2025 Margie & Robert E. Petersen NEUROENDOCRINE TUMOR RESEARCH SYMPOSIUM

BREAKTHROUGHS TODAY, CURES TOMORROW

November 17-19, 2025
Boston, Massachusetts

BREAKTHROUGHS TODAY CURES TOMORROW

NET NEUROENDOCRINE TUMOR RESEARCH FOUNDATION

2025 Margie & Robert E. Petersen
NEUROENDOCRINE TUMOR
RESEARCH SYMPOSIUM
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WELCOME TO THE 2025 MARGIE AND ROBERT E. PETERSEN NEUROENDOCRINE TUMOR RESEARCH SYMPOSIUM

We are thrilled to welcome you to this year's Symposium—the largest global gathering of neuroendocrine cancer scientists. Together, we will share discoveries, spark new ideas, and advance the science that drives progress for patients. Our Symposium is truly unique in its focus on basic and translational research and in fostering open, interactive discussion among attendees—sparking collaborations that move the field forward.

This year marks a special milestone—NETRF's 20th anniversary. What began as a small, patient-founded organization in Boston has grown into the largest global funder of neuroendocrine cancer research and a leading source of trusted patient education. Over two decades, we have invested more than $40 million across 76 institutions in 17 countries to deepen our understanding of tumor biology, identify new treatment targets, and pave the way for future clinical trials.

We are proud of the vibrant, collaborative research community that NETRF has helped cultivate. Over the next three days, you'll hear from leading experts, current and past grantees, and talented early-career scientists sharing new discoveries and progress. Our keynote speaker, Dr. Pamela Kunz, will reflect on how far research and treatment have come in 20 years—and the innovations that may lie ahead. We are also honored to include patient speakers whose stories remind us why this work matters so deeply.

NETRF's 20th year is not just an organizational milestone—it is a shared achievement made possible by you: the neuroendocrine cancer research community, Board of Scientific Advisors, Board of Directors, staff, and above all, our generous donors whose commitment has fueled our growth and impact. We extend our heartfelt thanks to our Symposium sponsors for helping make this gathering possible.

Thank you for being part of the NETRF community and for joining us in celebrating **20 years of progress, partnership, and hope.** Here's to an inspiring and energizing Symposium!

Elyse Gellerman
CEO

Todd Gilman
President, NETRF Board of Directors

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AGENDA

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All times listed are in Eastern Time

Presenting Sponsor: Exelixis

Monday, November 17, 2025

5:00–6:00 p.m. **Registration**
Location: The Connector

6:00–8:00 p.m. **Welcome Reception and Poster Session**
Location: Esplanade Room
Sponsored by Chimeric Therapeutics

Tuesday, November 18, 2025

8:00–9:00 a.m. **Registration and Breakfast**
Location: The Connector and Fenway Foyer

9:00–9:05 a.m. **Welcome**
Elyse Gellerman, MHS, NETRF Chief Executive Officer
Location: Fenway Ballroom

9:05-9:10 a.m. **Welcome and Meeting Logistics**
Anna Greene, PhD, NETRF Chief Scientific Officer

9:10–9:45 a.m. **Keynote – Advancing Neuroendocrine Tumor Research: Milestones, Innovations, and the Path Forward**
Pamela Kunz, MD, Yale University

9:45-10:00 a.m. **Patient Voice: Arrows in My Quiver**
Nancy Lewis

SESSION 1: NEW THERAPIES AND TARGETS

Session Chairs: Justin Annes, MD, PhD and Gregory Way, PhD

Location: Fenway Ballroom

10:00–10:15 a.m. **Inhibition of ROS Detoxification to Target GEP-NETs**
Jeffrey Frost, PhD, UT Houston Health Science Center

10:15–10:30 a.m. **BH3-mimetic Drugs Elicit Cell Death of Neuroendocrine Tumors in Preclinical Models: An Emerging Therapeutic Strategy for NETs**
Zoey Wang, MPhil, Sunnybrook Research Institute

10:30–10:45 a.m. **Discussion**

10:45–11:15 a.m. **Coffee Break**

11:15–11:30 a.m. **Tumor Cell Surface Targeting of High-grade Neuroendocrine Carcinomas**
C. Allison Stewart, PhD, University of Texas MD Anderson Cancer Center

11:30–11:35 a.m. **Pharmacologic and Genetic Disruption of SDH Sensitizes Tumor Cells to YM155-Induced DNA Damage**
Qianjin Guo, PhD, Stanford University

11:35–11:40 a.m. **DUSP1 is a Therapeutic Vulnerability in Neuroendocrine Tumors**
Majid Momeny, PhD, UTHealth Science Center

11:40–11:55 a.m. **Discussion**

11:55 a.m.–12:10 p.m. **Group Photo**

12:10–1:30 p.m. **Lunch**
Sponsored by ITM
Location: Fenway Foyer

SESSION 2: OMICS AND TUMOR SUBTYPES

Session Chairs: Chrissie Thirlwell, MBBS, PhD and Talya Dayton, PhD

Location: Fenway Ballroom

1:30–1:45 p.m. **Lung NETs in the Genomics Era: Past, Present, and Future of IARC's LungNENomics Project**
Nicolas Alcala, PhD, IARC – WHO

1:45–2:00 p.m. **A Cellular Map of Human Pulmonary Neuroendocrine Diversity and Proliferation**
Christin Kuo, MD, Stanford University

2:00–2:15 p.m. **Spatial Transcriptomics Reveals Local Subtype-specific Identity and Signaling within Multifocal Small Intestinal Neuroendocrine Tumors**
Akitada Yogo, MD, PhD, University of California, San Francisco

2:15–2:20 p.m. **Identification of PABPC Family, NOTCH1 and MTOR as Critical Somatic Mutations in Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) from Whole Exome Sequencing (WES) Analysis**
Hui Yu, MD, University of Colorado, Anschutz

2:20–2:35 p.m. **Whole Transcriptome Sequencing of Pancreatic Neuroendocrine Tumors Identifies Recurrent Fusion Genes in BEND2 as a Unique Oncogenic Driver that Correlates with Poor Patient Prognosis**
Aatur Singhi, MD, PhD, University of Pittsburgh

2:35–2:50 p.m. **Discussion**

2:50–3:30 p.m. **Coffee Break**

SESSION 3: TUMOR MICROENVIRONMENT

Session Chairs: Dawn Quelle, PhD and Mauro Cives, MD

Location: Fenway Ballroom

3:30–3:45 p.m. **A New Therapeutic Avenue Tackling Liver Metastasis and Antiangiogenic Resistance**
Minah Kim, PhD, Columbia University

3:45–4:00 p.m. **Analysis of the Tumor Microenvironment in Small Intestinal NETs**
Netta Mäkinen, PhD, Dana-Farber Cancer Institute

4:00–4:05 p.m. **Dissecting the Neuroimmune Landscape of Pancreatic Neuroendocrine Tumors with Single-cell Spatial Proteo-transcriptomics**
Jeanna Qiu, AB, Harvard Medical School

4:05–4:10 p.m. **TILs in Pancreatic Neuroendocrine Tumors (PanNETs): Towards Novel Cell Therapy Approaches**
Nada Chaoul, PhD, University of Bari Aldo Moro

4:10–4:15 p.m. **Single-cell Dissection of Cellular Crosstalk and Ligand-Receptor Networks Underlying Grade Transformation in Pancreatic Neuroendocrine Tumors**
Himanshu Singh, PhD, Memorial Sloan Kettering Cancer Center

4:15–4:20 p.m. **Unravelling the Molecular Mechanisms Behind Mesenteric Fibrosis: From Multi-omic Analysis to Target Gene Identification Using a Novel in Vitro 3D Patient-derived Model**
Harry Hodgetts, MSc, University College London

4:20–4:35 p.m. **Discussion**

4:35–4:40 p.m. **Travel Award Presentations**

4:40–6:00 p.m. **Extended Poster Viewing and Happy Hour**
Sponsored by ITM

6:00 p.m. **End of Day**

DAY 3 – Wednesday, November 19, 2025

8:00–9:00 a.m. **Registration and Breakfast**
Location: The Connector and Fenway Foyer

9:00–9:05 a.m. **Welcome**
Anna Greene, PhD, NETRF Chief Scientific Officer
Location: Fenway Ballroom

9:05–9:20 a.m. **Patient Voice: The Healing Garden**
Jake Dawson

9:20–9:45 a.m. **Challenge Address: Gaps in Basic and Translational Neuroendocrine Cancer Research**
Iacovos Michael, PhD, Sunnybrook Research Institute and University of Toronto

9:45–10:00 a.m. **Discussion**

SESSION 4: RADIOPHARMACEUTICALS

Session Chairs: Erik Mittra, MD, PhD and Daniel Halperin, MD

Location: Fenway Ballroom

10:00–10:15 a.m. **EphA2 Targeting Peptide Radiotheranostics for Lung Neuroendocrine Tumors**
Ajay Kumar Sharma, PhD, Johns Hopkins University

10:15–10:30 a.m. **Enhancer Landscape of Neuroendocrine Tumors Reveals Developmental Signatures with Theranostic Implications**
Yotam Drier, PhD, Hebrew University of Jerusalem

10:30–11:00 a.m. **Coffee Break**

11:00–11:15 a.m. **Results of the COPPER PET in NET Trial: A Randomized, Crossover, Readers Blind, Phase I/II Study Comparing 61Cu-NODAGA-LM3 and 68Ga-DOTATOC for the Detection of Neuroendocrine Tumors**
Guillaume Nicolas, MD, University Hospital Basel

11:15-11:30 a.m. **Computational Design and Preclinical Evaluation of Chelators for the Alpha-Emitter Pb-212**
Dongyoul Lee, PhD, Korea Military Academy

11:30–11:35 a.m. **Testing of Current and Novel FAPI Agents in Neuroendocrine Tumors**
Gina Kaup, BS, University of Michigan

11:35–11:50 a.m. **Discussion**

11:50 a.m.–12:20 p.m. **Break and Lunch**
Sponsored by Perspective Therapeutics
Location: Fenway Foyer

SESSION 5: BIOLOGY AND MODEL SYSTEMS

Session Chairs: Iacovos Michael, PhD and James Bibb, PhD

Location: Fenway Ballroom

12:20–12:35 p.m. **Using Patient-derived Tumor Organoids to Uncover Mechanisms of Pulmonary NET Progression**
Talya Dayton, PhD, European Molecular Biology Laboratory (EMBL), Barcelona

12:35–12:50 p.m. **Variable GLP-1 Receptor Expression Across Diverse Neuroendocrine Neoplasms: Implications for Incretin Therapies**
Andrew Bellizzi, MD, University of Iowa

12:50–1:05 p.m. **Sortilin in Functional Neuroendocrine Tumors: Marker and Target**
Felix Bolduan, MD, Charité Universitätsmedizin Berlin

1:05–1:10 p.m. **Establishing and Characterizing New Pancreatic Neuroendocrine Tumor Mouse Models**
Shifei (Samuel) Wu, BSc, Lunenfeld Tanenbaum Research Institute/ University of Toronto

1:10–1:15 p.m. **miR-375 Targets YAP to Regulate Neuroendocrine Differentiation and Tumorigenesis in PanNEN Cells**
Tashifa Imtiaz, BScH, MSc, Queen's University

1:15–1:20 p.m. **The Genetic Evolution of Low to High-grade Progression in Pancreatic Neuroendocrine Tumors**
Nancy Joseph, MD, PhD, University of California, San Francisco

1:20–1:35 p.m. **Discussion**

1:35–1:45 p.m. **Knowledge Gained, Horizons Ahead – Close of Meeting**
Mauro Cives, MD, University of Bari Aldo Moro

BREAKTHROUGHS TODAY CURES TOMORROW

NEUROENDOCRINE TUMOR RESEARCH FOUNDATION

Find it early. Treat it better. Cure it faster.

"I truly believe in the mission and the great work that NETRF is doing year in and year out. I want to be part of the solution — and I want to see a future where we find a cure."

— Steve Kaufer,
NETRF Board Member,
Co-Founder, TripAdvisor,
Co-Founder, Give Freely

For 20 years, NETRF has led the global charge to transform neuroendocrine cancer treatment.

Now, we have launched our most ambitious campaign yet — a **$25 million** effort to accelerate the bold science that will deliver new therapies and, ultimately, cures.

NETRF is advancing progress in three urgent and high-impact areas:

- **Early Detection** — So patients are diagnosed sooner, when treatment is more effective
- **New Therapeutic Development** — To expand treatment options and improve survival
- **Personalized Treatments** — To ensure every patient receives the right care at the right time

Bold ideas are waiting. They just need our support.

Your gift drives progress by:

- Funding life-changing research led by the world's leading scientists
- Powering innovations like CAR T-cell therapy from lab to lives
- Equipping patients and caregivers with trusted education and resources

As we mark 20 years of progress, let's celebrate by doubling down on our mission.

Make your gift today! Visit netrf.org/breakthroughs or scan the QR code to learn more.

Breakthroughs Today, Cures Tomorrow.

Our future starts now.

NET Knowledge Center

Help Your Patients Stay Informed, Engaged and Connected

Current and accurate patient education and information is essential for neuroendocrine cancer patients and caregivers. Finding credible information and resources can be challenging and difficult to navigate.

NETRF's NET Knowledge Center is a comprehensive resource organized to direct patients and caregivers to the information they need as they navigate a neuroendocrine cancer journey.

INFORMATION

Learn more about neuroendocrine cancers

A diagnosis of neuroendocrine cancer often comes with many questions and concerns. These resources explain the different kinds of neuroendocrine cancers, diagnostic tests, and risks so patients and caregivers can better understand their condition.

ENGAGEMENT

Take the next step post-diagnosis

With many different types of neuroendocrine cancer, it's important to find the best possible care and treatment. These resources assist patients and caregivers in finding specialists, treatments, and wellness practices.

COMMUNITY

Connect with more people and resources about neuroendocrine cancer

When it comes to neuroendocrine cancer, it takes a community. We offer numerous ways for patients and caregivers to access the latest information on treatments and research progress, as well as updates from the neuroendocrine cancer community.

Visit the NET Knowledge Center at netrf.org/for-patients or scan the QR Code.

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NET NEUROENDOCRINE TUMOR RESEARCH FOUNDATION

POSTER GUIDE

2025 Margie & Robert E. Petersen
NEUROENDOCRINE TUMOR
RESEARCH SYMPOSIUM
BREAKTHROUGHS TODAY, CURES TOMORROW

THEME 1 — PATIENT ACCESS, CARE AND OUTCOMES (POSTERS 1–6)

1. **Analysis of NET Digital Trial Finder Platform Usage and Challenges in Patient Referrals**
   Danielle Ralic, BS, Ancora.ai
2. **Quality of Life and Care Experiences in a U.S. Multi-Institutional Neuroendocrine Tumor Cohort**
   Tao Xu, PhD, University of Iowa
3. **Clinicopathological Characteristics and Survival Outcomes of Gastrointestinal Neuroendocrine Tumors in a Large Safety Net Hospital**
   Ramya Singhal, MD, Boston Medical Center
4. **Re-evaluating Follow-up Strategies in Medullary Thyroid Carcinoma: The Role of Postoperative Undetectable Calcitonin**
   Marijn van den Berg, BS, University Medical Center Utrecht
5. **Tobacco Cessation Improves Survival in Patients with Neuroendocrine Neoplasms. Possible Link to Adaptive Immune Cell Profiles**
   Nicolas Skill, PhD, Louisiana State University
6. **Feasibility Study for Delayed Ki67 Staining and Grading of Long-term Biorepository Neuroendocrine Tumors**
   Nicolas Skill, PhD, Louisiana State University

THEME 2 — GENOMICS (POSTERS 7–10)

7. **Molecular Characterization of Neuroendocrine Neoplasia (NENs): A Case Series Study**
   Luca Fiorini, MD, Azienda Ospedaliera Universitaria Integrata di Verona
8. **Proteogenomic Characterization of Pancreatic Neuroendocrine Tumors**
   Michael H. Roehrl, MD, PhD, Beth Israel Deaconess Medical Center and Harvard Medical School
9. **Deciphering Clonal Evolution and Tumor Microenvironment in Patients with DIPNECH**
   Fabien Lamaze, PhD, Centre de Recherche Institut universitaire de cardiologie et de Pneumologie de Québec – Université Laval
10. **Identification of PABPC Family, NOTCH1 and MTOR as Critical Somatic Mutations in DIPNECH from WES Analysis**
    Hui Yu, MD, PhD, University of Colorado Anschutz Medical Campus

THEME 3 — MECHANISMS, CELL OF ORIGIN AND MODELS (POSTERS 11–15)

11. **Hedgehog Signaling Drives Glial Cell Plasticity and Oncogenic Reprogramming in GEP-NENs**
    Suzann Duan, PhD, University of California, Irvine
12. **Alternative Splicing Contributes to Transcript Diversity in MEN1**
    Anassuya Ramachandran, PhD, University of Auckland
13. **Mechanisms and Models for Cdk5-dependent Neuroendocrine Tumors**
    Kylie Dickerson, MD, University of Arizona College of Medicine, Phoenix
14. **Establishing and Characterizing New Pancreatic Neuroendocrine Tumor Mouse Models**
    Shifei (Samuel) Wu, BSc, Lunenfeld Tanenbaum Research Institute/University of Toronto
15. **Loss of DAXX and ATRX Protein Expression Results in Increased Radiosensitivity and Ischemic Resistance of Bon-1 and QGP-1 Cells**
    Jessica Puzzuoli, PhD, CT(ASCP), Memorial Sloan Kettering Cancer Center

THEME 4 — TUMOR METABOLISM AND GROWTH DEPENDENCIES (POSTERS 16–19)

16. mTORC1 Signaling Drives Amino Acid Uptake in Pancreatic Neuroendocrine Tumors
Scott A. Oakes, MD, University of Chicago

17. Differential Expression of GLUT-1 and FASN Across Histological Grades of PanNENs
Erika Egal, DVM, MBA, PhD, University of Utah

18. miR-375 Targets YAP to Regulate Neuroendocrine Differentiation and Tumorigenesis in PanNEN Cells
Tashifa Imtiaz, BScH, MSc, Queen's University

19. UCHL1 is a Molecular Indicator and Therapeutic Target for Gastrointestinal and Pancreatic Neuroendocrine Tumors
Tanya Stoyanova, PhD, University of California, Los Angeles

THEME 5 — MICROENVIRONMENT, FIBROSIS AND SPATIAL BIOLOGY (POSTERS 20–23)

20. Dissecting the Neuroimmune Landscape of Pancreatic Neuroendocrine Tumors with Single-cell Spatial Proteo-transcriptomics
Jeanna Qiu, AB, Harvard Medical School

21. Single-Cell Dissection of Cellular Crosstalk and Ligand-Receptor Networks Underlying Grade Transformation in PanNETs
Himanshu Singh, PhD, Memorial Sloan Kettering Cancer Center

22. Unravelling the Molecular Mechanisms Behind Mesenteric Fibrosis Using a Novel 3D Patient-derived Model
Harry Hodgetts, University College London

23. Potential Biomarkers for Mesenteric Fibrosis in Small Intestinal NET Patients: An Exploratory Serum Proteomics Study
Leo J. Hofland, PhD, Erasmus MC

THEME 6 — RADIOTHERANOSTICS: CHEMISTRY AND TARGETING INNOVATION (POSTERS 24–28)

24. Optimized Automated Radiosynthesis of a Clinically-trialed [18F]F- Tyr3-octreotate Derivative for PET: Impact on the Development of a Novel GLP-1 Peptide Receptor Imaging Agent
Kevina Chavda, BSc, McMaster University

25. Testing of Current and Novel FAPI Agents in Neuroendocrine Tumors
Gina Kaup, University of Michigan

26. Computational Evaluation of Chelators for Actinium-225 and Its Decay Daughters Using DFT-based Modeling
Jeongyun Kim, PhD Student, Seoul National University

27. DNA-PK Inhibitors as Radiosensitisers of 177Lu-Dotatate Treatment for GEP-NETs
Cho Rong Hong, PhD, University of Auckland

28. [212Pb]VMT-a-NET for Advanced SSTR2+ NETs: Safety and Preliminary Efficacy (Dose-escalation Cohorts)
Perspective Therapeutics, Inc.

ABSTRACTS

2025 Margie & Robert E. Petersen
NEUROENDOCRINE TUMOR
RESEARCH SYMPOSIUM

BREAKTHROUGHS TODAY, CURES TOMORROW

TABLE OF CONTENTS

Computational Evaluation of Chelators for Actinium-225 and Its Decay Daughters Using DFT-Based Modeling

Clinicopathological Characteristics and Survival Outcomes of Gastrointestinal Neuroendocrine Tumors in a Large Safety Net Hospital

Alternative Splicing Contributes to Transcript Diversity in MEN1

Differential Expression of GLUT-1 and FASN Across Histological Grades of Pancreatic Neuroendocrine Neoplasms: Insights into Tumor Metabolism and Progression

Feasibility Study for Delayed Ki67 Staining and Grading of Long-term Biorepository Neuroendocrine Tumors to Enhance Translational Research

Tobacco Cessation Improves Survival in Patients with Neuroendocrine Neoplasms. Possible Link to Adaptive Immune Cell Profiles

DNA-PK Inhibitors as Radiosensitisers of 177Lu-Dotatate Treatment for GEP-NETs

Optimized Automated Radiosynthesis of a Clinically-trialed [18F]F- Tyr3-octreotate Derivative for PET: Impact on the Development of a Novel GLP-1 Peptide Receptor Imaging Agent

Re-evaluating Follow-up Strategies in Medullary Thyroid Carcinoma: The Role of Postoperative Undetectable Calcitonin – An International Multicenter Cohort Study

Deciphering Clonal Evolution and Tumor Microenvironment in Patients with DIPNECH

Molecular Characterization of Neuroendocrine Neoplasia (NENs): A Case Series Study

Proteogenomic Characterization of Pancreatic Neuroendocrine Tumors

Quality of Life and Care Experiences in a U.S. Multi-Institutional Neuroendocrine Tumor Cohort

mTORC1 Signaling Drives Amino Acid Uptake in Pancreatic Neuroendocrine Tumors

Hedgehog Signaling Drives Glial Cell Plasticity and Oncogenic Reprogramming in Gastroenteropancreatic Neuroendocrine Neoplasms

[212Pb]VMT-a-NET for Advanced SSTR2+ NETs: Safety and Preliminary Efficacy Results from Cohorts 1 and 2 of the Dose Escalation Phase

Mechanisms and Models for Cdk5-dependent Neuroendocrine Tumors

Potential Biomarkers for Mesenteric Fibrosis in Small Intestinal NET Patients: An Exploratory Serum Proteomics Study

UCHL1 is a Molecular Indicator and Therapeutic Target for Gastrointestinal and Pancreatic Neuroendocrine Tumors

Loss of DAXX and ATRX Protein Expression Results in Increased Radiosensitivity and Ischemic Resistance of Bon-1 and QGP-1 Cells

Inhibition of ROS Detoxification to Target GEP-NETs

Stephanie Planque, Zuo Yan, and Jeffrey A. Frost

Department of Integrative Biology and Pharmacology, UT Houston Health Science Center, 6431 Fannin St, Houston, TX 77030

Presenter: Jeffrey Frost, PhD

Background:

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogenous group of tumors that are generally slow growing and resistant to the majority of cancer therapeutics, which target cell proliferation. We have found that GEP-NET cells are sensitive to oxidative stress, and that combining agents that target distinct oxidative stress detoxifying proteins results in a synergistic killing of GEP-NET cells irrespective of their proliferative state. Cells generally use two mechanisms to protect against cytoplasmic reactive oxygen species (ROS), namely the thioredoxin and glutathione antioxidant systems. Our approach targets both of these systems.

