John Boccacino:

Hello and welcome back to the 'Cuse Conversations podcast. I'm John Boccacino, senior internal communications specialist at Syracuse University.

Robert Doyle:

Sometimes it's your nature, you enjoy science, and I always did. Chemistry then was just the one thing that... I enjoyed being in the lab. I enjoyed making things in a chemical sense. The specific area of medicinal chemistry and then into diabetes, and then ultimately from diabetes into obesity was an organic progression. I think I've always been interested in the aspects of the brain and how hormones can actually change your behavior. And so as a chemist, you would look at that and think, well, "Hey, if you can release something in your stomach that completely changes your behavior, naturally, can you do it chemically? Can you make a drug that you give somebody that would essentially change their neurological response to something?" And yes, I'm looking at glucose levels and I'm looking at appetite here, but I'm also thinking about addiction, aggression, depression.

John Boccacino:

Well, our guest on this episode of the 'Cuse Conversations podcast, he is Robert Doyle, the Jack and Laura H. Milton professor and dean's professor of chemistry, who's also an adjunct associate professor of medicine and pharmacology here in the College of Arts and Sciences. Now, Robert is a medicinal chemist with a focus on pharmaceutical drug development for the treatment of obesity and type two diabetes. His cutting edge research involves peptide-based treatments, which offer significant and consistent weight loss and glucose control. Doyle is joining us here on the podcast to discuss his significant weight loss research, his role as an endowed professor, the important role his students play in helping advance the research and how, through philanthropy, his research has really come to life here at Syracuse. Robert, thanks making the time to join us here on the podcast.

Robert Doyle:

Thank you, John. Pleasure to be here.

John Boccacino:

So I know it's a complicated, convoluted topic. In layman's terms, how would you describe the nexus of your research?

Robert Doyle:

Basically, we are medicinal chemists, as you mentioned, and we are focused on using peptides, so small proteins, to treat neuroendocrine disorders, so disorders that affect the brain primarily. And in that aspects, we are looking at addiction, we are looking at cravings, food intake, body weight reduction, glucoregulation, all of those complex endocrine issues that are really prevalent in today's society

John Boccacino:

I mentioned your cutting edge research, and we'll go through some of the discoveries that you've made that really give hope for people who might be battling obesity or type two diabetes. But what are some of the ways that this field has evolved since you've started off with your line of research?

Robert Doyle:

The big, I mean the major change that you've seen in the last 10 years is the creation of these GLP-1 drugs, exemplified by Ozempic and Zepbound, et cetera. Up until these drugs existed, there were no

really safe, viable weight loss alternatives. So diet, exercise have always been on the cards, of course. But for those people who needed a pharmaceutical intervention or wanted this pharmaceutical intervention, there was nothing that could achieve anything greater than the 5% body mass loss that you'd be looking for to have any kind of clinical benefit. So what you've seen early on with the creation of the first real breakthrough drug, which was Victoza, you were seeing that 5% BMI decline from a pharmaceutical. And that was a huge success. And I think it set everybody up for what subsequently happened, which is these newer, more potent, and more active weight-reducing drugs.

But those initial drugs were often once a day or twice a day injectables. And so patients, people, didn't want to do that necessarily, and that was slow to achieve breakthrough. So what you've seen really in these last few years is now what we have is upwards of 10% and greater body mass reduction coupled with once a week injectables. And that has really broadened the appeal and has honestly really created quite a phenomenon in the sense that you have Ozempic challenge on TikTok and you have celebrities taking these Ozempic medications now. And so it has really exploded in the last three to five years.

John Boccacino:

What was the linchpin that was able to take us from the first iteration of weight loss drugs to where we are now?

Robert Doyle:

Well, the discovery that this little hormone that you make in your stomach, if made long-acting and then injected into a human, could actually trigger food intake reduction. So essentially, by realizing that and doing pharmacological science on it to improve its half-life, make it hang around longer, so it would maintain what was normally only a very short activity in a human. But then through intervention, extending this lifetime and then driving that appetite off switch, if you will. And so really the discovery of GLP-1 and what GLP-1 could do is... It hasn't won a Nobel Prize yet, but it is going to. I wouldn't be surprised this year you're going to see the Nobel Prize awarded for the discovery of GLP-1 because it has revolutionized weight loss.

John Boccacino:

How would you explain the difference between GLP-1 and discoveries that your collaborators and yourself made of GEP44 and KCEM1 at the conferences of the American Chemical Society and the Obesity Society?

