviting me to [The Victory Summit](#) that was held in Birmingham, Alabama in April of 2009. That is where I first heard Dr. Guy Caldwell speak. As he described his research to an audience made up largely of Parkinson's patients and their families, I knew that he would make a great guest for the *Brain Science Podcast*.

Dr. Caldwell is a molecular biologist at the University of Alabama. He is doing some fascinating work with the tiny worm, [C. elegans](#), and he is optimistic that his work may actually lead to a cure for Parkinson's disease. Dr. Caldwell is probably the youngest guest I've had on the show, and I think his perspective will be of particular interest to those of you who are thinking about a career in neuroscience.

Because this interview is over an hour long, I have divided it into sections. In the first 15 minutes we talk about Dr. Caldwell's career, and in the second 15 minutes we talk about the role of *C. elegans*—not only why it is such an important animal in biology, but also why it has become important in neuroscience. And then in the last section of the interview we will get into the specifics of Dr. Caldwell's research.

Let's get on into the interview.

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INTERVIEW

Ginger: I want to welcome Dr. Caldwell on to the *Brain Science Podcast*. Guy, I'm really glad to have you on the show today.

Guy: Thank you, Ginger. I'm excited to be here.

Ginger: Can we start out by letting you tell us a little bit about yourself?

Guy: Sure. Let's see. If I go back to where I grew up, I'm actually a product of the public schools of northern New Jersey, and I grew up about 15 or 20 minutes from New York City. I actually grew up in the town of Caldwell, where I went to Caldwell High School. And I was essentially the Guy from Caldwell—no relation, as far as I know, to the person the town was named for, but my father likes to think that, as the dreamy artist type he is.

However, I really am the product of the upbringing of a Russian immigrant—my mother came directly from Russia after World War II—and my father, who was born down south, where I am now. My father was born in Atlanta, but has a southern family and upbringing. I'm a mix of that, but I did grow up up North.

I got interested in science primarily because of exposure to my grandfather, who was at one time considered the foremost orthopedic surgeon in the United States. I was named for him. He was Dr. Guy A. Caldwell, M.D. He was a Mississippi farm boy who grew up in Corinth, Mississippi. He went to Old Miss, and then off to Columbia Medical School in New York City. And after many years he returned down South and founded the [Ochsner Clinic](#), a famous medical center in New Orleans, along with his medical partner and good friend, [Alton Ochsner](#).

So, I used to travel every summer of my childhood from the New York area down south to New Orleans, where Ochsner Clinic is. Through that trip—which was by car, because my mother was afraid to fly—I got to learn the South. And since that time I've really had a southern education of sorts, because that trip exposed me to fun times in the South during my summer vacations, and I always associated with being in the South during good times.

And, sure enough, my own education after high school followed the path where I went to undergraduate university in Lexington, Virginia, at [Washington and Lee](#)

[University](#)—a famous historic university founded by George Washington, and later Robert E. Lee became president. And there I was a biology major. And I left Washington and Lee for graduate school at the [University of Tennessee](#) in Knoxville. I was there for receipt of a PhD in cellular and molecular biology.

Prior to entering the PhD program I actually was part of an innovative biotechnology degree program where I did some internships in the biotech industry—the pharmaceutical industry. I worked for a company called Burroughs Wellcome that is now [Glaxo](#). I did my doctorate in the field of cell biology, and really learned molecular biology, as I was studying the single-cell yeast *Saccharomyces cerevisiae*, the bread and beer yeast that we most commonly know—probably the best understood cell on the planet.

I was doing this yeast cell biology and understanding mechanisms related to how cells respond to what I would call cancerous-like situations. But I really was dissatisfied with the ability of only working on a single-celled organism. My interest yearned for far more than just single cells. And about this time—which was the early 1990s—my mother fell ill to dementia. And I watched her decline over the course of several years.

The impact of watching somebody—personally, or your own parent—dealing with something as traumatic as dementia was very strong on me. And I really wanted to find a way I could make an impact in the field of neuroscience. To this day, actually, I've never had a class in neuroscience. But I said to myself, well, wouldn't it be nice for me to go into the field of neuroscience. I think the 1990s was being heralded as the decade of the brain back then; and I thought, well, this would be a very interesting field to go into.

However, working on yeast cells didn't give me much background in neuroscience. So, I said to myself, how can I make that jump? I was looking for a way I could enter an organism that was simple enough that I could understand a

little bit about how its nervous system could work, without the necessary knowledge in brain anatomy and physiology that you have in what I would call hard-core neuroscience.

About that time I was at a cell biology conference and I heard a lead speaker at the conference, who was [Dr. Robert Horvitz](#) at MIT—a famous researcher in the field of worm biology, the microscopic nematode worm, *Caenorhabditis elegans*, or *C. elegans*. Dr. Horvitz is a leader in that field, and I was aware of his work. And I heard him speak at this meeting and I was enthralled by the power of this microscopic worm, and specifically how its nervous system was completely defined and understood, to the point that every neuronal connection, and connections between neurons and muscles, was already mapped out.

What was striking about Dr. Horvitz's lecture was that he also was making pronouncements that *C. elegans* was going to be the first animal of all animals on our planet to have its DNA sequence revealed. This was in advance of the [Human Genome Project](#), and *C. elegans* really became the model for that in many ways.

And I started putting two and two together, and said to myself, well, here's this organism that has a simple nervous system, and it has very defined genetics that's going to be coming out very shortly, and understanding its complete genome sequence. Isn't this going to be a wonderful organism for studying diseases of the nervous system? I said to myself, people that enter that field are going to have a bit of a head start over others in terms of being able to apply specific genetic sequences, and finding out what they might do in a simple nervous system like that of the worm.

At that point I decided that was the field I was going to go into for my postdoctoral work. So, following my doctorate at Tennessee, I said to myself this was what I wanted to work on. But I am an only child, and my mother was alone in the New York area with my father, and I really felt I needed to be closer to her

during this time of her life. So, I limited my postdoctoral search, really, to *C. elegans* researchers in the New York area. I did apply a couple other places, but in the end that's where I wanted to go.

So, I really honed in on the work of a specific individual at Columbia University, [Martin Chalfie](#). Marty Chalfie was another leader in the *C. elegans* field. His work had to do with understanding how microscopic worms respond to touch. And the neurons and the nervous system underlying touch response—or what's called mechanosensation—is pretty much still relatively unknown as far as the senses go. And I had pretty much decided at that point that I really wanted to work with Dr. Chalfie as my top choice for a postdoc.

I had my application all ready to go—this was 1994—and a friend of mine dropped *Science* magazine on my desk. Laying there on the cover of *Science* magazine was this beautiful picture of *C. elegans*, the worm. What was neat about this picture was it was lit up—it had this beautiful fluorescence throughout it. And my friend said to me, 'Isn't this the guy you want to go work for?' And sure enough, it was the first announcement of the discovery of the green fluorescent protein—or what's called [GFP](#).

GFP is, in fact, the protein from jellyfish that is responsible for their fluorescence. What researchers had done was they identified the gene that codes for this protein, GFP, and they had used it as a molecular light bulb of sorts, to light up different organs and nervous systems. And what this report was on the cover of *Science* was the first use of GFP in this manner, across species from jellyfish to worms, lighting up the nervous system of *C. elegans*. I realized at that point that this was going to be a pretty big discovery that was going to revolutionize how we do science. And I sent off my application that moment.

Ginger: Absolutely!

