Research and Clinical Update from
the Penn NET Center

April 13th, 2018

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Overview

• Overview of the Penn NET Center.

• Pheochromocytoma/Paraganglioma (Pheo/Para)

• Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)
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PENN NET Center Overview

- Medical Oncology
- Nuclear Medicine
- Pulmonary
- Gastroenterology
- Interventional Radiology
- Pathology
- Radiation Oncology
- Medical Genetics
- Endocrinology
- Surgery
- Nephrology
- Cardiology
- Head and Neck Surgery
- Cancer Biology
PENN NET Center Overview

Clinical Care
- Tumor sub-groups:
  - Pheochromocytoma/paraganglioma (Pheo/Para)
  - Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
  - Bronchial carcinoids

Research
- Basic science
  - Determine the mechanisms of NET formation and growth
  - Develop new treatments for NETs
- Clinical science
  - Understand the characteristics of patients with NETs
  - Understand the effects of NET treatments
  - Trial new treatments and/or treatment paradigms for NETs
Challenges associated with research in NETs

• Rarity and heterogeneity of NETs → limited numbers of patients for trials
• Few researchers compared to other fields
• Limited funding
• Limited/poor models for studying NETs in the lab
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Database and tumor collection

- Pheo/Para
  - 331 patients consented in the database
  - 111 tumor samples
Blood pressure variability and control by 24-hour ambulatory blood pressure monitoring before and after resection of catecholamine-secreting neuroendocrine tumors.

Jordana B. Cohen, MD, MSCE; Anirban Ganguli, MD; Bonita J. Bennett, RN; Raymond R. Townsend, MD; Debbie L. Cohen, MD

Summary of the results:
Following resection of catecholamine-secreting neuroendocrine tumors, individuals had a significant decline in 24-hour ambulatory blood pressure and blood pressure variability, on fewer antihypertensive medications compared to baseline.

Figure 1. Number of Antihypertensive Medications

- Pre-operative Antihypertensives
- Post-operative Antihypertensives
Clinical studies in Pheo/Para

Conclusions: Neuroendocrine tumor resection likely has greater cardiovascular prognostic significance than observed by changes in in-office blood pressure measurements and related parameters.
Clinical studies in Pheo/Para

MIBG avidity and progression-free survival in patients with metastatic pheochromocytoma are not dependent on germline SDHx mutation status

Fishbein L, Bennett B, Narayan V, Nathanson KL, Cengel K, Cohen DL, and Pryma DA

Conclusions: These data suggest no clinical predictors of response to MIBG therapy and do not support the notion that SDHB mutations carriers with metastatic PCC/PGL have a decreased response to MIBG therapy. All patients with MIBG avid metastatic PCC/PGL may benefit equally from MIBG therapy.
Clinical studies in Pheo/Para

Use of Somatostatin Analog Therapy in Patients with Advanced Pheochromocytoma or Paraganglioma and Somatostatin-Receptor Avid Disease

Vivek Narayan, MD MSCE; Lauren Fishbein, MD PhD; Katherine Nathanson, MD; Bonita Bennett, BSN RN; Daniel Pryma, MD; Debbie Cohen, MD

Conclusions: A significant proportion of advanced PGL patients demonstrate SSR-avid disease by conventional imaging. Such patients may be treated with SSA therapy (which may provide a delay in progression), either alone or in combination with other common systemic therapies.
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  • Database and tumor collection
  • Basic science and translational laboratory research
  • Clinical studies and trials
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  • Clinical studies and trials
Database and tumor collection

- GEP-NETs
  - 346 patients consented in the database
  - 224 banked blood samples
  - 96 tumor samples
GEP-NET Primary Tumor Location

- Unknown
- Pancreas
- Small Intestine
- Stomach
- Appendix
- Colon/Rectum
- Lung
- Duodenum
GEP-NET Type

- Non-functional
- Gastrinoma
- Carcinoid syndrome
- Insulinoma
- Somatostatinoma
- VIPoma
What do we do with the database and tissue?

