Speaker 1:

Welcome to the Eye on the Cure Podcast, the podcast about winning the fight against retinal disease from the Foundation Fighting Blindness.

Ben Shaberman:

Welcome, everyone, to the Eye on the Cure Podcast. I'm your host, Ben Shaberman with the Foundation Fighting Blindness and I am delighted to have as my guest today Dr. Rachel Wong. I met Rachel after her lecture at the 2022 ARVO meeting, it was the prestigious Friedenwall lecture. In case you didn't know, the ARVO meeting, it's a big international meeting on eye research held annually. This year it was in Denver in early May, and I loved her talk about retinal circuitry, and she was gracious to talk to me after her lecture, and then she agreed to be a guest on Eye on the Cure. Welcome, Rachel, it's great to have you.

Dr. Rachel Wong:

Thank you Ben, pleasure to be here.

Ben Shaberman:

Before we begin our conversation with Rachel, I wanted to give you a little background on her as a scientist. She is a neurobiologist recognized for her work on understanding the development and assembly of neuronal circuits. She was born in Kuala Lumpur, Malaysia graduated with a bachelor of science with honors in physics from Monash University, and a PhD in visual neuroscience from the Australian National University. She obtained postgraduate training at the National Vision Research Institute in Australia, and Stanford University, and the Vision Touch and Hearing Research Center in Australia. This all happened before joining the faculty at Washington University in St. Louis in 1994, and she is currently professor and chair of the Department of Biological Structure at the University of Washington in Seattle. You've done both Washington University and University of Washington. My first question, Rachel, is when did you realize you wanted to study the circuitry of the retina? It's not the most obvious thing that somebody jumps into for research or just a learning topic.

Dr. Rachel Wong:

This is true, especially for a physicist. I think my interest in the retina stems from my graduate school days in Australia in the early nineties, so a little while ago. I had joined the applied math department at the Australian National University, but at that time, I still wanted to be an experimentalist rather than a theoretical physicist. My math advisor introduced me to Abby Hughes at one of the leading vision science departments in the world at that time, [inaudible 00:02:54] by Peter Bishop at the John Curtin school. Abby put me onto a first project to introduce me to the retina and that was to determine whether a large population of small cells in the mammalian retina when neurons are clear, and charged me to find a way to correlate their morphology and the light microscopy with the outer structure using electron microscopy.

This was because the only way then that we confirmed the identity of a nerve cell was by the presence of synaptic connections. These where neurons talk to each other and communicate, and this really required reconstructing the retinal cells at nanometer resolution. When you come sort of up close and personal to a piece of tissue with that kind of project, I eventually was really struck by the beauty of the retinal cells and the highly organized connections that they make, and decided then as a graduate

student that I wanted to explore the developmental mechanisms that give rise the retina's structure and function. I think that began my long, many decades of journey working on the retina.

Ben Shaberman:

From your lecture and just some other exposure I've had over the years, I don't think we appreciate how vast and complex all the circuitry of the retina is, all those neural cells and tissue. In the world of retinal disease, at least in the world that we inhabit at Foundation Fighting Blindness, we're often talking about photoreceptors, because those are the cells that respond to light and kick off the visual cycle, they make vision possible. Sometimes we're also talking about RPE cells, which provide support for photoreceptors. But there are other really important cells in the retina and there are lots of them, and can you talk about some of these other cells, like bipolar cells, and ganglion cells, and the roles in processing visual information that's ultimately routed to the brain?

Dr. Rachel Wong:

I'm happy to do so, I think the focus on photoreceptors is certainly really important, because they are one of the cell types in the retina that undergo death in many diseases, and hence focus on photoreceptors. Without photoreceptors, we will not be able to see, so that's important. But I'll take you from what happens after light hits the photoreceptors, and as you say, when they absorb light and kick off the visual cycle. The signals from the photoreceptors have to pass through whole layers of neurons in the retina and information has to be processed before it is passed onto the brain. Really, the retina compresses of five major neuronal cell classes, as well as glial cells, the signals from the photoreceptors are conveyed to the retinal bipolar cells. They're called bipolar because they really look like they stretch on both sides.