Guy: And so, I was thrilled to receive a call from Dr. Chalfie, really within a couple days, inviting me for an interview up at Columbia. In a way it was a homecoming of sorts for me to return back to the New York area—to actually go back to the university where my grandfather started his medical career. And last year—2008—Martin Chalfie received the [Nobel Prize in Chemistry](#) for his discovery, along with two other scientists, for the use of GFP. So, just this past January I had the pleasure of returning back to Columbia for a Nobel Prize celebration in honor of Marty, along with a bunch of my former postdoctoral colleagues. We had a great big party, and it was a lot of fun.

But really my interest in Marty's work pre-dated GFP. It had more to do with this idea that this simple microscopic worm that had a completely defined nervous system could help us unlock the secrets of neurological disease. Even though I did primarily work on mechanosensory genes—these touch response genes—in worms as a postdoc at Columbia, always in the back of my mind I thought for my own laboratory and my own research someday I wanted to apply the power of *C. elegans*, and all the genetics and different methods that could be applied for *C. elegans*, to the process of studying neurological disease.

Which, at the time, and still to some degree right now, people that work on organisms like worms and fruit flies and yeast cells and these, what we call model organisms, had not been really applying these organisms for what I would call directed or applied research into disease mechanism. That has become more popularized in the last few years. But I had wanted to do that always from the get-go. And I think that this has really led to what our lab does now. But it was all an outgrowth of this path that I started, thinking about how the worm could be a leading system for that purpose.

Ginger: I want to talk with you in detail a little bit about the role of both molecular biology, and in specific, *C. elegans*, in neuroscience. But first, to finish

out your little biographical sketch, how did you end up at the University of Alabama?

Guy: Well, ending up at the University of Alabama has been a wonderful aspect of my career. My experience as a graduate student at Tennessee really was responsible for me considering work at the University of Alabama as a potential career path. I really enjoyed being at the University of Tennessee in Knoxville—a big university with lots of fun activities around it. And I said to myself that was a wonderful environment to be in. My own mentor and professor, [Dr. Jeff Becker](#), at the University of Tennessee, was one of the finest scientists there. And I saw what a wonderful career, and how much he enjoyed his life as a professor there.

And I said to myself, that would be a really nice job—a nice thing to do—to be a professor at what I would call a predominantly undergraduate university, but also obviously a research institution, where you have that mix between being a professor who teaches classes, as I do—I typically teach three days a week—and at the same time maintain an active research career. I would define myself as a researcher who teaches. And I really do like that balance between both. I think I would be incomplete without the teaching or the research.

But what happened was when I was a postdoc up at Columbia I had made a decision that I really wanted to begin getting on the job market. I was very fortunate because there was a grant that the University of Alabama had received from the [Howard Hughes Medical Institute](#). The HHMI sponsors undergraduate research programs at many universities across the country—40 or 50.

Alabama had apparently received one of these grants at this time, and was looking for somebody that could come in and establish and teach an undergraduate genomics lab course—genomics being a hot new area, using information from the Human Genome Project and genome projects of other organisms to help define how different genes interact and function inside

organisms. And Alabama had received this huge grant and was looking for somebody that could come in and teach a brand new genomics lab course.

I actually had experience with establishing and writing a textbook for a similar type of course when I was a graduate student at Tennessee. So, that gave me a heads-up for this job opportunity in Alabama. So, sure enough, I only applied to Alabama for my job search at the time. I also put a couple of other applications out, but Alabama was really what I probably fit best.

I got the interview, and got the job. However, there was an interesting aspect to this—and an interesting aspect to my own research lab. I actually share my lab, and my life, with my lovely wife, [Dr. Kim Caldwell](#). Kim is a PhD molecular biologist, as well, who had been a postdoctoral fellow at the Rockefeller University in New York while I was at Columbia. And then she moved over to Columbia University for a couple years, as well, because her boss had left Rockefeller and moved when he got married.

However, there was only one job opening at Alabama at the time. And Kim and I had always dreamed, back when we met in graduate school at Tennessee, about having a shared research program and shared lab. But we'd never really realized how that dream would come true. It's often very difficult to get two jobs at an academic institution. And, sure enough, there was only one job opening here.

I got it, and I was very excited to have that job. Kim was excited for me to have that. So, we made the decision at that point to, what I would say, invest in ourselves. And Kim joined the lab, where I taught her how to work with *C. elegans*. She and I built this mom and pop store together, is the way I view it. She worked in my lab for free for four years.

Ginger: Wow!

Guy: Fortunately Alabama is an inexpensive place to live, and we could have a home and still maintain a decent lifestyle on one salary. But it wasn't glamorous at the time. What happened was my concept of using *C. elegans* as an organism with which you could study neurological diseases really started to flourish. We received some substantial grant support, and some recognition for our students that were winning all sorts of awards for their research.

And we had a change of administration here at the University of Alabama, and a new president came in. And my wife had been teaching at the time, and she's an outstanding teacher. So, the rumors were spreading that the Caldwells were doing very well, I think. And the new president came and invited us to lunch, and at the lunch he told my wife that he was going to make her a tenure track professor. Suddenly our income doubled, and life got a lot better, and Alabama was really very supportive of us in that regard.

And I'm very proud to announce just last week my wife received tenure. I've had tenure for a couple years now. And so, our little dream of our mom and pop science store here—of having that pretty much forever now—seems to have become a reality. So, that's been a nice story for us. Alabama basically has been a wonderful place for us to establish and grow our joint careers here now together.

Ginger: Well, that's great. I'm glad that we had the opportunity to meet at The Victory Summit for Parkinson's disease in Birmingham, because otherwise I wouldn't even have known about your work. It's pretty exciting stuff.

Guy: Thank you.

Ginger: And I would say to my listeners that if you're wondering how guests get onto the *Brain Science Podcast*, sometimes there's a little bit of chance involved.

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The [Brain Science Podcast](#) is sponsored by [Audible.com](#). As I've mentioned in the past, I've been using Audible myself since 2003. This month I'd like to recommend a book that was suggested by listener, Jeff Kish. It's called *Think Smart: A Neuroscientist's Prescription for Improving Your Brain's Performance*, by Richard M. Restak. If you're not already a member, you can get this as a free audiobook download by going to audiblepodcast.com/brainscience.

Now let's return to my interview with Dr. Guy Caldwell from the University of Alabama. In this next section we will talk about the scientific importance of the tiny worm, *C. elegans*.

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Ginger: I'm sure at the beginning of our conversation some of my listeners were wondering why I might be interviewing a molecular biologist. And although I think you've already sort of given some good hints about that, I thought we might start by just talking a little bit about why it is that molecular biology has become such an indispensable tool for neuroscience. And before you talk about that, could you tell my listeners very briefly what molecular biology is?

Guy: Sure. Molecular biology, to me, is really the ability to manipulate things like DNA and the genetic code and the things that it codes for, such as RNA and proteins, that are the things that make our cells work. And the ability to understand how those molecules interact and function inside cells really is the core of molecular biology.

I harken back to when I was an undergraduate at Washington and Lee University, how I was thinking in terms back then of medical schools, and what I wanted to do in that regard; and I really didn't know anything about molecular biology. But what I distinctly recall to this moment was sitting in my basic undergraduate genetics course—and this, again, was the mid 1980s—and hearing my professor

talk about the phrase ‘recombinant DNA.’ And I said, ‘What does that mean? I’ve heard that before.’ Back then it was kind of a new phrase.