We use them to do research on NETs!!
PTCH 1 staining of pancreatic neuroendocrine tumor (PNET) samples from patients with and without multiple endocrine neoplasia (MEN-1) syndrome reveals a potential therapeutic target.

Buddha Gurung, Xianxin Hua, Melissa Runske, Bonita Bennett, Virginia LiVolsi, Robert Roses, Douglas A Fraker, and David C Metz.

Figure 1. Immunofluorescence for PTCH 1 in a normal pancreatic islet (A), a tumor not expressing PTCH 1 (B), and a tumor expressing PTCH-1 (C).
Research with others outside of Penn

• Tissue sharing collaborations:
  Dr. Andrea Califano (Columbia University)
  Dr. Juanita Merchant (University of Michigan)

• Data sharing collaborations:
  Collaborating on a large pancreatic neuroendocrine tumor study with Dana Farber Cancer Center and Mount Sinai
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Basic science and translational laboratory research

- Can we discover novel “targetable” pathways that are important for NET growth and tumorigenesis?

- Can Car-T therapy technology be effectively utilized to treat NETs?
Novel targetable pathways in NETs

Menin and Daxx Interact to Suppress Neuroendocrine Tumors through Epigenetic Control of the Membrane Metallo-Endopeptidase

Zijie Feng1,2,3, Lei Wang2,3,4, Yanmei Sun1, Zongzhe Jiang1, John Domsic3,5, Chiying An2,3,6, Bowen Xing1, Jingjing Tian1, Xiuheng Liu*, David C. Metz3,7, XiaoLu Yang1,3, Ronen Marmorstein3,5, Xiaosong Ma*, and Xianxin Hua3,5

Cancer Res; 77(2) January 15, 2017

Nude Mice
Novel targetable pathways in NETs

Menin and Daxx Interact to Suppress Neuroendocrine Tumors through Epigenetic Control of the Membrane Metallo-Endopeptidase

Zijie Feng$^{1,2,3}$, Lei Wang$^{2,3,4}$, Yanmei Sun$^1$, Zongzhe Jiang$^1$, John Domsic$^{3,5}$, Chiying An$^{2,5,6}$, Bowen Xing$^1$, Jingjing Tian$^1$, Xiuheng Liu$^4$, David C. Metz$^{3,7}$, Xiaolu Yang$^{2,3}$, Ronen Marmorstein$^{3,5}$, Xiaosong Ma$^1$, and Xianxin Hua$^{2,3}$
Novel targetable pathways in NETs

RESEARCH PAPER

BRD4 inhibitor IBET upregulates p27kip/cip protein stability in neuroendocrine tumor cells

Lei Wang\textsuperscript{a,b}, Smita Matkar\textsuperscript{b}, Gengchen Xie\textsuperscript{c}, Chiying An\textsuperscript{b,d}, Xin He\textsuperscript{b}, Xiangchen Kong\textsuperscript{b}, Xiuheing Liu\textsuperscript{a}, and Xianxin Hua\textsuperscript{b}

\textsuperscript{a}Department of Urology, Renmin Hospital of Wuhan University, Wuhan, P.R. China; \textsuperscript{b}Abramson Family Cancer Research Institute, Department of Cancer Biology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; \textsuperscript{c}Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P.R. China; \textsuperscript{d}Department of Endocrinology and Metabolism, The First Affiliated Hospital of Harbin Medical University, Harbin, P.R. China
Car-T therapy

T cells are isolated from patient

T cells are engineered to express CARs that recognize cancer cells

Modified T cells are grown and expanded in culture

Modified T cells are infused into patient
Car-T therapy

Camel and llama produce single variable domain antibodies or nanobodies.
Car-T therapy

Immunization of llama with somatostatin-expressing cells and construction of phage display library

