Episode 36 – Evert Njomen: Hacking our cellular recycling system to prevent the next deadly pathogen

Drew (00:03):

Howdy listeners and welcome home to Science Changing Life with me, of course, Drew Duglan. Today we learn a lesson in housekeeping, cellular housekeeping, that is. My Scripps Research guest is post-doctoral researcher, Evert Njomen in the chemistry lab of Professor Benjamin Cravatt, Evert studies, the process of autophagy, which is a critical way of cleaning up and recycling the internal machinery of our cells. What's more, she's working out how this pathway could be modified to create new defensive treatments against a variety of dangerous pathogens. So, let's settle down and join Evert as she discusses trading in medical school for a blossoming career in research.

Evert (00:44):

I grew up in Cameroon where I did my bachelor's degree in biochemistry and medical lab science. And even though I had a lot of, uh, hospital experience as a medical lab technician, there was really a limited experience when it came to research. Right? And my, one of the biggest thing my community needed was a medical doctor. And so with my love for science and pressure from parents and mentors, um, medical school was the obvious, next thing for me. So with limited availabilities, back in Cameroon, in terms of medical school, I decided to come here to the United States where you have more options, small options. And so the goal was to enroll into a master's program, get my prerequisite in place and then transition into medical school. But once I started, uh, research, I realized that's where my interest was, all those things that were being taught in those big biomed, uh, textbook and biochemistry textbook. And back in the day, I had this question of how did people get this knowledge, or how did they, this information while learning about in textbook comes about? And so when I started doing research, I realized, this is how all this information that we've been learning over the years actually come about. And so I told myself, doing research was much more interesting to me than actually going to medical school. And so instead of going to medical school immediately applied to another graduate program at Michigan State University, where I started my PhD.

Drew (02:36):

Wow. I was in the same boat. I really wanted to do medicine or I thought I did. And then I didn't get into any med schools. And so I ended up pursuing biomedical science and then I could have had the opportunity to then go into medicine. But I think perhaps like you are saying, I really enjoyed just learning about the, the sort of pathways underneath it all. Like all the mechanisms.

Evert (02:59):

Yeah. I got admission into medical school and graduate school. Then I put my medical school and hopefully, yeah, cause that was, I was at that spot where I was loving the research work, but at the same time, I came into the graduate program with the goal of medical school. So I decided to put that on hold for a year and see what graduate school really was.

Drew (03:22):

So what did your family think when you said you were gonna put your med school on hold and continue with the research?

Evert (03:29):

There were obviously disappointed, but at the same time, I think there was a financial factor that came into play as well. They couldn't pick up that financial responsibility at that time. And as a foreign student, I wasn't eligible for student loan either. So when I told them graduate school is the better option, both in terms of my interest and the financial part, it was disappointing, but okay. Because they couldn't take that loan to train me in a program that I was already losing interest in.

Drew (04:06):

Yeah. Right. And yeah, the costs of, of med school is, just exorbitant.

Evert (04:11):

Exactly. Yeah.

Drew (04:12):

Totally understand that decision. So now you mentioned you're in Professor Ben Cravatt's lab here at Scripps. So what is it that the lab does, uh, in broad terms and what, what kind of projects are you working on in, in the autophagy space?

Evert (04:26):

So directly the lab's interest is in findings molecules that regulate the function of proteins and then developing technologies that can actually allow them to study these different proteins and their role in different diseases with the goal that this could potentially lead to some new or better therapeutic. And when it comes to my research area, my focus has been to develop different chemical procure platforms that allow us to monitor small molecule protein interaction in cells. And in my case, a more interested in proteins that are involved in the autophagic pathway.

Drew (05:08):

And so with autophagy, I think doesn't it mean like auto is "self" and "phagy" is, is kind of eating like eating the cell, is that correct?

Evert (05:17):

Exactly. So it means self-easting. And this has to do with the fact that the cell is able to collect components within itself, for example, proteins that are damaged and no longer important organs like mitochondria, or even in certain cases, invading microorganisms like bacteria viruses or some para microbes. And eventually the component get degraded and the resulting outcome, uh, small building blocks like a minor acid, sugar like locus and even fatty acid, which in the case where the cell is under stress, like new trend stress or starvation, this component can be reused for importance cell function. And in the case of an invading microorganism, this is a way that the cell uses to sterilize itself from the pathogen.