And he said, ‘It’s recombining DNA, splicing and cutting things together, and generating new molecules of DNA that never existed before—usually for purposes of understanding how a protein or a molecule could work, but beyond that, for biotechnological processes of generating therapeutics and proteins. And this whole burgeoning field of biotechnology was waiting there. And I said to myself, you mean people get to cut and paste DNA and make new organisms for a living? And I said to myself, that’s a pretty cool job.

And I thought to myself, wouldn’t that be a nice way to help understand disease mechanisms and use these tools that really are the tools of molecular biology—recombinant DNA, protein biochemistry, and what I would call our understanding the molecules of life—and manipulate them for purposes of trying to discover how these molecules in our cells work together to function properly, or to dysfunction in terms of disease. So, to me, the phrase ‘molecular biology’ really is describing the process of understanding how the molecules that comprise our cells are functioning together, and manipulating them in those terms.

Ginger: So, that means the DNA and also the other molecules that DNA interacts with inside of a cell?

Guy: That’s right. In order for your DNA to—the phrase we use is to be transcribed—or to use that code that’s in the DNA to make a protein, there’s a host of different types of factors that need to sit down on the DNA, turn on the production of the molecules, which is RNA, and transcribe that, and have that translated then into the language of amino acids, which comprise proteins.

So, the proteins are the end product of what the DNA codes for, and how our proteins function and interact inside cells—the proteins can be hormones, they can be receptor molecules, they can be all kinds of different enzymes that are necessary for the function of our cells—that all is coded for within the DNA. But that process of going from DNA to protein really involves a host of molecules that are really the core of molecular biology.

Ginger: That's a huge field in and of itself.

Guy: It sure is. And applying it to neuroscience, as you asked earlier, really has flourished over the past, I'd say, 15 years or so. Mainly because people have designed all kinds of tools like the green fluorescent protein (GFP) that allow us to splice in a fluorescent protein from jellyfish, for example, into the DNA of a worm, or even a human cell now. We can then light up the nervous system of the worm, or a fruit fly, or a mouse, and light up different neurons and study whether or not those neurons are connecting properly, or functioning properly, or dying, for example.

We can take these tools of molecular biology and find genes that are coded for that are up-and-down regulated, for example, that are turned on or off in disease states. Lots of people are looking at what we would call expression patterns, or different types of responses that exist inside cells and in neurons in diseased individuals vs. non-diseased individuals. Of course, in mouse models and stuff, it's easier to do. And so, I'd say molecular biology is really at the forefront of unlocking the secrets of how neurons function. And the bigger challenges of how they connect and lead to cognition and other things are still way out there.

Ginger: But the tools of molecular biology, then, can be used in something as simple as a yeast, all the way up to a human.

Guy: Absolutely. One of the things I like to tell my students is DNA is DNA is DNA. And if you know how to work with the DNA of a fish, or a yeast cell, or a bacterium, you pretty much can apply that to a human cell. So, learning the basics of molecular biology if you're an undergraduate, or even a high school student, is really the foundation for understanding how you can use and manipulate DNA for studying any type of cell in the planet, including plants as well.

Ginger: I'm going to ask you a question that shows that I've been out of college for a long time. When my sister and I were in college over 30 years ago, she was studying microbiology. And now it's down a whole other level. So, do undergraduate students major in molecular biology, or would molecular biology be something you would study as a part of your biology degree?

Guy: That's a great question, actually. And as somebody that teaches undergraduates every day, I run into that a lot. There's this, not necessarily misconception, but there's the conception that molecular biology is microbiology. And that's not necessarily true. Molecular biology spans all different types of biology. It would span microbiology, cell biology, genetics, and biochemistry. Molecular biology is in the background of all those different fields.

Microbiology per se is really more of a focus on things like bacteria, and viruses, and fungi, and the small microscopic cells, which of course have DNA in them as well. And a lot of what we understand about molecular biology was because people studied microbial organisms and used those simple systems to unlock the secrets of molecular biology way back when—people like [Watson and Crick](#), the people that unlocked the genetic code. Those people were all studying microbiology back then.

But now, to say that microbiology is molecular biology really is not correct. I think that molecular biology spans other fields. And if you're an undergraduate

looking to enter the field of molecular biology, really what you're talking about is a basic biology major, in many universities. Some universities might offer a more specialized molecular biology major. Or, what I would call cell and molecular biology is very typical. So, if you're looking to get into the molecular biology field, those are the types of fields. But microbiology still is a fine background for that as well.

Ginger: So, let's talk about the famous nematode worm, *C. elegans*. You've been working with that for over 10 years now, right?

Guy: About 15, actually.

Ginger: Can you tell us what makes *C. elegans*—and I can't even pronounce its real name—so special?

Guy: Well, I don't even know if I pronounce it correctly—I say *Caenorhabditis elegans*. Well, *Caenorhabditis elegans*, or, *C. elegans* really is a special organism. It's special in that it's probably the most understood animal on our planet. It's the only animal for which we know how every worm forms invariantly from a single-celled egg that gets fertilized by a sperm. It's fertilized within the worm, because they're hermaphrodites—they have both egg and sperm, and so they can fertilize themselves, essentially, and lay the next generation of embryos.

But basically it's the only animal for which we know a complete cell lineage, meaning that from that first fertilized egg all the way to the adult—which only takes about three days to occur—that adult is comprised of exactly 959 cells. Over the course of about a decade in the 1970s [John Sulston](#), [Bob Horvitz](#)—who I mentioned—and the founder of the *C. elegans* field, [Dr. Sydney Brenner](#), spent a lot of time looking at that formation from a single fertilized egg to the 959-cell adult.

And what they had done is mapped out the complete lineage of how an animal forms: how all its organs form, how its nervous system forms, etc. *C. elegans* has a complete map of how that happens. Every cell has an actual name associated with it. It was a very tedious thing to do, but it was a very wise thing to do, because it helped us understand how different organs form, and how different cells divide, and die off, etc.

And in fact it was recognized with a [Nobel Prize back in 2002](#) because Brenner, Horvitz, and Sulston all received the Nobel Prize for their work in establishing the cell lineage, and more importantly, how it applied to understanding how different cells die off through a process of programmed cell death. So, *C. elegans* is very well understood in terms of its developmental biology.

The other thing I mentioned earlier is that it's also the only animal for which we know its complete neuronal connectivity. The way that was done is researchers—led by [John White](#), and again John Sulston, in the 1970s and 80s—what they did was they took the worm and they sliced and diced it in every way possible, and then basically, if you want to think of taking a microscopic worm and breaking it up into puzzle parts, and then spreading out those puzzle parts.

And if you think of the puzzle parts as being electron micrographs that would be shown underneath an electron microscope, those different photographs that came out of the worm's electron microscopy basically were pieced back together to find the connectivity of the nervous system. Again, this was an extraordinarily tedious process and it took a lot of care and time to do this. But the end result was that we understand exactly how every cell and neuron in the animal connects to each other. Again, this is the only animal for which we know that.

So, when you combine those two features with the fact that we know its complete DNA sequence through the sequencing of its genome – and *C. elegans* research was founded, as I mentioned, by Sydney Brenner. I'm very proud to tell my

students that I'm actually a scientific grandchild of Sydney Brenner, because Dr. Chalfie at Columbia, who I worked for, actually trained under Brenner; and so my own students are great-grandchildren of the founder of the worm field.

Brenner's vision for *C. elegans* was to find an organism that was simple enough that we could understand how its nervous system may function and how it can control basic responses of the nervous system—behaviors, for example—but not so complex that we can unlock those mysteries quickly. I believe his vision—many people now believe his vision—has borne a lot of fruit.