Robert Doyle:

So what we've done is partnered GLP-1. So what we have now is a system where GLP-1 is still present, still functional, but isn't the primary driver of the, or need to be the primary driver of the effect. Because the unfortunate thing about GLP-1 is that the weight loss is almost a side effect of its function. In other words, if you take enough of this particular peptide, you will lose weight. But it often does this through nausea, emesis, vomiting, malaise, you've got strict mobility changes. And so the side effects can be quite pronounced. And in fact, what we're seeing now, now that the drugs have been out there and are being utilized en masse, what we're seeing now is really patient tolerability is very low. And so, we now know that 70% of patients who start on these drugs are not taking them a year later, and 30% are not taking them within three months and will have achieved next to no weight loss whatsoever.

And so it seems like it's a hammer approach where maybe we need to maybe tone it down and maybe complement its functionality with some partners, if you will. And so the latest drug on the market does exactly that. It takes GLP-1 and it combines it with another incretin or another gut hormone that's called GIP. And working together in a specific ratio, you get better tolerability. It's still not good, but it's better

than the GLP-1 alone. And you actually get more pronounced weight loss. And so, once a week, more weight loss, better tolerability equals better drug.

And so what we're doing is we're figuring out, starting from that GLP-1, which combinations will work together and which ratio we need to get right between them to actually drive not just weight loss, but essentially to switch off those side effects. Because the side effects have shown to be the real clinical differentiator. If patients can't tolerate the drug, they can't take the drug, and it's as simple as that. And this is supposed to improve quality of life. Patients lose weight, they're supposed to gain more energy, they're supposed to be able to feel better and get out and about, and you can't do that if you feel sick and you feel low energy, malaise, et cetera, et cetera.

So our discoveries were really, we took two different routes. We took a combination of GLP-1 with another hormone called melanocortin stimulating hormone, so MSH, that's KCEM1. And then we also partnered it with another peptide called PYY. And PYY is a gut hormone that directly switches off appetite. And so it actually works in your brain to tell you, "Stop eating." And so if you've just had lunch, breakfast, or dinner, depending on when you're listening and you're feeling full, that was the PYY in your brain targeting a receptor that says, "You're full. You can stop eating now."

And so really, there's two concepts, two important concepts in terms of appetite, and that is satiety and satiation. So satiation is when you eat until you feel full. But satiety is how long is it between meals? And so it's not just initial consumption, but what is the time in between? And so if you can both decrease the initial consumption and then increase the amount of time between meals, you're going to lose weight. And if you can do that gradually and without triggering side effects, you're going to have a perfect combination of weight loss meets ready compliance, safety, tolerability, happy patient, losing weight, once a week injectable, move on.

And so we have been exploring those combinations of GLP-1 with these different peptide hormones. And what we see with our drugs and these new combinations are no nausea or emesis. So no overt side effects.

John Boccacino:

Effects. How troubling from a researcher was it knowing that the typical weight loss drugs out there did have a litany of side effects associated with them?

Robert Doyle:

Well, I mean, it's hard to really know how a medication is going to hold up in a population until it's out there in the population. And I don't mean that to be in any way skeptical of the process. The process is wonderful. What it is, is going through, in a phase three study, in a population that are affected by the disease we're talking about, or in this case we're talking about obese individuals or morbidly obese individuals. It's not a disease of course, but it's being treated like one in this case. If you decide to be a part of that trial, you're a highly motivated individual and you want to stay in the trial.

And so giving the medication to a population like that, where they're highly motivated, they're not necessarily going to want to quit. They're going to stick it out. And so, really, at the end of the trial, you're going to say, well, "Hey, we did these few thousand people who are morbidly obese and they lost an average of 11% of their body mass over X amount of time. Isn't that wonderful? And 88% of people who took the medication at the start, were still taking it at the end. So in other words, we had really good tolerability in the sense that the people in this trial stayed all the way through."

But that's, like I said, a motivated individual in a clinical trial being monitored and supported. The average person isn't in a clinical trial, isn't being supported, they're at home, they've got to get the kids to school, they've got to go and go to work, they've got to go and whatever needs doing. And they're obviously not as highly motivated. And so what happens is the psychology that isn't really there in the general population, as it is in the clinical trial, it manifests itself differently in the real world. And so I think what you find is that, while the tolerability, it's not great, but most patients still stuck it out, that did

not translate into the general population. Because as soon as you start feeling sick and ill, you just say, "Well, why am I taking this? This is not for me. I'm not part of this trial to see where it goes and I should stick it out. I'm just me trying to go to work today."