Methods:

BON1, QGP1, and HPNE cells were treated in vitro with a clinically approved inhibitor of thioredoxin reductase, auranofin, and different inhibitors of the SLCA11 cystine transporter. SLCA11 mediates cystine import, which is the precursor for cysteine, an essential component of glutathione (GSH). Cell proliferation was measured using CyQuant kits (Invitrogen) and crystal violet staining. Apoptosis was measured by flow cytometry using fluorescent Annexin-V and propidium iodide (Thermo-Fisher). Glutathione was measured using a GSH-GSSH colorimetric kit (ELabscience). To measure effects on tumor growth, nude mice were inoculated with BON1 cells. After tumors reached 100 mm3, mice were treated with saline, auranofin, imidazole ketone erastin (IKE), or auranofin plus IKE. Tumor growth and mouse weights were measured. Molecular indicators of tumor proliferation and angiogenesis were examined after tumor recovery.

Results:

Our data shows that the thioredoxin system inhibitor auranofin synergizes with the cystine transporter IKE to kill BON1 and QGP1 GEP-NET cells in vitro. The degree of synergy allows the use of doses of each drug that are ineffectual at inhibiting tumor cell proliferation on their own. Annexin V labeling shows that the cells die by apoptosis rather than ferroptosis. This is supported by the observation that the class II ferroptosis inducing agent RSL3, which blocks the ferroptosis gatekeeper GPX4, does not synergize with auranofin. In addition, auranofin and IKE synergize to reduce GSH levels, and the anti-oxidant N-acetylcysteine blocks cell death. When tested in vivo, we found that the combination of auranofin plus IKE inhibited BON1 tumor growth, while each drug alone did not cause significant effects. There was no effect on mouse weight, indicating that the drugs were not toxic.

Conclusions:

Our data indicates that simultaneous inhibition of the thioredoxin antioxidant system and the SLCA11 cystine transporter synergistically kills GEP-NET cells. Importantly, this approach inhibits the growth of BON1 tumors and is well tolerated in mice. As this approach does not specifically rely on cell proliferation, it has the potential to treat GEP-NETs that are resistant to other therapeutic approaches.

Back to Abstracts Table of Contents

BH3-mimetic Drugs Elicit Cell Death of Neuroendocrine Tumors in Preclinical Models: An Emerging Therapeutic Strategy for NETs

Zoey Wang[1,2], Justin Kale[1], Nilakshi Kulathunga[1], Uyen Le[1], Wiebke Schormann[1], Alberto Lens-Pardo[3], Betty Li[1], Rocio Garcia-Carbonero[3], Hubert Tsui[1,4], Calvin Law[5,6], Julie Hallet[5,6], Simron Singh[5,7], David W. Andrews[1,8], Iacovos P. Michael[1,2]

1. Biological Sciences Platform, Sunnybrook Research Institute, Toronto, ON, Canada; 2. Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada; 3. Oncology Department, Centro de Oncología Experimental, Grupo de Investigación en Tumores Gastrointestinales y Neuroendocrinos, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), CNIO, UCM, Madrid, Spain; 4. Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 5. Clinical Evaluative Sciences, Sunnybrook Research Institute, Toronto, ON, Canada; 6. Department of Surgery, University of Toronto, Toronto, ON, Canada; 7. Department of Medicine, University of Toronto, Toronto, ON, Canada; 8. Department of Biochemistry, University of Toronto, Toronto, ON, Canada.

Presenter: Zoey Wang, MPhil

Background:

Neuroendocrine tumors (NETs) are growing rapidly in prevalence, yet current treatments often yield limited efficacy and poor patient outcomes. As such, there is an urgent need to identify new and effective therapies. Analysis of single-cell transcriptomic data from NET patients revealed an elevated expression of the anti-apoptotic BCL2 protein family—comprising BCL-2, BCL-xL, BCL-w and MCL-1—which may contribute to cancer cell survival and persistence following treatment. We hypothesize that BH3-mimetics, a class of pro-apoptotic drugs targeting the BCL2 family, may induce cell death in NETs and present as an effective therapy, either alone or in combination with existing standard-of-care (SOC).

Methods:

NET patient-derived organoids (PDOs) were established from fresh, surplus surgical specimens, cultured for 3–4 weeks in hydrogel-coated 384-well plates, and treated with combinations of BH3-mimetics and SOC including Sunitinib, Cabozantinib, Everolimus, Octreotide, and 177Lu-Dotatate. Treatment response was assessed by confocal imaging using fluorescent, non-toxic dyes to measure metabolic activity and Annexin V to detect apoptosis. To mechanistically validate drug-induced apoptosis, NET cell lines were treated with BH3-mimetics, and the levels of BCL2 proteins and cleaved caspase-3 were examined by Western blotting.

Results:

We have established PDOs from primary (small intestine, pancreas) and metastatic (lymph node, liver) NETs with >90% success. Inhibition of all anti-apoptotic BCL2 proteins with the combination of Navitoclax (targets BCL-2, BCL-xL, and BCL-w) and S63845 (targets MCL-1) resulted in prominent cell death in all PDOs tested, indicating a critical role for the BCL2 family in NET survival. Targeted inhibition using BH3-mimetics specific to certain BCL2 proteins further identified BCL-xL and MCL-1 to be particularly important for NET cell viability. Importantly, combining Navitoclax with either Cabozantinib or 177Lu-Dotatate led to marked cell death in contrast to limited responses to single treatments, suggesting a synergistic effect. In human small intestine and pancreatic NET cell lines, induction of apoptosis was also validated by the drug-specific dysregulation of BCL2 proteins and increased levels of cleaved caspase-3 in response to BH3-mimetics.

Conclusions:

This study demonstrates that NETs depend on the activity of BCL2 family proteins for survival, especially BCL-xL and MCL-1. Inhibition of these proteins by BH3-mimetics effectively induces cell death and improves the efficacy of SOC agents in patient-derived preclinical models. Future work will elucidate the mechanisms allowing certain SOC to synergise with Navitoclax, for instance through dysregulating MCL-1. Overall, our findings illuminate a promising therapeutic strategy for NETs by combining BH3-mimetics with current SOC, providing strong rationale for future clinical evaluations.

Back to Abstracts Table of Contents

Tumor Cell Surface Targeting of High-Grade Neuroendocrine Carcinomas

C. Allison Stewart[1], Runsheng Wang[1], Kavya Ramkumar[1], Azusa Tanimoto[1], Ping Li[1], Alberto Duarte[1], Yuanxin Xi[2], Lixia Diao[2], Alexa Halliday[1], Shui Ping So[1], Jing Wang[2], Lauren A. Byers[1], Carl M. Gay[1]

1. Department of Thoracic/Head & Neck Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA, 2. Department of Bioinformatics and Computational Biology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Presenter: C. Allison Stewart, PhD

Background:

Personalization of therapy for high-grade neuroendocrine carcinoma (hgNEC) patients is challenging as these tumors are largely driven by loss of tumor suppressor function rather than actionable oncogenic addiction. However, recent therapeutic developments have focused on hgNEC-associated cell surface antigens which, when targeted with an antibody, can serve as beacons for delivery of cytotoxic or immunologic payloads. T-cell engagers (TCEs) and/or antibody-drug conjugates (ADCs) against hgNEC antigens including Delta-Like Ligand 3 (DLL3) and Seizure-Related Gene 6 Homolog (SEZ6) have demonstrated unprecedented responses in relapsed hgNECs. In some cases, such as small cell lung cancer (SCLC), the expression of these antigens is nearly ubiquitous and sensitivity to surface-targeting therapies is contingent primarily on payload. However, in other hgNECs, neuroendocrine features, including DLL3 and SEZ6 expression, are bimodal, which necessitates strategies for patient selection and alternative antigens for neuroendocrine-low hgNECs.

Methods:

We utilized expression data from public hgNEC cohorts, as well as our own curated institutional cohort, to characterize the relationship between established cell surface target expression (e.g. DLL3 and SEZ6) and various established biomarkers, including of neuroendocrine status, chemosensitivity, and immune sensitivity. Among hgNECs that were DLL3/SEZ6-low, we utilized gene expression and cell surface mass spectrometry to identify alternative cell surface candidates for therapeutic targeting, including both established and novel antigens. We then tested single-agent and combination treatments with ADCs, TCEs, and chimeric antigen receptor T-cell (CAR T-cells) against multiple antigens using patient-derived hgNEC models.

Results:

As expected, we determined that, unlike SCLC, expression of DLL3 and SEZ6 is heterogeneous in all other hgNECs. While those hgNEC tumors that express DLL3 (or SEZ6) are responsive to therapies targeting these antigens, neuroendocrine-low models (i.e. those driven by POU Class 2 Homeobox 3 (POU2F3) or Yes-Associated Protein 1 (YAP1)) are largely unresponsive. Instead, therapies targeting alternative surface antigens, such as Trophoblast Cell Surface Antigen 2 (TROP2) or Human Epidermal Growth Factor Receptor 2 (HER2) demonstrate superior efficacy in neuroendocrine-low models. In addition to TROP2 and HER2, alternative novel cell surface antigens were also identified for both neuroendocrine-high and -low hgNECs. Surprisingly, target expression is not the dominant predictive biomarker for many surface-targeting therapies as, instead, biomarkers of payload sensitivity (e.g. Schlafen 11 (SLFN11) for topoisomerase I inhibitor payloads) offer superior insight into efficacy.

Conclusions:

Surface-targeting therapies represent a new paradigm for hgNEC therapeutics. For hgNECs beyond SCLC, expression of DLL3 and SEZ6 varies widely depending on the underlying neuroendocrine status of the tumor. In neuroendocrine-low tumors, alternative targets will be necessary and candidates for those include TROP2, HER2, and various novel therapies. While DLL3- and SEZ6-targeting therapies are showing promise across all hgNECs, their impact will be limited outside SCLC without patient selection. Utilizing biomarkers, including those for target expression and, especially, for payload sensitivity, will be critical to optimize drug selection and sequencing in this new paradigm.

Back to Abstracts Table of Contents

Pharmacologic and Genetic Disruption of SDH Sensitize Tumor Cells to YM155 Induced DNA Damage

Qianjin Guo[1], Sooyeon Lee[1], Neali Armstrong[1], Brian Lim[1], Rebecca C. Schugar[1], David Tomz[1], Haixia Xu[1], Leor Needleman[1], Electron Kebebew[2,3], Justin P. Annes[1,3,4]

1. Department of Medicine, Division of Endocrinology, Stanford University, Stanford, CA, USA, 2. Department of Surgery and Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA, USA, 3. Endocrine Oncology Program, Stanford University, Stanford, CA, USA, 4. Chemistry, Engineering, and Medicine for Human Health (ChEM-H) Institute, Stanford University, Stanford, CA, USA

Presenter: Qianjin Guo, PhD

Background:

Pheochromocytomas and Paragangliomas (PPGLs) are rare neuroendocrine tumors arising from the adrenal medulla and extra-adrenal paraganglia, respectively. About 40% of PPGLs are hereditary, and a substantial proportion are caused by germline mutations in the succinate dehydrogenase (SDH) subunits. PPGLs can secrete harmful levels of catecholamines, cause mass effects, and harbor malignant potential. Although most PPGLs are curable by surgery, up to 20% are metastatic. Unfortunately, treatments for metastatic PPGL remain palliative. Succinate dehydrogenase subunit B (SDHB) deficiency confers a greatly increased risk for metastasis. As a result, SDHB deficiency accounts for almost half of the metastatic PPGLs. Hence, discovering novel therapeutic avenues that improve the prognosis for metastatic SDHB-PPGL patients, is an urgent and unmet need.

Methods:

Given the limited availability of human PPGL cell models, we employed SDHB-deficient UOK269 (KO) and SDHB-reconstituted UOK269 (WT) cells to investigate vulnerabilities caused by SDH loss. The cell model was characterized by MitoTracker and MitoSOX staining, transmission electron microscopy, and Seahorse metabolic analysis. A collection of mitochondria-targeted compounds was screened (96-well format) for SDHB-dependent cytotoxicity (treatment range [1nM-10,000nM]). After 72h exposure, relative cell viability was assessed using the Operetta CLS High-Content Analysis System. The best hit compound was subsequently validated in mouse pheochromocytoma (MPC) cells and primary human PPGL cells.

Results:

Chemical screening identified several compounds with preferential cytotoxicity toward SDHB-deficient UOK269 (KO) cells, with YM155 demonstrating the highest potency and an approximate fivefold lower IC_{50} compared to WT cells. To confirm selectivity, we re-evaluated YM155 in SDHB-reconstituted UOK269 (WT) cells with or without 3-NPA, a mitochondrial complex II inhibitor that mimics SDH dysfunction. YM155 exhibited enhanced cytotoxicity in the presence of 3-NPA, indicating that its effect is modulated by SDH inhibition. Additionally, recognizing the limitations of tumor cell-line screening, we evaluated the cytotoxic activity using a mouse primary cell model. To extend these findings beyond established cell lines, we validated YM155 cytotoxicity in 3-NPA treated mouse pheochromocytoma (MPC) cells and primary human PPGL cells. Mechanistically, YM155-induced cytotoxicity was found to be independent of Survivin- a known target. Instead, YM155 triggered DNA damage, and pharmacological inhibition or genetic disruption of KDM4 sensitized WT cells to its effects.

Conclusions:

Using a mitochondria-targeted small-molecule library screen, we identified YM155 as a compound with selective cytotoxicity toward SDHB-deficient cells. This selectivity was confirmed in mouse primary cells, MPC cells, and primary human PPGL cells, indicating potential applicability in animal model systems and beyond. Mechanistically, SDH dysfunction sensitizes cells to YM155-induced cytotoxicity through a Survivin-independent pathway involving DNA damage.

Back to Abstracts Table of Contents

DUSP1 is a Therapeutic Vulnerability in Neuroendocrine Tumors

Majid Momeny[1], Solmaz AghaAmiri[1], Servando H. Vargas[1], Jack T. Adams[1], Tyler M. Bateman[1], Sukhen Ghosh[1], Vahid Khalaj[1], Ali Azhdarinia[1]

1. The Brown Foundation Institute of Molecular Medicine, McGovern Medical School, The University of Texas Health Science Center at Houston, TX, USA

Presenter: Majid Momeny, PhD

Background:

Neuroendocrine tumors (NETs) are rare, heterogeneous malignancies that arise from enterochromaffin cells, primarily in the gastrointestinal tract and bronchopulmonary system. Surgery remains the standard treatment for localized NETs, but many patients present with metastatic or unresectable disease requiring systemic therapy. Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE targets SSTR2-positive NETs and improves progression-free survival and quality of life. However, its modest response rate (~18% in G1–G2 midgut NETs) and limitations on cumulative dosing often result in relapse, highlighting the need for rational combination strategies to improve efficacy.

Recent studies have identified phosphatases as key regulators of cancer signaling and resistance mechanisms, presenting novel therapeutic opportunities. Dual specificity phosphatase 1 (DUSP1), a MAPK phosphatase, selectively dephosphorylates JNK1/2 and p38 MAPKs. Elevated DUSP1 expression has been reported in multiple cancers and is frequently associated with enhanced metastasis, poor clinical outcomes, and therapeutic resistance. Inhibiting DUSP1 can sensitize tumors to therapy in several contexts. However, its expression pattern and functional role in NETs remain largely unexplored.

Materials and Methods:

To investigate the role of DUSP1 in NETs, we assessed its protein expression by Western blot in a panel of human NET cell lines—BON-1 and QGP-1 (pancreatic NET), H69 and H524 (small cell lung cancer), and IMR-32 (neuroblastoma)—and two patient-derived xenograft (PDX) models: 1452 (rectal NET) and 913 (pancreatic NET). The effects of DUSP1 inhibition were evaluated using the small molecule BCI. We measured cell viability (WST-1 assay), clonogenic survival, apoptosis (cleaved PARP), and activation of MAPK signaling (phosphorylated JNK, ERK, and p38). Bulk RNA sequencing was performed to identify transcriptional changes following BCI treatment. Publicly available transcriptomic datasets of pancreatic and small bowel NETs were also analyzed to compare DUSP1 mRNA expression in primary tumors versus lymph node and liver metastases.

Results:

DUSP1 protein was consistently expressed across all NET cell lines and PDX models. BCI treatment significantly reduced cell viability and clonogenic survival and induced apoptosis. Transcriptomic profiling and Western blotting showed activation of pro-apoptotic MAPK pathways, particularly phosphorylation of JNK1/2 and p38. Pre-treatment with the JNK inhibitor CC90001 partially rescued cells from BCI-induced cytotoxicity, confirming the role of JNK activation. Notably, combining BCI with ^{177}Lu-DOTATATE synergistically suppressed cell proliferation and enhanced apoptosis. In clinical samples, DUSP1 expression was elevated in lymph node metastases of patients with pancreatic and small bowel NETs compared to primary tumors.

Conclusion:

These findings identify DUSP1 as a novel and actionable therapeutic target in NETs. Inhibition of DUSP1 activates pro-apoptotic MAPK signaling and enhances the efficacy of PRRT with ^{177}Lu-DOTATATE. This study provides a strong rationale for further mechanistic studies and in vivo validation of DUSP1-targeted strategies to improve outcomes in patients with advanced SSTR2-positive NETs.

Back to Abstracts Table of Contents

Lung NETs in the Genomics Era: Past, Present, and Future of IARC's lungNENomics Project

Nicolas Alcala[#,*,1], Alexandra Sexton-Oates[#,1], Émilie Mathian[#,1], Noah Candeli[2], Yuliya Lim[1], Catherine Voegele[1], Alex Di Genova[3-5], Laurane Mangé[1], Zhaozhi Li[6], Tijmen van Weert[7], Lisa M. Hillen[7], Ricardo Blázquez-Encinas[8,9,10], Abel Gonzalez-Perez[11,12,13], Maike L. Morrison[14], Eleonora Lauricella[15], Lise Mangiante[1,16], Lisa Bonheme[1], Laura Moonen[7], Gudrun Absenger[17], Janine Altmuller[18,19], Cyril Degletagne[20], Odd Terje Brustugun[21-23], Vincent Cahais[24], Giovanni Centonze[25], Amélie Chabrier[1], Cyrille Cuenin[24], Francesca Damiola[26], Vincent Thomas de Montpréville[27], Jean-François Deleuze[28], Anne-Marie C. Dingemans[29], Élie Fadel[27,30], Nicolas Gadot[26], Akram Ghantous[24], Paolo Graziano[31,32], Paul Hofman[33], Véronique Hofman[33], Alejandro Ibáñez-Costa[8,9,10], Stéphanie Lacomme[34], Nuria Lopez-Bigas[11-13,35], Marius Lund-Iversen[36], Massimo Milione[25], Lucia Anna Muscarella[37], Sergio Pedraza-Arevalo[8,9,10], Corinne Perrin[38], Gaetane Planchard[39], Helmut Popper[40], Luca Roz[41], Angelo Sparaneo[37], Wieneke Buikhuisen[42], José van den Berg[43], Margot Tesselaar[44], Jaehee Kim[6], Ernst Jan M Speel[45], Séverine Tabone-Eglinger[46], Marco Volante[47], Thomas Walter[48,49], Gavin M. Wright[50,51], Justo P. Castaño[8,9,10,52], Lara Chalabreysse[53], Liming Chen[54], Christophe Caux[55], Nicolas Girard[56-58], Jean-Michel Vignaud[59], Esther Conde[60,61], Audrey Mansuet-Lupo[62], Luka Brcic[63,64], Giuseppe Pelosi[65], Mauro Giulio Papotti[66], Sylvie Lantuejoul[67,68], Jules Derks[29], Talya Dayton[2], Matthieu Foll[*,1] & Lynnette Fernandez-Cuesta[*,1]

1. Computational Cancer Genomics Team, Genomic Epidemiology Branch, International Agency for Research on Cancer (IARC-WHO), Lyon, France, 2. European Molecular Biology Laboratory, Barcelona, Spain, 3. Instituto de Ciencias de la Ingeniería, Universidad de O'Higgins, Rancagua, Chile, 4. Centro UOH de Bioingenieria (CUBI), Universidad de O'Higgins, Rancagua, Chile, 5. Centro de Modelamiento Matemático UMI-CNRS 2807, Santiago, Chile, 6. Department of Computational Biology, Cornell University, New York, USA, 7. Department of Pathology, GROW Research Institute for Oncology and Reproduction, Maastricht University Medical Centre, Maastricht, The Netherlands, 8. Maimonides Biomedical Research Institute of Cordoba (IMIBIC), Cordoba, Spain, 9. Department of Cell Biology, Physiology and Immunology, University of Cordoba, Cordoba, Spain, 10. Reina Sofia University Hospital, Cordoba, Spain, 11. Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona, Spain, 12. Centro de Investigación Biomédica en Red en Cáncer (CIBERONC), Instituto de Salud Carlos III, Madrid, Spain, 13. Department of Medicine and Life Sciences, Universitat Pompeu Fabra, Barcelona, Spain, 14. Department of Biology, Stanford University, Stanford, CA, USA, 15. Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", Bari, Italy, 16. Stanford Cancer Institute, School of Medicine, Stanford University, Stanford, CA, USA, 17. Division of Oncology, Department of Internal Medicine, Medical University of Graz, Graz, Austria, 18. Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany, 19. Berlin Institute of Health, Charité-Universitätsmedizin Berlin, Berlin, Germany, 20. Cancer Genomic Platform, Centre de Recherche en Cancérologie de Lyon (CRCL) INSERM U1052-CNRS UMR5286, Université de Lyon, Université Claude Bernard Lyon[1], Centre Léon Bérard, Lyon, France, 21. Institute of Clinical Medicine, University of Oslo, Oslo, Norway, 22. Section of Oncology, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway, 23. Institute for Cancer Research, Oslo University Hospital, Oslo, Norway, 24. Epigenomics and Mechanisms Branch, International Agency for Research on Cancer (IARC-WHO), Lyon, France, 25. First Pathology Division, Department of Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, 26. Pathology Research Platform, Cancer Research Center of Lyon, INSERM 1052, CNRS 5286, Lyon 1 University & Department of Biopathology, CNR MESOPATH NETMESO, Centre Léon Bérard, Lyon, France, 27. Department of Pathology, Hôpital Marie-Lannelongue, Groupe Hospitalier Paris Saint Joseph, Le Plessis Robinson, France, 28. Centre National de Recherche en Génomique Humaine (CNRGH), CEA-Institut de Biologie François Jacob, Université Paris-Saclay, Evry, France, 29. Department of Pulmonary Medicine, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, The Netherlands, 30. Paris Saclay University, Gif-sur-Yvette, France, 31. Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome, Rome, Italy, 32. Unit of Pathology, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy, 33. IHU RespirERA, Laboratory of Clinical and Experimental Pathology, FHU OncoAge, Côte d'Azur University, Nice, France, 34. Center of Biological Resources BB-0033-00035, University Hospital of Nancy, Vandœuvre-lès-Nancy, France, 35. Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain, 36. Department of pathology, Oslo University Hospital, Oslo, Norway, 37. Laboratory of Oncology, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy, 38. Hospices Civils de Lyon Biobank (CRB HCL), Tissu-Tumorothèque Est, Lyon, France, 39. Pathology Department, Caen University Hospital, Normandy University, Caen, France, 40. Pathology Institute for

Back to Abstracts Table of Contents

Diagnostics and Research, Medical University Graz, Graz, Austria, 41. Department of Experimental Oncology, Fondazione IRCCS - Istituto Nazionale dei Tumori, Milan, Italy, 42. Department of Thoracic Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands, 43. Department of Pathology, Netherlands Cancer Institute, Amsterdam, The Netherlands, 44. Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands, 45. Department of Pathology and Clinical Bioinformatics, Erasmus Medical Center, Rotterdam, The Netherlands, 46. Plateforme de Gestion des Echantillons Biologique, Centre Léon Bérard, Cancer Research Center of Lyon, Université de Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Lyon, France, 47. Department of Oncology, University of Turin at San Luigi Hospital, Orbassano, Turin, Italy, 48. Gastroenterology and Technologies for Health, INSERM UMR 1052 CNRS UMR 5286, Cancer Research Center of Lyon, University of Lyon, Lyon, France, 49. Department of Medical Oncology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France, 50. University of Melbourne, Melbourne, Australia, 51. Department of Surgery, St Vincent's Hospital, Melbourne, Australia, 52. CIBER Physiopathology of Obesity and Nutrition (CIBERobn), Cordoba, Spain, 53. Department of Pathology, Groupe Hospitalier Est, Hospices Civils de Lyon, Bron, France, 54. Department of Mathematics and Informatics, Ecole Centrale de Lyon, Lyon, France; Institut Universitaire de France (IUF), Paris, France, 55. CISTAR team, Cancer Research Center of Lyon, INSERM U1052, CNRS UMR5286, Université de Lyon, 8 Université Lyon 1, Centre Léon Bérard, Lyon, France, 56. Institut Curie, Paris, France, 57. Université de Versailles Saint-Quentin-en-Yvelines, Paris Saclay, Versailles, France, 58. EURACAN, Lyon, France, 59. Department of Biopathologie, Nancy University Hospital, Nancy, France, 60. Department of Pathology, Hospital Universitario 12 de Octubre. Universidad Complutense de Madrid, Madrid, Spain, 61. Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), CIBERONC, Madrid, Spain, 62. Department of Pathology, Cochin Hospital, APHP Paris Centre, Paris City University, Paris, France, 63. Department of Pathology, Hospital Graz II, Graz, Austria, 64. Department of Pathology, Medical University of Vienna, Vienna, Austria, 65. Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy, 66. Department of Oncology, University of Turin, Turin, Italy, 67. Grenoble Alpes University, Grenoble, France, 68. Department of Biopathology, Léon Bérard Cancer Center, Lyon, France

# These authors contributed equally; * These authors jointly supervised this work.

Presenter: Nicolas Alcala, PhD

Background:

Six years after the start of its support by NETRF, the lungNENomics project has born many fruits. Starting in 2019 in a field where lung NET research was the ever forgotten cancer of large genomic initiatives like the TCGA, lungNENomics is on the verge of providing a harmonized dataset of more than 300 samples—rivalling some of the largest TCGA and PCAWG cohorts in terms of size and data modalities. This multi-modal dataset has led to many discoveries that are already influencing the clinical management of the disease (Derks JTO 2025). Here, I will highlight the key discoveries from these past six years, discuss how rare cancer research can keep up with that of common cancers, and highlight open questions and challenges that we need to address to finally understand lung NET carcinogenesis and design the treatments of tomorrow.

