THE TRANSMITTER

Timothy Ryan on his pivotal switch from studying particle physics to decoding synaptic transmission

Dissuaded from pursuing theoretical physics and deterred by the "long feedback loop" in experimental physics, the National Academy of Sciences member took inspiration from "polymath" Watt Webb and "visionary" Stephen Smith—and learned to work "completely outside his comfort zone."

1 October 2024 | by BRADY HUGGETT

This transcript has been lightly edited for clarity; it may contain errors due to the transcription process.

[opening theme music]

Brady Huggett
This is "Synaptic." Welcome. You have found our podcast that looks at the people, the research and the challenges of the neuroscience space. You've joined us for Episode 18. My name is Brady Huggett, and I host the show.

[transition music]

OK, today let's go back to 1967. That year, Fermilab, the premier particle physics laboratory of the United States, was founded in Batavia, Illinois, about 35 miles west of Chicago. The goal of the lab was, and is, to expand humankind's understanding of matter, energy, space and time, and it is funded by the Department of Energy. It sits on 6,800 acres, has more than 2,000 employees, and every year more than 4,000 scientists from more than 50 countries visit Fermilab to use its accelerators, detectors, and computing capabilities.

Now, since its inception, about 2,535 people have received their Ph.D.s based on research done at Fermilab, but Timothy Ryan is not one of those people. That's our guest for today, Tim Ryan.

Tim spent time at Fermilab in the early 1980s. He had wanted to pursue theoretical physics, but his instructors at McGill University had eventually advised him against it. He didn't really have the chops for it, as he says on this podcast, so he began contemplating experimental particle physics instead, and part of his thesis work at McGill was spending time at Fermilab.

After his master's degree was done, he enrolled into a Ph.D. program at Cornell, where the faculty expected him to continue to study particle physics, but when he arrived at Cornell, he told them he'd experienced a change of heart. The issue, as he says in this episode, was the long feedback loop in particle physics, the time between starting research and finding out what to do next.

The projects he'd worked on at Fermilab, for instance, had been funded a decade before anything was published, and during his time in Batavia, he had seen the very long time horizon that can be associated with massive collaborations. Now, those, of course, can bring giant payoffs, he said, but he did not think he'd find that time scale enjoyable.

He began to lean toward the neuroscience field. We talked about that on this podcast. We also talked about him studying under Watt Webb, from whom he learned rigor of thinking and accuracy of measurement, and we talked about why he thinks he's currently doing the best science of his life. All of that coming up in the next hour.

I recorded Tim on August 20th, 2024, a very pleasant day in Manhattan, sunny, temperatures in the low 70s. We sat across a table in his office at Weill Cornell. Now, there was an air conditioning vent in the ceiling above us, blowing away. In fact, there was an AC vent on the ceiling in the backup room that we tried, too, and there was no way to turn it off. I've done what I can do to pull that out in post-production, but you can still hear a little wobble in the background.

OK, that should have you set up and ready to go. Here is your "Synaptic" podcast with guest Tim Ryan, starting right now.

[transition music]

OK, let's just see how we do here. The first thing I did want to ask you is, you've been at Weill Cornell, or Cornell, for decades.

Tim Ryan
There's two Cornells. There's the one in Ithaca, which I did do my Ph.D. on that campus, but they're relatively separate from this place. Financially, we're the same-

Brady Huggett
Umbrella?

Tim Ryan
-tip of the pyramid, but after that, they've always wanted to have a closer association with us, but in reality, you can have nothing to do with them if you barely know they exist, or you could decide, "I want to partner with them," so it's not very hands-on.

Brady Huggett
It functions as like a learning capacity for Cornell. It's a learning hospital for Cornell.

Tim Ryan
Yes. I think it started—I don't want to be quoted—over 125 years ago in the 1870s or '80s, because Cornell realized that they couldn't have a teaching hospital in rural New York near Ithaca. There wasn't enough of a population base to sustain that, so that's when they decided they would do it in the city, and it never varied from that.

Brady Huggett
OK, but I know—I think I know—that you were not born in New York. In fact, you may be—and I'm just guessing at this—you may have been born in Canada.

Tim Ryan
I was born in Canada.

Brady Huggett
That's because of McGill. That's why I'm thinking that.

Tim Ryan
Yes.

Brady Huggett
Where were you born?

Tim Ryan
I was born in Ottawa. I grew up in Ottawa for the first 17 years of my life.

Brady Huggett
How is it that your family was there?

Tim Ryan
Both parents emigrated there. My father moved to Canada from Ireland. He was born in- most iconic, he was born in Tipperary and grew up in Limerick and came to graduate school at McGill in, I think, the late '40s, early '50s, just postwar era, to do a Ph.D. in biochemistry. Then my mother was actually born in France but to a Canadian father and an American mother, and her father was a scientist. He was an entomologist working on infestation and biological control, and he spent most of his early career in Europe, and she came over during the war as well.

Brady Huggett
Oh, so she was not also born in Canada?

Tim Ryan
No, born in the south of France.

Brady Huggett
Both your parents were immigrants.

Tim Ryan
Yes.

Brady Huggett
And they met each other—

Tim Ryan
They met each other, I believe, in Ottawa.

Brady Huggett
Do you know how they met?

Tim Ryan
They were both academics. They both were professors. I'm not exactly sure if that was— I think it was true when they met, and I think it was at some—

Brady Huggett
Conference?

Tim Ryan
No, it wasn't. They were, no, different fields. My mother was an English professor. My father was a biochemist, so it was something more ethnic, like some Irish embassy thing that my father got invited to through some other friend. I actually don't remember quite the origin story of how they met, but I know it was at some social event.

Brady Huggett
What was your French mother doing at the ethnic Irish meeting?

Tim Ryan
Although she was born in France and ultimately did her Ph.D. in France, she was born a Canadian citizen too, because her father was actually a Canadian citizen and her mother was American, so she grew up speaking English, but she did happen to learn French completely because of where she was born and then ultimately had an affinity for going back to France.

Brady Huggett
Your parents meet, get married, have children, all in Ottawa?

Tim Ryan
Yes.

Brady Huggett
Do you have siblings?

Tim Ryan
Two.

Brady Huggett
Two?

Tim Ryan
I'm the youngest of three. I have an older brother who's four and a half years older and a sister who's two years older.

Brady Huggett
Sometimes I ask this question about how people get into a life of science, but in this case, it seems clear that you at least knew this sort of thing existed from your father's career.

Tim Ryan
I did. My grandfather was relatively— well, he was a bit of a— I was pretty young, so he loomed large in the sense that he was relatively famous. He had been elected a fellow of the Royal Society. He had sort of prominent positions within this field of biological control, and so science is always something that was talked about. Certainly my brother and I both liked talking about it and had an affinity for it. My brother, being older, sort of paved the way, had chemistry sets first, this kind of thing, and started going to science lectures and things, so it was sort of baked into the way I was growing up.

Brady Huggett
Your grandfather, that was all in Ireland when he was doing this?

Tim Ryan
No, that was my mother's father, and so he did most of his work— he was doing field work in the south of France, which is why my mother was born there and then was working in a lab in Cambridge, England, for a lot of time. He came here only after the war. He moved to Ottawa, actually, to take a job— I think it was in a government association of dealing with biological control and infestation problems.