The other problem is if you take it for a few months and you lose some weight and you're able to tolerate it, even if you don't feel great, you feel okay, and you can tolerate it, or maybe you feel fine and you can tolerate it just fine, great. But then it starts to wane. It stops working because of what's called tachyphylaxis. Eventually, essentially, your body just doesn't respond to it at that dose anymore. So the physician ups the dose. Now, you might hit a point where you do start to feel sick. Or if you already felt pretty ill, but you could just about tolerate it, but it's no longer working to cause weight loss, well then why would you keep taking it? Well, okay, you'd stop the physician will increase the dose. But at that point, you'll be so sick, you just can't tolerate it.

So the other thing about it is, when it gets out into a large population, taking it over a much longer period of time than the clinical trial, in theory, what happens is you get this need to continually up the dose to make it keep working. And if it already is poor tolerability, then more and more of it is just going to make you feel worse and worse, and so not a good combination. And so ultimately that's transpired with these drugs.

John Boccacino:

Is it true that you see there being an explosion coming in the days, weeks, months and years to come of these super safe, super effective weight loss medicines that'll be hitting the research markets?

Robert Doyle:

So right now there's over 100 weight loss medications of one form or the other in clinical trials. So yeah, absolutely. Short answer is, yeah. Five years from now, the field will look so different to the one you see right now. And I think you are looking at the first, like I said, salvo, the first wave of successful weight loss treatment. So to quote that old D:Ream song, "Things can only get better." And they're going to get better.

And what's really amazing, too, is that some of the effects that we've also learned, and I know I seem like I'm bashing these drugs, I'm not at all, they're wonderful.

John Boccacino:

Sure.

Robert Doyle:

And they've helped a lot of people. All I'm saying is that now that the dam has been breached, we can now really, really go crazy and really push through and learn from all of the science that's happened as a consequence of having these drugs. I mean, they're wonderful. But what we've also learned is that these drugs have a really positive effect on cardiovascular health. And cardiovascular health, of course, is still one of the biggest killers of men and women in the United States, worldwide. And so actually having a drug show percentage improvements in cardiovascular health, we haven't seen any really positive impact on pharmaceutical development in cardiovascular health since probably the 1970s. So to have something like this open up a whole new class of potential drugs to treat cardiovascular disease is pretty amazing. And I think you're going to see not just really super improved obesity drugs, you're going to see soon that these GLP-1 type drugs are going to be FDA approved for cardiovascular health.

They're also showing benefits, and this is what we've learned by being able to give it out to a population and study these drugs en masse, is that there seems to be a potential improvement in Alzheimer's disease progression. And again, if it's improving cardiovascular health, it's because it's improving vasculature

blood flow. And if one of the driving factors of Alzheimer's disease is a depletion of blood flow into the brain, so a decline in vasculature in the brain, then improving cardiovascular, or let's just broaden it to vascular health, would also play well with the brain.

And so a lot of the current theories about Alzheimer's disease obviously tie into plaque formation and neurofibrillary tangles, et cetera. But any effective drug that we've tried to remove those and reverse the disease just haven't worked. They haven't translated into humans at all. They haven't made any effect. And so I think re-looking at Alzheimer's disease as a vascular issue, and then seeing if these GLP-1s can stay the progression of the disease would be another amazing breakthrough.

So as much as we might say, "Oh, GLP-1s, they're terrible drugs, they make me feel sick." Well, for those people who can tolerate them, they're wonderful. And what's been born of them is going to be incredible, from a brain perspective, from a heart perspective, and then ultimately from the new generations that are going to be born of them to treat diabetes and to treat obesity. And so there's nothing but positives to come from all of this.

John Boccacino:

And is it true, Robert, that there's also a benefit to potentially treating... At least what I read, there's early evidence of opioid-addicted lab animals being helped with having their cravings reduced by part of the compound discovery. Is that something that you're hoping to maybe build upon or could give some hope for human treatment as well?

Robert Doyle:

Yeah. So one of the places, I don't look into the Alzheimer's or cardiovascular parallels with the GLP-1Rs and obesity, diabetes, I look into the use of them in not just obesity and diabetes, but addiction. And so along with my collaborators, again, at the University of Pennsylvania, we studied GEP-44, that you mentioned at the opening of the program, in opioid, specifically fentanyl-addicted rats. And what we were able to show is that we could reduce the craving, and we could then reduce the time in between relapse.