Methods:

The lungNENomics cohort comprises a comprehensive multi-modal dataset of 319 tumor samples (including 41 samples with multiple regions), with whole-genome sequencing, RNA-seq, methylation arrays, spatial transcriptomics and proteomics, and digitalized whole-slide images. We have performed agnostic multi-omic clustering to discover molecular groups of lung NETs as well as diverse comparative analyses to uncover their molecular profiles and molecular carcinogenesis processes. We have also generated patient-derived tumor organoids of lung NETs and used them for drug testing, and developed some of the very first deep-learning algorithms devoted to NETs.

Results:

Our multi-omic analyses have shown that lung NETs actually comprise four very different diseases (Alcala et al. Nat Commun 2019), affecting different patients and with different molecular drivers and characteristics. We also discovered supra-carcinoids as a new biological entity of lung NETs with NEC-like clinical and molecular features. The organoid models we have generated allowed us to discover new vulnerabilities in NETs (Dayton et al. Cancer Cell 2023). Finally, deep-learning analyses have shown the limitations of the current WHO classification system (Mathian et al. ESMO open 2024) and identified simple morphological characteristics that can help the identification of these diseases (Sexton-Oates et al. Under consideration in Nature). Overall, these results have promoted a new classification of lung NETs that will be proposed at the next WHO classification of

Back to Abstracts Table of Contents

tumors board meeting to guide clinical management. We have also provided open source resources to the NET community, including tumor maps to explore the data (https://tumormap.ucsc.edu/?p=RCG_lungNENomics/LNEN), bioinformatic pipelines to process it (https://github.com/IARCbioinfo), and provided public harmonized datasets to fuel other research programs (Gabriel et al. GigaScience 2020, Di Genova et al. GigaScience 2023, Alcala et al. GigaScience 2024).

Conclusion:

These past six years of funding by NETRF have allowed lung NET genomic research to keep up with common cancer research and generate results that are changing the way lung NETs are diagnosed and treated. The arrival of new technologies like high-resolution sequencing and AI provide hope to reveal the final secrets of the initiation and vulnerabilities of cancers, but continued efforts will be needed so lung NETs benefit from these advances, in particular to prevent and treat its most aggressive form, supra-carcinoids.

Back to Abstracts Table of Contents

A Cellular Map of Human Pulmonary Neuroendocrine Diversity and Proliferation

Parth Arora[1], Yue Zhang[1], Bailey Wallen[2], Daniel Chambliss[1], Christin S. Kuo[1]

1. Department of Pediatrics, Stanford University, Stanford, CA, 2. Department of Surgery, Stanford University, Stanford, CA

Presenter: Christin Kuo, MD

Pulmonary neuroendocrine cells (NECs) are rare airway neuroepithelial cells with diverse sensory, signaling, and stem cell functions. NECs have recently become one of the most intensely studied rare cell types of the mammalian lung, primarily using mouse models and this has led to a rich understanding of their development and function. In contrast, little is known about human NECs, including their anatomic distribution and molecular diversity. Neuroendocrine lung diseases originating from proximal airways have distinct clinical, histologic, and molecular features from those found in the distal airways. To translate the knowledge of normal NEC biology to human diseases, we systematically identified human NECs along the entire length of the airways from proximal to distal alveolar regions. In total, we fully re-constructed 826 solitary human NECs and quantified over 14,500 solitary and clustered NECs across five zones in the human lung. The cellular and molecular characteristics of human NECs differed locations within the airways, with clusters normally found only in two of the five zones. Within the distal airways, rare NECs proliferated under injury conditions. This new knowledge of the spatial organization of human solitary and clustered NECs under normal physiologic conditions establishes a foundational cell map with initial molecular profiles for subsequent studies to identify NE progenitor cells within their 'niches' and to determine the origin and functions of human NECs in diverse respiratory diseases with prominent neuroendocrine character.

Back to Abstracts Table of Contents

Spatial Transcriptomics Reveals Local Subtype-Specific Identity and Signaling within Multifocal Small Intestinal Neuroendocrine Tumors

Akitada Yogo[1,2], Naoki Akanuma[3], Grace E. Kim[3], Chrissie Thirlwell[4], Netta Mäkinen[5,6], Matthew Meyerson[5,6,7], Eric K. Nakakura[1,2]

1. Division of Surgical Oncology, Section of Hepatopancreaticobiliary Surgery, Department of Surgery, University of California, San Francisco, CA, USA, 2. Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA, 3. Department of Pathology, University of California, San Francisco, CA, USA, 4. Bristol Medical School, University of Bristol, Bristol, UK, 5. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, 6. Cancer Program, Broad Institute of Harvard and MIT, Cambridge, MA, USA, 7. Departments of Genetics and Medicine, Harvard Medical School, Boston, MA, USA

Presenter: Akitada Yogo, MD, PhD

Background:

Small intestinal neuroendocrine tumors (SI-NETs) frequently present as multifocal lesions, but the spatial and molecular mechanisms underlying their development and heterogeneity remain unclear. This study aimed to characterize the phenotypic subtypes of tumor cells across anatomical sites in multifocal SI-NETs and identify local microenvironmental factors influencing tumor development.

Methods:

Spatial transcriptomics was performed on 72 tissue microarray cores derived from four patients with multifocal SI-NETs, covering tumor and non-tumor tissues from various anatomical layers and metastatic sites. Unsupervised clustering, over-representation analysis (ORA), and ligand-receptor (L-R) pair analysis were used to define tumor subtypes and associated signaling networks. External datasets (GSE98894 and GTEx) were used for validation. Protein expression of selected genes was evaluated by immunohistochemistry.

Results:

Unsupervised clustering revealed four major tumor subtypes: mucosal, mesenteric, lymphatic, and deep, based on anatomical location and transcriptomic profiles. Each subtype exhibited distinct gene expression patterns and L-R interactions. Mesenteric and lymphatic subtypes exhibited distinct L-R pairs, such as NRG1 - ERBB3 and CXCL12 - CXCR4, respectively. 5HT - HTR1D was found in all subtypes except mucosal. Across the four subtypes, SST - SSTR1/2, PTN - NCL, MDK - NCL and GJD2 - GJD2 were consistently detected, suggesting fundamental roles in SI-NET biology.

Conclusions:

While further validation is needed, our findings indicate that multifocal SI-NETs consist of spatially distinct tumor subtypes affected by local cellular interactions, providing insight into SI-NET intra-tumoral heterogeneity, possible microenvironmental-triggered tumorigenesis, and potential subtype-targeted therapeutic strategies.

Back to Abstracts Table of Contents

Identification of PABPC Family, NOTCH1 and MTOR as Critical Somatic Mutations in Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) from Whole Exome Sequencing (WES) Analysis

Daniel T. Merrick[1], Hui Yu[1], Thomas Danhorn[1], Nathaniel Pakosz[1], and York E. Miller[1,2]

1. University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 2. Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, CO, USA

Presenter: Hui Yu, MD, PhD

Background:

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) is a recognized pre-malignant condition which is characterized by generalized proliferation of pulmonary neuroendocrine cells (PNEC). These premalignant lesions lead to life-threatening complications including multifocal carcinoid tumors and severe airway obstruction with respiratory failure. Surgical resection and lung transplantation have shown limited efficacy. The identification of the common somatic mutations in DIPNECH will allow us to understand the molecular basis of the disease to discover vulnerabilities that can be exploited to interrupt the development and progression of neuroendocrine tumors and to discover diagnostic and prognostic markers that can guide treatment planning decisions.

Methods:

A cohort of 47 patients with clinical and pathologic features of DIPNECH was identified. Lesions classified histologically as NECH, carcinoid tumorlets and carcinoid tumors were collected using micro-dissection from the archived formalin-fixed, paraffin-embedded (FFPE) tissue blocks. Genomic DNA from the micro dissected lesions and the germline DNA from lymph nodes or matched normal lung tissue were extracted and whole exome sequencing (WES) was performed to identify common somatic mutations in DIPNECH patients.

Results:

DNA was extracted from a total of 122 lesions from 47 patients collected by micro-dissection, including 87 NECH lesions, 12 tumorlets and 23 carcinoid tumors. After stringent filtering of polymorphisms and assessment of potential oncogenic impact, an average gene variant impact score (AGVIS) for each gene affected was calculated by reviewing frequency in tumor database such as COSMIC and using tools for predicting the effects of amino acid alterations such as SIFT and Polyphen. AGVIS ranges from 0 to 4 in our DIPNECH cohort where higher numbers represent potential higher impact of mutations in the gene on disease development and progression. We then identified a group of genes with a high frequency of somatic mutations (variants ≥ 10) and a high AGVIS > 2 in the DIPNECH cohort. With further confirmation of the potential tumorigenicity of these gene mutations using the cBioportal database and the predictive program Varsome, we identified the Poly (A) binding protein cytoplasmic family (PABPC), NOTCH1 and MTOR genes as harboring potential critical mutations in the pathogenesis and progression of DIPNECH.

When comparing cases with accompanying strong versus weaker clinico-radiographic evidence of DIPNECH, 453 bi-allelic and 449 single allelic polymorphisms showed raw statistically significant differences in frequency though none were significant when adjusted for multiple testing correction. In a similar comparison, where more stringent criteria in respect to thresholds for number of variants and overall reads as well as application of stricter variant caller programs were applied, an assessment of the frequency of common variants across all lesions within individual patient was performed. Strong evidence cases showed a higher rate of at least five variants that were shared between two or more lesions (12/19, 63.2%) compared to weaker evidence cases (1/4, 25%).

Conclusions:

PABPC 1/3, NOTCH1 and MTOR have been identified as potential critical alterations in the pathogenesis and disease progression of DIPNECH. Early analyses suggest that DIPNECH cases show evidence of clonal relatedness of spatially distinct lesions within patients.

Back to Abstracts Table of Contents

Whole Transcriptome Sequencing of Pancreatic Neuroendocrine Tumors Identifies Recurrent Fusion Genes in BEND2 as a Unique Oncogenic Driver that Correlates with Poor Patient Prognosis

Michelle A. Wood-Trageser, PhD[1], C. Tolson Nichols, MD[1], Danielle A. Hutchings, MD[2], Diana Bell, MD[1], Abigail I. Wald, PhD[1], Katelyn Smith, BA[1], Seung-Mo Hong, MD PhD[3], Claudio Luchini, MD PhD[4], Lodewijk A. A. Brosens, MD PhD[5], Anna Vera D. Verschuur, MD[5], Michele Bevere, PhD[4], Rita T. Lawlor, PhD[4], Aldo Scarpa, MD[4], Shannon Keating, PhD[1], James Tucker, PhD[1], Roderick J. O'Sullivan, PhD[6], Ta-Chiang Liu, MD PhD[7], Kevin McGrath, MD[8], Kenneth Fasanella, MD[8], Randall E. Brand, MD[8], Anne Marie Lennon, MD[8], Rohit Das, MD[8], Harkirat Singh, MD[8], Adam Slivka, MD PhD[8], Sultan Mahmood, MD[8], Amy E. Hosmer, MD[8], Asif Khalid, MD[8], Stephanie L. Romutis, MD [8], Amer H. Zureikat, MD[9], Herbert J. Zeh, MD[10], Melissa E. Hogg, MD[11], Kenneth K. Lee, MD[9], Alessandro Paniccia, MD[9], Geoffrey Nunns, MD[9], Melanie Ongchin, MD[9], Walter G. Park, MD[12], Patricio M. Polanco, MD[10], Jin He, MD [13], Diane M. Simeone, MD[14], Cristina R. Ferrone, MD[15], Dennis Hsu, MD[16], Janie Zhang, MD[16], Vikram Gorantla, MD[16], John Rhee, MD[16], Ralph H. Hruban, MD[17], Anju H. Singhi[1], Sara A. Singhi[1], Candice K. Wang[1], Nuha Shaker, MD, Robert Bubar, MD[1], Maria Grupillo, PhD[1], Yi-Tak Lai, PhD[1], Marina N. Nikiforova, MD[1], Christopher M. Heaphy, PhD [18,] Kevin M. Waters, MD PhD[2], Aatur D. Singhi, MD PhD[1]

1. Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA. 2. Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA.3. Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.4. Department of Diagnostics and Public Health, Section of Pathology, University of Verona, Verona, Italy. 5. Department of Pathology, University Medical Center Utrecht, Utrecht University, The Netherlands. 6. Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, PA, USA. 7. Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA. 8. Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA. 9. Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA. 10. Department of Surgery, University of Texas Southwestern, Dallas, TX, USA. 11. Department of Surgery, NorthShore University Health System, Evanston, IL, USA. 12. Department of Medicine, Stanford University, Stanford, CA, USA. 13. Department of Surgery, Johns Hopkins Medical Institutions, Baltimore, MD, USA. 14. Department of Surgery, New York University Langone Health, New York, NY, USA. 15. Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA. 16. Department of Medicine, Division of Hematology-Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA. 17. Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins Medical Institutions, Baltimore, MD, USA. 18. Section of Hematology and Medical Oncology, Boston University and Boston Medical Center, Boston, MA, USA

Presenter: Aatur Singhi, MD, PhD

Background:

Pancreatic neuroendocrine tumors (PanNETs) exhibit heterogeneous clinical behavior, and a growing number have been identified incidentally over the past few decades. Genetically, PanNETs are characterized by alterations in chromatin remodeling genes and genes associated with telomere elongation, such as ATRX and DAXX. ATRX and DAXX alterations occur in approximately 50% of metastatic cases and drive the metastatic progression of PanNETs. However, many PanNETs lack known driver alterations. Therefore, this study aimed to identify alternative oncogenic mechanisms and novel prognostic biomarkers in primary PanNETs.

Methods:

Whole transcriptome sequencing was performed on 224 non-syndromic PanNETs with extended patient clinical follow-up (>4 years). Findings were validated via immunohistochemistry in an independent multi-institutional cohort of 539 patients with a PanNET. Clinicopathologic correlation, molecular studies, and survival analyses were performed to assess the prognostic significance of identified biomarkers.

Results:

Based on unsupervised hierarchical clustering, transcriptomic profiling identified multiple distinct clusters, with Cluster 6, exhibiting aggressive features, including high WHO grade (G2/G3 vs G1), lymphovascular invasion, and distant metastases. Cluster 6 PanNETs were also uniquely wild-type for ATRX and DAXX alterations, but all cases harbored recurrent BEND2 fusion genes (CHD7::BEND2 and EWSR1::BEND2). Overall, BEND2 fusion genes were detected in 7% (15/224) of PanNETs and exclusively in Cluster 6. Gene Set Enrichment Analysis (GSEA) demonstrated that BEND2-fusion positive PanNETs had activation of telomere maintenance mechanisms

Back to Abstracts Table of Contents

via telomerase activation. Considering BEND2-fusion positive PanNETs exhibited elevated BEND2 RNA expression, a rapid and cost-effective immunohistochemical (IHC) assay for overexpression of BEND2 protein was developed in a CLIA/CAP-certified laboratory. All 15 PanNETs with BEND2 fusion genes were confirmed to overexpress the BEND2 protein. Orthogonal validation using BEND2 IHC on a separate cohort of 539 PanNETs showed patients with BEND2-positive tumors had significantly shorter disease-free survival (DFS, $p<0.001$) and disease-specific survival (DSS, $p<0.001$). All BEND2-positive tumors showed preserved expression for ATRX and DAXX, and were negative for alternative lengthening of telomeres (ALT) by chromogenic in situ hybridization. Multivariate analysis confirmed BEND2 expression as an independent negative prognostic factor for DFS ($p<0.001$) and DSS ($p=0.001$). Overall, ATRX, DAXX, and BEND2 alterations were present in 69% of metastatic PanNETs.

Conclusions:

This study identifies recurrent BEND2 fusion genes as a novel oncogenic mechanism in PanNETs and establishes BEND2 overexpression as an independent prognostic biomarker for poor patient outcome. These findings also emphasize the importance of telomere maintenance in the metastatic progression of PanNETs. The development of a rapid, cost-effective IHC assay enables the identification of BEND2-positive PanNETs in clinical practice, offering the potential for improved patient risk stratification.

Back to Abstracts Table of Contents

A New Therapeutic Avenue Tackling Liver Metastasis and Antiangiogenic Resistance in PanNETs

Yeonghwan Kim[1], An Lo[1], Juliette Shang[1], Tito Fojo[2], Minah Kim[1]

1. Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY, USA,
2. Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA.

Presenter: Minah Kim, PhD

Background:

Antiangiogenic therapies targeting the VEGF signaling pathway have demonstrated clinical promise for patients with pancreatic neuroendocrine tumors (PanNETs). However, therapeutic resistance and subsequent metastatic recurrence remain significant clinical challenges. Addressing these limitations requires a deeper mechanistic understanding of therapeutic resistance and the identification of novel targets to improve clinical outcomes.

Methods:

To explore mechanisms underlying resistance, we developed a spontaneous metastatic PanNET mouse model (RT2;AB6F1) that exhibits resistance to VEGF pathway inhibition (VEGF-Trap, REGN3) specifically in liver metastases. We performed single-nucleus RNA sequencing (snRNA-seq) on PanNET liver metastases post-VEGF inhibition to identify transcriptomic changes in malignant and endothelial cell populations. Candidate target genes identified through this unbiased approach were subsequently validated via immunohistochemistry, RNAscope, and functional assays.

Results:

Transcriptomic profiling via snRNA-seq of PanNET liver metastases after VEGF inhibition identified distinct differentially expressed genes in malignant and endothelial cells. Notably, VEGF-C was significantly upregulated in malignant cells, accompanied by elevated endothelial expression of its receptor, VEGFR3 (Flt4). Validation through IHC and RNAscope confirmed the increased expression of VEGF-C and VEGFR3 in PanNET liver metastasis. Ongoing functional studies indicate that VEGF-C/VEGFR3 signaling within blood endothelial cells establishes a supportive vascular niche facilitating liver metastasis progression and conferring resistance to antiangiogenic therapies.

Conclusions:

Our findings highlight VEGF-C/VEGFR3 signaling as a critical contributor to metastatic niche formation and therapeutic resistance in PanNET liver metastases. This work addresses a significant unmet clinical need by elucidating a novel vascular-targeted approach. Furthermore, it provides foundational data supporting the development of a bispecific antibody targeting VEGFR3 via a liver sinusoid-specific arm, an innovative therapeutic strategy we intend to advance through Columbia's Drug Discovery Program.

Back to Abstracts Table of Contents

Analysis of the Tumor Microenvironment in Small Intestinal NETs

Netta Mäkinen[1,2], Yosuke Kasai[3], Grace E. Kim[4], Chrissie Thirlwell[5,6], Eric Nakakura[3], and Matthew Meyerson[1,2,7]

1. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, 2. Cancer Program, Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA, 3. Department of Surgery, University of California, San Francisco, California, USA, 4. Department of Pathology, University of California, San Francisco, California, USA, 5. Bristol Medical School, University of Bristol, Bristol, UK, 6. Department of Oncology, UCL Cancer Institute, London, UK, 7. Departments of Genetics and Medicine, Harvard Medical School, Boston, Massachusetts, USA

Presenter: Netta Mäkinen, PhD

Background:

Small intestinal neuroendocrine tumors (SI-NETs) represent one of the major cancer subtypes of the small bowel and are often present as multiple concurrent lesions in the ileum. Previous high-throughput sequencing studies have shown that concurrent primary tumors from the same SI-NET patient display distinct somatic mutational profiles (despite few clear driver mutations). The independent clonal nature of these lesions suggests that other, non-genetic mechanisms are likely involved in their growth and development. The goal of this project has been to characterize the tumor microenvironment in SI-NETs and study its potential role in their pathogenesis.

Methods:

Our sample cohort included 11 primary tumors, six lymph node metastases, and 23 normal ileal mucosa specimens from 13 multifocal and 10 unifocal SI-NET patients. Single-nucleus RNA (snRNA) sequencing was performed using 10x Chromium Single Cell 5' High-Throughput v2 technology. We used Seurat (v5) and harmony for the data analysis and integration of the samples. Pseudobulk differential expression analysis was performed with DESeq2.

Results:

A total of 251,680 high-quality nuclei were available for our analysis. After the integration of snRNA sequencing data from normal ileal mucosa samples, we detected altogether 290 enterochromaffin cells (0.2%). Additionally, we identified 32,558 tumor cells (40.3%) among the primary tumors and 20,618 (45.6%) among the metastases. Smooth muscle cells and (myo)fibroblasts represented the most common types of stromal cells within the primary tumors. Differential expression analysis between tumor cells and enterochromaffin cells revealed several statistically significant differentially expressed genes that are involved in cell transport and cell cycle regulation.

Conclusions:

For the first time, we have been able to examine expression changes between tumor cells and their putative cells-of-origin in SI-NETs, elucidating mechanisms that are involved in the growth and development of these tumors. A deeper knowledge of the cellular and molecular mechanisms that underlie SI-NET development is essential for the non-invasive management, early detection and prevention of the tumors.

Back to Abstracts Table of Contents

Dissecting the Neuroimmune Landscape of Pancreatic Neuroendocrine Tumors with Single-cell Spatial Proteo-transcriptomics

Jeanna M. Arbesfeld-Qiu[1, 2, 3, 4, 5, 6, 7], Nicole Lester[1, 2, 3, 4], Beatrice Awasthi[1, 2, 3, 4], Mingjuan L. Zhang[8], Martin Hemberg[5], William L. Hwang[1, 2, 3, 4]

1. Center for Systems Biology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, 2. Department of Radiation Oncology, Massachusetts General Hospital, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA, 3. Krantz Family Center for Cancer Research, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, 4. Broad Institute of MIT and Harvard, Cambridge, MA, USA, 5. Gene Lay Institute of Immunology and Inflammation, Brigham and Women's Hospital, Massachusetts General Hospital, and Harvard Medical School, Boston, MA, USA, 6. Biological and Biomedical Sciences Program, Harvard University, Graduate School of Arts and Sciences, Cambridge, MA, USA, 7. Harvard/MIT MD-PhD Program, Harvard Medical School, Boston, MA, USA, 8. Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

Presenter: Jeanna Qiu, AB, PhD

Background:

Pancreatic neuroendocrine tumors (PanNETs) derive from neuroendocrine cells of the pancreatic islets that are physiologically innervated to regulate hormone production. About 15% of PanNETs exhibit perineural invasion (PNI), whereby cancer cells invade peripheral nerves in the tumor microenvironment (TME). Ours and others' transcriptomic studies in PanNET have also identified aggressive cancer cell states wherein genes related to neuronal development are upregulated. PNI is associated with worse clinical outcomes in PanNET and other cancers, yet tumor-nerve crosstalk in the PanNET TME is not well understood.

