You can find information about subscribing to this series at netrf.org/podcast, where you’ll also find helpful infographics, and videos that expand on this material.

If you’re new to NETWise, we strongly recommend you go back and listen to the first episode in this series. It will give you a solid grounding in 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, and wherever you get your podcasts.

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

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

***Symposium audio:*** *I would firstly like to thank NETRF, not only for giving me the opportunity to talk today and present our results, but also for giving me the opportunity to start this project actually.*

In November, at a hotel conference room in Boston, almost 100 NET researchers came together to share their work.

One by one, they stood at a podium in front of the room and presented their findings.

***Symposium audio:*** *I'm going to be talking to you today about the work we are doing on, uh, pancreatic neuroendocrine tumors.*

Some of the researchers had been looking into the nature of NETs…

***Symposium audio:*** *On the right, there's data to suggest that, each tumor, uh, each metastasis that you have has a potential to rise from a different primary tumor.*

Other researchers have been working to develop and improve treatments for NETs.

***Symposium audio:*** *So previous studies have shown that anti angiogenic treatment not only causes selective regression of immature blood vessels, but also improves vascular integrity and function…*

These presentations were the main event at NETRF’s annual research symposium.

The symposium brings the NET research community together every year, to discuss progress that's been made in understanding and treating neuroendocrine tumors.

***Symposium audio:*** *This is my fourth time attending this symposium, and it's always a great honor to be here. And I'm very happy to share our recent progress and ongoing work here.*

This is NETWise, a podcast for neuroendocrine cancer patients and caregivers that presents expert information and patient perspectives. I’m Jessica Thomas, Director of Patient Education at the Neuroendocrine Tumor Research Foundation.

Research is at the very core of what we do at NETRF. We believe it is the key to discovering cures and more effective treatments for neuroendocrine cancers. Today's episode is devoted to exploring that research.

We'll look back on some of the progress that’s been made in the past year. And we’ll look ahead to new developments that are on the horizon.

\_\_\_\_\_\_\_\_\_

Research is how we will unlock the mystery of neuroendocrine cancers, and ultimately, research is what we hope will one day bring us a cure.

***Greene:*** *Every day progress is being made by scientists, but foundationally we can't make advancements without research.*

Dr. Anna Greene is the Director of Research at NETRF.

***Greene:*** *So some of the questions they're trying to answer are fundamentally, what drives this cancer? Why does it crop up? What's causing it? How is it progressing? How can we better treat it?*

There are three main stages of research: basic, translational, and clinical.

***Greene:*** *So for basic research, this is where scientists are studying fundamental biology. So they might be asking a question about a gene and that gene might have a mutation in it. And it might be a mutation that appears in different types of cancers, but fundamentally they're just studying that gene.*

Translational research is when scientists take new knowledge about something like a gene mutation, and apply that information to a specific disease. It bridges the gap between fundamental biology and potential treatments.

***Greene:*** *And then clinical trials is when we've determined a treatment and we want to assess its safety and its efficacy in a patient population.*

All three stages of research are necessary to make new discoveries about NETs, improve diagnosis, and enhance treatment. We're proud that research supported by NETRF and others has pushed the needle in all of these areas over the past year.

In this episode of NETWise, we want to share some of the most important developments in NET research that happened in 2023.

Three areas that show particular promise in the research community are personalized medicine, immunotherapy, and the improvement of radionuclide therapies, such as PRRT.

We'll start with PRRT. It's something that NETWise listeners will be familiar with -- and you can learn more about the treatment in episode 28 of this series.

In a few short years, PRRT has gone from being an exciting new development to a mainstay treatment strategy for NETs that express somatostatin receptors. And as it grows in popularity, scientists are constantly working on ways to improve it

That includes investigating how the treatment could be combined with other drugs.

Dr. Dawn Quelle is a professor of neuroscience and pharmacology at the University of Iowa. She is a co-chair of NETRF's board of scientific advisors.

***Quelle:*** *There are a number of investigators who are finding that there are other drugs that can be given to those patients that will enhance their response to PRRT. That right there is really valuable because if you have a better response to that initial therapy, maybe you don't need to worry about other therapies down the line if we can eradicate the tumors.*

The key ingredient in PRRT is a radionuclide therapy called lutetium-177 dotatate. This was FDA-approved for treating gastrointestinal and pancreatic neuroendocrine tumors in 2018 after a landmark clinical trial called NETTER-1.

