Caring for Carcinoid Foundation and Stanford Cancer Center Neuroendocrine Tumor Patient Conference

NET Biology/Current CFCF Project

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Neuroendocrine Tumor Studies

Overview

- **Challenges for NET research**
- **NET biology: mTOR pathway**
- **Current CFCF Project**

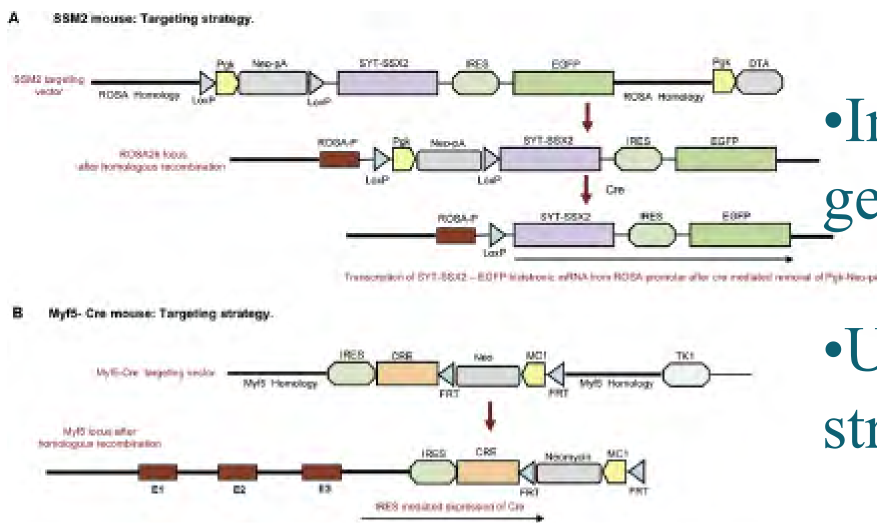
Neuroendocrine Tumor Studies

Challenges

- **Finding the right model**
- **Slow progress from bench-to-bedside**
- **Rare diseases, few patients**
- **Difficulty of clinical trials**

Neuroendocrine Tumor Studies

Finding the right model



- Insight into role of specific genetic events in a cancer
- Use to test new therapeutic strategies
- One part in translation of a discovery to the clinic

Haldar et al. Cancer Cell 2007

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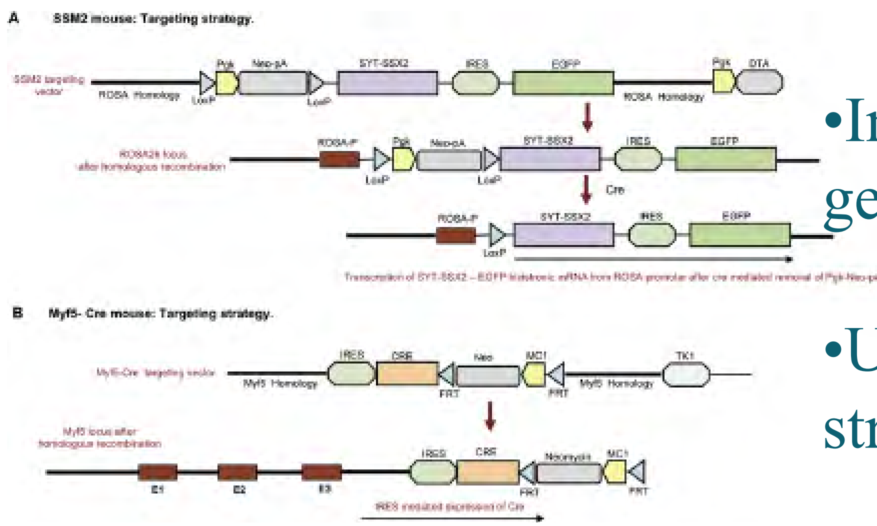
Finding the right model



- Insight into role of specific genetic events in a cancer
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- One part in translation of a discovery to the clinic

•We need better models to study NETs!