Methods:

We assembled a cohort of patients with PNI (n=12) and patients who had aggressive clinical courses (i.e. nodal or distant metastases or death due to disease) without PNI (n=9). We first performed a pilot study on two human PanNET surgical-resection specimens that were pathologically annotated to have PNI. We performed 1000-plex single-cell spatial transcriptomics (CosMx, Bruker) on 5 µm formalin-fixed paraffin-embedded sections. We sampled over 100 fields of view (FOVs) for each specimen prioritizing the presence nerves or immune aggregates in the chosen FOVs. Next, we performed immunofluorescence staining on consecutive sections of neurofilament-heavy chain (pan-nerve marker), synaptophysin (cancer marker), tyrosine hydroxylase (TH, sympathetic marker), sodium channel protein type 10 subunit alpha (Nav1.8, sensory marker), and vesicular acetylcholine transporter (VAChT, parasympathetic marker) to identify nerves and nerve subtype. We used semi-supervised clustering (Insitutype) to annotate broad cell types and identified nerve bundles by immunofluorescence. Next, we calculated the nearest-neighbor distance between malignant cells to nerves and identified differentially expressed genes between malignant cells proximal to and far from nerves.

Results:

Specimen P01 had extensive PNI, while P02 had fewer foci of PNI, although both specimens had abundant intratumoral nerves. We identified 42 nerves in P01 and 29 nerves in P02. All nerves were Nav1.8 positive, but without any TH or VAChT signal, suggesting an abundance of sensory nerves in the TME. After quality control, we recovered 102,412 cells with an average transcript count of 235 transcripts per cell for P01 and 128,914 cells with an average transcript count of 454 transcripts per cell for P02. Malignant cells proximal to nerves (< 200 µm) expressed genes related to the epithelial mesenchymal transition (e.g. DCN, MGP, CDH11) and axon-guidance (e.g. EPHA7, NOTCH2, SEMA3E), while malignant cells far from nerves (> 200 µm) expressed genes related to pancreatic endocrine cell identity (e.g. INS, GCG) and the apical junction (e.g. PFN1, CDH1).

Conclusion:

The results of this pilot study highlight the feasibility of running and integrating spatial transcriptomics and proteomics on human PanNET samples. We plan to run an expanded 33-plex spatial proteomics panel (COMET, Lunaphore) on consecutive sections of the specimens used in this pilot study to better characterize the immune cells and to expand this spatial proteo-transcriptomic study to the entire cohort of PanNETs with and without PNI. Ultimately, we hope to better characterize the spatial distribution and abundance of nerve subtypes in PanNET and better understand the phenotypes of malignant cells engaged in PNI and signaling interactions between malignant cells and nerves.

Back to Abstracts Table of Contents

TILs in Pancreatic Neuroendocrine Tumors (PanNETs): Towards Novel Cell Therapies Approaches

Nada Chaoul[1], Gabriella D'Angelo[1], Eleonora Pelle'[2], Alessandro Silvestris[3], Andrea Giglio[1], Eleonora Lauricella[1], Maria Laura Matrella[4], Gaetano Villani[4], Giovanna Giliberti[5], Giuseppe Ingravallo[5], Raffaele Palmirotta[1], Riccardo Memeo[6], Jaydira Del Rivero[7], Jyoti Choudhary[8], Graziano Pesole[2], Jerome Cros[9], Ilaria Marinoni[10], Camillo Porta[1], Jonathan Strosberg[2], Anguraj Sadanandam[11], Mauro Cives[1]

1. Department of Interdisciplinary Medicine, University of Bari ""Aldo Moro"", Bari, Italy; 2. Department of GI Oncology, Moffitt Cancer Center & Research Institute, Tampa, FL, USA; 3. Department of Biosciences, Biotechnologies and Environment, University of Bari ""Aldo Moro"", Bari, Italy; 4. Department of Translational Biosciences and Neurosciences, University of Bari "Aldo Moro", Bari, Italy; 5. Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro", Bari, Italy, 6. Unit of Hepato-Biliary and Pancreatic Surgery, "F. Miulli"; General Hospital, Acquaviva delle Fonti, Bari, Italy; 7. Developmental Therapeutics Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; 8. Cancer Biology Division, Functional Proteomics, Chester Beatty Laboratories, The Institute of Cancer Research, London, UK; 9. University Paris-Cité, Department of Pathology, Bichat Hospital (AP-HP), Paris, France; 10. Institute of Pathology, University of Bern, Bern, Switzerland; 11. Division of Molecular Pathology, The Institute of Cancer Research, London, UK.

Presenter: Nada Chaoul, PhD

Background:

Whether TIL therapy is feasible and effective in patients with panNETs is currently unknown.

Methods:

Samples of liver metastases were collected from 31 patients with well-differentiated, sporadic PanNETs (8 G1, 20 G2, 3 G3). Whole-exome sequencing and matched RNAseq were used to predict canonical and non-canonical neoantigens. Immunopeptidomics experiments were carried out on 8/31 randomly selected samples by LC-MS/MS. RNA-based TCR sequencing of TILs from different tumor regions and matched tumor tissue (4/31 patients) was performed, and antigen specificities were computationally modelled. HLA expression was assessed by IHC and validated in an external cohort by TMA. TILs were expanded using different protocols and phenotyped by flow cytometry. Multi-region functional analysis was conducted on 5/31 randomly selected tumors (120 fragments in total). TIL metabolism was assessed by Seahorse. Reactivity of TILs against autologous tumoroids was tested by ELISA, flow cytometry and live cell imaging.

Results:

Variant calling revealed a median of 10 pathogenic variants/exome. There was a median of 7 and 0 neoantigens predicted to strongly bind HLA-I and HLA-II respectively. No public neoantigens were identified, in the presence of a few shared non-canonical neoantigens. Immunopeptidomics experiments revealed considerable variations in the number of peptides presented by HLA-I across samples, with 919/22930 total epitopes identified as potential neoantigens. Striking differences were noted in the immunopeptidome of different regions of the same tumor, revealing spatial heterogeneity in antigen presentation. The TCR repertoire showed considerable intratumor diversity, with more limited temporal changes throughout TILs culture. TCR reactivities against cancer-testis antigens and lineage-related antigens were identified. HLA-I and HLA-II were expressed by tumor cells in 97% and 0% of the samples respectively. In an independent cohort of 97 primary panNETs, HLA-I and HLA-II expression was 80% and 0%. Extensive intratumor heterogeneity of HLA-I expression was noted. Endotheliocytes and immune cells expressed HLA-II within tumors, providing the basis for antigen cross-presentation. Clinically meaningful numbers of TILs were reached in 19/31 patients (60% of cases). A significant correlation was seen between TIL yield, tertiary lymphoid structures and number of HLA-II-bound neoantigens. T cells were the predominant population to grow in TIL cultures, with a CD4+/CD8+ ratio of 5:1. Most TILs exhibited a memory-progenitor stem-like phenotype (CD39-CD69-), known to be associated with antitumor activity. TILs deriving from different tumor regions widely varied in numbers, expansion dynamics, metabolic fitness and antitumor activity. When tested against autologous tumoroids, an average of 4/24 individual TIL cultures/patient showed HLA-dependent cytokine secretion accompanied by upregulation of activation and exhaustion markers. Tumor-reactive TILs effectively infiltrate autologous tumoroids. Tumor-reactive TILs show superior metabolic fitness as compared with non-reactive TILs.

Conclusions:

TILs from panNET liver metastases can be isolated and expanded to reach clinically meaningful numbers. Cancer-testis antigens and lineage-related antigens are recognized by the TCRs of expanded TILs. Anti-tumor reactivities appear to be confined to immune niches rather than dispersed throughout the tumor mass. Exploitable immunological vulnerabilities can be identified in PanNETs.

Back to Abstracts Table of Contents

Single-Cell Dissection of Cellular Crosstalk and Ligand-Receptor Networks Underlying Grade Transformation in Pancreatic Neuroendocrine Tumors

Himanshu N. Singh[1], Chenyang Zhan[2], Jessica C. Puzzuoli[1], Elias-Ramzey Karnoub[3], Jungeui Hong[2], Nitya Raj[4], Olca Basturk[2], Zeynep Tarcan[2], Christine A. Iacobuzio[2], Etay Ziv[1]

1. Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 2. Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 3. Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA, 4. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Presenter:

Himanshu Singh, PhD

Background:

Pancreatic neuroendocrine tumors (PanNETs) frequently metastasize to the liver, where a subset undergoes progression from well-differentiated low-grade (LG) to poorly differentiated high-grade (HG) forms. This transformation represents a pivotal clinical event, often marking the onset of therapeutic resistance and poor prognosis. Importantly, it is not consistently associated with recurrent genomic alterations, suggesting that non-cell-autonomous mechanisms—particularly those regulated by the liver microenvironment—may play a central role in driving tumor progression and resistance. We hypothesize that grade transformation in metastatic panNETs is accompanied by dynamic remodeling of the tumor microenvironment, including shifts in cellular composition and intercellular communication networks.

Methods:

We performed single-cell transcriptome profiling, capturing simultaneous scRNA-seq and scATAC-seq data from the same nucleus, to investigate transcriptional and epigenetic shifts within the liver tumor microenvironment during PanNET progression. Seurat was utilized to preprocess the sequencing data and unsupervised clustering was done to cluster cells. The annotation was done the basis of known markers, including PanNET tumor cells (with subgourps such as proliferative and aggressive), myofibroblastic and inflammatory cancer-associated fibroblasts (myCAF/iCAF), macrophages, endothelial cells, and hepatocytes. Cell-cell communication was inferred using CellChatDB ligand-receptor (L-R) database, and the relative contributions of specific L-R pairs were quantified in each grade. Comparative analyses were performed to delineate grade-specific shifts in cellular composition and signaling axes.

Results:

We observed remodeling of the TME with grade transformation. LG panNETs were characterized by a prominent interaction between hepatocytes and myCAFs, with the VEGFA–VEGFR1 axis emerging as the dominant L-R pair, followed by JAG1–NOTCH3 and VEGFB–VEGFR1. In contrast, HG PanNETs exhibited a marked expansion of aggressive and proliferative tumor cell populations, accompanied by increased direct communication between hepatocytes and PanNET cells. The L-R landscape in HG tumors was notably more complex, with a broader repertoire of signaling pathways, including multiple VEGFA–VEGFR and WNT–FZD interactions, as well as enhanced JAG1–NOTCH2/4 and WNT4/WNT2B–FZD4/5/6 axes. Notably, WNT signaling, largely absent in LG tumors, was highly enriched in HG PanNETs, implicating WNT-driven stemness and EMT programs in grade progression. The cellular composition data further corroborated these findings, with a significant increase in aggressive panNET and CAF populations in HG tumors, and a relative depletion of myCAFs and hepatocytes compared to LG counterparts.

Conclusions:

Our single-cell transcriptomic analysis reveals dynamic rewiring of ligand-receptor (L-R) signaling during panNET grade transformation, shifting from hepatocyte–myCAF interactions in LG tumors to a hepatocyte–panNET–driven, WNT/VEGF-enriched network in HG tumors. This highlights stromal remodeling and stemness pathways as key contributors to tumor aggressiveness. These findings support targeting specific L-R pairs (e.g., WNT–FZD, VEGFA–VEGFR) and stromal–tumor crosstalk to intercept grade progression. Consistency will be evaluated in expanded cohorts, and functional impact assessed using BON1, QGP1, and patient-derived organoid co-culture systems.

Back to Abstracts Table of Contents

Unravelling the Molecular Mechanisms Behind Mesenteric Fibrosis: From Multi-Omic Analysis to Target Gene Identification Using a Novel in Vitro 3D Patient-Derived Model

Maria C. Martins*[1], Harry Hodgetts*[1], TuVinh Luong[1,2,3], Andrew R. Hall[2,3], Eva van der Slik[4], Richard A. Feelders[4], Amy Webster[5], Christos Toumpanakis[6], Dalvinder Mandair[6], Peter van Koetsveld[4], Leo J. Hofland[4], Christina Thirlwell[7], Martyn E. Caplin[6] and Krista Rombouts[1]

1. Regenerative Medicine and Fibrosis Group, Institute for Liver and Digestive Health, Royal Free Hospital, University College London, London, UK, 2. Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust, London, UK, 3. Department of Cellular Pathology, Royal Free London NHS Foundation Trust, London, UK, 4. Department of Internal Medicine, sector Endocrinology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands, 5. University of Exeter - College of Medicine and Health, Exeter, United Kingdom. 6. Neuroendocrine Tumor Unit, ENETS Centre of Excellence, Royal Free London NHS Foundation Trust, London, UK, 7. University of Bristol Medical School, University of Bristol, Bristol, UK

Presenter: Harry Hodgetts, MSc

Background:

Mesenteric fibrosis (MF) affects up to 50% of small intestine neuroendocrine tumors (SI-NETs) patients, causing significant morbidity and mortality. MF pathophysiology is poorly understood, limiting the development of treatments and identification of biomarkers. A significant challenge in producing translational data for SI-NETs is a lack of robust methods to model the disease. This project aims to improve the understanding of MF and identify useful diagnostic and predictive molecular markers, further investigating and validating possible targets in a novel 3D SI-NETs/MF patient-derived in vitro model.

Methods:

RNA sequencing and DNA methylation analysis were performed on a cohort of 43 SI-NET patients classified into MF severity groups (minimal, mild, severe), including normal small intestine (N-SI), primary tumor (PT) and mesenteric mass (MM) tissues, and analysed by gene set enrichment analysis (GSEA) and differential methylation analysis, respectively. From this, candidate MF genes were selected and investigated in the 3D SI-NET hydrogels and through siRNA treatments. Briefly, for the 3D hydrogels, MF patient-resected N-SI or MM were decellularised, freeze-dried, milled into a powder and solubilised to obtain a non-fibrotic (N-SI) or fibrotic (MM) extracellular matrix (ECM) solution. Solutions were mixed with nanocellulose and a cell suspension to create hydrogels cultured for up to 14 days. Hydrogels were embedded with a mono-culture or co-culture of GOT-1 (SI-NET cell line) spheroids and/or primary fibroblasts isolated from SI-NET patient tissue, including N-SI, PT, normal mesentery (N-MES) or MM.

Results:

GSEA analysis revealed positive enrichment of ECM, fibrosis, fibroblast and inflammation reactomes in MM compared to PT, and in more severe groups of MF. From core-enriched genes of GSEA analysis, Collagen Triple Helix Repeat Containing 1 (CTHRC1), thrombospondin-1 (THBS1) and cathepsin k (CTSK) were selected for further investigation following a literature search. Epigenetics revealed differential methylation of several genes which also showed differential mRNA expression on RNAseq data. All selected genes which were expressed in primary fibroblasts were further evaluated in the 3D hydrogels, with only CTHRC1, THBS1 and CTSK mRNA being significantly upregulated in N-MES or MM fibroblasts when cultured in a fibrotic ECM hydrogel compared to non-fibrotic ECM. The three genes were functionally evaluated by performing siRNA knockdown, revealing significantly decreased mRNA expression of fibrosis associated genes COL1A1, COL1A2 and FN1 with THBS1 and CTSK knockdown in MM fibroblasts only, as well as aSMA decreased protein expression in N-MES and MM fibroblasts with CTHRC1, THBS1 and CTSK knockdown.

Conclusion:

We characterized MF through multi-omic RNAseq and epigenetic analysis, uncovering affected pathways and genes. We confirmed the role of candidate genes CTHRC1, THBS1 and CTSK in MF using a novel 3D patient-derived model and functional studies, highlighting their ability to modulate fibrogenesis and cell activation in pathogenic fibroblasts. These genes will be further investigated as therapeutic targets for MF.

Back to Abstracts Table of Contents

EphA2 Targeting Peptide Radiotheranostics for Lung Neuroendocrine Tumors

Ajay Kumar Sharma[1], Akhilesh Mishra[1] and Sridhar Nimmagadda[1,2,3,4]

1. The Russell H. Morgan Department of Radiology and Radiological Science, 2. Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center and the Bloomberg–Kimmel Institute for Cancer Immunotherapy, 3. Department of Pharmacology and Molecular Sciences, 4. Division of Clinical Pharmacology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, 21287, USA

Presenter: Ajay Kumar Sharma, PhD

Background:

Lung neuroendocrine tumors (NETs) represent a diverse group of neoplasms that originate from neuroendocrine cells found throughout the body and accounts for approximately 25% of all lung cancers. Despite advances in oncology, managing lung NETs remains challenging due to their heterogeneity and the lack of effective targeted therapies. Traditional treatment options, including surgery, chemotherapy, and external beam radiotherapy (EBR), often provide limited efficacy in advanced stages or in patients with tumors resistant to conventional therapies. In recent years, molecularly targeted nuclear medicine approaches have emerged as a promising strategy for the diagnosis and treatment of NETs. Radiolabeled peptides targeting somatostatin receptors (SSTRs), such as [68Ga] and [177Lu]Lu-DOTATATE, have shown significant clinical success in diagnosing and treating gastroenteropancreatic NETs (GEP-NETs). However, these approaches are limited in lung NETs, especially for patients with SSTR-negative tumors, which constitute approximately 50% lung NET cases. This gap in effective therapeutic options for SSTR-negative lung NETs underscores the unmet need for alternative molecular targets and novel theranostic approaches. EphA2 (Ephrin type-A receptor 2) is a member of the Eph receptor family, which is the largest subfamily of receptor tyrosine kinases. EphA2 is overexpressed in various cancers, including lung NETs, is a promising target for theranostic, as the majority of lung NETs show higher EphA2 expression compared to normal lung tissue. Here, we propose to develop a theranostic approach using AJ210, a peptide-based agent that targets the EphA2 receptor, which is highly expressed in lung NETs.

Methods:

A bicyclic peptide, AJ210, was synthesized via solid-phase peptide synthesis, and its binding affinity for EphA2 was measured using surface plasmon resonance. Lung NET cell lines NCIH69 and NCIH2286 were selected based on EphA2 expression, which was confirmed by flow cytometry. AJ210 was radiolabeled with Gallium-68, and its in vitro stability was evaluated in both PBS and serum. Cellular uptake studies of [68Ga]AJ210 were performed in NCIH69 and NCIH2286 cells. Additionally, pharmacokinetics and tissue distribution were assessed through ex vivo biodistribution studies in mice.

Results:

AJ210 exhibited high affinity for human EphA2, with a KD of 2.4 nM. Flow cytometry analysis confirmed higher EphA2 expression in NCIH2286 and low in NCIH69. In vitro stability confirmed the very high stability of [68Ga] AJ210 in PBS and serum up to several hours. Binding assay demonstrated higher uptake of [68Ga]AJ210 in NCIH2286 and low uptake in NCIH69 and competition with 1 μM non-radioactive AJ210 resulted in reduced uptake in NCIH2286, supporting EphA2-specific binding. Whole body ex vivo biodistribution of [68Ga]AJ210 in mice showed rapid clearance with the blood half-life of 5.2 min. Also, high accumulation in kidney suggested the renal clearance consistent with peptide-based radiotracers.

Conclusion:

AJ210 exhibits high stability and strong in vitro binding to EphA2, along with favorable pharmacokinetic properties of [68Ga]AJ210 for imaging applications. However, its in vivo tumor-targeting capability in lung NET is yet to be investigated. While the therapeutic efficacy of [225Ac]AJ210 remains to be validated, this novel agent holds promising potential for targeted radiotherapy in lung NETs and may have broader utility in other EphA2-expressing cancers.

Back to Abstracts Table of Contents

Enhancer Landscape of Neuroendocrine Tumors Reveals Developmental Signatures with Theranostic Implications

Yotam Drier[1], Merav Hecht[1], Shani Avniel-Polak[2], Simona Grozinsky-Glasberg[2]

1. The Lautenberg Center for Immunology and Cancer Research, IMRIC, Faculty of Medicine, Hebrew University of Jerusalem, Israel, 2. Neuroendocrine Tumor Unit, ENETS Center of Excellence, Division of Medicine, Hadassah-Medical Organization, and Faculty of Medicine, Hebrew University of Jerusalem, Israel

Presenter: Yotam Drier, PhD

Background:

Treating patients with neuroendocrine tumors (NETs) is challenging. Two main challenges are the lack of effective drug treatments and the lack of reliable biomarkers to guide management, since patients with the same tumor grade/stage often have different clinical courses, highlighting once more their heterogeneity. The genetic, epigenetic and developmental programs that drive NETs remain obscure, limiting our abilities to suggest new biomarkers and drug targets. We are working to systematically characterize the regulatory programs across a variety of NETs to address this gap.

Methods:

We are characterizing putative enhancers (by H3K27ac ChIP-seq), CTCF binding sites (by CTCF ChIP-seq) and transcriptomes (by RNA-seq) of NETs, to identify the regulatory networks the underlies these tumors. After profiling intestinal NETs, pancreatic NETs and lung NETs we are now focusing on pheochromocytomas and paragangliomas (PPGLs), and on comparisons across NETs of different origin.

Results:

We have characterized putative enhancers and transcriptomes of 22 intestinal NETs, 21 pancreatic NETs, 23 lung NETs and 13 PPGLs. We identified regulatory and developmental subtypes of pancreatic NETs, lung NETs and PPGLs. As previously demonstrated. integrative analysis of these data uncover biomarkers with clinical prognostic value, and new therapeutic targets (Cejas*, Drier* et al. Nature Medicine 2019; Davis*, Avniel-Polak* et al. PNAS 2024). We also identified NET-specific and shared super-enhancers across NETs, to develop better understanding of shared dependencies as well as patient specific sensitivities.

Conclusions:

Enhancer profiling of NETs helps uncover the regulatory networks driving these diseases and identify novel biomarkers for improved classification of tumors and new therapeutic targets.

Back to Abstracts Table of Contents

Results of the COPPER PET in NET Trial: A Randomized, Crossover, Readers Blind, Phase I/II Study Comparing 61Cu-NODAGA-LM3 and 68Ga-DOTATOC for the Detection of Neuroendocrine Tumors

Guillaume P. Nicolas[1], Damian Wild[1], Wolfgang A. Weber[2], Leila Jaafa[3], Melpomeni Fani[1]

1. Department Theragnostics, University Hospital Basel, Switzerland, 2. Department Nuclear medicine, Technical University Munich, Germany, 3. Nuclidium AG, Basel, Switzerland

Presenter: Nicolas Guillaume, MD

Background:

(Pre)clinical data suggest that somatostatin receptor (sstr) antagonists, when radiolabeled with gallium-68, offer superior imaging performance over agonists in patients with neuroendocrine tumors (NETs). ^{61}Cu-NODAGA-LM3 is a novel PET tracer targeting sstr subtype 2 that may overcome the production, resolution, and logistics limitations of [^{68}Ga]-based tracers. Copper-61 is cyclotron produced and has a longer half-life compared to Ga-68 or F-18, which are currently used for sstr2-targeting PET tracers, enabling delayed imaging and easier logistics. Additionally, Cu-61 has a higher positron fraction than Cu-64, enhancing image quality per administered activity. We report first-in-human data on safety, biodistribution, dosimetry, blood pharmacokinetics, image quality, and lesion detection with ^{61}Cu-NODAGA-LM3.