In fact, I mentioned two Nobel Prizes: There was also a third [Nobel Prize](#) this decade awarded to worm researchers. Dr. Andy Fire and Dr. Craig Mello had discovered a process known as RNA interference—or RNAi—which is a means by which cells kind of can protect themselves from aberrant types of infections from viruses and elements that cause DNA damage. This process of RNA interference has now been recognized as a basic cellular mechanism, that wasn't understood until worm researchers deciphered it. So, three of the last six Nobel Prizes have been given to *C. elegans* researchers. It's being pretty well recognized in the top echelons of the scientific community as being a very useful system.

What's really cool about the worm is it's transparent—meaning that underneath a typical microscope we can go in and look at its organs. And if you combine that with a fluorescent microscope, you can light up its different organs, including its nervous system, using the fluorescent protein from jellyfish. So, one of the things our lab likes to do is to light up neurons that produce certain types of chemicals—for example, the neurotransmitter dopamine. Dopamine is one of the signaling molecules in our nervous system that is necessary for responses and proper locomotion in humans, for example.

Worms have all these same simple types of molecules, like dopamine, serotonin, and acetylcholine. These are the neurotransmitters that cause our nervous

system to function properly. And worms have all those genes that code for those molecules. They use them in slightly different ways than we do, but they still use them for proper function. Coming back to the wonderful aspects of *C. elegans*—despite the fact that it is a microscopic nematode worm that only has 959 cells, 302, exactly, of those cells are neurons.

Ginger: A high percentage.

Guy: Yes, it is actually a fairly high percentage. It tells you how the nervous system is important for this organism. Actually you can dispense of almost all of those neurons and the animal still will survive. It has a simplistic nervous system, but still a level of complexity, and still codes for all these things like neurotransmitters and ion channels like sodium channels and potassium channels—these things that are controlled in neurons in order for them to fire properly and have electrical activity.

This allowed the worm to strike that balance between a level of simplicity that we can begin to understand; yet the level of complexity that it does have neurons, it does have a nervous system—unlike the yeast cell that I originally worked on—can allow us to begin asking questions about, for example, what is necessary for a dopamine neuron to survive and deal with the insults that might come either from the environment or genetic pathways.

Ginger: You mentioned that we know the genome for the *C. elegans*. Was that the first genome that was completely decoded?

Guy: It was. In fact I'm looking right now in my office at the cover of *Science* magazine from December of 1998, where the genome of *C. elegans* was announced. So, in many ways *C. elegans* served as the model for understanding how we could go about the technical aspects of decoding a genome and

sequencing it completely. But, yes, that was the first organism—the first animal, I should say, I think, not single-cell.

Ginger: OK. How much of that genetic material do we share with the worm?

Guy: We share approximately 50% of our DNA. Which is kind of a humbling figure if you think about the fact that the worm is only 1 mm long as an adult—which is about the size of a period on a page. About 50% of its overall DNA is shared. What's interesting if you start looking at disease genes—the genes that, when defective in us, lead to some sort of genetic disorder—that number actually goes up closer to 70%; where you might imagine that disease genes are more important for basic biological function and those processes would be conserved between lots of species.

But in general about 50% homology—is the word that's used—between worms and human DNA is found. But that gets a little higher when you talk about disease genes. So, for example, genes that are involved with Parkinson's disease, where people have identified 8 or 9 genes that are linked in families that have inherited forms of Parkinson's disease, the worm has all of those genes that have been identified so far, except for one. Which allows it to be a very useful model for studying Parkinson's.

Ginger: And we're going to talk about that in a few minutes. Recently I was talking to [Dr. Eye Marder](#)² about her work with the stomatogastric ganglion in the lobster, and she said something that confused many of my listeners. She said the lobster is not a genetic organism. And I assumed that what she meant was that since we don't have the genome for the lobster, we don't use it to knock out genes and see what happens—in contrast to what we can do with something like *C. elegans*. Would that be accurate?

² Dr. Marder was interviewed in [Episode 56](#).

Guy: Yes. That phrase is commonly used among different types of people, as when they say, ‘This organism is not a genetic organism.’ That doesn’t mean it doesn’t have a genome, or it doesn’t have DNA. All organisms do have that. But what it means is that the methodologies, and the techniques, and the ability to map and cross different genetic backgrounds has not been worked out yet for that system. I don’t know if people are actually working on that for lobsters.

But that type of basic science to understand the genetics and be able to do crosses, and systematically analyze genetic components and factors is relatively limited among organisms. The most famous one is the fruit fly. And of course we can do these things with mice. And worms are in that category. But the development of what are called model organisms, or systems that do have nice genetic tools to manipulate them, is still relatively rare. There are not too many organisms out there. So, I’m not surprised the lobster doesn’t have that yet.

[music]

Ginger: Before we get into the details of your work, will you talk a little bit about how *C. elegans* fits into the overall research approach to trying to unravel a human disease such as Parkinson’s disease? What I have in mind is the trail that goes, as I understand it from reading your papers, kind of from yeast, to *C. elegans*, to mice, to people.

Guy: Of course there are various ways scientists can try to attack problems associated with disease. There’s the top-down approach, which would be looking inside what we know from the human clinical condition, and then trying to model it down from the human into a mouse model, for example, and then try to get a behavioral, let’s say, deficit, or some sort of readout in a mouse that would be useful. That’s probably still a very common way to try to understand disease mechanisms.

Our approach has been a little bit different. We still actually do begin with what's known in the human disease, as you might imagine. But we kind of skip all the way from the human down to the worm, and sometimes, with collaborators, a yeast cell. What we do is—again it comes back to this idea that we had back when I was talking about what inspired me to enter this field was the fact that we do have the complete genome sequences of humans and things like yeast and worms.

What we can do is we can use powerful computer programs—what are called bioinformatics databases—that allow us to search for genes that are shared between humans and worms and yeast, and look for what are called homologous versions of those genes. Or even sometimes just take the human gene and put it into a yeast cell, or put it into a worm, and then see if in fact we can get some sort of readout.

One of the powers of these basic model organisms, like worms and yeast, is that we can manipulate them pretty rapidly using genetic tools. If we can then take a human gene, for example, that might be found in a Parkinson's patient and is defective in that patient; we can take that gene and create a readout. Now, Parkinson's in a yeast cell is not going to be the same as it is in a human being, or a worm, for that matter.

But the cellular defect that might be associated with taking an aberrant human gene and putting it into a yeast cell or a worm could lead us to a readout or a function in that animal that allows us to then manipulate the animal and find out what modifies that function—what prevents it from doing what it would do in the disease state—or what type of drugs would prevent that from happening. Those kind of questions can be answered much more rapidly in a single-celled yeast or a simple worm.

What we do in this regard is create a sort of a pipeline, is the way I like to think of it. Let's say a gene has been identified as responsible for Parkinson's in a human patient. We can then either look for that same gene in the worm genome or the yeast genome. Then we can take that gene and look for any sort of defect in the yeast cell, and then screen for factors that prevent that defect from occurring—seeing if in fact those factors then could be taken into a worm where we might have a similar type of defect.

Then we can see if the worm responds the same way to the modifying factor that we would identify. And that modifying factor can either be a gene, it can be another gene that's coding for a protein that is affecting that, or it could be a drug that we could use to modify something. And then, if it works in the worm, then we would go to our friends that work with mice, or human cell cultures, or even rodent cell cultures, neuronal cultures—thing like cultured neurons, for example—and see if in fact the factor that was screened originally in the yeast, that validated in the worm, holds true when we take it into the mammalian system.