Dr. Pamela Kunz is a GI medical oncologist at Yale Cancer Center, where she’s the director of the Center of Excellence for GI Cancers. She is a NET specialist, and her work is focused on clinical trials.

***Kunz:*** *We know that the lutetium dotatate was more effective in terms of prolonging sort of stability – in the clinical trial lingo that's called “progression-free survival.” About one in five patients had tumor shrinkage. So we're building on that.*

In addition to combining PRRT with other drugs, researchers are looking into the timing of this treatment. It's possible that starting PRRT sooner could increase its effectiveness. One trial is studying the possibility of lutetium-177 dotatate as a first treatment option.

***Kunz:*** *So actually, there's a big clinical trial that will be presented in January called NETTER-2, um, there was a press release that said it was a positive study. So we don't know the details yet, but I'm really excited to see that presentation.*

Another way scientists are trying to improve these radionuclide therapies is by trying out different kinds of radioactive particles. For example, there's a treatment called alpha therapy which uses a different kind of energy particle than PRRT currently uses. These therapies emit alpha particles, which travel shorter distances and have higher energy -- and hopefully, will prove more effective.

But this work on radionuclide treatments is only the beginning.

Immunotherapy is another kind of treatment that members of the NET community have probably heard a lot about.

Immunotherapy is when a patient's own immune system is harnessed to fight cancer. It has long been thought that this could have the potential to treat NETs.

So far, the immunotherapy treatments that have been tested have had disappointing results. But researchers are working hard to develop immunotherapy options for NET patients.

One kind of immunotherapy that has shown promise is called CAR-T cell therapy

***Quelle:*** *The “CAR” stands for chimeric antigen receptor. And what researchers can do is they can take the immune T-cells out of a patient from their blood. They can then educate those T-cells by mixing them with antigens or proteins that are specific to the tumor. And then they can take those T cells that have been educated and put them back into the patient. And now the patient has immune cells that can kill the tumor.*

CAR-T has been successful in treating blood cancers. So more than a decade ago, NETRF reached out to a team of investigators at the University of Pennsylvania who were studying CAR-T cell therapy, and asked them to study how it could be used for NETs. That basic and translational research has now led to the first CAR T cell clinical trial for NETs, which will begin in 2024.

***Quelle:*** *10 years is pretty quick for that progress to have taken place. So that's really exciting.*

As exciting as that is, researchers are working on something even more exciting: personalized medicine.

Right now, treatments tend to be generalized. If you have a diagnosis, there is a standard form of treatment for that diagnosis.

Personalized medicine could lead to a paradigm shift, where patients are treated in an individualized way. And there's good reason for this:

***Greene:*** *When two patients have been diagnosed with the same disease, sometimes they have different outcomes. And so some researchers are trying to figure out how we can better treat them, knowing that their outcomes could potentially be different, because we don't want to over-treat or under-treat a patient. So: can we better tailor their therapy in a more personalized way?*

One way doctors could one day be able to better tailor therapies for NET patients is by using diagnostic tests. These tests can identify certain qualities about a tumor, which can tell doctors about how the patient may respond to a treatment.

Some of these diagnostic tests look for what are called biomarkers. A biomarker is a biological component, like a protein in a cell, that is unique to a particular tumor type.

***Quelle:*** *We look for markers that discriminate tumors from normal cells because then we can either use that marker to run a test and say, ‘Oh, this person has this particular type of tumor,’ or, ‘they have a particular subtype of neuroendocrine tumor.’ Or we might use it to classify them as a higher grade as opposed to a lower grade. Or we might use it to say this biomarker is a really good drug target.*

*And now we're thinking towards personalized medicine, this might be something where we could use drug X or Y or Z to give to that patient because they have particularly high levels of that biomarker on their tumors.*

One particular biomarker appears to be predictive of relapse in pancreatic NETs.

***Quelle:*** *And it's called alternative lengthening of telomeres, or ALT. And that is something that has become of interest because it looks like it will be a good prognostic marker for how well a patient will respond and or their survival.*

For example, one researcher has developed a test for ALT that is accurate, easy for hospitals to run, and a good indicator of the survival prognosis for patients who may have pancreatic NETs.