Methods:

This ongoing, randomized, crossover, controlled, reader-blind, phase I/II PET/CT study (NCT06455358) enrolls 22 patients with sstr2-positive well-differentiated gastroenteropancreatic or bronchopulmonary NETs. Each patient undergoes both ^{61}Cu-NODAGA-LM3 PET/CT (at 1h and 3h post-injection) and ^{68}Ga-DOTA-TOC PET/CT (at 1h post-injection) on the same scanner within 28 days. The order of radiopharmaceutical administration is randomized, with imaging scheduled, if applicable, 14±2 days after the last somatostatin analogue injection. Co-primary endpoints are safety and sensitivity of ^{61}Cu-NODAGA-LM3. Sensitivity will be tested for noninferiority against ^{68}Ga-DOTA-TOC using a mixed-effects logistic regression model. Biopsy and/or composite imaging during 2–7 months of follow-up serve as gold standard. Adverse events will be monitored up to one day after administration using the Common Terminology Criteria for Adverse Events version 5.0. Main secondary outcomes are biodistribution, pharmacokinetics, dosimetry, and lesion detection. Six patients undergo additional PET/CT 18h post-injection (p.i.) for dosimetry. The PET/CT results at 1h and 3h p.i. are compared to determine optimal imaging time.

Results:

To date, 18 patients have completed imaging among which 6 have completed full dosimetry without any clinically significant adverse events. ^{61}Cu-NODAGA-LM3 demonstrated rapid blood clearance (median clearance: 242 mL/minute [162–365]). Preliminary data showed a favorable biodistribution, with 49% lower median liver SUVmax 3.1 [2.6–3.3]) and 63% lower median spleen SUVmax (9.0 [5.5–10.8]) at 1h p.i. compared to ^{68}Ga-DOTA-TOC (liver: 6.4 [3.9–7.1], spleen: 24.0 [18.0–25.8]), wilcoxon p-value <0.001 and 0.002, respectively. Median of the mean tumor uptake (SUVmax), for the three hottest matched lesions, was 12% higher with ^{61}Cu-NODAGA-LM3 (19.6 [9.1–22.8] vs. 16.9 [11.7–24.8]) at 1h p.i, improving lesion detectability and tumor-to-background contrast. The median effective dose was 5.0 mSv [4.2–5.7]. Image quality was rated superior with ^{61}Cu-NODAGA-LM3 in 15/18 cases in blinded review.

Conclusion:

^{61}Cu-NODAGA-LM3 demonstrated excellent safety, favorable pharmacokinetics, biodistribution, dosimetry, along with superior lesion detectability in patients with NETs. These preliminary findings support the clinical value of sstr2 antagonists and suggest potential for broader applicability in clinical routine.

Back to Abstracts Table of Contents

Computational Design and Preclinical Evaluation of Chelators for the Alpha-Emitter Pb-212

Dongyoul Lee[1], Jeongyun Kim[2], Ku Kang[3], Na Yeon Han[4,5], Changkeun Im[4], Choong Mo Kang[6], Jae Hun Ahn[4,7], Sairan Eom[4], Ayman Muzammal[4,5], Yong Jin Lee[4,8], Kyo Chul Lee[4,5], Won Bo Lee[2], Michael K. Schultz[9]

1. Department of Physics and Chemistry, Korea Military Academy, Seoul, Republic of Korea, 2. Department of Chemical and Biological Engineering, Seoul National University, Seoul, Republic of Korea, 3. Chemical, Biological, Radiological Defense Research Institute, Seoul, Republic of Korea, 4. Division of Applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea, 5. Radiological and Medico-Oncological Sciences, University of Science and Technology, Seoul, Republic of Korea, 6. Department of Nuclear Medicine, Samsung Medical Center, Seoul, Republic of Korea, 7. Graduate School of Translational Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea, 8. Korea Radioisotope Center for Pharmaceuticals, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea, 9. Perspective Therapeutics Inc, Coralville, IA, USA.

Presenter: Dongyoul Lee, PhD

Background:

Targeted alpha-particle therapy has emerged as a promising approach due to its high linear energy transfer and short tissue penetration range. Among alpha-emitting radionuclides, lead-212 (212Pb) is of particular interest owing to its favorable half-life and decay characteristics. A critical requirement for the success of 212Pb-based radiopharmaceuticals is the ability of the chelator to stably bind 212Pb and retain its daughter nuclide, bismuth-212 (212Bi), after decay. However, conventional chelators often fail to accommodate the differences in ionic radius and charge between Pb2+ and Bi3+, potentially leading to dissociation of 212Bi, which may compromise therapeutic efficacy and safety. To address this challenge, improved chelator designs with enhanced binding stability are needed. In this study, we employed density functional theory (DFT) modeling to identify the thermodynamic factors governing Pb and Bi coordination, and synthesized multiple chelator-peptide conjugates to evaluate their radiolabeling efficiency, complex stability, and biological performance in vitro and in vivo.

Methods:

Density Functional Theory (DFT) calculations were performed using the ORCA software package. The TPSSh (meta-GGA) functional and SARC-ZORA-TZVP basis set was employed for Pb and Bi. Solvent effects were modeled using the Conductor-like Polarizable Continuum Model (CPCM) to simulate an aqueous environment. Additionally, Grimme's D3BJ dispersion correction was applied to improve the accuracy of weak interaction modeling. Multiple peptides conjugated with conventional chelators—including DOTA, PSC, and DOTAM—as well as newly developed chelators, have been or are currently being synthesized with Tyr3-octreotate (TATE). Chelation properties, complex stability, in vitro cellular uptake in AR42J cells, and in vivo SPECT imaging studies will be conducted using 203Pb as an elementally matched surrogate for 212Pb.

Results:

DFT calculations revealed that cavity size (which accommodates the ionic radius of the radionuclide), the preferred coordination geometry of the chelator–radionuclide complex, and charge matching are key factors governing thermodynamic chelation stability. A series of known chelators—including NOTA, TETA, NODAGA, DOTA, DOTAM, and PSC—were investigated to evaluate their coordination behaviors with Pb2+. Among these, chelators with relatively larger cavities and divalent metal compatibility, such as DOTA, DOTAM, and PSC, consistently formed square antiprismatic geometries, which are considered thermodynamically favorable configurations for Pb2+ chelation.

Focusing on the comparison among DOTA, PSC, and DOTAM, PSC exhibited the lowest interaction energy with Pb2+, followed by DOTA and DOTAM, indicating that PSC is the most suitable chelator for 212Pb among those examined. Furthermore, based on the hypothesis that structural flexibility may aid in retaining the decay daughter 212Bi—due to the need to accommodate the charge and size change from larger 212Pb2+ to smaller trivalent 212Bi3+—several novel chelator compositions were identified that show potential for dual retention of both 212Pb and its daughter. In vitro and in vivo studies using 203Pb as a surrogate for 212Pb are currently underway to experimentally validate these computational predictions.

Conclusion:

Key factors governing chelation stability—including cavity size, charge matching, and structural flexibility—were identified through computational modeling. Based on these insights, multiple chelator compositions were developed to improve interaction energy and accommodate structural changes during radionuclide decay. These findings suggest a promising strategy to enhance the stability, safety, and therapeutic efficiency of radiopharmaceuticals, supporting the development of refined chelator designs for targeted alpha therapy.

Back to Abstracts Table of Contents

Testing of Current and Novel FAPI Agents in Neuroendocrine Tumors

Gina Kaup[1], Harshad Kulkarni[2], Jason A. Witek[1], Allen F. Brooks[1], Peter J. H. Scott[1,3], Benjamin L. Viglianti[1]

1. Department of Radiology, University of Michigan, Ann Arbor, Michigan, USA, 2. BAMF Health. Grand Rapids, Michigan USA, 3. The Interdepartmental Program in Medicinal Chemistry, University of Michigan College of Pharmacy, Ann Arbor, Michigan, USA

Presenter: Gina Kaup, BS

Introduction:

Tumor associated fibroblasts have become a new method to target tumor given their expression Fibroblast Activation Protein (FAP) on their cell surface. This expression of FAP during cancer cell growth has led to its targeting by inhibitory molecules for imaging and therapy, similar to somatostatin PRRT for NET. Unlike PRRT, FAP expression is thought to be present regardless of NET grade/NEC unlike somatostatin which has decreased uptake at increasing grade or when carcinoma is present. We recently developed a new FAPI agent, labeled with F18 and at ½ the molecular weight of current FAPI agent. We plan to test this agent along with current FAPI agent in NET of varying grades and compare to current somatostatin imaging with the goal of offering another option to patient for PRRT therapy other the somatostatin targeting.

Methods:

We have recently made FluroFAPI labeled with F18 and are completing the final steps to apply for an IND with the FDA. We recently obtained regulatory approval (UM to test FAPI-04 and at BAMF Health to test FAPI-46/74) in patients that have NET of varying grades and compare it to somatostatin imaging.

Results:

We have demonstrated effective synthesis and safety of our FluroFAPI agent and await FDA IND. We are in the process of imaging patients and expect that FAPI will not only image low Grade NET similar to somatostatin, but also image high Grade NET and NEC.

Conclusion:

If successful, FAPI will offer another method to target NET and more importantly high grade NET/NEC giving patient the potential of other therapeutic options for the cancer care.

Back to Abstracts Table of Contents

Using Patient-derived Tumor Organoids to Uncover Mechanisms of Pulmonary NET Progression

Heleen Jüngen[1], Rossana Passannante[1], Noah Candeli[1], Jacqueline Severino[1], Alexandra Sexton-Oates[2], Nicolas Alcala[2], Lynnette Fernandez-Cuesta[2], Matthieu Foll[2], and Talya L. Dayton[1]

1. European Molecular Biology Lab (EMBL) - Barcelona, 2. Computational Cancer Genomics team, Genomic Epidemiology Branch, International Agency for Research on Cancer

Presenter: Talya L. Dayton, PhD

Background:

Pulmonary neuroendocrine tumors (NETs), or carcinoids, show a range of clinical behaviors, from a slowly progressing disease to clinically aggressive cancers with poor prognosis. A newly characterized subtype, the "supra-carcinoid," exhibits morphological features of carcinoids but molecular features of carcinomas, and a more aggressive clinical course than other carcinoid subtypes. This heterogeneity in clinical outcomes for patients with pulmonary NETs presents a major clinical challenge and means all patients require lengthy follow-up, underscoring the need for biomarkers predictive of aggressive disease and effective therapeutic strategies for the treatment of all pulmonary NETs.

Methods:

We leverage novel patient-derived tumor organoids (PDTOs) from low-grade pulmonary NETs and including the first described supra-carcinoid PDTO, to investigate genetic and growth-factor driven mechanisms of tumor progression.

We are applying CRISPR/Cas9-mediated gene editing to introduce MAPK- and PI3K-activating mutations into pulmonary NET PDTOs and assess their phenotypic and molecular effects through proliferation assays, RNA sequencing and ATAC sequencing. In parallel, we are using bioinformatic analyses of bulk and single-cell lung NET transcriptomes to identify and prioritize candidate ligands that support NET growth and survival.

Results:

We optimized a nucleofection protocol for NET PDTOs and validated our gene-editing pipeline by introducing a TP53 loss-of-function mutation into a supra-carcinoid PDTO (LNET10). Edited cells showed clonal expansion, nutlin-3 resistance, and accelerated proliferation – demonstrating that TP53 loss can further drive progression of an already aggressive NET subtype. This finding provides proof of principle and new mechanistic insight into NET progression. Constructs targeting NF1 and PTEN have been generated, and additional lines are being expanded for further gene-editing experiments.

Transcriptomic deconvolution revealed distinct stromal and immune profiles across NET subtypes and identified enrichment of lower airway progenitor (LAP) cell signatures in supra-carcinoids. Using NicheNet, we identified ligands predicted to drive LAP-to-neuroendocrine differentiation. We are currently conducting growth-factor screens in PDTOs and implementing automated imaging pipelines for high-throughput ligand testing.

Conclusions:

We have established robust gene-editing pipelines in pulmonary NET PDTOs, the only long-term in vitro model system for this disease. Our data show that TP53 loss can accelerate progression of a supra-carcinoid toward a more aggressive state, highlighting a potential stepwise model of NET progression and suggesting these tumors can progress to full-blown carcinomas.

Our parallel bioinformatic analyses show that supra-carcinoids retain features of immature airway progenitors and our ongoing work is aimed at determining whether targeted ligands can induce differentiation and suppress aggressive phenotypes in these tumors. The results of our experiments are expected to identify potential vulnerabilities of pulmonary NETs that can be exploited for therapeutic purposes. Our work aims to facilitate the development of strategies to stratify and treat patients with pulmonary NETs and to prevent the transition of their tumors to aggressive disease, ultimately improving patient outcomes.

Back to Abstracts Table of Contents

Variable GLP-1 Receptor Expression Across Diverse Neuroendocrine Neoplasms: Implications for Incretin Therapies

Po Hien Ear[1*], Sophia A. Hueser[1], Reese E. Townsend[1], Ellen Abusada[2], Carlos HF Chan[1], Dawn E. Quelle[3], Joseph S. Dillon[4], James R. Howe[1], Andrew M. Bellizzi[2*]

1. Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, IA, 2. Department of Pathology University of Iowa Carver College of Medicine, Iowa City, IA, 3. Department of Neuroscience and Pharmacology, University of Iowa Carver College of Medicine, Iowa City, IA, 4. Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA

Presenter: Andrew Bellizzi, PhD

Background:

Neuroendocrine neoplasms (NENs) are rare cancers originating from neuroendocrine cells and are further classified as well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Commonly used drugs such as proton pump inhibitors can promote gastric NEN growth and result in poor prognosis. Nowadays, incretin mimetic drugs such as the glucagon-like peptide 1 receptor (GLP-1R) agonists have gain extensive popularity for treatment of diabetes and obesity. These drugs target GLP-1R and their use in neuroendocrine cancer patients with medullary thyroid carcinoma (thyroid NET) or multiple endocrine neoplasia syndrome type 2 is deemed contraindicated. Previous studies investigated GLP-1R expression in small subsets of NEN.

Methods:

We assessed GLP-1R expression by immunohistochemistry in a large collection of 576 patient NENs from 13 sites of origin. We identified 7% of NENs stained positive for GLP-1R. GLP-1R expression and function were validated using novel patient-derived NET spheroid models.

Results:

They were from 5 NEN types: duodenal NETs (dNET), gastric NETs, pancreatic NETs, pheochromocytomas, and lung NETs. We then validated the dNET spheroids for response to an incretin mimetic drug and found activation of the MAPK pathway.

Conclusion:

While GLP-1R agonists are contraindicated in patients with thyroid NET, none of our 29 thyroid NETs expresses GLP-1R. Hence, in contrast to rodent studies, GLP-1R agonists may have no effect on human thyroid NETs since they do not express the receptor. Interestingly, ileal NET also showed no expression of GLP-1R. More preclinical research examining potential oncogenic effects of incretin mimetics on the 5 subtypes of GLP-1R positive NENs is needed to better understand their safety.

Back to Abstracts Table of Contents

Sortilin in Functional Neuroendocrine Tumors: Marker and Target

Felix Bolduan[1], Yvonne Giesecke[1], Ines Eichhorn[1], Natalia Alenina[2,3], Michael Bader[2,3,4,5], Thomas E. Willnow[2,6], Niklas Müller-Bötticher[7], Naveed Ishaque[7], Bertram Wiedenmann[1] and Michael Sigal[1,8]

1. Department of Hepatology & Gastroenterology, Charité Universitätsmedizin Berlin, Berlin, Germany, 2. Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany, 3. German Center for Cardiovascular Research (DZHK), Berlin, Germany, 4. Charité-Universitätsmedizin Berlin, Berlin, Germany, 5. University of Lübeck, Institute for Biology, Lübeck, Germany, 6. Department of Biomedicine, Aarhus University, Aarhus, Denmark, 7. Center of Digital Health, Berlin Institute of Health at Charité Universitätsmedizin Berlin, Berlin, Germany, 8. Berlin Institute for Medical Systems Biology (BIMSB), Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany

Presenter: Felix Bolduan, MD

Background:

A subset of neuroendocrine tumors (NETs) causes a hormone related disease (functional syndrome); e.g. the carcinoid syndrome due to over-secretion of mainly serotonin. This functional syndrome causes a tumor independent poor prognosis in NET patients and current pharmaceutical treatment options are limited. Notably, on a molecular level it is unknown what distinguishes this subset of functional NETs from nonfunctional tumors. Furthermore, accurate models of functional NETs are missing.

Sortilin is a widely expressed transmembrane receptor found in many cancer cells. It is involved in secretion processes and may itself be secreted into the bloodstream; however, the significance of sortilin in NETs remains unclear.

Methods:

Tissue samples from both functional and nonfunctional NETs were analyzed for sortilin expression using immunohistochemistry. The transcription levels of sortilin were assessed through bulk RNA sequencing from a separate cohort. To investigate the functional role of sortilin in NETs, its activity was inhibited using a small molecule inhibitor in a cell culture model of NETs (BON cells). The serotonin content was then measured using high-performance liquid chromatography (HPLC). Additionally, murine organoids were treated with inhibitors of the NOTCH and EGF signaling pathways to enrich neuroendocrine cells as shown previously. The serotonin content in these neuroendocrine organoids was also measured by HPLC, both with and without sortilin inhibition.

Results:

Sortilin is highly expressed in functional NETs compared to nonfunctional NETs and its inhibition in BON cells causes decreased serotonin levels. Interestingly, there was no difference in sortilin transcription between functional and nonfunctional tumors, arguing for a posttranscriptional mechanism. Murine intestinal organoids were enriched with neuroendocrine cells and these neuroendocrine organoids produce sufficient amounts of serotonin for detection by HPLC. Sortilin inhibition in these organoids yields to diminished serotonin concentrations.

Conclusions:

Sortilin expression discriminates functional from nonfunctional NETs and enables therapeutic targeting. Neuroendocrine differentiated organoids could serve as a novel model for investigating the serotonin metabolism in functional NETs. In ongoing measurements, we are now examining the blood levels of sortilin in NET patients.

Back to Abstracts Table of Contents

Establishing and Characterizing New Pancreatic Neuroendocrine Tumor Mouse Models

Shifei Wu[1,2], Sebastien Martinez[2], Iacovos P. Michael[3,4], Trevor J. Pugh[3,5,6], Daniel Schramek[1,2]

1. Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada 2. Lunenfeld Tanenbaum Research Institute, Toronto, Ontario, Canada 3. Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada 4. Sunnybrook Research Institute, Toronto, Ontario, Canada 5. Princess Margaret Cancer Centre, Toronto, Ontario, Canada 6. Ontario Institute for Cancer Research, Toronto, Ontario, Canada

Presenter: Shifei (Samuel) Wu, BSc

Background:

Pancreatic neuroendocrine tumor (PanNET) patients have a 60% overall mortality rate. Most of them have an unpredictable, highly variable clinical course. Insufficient understanding of PanNET biology hinders the development of effective therapies and doctors from stratifying patients into 1) those with rapidly progressing tumors who will benefit from early aggressive therapies and 2) those with indolent tumors who could be spared from unnecessary treatments and their toxic side effects.

Recent studies have identified strong associations between MEN1/ATRX/DAXX mutations, alternative lengthening of telomere (ALT), copy number alterations (CNAs), and poor clinical outcomes. High-grade PanNETs frequently harbor alterations in mTOR pathway genes, TP53, and CDKN2A. Additionally, the resemblance of PanNETs to pancreatic alpha or beta cells carries prognostic significance.

However, the mechanisms by which these genetic alterations drive PanNET progression remain poorly understood. It is also unclear whether the alpha or beta cell-like PanNET subtypes reflect differences in the cell of origin or are driven by transdifferentiation programs initiated by genetic alterations. Genetically tractable PanNET mouse models are needed to address these questions, improve our understanding of PanNET etiology, and guide clinical management and therapeutic development.

Methods:

We aimed to develop novel mouse models with high-grade, metastatic PanNETs that recapitulate genomic, transcriptomic, molecular, histological, and clinical features seen in human PanNETs. To achieve this, we used late-generation Tert-mutant mice to create telomere-short, telomerase-deficient cells. Using in vivo CRISPR/Cas9-mediated gene editing and genetically engineered mice, we knocked out various combinations of mouse homologs of tumor suppressor genes frequently mutated in human PanNETs in a stochastic manner.

A pooled sgRNA library targeting 22 candidate tumor suppressor genes (sgPNET-TSG-22) was delivered via high-titer AAV into Men1-deficient, Atrx-deficient, telomere-short, telomerase-deficient, Cas9-expressing beta cells. Tumor-promoting combinations of CRISPR/Cas9-induced mutations were identified through targeted deep sequencing of resulting tumors, leveraging the principle that growth-promoting mutations will be enriched.

Results:

All mice receiving the sgPNET-TSG-22 library developed large tumors within ~17 weeks, sometimes with liver metastases. In contrast, mice receiving a control library remained healthy. Targeted deep sequencing of high-purity tumors from these mice revealed five to thirteen CRISPR/Cas9-induced mutations, with none detected in adjacent normal tissues. Notably, a small subset of these tumors exhibited ALT and CNAs. Most of these tumors have concurrent mutations in Pten, Trp53, and Rb1. Subsequent experiments validated that disruption of just these three genes was sufficient to drive aggressive tumor formation in Men1-deficient, Atrx-deficient, telomere-short, telomerase-deficient, Cas9-expressing beta cells. The mutation burden and apparent clonal nature of these tumors suggest that our system enables simultaneous knockout of many genes in beta cells in vivo.

Conclusions:

We have developed a flexible in vivo system for modeling PanNET progression driven by loss of multiple tumor suppressor genes. We are now applying this system to Cas9-expressing alpha cells to assess the effect of cell type and various combinations genetic alterations—including Men1, Atrx, Pten, and Trp53/Cdkn2a—on tumorigenesis. Moving forward, we aim to compare genetic drivers, tumor aggressiveness, histology, ALT and CNA prevalence, transcriptomes, and epigenomes across models and with human PanNETs.

Back to Abstracts Table of Contents

miR-375 Targets YAP to Regulate Neuroendocrine Differentiation and Tumorigenesis in PanNEN Cells

Tashifa Imtiaz[1], Xiaojing Yang[1], Simona Damiani[1], Kathrin Tyryshkin[1], Neil Renwick[1]

1. Department of Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada

Presenter: Tashifa Imtiaz, BScH, MSc

Background:

Pancreatic neuroendocrine neoplasms (PanNENs) are diverse tumors or cancers that arise from pancreatic islets cells and remain poorly understood. microRNAs (miRNAs, miRs) are short, non-coding RNAs that negatively regulate gene expression. Some miRNAs are disease specific and regulate molecular networks in pathogenesis. We previously showed that miR-375 is elevated in NEN tissues. In vitro, we found that miR-375 targets YAP to regulate neuroendocrine differentiation and tumorigenesis in lung carcinoid cells. Preliminary work found that YAP absence is colocalized with miR-375 and neuroendocrine marker positivity in clinical PanNEN tissue samples. To assess the functional role of this axis in PanNENs, we characterized the effects of miR-375 knockout or YAP overexpression in pancreatic carcinoid and carcinoma cells.

Methods:

We established miR-375 depleted, and YAP overexpression cell lines with a lentivirus-mediated approach in PanNEN cells: BON-1 and QGP-1. We evaluated the effects of miR-375 depletion and YAP overexpression on neuroendocrine differentiation, cell growth, and colony formation using western blot analysis for neuroendocrine markers, proliferation, and soft agar assays, respectively. Next, we assessed transcriptomic changes using RNA-sequencing on miR-375 knockout or YAP overexpression, and control cells.

Results:

miR-375 knockout and YAP overexpression in BON-1 and QGP-1 cells led to a significant reduction in neuroendocrine marker expression, cell growth, and colony formation. When miR-375 knockout cells were treated with siYAP, neuroendocrine marker expression and cell proliferation were partly rescued – indicating YAP expression is partly responsible for the observed effects. To further explore the mechanistic implications of this axis, we identified 124 and 44 commonly dysregulated genes in modified BON-1 and QGP-1, respectively. This included downregulation of well-known oncogene, RET, and neuroendocrine specific transcription factors and hormones: HES6, INSM1, ASCL1, and SST (somatostatin). These downregulated genes likely contributed to the observed decrease in neuroendocrine features and cell growth in knockout and overexpression cell lines.

Conclusion:

miR-375 targets YAP to regulate neuroendocrine differentiation and tumorigenesis in pancreatic carcinoid and carcinoma cells. Since YAP depletion in miR-375 knockout cells only partially rescued the observed effects, there are likely additional miR-375 targets involved. To identify these targets, we will profile miR-375 bound transcripts using a cross-linking approach. Given our consistent findings in pancreatic and lung NENs, this axis may be preserved in NENs from different sites. Future work continuing to uncover this molecular network surrounding miR-375/YAP will help deepen our understanding of NEN biology and identify potential therapeutic targets.

