Episode 41:
2024 Year in Review
Transcript

If you're new to NETWise, we highly recommend you go back and listen to the first episode in this series. It goes over the basics of neuroendocrine tumors and how they're treated. And you can find a whole library of episodes on different topics at netrf.org/podcast, where you'll also find infographics and videos that expand on this material.

If you have a story to tell about your own NET journey, please email us and let us know – podcast@netrf.org.

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In late October, more than 100 people traveled to Boston from across the United States and 11 countries for NETRF's 17th annual research symposium. They included scientists, doctors, patients, and other members of the neuroendocrine cancer research community.

> ***Vox pop:*** *So hi, I'm Eleonora Pelle. I'm a medical oncologist. I work currently as a postdoctoral fellow at the Moffitt Cancer Center in Tampa.*
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> *I'm Andy Liao. I'm a medical oncologist from the University of Chicago.*
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> *I'm Xiangsheng Zhu. I'm an associate professor at MD Anderson, GI Medical Oncology.*
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> *I'm Brittany Holzhauer, I'm a NET patient, and I also have a non profit, the CureNet Project*

Over the course of the three-day symposium, there were panel discussions, slide presentations, and posters.

PhD students struck up conversations with seasoned scientists, and donors talked with researchers putting their funds to good use.

> ***Vox pop:*** *Hi! I'm, uh, Richard Fielders from, uh, Rosses Medical Center, Rotterdam, the Netherlands, and, uh, I*

work on neuroendocrine tumors, but also adrenal tumors and pituitary tumors.

My name is Samuel. I am a PhD student in Daniel Shermack's lab, and my project is about building a mouse model to study pancreatic neuroendocrine tumors.

I'm Julie Mebane. I'm involved on the board of directors. I'm the vice president of the board and the chair of the development committee. And I'm also a patient, so, uh, it's just great to see this science in action.

You're listening to NETWise. I'm Jessica Thomas, Director of Patient Education at NETRF.

In each episode of this podcast, we share expert information and patient perspectives to help neuroendocrine cancer patients and caregivers navigate their journeys.

The mission of NETRF is to fund research to discover cures and more effective treatments for neuroendocrine cancers.

And in this episode, we're continuing an annual tradition, where we look back on the work that's been done in the past year, and celebrate the progress that's been made.

Welcome.

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At NETRF, we look forward to the research symposium every year. Over the course of a few days, scientists leave their individual labs and come together to create a large picture of progress.

We bring this community together and invest in this work because we know that robust research like this is the key to one day putting an end to neuroendocrine cancer.

Elyse Gellerman is the CEO of NETRF.

> ***Gellerman:*** *We strongly believe that if we don't understand how these tumors form, how they spread, then we can't really develop effective treatments.*

There is a lot we still need to understand about neuroendocrine tumors. They are complex and heterogeneous – they take many forms, and can appear in many locations throughout the body. Research is how we can unlock this understanding.

> ***Gellerman:*** *You know, those treatments emerge after years of working in laboratories and looking at cells under microscopes and sequencing the DNA in those cells. That's where really the thought process and the discovery process begins.*

Research is all about discovery. It's about trying to figure out how something works, and applying that knowledge to make progress.

> ***Bibb:*** *The point of what we do is to try to understand medical problems and then to drill down on them, and take it into the back room and start to pull it apart and look at it from as many different angles as possible, and with as many advanced technologies and innovative approaches as possible, to understand what's the cause of this problem. In this case, what's the cause of neuroendocrine cancers.*

James Bibb is a scientist, and chair of the department of Translational Neurosciences at the University of Arizona College of Medicine.

> ***Bibb:*** *And then with that relationship between our physicians and with the help of what they learn from their patients, we're able to start to make new observations about what causes this? And then where are the vulnerabilities? Where is there something that we can*

> *see that we could target to disrupt and interfere with this process? And then bring something that we can test in our models that we've built. And if we have a drug that is working in our models, then the question really is, can we bring this to the clinic?*

What drives all research is the desire to improve human health. And the process of conducting meaningful research exists along a spectrum, with the lab on one end and patients on the other.

As longtime NETWise listeners will remember, this spectrum consists of three essential kinds of research: basic, translational, and clinical.

Dawn Quelle is a cancer researcher at the University of Iowa, and a co-chair of NETRF's board of scientific advisors. Her work focuses on understanding what drives the growth and metastasis of neuroendocrine tumors.

