

2024 Highlights in Neuroendocrine Cancer Research

At NETRF, 2024 was defined by groundbreaking progress fueled by innovative research and strategic scientific collaborations. This year brought major therapeutic advances, including FDA approvals and breakthrough therapy designations, that accelerated the development of new treatments and personalized care approaches. Equally important were foundational discoveries in basic research, which deepened our understanding of neuroendocrine cancer biology and revealed new targets for future therapies. Together, these milestones reflect meaningful strides toward improving outcomes for all patients facing neuroendocrine cancer.

NETRF-Funded Basic and Translational Science Highlights

In 2024, significant progress was achieved in neuroendocrine cancer research. Scientists are developing promising new therapies, including a novel radiopharmaceutical, 225Ac-crown-TATE, showing strong efficacy in preclinical models, and NET-Smart compounds demonstrating selective toxicity toward NET cells. New insights emerged in understanding tumor biology, such as ANGPT2's role in pancreatic NET liver metastasis, the Wnt pathway's regulation of somatostatin receptors, DNA-repair mechanisms influencing PRRT sensitivity, and the transformation pathways of high-grade pancreatic NETs. Additionally, researchers advanced therapeutic strategies by enhancing CAR T-cell activity through IL-23 and CD226, uncovering drug-resistant cell populations in high-grade carcinomas, identifying the microbiome's role in NETs, using statins to improve receptor-targeted therapies, and establishing novel patient-derived tumor models. These discoveries offer promising pathways toward better diagnosis, personalized treatment, and improved patient outcomes in neuroendocrine cancers. Learn more about some additional basic and translational research highlights below:

- <u>Targeting Cancer-Associated Fibroblasts (CAFs)</u>: Research has explored CAFs in neuroendocrine tumors (NETs) as potential therapeutic targets, particularly for tumors that lack somatostatin receptor 2 (SSTR2).
- **Defining Lung NET Subtypes:** Emerging studies have identified new lung NET subtypes with <u>specific</u> <u>treatment sensitivities</u>. One key finding emphasizes the need to improve lung NET classification by <u>integrating molecular markers</u> to support more accurate diagnoses and tailored therapies.
- <u>Profiling of PanNETs</u>: Combining protein expression data with genetic information allows for more precise subtyping of PanNETs, helping predict tumor aggressiveness and patient outcomes beyond what current classifications provide.
- **Development of New Research Models:** Recent advances include new <u>patient-derived models</u> for lung NETs, <u>patient-derived xenograft models</u> of gastroenteropancreatic neuroendocrine cancers, and <u>mouse</u> <u>models</u> for pancreatic NETs, enabling more effective translational research.
- <u>Improving PRRT Treatments</u>: Research on somatostatin receptor antagonists like Lu-DOTA-JR11 revealed improved treatment efficacy and insights into bone marrow radiation absorption.



• <u>Exploring the Gut Microbiome</u>: A 17-species microbial signature was found to be predictive of midgut NETs, offering promise for the development of microbiome-based diagnostic tools to aid in early detection and intervention.

Therapeutic Advances

This year marked incredible progress in the treatment of neuroendocrine cancer with new FDA approvals, expanded indications, and breakthrough designations. From targeted radiotherapies and pediatric approvals to new small-molecule therapies, these advances represent major steps forward in improving outcomes and expanding options for neuroendocrine tumor (NET) patients.

- <u>Cabozantinib FDA Approval</u>: The FDA approved cabozantinib for previously treated advanced NETs based on the CABINET trial, significantly improving patient outcomes in pancreatic and extra-pancreatic NETs.
- <u>Lutathera for Pediatrics</u>: Lutathera received FDA approval for pediatric patients aged 12+ with gastroenteropancreatic NETs (GEP-NETs), marking the first pediatric radiopharmaceutical approval.
- <u>Lutathera as First-Line Treatment</u>: The NETTER-2 trial found that Lutathera as a first-line treatment reduces the risk of disease progression or death in those with newly diagnosed G2/G3 advanced GEP NETs.
- <u>Histotripsy for Liver Tumors</u>: A noninvasive, focused ultrasound treatment was FDA-approved for liver tumors, including NETs.
- <u>AlphaMedix Breakthrough</u>: AlphaMedix (212Pb-DOTAMTATE), a targeted alpha therapy, received FDA Breakthrough Therapy designation for advanced GEP-NETs, accelerating therapy development.

New Clinical Trials & Novel Therapies

Building on recent scientific insights, several first-in-human studies were launched in 2024 to tackle hard-to-treat neuroendocrine cancer. From an antibody-drug conjugate targeting DLK1 to two CAR T-cell therapies directed at CDH17 and IL13Rα2, these trials aim to translate cutting-edge preclinical discoveries into new, life-extending treatments for patients.

- <u>CDH17 CAR T-Cell Trial</u>: A landmark clinical trial began testing a novel CDH17 CAR T-cell therapy for gastrointestinal NETs. NETRF funded the preclinical research that led to the trial.
- <u>ADCT-701 Trial</u>: A phase I trial that began evaluating an antibody-drug conjugate, ADCT-701, targeting DLK1 in neuroendocrine cancer.
- <u>IL13Rα2 CAR T-Cell Trial</u>: A phase I CAR T-cell clinical trial began evaluating the molecule IL13Rα2 found on the surface of some NETs, including pheo/para.

NETRF's Commitment to Research

NETRF has invested an all-time total of about \$40 million in <u>global</u> neuroendocrine cancer research funding, highlighting our <u>commitment</u> to accelerating progress in this complex and often under-recognized disease. In 2024, this investment catalyzed a wave of innovation across basic, translational, and clinical science, driving



discoveries that deepen our biological understanding of neuroendocrine cancer. These 2024 research advancements represent substantial progress and steps toward transforming diagnosis, treatment, and patient care in neuroendocrine cancer. Through strategic funding and collaboration with investigators worldwide, NETRF continues to lead efforts that not only expand scientific knowledge but also bring hope to patients and families by making a real-world impact in care and outcomes.

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