Brady Huggett
Your mother's father was a scientist?

Tim Ryan
Yes.

Brady Huggett
Your father's a scientist?

Tim Ryan
Yes.

Brady Huggett
In that way, your mother married her father?

Tim Ryan
I suppose you could say that. [laughs]

Brady Huggett
Did she ever say that?

Tim Ryan
No.

Brady Huggett
No? With both your parents, I guess more on your father's side, was there a tie to Ireland for you? Were you going back to see family?

Tim Ryan
Not very often. I was born in 1961, so travel was a little less common than it is now. It sort of was a wealth separator, basically. Now everyone travels, but then it was only if you had means. We did go over as a family once when I was very young. I went back again just finishing college with a backpack. Then I've only been back once since, which was last summer. I was at a conference in Dublin.

Brady Huggett
Sometimes people have this like strong tie to that country. They go back a lot. That's not been your-

Tim Ryan
No. I feel tied to it only because I can imitate and understand Irish accent. I'm not fooled by Irish accents in the sense that I can

understand them instantly. It must be, my father had a slight brogue that I didn't ever realize, but it sort of— my brain became wired this way. I always enjoy meeting Irish people because it just makes me— I'm very familiar with it.

Brady Huggett
It feels like family.

Tim Ryan
It does, yes.

Brady Huggett
You have an older brother who's into science for sure, chemistry sets, etc., and so you're just sort of following along, doing those same things as your brother's doing?

Tim Ryan
Yes. I think one was always excited by— we were all always excited, it seems, about learning ideas about how things worked in the world and what the principles were behind it. That's still true today. I guess I was one of these people that pretty early on got a sense of how exciting the process of discovery was and appreciated that, learning about big discoveries, period. Even personally, just when you hear about them and you understand something, that's kind of your own discovery. Even if you're not making the discovery, it's your own discovery of something you didn't understand before; I always found very satisfying.

Brady Huggett
Right, so even if you didn't make the discovery, but you learn about, it sort of lives in you as a new discovery.

Tim Ryan
Yes.

Brady Huggett
I never really thought of it that way. Every time someone comes across that, it's a new discovery again for that person. Now, your mother, with the English history, were you getting that side growing up as well?

Tim Ryan
Yes, always appreciated. She was a comparative literature professor, so there was always an appreciation for the humanities, but I would say the science sort of dominated in what we ended up thinking about.

Brady Huggett
She wasn't reading literature before bed or anything like that?

Tim Ryan
No.

Brady Huggett
No? It was all science? [laughter] Did you have other interests growing up? Did you think you wanted to be a scientist or just, that's like the family tree?

Tim Ryan
The only thing I ever entertained— and I found architecture fascinating, probably from purely the aesthetics. I realized I enjoyed certain forms of buildings and things and reading about it, but I don't think I ever had any what I felt was an essential talent you probably needed for that, which was artistic skills. It sort of never came to me naturally, but that was the only other thing I sort of always entertained as something I found really quite appealing. It wasn't so much intellectually appealing as aesthetically pleasing.

Brady Huggett
It didn't ping your curiosity in the same way? How was that building made or how is it—?

Tim Ryan
No, not till much later. After I began to appreciate physics and engineering, then it suddenly dawned on me, "Oh, this is actually interesting. Why does this bridge stand up?"

Brady Huggett
Right. That's right, for hundreds of years or less. Anyway, you're moving through high school. Did you do well in sciences in high school?

Tim Ryan
I did, yes. My parents ended up sending me to a French— so I grew up mostly speaking French in school, English at home, but it was a 100 percent immersion French school for 10 years. I did that for sort of grade 1 through 10.

Mostly, my parents as new immigrants weren't thrilled with what they were sampling with my siblings in the local educational system. They'd heard about this school that was essentially following the French government's curriculum for education. It had teachers imported from France. It was really a French *lycée*. We were sort of guinea pigs. My brother was really a guinea pig. He went to the school when it had two years of classes, and they just added a year every year as they moved up. I went in the first layer of expansion, where they sort of doubled the size at two grade ones coming in.

It was an interesting challenge because I distinctly remember the first day of class. They refused to speak English. I don't think they spoke much English, but they certainly refused to do it. I spoke no French, so the first six months, or three months probably, it was just like, you had to figure it out, but 6-year-old brains can do this.

Brady Huggett
Right, so I guess you wouldn't start someone— well, I guess you could, but like in eighth grade, it had to be really young just to drop you in like that. That's also what your brother did?

Tim Ryan
Yes.

Brady Huggett
But you're the third child.

Tim Ryan
Yes, and they did not do it, for reasons that were never clear to me, to my sister. They kept her in a different track in a public school, or actually a parochial school, I think she was in. They kept her in that for a fairly long time. With me, I only ever tried the one school. They've just had me in this— and it was interesting because certainly, you learned much a different view of the world because it was all people from another country teaching you. For example, our history curriculum in ninth grade was the French Revolution, nothing else. [laughs]

Brady Huggett
That's it?

Tim Ryan
That's it.

Brady Huggett
All year?

Tim Ryan
All year.

Brady Huggett
Wow.

Tim Ryan
You definitely have a different perspective. We actually had a separate history class for history of Canada because they felt

like, “Oh, it’s important, we are in this country, we’ll learn the history.” It was actually taught by a separate person, and it was a separate actual class. It was good.

Brady Huggett
These were not French Canadians? These were from France?

Tim Ryan
No, these were French. The school had a mixture of a small number of people like myself, which would be called anglophone, native English speakers. I would say the majority were French Canadian families. Then because Ottawa is a capital, it hosts a lot of embassies, so people associated with French-speaking country embassies-

Brady Huggett
Would send their kids.

Tim Ryan
-which there are plenty, would send their kids there.

Brady Huggett
In that way, it’s to keep French alive in their kids who are— it’s otherwise an English-speaking country, right?

Tim Ryan
Exactly, although it’s officially a bilingual country.

Brady Huggett
Every province is that way?

Tim Ryan
Yes, federally, officially a bilingual country, but Ottawa being the capital and right on the border of Ontario and Quebec, and Quebec is-

Brady Huggett
Quebec, of course, right.

Tim Ryan
-very French. It’s more French than most cities that aren’t French cities.

Brady Huggett
This first three months or so— obviously, you still remember this, just like, I didn’t catch anything today, going home the next day, I didn’t really understand that. Eventually it starts to sink in.

Tim Ryan
Yes, I don’t actually really remember how I got through it. I do remember on the first day, there was another anglophone classmate, a 6-year-old girl who just stood up and cried the whole time. [laughs]

Brady Huggett
Oh, man.

Tim Ryan
Eventually, I’m sure it was much faster than by Christmas. It must’ve been a relatively quick thing where you pick it up. I’m not the first experiment that this was done on me. [laughs]

Brady Huggett
I guess because they’re also teaching you things like the alphabet in first grade. Maybe that’s perfect for learning a language anyway. Do you still speak French?