Back to Abstracts Table of Contents

The Genetic Evolution of Low to High-Grade Progression in Pancreatic Neuroendocrine Tumors

Sarah E. Umetsu[1], Stephanie Wang[2], Emily Bergsland[2,3], and Nancy M. Joseph*[,1]

1. Department of Pathology, University of California San Francisco, SF, CA, USA, 2. Helen Diller Family Cancer Center, University of California San Francisco, SF, CA, USA, 3. Department of Medicine, Division of Hematology/Oncology, University of California San Francisco, SF, CA, USA

Presenter: Nancy M. Joseph, MD, PhD

Background:

Pancreatic neuroendocrine tumors (PanNETs) are a heterogenous group of tumors and now include an aggressive high-grade category (grade 3, G3) introduced in the 2017 WHO classification. Challenges in pathologic diagnosis have limited our understanding of the G3 PanNET category and how to optimally manage patients with G3 PanNET. Estimates of the propensity for PanNETs to progress to G3 vary considerably, and in most cases we lack biomarkers that predict which patients will progress and which will not. PanNETs have been shown to harbor frequent mutations in MEN1, DAXX, ATRX, mTOR genes (TSC1/2, PTEN), SETD2, and CDKN2A, but the sequence of alterations acquired during tumor progression remains poorly understood. This study aims to gain a deeper understanding of the genetic evolution over time in PanNET progression.

Methods:

PanNET patients who had serial biopsies over time, including patients with stable low-grade disease (grades 1 and 2, G1/G2) over time and patients with disease that progressed from low to high-grade (G1/G2 * G3) were identified using the UCSF Pathology database and an IRB-approved outcomes database of patients seen at the UCSF Center for Neuroendocrine Tumors. Capture-based DNA sequencing of ~500 cancer genes was performed on 57 longitudinal archival PanNET samples from 15 patients with low to high-grade progression and 9 patients without grade progression.

Results:

PanNET samples (n=39; 7 G1, 14 G2, 18 G3) from the 15 patients with low to high-grade progression demonstrated frequent alterations in MEN1 (85%), DAXX or ATRX (56%), and TSC1/2 (31%), which were present in all grades and sometimes acquired during progression to G3 (seen in 7%, 13%, and 33% of patients, respectively). Alterations in CDKN2A were present in G2 and G3 tumors and acquired during progression to G3 in 33% of patients. TP53 alterations were exclusive to G3 tumors and frequently acquired during progression to G3 (66% of patients). PanNET samples (n=18; 1 G1, 17 G2) from the 9 patients without grade progression over the same length of time also had recurrent alterations in MEN1 (66%) and DAXX or ATRX (39%), but alterations in TSC1/2, CDKN2A, and TP53 were absent.

Conclusions:

PanNET progression to G3 most commonly involves acquisition of TP53 alterations, which were exclusively seen in G3 PanNET. CDKN2A deep deletions and alterations in TSC1 or TSC2 were also commonly acquired during G3 progression, but alterations in these genes were observed in lower-grade PanNETs as well. A larger cohort of samples will be examined to confirm these results, which may suggest biomarkers to help risk-stratify patients and improve management for patients with high-grade PanNETs.

Back to Abstracts Table of Contents

Analysis of NET Digital Trial Finder Platform Usage and Challenges in Patient Referrals

Danielle Ralic[1], Katie Vieyra[2], Josh Mailman[3]

1, 2. Ancora.ai Zurich, Switzerland, 3. NorCal CarciNET Oakland, CA USA

Presenter: Danielle Ralic, BA

Background:

Neuroendocrine tumors (NETs) represent a diverse group of cancers for which patient access to specialized care, clinical trials, and information is critical. Finding relevant clinical trials is quite a challenging task and so the Ancora.ai platform, an AI-powered digital trial finder, was developed to bridge this gap, aiming to connect NET patients with relevant research opportunities. Understanding how patients use the platform and, critically, identifying barriers to successful patient referral is essential for optimizing patient access to clinical trials and advancing NET research.

Methods:

This project analyzed Ancora.ai platform usage statistics from August 29, 2024, to May 30, 2025. Data points included unique visitors to the trial finder, contributing drivers to the trial finder, patient trial referral requests and outcomes of these referrals (successful, no response from trial /trial closed, or patient no longer interested). The analysis focused on identifying patterns in platform engagement and specific bottlenecks impacting the success of the patient referral process.

Results:

In this 9 month period, Ancora.ai attracted 1879 unique visitors searching for NET clinical trials. The main organizations driving traffic to the NET trial finder included NETRF (42%), Ancora.ai itself (24%), INCA (10%), NorCal CarciNET (7%), and the Pheo Para Alliance (6%), demonstrating robust engagement from the NET community across 8 countries (US, UK, Canada, France, Spain, Brazil, New Zealand, Philippines). In this 9 month period, patients found and initiated 58 trial requests through the Ancora.ai platform. However, despite this patient demand, only 2 patient trial referrals were successfully made. An overwhelming 45 referrals (78% of all patient trial requests) received no response from the trial sites or sponsors, or the trials were already closed. Notably, 38 of the 58 patient-requested trials were non-industry sponsored, indicating a strong patient interest in a broad range of research.

Conclusion:

NET patient organizations are effective drivers to the Ancora.ai platform where patients are able to search for and request relevant clinical trials. Despite this proven patient demand and platform usage, the ability for patients to get connected to a clinical trial is significantly hindered by a lack of responsiveness from trial sites and sponsors. This suggests a bottleneck in the communication and follow-up process on the part of the research institutions and sponsors, rather than a lack of patient interest or platform utility. Next steps must focus on establishing more robust communication protocols with trial sites and sponsors and exploring methods to streamline the referral process to better support interested patients in enrolling in NET research.

Back to Abstracts Table of Contents

Computational Evaluation of Chelators for Actinium-225 and Its Decay Daughters Using DFT-Based Modeling

Jeongyun Kim[1], Ku Kang[2], Jin Yoo[2], Won Bo Lee[1], Michael K. Schultz[3] and Dongyoul Lee[4]

1. Department of Chemical and Biological Engineering, Seoul National University, Seoul, Republic of Korea, 2. Chemical, Biological, Radiological Defense Research Institute, Seoul, Republic of Korea, 3. Perspective Therapeutics Inc., Coralville, IA, United States, 4. Department of Physics and Chemistry, Korea Military Academy, Seoul, Republic of Korea

Presenter:

Jeongyun Kim, PhD Student

Background:

Actinium-225 (225Ac) is a potent alpha-emitting radionuclide used in targeted radionuclide therapy (TRT). Its relatively long half-life (~10 days) allows for extended therapeutic action but also imposes a stringent requirement for prolonged in vivo chelation stability. Clinical application is further complicated by the complex decay cascade of 225Ac, which produces daughter radionuclides (e.g., Fr-221, At-217, Bi-213) with distinct chemical properties and substantial recoil energies. While existing chelators such as DOTA, macropa, and crown ether derivatives show moderate success in coordinating Ac^{3+}, their ability to retain both the parent and daughter radionuclides under continuous alpha decays raises critical questions. In this study, we computationally modeled chelators (i.e., DOTA-, macropa-, and crown-based ligands) and determined their thermodynamic and structural stability with 225Ac and its decay progeny.

Methods:

Density Functional Theory (DFT) calculations were performed using the ORCA package. A TPSSh functional with def2-TZVP basis sets (and SARC-ZORA-TZVP for Ac) was used with Grimme D3BJ dispersion correction and the CPCM water model. Multiple trivalent chelator scaffolds, including DOTA, macropa, and crown-based ligands, were modeled in conjugation-ready forms (linked via ethylamine). The interaction energies, coordination geometries, and charge distributions of chelator-metal complexes were systematically evaluated.

Results:

DFT-based structural optimization of Ac^{3+} complexes revealed distinct coordination behaviors depending on the chelator type. The DOTA-conjugated ligand formed a rigid 8-coordinate geometry, while macropa- and crown-based ligands adopted more flexible coordination environments with 11- and 10-coordinate structures, respectively. These macrocyclic chelators exhibited up to 0.4 eV lower interaction energies compared to the DOTA counterpart, indicating enhanced thermodynamic stability. While the compact geometry of the DOTA complex suggests strong directional binding, the increased coordination numbers and cavity adaptability observed in macropa- and crown-based ligands offer structural advantages for accommodating the large trivalent ion Ac^{3+}, and potentially its decay daughters.

Our modeling study is currently focused on evaluating known chelators for 225Ac; however, future work will expand toward the potential development of multivalent-compatible or cavity-adaptive chelators capable of coordinating not only 225Ac but also its decay daughters, which exhibit distinct ionic sizes and coordination preferences—such as ^{221}Fr (monovalent, alkali-like), ^{217}At (multiple oxidation states, borderline halogen), and ^{213}Bi (trivalent, borderline-soft).

Conclusion:

This study provides a computational framework for evaluating chelator structures suitable for 225Ac and potentially its decay daughters. Although no single chelator is currently known to retain all progeny, our modeling approach allows systematic exploration of chelators with adaptable cavities and charge-balancing properties. Future efforts will focus on daughter-specific modeling to support the development of chelators with improved radiochemical retention and safety profiles for clinical TRT.

Back to Abstracts Table of Contents

Clinicopathological Characteristics and Survival Outcomes of Gastrointestinal Neuroendocrine Tumors in a Large Safety Net Hospital

Ramya Singhal, MD[1,2], Grace Kim, MD[1,2], Isa Jacoba, MD[1,2], Qing Zhao, MD[1,2], Haesook T. Kim, PhD[3], Horst C. Weber, MD[1,2,4]

1. Boston Medical Center, Boston, MA, United States, 2. Boston University Chobanian & Avedisian School of Medicine, Boston, MA, United States, 3. Dana-Farber Cancer Institute, Boston, MA, United States, 4. VA Boston Healthcare System, Boston, MA, United States

Presenter: Ramya Singhal, MD

Background:

Neuroendocrine tumors (NETs) are heterogeneous, rare tumors predominantly of the gastrointestinal (GI) tract. Overall survival (OS) and prognostic factors of GI-NETs remain poorly understood. This study aimed to determine the clinicopathological characteristics and OS outcomes of GI-NETs in a demographically diverse population.

Methods:

All patients at a large tertiary safety-net hospital with a pathology-proven GI-NET diagnosis from 2001 through 2022 were identified. Demographic and tumor characteristics were collected from medical charts.

Results:

Six primary GI sites and liver metastases were identified. Of these primary sites, rectum was the most frequent (27.4%). OS was the highest for appendiceal NETs (5-year OS 95%) and lowest for stomach NETs (5-year OS 76%). Prognostic factors included age (5-year OS: 92% vs 67% for <65 and >=65, respectively, p<0.0001), stage (5-year OS: 89%, 91%, 84% and 50% for stage I, II, III, IV, respectively, p=0.01), size (5-year OS: 91%, 91% and 75% for <1cm, 1-<2cm, >2cm, respectively, p=0.0025), and grade (5-year OS: 92% and 39% for well/moderately and poorly differentiated, respectively, p<0.0001). In multivariable analysis, age (hazard ratio (HR) 3.33, p=0.0002), high tumor stage (HR 2.24, p=0.02), larger tumor size (HR 2.76, p=0.0028), and poor grade (HR 6.03, p=0.0003) were significantly associated with poor OS.

Conclusions:

In this large, single-site retrospective analysis of GI NET, we report the anatomical distribution of GI NETs and survival among GI NETs. Survival among various GI-NETs is generally favorable and no racial difference was observed. These novel findings expand on our knowledge of GI-NET survival and prognostication.

Back to Abstracts Table of Contents

Alternative Splicing Contributes to Transcript Diversity in MEN1

Alex McLean[1], Polona Le Quesne Stabej[1], Veronica Boyle[2,3], Marianne Elston[2], Sharon Pattison[4,5,6], Ben Lawrence[6,7], Cristin Print[1], Anassuya Ramachandran[1]

1. Department of Molecular Medicine and Pathology, School of Medical Sciences, Faculty of Medical and Health Sciences, University of Auckland, New Zealand, 2. Endocrinology Unit, Te Whatu Ora Waikato, Hamilton, New Zealand, 3. School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, New Zealand, 4. Te Whatu Ora Capital, Coast and Hutt Valley, New Zealand, 5. Department of Pathology, Otago Medical School, University of Otago, New Zealand, 6. Department of Oncology, School of Medicine, Faculty of Medical and Health Sciences, University of Auckland, New Zealand, 7. Department of Medical Oncology, Te Toka Tumai, Health New Zealand, Auckland, New Zealand

Presenter: Anassuya Ramachandran, PhD

Background:

While the causal genetic link between mutations in the gene MEN1, its encoded protein MENIN, and multiple endocrine neoplasia type I (MEN1) syndrome is very well established, the mechanism underpinning this link is incompletely understood. These loss of function mutations provide strong evidence that MEN1 acts as a classic tumor suppressor. Nevertheless, MENIN also has pro-oncogenic activities in several cancer types. We believe that the complexity of MEN1 biology remains to be fully appreciated and propose that alternative splicing of MEN1 could account for some of these differences.

Methods:

In silico data mine, along with in vitro studies are being used to characterize MEN1 transcript diversity in relevant cell lines and pancreatic neuroendocrine tumors.

Results:

In silico datamining has revealed multiple alternative splicing events, including alternative splicing of exons and intron retention events. In addition, in vitro studies have revealed the use of a novel exon from within intron 7 of the gene.

Conclusions:

Our work has revealed strong evidence for alternative splicing in MEN1. We are currently using long-read PCR to characterize the full length transcript isoform landscape of MEN1 and future work will be aimed and characterizing the biological effects of different MENIN isoforms.

Back to Abstracts Table of Contents

Differential Expression of GLUT-1 and FASN Across Histological Grades of Pancreatic Neuroendocrine Neoplasms: Insights into Tumor Metabolism and Progression

Erika SA Egal[1], Reydson AL Souza[1], Rodrigo A Maioral[1], Jeffrey Stanley[1], Moises WA Gonçalves[2,3] Tayna Figueiredo-Maciel[2,3], Wei Zhang[1], Ingrid I Damas[4], Gillian L Hale[5], Chris Fillmore[1], Heloisa P Soares[6]

1. Biorepository and Molecular Pathology, Huntsman Cancer Institute, University of Utah (UU), Salt Lake City, Salt Lake City, Utah, USA, 2. Department of Pathology, School of Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas, São Paulo, Brazil, 3. Department of Oral Diagnosis, Piracicaba Dental School, Universidade Estadual de Campinas (UNICAMP), Piracicaba, São Paulo, Brazil, 4. Brazilian Center for Research in Energy and Materials (CNPEM), Campinas, São Paulo, Brazil, 5. Department of Pathology, University of Utah (UU), Salt Lake City, Utah, USA, 6. Division of Oncology, Department of Internal Medicine, Huntsman Cancer Institute, University of Utah (UU), Salt Lake City, Utah, USA.

Presenter: Erika Egal, DVM, MBA, PhD

Background:

Pancreatic neuroendocrine tumors (PanNETs) are a heterogeneous group of tumors that exhibit variable clinical behavior. Understanding metabolic alterations across tumor grades may reveal diagnostic and therapeutic opportunities. In this study, we examined the expression of two critical metabolic proteins, glucose transporter 1 (GLUT-1) and fatty acid synthase (FASN), in various histological grades of PanNETs and metastatic lesions. Methods: Seventeen formalin-fixed, paraffin-embedded PanNET samples were selected retrospectively from the Huntsman Cancer Institute (University of Utah) and classified using the current World Health Organization (WHO) grading criteria. The samples were classified as follows: grade 1 (n = 7), grade 2 (n = 8), grade 3 (n = 1), and metastatic (n = 1). Immunohistochemistry for GLUT-1 and FASN was performed using an automated Leica Bond platform. Staining quantification was carried out using QuPath software with a compartment-specific analysis. GLUT-1 staining was defined as both cytoplasmic and membranous, while FASN staining was defined as exclusively cytoplasmic. Five representative regions per tumor were analyzed, and data were subjected to statistical comparison using the Kruskal-Wallis and Dwass-Steel-Critchlow-Fligner post-hoc tests (Jamovi v2.3.28.0), with $p < 0.05$ considered significant.

Results:

GLUT-1 expression was limited to the islets of adjacent normal pancreatic tissue, whereas the neoplastic areas exhibited diffuse cytoplasmic and membranous staining. Grade 3 tumors showed markedly lower GLUT-1 expression (8.5%) and lower staining intensity (0.11) than grades 1 (56.1%, intensity 0.30) and 2 (61.3%, intensity 0.26). Significantly, higher GLUT-1 expression was observed in grades 1 and 2 compared to grade 3 ($p < 0.05$ for both comparisons). A similar pattern was observed for staining intensity, however, a statistically significant difference was found only between grades 1 and 2 ($p < 0.05$). FASN exhibited strong, diffuse cytoplasmic staining in both normal pancreatic tissue and neoplastic tissue, with relatively lower expression in normal islets. In neoplastic cells, FASN expression remained high across most groups, with over 93% of cells staining positive in grades 1 and 2 and metastatic tumors, but staining positivity decreased to 65.6% in grade 3 tumors. The mean staining intensity was highest in grade 1 tumors (0.65), followed by metastatic tumors (0.60) and grade 2 tumors (0.51). It was lowest in grade 3 tumors (0.33). While the percentage of FASN-positive cells did not differ significantly among the groups, staining intensity was significantly higher in grades 1 and 2 than in grade 3 ($p < 0.05$ for both comparisons).

Conclusions:

GLUT-1 expression is markedly reduced in well-differentiated (grade 3) PanNETs, suggesting impaired or altered glucose uptake pathways in high-grade tumors. In contrast, FASN remains highly expressed across tumor grades, although staining intensity progressively decreases in grade 2 and 3 well-differentiated tumors, but increases in the metastasis. These findings underscore the distinct metabolic profiles across PanNET grades and suggest that GLUT-1 downregulation may be a marker of aggressive behavior. Further studies in larger cohorts are necessary to validate these biomarkers for clinical application.

Back to Abstracts Table of Contents

Feasibility Study for Delayed Ki67 Staining and Grading of Long-term Biorepository Neuroendocrine Tumors to Enhance Translational Research

Nicholas J. Skill, Mary A. Maluccio

Louisiana State University Health Science Center, New Orleans, LA

Presenter: Nicholas J. Skill, PhD

Background:

Biobanking of pathological specimens for research purposes is a staple of most academic institutions. However, repository tissues are sometimes not fully annotated for tumor grade which makes there use in translational research limited. The purpose of this project is to evaluate the impact of two tissue processing protocols (-86oC in RNALater vs LiqN2 in FBS/DMSO) on delayed Ki67 staining. The overall goal is to annotate bio-banked neuroendocrine neoplasms (NEN) for research purposes. NENs are a family of rare metastatic tumors that originate from neuroendocrine cells located throughout the body, primarily in the small bowel, pancreas, lung, stomach and rectum. Grading of NENS is a key prognostic factor and is based on Ki67 staining (G1 <3%, G2 3-20 %, and G3 >20% Ki67 positive cells).

Methods:

The Louisiana State University Health Science Center – New Orleans has the largest dedicated biorepository for rare NEN tumors. The repository began in 1995 to screen anti-angiogenesis phytomedicinal and pharmaceuticals compounds against NEN tumors and contains over 2000 samples. Tumor samples were collected at the time of surgery and processed/stored to facilitate subsequent ex-vivo angiogenesis assay and gene array analysis. In brief, tumors were either: 1) micro dissected (1mm fragments), media/FCS/DMSO (70/20/10) -86oC overnight, and long term storage LiqN2 (-196oC), or, 2) RNALater and -86oC. The sample biorepository database was queried for samples with unknown Ki67 staining levels. Twenty five random tumors (12 RNALater and 13 LiqN2) were retrieved and subjected to routine histology processing and KI67 staining. Result slides were digitized and subjected to image-analysis using HELO imaging/quantification software to compute percentage KI67 staining.

Results:

Long-term storage had minimal impact on tissue integrity. All tissues were successfully processed, embedded, sectioned and stained. Microdissection of tumors didn't prevent histological analysis or Ki67 staining. In contrast, although tissue architecture was better preserved with RNALater Ki67 staining was absent in all tissues. In RNALater preserved tumors Ki67 staining was observed in the extracellular matrix and the hematoxylin staining of nuclei was diffuse which made HELO analysis inaccurate.

Conclusion:

Delayed Ki67 of long-term NEN tumors is feasible. However, tumor processing does impact success. While studies by others have shown successful immunohistochemistry in RNALater stored samples this study contradicts its use for Ki67 staining of NEN tumors. This was an initial feasibility study in previously ungraded tumors. This approach was chosen to avoid unnecessary loss of annotated tissues with known grade when determining practicality. Subsequent analysis will determine the accuracy of delayed Ki67 staining by comparing delayed Ki67 staining levels with pathologists quantification in patients chart.

Back to Abstracts Table of Contents

Tobacco Cessation Improves Survival in Patients with Neuroendocrine Neoplasms. Possible Link to Adaptive Immune Cell Profiles

Nicholas J. Skill, PhD and Mary A. Maluccio, MD

Louisiana State University Health Science Center, New Orleans, Louisiana

Presenter: Nicholas Skill, PhD

Background:

Neuroendocrine neoplasms (NEN) are rare cancers that originate from unique neuroendocrine cells distributed in most organ systems. Currently, the influence of tobacco exposure and cessation on NEN cancers is not fully known. The purpose of this study was two-fold. 1) better understand and quantify the impact of tobacco use and cessation in NEN patients. 2) measure changes in adaptive immune cell profiles contemporaneous with tobacco use and cessation.

Methods:

The LSUHSC-NO NEN database (n>8000 patients) was searched for tobacco use and cessation. Six factors, 1) tobacco use, 2) overall survival (OS, 3) loss of predicted life, 4) primary tumor site, 5) lymphocyte levels, and 6) patient demographics were extracted for analysis in order to evaluate 3 topics: A) demographic differences, B) survival, and C) adaptive immune cell profiles.

Results:

Cohort (n=1024), 1) Demographics: 56% female, 75% White/Caucasian (CA), 22% Black/African American (BL). 2) NEN patients' current smoking incidence rate was low (8%) when compared to the national average (12%). NEN patient tobacco cessation rate was greater (35%) when compared to the national average (9%). Amongst BL patients' tobacco use was higher (11%) and cessation was lower (26%) when compared to CA. The average age at NEN diagnosis was significantly earlier for tobacco consumers (55) when compared to non-smokers (59yrs, p=0.03). 2) Survival: OS and loss of predicted life (LOPL) were significantly inferior in current tobacco users (1994days & 13yrs) when compared to no tobacco exposure (2474days & 9yrs. respectively). Tobacco cessation was linked to an improvement in both OS (2374days) and LOPL (4yrs). 3) Immune profiles: There was a significant increase in Th, Tx, and B immune cells in current tobacco users when compared to both never and former users. TREG cell levels were higher in both current and former tobacco users when compared to never users.

Conclusion:

Tobacco exposure has a calculable negative impact on NEN cancer diagnosis and survival. Moreover, tobacco cessation in NEN cancer patients was linked to increased survival and an amelioration of increased immune cell populations. This is a preliminary study; future analysis will focus on 1) timing of cessation in relation to cancer diagnosis and quantification of immune cell populations before and after smoking cessation, and access to smoking cessation resources and cancer preventative healthcare.