Haldar et al. Cancer Cell 2007

UCSF University of California San Francisco

Translational Studies

Slow progress from bench-to-bedside

DISCOVERIES LEADING TO FDA APPROVAL OF STI571/Gleevec FOR TREATMENT OF CHRONIC MYELOGENOUS LEUKEMIA

1960

1960 – Abnormal chromosome 22 (Philadelphia Chromosome) observed in CML patients

1970

1973 – Chromosome 22 and 9 translocation observed by new staining techniques

1980

1982 – *abl* Proto-oncogene identified in chromosome 22 translocation

1984-1987 – BCR-ABL protein identified as possible cause of CML

1990

1990 – *bcr-abl* Gene identified as cause of leukemia in mice

1993 – First STI571/Gleevec laboratory studies begin

1998 – First human tests begin

1999 – First human results reported

2000

2001 – April: Larger study confirms earlier findings

2001 – **May:** FDA approves STI571/Gleevec for treatment for CML

- After a long and careful research process
- Necessary to find out if new treatment is safe and effective in patients
- Need patients to participate

http://www.cancer.gov

2002 – February: FDA approve Gleevec for treatment of advanced GIST

Translational Studies

Rare diseases, few patients

RTOG S-0124, A Phase II Study of Multimodality Therapy for Primary and Recurrent Retroperitoneal Sarcomas, (closed to accrual on 7/22/03 due to unacceptably slow accrual) was terminated on March 25, 2004.

Effective immediately, no further data and/or forms should be submitted to RTOG Headquarters.

http://www.rtog.org

Neuroendocrine Tumor Studies

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Neuroendocrine Tumor Studies

