Carcinoid-NeuroEndocrine TUMOUR SOCIETY CANADA

SOCIÉTÉ DES TUMEURS Carcinoïdes-NeuroEndocrines DU CANADA

Highlights of research projects funded by CNETS Canada and outcomes

Prof. Girish Shah

Chair of Scientific and Medical Advisory Board of CNETS Canada
and
Professor and Researcher at Laval University Hospital Research Centre in Quebec City

2017 NATIONAL NET PATIENT CONFERENCE:

CNETS CANADA & CANM JOINT MEDICAL SESSION

April 21-22, 2017, Westin Harbour Castle, Toronto (ON) Canada

Research closes the gap between "What is…and what could be"

Today's NET therapy was Yesterday's Research

How far in yesterday?

(1) ^{60}Ga : 50 years old (Prof. Roland Hustinx)

(2) STZ (Stretozotocin), 5-FU (5-fluoruracil) etc

Tomorrow's NET therapy will be Today's Research

Supporting Research is among the top 4 priorities for CNETS Canada

- Research can be game-changer that will help us understand the causes of NET cancers; expedite and improve diagnostics and develop state-of-the-art treatments of the future
- There has been unanimous and strong support among NET community and NET practitioners that research support remain an integral part of the larger vision of CNETS Canada.

How to support research in a “rare” or an “orphan” disease such as NET?

- Role of serendipitous discovery has been oversold in research folklores: Newton & apple, or Fleming & penicillin)
- Research findings do not occur in vacuum: they need fertile minds to bloom research ideas into clinically applicable practices
- CNETS Canada’s approach has been to increase the awareness of conducting NET research in Canada to:
  (a) Improve current methods of diagnosis and therapy
  (b) To examine the causes of NETs, and improve the range of therapeutic options by identifying new targeted or personalized therapies.

CNETS Canada Research Support-A (2010-14)

CNETS & Cancer Research Society Inc.

1:1 Matching Program: 60K per year for 2 years

- **2010: Herman Yeger**, Hospital for Sick Children, Univ. Toronto
- **2011: Nahum Sonenberg**, Goodman Cancer Res Ctr., McGill Univ. Montreal
- **2012: Lois Mulligan**, Cancer Research Institute, Queen's Univ., Kingston
- **2013: Nahum Sonenberg**, Goodman Cancer Res Ctr., McGill Univ. Montreal
- **2014: Trevor Pugh**, Princess Margaret Cancer Ctr, Univ Toronto

CNETS Canada Research Support-B (from 2016)