Tim Ryan
I do. I do. It's interesting when I— I'm very comfortable speaking French, although what you lose is vocabulary that you don't use anymore. Another fascinating thing about the brain is when I go to France and if I'm there for just a few days or more, suddenly words start coming back to me that I'd forgotten. They're like, "Oh, I know that word." I won't even be thinking about it. They just somehow unlock this special part of my brain and now it's accessible again, whereas right now, I might struggle to think of the word for monkey wrench.

Brady Huggett
Have you looked at that at all in your work?

Tim Ryan
No, I have not.

Brady Huggett
That's fascinating though, right?

Tim Ryan
I do find it fascinating. There's many features like this about— shows you how humbled we are about the brain, about these fundamental things that we don't understand.

Another example— I find it motivating. It's not the scale that I work on, but if you learn to play an instrument at all as a kid, maybe you do it like- I took piano, like many, for five or six years and then got too busy, but I could still— somehow, if I sat down at a piano for more than 10 minutes, suddenly— I remember this happened to me as an adult where I sort of tried to play again a little bit more regularly. Suddenly, like this is if someone downloaded a program and I was playing this like I didn't know where this came from. There was some stored muscle memory, but from decades ago, that I unlocked.

Brady Huggett
It almost feels like everything in your life is in there someplace, but we just can't access it.

Tim Ryan
Right, yes, exactly. I find it humbling that there's a lot to understand about the brain, but that being said, my work doesn't try to approach that problem.

Brady Huggett
You're finishing this, so for 12 years—

Tim Ryan
I actually only did 10. The school was accelerated as well, not on purpose. They just ended up being accelerated and I left after 10th grade and went to university.

Brady Huggett
At 16?

Tim Ryan
Yes.

Brady Huggett
The whole thing was French immersion?

Tim Ryan
Yes.

Brady Huggett
Then you went to McGill?

Tim Ryan
Actually, I did one year at the local University of Ottawa. That was already my first instruction in English other than an English class. There it was mixed. I had both because it was a bilingual university. I had some of it in French, some in English. I did that for one year and then I decided to transfer to McGill.

Brady Huggett
This first year where it's just English, did you find that odd?

Tim Ryan
No, it wasn't.

Brady Huggett
No problem?

Tim Ryan
It was my native language, [laughter] so there was no problem.

Brady Huggett
Can you tell me why you started at that school and then transferred? Were you aiming for McGill?

Tim Ryan
I don't know. It's a good question. I found it pretty easy even though I had jumped in fairly young.

Brady Huggett
Was that part of it? It was the reason you didn't go for McGill is you're like, "I'm only 16"?

Tim Ryan
No, I didn't even think of it then. I think it was purely social. The school was accelerated and a handful of us, my friends— I wouldn't have done it if I didn't have peers doing it, I'm sure, at 16. A bunch of us left all at the same time, realized that this university would let us in because the school was on a faster pace. There were a handful of us, six or seven, that all went into the same first year at the same time. I wouldn't have done it, I think, without sort of peer support. I wasn't thinking of, at 16, going off to another city.

After a year, yes, I found it was— it was interesting. My brother had gone to that school for four years. He was in his senior year when I was beginning, I guess, or something, so I was— I don't know. Somehow, my eyes began to open up, and I thought maybe it'd be interesting to go somewhere else.

Brady Huggett
This French school— back to this, it was not designed to end at 16.

Tim Ryan
No, no. It had two more years.

Brady Huggett
Oh, but at 16, you realized you'd learned enough to be on a college track, or you obviously have someone—

Tim Ryan
I knew I could get into college because—

Brady Huggett
Your friends were doing it.

Tim Ryan
Yes. It had happened a year before, not nearly as many, but the floodgates open. It's like, "Oh, yes, we have learned enough to basically, we could skip two right away.

Brady Huggett
Huh. I'm not sure I would have wanted to do that at 16.

Tim Ryan
It's a good question. As I said, I wouldn't have done it without peers doing it, so in some ways, it didn't feel quite as foreign. I still lived at home, so it wasn't the real college experience. The other thing in Canada, the college experience didn't use to be the same as I've come to learn it is here, which is, it's such a big thing in the American culture, the college experience. It's been advertised, movies are made, so so much focus is made on, "Oh, you want to optimize this thing. The peak of your life might happen there."

Brady Huggett
Right. You're away from your parents, you're still young, you're living in a dorm with other people, they might be crazy, whatever, like a party scene.

Tim Ryan
But in Canada, most people simply go to the college in the town they live in, and you typically don't. When I went to McGill, all of my classmates lived at home, practically. They were all Montrealers.

Brady Huggett
There's not that—

Tim Ryan
I did live in a dorm. There obviously were dorms because there were people that came from all over the world and all over Canada, but mostly the schools tended to rely on local populations.

Brady Huggett
At 17 you decide it's not that the school that you're at was poor or anything like that.

Tim Ryan
No, no, no.

Brady Huggett
You thought, "I'm not being challenged enough. I want to go to McGill."

Tim Ryan
It was a mixture of things I somehow— my father had done his Ph.D. there. I sort of knew about Montreal. I don't know, sometime I got a bee in my bonnet one day, and I wrote for the booklet, which there was no online presence then, and I got sent a course catalog. That's what you looked at. I was like, "Oh, look at these exciting classes." I decided, "Oh, this might be— " and I talked to my parents, and they were very both quite supportive of it. They thought, obviously, he had come and gone to McGill and thought highly of it, so they didn't see any reason that this would be a problem.

Brady Huggett
You probably will not remember this, but do you know what courses you saw that you thought, "Oh, I want to take that?"

Tim Ryan
I went straight into honors physics. McGill adhered a little bit more closely to the British educational system of being highly focused. They assume that when you were a high school student, you got a well-rounded education, and then by the time you got to college, you focused. I would say in America, especially at liberal arts colleges, it's meant to be broad right through— or Columbia or Chicago, there's very core curriculum type of things. This was not— I just saw this exciting-looking challenging program in physics, so that's what got my eye.

Brady Huggett
OK, so actually, I saw this in some of your background that you did study physics first.

Tim Ryan
Yes.

Brady Huggett
In the classic sense?

Tim Ryan
In the classic sense.

Brady Huggett
That was the main thing that you were curious about. How do things work? What is force? What is mass? How does—

Tim Ryan
Everything, and you sort of get this— the people that I found that are attracted to physics, they're really trying to understand how things work, and then you realize that you can get more and more fundamental with it. It'd start out with sort of Newtonian things, which we figured out in the 17th century. Then you learn about electricity, magnetism from the 18th century, and then slowly— then this next— like the quantum era, which, even though it was the beginning of the 20th century, was still quite modern feeling, because it's how devices work and lasers and all these things. It definitely felt like this was the frontier, and I felt like, "That's where all the exciting discoveries are going to happen."

Brady Huggett
This is fascinating. All right, so you finished your undergrad at McGill.

Tim Ryan
Yes.

Brady Huggett
I think you stayed for a master's in physics, too, right?

Tim Ryan
I did. I did.

Brady Huggett
What area physics were you looking at specifically?

