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Do you have a story to tell about your own NET journey? If you're a NET patient who would like to participate in a future episode, please email us and let us know! podcast@netrf.org

Welcome to NETWise. This is a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. I'm Elyse Gellerman, from the Neuroendocrine Tumor Research Foundation.

Today, we're going to pick up where we left off in the last episode of NETWise – looking at how scientists do the research that we hope will yield the next generation of effective treatments for NETs. Today, we're going to look specifically at the important role NETRF plays in this process, and how and why we choose the researchers we support.

We're in an interesting time for NET research. There is still an awful lot we don't know about NETs, but we also know more now

than we ever have in the past. When NETRF was founded, in 2005, we knew very little about the biology of neuroendocrine cancers. Here's Dr. John Kanki, NETRF's Director of Research:

Kanki: *"Fifteen years ago, we knew nothing about how the disease formed. And the treatments, at the time, were relatively ineffective because they were really treatments for other kinds of cancers that didn't work as well on NETs because we didn't know how NETs formed in the first place and why they formed in the first place. Once the foundation was started and funding started going to research to understand the basis, the biological basis of NETs, then we started to understand a little bit about the disease."*

And we're proud that our work since then has been instrumental in transforming the way NETs are understood and treated.

Kanki: *"The initial research from the foundation has contributed to the development of the current therapeutics now used to treat NETs."*

The reason our support has been so effective is that we directly addressed a major gap in public funding for NET research, support for basic and translational research – work in which scientists ask the kinds of questions that lead to understanding of the fundamental biological mechanisms of this uncommon cancer.

The National Institutes of Health and other large government agencies provide essential support for medical research, but they have a tendency to favor funding research for cancers that are more prevalent. They also tend to favor research that could move more quickly to lead to the development of new therapies. They're less likely to fund research that could break new ground in the field. A problem is that without the freedom to look in new places and try new approaches, scientists can't test the innovative and different ideas that may be needed to target this unique type of cancer. This is where NETRF has always felt it could be the most useful.

Kanki: *"It's what we tend to call "high risk, high reward" type research. It's taking jumps, it's taking leaps. This is the way that NETRF tries to fill the gaps in the overall funding of NET research. Try and fund research that will lead to the creation of new ideas, new cutting edge technologies, the use of new technologies to be able to address NETs in different ways. And really to also make sure that we focus on understanding the disease more, not just its treatment."*

Here's Dr. Dawn Quelle, a Professor of Pharmacology and Neurology at the University of Iowa, followed by Dr. Ramesh Shivdasani, an Oncologist at the Dana Farber Cancer Institute at Harvard University. Both are members of NETRF's Board of Scientific Advisors.

Quelle: "A lot of times you can't get significant research funding from NIH or other federal agencies unless you have a lot of data or you've already been demonstrating key findings for years and years in that field. So, what we're trying to do is we need to get preliminary data that support an initial idea. And frankly, that's where NETRF comes in as this major enabler for researchers. We're looking at very high-risk ideas that may not be successful but there's enough excitement, justification, or rationale to support them."

Shivdasani: "There's a real push from Congress, from policy makers, from patient advocates. 'Get me the treatment. Get me the treatment. My mom has cancer. She's not going to live long enough for your research to bear fruit.' The patients' needs, the public's demands are not unreasonable but they can be somewhat shortsighted. Nobody, and I repeat nobody, is really smart enough to predict where the discoveries are going to come from."

Kanki: "It's only understanding the basis of the disease that you can actually cure or prevent it. And to me, that's the gold medal. That's what we're really trying to shoot for. NIH tends to be careful with its money. It doesn't want to fund research that's going to be risky. The bigger ideas, the high impact ideas with less preliminary data will not be funded by NIH, and that's the gap."

Another very important aspect of supporting NET research is NETRF's efforts towards building and sustaining a collaborative, connected, global community of NET researchers. This is particularly necessary for NET research so scientific advancement can be as effective and cost-efficient as possible.