***Quelle:*** *And there are other biomarkers that my group is studying, that other people are studying. And so there's been a lot of advancement in pathways that could be used for treating neuroendocrine tumors.*

Improving radionuclide therapies, advancing immunotherapy, and developing personalized medicine are some of the main areas researchers have been focused on. But there is even more exciting work being done.

***Kunz:*** *We're also looking at, are there more effective drugs that really yield tumor shrinkage?*

*A trial that I had the opportunity to lead – we just published this last year – this is with CAPTEM or capecitabine and temozolomide.*

*So this has the highest published shrinkage rate for pancreatic nets at 40%. So really for patients who are having symptoms from tumor bulk or symptoms from if their pancreatic NET secretes hormones, or if they have a more rapid pace of growth, CAPTEM has really now become the standard for treating those patients.*

*Another clinical trial of a medication called cabozantinib examined patients with both pancreatic NETs and non-pancreatic NETs. And in both groups, cabozantinib was effective in terms of slowing growth and also in terms of some modest tumor shrinkage. So it's not officially FDA-approved yet, but I anticipate that that will get FDA approved in 2024, so I'm looking forward to hearing that.*

There is work like this happening around the world, and every day researchers make progress. Sometimes that progress is just an inch forward, and sometimes, it can completely change the lives of patients.

It can take many years, and lots of hard work, but eventually discoveries that are made in the lab can make their way to new treatments.

***Kunz:*** *Even in the time that I've been practicing, so as a, you know, full fledged oncologist for the last 15 years or so, in that period of time, I've had patients who, in their lifetime, they're benefiting from drugs that are being researched, go through those hoops, and make it to FDA approval. And so I think that it provides treatment options and hope for patients.*

Despite all the progress that's being made, there are still a lot of questions about NETs that need to be answered. We still don't know, at a fundamental level, how these tumors arise and how they progress. And there are some roadblocks in the way of answering those questions.

One longtime difficulty in NET research has been a lack of research models. Models allow scientists to study a disease in systems that mimic or replicate how the disease might exist in a human body.

But because of the complex and unique nature of NETs, models have been difficult to develop, and there aren't enough of them.

***Quelle:*** *In other types of cancer, like breast cancer or colon cancer that are very common, you have probably hundreds, if not thousands of model systems that you can leverage. It's very difficult in NETs and we have handfuls of models.*

Scientists are working to solve this problem. For example, one researcher is developing a new kind of model, using chick embryos.

***Quelle:*** *Basically, you have eggs and you isolate the embryos from there and you can use those chick embryos to host patient-derived tumors, pieces that you put in there. And they will develop a vasculature and you can keep them going and you can test drugs and you will hopefully be able to identify some therapies.*

And then they are learning more about the biology of the tumors as well.

A lack of models is a problem that scientists may one day be able to overcome. But the most significant challenge faced by NET research isn't one that can be addressed in a lab. That problem is a lack of funding.

***Quelle:*** *The state of funding for NETs is always in flux. Federal agencies like the National Institutes of Health in the U. S. and I think it's NSF, the National Science Foundation in the UK, they typically want to fund research that is much further along and has guaranteed output.*

This is where NETRF comes in. Our foundation works to fill that funding gap, supporting researchers who are using new techniques and asking high-quality questions.

To make significant strides in treating NETs, we have to invest in learning as much as we can about the disease.

NETRF supports all kinds of research, with a focus on basic and translational research. We can have the greatest impact if we support the understanding of NETs at a fundamental level; this will help identify new treatments and advance new therapies into clinical trials.

***Quelle:*** *NETRF is the leader in the world as far as studying neuroendocrine tumors and providing resources, especially for innovative discovery based research that might not be fundable by large agencies. And what NETRF has done– has chosen to fund really innovative ideas and to welcome new investigators into the NET research fold.*

We do this by awarding grants to researchers. Each of our six grant programs is designed to support a different type of research into neuroendocrine cancer.

The grants are awarded every year, after a rigorous selection process and approval from NETRF’s Board of Directors.

***Greene:*** *These funds aren't given as a blank check. It's really important that we steward donor money appropriately. And so these grants are given under a grant contract and we're monitoring these grants every six months with a progress report and an updated financial report to make sure the project that we funded is being conducted.*

Almost three-quarters of all donations NETRF receives are directly invested into research projects.