Tim Ryan
There, I worked in high-energy particle physics. In all honesty, when you're an undergraduate in physics, you become good at doing problem sets. That's how you learn, right? You're given a lot of homework, a lot of problems, fair amount of math, and you solve these more and more challenging problems. That's what you know, so you've sort of had this impression like, "This is physics, it's like doing this kind of more theoretical work." I thought that's what I wanted to do is to try and do theoretical physics, only really to come to the harsh realization that I didn't really have the chops to make it in theoretical physics. Very few do. I mean, plenty do, but I was not one of them.

I still love physics, so I thought, "Oh, this is still a fundamental area," so I joined a group that was in experimental particle physics. That was a circle where those— it was interesting because I got to experience other things, though, even at that time, particle physics only happened at large centers. It's much smaller scale than today, but it was still large scale compared to anything that existed. The groups might have been 25 to 40 people from all over the room—the world, sorry—that came to work together. There were different universities, and different universities were sort of in charge of different aspects of the experiment, so I just got tacked on as a master's student as a helper.

Brady Huggett
I see. OK. At that point, especially when you're chasing this master's, what did you think your career might be?

Tim Ryan
I probably assumed I would head towards academic physics.

Brady Huggett
But not on a theoretical side.

Tim Ryan
No. Then once I sort of came to this disappointing acceptance that was, I was not cut out for doing theoretical physics as a profession, I would explore whether I was cut out for doing experimental physics. [laughs]

Brady Huggett
Was there one moment where, I don't know, you went into a course, and you took your first test, and you thought, "Whoa, this is beyond me"? How did you know that you were not cut out to be a theoretical physicist?

Tim Ryan
I went to talk to faculty, and they made it clear. It was very tough.

Brady Huggett
You said, "I'm thinking about this for a career," and they said, "You should think about something else, Tim"?

Tim Ryan
Yes. I don't remember the exact words, but it was more or less along that line.

Brady Huggett
Yes, that does sound—

Tim Ryan
I give them full respect. They did what they were supposed to.

Brady Huggett
Right. Did they push you in any new angle, like you might be good at—

Tim Ryan
No, they didn't. It wasn't a counseling session. [laughter]

Brady Huggett
It's more direct than that. OK, so then you get your master's in McGill, and then you have to make some decisions, right?

Tim Ryan
An important part of McGill's— during that time, I was doing my thesis work there, but because it was work in an international group, the center of the work was actually at Fermilab in Batavia, Illinois, which was, at the time, the center of particle physics in the United States. The only counterpart was CERN in Switzerland. It was sort of exciting because now it's a national lab. It's thousands of physicists gathered from all over the world, you're surrounded by these big machines.

That part was very exciting to get to get a flavor of this, even though the part we're playing is really a tiny cog and something. I also even got to go to SLAC, the Stanford Linear Accelerator, connected to the Stanford campus, right under 280. That was also exciting because I got to sample it there. Mostly what I took away from this is that I still like particle physics. And I thought, "I will try and continue in this," but one thing I don't want to do is have to live in Batavia, Illinois, [laughs] because it really was isolated. For students, it's exciting in lots of ways, but not in lots of many other ways. I said, "I only want to go to a place where I could do this on campus."

Brady Huggett
You were probably 20 at that point.

Tim Ryan
Yes.

Brady Huggett
I understand, yes.

Tim Ryan
That sort of narrowed down what my choices would be going for the next stage. One of the places I applied was Cornell, because they had their own synchrotron. I said, "Well, I'll look at only places that where you could do it locally," and that narrowed down to Stanford or Cornell, basically, where those would be viable. I chose to go to Cornell, but by the time I got there, I'd also changed my mind about particle physics.

Brady Huggett
All right, that's what I want to get at. You enroll in this Ph.D. program, I think, right?

Tim Ryan
Yes.

Brady Huggett
You got a master's, another master's, but you were there for the Ph.D. program.

Tim Ryan
At Cornell, yes.

Brady Huggett
Yes, at Cornell, right. You went in thinking that, OK, I'm not going to be a particle physicist?

Tim Ryan
Yes, by the time I got there, but when you apply, I was still thinking— it must've been fall of the previous year. I was thinking it was what I want to do, but now come spring, when a letter, I opened a letter, I've been accepted, and I decide, "OK, I'll go there," I was immediately assigned some person in particle physics as my graduate adviser, but as soon as I got there, I made it clear I sort of had a change of heart. They're very open. It's a graduate program. It's a big graduate program. There were 40— I had 45 classmates all going into a Ph.D. in physics.

But the other thing, it was a bit of a safety valve. The reason I didn't go in completely blinded, I noticed that Cornell did have a pretty rich spectrum of physics going on across the board, so not only did it have its own particle physics thing where some of it was local, but it also had strengths in many other areas, so that's why I felt, "I'll find something."

Brady Huggett
Between that fall and the spring, what happened where you decided, "No, that's not going to be my focus"?

Tim Ryan
I realized one thing I was missing— and I probably had not yet experienced it truthfully in any scientific endeavor, but I felt like the feedback loop between working and finding a result and then making a decision about what to do next, that was a 10-year time span in particle physics. The project I worked on, the grant proposal was put in— let's just say it was 1977, and that team was funded worldwide, a team assembled. I participated for a couple years right in the middle. The big papers that came out of that were published in 1987, so it was a very long time horizon to pull off these sort of scales of work.

That's still true, and there can be giant payoffs, incredible discoveries. I still follow it, I still find it fascinating, but to me, that time scale was too slow for any satisfactory feedback loop that I figure something out, and it's like, "Ah, this is what we'll try next." That was missing for me, which I find that a little bit too frustrating, that it was a bit more like, I have a job to play, it's kind of an engineering role, like we're going to be analyzing this, and it'll be plugged in places, and I just realized that I wouldn't find that enjoyable.

Brady Huggett
When you say "feedback loop," do you mean that you would do your work, and because you're this cog in this mighty machine, you wouldn't know if the work was good? You wouldn't get feedback saying, "That's a great job, Tim, keep going," or you're saying that when you started to get results, it would take you 10 years before you'd know what the next step was?

Tim Ryan
It was more that, yes.

Brady Huggett
It's almost like the impatience of it, of having to do a 10-year project.

Tim Ryan
Some people luckily have the patience for it, because it's still a very important endeavor about understanding the world we live in, but that was another way I realized I wasn't cut out for it for other reasons.

Brady Huggett
Then I think your adviser for this program ends up being Watt Webb?

Tim Ryan
Yes.

Brady Huggett
OK, so did you identify him?

Tim Ryan
Pretty early on, yes. He was a bit of a polymath. He had worked in all kinds of areas of physics. It's funny, I had a taste, very indirect. I had took almost no biology. I took one required class at McGill. I hated it.

Brady Huggett
Why?

Tim Ryan
I felt it was everything I didn't like about science. What I liked about science was like— the work of doing problem sets was figuring something out. The biology, really, at the introductory level, was, "This is how things work. This is the way we understand it now, and you are going to be tested on whether or not you know what we know.

Brady Huggett
Whether you've ingested this and retained it.

Tim Ryan
Yes. It's the only time I ever took a multiple-choice exam.

Brady Huggett
Oh, really?

Tim Ryan
Yes.