Back to Abstracts Table of Contents

DNA-PK Inhibitors as Radiosensitisers of 177Lu-Dotatate Treatment for GEP-NETs

Cho Hong[1], Lydia P. Liew[1], Way Wong[1], Stephen M. F. Jamieson[1], John Mak[2], Ben Lawrence[2,3], William R. Wilson[1], Michael P. Hay[1]

1. Auckland Cancer Society Research Centre, University of Auckland, Auckland, New Zealand, 2. Auckland City Hospital, Auckland New Zealand, 3. Department of Oncology, University of Auckland, Auckland, New Zealand

Presenter: Cho Rong Hong, PhD

Background:

177Lu-Dotatate is an FDA-approved radionuclide-peptide receptor radionuclide therapy (PRRT) for somatostatin receptor-expressing gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Despite impressive increases in progression free survival outcomes compared to high dose octreotide in recent NETTER-1 (Strosberg, NEJM 2017) and NETTER-2 (Singh, Lancet 2024) trials, there remains a need to improve patient survival, especially in advanced well-differentiated GEP-NETs. Patients typically receive 2-4 cycles of 177Lu-dotatate at 7.4 GBq, irrespective of patient characteristics such as size and weight, 68Ga-dotatate positivity or the inherent radiosensitivity of the tumor. Consequently, there is potential for radiosensitization of 177Lu-dotatate in GEP-NET patients who have received sub-optimal doses of 177Lu-dotatate.

DNA-dependent protein kinase (DNA-PK) plays an essential role in non-homologous end-joining repair of radiation-induced DNA double strand breaks in human cells. As a result, DNA-PK inhibitors (DNA-PKi) are highly effective sensitisers to all forms of ionising radiation, including beta emitters such as 177Lutetium (Waldeck, Theranostics 2023, Reuvers Theranostics 2023). We have developed novel, potent and selective DNA-PKi exemplified by our lead compound DDRx-124. We consider there is a clear opportunity to combine DDRx-124 with 177Lu-dotatate for patients with advanced GEP-NETs to increase treatment efficacy.

Methods:

Potential DNA-PKi were developed through structure-activity studies using biochemical screening against DNA-PK and related PIKK and PI3K enzymes, and radiosensitisation (60Co irradiation) of HCT116 colorectal carcinoma cells using a growth inhibition assay. Compounds were further evaluated as radiosensitisers in vitro against a human tumor cell line panel using a clonogenic survival endpoint. Lead compounds were evaluated in mice for tolerability, pharmacokinetic profile and radiosensitisation of human tumor xenografts using an ex vivo clonogenic survival assay. Sensitisation of H1299-7 cells expressing somatostatin receptor 2 treated with 177Lu-dotatate was evaluated in a growth inhibition study.

Results:

A novel class of DNA-PKi based on an imidazo[4,5-c]pyridinone scaffold was identified and SAR studies pinpointed lead analogues with low nM potency against DNA-PK and high selectivity against related kinases in biochemical screens. Compounds selectively inhibited growth of HAP1 PRKDC wild-type cells when combined with radiation, but not the corresponding PRKDC-/- cells. DDRx-124 was an effective radiosensitisers of colorectal carcinoma (HCT116), non-small cell lung cancer (H460, H1299, A549), pancreatic (BxPC-3, PANC-1, MiaPaCa-2) and head and neck squamous cell carcinoma (FaDu, UT-SCC-74B) cells. DDRx-124 displayed high oral bioavailability. When administered PO at a range of non-toxic doses, DDRx-124 provided significant additional tumor cell killing of HCT116, UT-SCC-74B, and BxPC-3 tumor xenografts in combination with a single (13 Gy) radiation treatment. DDRx-124 potentiated tumor cell growth inhibition by 177Lu-dotatate in vitro.

Conclusions:

DDRx-124 is a potent, selective inhibitor of DNA-PK and effective radiosensitizer of human tumor cells in vitro and in vivo in conjunction with external beam radiotherapy. Preliminary results show that DDRx-124 is also a potent sensitizer of 177Lu-dotatate treatment in vitro. We continue to develop preclinical data to explore the opportunity to combine DDRx-124 with PRRT in patients with GEP-NETs and to advance the compound to clinical studies.

Back to Abstracts Table of Contents

Optimized Automated Radiosynthesis of a Clinically-trialed [18F]F- Tyr3-octreotate Derivative for PET: Impact on the Development of a Novel GLP-1 Peptide Receptor Imaging Agent

Kevina Chavda[1], Shereecia M. Bangura[2] and James A.H. Inkster[1]

1. Dept. of Chemistry & Chemical Biology, McMaster University, Hamilton, Ontario, Canada,
2. Nuclear Operations & Facilities, McMaster University, Hamilton, Ontario. Canada

Presenter: Kevina Chavda, BSc

Background:

PET imaging with radiolabeled somatostatin analogues permits NET diagnosis and treatment planning. Radiopeptides labeled with 18F (t½ =110min) hold advantages over 68Ga (t½=68min) in terms of image resolution, the ability to transport doses, and the imaging of multiple patients with one dose. Unfortunately, the development of 18F-somatostatins is complicated by the elevated temperatures and basic conditions used in traditional 18F-fluorination, leading to a reliance on multi-step syntheses using 18F-labeled 'tags', which impedes clinical production using automated synthesis units (ASUs). Silicon Fluoride-Acceptor (SiFA) chemistry allows for the direct ('one-step') labeling of di-tert-butylphenylfluorosilane-bearing vectors via '19F-for-18F' exchange at RT. SiFA was used to prepare [18F]SiTATE, a clinically-trialed octreotate derivative with favourable tumor uptake and biodistribution vs. [68Ga]DOTATATE. However, the reported synthesis employs a highly basic Kryptofix-OH complex to elute the [18F]fluoride off QMA columns. Counteracting the basicity necessitates two liquid transfers in volumes incompatible with ASUs (<300µL). We have merged SiFA with a non-standard [18F]F- extraction method called "non-anhydrous, minimally basic" (NAMB) chemistry that employs non-basic anions to elute small QMA columns, and the resulting eluates can be used in 18F-fluorinations without removing water (1-6% final water content). Furthermore, NAMB eliminates the low-volume steps associated with Kryptofix-OH (pH titration, late precursor addition). Using 'SiFAxNAMB', we report here a highly optimized automated synthesis of [18F]SiTATE and introduce [18F]SiFA-AoA-[Lys40]-exendin-4 ([18F]SiEX), a novel probe for insulinoma imaging.

Methods:

[18F]SiTATE and [18F]SiEX were synthesized on a FastLab1™ ASU. [18F]F- was eluted from smaller-than-usual QMA columns (12 mg) using 25 µmol tetraalkylammonium tosylate (TEAOTs) or dihydrogen phosphate (TBADP) in MeCN:H2O (8:2;300µL). Eluate was added directly to 19F-precursor (50 nmol) in a MeCN:DMSO mixture (final volume=1mL, 6% H2O). Reactions were stirred at RT for 10 min before C18 cartridge purification (final matrix: 10% EtOH in PBS/Tween 20/Na ascorbate). Two important optimizations from our previous attempts were the introduction of more DMSO (+30%) and TBADP usage.

Results:

Non-decay-corrected radiochemical yield (NDC-RCY) of [18F]SiTATE was 49±7% (n=3) over 25 min, starting from 167±8 mCi. Molar activities (Am) were 61±10 GBq/µmol. A high-activity run (1 Ci) was completed under similar conditions (52% NDC-RCY; Am=440 GBq/µmol). In the presence of ascorbate, no significant radiolysis was observed (95% pure after 1 h), despite the large amount of tracer produced (594 mCi). A manual synthesis of [18F]SiEX resulted in 16% NDC-RCY. The final product appeared radiochemically pure by C18-HPLC, but not by TLC (silica; 78±<1%). Exendin-4 is a long (39 amino acid), unmodified neuropeptide and may degrade or differentiate on silica. Translation to ASU resulted in an NDC-RCY of 13±3% (n=2) and Am of 14±4 GBq/µmol. These results are comparable to the indirect synthesis of another 18F-exendin; however, that approach used a maleimide-bearing 18F-tag and required four radiochemical steps.

Conclusion:

Using 'next-gen' radiofluorination methods, somatostatin agonist [18F]SiTATE was prepared in exceptionally high yields, suitable for the sequential PET imaging of multiple NET patients. It was also used to synthesize a novel GLP-1r ligand, albeit in lower yields. Next steps will focus on optimizing RCY and Am of [18F]SiEX and evaluating its affinity and specificity for pancreatic tumor cells.

Back to Abstracts Table of Contents

Re-evaluating Follow-up Strategies in Medullary Thyroid Carcinoma: The Role of Postoperative Undetectable Calcitonin – An International Multicenter cohort study

Marijn L. van den Berg[1,2], Hannelore I. Coerts[3,4], Dilay Aykan[1], Eline C. Jager[4], Paige McKinley[2], Bahar Golbon[2], Schelto Kruijff[4], Jesse D. Pasternak[2], Joaquín Gómez Ramírez[5], Tesse M. van Ginhoven[6], Lutske Lodewijk[1], Menno R. Vriens[1]

1. Department of Endocrine Surgical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands, 2. Department of Endocrine Surgery, University Health Network, Toronto, Ontario, Canada, 3. Department of Radiology and Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands, 4. Department of Surgical Oncology, University Medical Center Groningen, Groningen, The Netherlands, 5. Department of Endocrine Surgery, University of Madrid, Madrid, Spain, 6. Department Surgical Oncology and Gastrointestinal Surgery, Erasmus Medical Center, Rotterdam, The Netherlands

Presenter: Marijn van den Berg, BS, MD candidate

Introduction:

After thyroid surgery for sporadic Medullary Thyroid Carcinoma (MTC), lifelong postoperative follow-up using the tumor marker calcitonin is recommended, even for those with a seemingly favorable undetectable calcitonin 3-6 months post-surgery. This study aims to assess long-term outcomes of sporadic MTC patients with initially postoperative undetectable or normalized calcitonin levels.

Methods:

Sporadic MTC patients who underwent thyroid surgery between 2000 - 2020 and had known postoperative follow-up across five international hospitals in Europe and North America were retrospectively included. Clinicopathological characteristics, biochemical recurrence, structural recurrence and disease-specific survival were investigated. Predictive factors for recurrence and disease-specific survival were identified.

Results:

Of 330 MTC patients who underwent thyroid surgery, 310 patients with a known follow-up were included. 120 (39%) had an initially (3-6 months post-surgery) postoperative undetectable calcitonin. During follow-up, 12 (10%) of the patients with an initial undetectable calcitonin experienced biochemical or structural recurrence after a median time of 6.5 years (IQR 2.8 – 9.5 years), of which six (5%) died due to MTC after a median time of 3 years (IQR 1.0 – 6.5 years). The 5-year recurrence free survival in this initial undetectable patient group was 97% and the 10-year recurrence free survival is 91%. The 5-year MTC-related survival in this group was 96% and the 10-year recurrence free survival is 92%. Tumor size and the presence of neck lymph node metastasis were significantly associated with recurrence of MTC, respectively OR 1.05 (CI 1.01 – 1.10) and OR 6.24 (CI 2.03 – 19.15).

Conclusion:

This study illustrates that in patients with MTC who have initially undetectable calcitonin after thyroid surgery, the 5-year recurrence free survival is 97% and the 10-year recurrence free survival is 91%. These data highlight the importance of continuing surveillance for at least five to ten years after initial treatment. Further research with a longer follow-up duration is needed to determine whether lifelong follow-up is warranted in MTC patients.

Back to Abstracts Table of Contents

Deciphering Clonal Evolution and Tumor Microenvironment in Patients with DIPNECH

Fabien C. Lamaze[1], Donate Weghorn[2], Philippe Joubert[1,3]

1. Centre de Recherche Institut universitaire de cardiologie et de Pneumologie de Québec – Université Laval, Québec, QC, Canada, 2. Center for Genomic Regulation, Barcelona, Spain, 3. Département de biologie moléculaire, de biochimie médicale et de pathologie, Université Laval, Québec, QC, Canada

Presenter:

Fabien Lamaze, PhD

Background:

Lung cancer remains the leading cause of cancer mortality in North America, with neuroendocrine neoplasms (NENs) comprising ~25% of cases. Among these, Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) is a rare, underrecognized entity characterized by diffuse proliferation of neuroendocrine cells, often progressing to carcinoid tumors. Predominantly affecting women, DIPNECH is increasingly diagnosed due to high-resolution CT imaging. Most patients present with multifocal, bilateral disease, limiting surgical options and leaving surveillance or low-efficacy chemotherapy as primary management. Unlike other lung cancers, DIPNECH lacks molecular characterization, hindering targeted therapy development. Investigating DIPNECH through genomic and tumor microenvironment profiling offers a unique opportunity to uncover shared molecular drivers and biomarkers.

Methods:

For this project we plan to examine the somatic mutational profile using a combination of whole exome sequencing (WES) and ATAC-seq and the tumor microenvironment composition during the development of preneoplastic/neoplastic lesions characterizing patients with DIPNECH using a spatial transcriptomic and proteomics-based technologies. Since these patients generally develop multiple foci of neuroendocrine hyperplasia/tumorlets and carcinoid tumors, our interest is also to investigate the profile of both lung tumor and non-tumor lung parenchyma to fully understand the sequence of events leading to the development of DIPNECH. Chromatin accessibility reflects the degree to which transcription factors and associated transcriptional machinery can bind to the DNA and transduce a regulatory signal for cancer development. Therefore, profiling the chromatin accessibility using Assay for Transposase-Accessible Chromatin (ATAC) sequencing on archived FFPE samples is a crucial step for our understanding of gene regulation during the transition between non-tumor parenchyma and carcinoid.

Results:

Over recent years, a cohort of 30 DIPNECH patients was clinically and pathologically characterized. A microdissection protocol was developed to isolate DIPNECH lesions from glass slides, enabling high-quality whole-exome sequencing (WES) with 500X coverage. This included samples from blood, non-tumor lung tissue, neuroendocrine cell hyperplasia (NCH), tumorlets, and carcinoids. We applied post-processing to reduce formalin-related artifacts. A complementary method using height fresh frozen samples during surgery was also established to ensure high quality structural variants calling and ATAC-seq. Additionally, a spatial transcriptomics pipeline using Visium (10X) was also developed for tissue microarrays (TMAs), which will be applied in this project to explore tumor evolution and microenvironment in DIPNECH.

Conclusions:

Given the clinical homogeneity often observed in DIPNECH patients, this approach may reveal common signatures that could inform novel diagnostic tools and therapeutic strategies, addressing a critical unmet need in pulmonary neuroendocrine oncology.

Back to Abstracts Table of Contents

Molecular Characterization of Neuroendocrine Neoplasia (NENs): A Case Series Study

Luca Fiorini[2], Laura De Bona[2], Chiara Agnoletto[1], Elena Trevisani[2], Michele Borghesani[2], Luca Landoni[3], Claudio Luchini[1,4], Rita T. Lawlor[4], Aldo Scarpa[1,4], Michele Milella[2], Andrea Mafficini[4,5], Sara Cingarlini[2], Agnoletto C.[1], Landoni L.[3], Luchini C.[1,4], Lawlor R.T.[4], Scarpa A.[1,4], Mafficini A.[4,5]

1. Department of Diagnostics and Public Health, Section of Pathology, University and Hospital Trust of Verona, VR, Veneto, Italy, 2. Section of Oncology, Department of Engineering for Innovation Medicine, University and Hospital Trust of Verona, VR, Veneto, Italy, 3. Department of Surgery, Pancreas Institute, University and Hospital Trust of Verona, VR, Veneto, Italy, 4. ARC-Net Centre for Applied Research on Cancer, University and Hospital Trust of Verona, VR, Veneto, Italy, 5. Section of Innovation Biomedicine, Department of Engineering for Innovation Medicine, University and Hospital Trust of Verona, VR, Veneto, Italy

Presenter: Luca Fiorini, MD

Background:

NENs are rare highly heterogeneous neoplasia originating from the neuroendocrine system, requiring a multidisciplinary approach for diagnosis and treatment. Comprehensive genomic profiling (CGP) data of real-world cases is expected to recapitulate such heterogeneity for patient stratification and to plan informed precision therapy.

Methods:

A retrospective monocentric cohort of 113 patients diagnosed with gastrointestinal neuroendocrine carcinomas (GI-NEC) and tumors (GI-NET) between 2021 and 2024 were subjected to Next Generation Sequencing (NGS) on liquid or tissue biopsies using FoundationOne® (324 genes) and CORE (174 genes) panels. Detected variants were classified according to the ACMG-AMP 5-tier classification and the ESCAT ESMO Scale of actionability in order to identify potential targetable alterations for precision medicine

Results:

Profiled samples included 28 GI-NEC (25%), originating from pancreas (14), stomach (5), ampulla (4), rectum (3) and colon (2), and 85 GI-NET (75%), with the great majority having a pancreatic origin (82). As for NET grading (G), 8 were G1, 41 G2 and 36 G3 tumors. Coherent with literature data, the most common mutations in NEC tumors are TP53 (89%), RB1 (50%) and KRAS (46%), yet NET presented a high prevalence of alterations in MEN1 (39%), TSC2 (28%), CDKN2A/B (24%), DAXX (24%), ATRX (19%) and PTEN (15%). 45% of mutations in NEC and 42% in NET were Class 4,5. Potentially targetable gene alterations identified in agnostic mode, ESCAT Level of evidence (LOE) I-II, were 17 (Single Nucleotide Variants, SNV n=9; Copy Number Variants, CNV n=7; Structural Variants, SV n=1) in NEC and 59 in NET (SNV n=39; CNV n=17; SV n=3). Further, most of NENs (104 cases, 92%) have low tumor mutational burden value, with a potential indication for immune checkpoint Inhibitor therapy with LOE I-C for 3 NEC and 6 NET patients. Patients have been discussed interdisciplinary receiving indication for therapy, which access has been possibly guaranteed through off-label prescription or early phase clinical trials.

Conclusions:

CGP allows the identification of actionable alterations in a significant subgroup of NEN patients, thus eligible to novel target therapies, offering an opportunity for these rare tumors.

Back to Abstracts Table of Contents

Proteogenomic Characterization of Pancreatic Neuroendocrine Tumors

Atsushi Tanaka[1,2], Yusuke Otani[1,2], Michael H. Roehrl[1,2]

1. Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA, 2. Harvard Medical School, Boston, MA, USA.

Presenter:

Michael H. Roehrl, MD, PhD

Background:

Pancreatic neuroendocrine tumors (PanNETs) represent well-differentiated endocrine neoplasms with variable clinical outcomes. Predicting patient outcomes using the current tumor grading system is challenging. In addition, traditional systemic treatment options for PanNETs, such as somatostatin analogs or cytotoxic chemotherapies, are very limited.

Methods:

To address these issues, we characterized PanNETs using integrated proteogenomics and identified four subtypes.

Results:

Two proteomic subtypes showed high recurrence rates, suggesting clinical aggressiveness that was missed by current classification. Hypoxia and inflammatory pathways were significantly enriched in the clinically aggressive subtypes. Detailed analyses revealed metabolic adaptation via glycolysis upregulation and oxidative phosphorylation downregulation under hypoxic conditions. Inflammatory signature analysis revealed that immunosuppressive molecules were enriched in immune hot tumors and might be immunotherapy targets.

Conclusions:

In this study, we characterized clinically aggressive proteomic subtypes of well-differentiated PanNETs and identified candidate therapeutic targets.

Back to Abstracts Table of Contents

Quality of Life and Care Experiences in a U.S. Multi-institutional Neuroendocrine Tumor Cohort

Michael A. O'Rorke[1,4], Tao Xu[1,4], Rhonda R. DeCook[1], Bradley D. McDowell[1,2,4], Brian M. Gryzlak[1], Nicholas J. Rudzianski[1], Kimberly C. Serrano[1], Abigayle M. Wehrheim[1], Udhayvir S. Grewal[3,4], Chandrikha Chandrasekharan[3,5], Joseph S. Dillon[3,4], Thorvardur R. Halfdanarson[6], T. Clark Gamblin[7], Lindsay G. Cowell[8], Tobias Else[9], Heloisa P. Soares[10], Vineeth Sukrithan[11], Sravani Chandaka[12], Hanna K. Sanoff[13], Fiona C. He[14], David Geller[15], Robert A. Ramirez[16], Mei Liu[17], William Lancaster[18], Josh A. Mailman[19], Heather Moran[20], Maryann Wahmann[21], Elyse Gellerman[22], Elizabeth A. Chrischilles[1,4], on behalf of the NET-PRO Study Investigators

1. College of Public Health, Department of Epidemiology, University of Iowa, Iowa City, Iowa, USA, 2. Population Research Core, Holden Comprehensive Cancer Center, University of Iowa, Iowa City, Iowa, USA, 3. Department of Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, Iowa, USA, 4. Holden Comprehensive Cancer Center, University of Iowa, Iowa City, Iowa, USA, 5. Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, 6. Mayo Clinic, Rochester, Minnesota, USA, 7. Medical College of Wisconsin, Milwaukee, Wisconsin, USA, 8. O'Donnell School of Public Health, UT Southwestern Medical Center, Dallas, Texas, USA, 9. Department of Internal Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, Michigan, USA, 10. Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA, 11. Division of Medical Oncology, Department of Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA, 12. University of Kansas Medical Center, Kansas City, Kansas, USA, 13. Division of Oncology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, 14. Allina Health Cancer Institute, Minneapolis, Minnesota, USA, 15. University of Pittsburgh, Pittsburgh, Pennsylvania, USA, 16. Department of Internal Medicine, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, Tennessee, USA, 17. Department of Health Outcomes and Biomedical Informatics, College of Medicine, University of Florida, Gainesville, Florida, USA, 18. Department of Surgery, Medical University of South Carolina, Charleston, South Carolina, USA, 19. NorCal CarciNET Community, Oakland, California, USA, 20. The Healing NET Foundation, Los Angeles, California, USA, 21. Neuroendocrine Cancer Awareness Network, Fort Mill, South Carolina, USA, 22. Neuroendocrine Tumor Research Foundation, Boston, Massachusetts, USA

Presenter: Tao Xu, PhD

Background:

Neuroendocrine tumors (NETs) are uncommon, heterogeneous neoplasms associated with prolonged survival and substantial symptom burden. However, patient-reported outcomes (PROs) across NET subtypes remain poorly characterized, particularly in real-world settings.

Methods:

The Neuroendocrine Tumors–Patient Reported Outcomes (NET-PRO) study is a prospective, multi-institutional U.S. cohort funded by the Patient-Centered Outcomes Research Institute (PCORI), conducted across 14 sites. Adults aged ≥18 years with incident small intestinal (SI-NET), pancreatic (panNET), gastroenteropancreatic (GEP), or lung NETs diagnosed from January 2018 through September 2024 were enrolled using a validated EMR-based computable phenotype. Baseline surveys assessed health-related quality of life (HRQoL), symptoms, care experiences, and clinical characteristics using validated instruments. Descriptive statistics and standardized mean differences (SMDs) compared responses by NET site and time since diagnosis.

Results:

Among 2,367 participants (mean age 57.8 years; 57.3% female), 1,974 had GEP-NETs (659 SI-NET, 555 pNET) and 393 had lung NETs. Fatigue (mean 33.0), insomnia (32.5), and diarrhea (25.7) were the most burdensome symptoms. Lung NET patients reported worse dyspnea (SMD = 0.58, $p < 0.001$) and lower physical, role, and global QoL scores than those with GEP-NETs. Patients with pNETs reported better functioning and lower symptom burden. Diarrhea worsened over time, especially in SI-NETs. Most rated care highly (75.3%) and reported good coordination, but concerns about treatment side effects (80.4%), costs (60.7%), and travel burden (58.8%) were common.

Conclusions:

This large U.S. cohort highlights substantial, persistent symptom burden among NET patients, with variation by tumor site and disease duration. Findings support longitudinal assessment of HRQoL in this growing patient population.