Kanki: *It turns out that over the last 15 years that NETRF, while the grants tend to be smaller than NIH, it's funded a greater number of NET research investigators. And this is really important because this larger number of investigators that it has supported through the years that is really responsible for creating and maintaining a research community. And a research community that's dedicated to NETs is really important. You need that kind of collaborative and cooperative interaction between investigators in a given field in order to really drive that research and advance that research as effectively and efficiently as possible. You want people to share their data. You want them to be able to learn from each other so that collectively they move the field forward together."*

Here's Dr. Chrissie Thirlwell, Professor of Cancer Genomics at University of Exeter in England and Co-Chair, along with Dr. Quelle, of NETRF's Board of Scientific Advisors.

Thirlwell: *"What is great to see is there are researchers globally, who, again, through NETRF have been encouraged to work together and collaborate through some of the funding*

streams and through lots of other mechanisms. And there is such determination to really get further and to crack this.

And we actively encourage people who haven't worked in the NET field before because some of our biggest advances have been by people who are brilliant scientists in other areas, who've then started working on NETs. And quite a few years ago, NETRF would sometimes approach labs that were doing brilliant work in cancer research but hadn't actually worked in NETs before and said, "Would you be interested in doing that? And for me, that was a really refreshing and innovative approach to take in scientific research and endeavor."

Quelle: *"This has been a small group of researchers that, in my understanding, has grown in leaps and bounds in the last 10 to 15 years. I think NETRF has really helped this because you're really the flagship organization that is driving a lot of this basic research. And I'm seeing just a wealth of new investigators interested in joining the field. So, that to me is really exciting to see all of these people coming in who have expertise in other cancer systems and they're applying their expertise now to neuroendocrine tumors. So, hopefully we can keep seeing more advances over the next five to 10 years as we have this influx of new investigators."*

NETRF supports researchers with a variety of different grant programs, aimed to help scientists doing different kinds of work at different stages of their careers.

Kanki: *"There are four different awards that we currently have. The largest is called an Accelerator Award, which is really to provide funding for more than one investigator for them to work as a collaborative with other groups and to collectively address a particular problem in NETs.*

Then we have what's called an Investigator Award, which is for a single investigator driving research on a hypothesis or an idea that they have singularly developed. And they want to test that hypothesis and based on their findings, then they might be able to move that research forward.

Probably my favorite award is the Pilot Award. These are very small one year awards. They provide funding for people to think outside of the box and to try and come up with ways that haven't been tested before that may really contribute to advancing our understanding of NETs or the treatment of NETs.

And then we also have what's called a Mentored Award. And this is an award that goes to a young scientist that's still working within the lab of their mentor, who is generally a senior investigator in NET research. And that young investigator needs to be funded in order for them to, for example, develop their own ideas and their own NET

research that they can potentially take with them as they go out, look for a job as an investigator to start their own laboratories. And then having that preliminary data, they might be able to go to another funding source such as NIH, that then sees that the background data is there, that this is likely to work and they can take their idea further."

The ability to support young NET investigators is critical to establishing a pipeline of NET researchers to advance the field. That first grant can launch a career.

Thirlwell: *"I can talk from a very personal perspective here. I've actually been involved one way or another for over 12 years with the organization before it became NETRF, and my very first grant that helped me get my first big clinician scientist grant came from the organization and that gave me such a pivotal stepping stone."*

And research grants are just one way that NETRF supports scientists and the scientific community

Thirlwell: *"I think the other element about NETRF, which is great for early career and junior researchers, is the annual symposium that we have because it is very open. It's a very safe place to discuss your results. People discuss results before they're published in a safe environment and in a very supportive environment. And I've always found that a really, really helpful and positive experience*

through my career. And it also helps build collaborations as well. So, I've formed my longest and most productive collaborations through NETRF. That's been a really good experience for me personally."