These bipolar cells collect information from the photoreceptors and they pass that information through a layer of what we call other interneurons that eventually will reach the retinal ganglion cells. The ganglion cells are also really important, they tend to die also in some diseases, like macular degeneration, for example. They're important because it's the ganglion cells that collect all the information from the photoreceptors, for example, and they are the sole output cells of the retina. These ganglion cells form long cables called axons that connect to the brain, and is in the brain, of course, the final processing is done before we actually see. Now, within the retina, the signals from the photoreceptors or the bipolar cells are modulated by two classes of interneurons called horizontal cells and amacrine cells. You don't only have a vertical pathway from photoreceptors to bipolars to ganglion cells, but you also have lateral connections that shape eventually that output of the ganglion cells through interactions with horizontal cells and amacrine cells.

Why do we care about the rest of these cells? It's because really, circuits within the retina formed by these five neuronal classes, process and relay all kinds of visual information, not just like intensity changes or contrasts. In fact, there are many, many types of retinal ganglion cells connected to many, many types of bipolar cells and amacrine cells. Each ganglion cell type has specific properties, they are feature detectors and it's their circuit patterns that dictate what the major features might be that a particular ganglion cell type interested in. For example, there are ganglion and cells that respond well to one particular direction of movement. Their preference to that direction is really shaped by connections, very asymmetric types of connections, with one particular type of amacrine cell. You can see, the retina is very built with many, many micro circuits using all five neuronal cell classes to collect all that rich information to give us essentially vision, not just light detection but vision.

Ben Shaberman:

Right, and you were talking about perception of movement and I don't think we appreciate how well our retinas adapt to moving objects and how well we can see relatively fast moving objects. But there are also a lot of other things changing in our visual landscape, light, contrast, colors, and all these things are happening in real time. If I understand correctly, it's some of these other cells in the retina, like ganglion cells that are helping us perceive that changing environment. Is that correct would you say?

Dr. Rachel Wong:

Yes, that's definitely correct. I brought up only direction selectivity as one feature, but of course, there's color, there's contrast, there's orientation, so you might prefer particular orientation of a [inaudible 00:08:59] versus another. There is photo processing of course in the brain as well, we talk about the output of the retina, that goes to many visual centers in the brain and where visual brain cells are also important for detecting and processing motion, for example, different directions as well. One thing that of course the brain is really important for is also binocular vision, because now you have to integrate process signals from both retinas, not just retina. [inaudible 00:09:30] of blindness really occurs you to disruptions to the retina in the eye or to visual centers in the brain. We certainly also have to understand the connections between the retina and the various brain centers.

Ben Shaberman:

The complexity is daunting, the more you dive into it, but that's exactly what you're doing. Can you tell us more about the work in your lab and why it's so important for the development of treatments and cures for retinal degenerations and other conditions of the retina?

Dr. Rachel Wong:

Yeah, sure. I think as I mentioned, blindness is often caused by death of retinal photoreceptors or the ganglion cells, so the input side to the retina and the output side of the retina. There is much work and also a lot of progress in replacing these cells that have been lost through injury or disease, so still long way to go, but there's tremendous efforts in replacing photoreceptors, and also more recently, in retinal ganglion cells. But we have to think about what environment we are putting these new cells back into, and whether these new cells can really reconnect with the rest of the cells that have been left behind and survived the disease or the injury. We hope that our studies can help strategize rewiring of the retina in cell replacement, I think therapies in two ways, at least hopefully in two ways. First, we would like to discover the mechanisms that normally ensure that retinal neurons wire together appropriately to form the various retinal circuits, and we have mentioned that there are many.

I think that such knowledge would help us better understand what factors are critical for facilitating accurate reconnection of retinal cells. Secondly, we are trying to get a deeper understanding of the structural and functional changes that occur in retinal circuits after some populations of cells, such as photoreceptors, die. This is about the environment the new cells have to sit in, I think knowing the extent that time course and circuit specificity of these cellular rearrangements could help us better tailor strategies for circuit repair. For example, we can ask when must reconnection renew cells occur in order to be able to recover the original circuit patents, or what kind of therapy needs to be designed to enable adult cells to reengage developmental mechanisms that guide formation of proper circuits? Although, much of our studies focus on neural development, how retina circuits of various types become assembled properly. We have also been interested in looking at what happens after those circuits are formed, what keeps them in place and what causes perhaps rearrangements after this disruption.