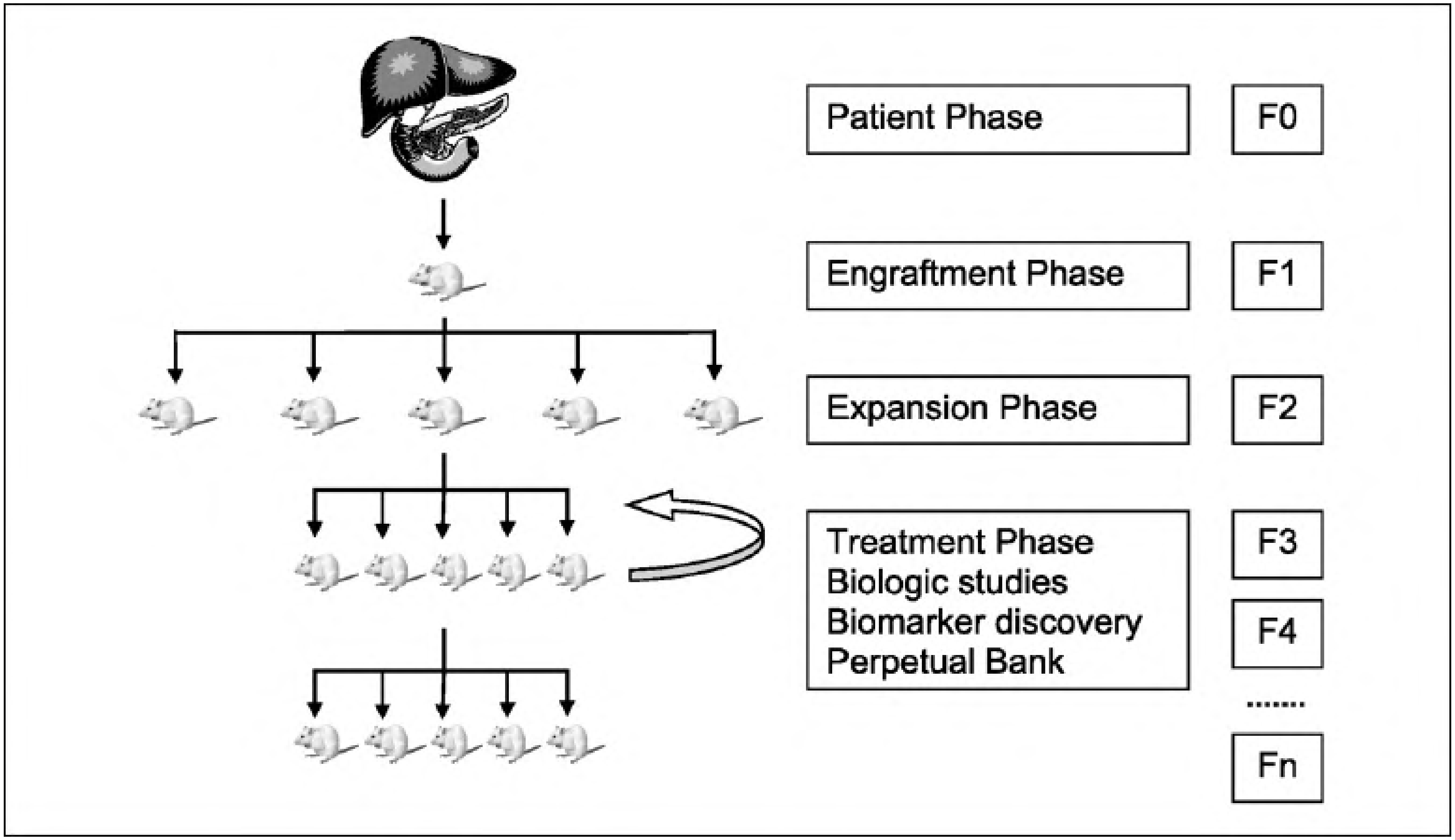
mTOR Pathway

- **Dysfunction of mTOR pathway is a critical event in pancreatic NETs**
- **Everolimus, a partial mTOR inhibitor, showed unequivocal anti-tumor activity in a phase III clinical trial**
- **Everolimus is approved for the treatment of pancreatic NETs**
- **However, therapeutic resistance emerges over time**