NETRF's Board of Scientific Advisors, or "BOSA", is a group of more than a dozen global leaders in NET research, representing a wide range of specialties from Oncology to Pathology, Gastroenterology to Genetics, and well beyond. Their process for choosing who should receive NETRF's research awards is a painstaking one, carefully reviewing each proposal to make sure we choose the ones that will be the best fit for our support.

Thirlwell: *"We spend hours on our scientific advisory board reviewing these and discussing them together. And each review has about three or four different people looking at it all from slightly different angles. There are usually three general areas we look at. We want to see what the group of people, what the individual or the group of people putting the application in, have done and what expertise they're bringing to NET research. So, we look at the background and the collaborations or the work that those people have done. Then we obviously look very, very closely at the proposal that's coming to us. And it's a very, very well thought out and very thorough review of the application. We want to see, 'Is this new? Is this exciting? Is this the right place to do this research, in terms of literally down to, is there the right equipment?"*

What's the track record of that physical place or that institution? Do these people or does this group have everything they need to do that? Will they be able to get the samples they say they're going to work on? Is this a model that we think might be a goer?' And then the actual real crunch point. We have to think, 'What's the translation? What's the clinical impact? Where will this take us?' So, you kind of... in very simple terms, it's sort of people, place, proposal, but it's the science. Is it novel and will it really help us take our understanding one step further?"

Quelle: *"They all need to have the most rigorous justification and the most compelling design for their studies that we think will actually yield beneficial information, interpretable data and that would actually address the question that they're trying to ask. So, we look for very rigorous experimental designs and they need to justify what they're doing."*

Thirlwell: *"And if not, we give feedback, we make suggestions and we have in the past linked different researchers up together so that they can actually collectively have a far more impactful review. And again, I find that very refreshing. When I've sat on other grant review bodies, it can be less open in terms of actually giving a lot of feedback or actually suggesting, 'Perhaps you might want to work with such and such a group. They've*

got experience in this area.' So, I find it a really refreshing and positive review process to be part of."

Quelle: *"Good science is what gives you good information and that's all we're looking for."*

So what kind of work is being done right now by this global community of researchers? We thought a good way to present a cross-section of current research would be by looking at the work being done by the scientists we spoke to here. All are members of our Board of Scientific Advisors, and accomplished researchers, many of whom have received support from NETRF grantmaking at crucial moments in their career. Let's hear a little from each of them about the questions that are currently being asked in their laboratories, and the potential they have to help us work toward new and better treatments for neuroendocrine cancer.

To begin with, Dr. Shivdasani and his colleagues are asking very fundamental questions – looking past the formation of NET cancers all the way to the formation of neuroendocrine cells themselves. If we better understand how healthy neuroendocrine cells form and reproduce, we can then better understand how that reproduction might go wrong.

Shivdasani: *"There are endocrine cells in the pancreas, in the lung, in the digestive tract that make a panoply of different hormones. So, any of these tissues will have half*

a dozen to a dozen, very diverse cell types that together make up the tissue. Neuroendocrine cells are one tiny minority in that population. All of these different cell types begin with a primordial cell that we call a stem cell because it has the capacity to branch into multiple different distinct cell types, all in the same tissue. One of those is the neuroendocrine cell type. We understand very well or we understand better how each of the other cell types in the pancreas or the intestine or the lung comes to be. But we know almost nothing about how the endocrine cell comes to be. And we also therefore know very little about what the steps might be that would turn that cell into a bad actor, into a cancer. And so, we are putting the cancer question itself almost on the side and saying, "We'll get to that," but we have no hope of understanding the cancer without first understanding the blueprint of the normal cell.