The beautiful thing about yeast and worms is they're pretty cheap to work with. We can screen through thousands of animals, and hundreds of animals very rapidly. But mice are expensive. They're very expensive. It can cost hundreds of thousands of dollars to keep a typical mouse colony at a lab working for a year. It's much more bang for your buck to understand these things at a basic process first, and then seeing if it translates more into the more expensive and more challenging models that we have. I won't even get into primates, because that's really expensive.

Lots of cellular mechanisms are shared between these species—much like the DNA in themselves. The things that make a neuron function properly—you know neurons are just cells that are a little more specialized—the things that make a neuron function properly actually may be necessary for a yeast cell to survive, or may be necessary for a worm neuron to function properly. And if you can begin

to understand those things in a yeast or a worm first, you save a lot of time before going on to the more complex models.

Now, having said that, you do have to go on to those models. No one's going to take a drug that was really just discovered in a yeast cell and think it's going to work directly in a human. And the FDA would probably not like that very much. What we can begin to do is get clues. What I like to say is, you screen and then you validate.

We've been doing a lot of this in the last few years. What we're finding is a lot of the things that work in a yeast and a worm cell actually do work in mammalian cells. So, it's been very satisfying in understanding that basic cellular processes that are not working right in disease states can be studied in these systems.

Ginger: You mentioned early on that you got interested, sort of, in neuroscience because of your mother having Alzheimer's disease. Your work now is mainly focused on Parkinson's disease?

Guy: Our lab works on several neurological disorders. We're probably best known for our work in Parkinson's. Which is kind of ironic, because when I started the lab 10 years ago I never even thought about Parkinson's disease. That's one of the beautiful things about having your own research lab and being in academic science, is if you suddenly have an idea and can convince somebody to give you money to do it, you can change your entire career path, or at least modify it to some degree.

But we actually work on Parkinson's, we work on another human movement disorder that's called dystonia, and we also work on epilepsy. We are, in fact, beginning some work now recently on dementia as well, and Alzheimer's. So, we kind of are using the worm to study a gamut of neurological diseases, but most of our published work to date has been on dystonia, and Parkinson's, and epilepsy.

One of the stories I like to tell is being in an undergraduate university such as the University of Alabama, is very rewarding at times, because having a population of a hungry undergraduate, often pre-medical, students who are looking to impress and do well in undergraduate, can be a very useful breeding ground for testing out one's crazy ideas. Whereas, if I was running a lab at a medical center, for example, or an institute, I would be less likely to test out a crazy idea on the career of a postdoctoral fellow or a medical resident who might be working in my lab. I can test out some crazy ideas with some of my undergraduates and realize it's not going to ruin their career if it doesn't work.

So, about six years ago now, I had an idea that one of the genes we had been working on that actually is linked to the human movement disorder, dystonia, might also play a role in a protective capacity against Parkinson's disease. I won't get into the details of that, but basically we had a theory that this might be a way that we could get into the Parkinson's world. I said to myself, this would be great, but I don't have any money to do this.

And, sure enough, one of my ambitious undergraduates pulled out a grant application that she found online, and handed it to me and said, 'Why don't you apply for this grant?' And I realized the deadline was almost in two days. It was a grant from a brand new foundation at the time that was looking to fund innovative research into Parkinson's. This was the [Michael J. Fox Foundation](#). And I had two days to put in an application. And I said, well I don't have any real—very minimal—preliminary data on this. And they said they didn't need much.

Sure enough, I decided to spend basically two nights writing this grant, and put it off to the Michael J. Fox Foundation, and it was funded. We were one of the first labs in the world that was in fact selected by the Fox Foundation, which has now grown into, obviously, the most well-known philanthropy for Parkinson's in the world. They've been funding our lab now almost continuously for the past six

years. We're very grateful for their support. But really what happened was, overnight I became a Parkinson's researcher.

It's a great example of how if you just want to pursue some of your ideas and you can convince somebody to let you do that, you can enter into a whole new world. And as you know, where we met and discussed our research at Victory Summit, was in fact a lecture that I was giving to a room full of Parkinson's patients—about 500 or so. And so, since that time it's been very rewarding to know that our work is actually out there reaching, and hopefully inspiring, some patients to have some hope that what we're doing may make a difference for them.

So, we work on Parkinson's primarily, but we also do work on dystonia and epilepsy—to answer your original question.

Ginger: Do you want to talk a little bit about how you're using the *C. elegans* to try to come up with ideas for Parkinson's?

Guy: Sure, absolutely.

Ginger: Do you think we need to talk just a little bit about Parkinson's disease before you start?

Guy: Well, Parkinson's disease, as most people know, is a movement disorder, and results in people having involuntary movement and tremors, and basic biological functions become uncontrolled. It's a devastating disorder that affects over a million Americans, and many more worldwide. It's the second most common neurodegenerative disorder, after Alzheimer's disease. It, of course, is growing in numbers as we age as a population.

It's a disease in which the neurons that produce the chemical, dopamine—as I mentioned earlier, the neurotransmitter, dopamine, inside our brains—those neurons progressively die off over the course of aging. What people have found

over many years of outstanding human genetic studies is that different genetic factors that are shared in families where Parkinson's is inherited have begun to give us clues into what cellular pathways and mechanisms inside our neurons may be defective.

However, we really are in our infancy in trying to understand how those pathways are impacting the clinical or disease state. But what we know is these pathways somehow are regulating whether or not those dopamine neurons are surviving or not. The idea that we had was what if we could take some of these—specifically, one of these—genetic factors that's found in humans, that if you have too many copies –

Most of you know that we have one copy of our genes from our mother, one copy from our father. Some Parkinson's patients actually have an extra copy of a gene that encodes a protein called [alpha-synuclein](#). And alpha-synuclein has been found as a protein that in the brains of Parkinson's patients, after they die, if you actually were to dissect out the brain tissue and look inside the brains, what you would find are these inclusions, or what are called [Lewy bodies](#). They're these clumps of protein that are around the dead neuronal tissue.

And these clumps of proteins primarily are comprised of this one protein I was calling alpha-synuclein. There are many other proteins associated with them, but alpha-synuclein is there in high levels. And, sure enough, what some Parkinson's patients' families have—in rare cases, actually—are extra copies of this protein. But what we found is that the levels of alpha-synuclein really seem to be important for whether or not a dopamine neuron will survive.

The clumping of the protein is interesting, as well, because the protein aggregates and forms a misfolded type of state. If you think of proteins inside our cells floating around normally, and being soluble in the cells—which are mostly water, of course—what happens is sometimes they fall out of their normal shape. They'll

lose their three-dimensional shape and they'll clump and they'll aggregate. And if there is too much of a protein, it will aggregate sometimes. And that's what happens in the case of alpha-synuclein in a Parkinson's patient.

And so, we thought to ourselves, this process of alpha-synuclein having too many copies, and aggregating and forming clumps could be something we actually could make happen inside a worm. Well, what we did is we actually took the human DNA for alpha-synuclein and we put it inside the worm's dopamine neurons. And, as I mentioned, the worms have 302 neurons of their complete nervous system. But precisely 8 of those neurons produce dopamine. Again, having a precise number that we can count, animal to animal over a course of hundreds of animals, allows us to get very definitive data on whether or not a factor like alpha-synuclein, for example, would cause those 8 neurons to die more rapidly.