> ***Quelle:*** *Basic research is trying to determine the fundamental mechanisms of biology and biochemistry or chemistry, and trying to then take that knowledge and move it towards an actual system is more what we call translational research.*

Translational research is where the observations made about tumor *cells* are tested on tumor *models*.

> ***Quelle:*** *So if we learn that there is a particular kinase or enzyme that's really active in the tumor cell in the basic research, now we can say, is there a drug that targets that enzyme or protein? And can we now treat an animal that has that kind of tumor and show that we can decrease the growth of the tumor? That's translational research.*

And then in clinical research, researchers assess how safe and effective a drug might be in a patient population.

> ***Quelle:*** *We can predict whether that tumor would grow faster, or whether there's a good chance for longer survival for that patient, or whether they should not go into a certain clinical trial because they don't have the right mutation in their tumor. So there are differences. There's a continuum of research, basic to translational to clinical.*

In this episode, we're going to talk about some ways the needle has been pushed in each area of research in the past year. We'll start with advances in basic research, and move through the spectrum to finish with updates that have clinical applications.

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In basic and translational research, some of the biggest developments come from the use of technologies that make science more detailed and precise.

The first one we want to talk about is something called omics.

"Omics" is a way of referring to a group of technologies that examine specific aspects of a tumor. These include things like genomics, which detects genes in a biological sample, and proteomics, which looks at proteins in a sample. Together, omics can create a rich picture of the molecular makeup of an individual tumor or tumor type.

Iacovos Michael is a researcher at Sunnybrook Research Institute in Toronto, and a NETRF grantee.

> ***Michael:*** *You can think about it as this very high resolution image we can take of a tumor. You can compare it with the old cameras we had on our phones compared to the new phones' sophisticated cameras that give you this high resolution. And in addition to having the image, maybe you have some specific parameters [like] where was the image taken, what day was, uh, what time, what was the temperature, the elevation and all that.*

This creates a whole new world of data that researchers are using more in their work.

A multi-omic approach can generate large libraries of information from hundreds of tumors, which could open new windows into understanding them.

> ***Quelle:*** *And we're mining that information and we're getting deeper and deeper into the weeds, but that actually gives us more insight into what's different between the tumor cells and the normal cells. And I think that's really where we've made tremendous advances in the past year, but also the past five to ten years.*

The second advancement in basic & translational research that we want to talk about is something you've definitely heard of: artificial intelligence.

These omics we've been talking about generate enormous amounts of data, more than researchers could process and analyze on their own. AI can assist in the work of organizing and interpreting all that data.

> ***Bibb:*** *Once you teach these programs how to analyze that data, then you can go and drink a coffee and when you come back, you've got this new organization of data where before it was just a huge heterogeneous forest. Now we can see everything, all of the individual leaves in that forest and we can pick the leaves that we want to examine closer.*

With the help of AI and omics, the hope is that our understanding of these cancers will improve more quickly and precisely than before.

In fact, the combination of omics and AI is already helping to fill in gaps caused by a lack of models.

This has been a longstanding challenge in neuroendocrine cancer research. Models are an essential research tool which

allow scientists to study cancer outside of the human body. They include cells grown in a petri dish, animals in a lab, and digital simulations of living cells. But the complex and unique nature of neuroendocrine neoplasms have made models more difficult to develop than they are for other cancers.

Now, with these new tools, scientists can extract more data from the *available* models.

> ***Michael:*** *It will allow us to understand whether the patient- or predict whether the patient will respond to the same therapy the patient will get. And if it doesn't respond, we can use the omics technologies, to dissect why it didn't respond. And then we'll ask ourselves: is there a second treatment that maybe is already approved that we can give to this patient so we can extend the survival and maybe shrink the tumor at the end?*

The use of all these technologies together can help deepen our understanding of neuroendocrine cancers.

Like Dr. Michael just mentioned, one example of something scientists are working to better understand is why a tumor might not respond to a given treatment, or become resistant to it over time.

Investigating these "mechanisms of resistance" is an important area of basic research at the moment.

> ***Quelle:*** *We're hearing it from folks who do drug screens, and they identify which particular drugs are able to kill either small bowel or pancreatic or other types of neuroendocrine tumors, and they also identify what drugs those tumors are naturally or intrinsically resistant to.*

Understanding what causes this resistance can help target and prevent it. This could help make treatments more effective.

And that's the point of basic and translational research as a whole: scientists are adding to our understanding of these

tumors, which results in new and better treatments down the line.