Drew (06:15):

Gotcha. Okay. I see in the scientific space, there's a lot of link of autophagy to lots of different diseases. And I guess is that because these components that autophagy would usually digest can sort of misfold and cause lots of different problems in the cell.

Evert (06:31):

Exactly. So if you take like the case of neurodegenerative disease, for example, I think a common hallmark for this disease is the accumulation of protein aggregate. You can think of it in the form as think of your bedroom when everything is just everywhere. You can even easily access, say your glasses. So everything slows down, right? And that is what happened in neurodegeneration where you have all this accumulated stuff, particularly protein aggregate that tend to slow down cell function. And so if you can find a way by which this protein aggregate at getting rid of, then you have the possibility of at least reducing the phenotype that you see in these diseases.

Drew (07:21):

I see, like with the analogy you just made, kind of keeps the cell clean, I suppose.

Evert (07:27):

Exactly. Housekeeping

Drew (07:29):

Yeah. Got it. So you said, it seems to be at work to protect against different microorganisms. Are some of these invading threats, are they able to change like these autophagy pathways or switch them off? Do you know?

Evert (07:47):

Actually, some microorganisms that would take advantage of these to multiply, right? They could, they could change the, the composition of the membrane or even sequester some cellular components like lipids which are probably essential for the fusion step and prevent that from happening. So we know a few cases where the microorganism actually hijacks the autophagy pathway to promote its own replication.

Drew (08:15):

As with so many things, the process of autophagy is tightly controlled, not too much, not too little. Evert is using chemical tools in the lab to screen for compounds that have the ability to tip the balance towards activation of autophagy, which could represent a completely new approach to dealing with infectious disease.

Evert (08:34):

Our goal is to find molecules that can up the activity of this autophagy pathway. Like almost every system, our body, you have negative regulation, right? The body has to make sure that it's not happening excessively. And so one of the question we're trying to access find small molecules that regulate proteins in this pathway, particularly those that act as negative regulators to slow down the activity of the pathway and whether this type of molecules can actually transition into promoting our ability to quickly clear this microbe and even reduce that rate of replication.

Drew (09:17):

It seems like this could have major implications for some of these bacteria that already seem to be resistant to different antibiotics because that's a really growing problem, right?

Evert (09:27):

It is a big one in the field of infectious disease, right? So this approach would going directly after a host, you refer to it as a host directed mechanism, which means instead of targeting something specifically in the bacteria of virus like traditional antimicrobial agents, would you, you're rather trying to up the activity of your own immune system. And so even though resistance is something that could potentially happen, it's less likely compared to when the small molecule is directed at the pathogen. And the second advantage to this is you don't have to develop the molecule for every single pathogen, right. Just one molecule that is able to kill all the pathogens.

Drew (10:14):

Right? Yeah. That's so cool. So if it's the same pathway that would be at work clearing all these different pathogens, I guess this is almost like a new type of immunotherapy, right. If it's working on our own cellular systems?

Evert (10:28):

Right.

Drew (10:28):

So have you found any promising molecules that, that can do this and have you tested them?

Evert (10:35):

So far, we've found molecules that bind proteins in the autophagy pathway, but we haven't moved yet to the next step of demonstrating what these molecules actually have activity in autophagy or the ability of autophagy to prevent infection. So that would be the next step in this program.

Drew (10:56):

Seems to me that I come across aji in sort of the research on like intermit and fasting. So can this be activated with changes to diet or exercise or other environmental triggers?

Evert (11:10):

Yes. It's actually known as starvation-induced pathway in the sense that the whole idea of self-eating is that when the cell eat or degrade components that are not needed at that time, it's able to generate this small building block that it's able to use for immediate cellular function or need. And so each time you starve the cell of those nutrients, it automatically turn on this pathway in order to generate those building blocks that it needs. And of course, activities like exercise, where you are using a lot or where you need these nutrients. And you also tend to generate some sort of hypoxic condition or low oxygen, which often stimulates autophagy.

Drew (12:00):

Do you do any fasting?

Evert (12:03):

I don't love breakfast, so….

Drew (12:05):

Yeah, me neither.

Evert (12:07):

Yeah. So that that's, that's my form of fasting mostly

Drew (12:12):

Yeah. Time-restricted feeding there. Cool, so you were talking about neurodegenerative disease and how, you know, defects in autophagy and sort of cellular cleanup can lead to some of these clumping effects, you know, with the plaques in the cells. So is there a system-wide loss of housekeeping function as we get older?