What we could do with those 8 neurons, actually, is do that trick that I learned back at Dr. Chalfie's lab—take that fluorescent jellyfish protein and light up those neurons. We can light up those 8 dopamine neurons of the transparent worm, and then we can take human alpha-synuclein and give the worm extra copies of it—extra dose of it—like would be found in the families that have Parkinson's. And, sure enough, over the course of the worm's lifespan, which is only two weeks –

It's a wonderful organism for understanding the diseases of aging because it has a very short lifespan. In fact, mark my words, one of the future Nobel Prizes will be given to worm researchers for unlocking aging itself. [Cynthia Kenyon's](#) lab and other fine researchers have been working on that for years.

But, coming back to the dopamine neurons, what we can do is light them up with the fluorescent protein, we can give them human alpha-synuclein, and sure enough, over the course of its lifespan those neurons will accelerate their death—their death will be more rapid. We can then look for other genetic factors that

prevent that from happening—things inside a worm that are shared between worms and humans; part of that 50-70% of genes that I was talking about. We can begin looking at which ones of those factors either accelerate the death if they're defective, or protect the death from happening.

If you think about identifying a new genetic factor that is shared in all of us that protects a dopamine neuron from dying, well, that's wonderful. But what a drug company looks at is that's a new target for a drug development program. And so, what our lab has done is, we have used the worm and the power of genetics in the animal to screen for lots of genetic factors and find those that may cause the worm to have enhanced protection—what's called neuroprotection—against dopamine neuron death induced by alpha-synuclein.

This has led us to get a short list of about 20 or so targets—5 of which we've been studying pretty intensively—that are new therapeutic targets for Parkinson's disease. This was originally funded by the Michael J. Fox Foundation. And they've continued their funding with one of the factors that we've identified—one of our lead candidates is a gene that actually protects dopamine neurons from dying over the course of worm aging—and in collaboration with very fine researchers at the [University of Alabama Medical School](#) in Birmingham.

Those researchers, who work on mammalian cells and neurons, found in fact that the factor that we discovered in worms actually does protect human dopamine neurons from dying. So, we're very excited about this, and the fact that we may have identified a new therapeutic target that we can then look for drugs that activate this target, or use that target itself in a therapeutic manner through something like gene therapy.

[music]

I want to take a moment to thank those of you who support my work with donations. Starting next month I'm going to give away a free book each month. Everyone who donates at least \$25 is eligible. The first winner will be chosen on August 7th and will be announced on the August 14th episode. After that I will draw one name a month. To learn more, just go to brainsciencepodcast.com and click on the tab at the top of the page labeled '[Donations and Subscriptions](#).'

I will discuss this in more detail later. But let's get back to Dr. Guy Caldwell. In the last part of this interview we spend about 20 minutes talking about Dr. Caldwell's research, and then Dr. Caldwell shares his advice for those of you who might be thinking about a career in science.

[music]

Ginger: Does the stuff that you do help to unravel any of the pathophysiology of Parkinson's disease?

Guy: Probably not so much. The pathophysiology of Parkinson's disease can be fairly controversial, actually. People aren't sure that these Lewi bodies—these clumps of protein that are in the brain—are actually evidence of a horrible thing or not. Some people think they might have been evidence of the cells trying to protect themselves and sequester the extra alpha-synuclein or other factors that are causing neurons to die—kind of like taking out the trash and moving it over to the side or something. And so, I'd say the worm system is not ideal for that type of work.

Ginger: But it is idea for trying to find what makes things worse and what makes things better at the basic level.

Guy: I think so. I think it's been very good in terms of finding out what types of factors are protective, or actually can enhance degeneration. Another project that I alluded to earlier, that we've been working on in more specifics, is taking

genetic factors that have been screened out in yeast cells. As I mentioned, alpha-synuclein can form multiple copies and aggregates and cause neurons to die.

Well, what the lab of [Susan Lindquist](#)—a very fine geneticist at the [Whitehead Institute](#) at MIT in Boston—what Sue Lindquist’s lab has done is they’ve taken human alpha-synuclein and, again, attached it to that fluorescent protein GFP, and they’ve shown that extra copies of alpha-synuclein cause it to clump in yeast cells, and that clumping is associated with the dying of the yeast cell. So, what the Lindquist lab has done is screen through genetic factors that can prevent the yeast cells from dying.

And what we’ve done is taken some of those factors, put them into our worm dopamine neurons, and shown if in fact what prevents the yeast cell from dying from alpha-synuclein dependent degeneration can protect the worm dopamine neurons from alpha-synuclein dependent degeneration. And, sure enough, we have found a suite of different factors (published across various papers now) that work in both worms and yeast; and actually go to the next step.

And the lab of [Chris Rochet](#), who is at Purdue University, has a wonderful system for studying primary midbrain cultures of rat neurons. They can take the rat neurons that have alpha-synuclein in them, and show if in fact the things that work in the yeast and the worm actually work in the rodent model. So, we have this pipeline of sorts, that’s been very exciting, to take and validate the findings that our hope that these targets that we’re identifying will represent, again, new therapeutic targets or potential gene therapy targets.

A project that we’ve just recently entered into—again with Dr. Lindquist and Rochet—is very exciting in the world of stem cell research. Most people who are focused on Parkinson’s understand that there’s a lot of hope from stem cell research to replace those dopamine neurons that have died off over the course of aging inside the brains of Parkinson’s patients. One of the hopes is that we can

transplant neurons that have been grown up from a stem cell state, that have been differentiated or coaxed into—if you will—producing dopamine, and take those neurons and transplant them back into a Parkinson’s patient.

One of the problems with taking anything and doing a transplant, as most people know, is that it can be rejected by the immune system. So, taking neurons or something from somebody else and putting it into your brain might not be ideal. But taking them from yourself—where you have your own neurons and they’ve been cultured and made into dopamine neurons—that would be ideal.

So, last year *Science* magazine, actually—the premier journal in all research—selected what would be called the discovery of the year, which was called the reprogramming of cells—the production of what are called induced pluripotent stem cells. That’s a big word for basically saying that we can take adult cells, like skin cells, for example, and reprogram them back into the stem cell type state, and then differentiate them back into whatever we want them to be. In our case we want them to be dopamine neurons.

And several labs in Japan, in Boston, and others, have pioneered this IPS cell technology, and it’s really revolutionizing the ability to generate stem cells without any of the controversies that are associated with embryonic stem cell research. So, this is a very exciting field. And we’ve recently been funded by the Howard Hughes Medical Institute as, again, part of a pipeline, with the Lindquist lab at MIT, and the Rochet lab, and human geneticist [Richard Myers](#) of Boston University, who actually has done a lot of Parkinson patient genotyping, or genetics.

And the most important aspect of this is the lab of [Dr. Rudolph Jaenisch](#) at MIT, at the Whitehead Institute. Dr. Jaenisch is an expert in reprogramming these skin cells into the pluripotent stem cells. What this project is aimed at doing is finding these protective factors that we’ve screened through in yeast, and then

worms, and then validated in the rat system, and putting them back into these reprogrammed stem cells of actual Parkinson's patients themselves—since you can not have that immune rejection problem.

As you might imagine, the cells of a Parkinson's patient have a problem—they cause Parkinson's. So, we have to fortify them, we have to protect them. And the way we can do that is to find these protective factors in worms and yeast, and make those cells a little bit better than they would be normally. And then have them in a state that they wouldn't be rejected by the immune system. And so, that is a new project that we just started this past November, and we're very excited to say we already have some good protective factors we found in yeast and worms, and we're moving them up the pipeline, hopefully toward those pluripotent stem cells eventually.