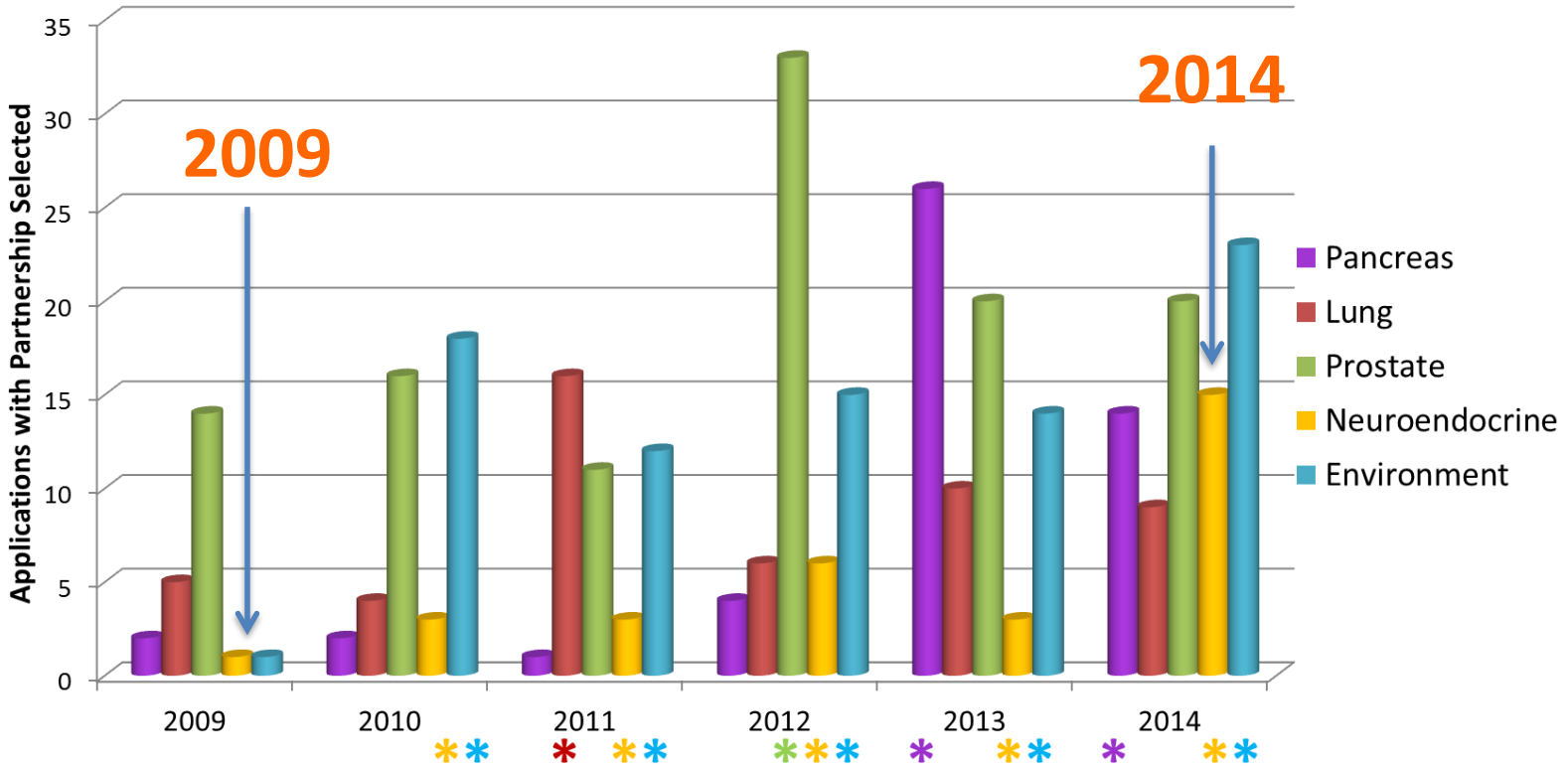
CNETS designed its own program:
Two grants of 40K per year

- **2016-A: Hagen Kenecke***, British Columbia Cancer Agency, Univ. British Columbia (*Jean-François Bernard)
- **2016-B: Jean-Mathieu Beauregard**, Quebec Hospital Centers (CHU-Q) Université Laval, Quebec City
- 2017: Ongoing competition: Two awards to be announced in summer-2017

How does CNETS Canada measure "return on investment" in Research?

- Is more attention being paid to NET research in NETS in Canada?
- Are we stimulating more work or more researchers to think about doing research with a NET problem?
- Are we improving therapy for NETS?
- Are we heading towards development of new therapies in NETS?

Outcome 1: Is there more interest n doing NET research in Canada?



- The number of applications received on neuroendocrine tumours went from one (1) in 2009 to 14 in 2014.
- Although two applications on neuroendocrine tumours had score above 8/10 in 2015, none could be funded due to lack of funds

From:: Dr. Lucille Beaudet, CRS

Output from Previous Grant-1?

Herman Yeger: Grant of 2010-12

Project: Role of hypoxia/hypercapnia chemo-sensing in the pathophysiology of malignant progression of carcinoids

Papers and Presentations

1) BMC Cancer. 2013 Aug 8;13:378. doi: 10.1186/1471-2407-13-378. **Combination of carbonic anhydrase inhibitor, acetazolamide, and sulforaphane, reduces the viability and growth of bronchial carcinoid cell lines.** Mokhtari RB[1], Kumar S, Islam SS, Yazdanpanah M, Adeli K, Cutz E, Yeger H.