Jiao et al. Science 2011; Yao et al. NEJM 2011

Translational Studies

Human cancer xenografts



Rubio-Viqueira et al. Clin Cancer Res 2006

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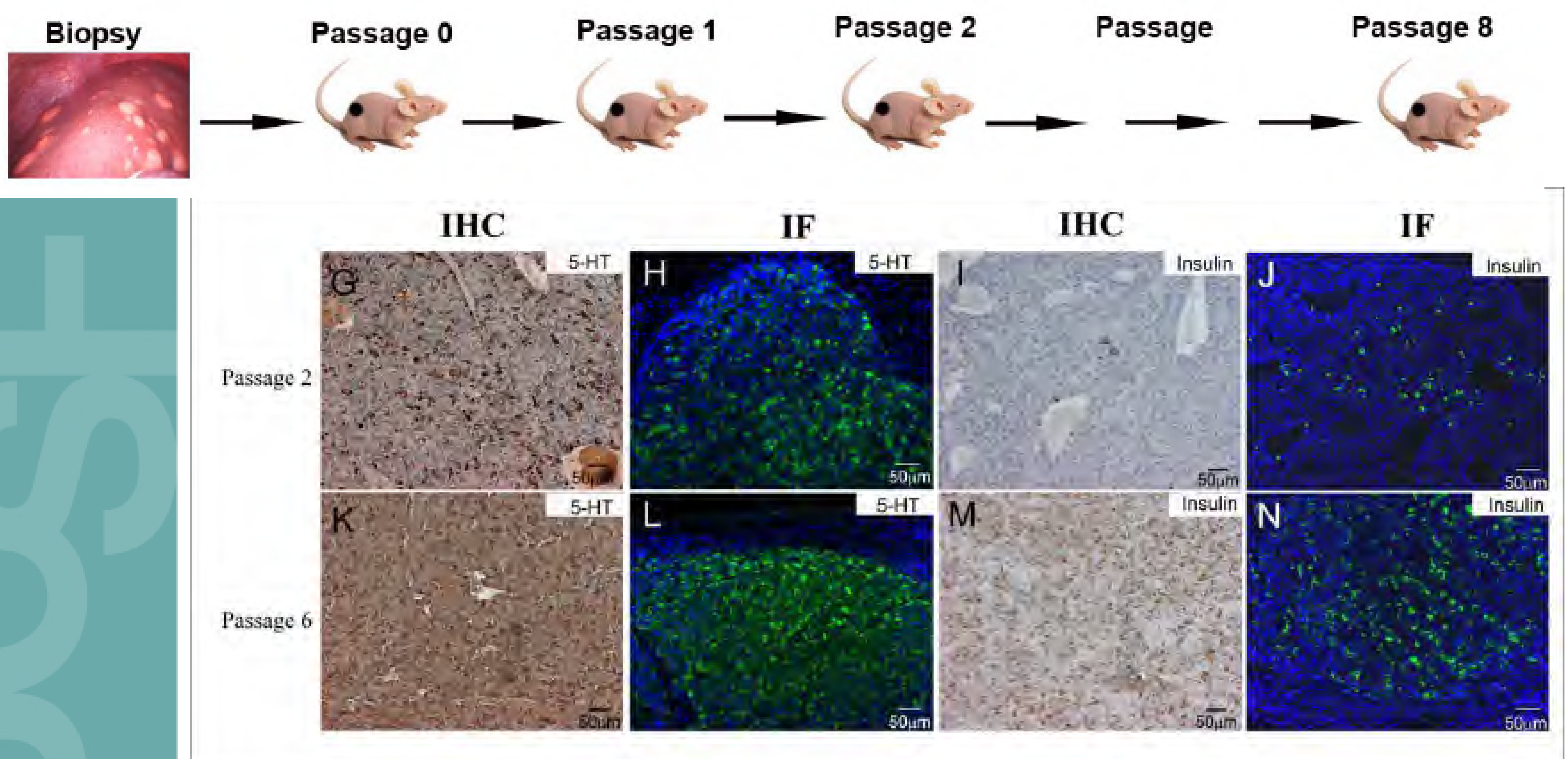
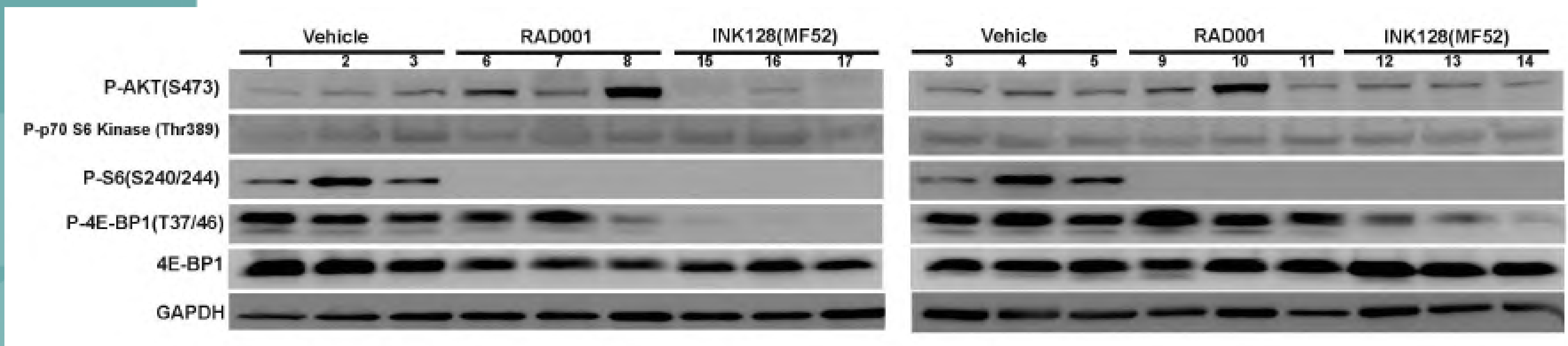
Models of rare human cancers