Ginger: That sounds exciting, because from what little I've read about Parkinson's, it seems like I read when they tried to transplant some dopaminergic cells into Parkinson's patients, the cells usually in the past have then died.

Guy: Right. Or they didn't stop growing—they formed a cancerous-like state. And that trick is still not worked out. It still needs to be done. But the hope is that while that's being figured out we can begin to get these type of fortified cells that would be more useful for patients. One of the sad aspects of Parkinson's disease is that it is degenerative. So, often by the time a patient is showing the clinical symptoms of Parkinson's—the tremor, for example—about 80% of their dopamine neurons have already been lost.

So, most drug discovery right now, including work in our lab, has been focused on halting the death of those remaining 20%, for example—keeping those alive, keeping people alive with those, without replacing that 80% that's lost. That's been where most of the efforts in drug development have been, is at halting the progression of the disease. What's beautiful about the stem cell based projects is

it doesn't have the promise of only halting the disease, it has the promise of curing it forever—of being able to replace those cells and keep people off drugs that they would need to be taking forever. That's the real beauty of this type of approach.

Ginger: What's the most exciting thing that you've discovered? Is there one thing that stands out in your mind?

Guy: Sure. Actually, among the most exciting things we've done recently is used the worm model for identifying neuroprotective factors. I mentioned earlier our lab work on a disease called dystonia. Dystonia is a movement disorder that is classified by different types of abnormal postures, and contortions, and twisting-like clinical symptoms in patients. It could be very mild. It could be as mild as a writer's cramp—that's a form of dystonia, actually. It could be as severe as to put somebody in a wheelchair, where they're bent over and unable to feed themselves, for example, and have a very painful existence.

There are different forms of dystonia³. It's kind an umbrella term. One of the things our lab has been working on is the most severe heritable form of dystonia that affects children, typically at around age 8 or 10 in childhood. It can change their gait and their ability to walk properly or run properly, and it can put them in the wheelchairs. What we've been working on is to understand the protein that causes this most severe form of childhood dystonia. It's a protein called torsin.

Torsin is coded for in all our bodies. We all have normal versions of torsin. People that have dystonia have an abnormal version of torsin that has been inherited from a parent. It's a dominant disease such that if you inherit one copy of the bad torsin gene, you're going to have a chance of getting the disease.

³ http://en.wikipedia.org/wiki/Torsion_dystonia

So, we've been trying to understand what goes wrong inside the cells of patients that have defective torsin. And one of the things we've been able to do in the microscopic worm is to understand what cellular processes might be defective if you, in fact, cause human torsin to be turned on in the worm cells, and look at what might be going on. What we find is that the torsin protein is very critical for regulating how these cells can manage stress—the stresses that are caused by protein damage inside cells, or other types of stress that can cause our neurons, for example, to not function properly.

It was our work on torsin that led to our work on Parkinson's, because we were very interested in what might be the function of normal torsin. We know that when it's defective it causes dystonia. But one of the things we always want to do in understanding disease is find out what's the protein normally doing in us. We found it serves in a protective role against different types of stress, including the type of stress that is associated with protein misfolding, like I mentioned in the example of Parkinson's in alpha-synuclein.

In fact, what led us to the Parkinson's world was that we found that torsin can protect dopamine neurons from dying because it can protect against the misfolding of alpha-synuclein and the aggregation and clumping of that protein. So, we kind of entered the Parkinson's world because of our work on dystonia. But what we had done over that time, while we were working on Parkinson's, was we also started taking worms that had defective torsin in them and had an inability to combat stress responses inside of the worm, and we screened for drugs that would enhance the activity of torsin, specifically, and looked for drugs that could reverse the effects of the mutant protein and compensate for that by enhancing the wild type—the normal gene activity.

Sure enough, we found some drugs that, if you're a worm with a defective torsin or dystonia protein, we could reverse that. We then made a collaboration with a very fine lab at Harvard University—that of [Xandra Breakefield](#), who discovered

the torsin gene, back in 1997. And we asked Xandra if she had any human patient cells that came directly from dystonia patients, and if they had a defect in this response of protein regulation and stress responses. And, sure enough, the drugs that we found in the worm model actually reversed the effect in the human cells.

Then, at the same time, there was a very good mouse researcher at our medical school in Birmingham, who had developed a mouse model of this same form of dystonia, in which he had taken these mice that had aberrant type of movement. They would do a behavioral test where mice would normally walk very rapidly across an elevated beam—mice can just run across these beams very easily—but the mice that had the dystonia mutation could not do that. They would fall off the beam—they'd slip off repeatedly.

Sure enough, the drug that we discovered in the worm model that was validated in the human patient cells also restored the movement to the mice. So, here was a really wonderful validation of the idea that if you take a defective protein that's linked to a human disease, try to get some sort of functional readout inside an organism like a worm, use that readout to define modifiers of that (those modifiers could be either genetic or chemical; in our case they were chemical modifiers, they were drugs) we could then use that system to screen and then validate in higher systems—in mammalian models.

So, we're excited, because this drug that we found (I can't tell you what it is; I'd have to kill you) is something that has been licensed by the pharmaceutical industry. They are interested in now taking them to human clinical trials for dystonia. And we're very excited by that, because dystonia actually is a fairly rare disorder—it's like an orphan disease in that there are not a lot of people that have this form of dystonia.

It's our hope that the molecules we found in our system can be accelerated toward clinical paths. Not only because we've found them now. There's not been

a new drug for dystonia for over 30 years. Currently the main way of trying to correct dystonia in patients is to do brain surgery—deep brain stimulation surgery—which is very risky, and obviously, challenging. And so, we're hopeful that the molecule we found in the worms will be taken through the clinical path toward humans.

What's exciting about it is that the set of molecules we used in our original worm screen were already FDA approved drugs. They're molecules that have been out there, they've been taken by people for years for different purposes. And the molecule that we have is actually something that is fairly well-known, and has been taken for other purposes. So, this is the idea of teaching an old dog a new trick. It's never been used for purposes of neurological disease before, so we're excited about the prospect that this drug can accelerate its way through the clinical trials and FDA approval, because it actually has a lot of information on there.

Ginger: One of the things about your screening system, where you can screen a lot of things through the yeast and then the *C. elegans*, is that that allows you to be pretty liberal in the kinds of things that you can screen.

Guy: That's right. Pretty much no one cares what we do to the worms and yeast cells. So, that allows us to screen a lot. The drawback of these systems is that, for example, the worm has a very thick cuticle on it—a kind of a thick skin to it—and so, lots of drugs may not penetrate that cuticle. So, I like to think in terms that if something works it means something, but if it doesn't work it doesn't mean anything. It could mean that the drug just didn't get to the right place, or it didn't get into the worm.

Ginger: Yes. So, do you have anything else you want to talk about before I ask you a few closing questions?

Guy: Yes. The one neat thing about this drug discovery program that we have going for torsin-related therapeutics—which I should mention has been funded by a pharmaceutical company called [QRX Pharma](#)—is that I mentioned earlier that one of our discoveries that helped us enter the Parkinson’s world is that we’ve found that torsin actually can protect against the degeneration of alpha-synuclein-dependent neuronal degeneration.

So, you might imagine that if you have a drug that may work for enhancing dystonia via a torsin-dependent mechanism, that same drug might work for enhancing torsin for Parkinson’s. So, whereas dystonia is in fact a rare disorder with a limited patient population, Parkinson’s is not. It’s our hope that the molecules we’re identifying that are useful for dystonia could also be potentially useful for Parkinson’s disease.