Brady Huggett
Oh, wow. That's so funny. You said earlier that you had this curiosity about the way things work. Biology does feed into that. Here's the way your body works—

Tim Ryan
Absolutely. I was extremely curious and very ignorant because I didn't really take it for very much. It was also a survey, broad, broad biology class which covered all—

Brady Huggett
A hundred students in the class kind of—

Tim Ryan
Hundreds, and it covered botany too, everything, so I really did not get very much out of it. There were interesting things, but I was sort of too embedded in something else. I had friends doing— actually, I had a friend working more closer to neuroscience, and I would just learn about it from him, and I realized, oh, it's fascinating things. The way a lot of people are attracted to neuroscience because of psychology.

Brady Huggett
Yes, or the brain.

Tim Ryan
We're all curious about how we work, so I found this fascinating. Webb had nothing extremely direct at the time, but he had written some things showing some interest in these problems and why studying these very fundamental things might have impact on it. The first time I went to talk to him was a little bit because of that, just because something he had written in one paper or something on some blurb about his lab caught my attention.

Brady Huggett
You're saying he was also sort of multidisciplinary in that way?

Tim Ryan
Yes.

Brady Huggett
He had some physics, obviously. He also had some biology in there.

Tim Ryan
At the time he was chairman of applied and engineering physics. He had his own very interesting route into that role, but he had made many sort of— as a master developing and applying, sort of, advanced techniques of how to analyze data from— really, that ended up being important in both chemistry and biology, even though it was really because he was a physicist that he could do it.

I used to call it applied statistical mechanics because he was really very adept at looking at statistical systems and ensembles and seeing how you could extract new information with novel kinds of measurements. It turns out that ended up being a really useful thing for biology, eventually. He had sort of marched through and some of the times he thought, "Well, we can make an impact on this biological problem," so he would go into it, both feet.

Brady Huggett
When you came to him and said, "I'm thinking about maybe— can I work with you? I came for this program, but I want to focus on something different," you didn't have any bio other than this one course. Was that a problem, or what did he say?

Tim Ryan
No, he was pretty used to this background coming in, being in a physics— and half his students were either getting their Ph.D.s in applied physics, or half of them were getting them in straight physics, so it wasn't unusual. He just says, "Oh, if you're interested in this, I suggest you take this class or audit this class," and they would be outside of physics.

Brady Huggett
What did you learn working with him? This feels like the big shift in your career.

Tim Ryan
It was the big shift, yes.

Brady Huggett
What was he showing you? When did you start to think, "OK, I'm really going to start to focus on straight neuroscience"?

Tim Ryan
It wasn't that time because I did not do that while I was a Ph.D. student. Although I worked on things that were sort of biological problems, it was really still using a lot of physics to study things. What I really learned from him was rigor of thinking and accuracy of measurement. I remember lots of these. He was very challenging. He would challenge your thinking. You would try and explain something to him, and he would find all the flaws that you didn't realize you weren't thinking about this rigorously.

He could be a bit scary. He was, but for some, quite a scary personality, I suppose, but that was a real trial by fire in some ways. That's when I really began to appreciate— I realized that he was complaining— we had not measured something well enough, and I didn't see the relevance of it. I really thought like, "Why waste my time?" and he was adamant. Probably a year later, I realized, oh yes-

Brady Huggett
He was right.

Tim Ryan
-he knew what he was talking about. We should have made that much— right. It's part of the practice of becoming a scientist in lots of ways. There's probably a thousand versions of this arc.

Brady Huggett
When you say he was scary, meaning that he would just approach you and say, "That's wrong, do it this way," and some students did not appreciate that-

Tim Ryan
He didn't hold back.

Brady Huggett
But you didn't have a problem with that?

Tim Ryan
No. I guess I had a tough enough skin at the time. There was a full spectrum of personalities in physics. There were 45 students who were accepted in, which is a pretty large graduate class. Sure, they're not that size anymore. I remember, I think 30 of us probably felt that they had— because it was 50 percent larger than normal. I think at least three-quarters of us thought that we were in the 50 percent extra that they didn't normally let in. [laughter]

Brady Huggett
You're like, "I'm the weak link. We're the weak link." You stayed there, I think, five years or something in the Ph.D. program. Then you did a postdoc.

Tim Ryan
Yes. So—

Brady Huggett
Go ahead.

Tim Ryan
Right, so it was during that period I began to get a little bit more exposure to biological sciences and what the problems were. Even then, though, there was— I'll tell you that there was a memorial symposium for Watt Webb. He passed away a handful of years—

Brady Huggett
Yes, in 2020 or something.

Tim Ryan
Yes, and two years ago, there was a memorial symposium in Ithaca that I was invited to and I spoke at and was seeing a bunch of people. I remember it because he had a very long career covering all kinds of things. I remember advertising the reason I chose even what I work on today, the origin was a paper he handed to us all, probably a paper from around 1982. It was actually an internal preprint. There was no preprint servers, even for physics then. It was from Bell Labs, and it was from a former student of his who became a very famous neuroscientist, David Tank. He had just sent along some papers that they were working on, and it was a purely theoretical paper about neural networks, and it was from Tank and a guy named John Hopfield. It was sort of foundational paper. I read this, and I was transformed because it was so simple. What the paper ultimately showed was that you could wire up a set of op-amps in some ways and give them really simple properties, and all

that mattered is like if you— the weights of how well the output of one op-amp influenced the input of another one would be predictive of certain properties of the network that could be used to do useful computations.

They built devices like this, and this was the Hopfield network, and the parameters that you could tune were the synaptic weights. That's what I realized, oh, synapses. I sort of went whole- I bought- I said, synapses are probably the be-all and end-all of ultimately controlling what you can do with the brain. Even though I didn't work on them in the least bit as a graduate student, the seed was planted then really like, "Oh, this is a piece of biology that's going to be fundamental to understanding in neuroscience.

Brady Huggett
Well, you were right about that for sure.

Tim Ryan
Basically, that's when I left to do a postdoc then at Stanford, that's when I decided to jump in, and I wanted to work on synapses.

Brady Huggett
Right. Then your postdoc is like cellular and molecular physiology or something.

Tim Ryan
Yes.

Brady Huggett
When I was looking at your background, I thought this was the big shift for you. You're saying, no, actually, maybe the Ph.D. with Watt Webb was.

Tim Ryan
I became sensitized during the Ph.D., but it's true. The real shift was then I had to go outside of my comfort zone completely. I joined a lab not really knowing what I was going to do. I happened to join a lab that also wasn't giving tons of direction, for better or worse, but mostly discussing ideas. I came up with some things that were interesting. Truthfully, they weren't related to synapse. I was sort of holding off until I saw that opportunity and basically fussed around for the first year or so and then landed upon something where I could use my skills, and it turns out I could work on synapses.

That was the turning point. Probably 1992 even was roughly when that happened.

Brady Huggett
This was with Stephen Smith?

Tim Ryan
Yes.

Brady Huggett
Was he not giving direction? It was a free-flowing lab?

Tim Ryan
It was pretty free-flowing. Stephen is honestly a visionary person, but because he's wired this way, he gets extremely enthusiastic about fundamental ideas that he likes, and he tends to spread himself around these areas. For him, it's been a very satisfying career to move from exciting thing to exciting thing and seeing what they can contribute. For the people that train with them, it depends on how it goes. With mine, it wasn't really— the thing that I ended up locking on, I have to say, was not really directed by Stephen. He was fully supportive.