2) Am J Respir Cell Mol Biol. 2015 Feb;52(2):183-92. doi: 10.1165/rcmb.2014-0054OC. **Carbonic anhydrase II mediates malignant behavior of pulmonary neuroendocrine tumors.** Zhou Y[1], Mokhtari RB, Pan J, Cutz E, Yeger H.

Perspective:

1) Improved chemotherapy for Lung NETs: An enzyme in lung NET cells: Carbonic anhydrase II, holds the key to their ability to resist chemotherapy: therefore a a combination of chemo with inhibition of this enzyme can improve chemotherapy

2) To create NET tumor bank as a resource for all for NET researchers

Output from Previous Grants 2-4?

Nahum Sonenberg: Grants of 2011-13 & 2014-15
Project: mTOR inhibition and translational control of pancreatic NETS

Papers, Book Chapters and Presentations

1) Nature Communications. 2016 Jun 20;7:11776. doi: 10.1038/ncomms11776.
Translation control during prolonged mTORC1 inhibition mediated by 4E-BP3.
Tsukumo Y[1], Alain T[2], Fonseca BD[2], Nadon R[3], Sonenberg N[1].

2) Bhat M, Metrakos P, Ramon y Cajal S, Sonenberg N, Alain T. (2014). Pancreatic Neuroendocrine Tumours. Parsyan, A**. Translation and Its Regulation in Cancer Biology and Medicine. :** 631-64.. Published, Springer Netherlands,

3) Submitted articles:
Tsukumo Y, Alain T, Nadon R, Sonenberg N. Transcriptional activation of 4E-BP3 suppresses cell proliferation through cap-dependent translation repression during prolonged mTOR inhibition. *Mol Cell submitted*

Perspective:

1) Improved therapy for PNETs with mTOR inhibitors Everolimus and 2nd generation of mTOR inhibitors: Expression of translation initiation factor 4E (eIF4E) and its repressor 4E-binding proteins (4E-BP3) and 4E-BP2) controls therapeutic response to mTOR inhibitors: **Personalized therapy**

Output from Previous Grant-3?

Lois Mulligan: Grant of 203-14
Project: Isoform-specific regulation of RET receptor tyrosine kinase

Papers and Presentations

1) Hyndman BD, Crupi MJF, Peng S, Bone LN, Wagner SM, Rekab AN, Antonescu CN **Mulligan LM.** Differential recruitment of E3-ubiquitin ligase complexes regulates RET isoform internalization. Submitted J Cell Sci, In revision. Crupi MJF, Yoganathan P, Bone LN, Lian E, Fetz A,

2) Antonescu CN, **Mulligan LM** (2015). Distinct temporal regulation of RET isoform internalization: roles of clathrin and AP2. Traffic 16: 1155-1173. Epub Aug 25, 2015. DOI: 10.1111/tra.12315

3) Crupi MJF, Richardson DS, **Mulligan LM** (2015). Cell-Surface Biotinylation of Receptor Tyrosine Kinases to Investigate Intracellular Trafficking. In: *Receptor Tyrosine Kinases: Methods and Protocols* Ed. Germano, S. Springer Science, New York, USA Methods in Molecular Biology 1233: 91-102. DOI: 10.1007/978-1-4939-1789-1_9

4) Mulligan LM (2014). RET Revisited: Expanding the Oncogenic Portfolio. Nature Reviews Cancer 14(3): 173-185.

Perspective: In MEN2 expressing NETS, the RET receptor tyrosine kinase protein binds cellular growth factor and activates transduction pathways. These studies suggest better targeting of MEN2 NETs.

Output from three other Grants

- Trevor Pugh (Grant 2014-15)
- Hagen Kenecke (Grant 2016A)
- Jean-Mathieu Beauregard (Grant 2016B)

- Exploring new ways to treat gastrointestinal and pancreatic NETs
- Personalized PRRT radiotherapy for NETs
- Potentiation of PRRT radiotherapy for NETs