To date, NETRF has funded 133 projects, for an investment of 36-million dollars. And these projects have *very real* outcomes.

In the last five years alone, 8 NETRF-sponsored researchers have received patents or have patents pending for their discoveries. And researchers have begun 5 industry partnerships or spin-off companies that are designed to bring new treatments to patients.

***Greene:*** *And when we look at our research outcomes, we have funded, all time, 20 clinical research projects and clinical trials, and we're seeing movement from basic and translational research into the clinic. And this is how we're going to move toward better treatments and one day a cure for neuroendocrine cancers.*

Scientific advancements like this don't happen in silos. They involve creativity, cooperation, and collaboration. NETRF seeks to foster that, and researchers have reported 80 new collaborations between themselves as a result of NETRF funding over the past 5 years.

A big part of this is NETRF's annual research symposium, which we heard about at the top of the episode.

Each year at this event, all of NETRF's grant recipients, along with dozens of other researchers, come together to share their work.

***Greene:*** *It's primarily a combination of talks. So presentations by researchers combined with breaks where you have those more informal discussions where collaborations can start.*

*And so researchers are typically seated in classroom style tables looking toward a podium where there will be a presenter.*

*And then after the presentation, there's a question and answer session. And that's where scientists have the opportunity to ask questions and really engage with the work.*

***Quelle:*** *That's, I think, one of the most vibrant parts of this meeting. Everybody gets involved. And people are having really challenging discussions at times if they don't agree on the science, it's always very professional and very collegial, but we might discuss novel ideas that weren't considered before, or challenges that we're all facing and how can we overcome them. And so I think it's very much a team feeling.*

***Greene:*** *There are multiple times when someone would stand up and ask a question and the presenter would respond and say, ‘Hey, that's a great idea. We should collaborate.’ And so that's the atmosphere we're trying to, to sponsor at these events.*

Having nearly a hundred researchers who are devoted to better understanding NETS gather in a room together was an inspiring way to end 2023.

There's so much progress in NET research from the past year to celebrate, and a lot to look forward to in the year ahead.

***Greene:*** *In a few weeks, we're going to announce our new slate of grant funding for the next year. And a big theme again, it's just studying the basic biology of this disease. Trying to learn more about what's driving these cancers, more about how they progress. And we're hopeful that we'll gain some answers from these projects.*

And the ultimate hope is that one day, this work will lead to a cure.

***Quelle:*** *And that's the goal. And I think we're getting there. Every step forward gets us closer to the end goal. And it does take a village or a large community to do it and our NETRF funded research community is growing constantly and it's supporting researchers globally. You know, the reach of NETRF is far beyond that of any other agency or foundation to study neuroendocrine tumors.*

***Kunz:*** *I think there's a lot to be hopeful for in the field of neuroendocrine tumors. And I really think that this is driven by a mix of really wonderful, basic and translational research that then gets translated to the clinic and to clinical trials. And the reason I'm hopeful is that we've seen just extraordinary growth and advances in the last decade, and I think it will be no different for the upcoming decade.*

Whatever happens next year and beyond, NETRF is here for you.

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 visit our website, NETRF-dot-org. While you're there, you can make a donation, find out more about our community of researchers, and find other resources to help you on your NET journey.

\_\_\_\_\_\_\_

Thanks for listening to NETWise. I’m Jessica Thomas, Director of Patient Education for the NET Research Foundation.

Our Production Partner for this series is CitizenRacecar.

This episode was produced by Anna Van Dine; Post-Production by José Miguel Baez; Production Manager, Gabriela Montequin. Executive producer, David Hoffman.

It was made possible by the generous support of Ipsen; Novartis; TerSera Therapeutics; Boehringer Ingelheim.

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

This is a production of the NET Research Foundation. 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.

This podcast is not intended as, and shall not be relied upon as, medical advice. The Neuroendocrine Tumor Research Foundation encourages all listeners to discuss any scientific information found here with their personal oncologist, physician, and/or appropriate qualified health professional. Listening to this podcast does not constitute a patient-physician relationship. The Neuroendocrine Tumor Research Foundation does not represent that any information provided here should supplant the reasoned, informed advice of a patient’s personal oncologist, physician, or appropriate qualified health professional.A close up of a sign

Description automatically generated