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This brings us out of the lab and over to the clinical end of the research spectrum. This is where potential new treatments are carefully tested in a series of trials, determining their safety and efficacy in a given patient population.

One of the most-discussed possible new treatments in this space is immunotherapy.

> ***Quelle:*** *I think immunotherapy is definitely the biggest area that I have with a growth and interest in potentially treating neuroendocrine tumor patients.*

Immunotherapies harness the immune system to fight against cancer. Historically, they haven't worked well for neuroendocrine tumors. But new approaches have brought immunotherapy back onto the scene as a potential treatment for neuroendocrine cancer. There are several kinds of immunotherapy currently being investigated, which you can learn about in-depth in episode 39 of NETWise.

Most of these are in earlier stages of research, but two have moved through the basic and translational stages and are headed into clinical trials.

The first of these two immunotherapies is CAR-T cell therapy.

> ***Michael:*** *This is a very exciting area in which now you use the immune cells for the treatment of cancer from the patients. You engineer it to attack neuroendocrine tumors. Um, we're going to hear about early stages of phase one clinical trials, with specific CAR-T cells, which can recognize neuroendocrine cells and neuroendocrine tumors. And I think that's something we'll have to follow up the next two, three years. And I'm very excited about this area of research.*

There is a phase 1 clinical trial for CAR-T currently enrolling patients with GI neuroendocrine tumors.

In addition to CAR-T, there's a second immunotherapy drug that is headed to clinical trial.

Dr. Jaydira Del Rivero is a medical oncologist and endocrinologist working at the National Cancer Institute at the National Institute of Health.

> ***Del Rivero:*** *NCI, where I work, we also have a study of an antibody drug conjugated against a protein that is expressed also in neuroendocrine tumors, it's called DLK1, and that's also for neuroendocrine tumors and neuroendocrine carcinomas.*

This is also a phase one trial, set to begin in 2025. It is enrolling patients with neuroendocrine tumors and neuroendocrine carcinomas.

Both of these trials will give researchers crucial information to improve these potential treatments. If phase one goes well, they will move into several more rounds of testing.

> ***Quelle:*** *We try it, we learn from it, we keep going back to it. And it will be an iterative process where hopefully we can keep improving it.*
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> *I would caution people not to be too excited that we're going to see cures immediately. It is a process, probably a five to ten year process. Just getting to the point of these clinical trials has been a huge advance and now we need to work our way through that.*

This past year of research didn't just see these potential treatments reach the clinical trial stage – we also got final results from two important clinical trials that have been underway. These were both phase 3 trials, which is the final stage of testing.

The first of these was a trial called NETTER-2. This tested the efficacy of Lutetium-177 dotatate as a first-line treatment for high-grade, well-differentiated gastroenteropancreatic NETs.

Lutetium-177 dotatate is the key ingredient in PRRT. In 2018, it was approved by the FDA as a treatment for gastroenteropancreatic NETs after a landmark clinical trial called NETTER-1. NETTER-2 followed up on those results, testing whether starting this treatment sooner could have a positive effect.

> ***Del Rivero:*** *So the NETTER-2 is a randomized study of Lutathera, of 177 Lutetium dotatate in the first line setting, uh, compared to high dose octreotide. And, um, the results were quite surprising in the sense that they saw a clinical benefit of using 177 Lutetium dotatate in the first line setting for higher grade neuroendocrine tumors.*

The study concluded that PRRT with Lutetium-177 dotatate as a first-line therapy should be considered a new standard of care for patients with these NETs.

These are significant results — until now, there was no universally accepted first-line therapy for higher grade, well-differentiated gastroenteropancreatic neuroendocrine tumors.

The second phase 3 clinical trial that concluded this year tested a drug called cabozantinib. This has been used to treat certain types of thyroid, liver, and advanced kidney cancers.

> ***Del Rivero:*** *The data that was presented was the benefit of this drug, not only for pancreas neuroendocrine tumors, but also for extrapancreatic neuroendocrine tumors, including small bowel and lung neuroendocrine tumors.*

The data showed the benefit on progression free survival, meaning the stabilization of tumors, uh, growth. But also the quality of life as well that has been reported.

In August, the FDA accepted a supplemental new drug application for cabozantinib to treat advanced NETs. The agency is expected to complete its review in the spring of 2025. If approved, cabozantinib could become a new standard of care for patients with advanced NETs.

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Going through this spectrum of research takes a lot of time and resources. It takes many years of hard work to go from the bench in a laboratory to the bedside of a patient.