So the idea is taking this initial compound and developing it for addiction would be that you would take it as a once a week injectable. And what happens is over that time course, you're craving for going out and getting the opioid, getting the fentanyl, would be off. And so essentially, while you're going through detox and while you're going through drug rehabilitation, et cetera, relapse is always the one big cloud that hangs over your head. You're always an addict, as they say. And so you're always just one dose away from relapse.

And so if you had a medication that essentially made it that that craving was under control, that would be obviously an enormous benefit physiologically just in terms of staying off of it. But I think would also be an enormous helping hand to the person who was going through this to know they have got something that's going to help them manage this. It's almost like a positive circle of, "Okay, I'm not going to relapse because I have the drug." And then with the drug and the fact that they know they're not going to relapse because they have the drug, they don't relapse. "I've got this. This is okay, this is under control." And so there's nothing but, again, positive mental and physiological outcomes to being able to give someone who's trying to get off fentanyl, for example.

And so early studies that we have with GEP-44 in fentanyl addicted rats have been very positive. The one thing we actually want to do, ironically, is we want to dose it so low that it works for fentanyl addiction but does not cause side effects, because we cannot induce nausea and vomiting in a recovering addict or weight loss. Because again, the conventional feeling in the addiction space is addicts cannot afford to be any more dietarily restricted. They're often already underweight or have nutritional deficiencies. And so we're trying to make it so it's potent enough to maintain that fentanyl craving off switch, basically. But we want it to stay below the threshold that triggers food intake reduction and obviously the side effects. So that's the line we're walking with addiction right now.

John Boccacino:

Could you give a little example to our audience of the role that Syracuse's Center for Science and Technology has played in acting as a mini pharmaceutical design and manufacturing center to enhance your research?

Robert Doyle:

So the CST is where I'm housed. I'm located in the Department of Chemistry here in the Center for Science and Technology. And so within my own lab, we have multiple large scale peptide synthesizers that allow us to produce really gram quantities of these drugs. We have multiple purification setup systems so that we're able to purify to 99% purity. We also have multiple screening facilities here. So we have cell labs that we can screen for the required receptor binding. We have AI and what we call molecular operating environment, or essentially these computational chemical approaches to aid in design. So really, we can start from a concept on a piece of paper, we can then begin to design that computationally. We then move that into the lab and we actually physically make it. We then purify it, we then screen it for binding for function, et cetera, et cetera.

And if it makes the grade, and we'll set some target product profile, and we'll put something in place that says we want the drug to be able to do the following criteria. And if it meets those criteria, it goes out into preclinical animal models, which would be at the University of Pennsylvania in this case. And that's where the rubber meets the road. So we'll actually look and see if what we've created here is manifesting the effect we want it to in that preclinical model. And if not, we go back to the drawing board. And if it does, we call that a hit, and we'll then take that hit and we'll begin the process of optimizing it for development.

John Boccacino:

How can you describe the valuable role that you get out of working with our students to help advance your research?

Robert Doyle:

You spend years becoming a really good chemist and learning the tools of the trade, and then you become a professor and your job becomes about resources and acquiring funding and conceiving of projects, and you don't have time to be in the lab anymore. You have to train the students and get them in there. And then they're the ones who actually drive the car. So day in and day out, they're the ones who are in there grinding out the production, the purification, the screening, the failures, the redesigning. They bring the passion, and they bring really the intellect, and they're wonderful. They roll up their sleeves, they jump wholeheartedly into the medicinal chemistry and the biochemistry and the physiology and the preclinical and the intellectual property and all the aspects of drug development. And they do it with good grace and hard work, and like I said, a lot of smarts. We have some really great students here at SU. And with the right resources and support, as we're seeing from the work coming out of the group now, there's really no reason why this level of success can't be manifest here at SU. Absolutely.

John Boccacino:

Is there anything tangibly you can come up with of how the students challenged your ideas or perceptions to help advance it moving forward?

Robert Doyle:

No, I'm way too clever. So there's nothing they can teach me. No, absolutely not. No, I mean, obviously day in and day out, they know the system so much better than me. And so what they've taught me over the years is, if I have eight to 10 projects up in the air, I can picture in broad strokes what everything is for

and where everything is going, but what they've taught me over the years is I have to be humble. I know my comment didn't suggest it there, but I have to be willing to step back and let them take the reins. I have to be willing to trust them that they'll do it and they'll do it right.