I could go in a little bit and say that our lab really applies therefore microscopy techniques, this stems for my old days as a graduate student. But we collaborate also with really wonderful colleagues, who are

experts in probing retinal function through electrophysiology and also in identified gene expression in retinal cells. I think a multidisciplinary approach is necessary in order to advance our understanding of normal retinal circuitry and function, and also in restoring such circuits and their function in disease. Collaborative work, not just work from our own laboratory should be supported, and I think would trigger faster progress.

Ben Shaberman:

Right, and I'm really glad you talked about the environment for connecting new cells, transplanted cells, into the retina. Because from my understanding, that's really perhaps the biggest challenge with cell-based therapies now is you can grow new photoreceptors, but to get them to integrate and survive in the host retina is a really big challenge. We appreciate the work you're doing to understand the environment that we're putting these cells in. One thing I want to add for our listeners, for those that can see, you have some wonderfully beautiful images on your webpages when I was doing a little research.

Dr. Rachel Wong:

Thank you, Ben.

Ben Shaberman:

You take beautiful pictures of the retina, and it really is a beautiful piece of tissue and you capture that beauty really well. One thing that I think is important about your lab is that the people in your lab, you've had some pretty remarkable people come out of your lab. I really have two questions. One, what's it like to run a lab and be a mentor for all these younger scientists, mostly younger scientists, and can you talk about some of the personalities? I know Rachel Huckfeldt, Jeff Mumm, some people that have been funded by the foundation have come out of your lab.

Dr. Rachel Wong:

Sure, I think first of all I should say that running a lab is really about being committed, not only to solving scientific problems but also to the training of young scientists to become outstanding researchers in their own right. I think that certainly apart from scientific discoveries, this is the most satisfying aspect of running a lab, that is to see one's trainees grow as scientists and also as individuals. Really, I think the discoveries in the lab belong to the trainees and our support staff, I think I'm the facilitator. It's extremely rewarding to see trainees like Rachel and Jeff pertain their career goals and make an impact in the vision world.

After they've established their own labs, for example, and very, very successfully. I have worked with many graduate students who also train as physicians, such as Rachel, and I've watched them become outstanding physicians. Three have become ophthalmologists, perhaps not surprisingly, and also excellent researchers. I think this really makes me really, really happy, because I think in the end, it's not just what we might find together while we are in the lab, but also beyond that, all the discoveries and the impact, even in terms of patient care, that really is really important. I'm happy to be part of that, rather than be the person who has done it.

Ben Shaberman:

Well, thank you for being such a great mentor. For our listeners who don't know, Rachel Huckfeldt, who we've been talking about, is an outstanding clinical researcher and is involved in several clinical trials at

Mass. Eye and Ear, and Jeff Mumm is a zebrafish expert, I believe he is still at Hopkins, I haven't talked to Jeff in a little while.

Dr. Rachel Wong:

Jeff's at Hopkins.

Ben Shaberman:

He's looking at therapies and retinal regeneration in zebrafish, which is a really important aspect of our world. Keep churning out the great talents, Rachel, we appreciate that. I'd like to thank you for taking time today to talk about your great work. It's an important aspect of the effort to get treatments and cures into clinical trials, to understand how especially cell-based therapies can work. You might not get the visibility in our space, because you're not directly involved in developing treatments and cures, but the work you're doing makes them much more likely to succeed. Thank you just for taking time and talking about the circuitry of the retina, it's very cool. I wish you the best moving forward.

Dr. Rachel Wong:

Thank you very much, I'm glad to have the opportunity to share some of my thoughts.

Ben Shaberman:

I hope to see you next year at ARVO, I think it's in New Orleans, so that should be [inaudible 00:17:22]. Thanks, as always, to our listeners for joining the podcast and we look forward to having you back for the next episode. Take care, everyone.

Speaker 1:

This has been Eye On the Cure. To help us win the fight, please donate at foundationfightingblindness.org.