Joe Zhou – who is my co-investigator on the Accelerator Award from NETRF – he had the wherewithal to create a cell system. He borrowed a concept that originally was developed in the skin and did the same thing in the intestine where he took primary cells from human surgical specimens or biopsies, cultured them in a petri dish in a very specialized way that allowed the stem cells to expand. And they expanded in this way, indefinitely. This has not been done before. To this, he added a single factor that converts those stem cells into hormone producing endocrine cells. And this allows those cells over the course of the

next five days to go from completely primitive cells that could have moved in any direction. They're particularly flexible stem cells. And now 98% of them turn into completely terminal endocrine cells. At the same time, there were other developments in molecular biology in general that allow you now to follow a trajectory of cells and break it down at the resolution of single cells. So, you can ask any given cell as it's inching its way along this path to get to the end point. You can look at every population of cells and ask at any given time, "What is the state of a single cell?" This technology did not even exist even in my imagination when we wrote this grant five years ago. And so, we took advantage of that. And we now have, for the first time, a complete map of the path that cells take in order to achieve this endgame."

One of the reasons this work is so exciting is that it could potentially open up entirely new treatment strategies for NETs. Perhaps, instead of killing cancer cells we could rehabilitate them... somehow causing them to revert to a normal, healthy rate of growth. We're very far from actually accomplishing this, but if we did it would be a game-changer for cancer treatment.

Shivdasani: *"The vast majority of energy has been focused on how to kill the cells, which makes perfect sense. These are cells that don't belong. They're not doing you any good. And if you can kill them, all the power to you, and almost all cancer therapy is focused on killing the cells. And it works but only a tiny fraction of them are curative."*

And the reason for that is because you can't possibly kill every last cell. You can kill 99. You can often kill 99.99% but all you need is to leave a handful of cells behind and they'll grow back. So, the fundamental problem is, how can you kill the very last cell but not also kill the patient in the process? And therefore all of cancer treatment grapples with the issue, what we call the 'therapeutic window'.

Sure, I can give you enough chemotherapy right now to kill every last cancer cell in your body. But before I kill that last cancer cell I'll have destroyed your liver, your heart and your kidneys. So, there's no point in that. So, what has to continue with the research on how to kill cancer cells, it's still a powerful weapon, but if you could devise an alternative strategy, which is to push the cells back into a normal physiologic state where they can't do harm. They can't spread, they can't travel, they can't overgrow, then you've effectively cured the patient. And so, a fundamental premise of our approach is that we will endeavor to understand how cells that have broken the rules can be forced not to die necessarily but to return to obeying rules that will prevent symptoms, disease or death."

Dr. Quelle's team is working a little later in the life cycle of NETs, studying a particular protein that seems to be related to

the process of turning healthy neuroendocrine cells into cancerous ones.

Quelle: *"So, in my group, we study a protein called RABL6A. It's a tumor promoting protein. We've been studying for the past 15 years, how it works. How does it tell a tumor cell to keep growing and to stay alive when it shouldn't stay alive? Or how does it tell a tumor cell or enable it to migrate and metastasize to it, a new site? And what we've learned is that this protein is really highly expressed in neuroendocrine tumors, both at the pancreas and the small bowel. And we learned that if we get rid of it in mice, we can actually slow down the formation of insulinomas in a very common mouse model. So, we've learned about what does RABL6A do to promote cell growth? Who actually carries out its actions within the cell? And so, by identifying its effector proteins, we have figured out, "Well, there are lots of very prominent effector proteins that we can target with drugs."*

They include AKT, kinase, which is one of the drug targets that is being used in neuroendocrine tumor therapy today when you have AKT mTOR inhibitors like everolimus. So, we were excited that RABL6A is controlling a relevant pathway that normally is controlling neuroendocrine tumor growth but we know that that therapy on its own also will ultimately lead to drug resistance. So, we wonder about other targets of RABL6A. And the exciting thing is that we've found lots of different targets of RABL6A and what

we're doing is using current drugs that are in the clinic and used to treat other cancers and we're combining them with existing drugs as well as new drugs. And we're finding that there are particular drugs that work really well together. And so, they synergize to kill the tumor cells and prevent them from expanding and growing. And that's really what we're hoping to translate from our animal models. And we're working with our clinical colleagues to develop clinical trials where we test these combination therapies."