Stephen can tell when something— I remember when I was working with someone who actually had come on sabbatical to Stanford, and it was a well-established scientist, and we ended up working on this. It was a technique to use fluorescent dyes to label synapses. It's not the very first time, but one of the first times. I realized we could exploit this and learn lots of new things. I remember once we had a dataset analyzed, and it was over Christmas this year, and I was showing Stephen it.

Stephen, he nailed it because what he said was, this is going to change what you do. He could see this was going to be a big deal, and this is going to change what you do.

Brady Huggett
What part was going to change it? The ability?

Tim Ryan
Just when he saw the potential that we tapped into, being able to visualize synapses and study their properties in ways that had never been done before.

Brady Huggett
By using dye?

Tim Ryan
By using just dyes. He said, this is going to change how you're going to do things and how many people will do things. He sort of had this inkling that was, and he's right.

Brady Huggett
Yes, he was right. Yes. OK. I think, now tell me if I'm wrong, but it's '97 you finished that or something?

Tim Ryan
Yes.

Brady Huggett
Then it was time to get, like, a job.

Tim Ryan
Yes, time to get a job.

Brady Huggett
Then you came here. Yes. This was like an assistant professor or something.

Tim Ryan
Assistant professor, yes. In a brand-new department that was being rejuvenated because it had essentially mostly died off. A new chairman had been hired, who was someone who I had met. His name is Fred Maxfield. He's still here. He's no longer the chairman. It's funny how close these circles are. When I was a graduate student, Watt Webb had applied for major funding from the government to make his lab a national resource center, amazingly with the goal of not providing a service to anybody, but just to fund the discoveries that his lab is good at doing.

He convinced people to do this. One of the site visitors to come and review this was Stephen Smith. Another one was Fred Maxfield. They were both there. Of course, this was a session where the students, a handful of students, are giving talks to this panel of experts about this is what Watt Webb's lab does. Right? It's odd that I realized that there were two people that changed the course of my career that were both there to show you, well, you never know who's going to be listening.

Brady Huggett
Yes. Did you talk at that?

Tim Ryan
I did.

Brady Huggett
It must have gone well, then.

Tim Ryan
They got the center? Well.

Brady Huggett
Yes. OK. When you come here, not long after, in 2000, you win the McKnight Technological Innovations in Neuroscience Award, right?

Tim Ryan
Yes.

Brady Huggett
This was for, I think, what you're just talking about, ways to better monitor what's happening at the CIPS.

Tim Ryan
Yes.

Brady Huggett
I had not heard of that award, honestly, until I saw that you won it. What did that do for your career, other than some funding, obviously?

Tim Ryan
Yes. The funding was probably less important, honestly, because it's still in early phase where I'm living off startup funds. Honestly, in that era, also, I had managed to get an NIH grant, the first crack. I was sort of off and running. These are more what it's joked about as the Young Turk Awards, like you want to try and get into these networks of people. It was before networks were known to be truly a thing that all these places want to build on purpose for young people.

Brady Huggett
You mean universities, academic centers?

Tim Ryan
Universities, funding like Simons, Chan Zuckerberg, they're all about making these networks for the benefit of science. You realize when you get this, you go to their meeting, you're meeting sort of the who's who of people in science. You get to hear about interesting ideas. Yes.

Brady Huggett
Then you win it again 10 years later.

Tim Ryan
Yes.

Brady Huggett
I know that data is a little like, we're using data a little bit too much maybe in reporting, or certainly maybe sports reporting, but you're the first person to ever win that twice.

Tim Ryan
Probably, yes.

Brady Huggett
At the time, that was true. Maybe it's still true. I don't know.

Tim Ryan
No, the board doesn't even exist anymore.

Brady Huggett
Oh, so the doors closed on that. You're the only one. This time it was to look at ATP.

Tim Ryan
Yes.

Brady Huggett
You were going to use luciferase, I think, for this, which comes from fireflies.

Tim Ryan
Yes.

Brady Huggett
I don't know if you bioengineered that, or is that naturally the way that, so luciferase lights up when it is in contact with ATP in the firefly itself, or did you have to bioengineer it?

Tim Ryan
We didn't have, it wasn't that heroic. I'll give you a bit of the background. Truthfully, the idea for ATP was not well grounded in the sense that literally was the feeling, this might be a cool thing to measure. This is my roots of Watt Webb:You don't necessarily know what you're going to learn. The motive is, let's figure out how to make a better measurement, then we'll see. Because the history of physics has taught us that the basis of discovery is in better measurements. That's sort of rooted in me. It's what I breathe.

I believe this is always something that's going to be useful, if you do it well. If you do it sloppily, you won't learn much. That was always, and I was thinking about it, I was like, "Oh, I wonder," and I knew luciferase was a tool that had been used because in a test tube, all it takes is ATP and a small molecule called luciferin, and it glows. It had been used as a reporter gene in a variety of systems because you can make things glow like this. No one had really tried to use it in a quantitative way. I reasoned, "Oh, maybe we could stick this into synapses and watch them glow and figure out a clever way to calibrate it so we could tell how much ATP was there to drive this reaction."

Brady Huggett
It was known that ATP was there at the synapse.

Tim Ryan
Yes.

Brady Huggett
What you wanted to do was to figure out exactly how much, when it was used, etc., like better monitoring for what was happening there?

Tim Ryan
Yes, that's exactly right.

Brady Huggett
I think what happens is this paper that comes out in *Cell* in 2014, that shows not only is ATP present, but it is locally synthesized, right?

Tim Ryan
Yes, that's right.

Brady Huggett
That I think was a first.

Tim Ryan
I think so, yes.

Brady Huggett
To me, I read the paper and I was like, that's super, super interesting. I'd never considered it, but like once you read it, you're like, of course.

Tim Ryan
Yes, no, I think that there was certainly an appreciation that all cells, in some ways, the definition of a living cell is a cell that

can make ATP. Because that's what sustains the life of the cell. Maybe it's circular in the end how you want to define a living cell. Neurons, for sure, have to make, all living things make ATP. I think what is often not appreciated about the architecture, I like to think of neurons, they're very specialized because I think of them as a sort of biology at the extreme because there's no bigger cell in our body really than, maybe exceptions, but individual neurons can cover enormous distance scales.

It's now known even in a mouse brain, forget about the spinal cord, a single axon might cover tens of centimeters, even in the cortex, even much more than the linear dimension of the mouse. Everything is happening very far away. Our classical biochemistry has all come from studying sort of muscle, the muscle, the biochemistry of ATP synthesis. A lot of it came from studying pigeon muscle. This is not nearly as, it's got its own complexities and architecture, but it's all relatively compact. It's full of all this machinery.

Neurons have this other problem with like, they have to ship things really far away. The rules are going to be interesting and different and create different opportunities and vulnerabilities. I also find that interesting. Another reason why making measurements of things out there, we might learn things that were not expected.