And so they've taught me and surprised me many times by coming up and saying, "Hey, you know what? I saw this and I made this change and this is what it does," and my instinct would've been no way that will do that. And they were like, "Well, I thought that too. But then I saw this paper from 10 years ago and this left turn turned out to be a right turn. And so I thought, I'm going to put that in here and see what happens." And so that sense of confidence and inquisitiveness and can-do, and it's still wonderful. So it's taught me that, you know what, I'm not always right and I shouldn't even conceive of that. And they keep my feet on the ground and they surprise me every day with some wonderful question or some clever idea.

And I always tell them if, "Unless you're redefining the laws of physics or the experiment is going to cost a million dollars, then do it." I always tell them, "Look, if you've had an idea, and as long as it's scientifically feasible and isn't going to bankrupt the lab, go for it." Because the science never fails to surprise. And sometimes those loose threads, when you pull them, are the best science. You actually end up being better than the sweater you were trying to knit in the first place.

John Boccacino:

Well, there is a loose thread I want to connect back, Robert, to get your perspective on this. How did you get interested in this line of work, in this field of study in the first place?

Robert Doyle:

Yeah, I get asked that a lot. I think it's like sometimes it's your nature, you enjoy science, and I always did. Chemistry then was just the one thing that... I enjoyed being in the lab. I enjoyed making things in a chemical sense. The specific area of medicinal chemistry and then into diabetes, and then ultimately from diabetes into obesity was an organic progression. I think I've always been interested in the aspects of the brain and how hormones can actually change your behavior.

And so as a chemist, you look at that and think, "Well, hey, if you can release something in your stomach that completely changes your behavior, naturally, can you do it chemically? Can you make a drug that you give somebody that would essentially change their neurological response to something?" And yes, I'm looking at glucose levels and I'm looking at appetite here, but I'm also thinking about addiction. You're also thinking about aggression. You're also thinking about depression. There are all of these often intractable diseases that you track back their source, it's to the brain and it's often to some chemical mismatch or some hormonal mismatch or et cetera, et cetera. And I think, even as I say it now, it's still fascinating. I mean, there's still so much we can still do, and the sky's the limit.

John Boccacino:

If you had to look into a crystal ball, what's up next with your research into this field?

Robert Doyle:

So if we take what we're doing and we flip it on its head, what we can conceive of then is something that facilitates weight gain. Why would you want to do that and where? So ideally, what we would like to do and what we've actually created and SU actually has a patent and a couple more coming along that are born of my lab whereby we can actually switch off the vomiting. So again, we're talking about switching it off, but at this time associated with chemotherapeutic induced nausea, vomiting. So in other words, a major problem with chemotherapy is, of course, the same sort of problems you're having with GLP-1s, nausea and vomiting, malaise, lethargy, and an inability to achieve maybe an ideal clinical dosing target because you're too sick to achieve that level. You just cannot tolerate the drug.

And so if you could actually make it so that you could still give that drug, but you could give it at much higher doses and a dose that the physician would be much happier if you were taking, then that would obviously give you a greater chance for an improved prognosis. But also if we removed the nausea, vomiting, so you could do that, we'd also be removing the nausea and vomiting so you would have a better quality of life. And so what we've designed is a drug that is an anti-emetic, so it switches off the emesis and also rebounds your appetite. And so what you would do is, if you were undergoing chemotherapeutic and my crystal ball head as you mentioned, what I would say is, wouldn't it be wonderful if you had to go in to take your regimen, but they could pre-dose this so that you would still feel absolutely fine, or at least much better, you could take more of the drug, so have a better treatment efficacy, and at the same time, you wouldn't lose all of that weight that goes hand in hand with chemotherapy?

So there hasn't been anything new in terms of dealing with the nausea, vomiting, weight loss, cachexia associated with chemotherapy since the setron drugs like, I don't know, 40 years ago. And so if we can come up with a new way to do this, I think that would be pretty groundbreaking, and I think you'd have an entire population who would have a better treatment outcome coupled with a much better quality of life. And so to me, that's a huge double whammy of a benefit.

John Boccacino:

Well, it's really been a fascinating conversation here on the podcast. I want to thank Robert Doyle, the Jack and Laura H. Milton professor and dean's professor of chemistry. We cannot wait to see what's next as you continue with your fascinating research. Robert, thank you so much for making the time to join us today.

Robert Doyle:

Thank you, John.

John Boccacino:

Thanks for checking out the latest installment of the 'Cuse Conversations podcast. My name is John Boccacino, signing off for the 'Cuse Conversations podcast.