Back to Abstracts Table of Contents

mTORC1 Signaling Drives Amino Acid Uptake in Pancreatic Neuroendocrine Tumors

Greg Malnassy[1], Eliza M. Rosen[1], Jenny Hu[1], Dylan Kerr[1], Anjali Kotamarthi[1], Tatsuki Ueda[2], Nicolas Chevrier[2], Scott A. Oakes[1,3,4]

1. Department of Pathology, University of Chicago, Chicago, IL, USA, 2. Pritzker School of Molecular Engineering, University of Chicago, Chicago, IL, USA, 3. Committee on Cancer Biology, University of Chicago, Chicago, IL, USA, 4. Committee on Molecular Metabolism and Nutrition, University of Chicago, Chicago, IL, USA

Presenter: Scott A. Oakes, MD

Background:

mTORC1 is a master regulator of cellular activity that responds to a wide range of growth factors, environmental cues and nutrient supplies to control cell growth and proliferation. It is well established that mTORC1 is hyperactivated in most pancreatic neuroendocrine tumors (PanNETs) due to altered expression of pathway components, mutations or epigenetic silencing of endogenous inhibitors (e.g., PTEN, TSC1/2), or aberrant signaling from the loss of negative regulators of the pathway such as menin (MEN1). The mTORC1 inhibitor everolimus was FDA approved in 2011 for patients with advanced PanNETs; however, its benefits are relatively modest and short-lived. Unfortunately, we still have limited insight about mTORC1 effectors that drive PanNET tumorigenesis and the escape mechanisms that allow tumor cells to resist mTORC1 inhibition.

We recently discovered that ongoing mTORC1 signaling in PanNETs results in upregulation of the transcription factor ATF4, which is best known as the primary pro-survival output of the integrated stress response (ISR). Under conditions where amino acids are limiting, ATF4 transcriptionally upregulates genes that promote amino acid transport and biosynthesis. However, the connection (if any) between mTORC1, ATF4 and amino acid supply has not been extensively studied in PanNETs.

Methods:

To elucidate potential mechanisms behind everolimus resistance, we analyzed ATF4 expression and target genes in BON-1 and QGP-1 human PanNET cell lines before and after a timecourse of everolimus treatment. In addition, we generated everolimus resistant BON-1 and QGP-1 cell lines by culturing them in the presence of clinically relevant concentrations of everolimus over several months and subjected them to RNA-Seq analysis to identify differentially expressed genes and potentially modulated pathways.

Results:

We identified SLC1A5, a glutamine transporter, as one of the most highly upregulated ATF4 targets in PanNETs. We find that the expression of SLC1A5 rapidly falls in both QGP-1 and BON1 cells following mTORC1 inhibition, and that forced overexpression of ATF4 strongly upregulates SLC1A5. We show that shRNA-mediated knockdown of SLC1A5 leads to striking decreases in QGP-1 and BON1 cell proliferation. To confirm the dependency of PanNET cell lines on glutamine intake, we cultured QGP-1 and BON1 in glutamine-depleted media and observed profound decreases in cell proliferation. Additionally, treatment with a selective SLC1A5 inhibitor, V-9302, produces dose-dependent decreases in QGP-1 and BON1 growth as assessed by colony formation and cell proliferation assays. Furthermore, SLC1A5 is significantly upregulated in everolimus-resistant QGP-1 and BON1 cell lines, both of which remain equally sensitive to V-9302 treatment when compared to parental cell lines. Preliminary results suggest that knocking down SLC1A5 in QGP-1 and BON1 cells impairs their ability to grow in immunocompromised mice.

Conclusions:

The TORC1 signaling pathway in PanNETs induces expression of the ATF4 transcription factor and its downstream target the SLC1A5 glutamine transporter. Everolimus resistant PanNET cell lines demonstrate upregulation of ATF4 and SLC1A5 in the absence of mTORC1 signaling, and activation of the integrated stress response (ISR). SLC1A5 knockdown or glutamine depletion reduces PanNET cell growth. Studies are ongoing to fully understand the roles of ATF4, SLC1A5 and glutamine metabolism downstream of mTORC1 signaling in PanNETs.

Back to Abstracts Table of Contents

Hedgehog Signaling Drives Glial Cell Plasticity and Oncogenic Reprogramming in Gastroenteropancreatic Neuroendocrine Neoplasms

Suzann Duan[1,2], AnneLeigh B. Twer[2], Ateh Zinkeng[2], Ricky A. Sontz[2], Juanita L. Merchant[2,3]

1. Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University of California, Irvine; Irvine, California, USA, 2. Division of Gastroenterology and Hepatology, Department of Medicine, University of Arizona College of Medicine; Tucson, Arizona, USA, 3. University of Arizona Comprehensive Cancer Center; Tucson, Arizona, USA.

Presenter: Suzann Duan, PhD

Background:

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) represent heterogenous malignancies whose cellular origins remain poorly understood. Men1-driven reprogramming of neural crest-derived glial cells was previously implicated in GEP-NET development. In these studies, hyperactivation of the Sonic hedgehog (SHH) signaling pathway coincided with NET development, yet the underlying mechanism of SHH activation and the potential for pharmacologic intervention in preclinical models of GEP-NETs have not been thoroughly evaluated. In the current study, we investigated the premise that GEP-NETs might originate from enteric glial cells that are instructed by SHH signaling.

Methods:

Men1 was deleted in glial cells by expressing Cre recombinase downstream of the human glial fibrillary acidic protein promoter (ΔMen1). Hedgehog (HH) activation of Men1-deficient glial cells was blocked by deleting the gene encoding primary ciliary protein KIF3A required for transducing SHH signaling. We evaluated the resulting ΔMen1 mice for NET development and dysregulated hormone activity. We further confirmed the induction of HH signaling in primary ΔMen1 mouse enteric glial cultures. Hyperactivation of SHH in human and mouse GEP-NETs was evaluated by immunofluorescent staining and western blot. Human and mouse NET tumoroids were treated with an agonist and inhibitors of HH signaling and evaluated for ERK/AKT activation, proliferation, and transcript fluctuations indicative of neural crest cell reprogramming.

Results:

We demonstrated that human GEP-NETs overexpress HH signaling pathway components, including SHH and its cognate receptor PTCH1. We showed that patient-derived pancreatic NET tumoroids proliferate in response to SHH pathway agonists. In contrast, pharmacologic inhibition of GLI1/2, but not inhibition of SMO alone, attenuated tumoroid growth. Genetic deletion of Men1 in GFAP+ and SOX10+ glial cells caused the development of pancreatic and small intestinal NETs that overexpress HH proteins. Further use of tdTomato+ mice demonstrated the involvement of GFAP+ and SOX10+ glial cells in these tumors. Tumoroid cultures of mouse pancreatic and small intestinal NETs recapitulated the drug response shown by patient-derived tumoroids. Lastly, Men1-deficient enteric glial cultures showed a glial-to-neuroendocrine transition that was alleviated upon HH inhibition, and these events were reproduced in genetic mice harboring GFAP+ cells with impaired primary cilia.

Conclusions:

Our observations implicate neural crest-derived glial cells as potential neuroendocrine cell precursors that are susceptible to transformation through increased SHH signaling upon loss of Menin. By establishing that NETs can arise from a glial cell that responds to SHH, our findings prompt a reassessment of HH inhibitors for potential therapeutic intervention in GEP-NETs that may include targets beyond inhibiting SMO.

Back to Abstracts Table of Contents

[212Pb]VMT-a-NET for Advanced SSTR2+ NETs: Safety and Preliminary Efficacy Results from Cohorts 1 and 2 of the Dose Escalation Phase

Halfdanarson T[1], Wahl R[2], Solnes L[3], Balaraman S[4], Sibley G[5], Anthony L[6], Mancini B[7], Starr J[8], Sukrithan V[9], Liao CY[10], Mehr S[11], Baratto L[12], Yang W[12], Hanna A[12], Keefe S[12], Puhlmann M[12], Prasad V[2]

1. Mayo Clinic Rochester 2. Washington University School of Medicine 3. Johns Hopkins 4. Profound Clinical Research 5. Virginia Cancer Specialists 6. University of Kentucky 7. BAMF 8. Mayo Jacksonville 9. Ohio State University, 10. University of Chicago 11. Nebraska Cancer Specialists 12. Perspective Therapeutics

Presenter: Lucia Baratto, MD

Background:

Somatostatin receptor subtype 2 (SSTR2) is expressed in neuroendocrine tumors (NETs), and it is an important target for both diagnosis and therapy. [212Pb]VMT-a-NET is an alpha therapy agent targeting SSTR2-expressing NETs. Here, we report the results of a prospective, open-label, Phase I/IIa clinical trial evaluating the safety, tolerability, pharmacokinetics, and preliminary efficacy of [212Pb]VMT-a-NET [NCT05636618].

Methods:

Adults with well-differentiated unresectable or metastatic SSTR2-expressing NETs, who are peptide receptor radionuclide therapy (PRRT) naïve, and who progressed on at least one prior line of systemic therapy, are eligible. The study design follows a Bayesian dose-finding algorithm. Participants receive up to four doses of [212Pb]VMT-a-NET on 8-weeks intervals at the assigned dose level. Efficacy is assessed by investigators according to RECIST criteria v1.1.

Results:

As of 30-Apr-2025, nine participants were enrolled for dose-limiting toxicity (DLT) observation into cohort 1 (n=2) and cohort 2 (n=7) at dose levels of 92.5 MBq [2.5 mCi] and 185 MBq [5 mCi], respectively. Thirty-three (33) additional patients were enrolled into cohort 2 to further evaluate safety and efficacy at the selected dose. Safety was assessed for all participants treated (n=42), while efficacy was evaluated for the nine participants enrolled for DLT-observation. Among all participants treated with [212Pb]VMT-a-NET (n=42), no DLTs, no grade 4 or 5 adverse events (AEs), no treatment-related discontinuations, no serious renal complications or myelosuppression, and no dysphagia were observed.

Four out of seven participants (57%) enrolled for DLT-observation in cohort 2 achieved an objective response with a median follow-up time of 52 weeks (range: 6,64). Three objective responses were confirmed, while one was pending confirmation at the time of data cut-off (DCO). Overall, seven of the nine participants (78%) enrolled for DLT-observation both in cohort 1 and 2 were without progression as of the DCO, with a median follow up time of 56 weeks (range: 6,77). Cohort 3, at a dose level of 222 MBq [6 mCi], has recently been opened for enrollment. Safety data for all treated participants and efficacy results for a mature subset will be presented at the research symposium.

Conclusions:

[212Pb]VMT-a-NET is a well-tolerated therapy for patients with advanced NETs, and it has shown promising clinical benefit at the dose level of 185 MBq [5 mCi]. The study is ongoing and open for enrollment in cohort 3.

Back to Abstracts Table of Contents

Mechanisms and Models for Cdk5-dependent Neuroendocrine Tumors

Kylie Dickerson[1,2], Priyanka Gupta[2], Andres Diaz[2], Kuldeep Gupta[1], Renata Jaskula-Stzul[3], Michael Choti[1], James A. Bibb[2]

1. Department of Surgery, University of Arizona College of Medicine Phoenix, Phoenix, AZ 85004, USA, 2. Department of Translational Neurosciences, University of Arizona College of Medicine Phoenix, Phoenix, AZ 85004, USA, 3. Department of Surgery, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL 35233, USA

Presenter: Kylie Dickerson, MD

Background:

Neuroendocrine tumors (NETs) occur in various forms sporadically or as the consequence of causally-linked mutations. They are generally characterized by their indolent course, debilitating symptoms, and untreatable lethality. Advances that have improved outcomes for these cancers have been limited. Following the serendipitous discovery that mechanisms that cause neurodegeneration in the central nervous system can also cause NET tumorigenesis, we have been studying various types of NETs to understand the mechanistic causes, create clinically accurate models, identify diagnostic biomarkers, and test new treatments. Our hypothesis is that diverse genomic variations converge upon common pro-neoplastic signaling mechanisms such as the aberrant activation of the protein kinase Cdk5 to drive progression of most Neuroendocrine tumors.

Methods:

Experimental models such as human tumors, cell lines, and organ-specific inducible bitransgenic animal models were utilized for the characterization of NETs. Whole exome sequencing, bulk transcriptomics, phosphoproteomics, and immunohistochemistry tissue microarray profiling were performed. Biomarker directed anti-Cdk5 targeted therapies will be tested in vivo using inducible autologous bi-transgenic tetracycline response element mouse models of PNETs, PCs, and GINETs. Cdk5 inhibitors with broad therapeutic windows will be used as the biomarker-directed therapy.

Results:

Here we will summarize some of the most notable advances made in our NET research program. We will overview the models we have created including those for medullary thyroid carcinoma (MTC), pheochromocytoma (PC), and pancreatic NETs (PanNETs). We will describe some of our latest mechanistic and multi-omic studies, and present selected findings on the potential of experimental and preclinical treatment approaches for Cdk5 dependent NETs.

Conclusions:

The inducible mouse models provide a useful preclinical tool for testing new therapies. The downstream effectors of Cdk5 can serve as predictive molecular signatures for the early detection of tumors in NET patients. The next step involves developing a clinically relevant multiplex assay system that could allow infallible quantitation of biomarker levels from the core biopsies of patient tumors. The extended current and future directions for this research will be discussed. The information, tools, results, databases, models, and drugs described in this study will be openly shared with the NET cancer research communities.

Back to Abstracts Table of Contents

Potential Biomarkers for Mesenteric Fibrosis in Small Intestinal NET Patients: An Exploratory Serum Proteomics Study

Leo J. Hofland[1], Eva van der Slik[1], Richard A. Feelders[1], Anand M. Iyer[1], Peter van Koetsveld[1], Maria C. Martins[2], H. Hodgetts[2], Martyn E. Caplin[3], Krista Rombouts[2], Wouter W. de Herder[1]

1. Department of Internal Medicine, sector Endocrinology, ENETS Centre of Excellence, Erasmus MC Cancer Institute, Rotterdam, The Netherlands, 2. Regenerative Medicine and Fibrosis Group, Institute for Liver and Digestive Health, Royal Free Hospital, University College London, London, UK, 3. Neuroendocrine Tumour Unit, ENETS Centre of Excellence, Royal Free London NHS Foundation Trust, London, UK

Presenter:

Leo J. Hofland, MD

Background:

Mesenteric fibrosis (MF) significantly contributes to morbidity in patients with small intestinal neuroendocrine tumours (SI-NETs), primarily due to its role in causing mesenteric ischemia and bowel obstruction. Additionally, the presence of MF complicates surgical intervention. Currently, the diagnosis and grading of MF in preoperative or nonoperative patients remain suboptimal, relying solely on radiological scoring systems. However, comparative studies have demonstrated that radiological assessments underestimate MF severity by up to 40% when compared to histopathological findings. This underscores the need for improved diagnostic tools. We conducted an exploratory study to identify potential serum biomarkers for MF in SI-NET patients.

Methods:

Serum proteomic profiling was performed using the RayBiotech L-2000 microarray, targeting 2,000 proteins. Sera were collected from 18 treatment-naïve, stage IV SI-NET patients via the Erasmus MC Biobank. Patients were stratified into three matched groups (n=6 each): (1) with mesenteric metastasis (MM) and moderate/severe MF, (2) with MM and none/mild MF, and (3) without MM. Matching criteria included sex (50% male), tumour size, and urinary 5-HIAA levels. MF severity was assessed radiologically by evaluating the number and width of radiating strands surrounding MM.

Preliminary results:

Unsupervised clustering analysis did not reveal distinct patient groupings based on MF status. Differential expression analysis identified 15 proteins with significant changes ($P<0.05$) between severe and none/mild MF groups—2 upregulated and 13 downregulated. Approximately half of the proteins were associated with oncogenesis, with regulation of the Ras/MAPK signalling pathway appearing particularly altered. Other enriched pathways included extracellular matrix (ECM) remodeling, cellular stress response, and immune dysregulation. Notably, Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF), a stress-response protein upregulated in kidney fibrosis, showed >2-fold increase in severe MF cases.

In comparing SI-NET patients with and without MM, four proteins were upregulated, including Syndecan-1 and Thymic Stromal Lymphopoietin (TSLP), both implicated in fibroblast activation and proliferation. Additionally, hierarchical clustering suggested potential associations with tumour grade, and 47 proteins differentially expressed between grade 1 and grade 2 tumours are currently being analysed further.

Conclusion:

In this exploratory study, we did not observe a clear-cut differentiation of MF status in SI-NET patients based on the abundance of 2000 proteins, underscoring the challenge of detecting localized fibrotic processes from patient sera.

Nevertheless, we identified a limited but potentially meaningful subset of differentially expressed serum proteins correlating with MF severity. These proteins may reflect ongoing fibrotic remodelling, chronic inflammation, and altered oncogenic signalling pathways. Whether changes in serum protein expression—such as MANF—are sufficiently sensitive and specific to serve as biomarkers for MF requires further investigation. Ongoing analyses will compare these serum findings with established protein expression profiles from SI-NET tissue samples to better elucidate their biological and clinical significance.

This research into mesenteric fibrosis is funded by NETRF Accelerator Grant 702627 (UCL/Exeter/Erasmus)

Back to Abstracts Table of Contents

UCHL1 is a Molecular Indicator and Therapeutic Target for Gastrointestinal and Pancreatic NeuroendocrineTumors

Kewei Le[1], Shiqin Liu[1], J. Randolph Hecht[2], Tanya Stoyanova[13]*

1. Department of Molecular and Medical Pharmacology, University of California Los Angeles, Los Angeles, CA, USA, 2. Department of Clinical Medicine, University of California Los Angeles, Los Angeles, CA, USA, 3. Department of Urology, University of California Los Angeles, Los Angeles, CA, USA

*Corresponding Author: tstoyanova@mednet.ucla.edu

Presenter: Tanya Stoyanova, PhD

Background:

Neuroendocrine neoplasms can be categorized into well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas. Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) include carcinoid tumors of the gastrointestinal tract and pancreatic neuroendocrine tumors (pNETs). While some NENs are localized at the time of diagnosis, the majority of small intestinal and PanNENs have metastasized by the time of diagnosis, and thus the diagnosis and prognosis of GEP-NETs remain a major clinical challenge. Serum markers for diagnosis and follow up such as chromogranin-A and pancreastatin are controversial due to poor sensitivity and specificity. In our recent study, we demonstrate that UCHL1, a deubiquitinating enzyme, is overexpressed in gastrointestinal and pancreatic NE tumors. Importantly, we show that UCHL1 is markedly elevated in both tumor tissues and patient blood samples with NE features, underscoring its potential as a marker for identifying and classifying NE tumors as well as a promising therapeutic target. Here, we establish UCHL1 as a molecular indicator of gastrointestinal (GI) and pancreatic NE tumors and further evaluate its potential as a novel therapeutic target for these diseases.

Methods:

UCHL1 expression was assessed in normal pancreas, pancreatic adenocarcinoma, and pancreatic NE tumors by immunohistochemistry (IHC) staining. Patient samples included 3 normal pancreatic tissues, 16 pancreatic adenocarcinomas, and 15 pancreatic NE tumor tissues. UCHL1 staining was scored on a scale of 0–3, where 0 indicated negative, 1 low, 2 medium, and 3 strongly positive expression. In addition, UCHL1 mRNA levels in GI cancer cell lines were examined using the CCLE datasets. UCHL1 protein expression in COLO320DM (NE-like) and COLO201 (adenocarcinoma) cell lines was analyzed by Western blot. To evaluate the therapeutic potential of targeting UCHL1 in NE tumors, cell viability assays were performed in COLO320DM and COLO201 cell lines using two UCHL1 inhibitors, LDN-57444 and IMP-1710.

Results:

Immunohistochemical analysis revealed that normal pancreatic tissues showed no detectable UCHL1 expression, pancreatic adenocarcinomas exhibited low to moderate expression, and pancreatic neuroendocrine tumors displayed the highest expression levels. These findings indicate that UCHL1 is specifically enriched in pancreatic neuroendocrine tumors and suggest its potential as a tissue biomarker to improve diagnosis of patients with this disease. Among the three large intestine adenocarcinoma cell lines UCHL1 mRNA levels were uniformly low. In contrast, the colon cancer cell line with neuroendocrine features exhibited remarkedly elevated UCHL1 mRNA expression. To validate these findings, we compared UCHL1 protein levels by Western blot a colon cancer cell line with neuroendocrine features and adenocarcinoma. Consistent with the transcriptomic data, UCHL1 protein was highly expressed in colon cancer cell line with neuroendocrine features when compared to adenocarcinoma. We next evaluated the sensitivity of colon cancer cell lines with neuroendocrine features to UCHL1 inhibitors and demonstrated high sensitivity. Together, these results demonstrate that UCHL1 is selectively upregulated in colon cancer cells with neuroendocrine features and that pharmacologic inhibition of UCHL1 impairs their viability.

Conclusions:

Our findings strongly support that UCHL1 could serve both as a diagnostic marker and as a promising therapeutic target for NE tumors, particularly those arising in the GI tract and pancreas.

Back to Abstracts Table of Contents

Loss of DAXX and ATRX Protein Expression Results in Increased Radiosensitivity and Ischemic Resistance of Bon-1 and QGP-1 Cells

Jessica C. Puzzuoli PhD, CT(ASCP)[1], Caleb Solivio BS[2], Christopher M. Heaphy PhD[3,4], Mindy K. Graham PhD[4], Anthony J. Rizzo BS[4], Diane Reidy MD[1], Eric Chan BS[1], James Russell PhD[1], Etay Ziv MD, PhD[1]

1. Memorial Sloan Kettering Cancer Center, 2. California University of Science and Medicine, 3. Boston University Chobanian & Avedisian School of Medicine, 4. The Johns Hopkins University School of Medicine

Presenter: Jessica C. Puzzuoli PhD, CT(ASCP)

Background:

Well-differentiated pancreatic neuroendocrine tumors (PNETs) often present late with unresectable liver metastases. These are often treated with liver-directed therapies including ischemia-based trans arterial embolization (TAE) or radioembolization (TARE). DAXX and ATRX mutations are relevant in PNETs. Our previous clinical data has shown poor response to TAE in DAXX-mutated PNETs; however, an association with response to TARE has not been reported. The purpose of this study was to evaluate the effect of loss of DAXX or ATRX protein expression on radiosensitivity and ischemic sensitivity in two PNET cell line models and compare TARE responses in patients with and without DAXX and ATRX mutations.

Methodology:

CRISPR/Cas9-generated knockouts (KOs) were made in two PNET cell lines: DAXX KOs were derived from Bon-1 cells (C16, C45) and ATRX KOs were from QGP-1 cells (QAX12, QAX24). Cells were treated in normal conditions or ischemia and tested for viability at different timepoints. Cells were irradiated with varying doses and colony formation was counted. To assess apoptosis, a Caspase-3 assay was performed for ischemia and radiation. The cohort study was approved by the IRB at MSKCC. Consecutive participants with PNET who underwent TARE were identified retrospectively (n=20) and clinical and treatment covariates were recorded as well as DAXX/ATRX mutation status. Time to local progression was measured and competing risk analysis was performed using Grey test.

Results:

All KOs demonstrated increased viability in comparison to the Bon-1 and QGP-1 cells at days 3 and 5 post-ischemia. Bon-1 demonstrated increased apoptotic activity compared to C16 and C45 cells at days 1, 3, and 5 post-ischemia ($p<0.0001$). All KOs exhibited greater sensitivity to radiation treatment in comparison to the Bon-1 and QGP-1 cells. Bon-1 and QGP-1 cells had increased survival fraction post-radiation ($p<0.0001$). Moreover, C16 and C45 cells demonstrated higher apoptotic activity than Bon-1 at 48 and 72 hours post radiation ($p<0.0001$). There were 11/20 (55%) patients with a DAXX/ATRX mutation. The median ki67 was 19% (IQR: 18%), there were 11/20 (55%) grade 2 and 9/20 (45%) grade 3 tumors, 6/30 (30%) had greater than 50% tumor burden, and most patients had prior treatments with PRRT (60%), TAE (75%), or chemotherapy (65%). We did not detect any differences between wild type and DAXX/ATRX mutant patients in terms of age, grade, tumor burden, prior treatments or dose delivered. Competing risk analysis showed longer time to local progression after TARE in patients with DAXX/ATRX mutations ($p < 0.001$). The median time to local progression after TARE was 8 months in DAXX/ATRX wild type patients compared with 24 months in DAXX/ATRX mutant patients.

Conclusion:

In correlation with our clinical data from patients treated with TAE and TARE, loss of DAXX and loss of ATRX protein expression in their respective PNET cell lines resulted in increased ischemic resistance and increased radiosensitivity compared with Bon-1 and QGP-1 wildtype cell lines. Current and future studies include investigation of signaling pathways contributing to these outcomes as well as the cellular mechanisms involved.

Back to Abstracts Table of Contents


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