Brady Huggett
First off, I just want to say, you were talking earlier about how when a discovery happens, then you learn about the discovery. When I read that paper, I was like, "Oh, it never occurred to me." I think I was like telling my wife about it, right? Because it has a sense of discovery. I just figured out what's happening and why ATP is necessary. I thought it was just a fascinating paper. That, I think, seems to have set your career on a new trajectory. For sure. Can you tell me what that meant? It's still, I think, your most cited paper, number one. Yes.

Tim Ryan
Having an impactful paper probably makes people think, give you more of the benefit of the doubt when it comes to—

Brady Huggett
On your next paper?

Tim Ryan
Your next paper, or scoring a grant or these kinds of things. Those are tangible things that you're not in the room when it happens, when they make decisions. It got appreciation. Certainly, that's true. It's nice. Our egos all like being validated. There's no question. We're all human. What it did was open up a door to new, interesting questions. Because knowing that it was important, it had to be made locally, then said, well, how does that all work? I would say, in parallel to that discovery, another part of that paper, which we had actually made before we understood the role of the ATP, was we recognized also that synapses are incredibly sensitive to the need to make ATP on demand. If you don't let them do it, they collapse really quickly. I realized that was probably extremely important property of synapses that we need to worry about.

Brady Huggett
Why is it important to be able to make ATP on demand? I think this has to do with vesicle recycling. Is that right?

Tim Ryan
Yes. We discovered through our work that the first thing that seems to break if you don't have enough ATP is the process of recapturing the proteins of a synaptic vesicle after it releases neurotransmitter, because it's fused through a process called exocytosis. Those things all have to be recaptured so you can remake the vesicle. That is the process that breaks when you don't have enough ATP. That, of course, means you will run out of vesicles. If you run out of vesicles, you will no longer be secreting neurotransmitter.

Brady Huggett
Which means it may lead to disease.

Tim Ryan
Yes.

Brady Huggett
I think the first thing people thought about, maybe that's not true, but it was like Parkinson's.

Tim Ryan
Yes. That is the direction we currently are working on very heavily.

Brady Huggett
I think you have a grant. You have a couple from NINDS now. One extends to next year and one extends to 2029.

Tim Ryan
Yes.

Brady Huggett
You have some Michael J. Fox funding as well. Obviously that's Parkinson's. You said before, when you're in that room and people are looking at your grants, that stuff is probably— you're awarded those grants based on this work. Has it become easier for you to win grants now than back in 2001?

Tim Ryan
No, I don't think so. I don't think so. You're only given so much credit for retrospective contribution. It's mostly about what are you proposing to do? That's really what's evaluated. They're not gold stars. They are literally saying, what are you proposing? Then you're competing with a bunch of other people with good ideas as well.

Brady Huggett
In this case, you're able to say, "Look, we did this, we're pushing it in this direction.

Tim Ryan
It certainly helps. It's a bit hard to answer that question fairly because whether it's easier or not, I've had a typical career. I've been luckily able to sustain continuous funding, not without rejections. They still happen. I feel more confident that the work is so interesting and it has led us to make discovery after discovery. That's what I feel to me has been impactful. It just kept it incredibly exciting the whole time, including today. It's still as exciting as it's ever been.

Brady Huggett
You're also, I think, associated with Janelia, somehow. I think that maybe started in 2018 or something like that.

Tim Ryan
Yes.

Brady Huggett
Tell me what you're working on now.

Tim Ryan
OK. Because of the discoveries we made about the importance of ATP, I became interested in where this impacts neuroscience. There's two flavors, one of which we're not working on, but it's a good story to convince the public. There's a paper that was published about 25 years ago. It's a human psychology experiment in some ways. It's just take a room full of people, divide it into two groups. Give half the group an oral dose of artificial sweetener, aspartame, and give the other half the group an oral dose of glucose.

Then give them a list of 25 words and test their recall on various time scales. The conclusion is, the people that got glucose did twice as well as the people that got a aspartame.

Brady Huggett
Did they switch them?

Tim Ryan
No. It was just, it wasn't meant for more complicated than that. Of course, we've all experienced this. I'm sure you've had a snack that's improved your ability to focus and edit your podcasts. That was a realization of humans is, oh, our synaptic, it doesn't have to be synaptic performance, but given how sensitive synaptic performance is to fuel availability, the implication

is that we're actually not running it off to them a lot of the time, which is not something I would say most people appreciate. On the other hand, it's hard to, this data is so simple. There's probably evolutionary reasons for why.

We weren't perfected. There's some headroom to get better. There's also a lot of room to get worse. I use this in a lot of my public talks and things because it's easy to convince people, there's an angle we're not thinking about. Then I bring them into, synapses are sensitive to this. The flip side is then we also know that as we age, our fuel delivery systems to the brain get worse. They get worse to the whole body, actually, not just, that's why elite athletes stop being elite athletes for lots of reasons with age. But one of them is that they're not able to deliver fuel and oxygen as efficiently as they were when they were 25.

Now, Parkinson's was, I'll tell you the honest truth. I was having lunch about four years ago with a colleague at Rockefeller. This is the importance of networks. I was telling a little bit what I, some interesting things. We had some ideas about Parkinson's, about why the neurons that die in Parkinson's might be particularly vulnerable because we had thought we'd figured out that they might be consuming, there's a reason they might be consuming way more ATP than most other neurons. That was sort of a hypothesis at the time.

One we're still testing actually to this day, but like a couple of weeks later, I ran into him and he says, "Oh, I just heard this interesting talk. You might want to look this up." He didn't really recall too much. He gave me the name of the person, and I went and read this paper. It was a study starting with a paper 10 years ago where a group had decided to see if they could keep flies from dying from a genetic perturbation. The genetic perturbation was the turn on a cell death pathway. The experiment was feed the flies drugs that humans take, FDA-approved drug panel.

Brady Huggett
What drugs?

Tim Ryan
In principle, you would like to do everything, in practice, that's a couple of thousand. You don't inject drugs into flies. You put it in their foods. It's very inefficient. Everything was expensive and laborious. They cherry picked a couple of dozen for reasons that are too complicated and not worth going into. Amazingly, they found a drug that seemed to double survival. That was, then they tried to track this down and it didn't make any sense. The known target for the drug, the reason it's used clinically was an adenosine, an adrenergic receptor, not adenosine, an adrenergic receptor.

It's only used for one clinical indication largely, which was because this receptor happens to be in the endothelia that line the urinary tract. If you are having trouble with urination because you've had something impeding the flow, like a growing prostate, this is meant to relieve that symptom. It's a local blood pressure drug. OK. If you fast forward, it's about, it doesn't seem like, what would this have to do with, and it's a fly, they don't even have epinephrine, for example. They tracked down, they realized it's probably not that target.

They did other biochemical experiments. They went fishing and what they did, the hit they got was the first ATP producing enzyme in glycolysis. They thought that the drug did not inhibit it, but actually it made it slightly better. That, and they had other types of measurements, again, a bit crude, grinding up flies, measuring ATP and pyruvate when the flies were on the drug from the brain, all look like, yes, it looks like it's making things a little bit better. Then you fast forward a few years, they made a slightly bigger team or they teamed up with other people and they tested this in Parkinson's models in mice, flies, and rats.