UCSF Surgical Oncology Laboratory

Neuroendocrine Tumor Studies

In vivo platform for drug development



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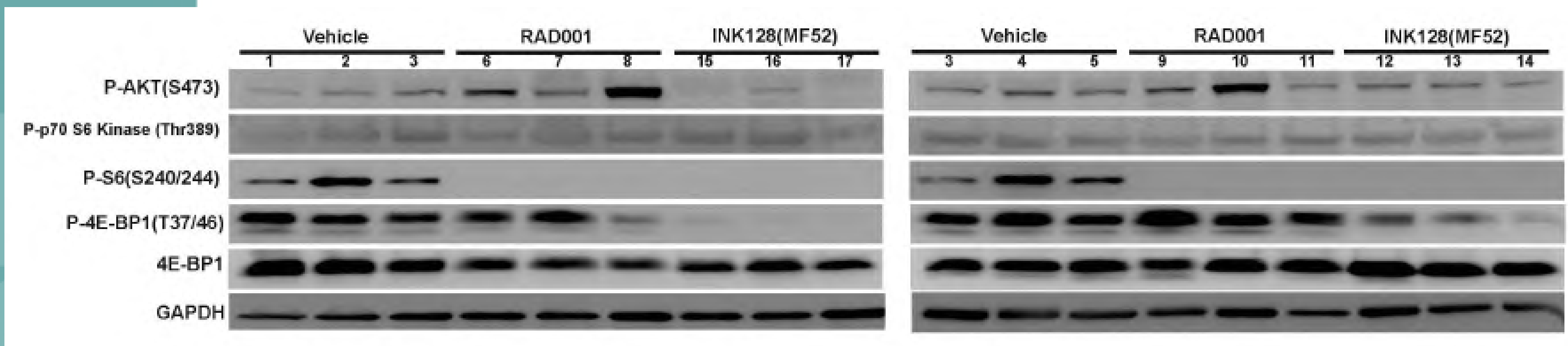
In vivo platform for drug development



•INK128 is a superior mTOR inhibitor to everolimus (RAD001)

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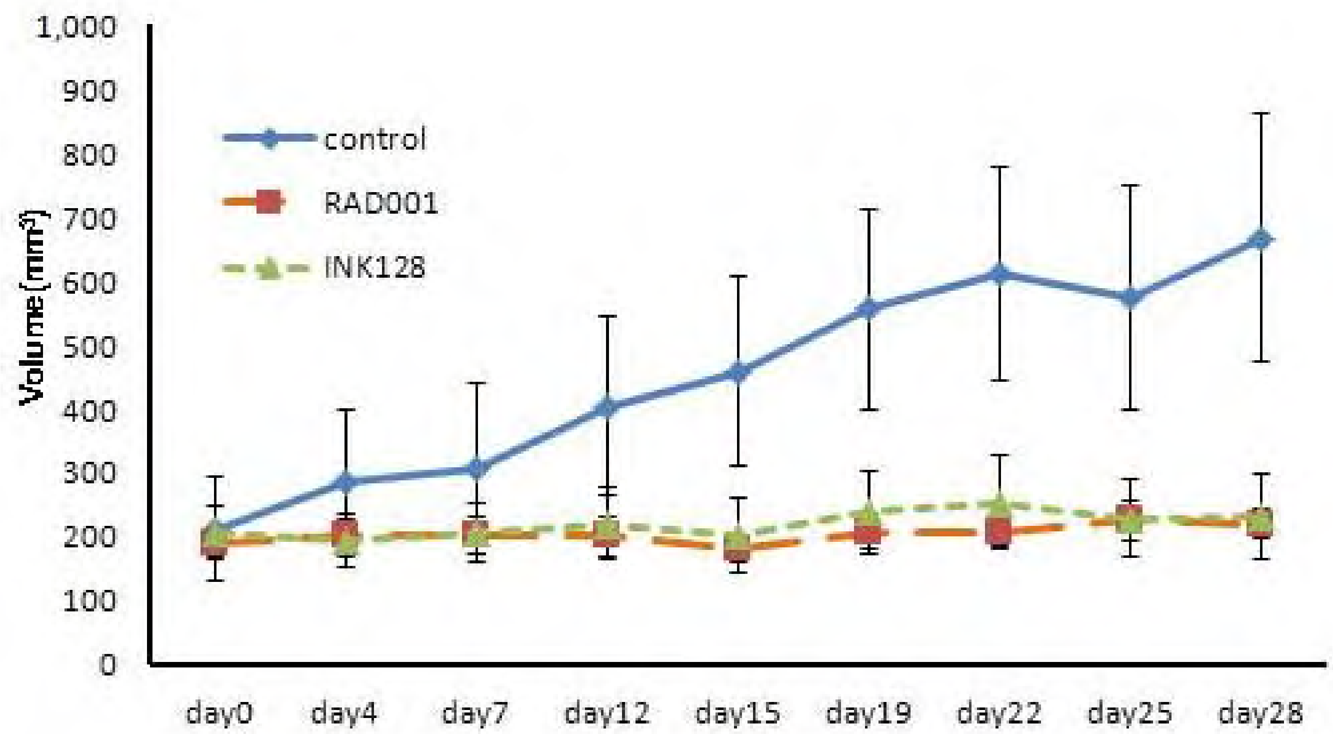
In vivo platform for drug development