Gellerman: *And that is because of all of that basic research, isolating, whether it's a new drug or a new approach, to treat neuroendocrine cancer. And then the process of testing a drug, or a treatment can take years and billions of dollars.*

While there's a lot of money for research into more common cancers, neuroendocrine cancers draw less funding. NETRF invests in research to fill that critical gap.

Dr. Ramesh Shivdasani has been involved with NETRF since the organization began 20 years ago.

Shivdasani: *NETRF has really been at the forefront of developing and catalyzing the application of the translation, as we call it, of research from the laboratory and from preclinical or early clinical research into clinical practice.*

Since our organization was founded in 2005, we have put almost 38 million dollars towards this work. All these funds are from generous donors; we don’t receive government funding.

We make our investments in the form of grants to scientists whose research shows particular promise. As a result of the work we've funded in the past decade alone, 8 patents have been issued or are pending. We've seen five industry partnerships, where technology developed by researchers has been taken to market.

And NETRF's investment isn't just financial — we also work to create a community of scientists and clinicians.

> ***Gellerman:*** *There's about 88 collaborations that we've documented between researchers, between institutions, across countries. We truly are global now. We started out as a small organization in Boston and now we are truly global. We're the largest global funder of neuroendocrine cancer research.*

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> ***Hua:*** *Good morning, everyone.*

At the research symposium this year, Dr. XianXin Hua presented his work on CAR-T immunotherapy, which we talked about a few moments ago.

> ***Hua:*** *This technology has been licensed to the, uh, Chimerica Therapeutics by Penn Center Innovation, and now the Phase I, II clinical trial has opened at the University of Pennsylvania.*

In 2014, CAR-T was approved as a treatment for leukemia. NETRF took notice of CAR-T's potential, and invested in developing CAR-T as a treatment for neuroendocrine cancer. This played a key role in bringing it to clinical trial in just 10 years.

> ***Hua:*** *Our work on developing novel CAR T therapies from the beginning was, uh, supported by NETRF, which, uh, also helped us bridging the gap of research when the funding was really tough. So eventually, uh, leading to*

the discovery of this new target and antibody, uh, that led to the CAR T for clinical trial.

We're proud to have been instrumental in the development of this new treatment, and we're excited to see the results of this clinical trial.

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As much as we want to celebrate all that's been accomplished in the past year, we know how much more there is to be done. We will continue to work hard to develop treatments – and one day, cures – that will improve the lives of people living with neuroendocrine tumors and carcinomas.

With persistence and dedication, we know that the hard work of scientists, researchers, and clinicians pays off in the long run. In the past 20 years that NETRF has been around, we've seen that prove true.

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Harry Proudfoot was one of the attendees at this year's research symposium. He's been involved with NETRF since the early days. His wife, Jane, died of neuroendocrine cancer in 2010. She had her first symptoms all the way back in 1980.

Proudfoot: *When I went online, when my wife was first diagnosed, there were seven entries on the internet, total. Three of them went to the Carcinoid Cancer Foundation in New York. One of them came to this organization. One of them was a paper. That was it.*

In the decades since, things have changed immensely. There are more treatments, better diagnostic tools, and a deeper understanding of these cancers. There are more researchers working on this than ever before.

Proudfoot: *To see it– how much it has grown and changed means that people are living longer. People are having*

better quality of life, all of that kind of stuff is happening and people are finally beginning to sort of understand what the foundational science- that we have to have before we can even think about a cure for this.

You know, we're still on the stage where we have to ask really fundamental questions before we can figure it out, what it is that's going on here. And until you understand that, you don't have targets to shoot at. You don't have a way to begin to develop anything that looks like a treatment or a cure.

But after seeing all the progress that's been made over the past several decades, Harry believes that more effective treatments – and eventually, a cure – are possible. So do we: that's why NETRF will remain committed to funding research for years to come.

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Thanks for listening to NETWise. I'm Jessica Thomas, Director of Patient Education at NETRF.

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If you would like to join NETRF in our mission to fund research for NET cancer or help support educational programs like this NETWise podcast, please go to netrf.org/donate.

Special thanks to everyone we interviewed for this episode. We are grateful for your expertise.

NETWise is a production of NETRF. We're committed to improving the lives of patients, families, and caregivers affected by neuroendocrine cancer. We fund research to discover cures and

more effective treatments, and we provide information and educational resources. Please visit us at netrf.org.