Evert (12:34):

Yes. Housekeeping function drops with age. You see that for both autophagy as well as for the proteasome, which are the two systems that carry out this cleaning role. And for autophagy aha, there have been some postulation to things like reduced sensitivity to things like insulin and glucagon, because when you lose sensitivity to those molecules, we don't have uptake of the required basic amount of glucose or maybe the glucose level in the cell is not regulated the way it's supposed to. And so the system, which is autophagy that is in place to check for that, tends to drop if you're not detecting the right amount.

Drew (13:16):

I see. And that could that, explain why, you know, we're at greater risk for diabetes because we lose those the control. Right. Um, from those hormones, do you think we'll ever have a good measure of, well, should I say, can we measure autophagy? Like how easy is it to measure and could we ever have a simple test for it? The way we measure like blood glucose, for example.

Evert (13:38):

That has been the biggest challenge in the field. Being able to monitor it *in vivo* or in a human. Anyone that comes up with that technology, that would, that would be one of the biggest breakthroughs in field. And I think right now you, you have a few autophagy inhibitors in clinical trials for different types of cancer. But even with that, I think one of the biggest challenges is actually being able to measure autophagy activity in humans at that stage, right?

Drew (14:12):

I see to know if it's working. Yeah.

Evert (14:14):

To know if it's working.

Drew (14:15):

I love this idea of having immunotherapy could just target ourselves in a way and then take care of so many different pathogens. Would this be extended to other parasites and things like that and not just bacteria?

Evert (14:29):

Yes. Because you have certain viruses like herpes simplex virus and then parasites like Toxoplasma gondii that also get integrated through this system.

Drew (14:41):

That would be big. Yeah. That would be really big. It's definitely outside the box to go that way and not just, you know, try to hit the, the pathogen.

Evert (14:51):

I think it's really high time. We start thinking of these complimentary strategies, given a lot of drug resistance that we're getting with different, uh, antimicrobial agent and also the fact that this is paralleled by a dramatic decline in the number of antibiotics that are going into the market. So we need to find strategies that will complement the few antimicrobial agents that are out there.

Drew (15:19):

Yeah. Well, yeah, you're on the cutting edge there and it's, it's a scary prospect, isn't it? It's just like we, we haven't got that long left, maybe, of using these.

Evert (15:28):

I think also particularly after we faced this pandemic, you have to also start thinking of ways that in the face of, of a microbial agent that we have no understanding of how it works or how it causes a disease - how do you get your body really to start providing that first line of defense?

Drew (15:50):

Sure. Yeah, because it takes so long to realize the mechanisms at work for this, you know, newly identified pathogen and by that time it's already spread and it's dangerous….

Evert (16:00):

Exactly. Yeah.

Drew (16:01):

To have that first line defense is a really good idea. Wow. Well, Hey, we could just transition very briefly away from the science. And I was just curious if you had any, uh, major hobbies and passions when you're not looking at small molecules in the lab.

Evert (16:15):

I think that's the most difficult question of them all! I love gardening so that means I also tend to spend a lot of time in the kitchen cooking the stuff from my garden.

Drew (16:26):

Oh, you have like herbs and stuff.

Evert (16:28):

Yes.

Drew (16:29):

Great.

Evert (16:30):

Lots of tomatoes, carrots and all those little spices you can think of.

Drew (16:34):

Oh, that's great. That's kind of the dream to have like my own like vegetable and herb garden. All right. Well just maybe ask my final round-up question, which is something I'd like to throw at all of our guests. So, you know, if you could give your one piece of advice or, or wisdom to anyone in either work or career progression, life health, self-improvement, what do you think it would be and why?

Evert (16:57):

Career-wise, particularly in the field of science, I would say be passionate about what you do and be patient. I know this is something we hear a lot from day to day, but when it comes to science, almost 90% of the things that we do the first time they fail. It's that passion and resilience that get you to do that next step, that ends up being a success or so keep that passion as you end embark on this journey.

Drew (17:29):

There, we have it, the value of failure and resilience, many thanks to Evert for coming on and sharing this exciting work and really elegant approach to protecting against all kinds of infectious threats. We'll have more about this topic as well as other Scripps Research content in the show notes. So make sure to take a look, thank you very much for listening. We really do appreciate you tuning in and you can revel in the spirit of gratitude by leaving us that five-star review and sharing the podcast with your friends and family. We'll be back soon with more impactful stories. So until then stay sharp, be wise and take care.