Currently the Michael J. Fox Foundation is funding enhanced studies with mammalian models of Parkinson’s at [Southern Research Institute](#) in Birmingham, where they’re taking some of the molecules we found for dystonia and seeing if in fact they work in mammalian models of Parkinson’s disease. So, we’re hoping that we have a double whammy here with some of our hits that would be useful for both movement disorders.

Ginger: That’s pretty exciting. (I guess that’s an understatement.)

Guy: We are very excited about it. When we think back to the fact that we really didn’t do our first experiments on Parkinson’s until about six years ago, I think the hope for Parkinson’s disease is tangible. Among the researchers in the field, when you see how rapidly the discoveries are coming around, I do in my heart of hearts believe that this is a disease we’re going to see a cure for in hopefully a decade or less.

I think that the overwhelming evidence that's coming out in terms of the type of cellular mechanisms and pathways that might cause degeneration, and the ways in which we are attacking that through a host of systems, going, again, from yeast all the way to humans, I think that there's just such a very beautiful concerted effort that's going on to hopefully combat the disease.

And foundations like the Fox Foundation, American Parkinson's Disease Foundation, and others, are really doing a wonderful job of funding innovative studies that are going to accelerate the path to a cure. I do think that when you combine that with the hope of things like the stem cell technologies, we will hopefully see a cure in the next few years. But we can never know.

But what's more exciting to me is that lots of these diseases of the nervous system have this common feature that I mentioned earlier of protein misfolding and aggregation. Alzheimer's, for example, involves the misfolding and aggregation of a protein called beta-amyloid. And we have a worm model in which we're looking at that, as well. It causes age-dependent degeneration of worm neurons also, if you take human beta-amyloid.

It's our hope that there are commonalities; that mechanisms that might be involved in understanding how neurons respond to stresses and protein misfolding aggregation, that these basic cellular pathways that are leading to one disease may also impact another disease. And there are really good reasons to think that might be true.

Because sometimes you'll find rare patients that have different types of plaques. They may have Lewi bodies, they might have Alzheimer's plaques, and they might have a bunch of different pathologies that are linked to different diseases. And it leads you to think that there's a common mechanism that could be manipulated to hopefully understand and find cures for multiple diseases. So, it's our hope if you can unlock one, you can maybe begin to get therapeutics for others, too.

Ginger: That's really exciting. So, I guess then I don't have to ask you if you think molecular biology is a good field for students who are interested in neuroscience.

Guy: Absolutely. I think if you're interested in neuroscience, if you're interested in brain science, that learning the tools and the background of molecular biology is essential, almost, these days—combining those tools with things like physiology, and understanding how our neurons fire, how we can measure those things, and combining those with the exciting world of bio-imaging that's occurring with things you can do now in brain imaging.

If I were a new student entering the field of biology, or thinking about medical school, or doing medical research, or something, I think those would be the areas I would get in. I would get in a background of molecular biology where you know how to manipulate the DNA—you can make models of organisms like mice, for example, or worms—and understand these basic processes.

But then I think I would combine that knowledge with areas in physiology and imaging—maybe as you become more senior in your career path toward medical school, or residency, or postdoctoral research—so you can begin to apply those tools that are really more unique to higher systems. That combination, though, of molecular biology and genetics, with those other aspects of physiology, is a very powerful way to approach holistically the problem of what happens inside our brains.

Ginger: Your work demonstrates the reality of modern research, which is that it's becoming very multidisciplinary. Could you talk just briefly about what you see as the special challenges that are involved in doing work across disciplines?

Guy: Well, I think the challenges that come when working across disciplines is really speaking the language of the different disciplines, and organizing thought.

We have projects that are working with ecologists, for example, and trying to understand what type of environmental factors might lead to Parkinson's disease.

The wonderful thing nowadays about doing interdisciplinary research is that we have this thing that we call the Internet—that has beautiful podcasts on it, for example. I speak more often with researchers at Harvard and MIT than I do with people down the hall from me. It's a wonderful way in which people working in different disciplines can connect to each other, and communicate, and share their data very rapidly. Whereas it used to be if you weren't in certain labs on the East Coast or West Coast, or certain places, you couldn't get any kind of research done. We're really so connected now.

The challenge is to be able to convince organizations that these types of interdisciplinary projects are worthwhile. They're usually more risky for funding. There is emphasis on that nowadays; which is good. Those types of projects have a higher failure rate, I'd say, in general. But there is a growing appreciation for the power of combining different model systems, for example, and applying those together in different ways. But, as with everything, the biggest challenge is getting funding.

Ginger: You touched on this briefly, but, any other advice for students who are interested in science?

Guy: My biggest piece of advice to students is really to go where your heart is. Don't force yourself to think that what you think you know is good for you is where you need to be going. I think what you really need to do is go with your gut and feel what really excites you. What is it that you like to listen to? If you like listening to this podcast, for example, that's telling you, well, you may like working in the field of neuroscience. What really excites you could be something very different than what you think at the beginning of college, for example, you might be going into.

And my example is I thought I wanted to enter cancer research, then I wanted to be an oncologist and physician. But it wasn't until I heard about the world of molecular biology and recombinant DNA that I really thought that was a very cool way to pursue a career path. And to this day I still get extremely excited when an undergraduate in my lab may create a new strain of worm, or something. And I'll sit around and say, 'Do you realize you created an organism that never existed before on this planet?' If that can't turn you on, then nothing else can.

I think that's still a very cool thing to do. And that kind of excitement, if you can find that for yourself – I think the process of college is more about discovery. Not only discovering things in a research lab, but discovering who you are. What excites you? What really might be the future that you want to have for yourself? Don't pigeonhole your thoughts into one career path. Just really think of yourself in terms of what am I reading, what have I heard that really gets me excited. And then you'll be good at it. Beyond that you might really find a career path that you deeply enjoy.

Ginger: Thank you. If my listeners want to learn more about your work?

Guy: We have a website for our lab that, again, I share with my lovely wife, Kim. Our website is www.bama.ua.edu/~gcaldwel.

Ginger: And I'll put a link to your lab in the Show Notes, too.

Guy: Great. And you can find us just by searching on the web for my name; or [The Worm Shack](#) is the nickname of our lab.

Ginger: That's actually what I did when I wanted to track you back down, because I remembered when I heard your talk that you put up the little logo for The Worm Shack. So, I actually just Googled 'Worm Shack University of Alabama' and went straight to you.

Guy: Yes. Well, we actually named our lab after a bait and tackle store—which unfortunately no longer exists—here is Tuscaloosa. We were driving by it one day and said, ‘Oh, The Worm Shack. That’s a great place. We should name our lab that.’ And the reason we named our lab that is they had a lot of cool t-shirts that you could buy, and we could give them to people that worked in our lab.

Ginger: Guy, I really appreciate you coming on the show, and I look forward to talking to you again soon.

Guy: It’s my pleasure, Ginger. Thank you for having me. I appreciate it, and wish you the best.

[music]

I want to thank Dr. Guy Caldwell for being on the *Brain Science Podcast*. His enthusiasm for his work is quite contagious, and I think his students at the University of Alabama are lucky to have someone who is committed to both teaching and to research. This is a very rare combination.

I want to remind you that you can find detailed Show Notes, links, and an episode transcript at brainsciencepodcast.com. You can share your ideas at our Discussion Forum at brainscienceforum.com and on our new Facebook fan page. You can also send me email at docartemis@gmail.com.

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Thanks again for listening, and I look forward to talking with you again next month.

[music]

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