Dr. Thirlwell's team is also trying to understand the factors that cause healthy neuroendocrine cells to turn into NETs, by looking at epigenetic factors that may be involved. This means things in your cells that are not genetic code, but can affect the way genes reproduce.

Thirlwell: *"For the last 10 years or so, we've been looking at the DNA sequence of different neuroendocrine tumors. Our first five years of work, which was a collaborative piece of work with Matthew Meyerson's team at the Broad, was in sequencing the intestinal NETs. We couldn't find any actionable mutations. Pancreatic and lung tumors as well, they have pretty much the lowest background mutation rate of any cancer. There's very little going on. And in the intestinal NETs, only 8% of them had a mutation in one gene, which we couldn't give a drug to. And then when we looked to see if that gene told me as a cancer doctor, if*

those patients did better or worse, it didn't actually help with that. And it wasn't from ones who tried. So, it was at that point with my group, I thought, 'Well, we can't get the answer with the sequence here. We need to focus on the epigenetics and look at other ways that this biology might be evolving to make this normal cell cancerous.'

So, a genetic change is a change in a DNA sequence. An epigenetic change is something that doesn't change the sequence but it can still switch your genes on and off. And that's where our work's focused. And what we found with that is we found different groups of intestinal NET, which when you look at them down microscope are all the same. So, a pathologist would give them all the same label but we found three different groups and they have different clinical outcomes. So, that in itself is helpful because it can tell us whether a patient's tumor might be more aggressive or less aggressive. And in their pancreatic and lung neuroendocrine tumors, around 40% of them have mutations in the epigenetic machinery. There are things called histones, which you wrap your DNA around and it condenses the DNA so it fits into that tiny nucleus. And this forms a micro chromatin. So, in the pancreatic and the lung NETs, we find mutations in the histone modifiers and chromatin remodelers. And that's in about 40% of cases.

So, those are some of the areas where we've been learning a lot more about the biology but unfortunately it hasn't led

to a change in the treatments that we actually use in clinics so far."

But that's ok. As we've said throughout these last two episodes, it's only by asking these fundamental, high-risk, high-reward research questions that we're truly going to understand neuroendocrine cancers. And that deep understanding will lead to truly innovative treatments.

We're very proud that taking this approach for the last fifteen years has already shown real results.

Kanki: *An analysis that I did last year, looking at some of the first studies that were funded by NETRF show that they indeed were being translated into the clinic. And you can tell that by looking at the kinds of citations and how other researchers in the field are taking that data from those research projects and using it in their own research to move towards potential therapeutic realization.*

And we're just getting started. By staying this course of supporting gifted researchers asking deep, fundamental questions, who knows what the next fifteen years will bring?

Thirlwell: *"I'm just so incredibly proud to be part of the working organization in the BOSA. It's fantastic seeing how NETRF has evolved and grown and seeing its global reach. It gives the best funded and well-resourced research funding*

globally. It's been just fantastic to see the organization grow and just the global reach it has now."

Thanks for listening to NETwise. I'm Elyse Gellerman, CEO of the NET Research Foundation. This episode was written and produced by David Hoffman of CitizenRacecar; Post-Production by Garrett Tiedemann (*TEE-da-min*); Production Manager, Gabriela Montequin (*mon-ta-KEEN*). It was made possible by the generous support of Ipsen; Advanced Accelerator Applications, a Novartis Company; TerSera Therapeutics; and Progenics Pharmaceuticals, a Lantheus Company. Special thanks to everyone we interviewed for this episode. We are grateful for your expertise. This is a production of the Neuroendocrine Tumor Research Foundation. We're committed to improving the lives of patients, families, and caregivers affected by neuroendocrine cancer by funding research to discover cures and more effective treatments and providing information and educational resources. Please visit us at NETRF.org

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