Amazingly, the drug was incredibly protective now in all these cases. I saw this and I was really excited because I was already thinking there was a bioenergic root of maybe Parkinson's, but no data, I just literally had some hand-waving reasons why I thought this. I said, this really looks like something. I said, I wondered if this is related to the fact that when we had looked explicitly at Parkinson's mutants, not looking at ATP, we had blinders on, we were looking just at what was it doing to synapse function, vesicle recycling. We'd noticed a bunch of these different known Parkinson's mutations seem to slow vesicle, they slowed it down.

Oddly enough, metabolic problems slow it down too. I had not made the connection until I'd read their paper going, "Oh, I wonder if it's all bioenergetic and this is the root." A subgroup of the people that were participating in that paper published in 2019, now they had looked a little bit at humans in this paper, but they did a more serious look back and said, "Listen, there's a bunch of data from people taking this drug." Now you can do what's called a retrospective analysis.

The conclusion was, and this was published two years ago by a group of epidemiologists and quite a famous scientist named Mike Welsh, who is responsible for, in my opinion, at least in part, for the reason cystic fibrosis patients are living two decades longer. It's because of fundamental work he did in the '90s. He happened to be participating in this, and they showed that men taking this drug reduced the likelihood of getting Parkinson's by 37 percent, which is the biggest effect ever claimed for neurodegeneration.

It's all incredibly exciting, but I thought one of the weaknesses of it all, and then I realized why drug companies, I don't have a full analysis of what their interest level is or was, but one, of course, it's a known generic drug now. The other is the data that it was really working on this enzyme is the weakest. Because if you say, what's the gold standard? Purify this enzyme in a test tube, measure the enzymatic activity and add the drug and how much does it make it work better? That was a very small effect, like a few percent.

Then it's like, that's a bit of a cross your fingers that that's really the target. Because we're not saying the drug doesn't protect against Parkinson's, but is the drug really doing it by this bioenergetic problem and really via this enzyme? We set out in the last few years to determine whether this holds water at the level of, is this enzyme really that key in this problem? Is the drug acting like there's more enzyme there or not? I'm happy to say that paper is coming out in the press two days from now.

Brady Huggett
Oh God, OK.

Tim Ryan
Basically, everything that came before seems to hold true. We even did experiments where we just sort of did a gene therapy version in a mouse, where you use a virus to deliver this enzyme. The enzyme is called phosphoglycerate kinase one. We just have the striatal neurons in the midbrain express more of this. It really is strongly protective against the kinds of lesions people use in experimental Parkinsonism.

Brady Huggett
The thing that's made me think of, and it's sort of related, but like, so there's a certain percentage of cases of like ALS that are genetic, that's known, but the rest are spontaneously arising. Maybe it's something like this, that's doing it. Every, when you ask, we don't know why. It's just at some point things break down and the muscles start to die.

Tim Ryan
Yes, so it's actually more optimistic than that from my point of view. In Parkinson's, I believe the experts in human genetics say it's about 15 percent of the cases are known genetic drivers. 85 percent are called sporadic. What's amazing is that the tests of the drug have been done in a bunch of the different known genetic drivers. The human data is presumably because it's random, is largely the sporadic. The fact is, it's working in both. I actually think, to me, that tells me this is probably the root of it. There may be exceptions, of course.

We actually found one in this paper that's coming out that one of the initial names for these genes were called Park genes for Parkinson's. These are attempts in human genetics where you find families and you sequence family members that are affected, and you narrow it down to a gene. For a while, for the 25-year period, they were called the Park genes, Parks 1 through 23. That name isn't used anymore, I don't know why, but Park 7 is a small molecule, it's a protein called DJ1. What we discovered, by a little bit of chance we've been following the lead, that we found it was a claim that DJ1 might interact with this enzyme PGK1.

What we discovered is that when we removed DJ1, this drug doesn't work anymore. It actually creates a massive metabolic problem on its own. The gene therapy doesn't work anymore. This may be one we can't fix because it's too intimately connected to the problem. Can't fix currently, I should say. Not with this trick anyway. It's looking like many of them actually will be, I'm confident they're going to be connected to this. What I'm hopeful is that, even though we don't still understand how the drug works, but we have much higher confidence, I do now, that it's really via this enzyme, perhaps with the partnership of this other Parkinson's gene.

This is what you need as the toolkit. If you want to try and help the world make a better version of the drug, this would be the starting point. For that reason, I'm excited.

Brady Huggett
OK. All right, there's two things I want to ask you to finish this off. One is, you just said, when you give talks and stuff. I think in 2022, you gave a talk at the International—

Tim Ryan
The Brain Energy?

Brady Huggett
International Brain Energy Metabolism Conference, right?

Tim Ryan
Yes.

Tim Ryan
Then I think 2023, the Korean Society for Brain and Neural Sciences. Then I think last year, you were elected to the National Academy of Sciences, right?

Tim Ryan
I was.

Brady Huggett
My first question is, do you think you're doing the best science of your life now?

Tim Ryan
Yes.

Brady Huggett
The follow-up is, is that rare? I don't know what's the corollary, but I don't know that certainly athletes aren't doing their best work in the last third of their career. I don't know that Bruce Springsteen's writing the best music in the last third of his career. For science, even for science, is it rare to be doing your best work in the last, maybe, I don't know how long you do this, Tim, maybe the last third of your career? I don't know.

Tim Ryan
It's a tough question to ask. In physics, there's this old thing, theoretical physics, of course. The problem is, there's a few data points of absolutely brilliant contributions from guys in their 20s and 30s. You could say, well, Werner Heisenberg and Paul Dirac, their big breakthroughs came roughly at the age of 30, right? Now, at the same time, it's hard to top what they did. There's no way they could do it again, they could do better, because those are singular moments in the history of science, right?

I never liked that example, because it doesn't mean that their capacity for doing great stuff changed, it's just that they peaked.

Brady Huggett
They found a moment early.

Tim Ryan
They found a moment early. The example that is often used is Giuseppe Verdi, great composer, continued composing his most famous operas well into his 80s, right? I feel incredibly fortunate that I get to continue to experience the excitement that I did very early on, but it got me excited about just, I didn't expect this result. This is, I have to think about this. That's exciting. I'm really happy that that happens today still.

Brady Huggett
OK, that's it. Thank you very much.

[transition music]

I'm still thinking about the way discovery lives on, how it is reborn as a new discovery for every single person that learns about it. I love that. Thank you, Tim, for a great talk and for hosting me in your office. OK, this podcast will be archived on the transmitter.org where we have also included a transcript. In the transcript, we have inserted links to some of the papers discussed. Check that out if you'd like more information. This show can be found wherever you get your podcasts, Apple, YouTube, Spotify, or in whatever podcast app you use.

Some of the information for our intro came from the website and educational materials for the Fermi National Accelerator Laboratory. If you'd like to comment on this show or whatever we do with the transmitter, you can find us on the social media platforms, X, Mastodon, Blue Sky, and LinkedIn. Our theme song was written and performed by Chris Collingwood. Thank you for listening to "Synaptic." Until next time.

[ending theme music]

Tough question, but is it possible to silence that?

Tim Ryan
Yes.

Brady Huggett
OK, we will—

Tim Ryan
I wish I could say yes, but I have no control over it.

Brady Huggett
That's fine. We'll just get close to the mics.