Neuroendocrine tumor-like cells

Screen the phages for those that recognize neuroendocrine tumor-like cells

Separate out the nanobody producing cells

Isolate sequence of the nanobodies and put into a phage display library

Isolate the specific antibody sequence that is positive

VHH
Car-T therapy

NET-specific nanobody-directed CAR-T cells kill NET cells, but not non-NET cells
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Interventional Radiology Trials

• RETNET Trial - Accruing

• Capecitabine/temozolomide + Y90 radioembolization
  – Pilot completed and accepted for publication
SPINET Trial

Efficacy and Safety of Lanreotide Autogel/Depot 120 mg vs. Placebo in Subjects With Lung Neuroendocrine Tumors (SPINET)

• Principal Investigator: David Metz
• Sub-Investigator: Bryson Katona

• Phase 3, prospective, multi-center, randomized, double-blind, study evaluating the efficacy and safety of lanreotide in well-differentiated, metastatic and/or unresectable, typical or atypical lung NETs.

• Recruiting!
Efficacy of Peptide Receptor Radionuclide Therapy in a United States–Based Cohort of Metastatic Neuroendocrine Tumor Patients

Single-Institution Retrospective Analysis

Bryson W. Katona, MD, PhD,* Giorgio A. Roccaro, MD,*† Michael C. Soulen, MD,‡
Yu-Xiao Yang, MD, MSCE,*† Bonita J. Bennett, BSN,* Brian P. Riff, MD,§ Rebecca A. Glyn, BS,*
Damian Wild, MD, PhD,|| Guillaume P. Nicolas, MD,∥ Daniel A. Pryma, MD,‡
Ursina R. Teitelbaum, MD,¶ and David C. Metz, MBChb*

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Analyzed data from all patients from Penn who underwent PRRT (primarily in Europe)

Examined how well PRRT worked → tumor progression

Looked at different factors that may play a role in how well PRRT worked
PRRT was effective in our USA based patient population.

PRRT was more effective:
- Grade I/II NETs
- When used prior to systemic chemotherapy
Endoscopic Resection of Duodenal Carcinoid Tumors: A Single Center Comparison between Simple Polypectomy and Endoscopic Mucosal Resection

Nadim Mahmud, Yutaka Tomizawa, Kristen Stashek, Bryson Katona, Gregory Ginsberg, David Metz

• Goal: To compare simple polypectomy (less morbid) to advanced resection techniques (more morbid)

• Findings:
  • No differences in complete resection margins or local tumor recurrence between methods
  • Simple polypectomy may be adequate treatment for small duodenal carcinoid tumors (≤6mm in size)
Endoscopic Resection of Duodenal Carcinoid Tumors: A Single Center Comparison between Simple Polypectomy and Endoscopic Mucosal Resection

Nadim Mahmud, Yutaka Tomizawa, Kristen Stashek, Bryson Katona, Gregory Ginsberg, David Metz

• Results will be presented as a talk at the Digestive Disease Week Conference in Washington, D.C. in June 2018

• Manuscript has been submitted to the journal of Gastrointestinal Endoscopy
Risk of Metastasis in Patients with Rectal Neuroendocrine Tumors

Ian W. Folkert, Andrew J. Sinnamon, Douglas L. Fraker, Bonita Bennett, David C. Metz, Kristen M. Stashek, Robert E. Roses

- Rectal NETs account for a significant portion of all GEP-NETs
- Goal: To identify risk factors for the development of metastatic disease in patients with rectal neuroendocrine tumors
Risk of Metastasis in Patients with Rectal Neuroendocrine Tumors

Ian W. Folkert, Andrew J. Sinnamon, Douglas L. Fraker, Bonita Bennett, David C. Metz, Kristen M. Stashek, Robert E. Roses

• Main Conclusions:
  • Patients with small intermediate grade rectal NETs remain at risk for developing metastatic disease
  • >2 cm G1 or any G2/G3 tumors
    • → complete staging
    • → more aggressive surveillance/management

• Results were presented as a talk at the Society for Surgical Oncology Annual Meeting in Chicago, in March 2018.

• Manuscript in preparation.
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Thank you!

- **Our patients**
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