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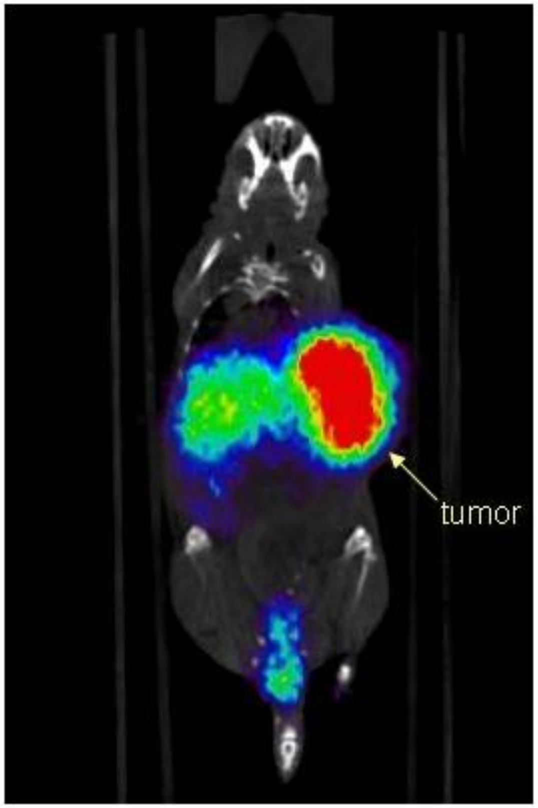
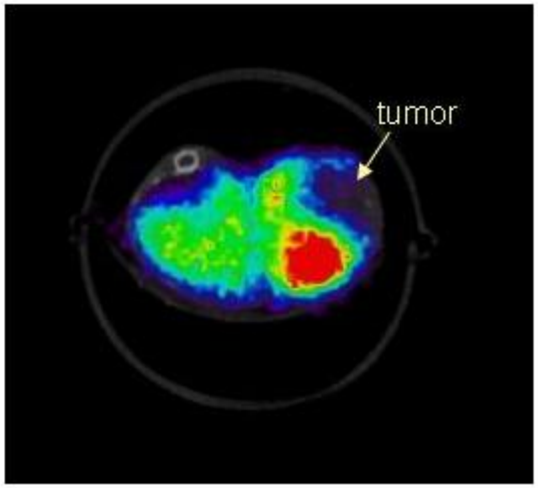
In vivo platform for biomedical imaging



•Ga-68 DOTATOC PET-CT



UCSF Surgical Oncology Laboratory

Neuroendocrine Tumor Studies

Multidisciplinary team

- **Kevan Shokat: Drug design**
- **Henry VanBrocklin: Biomedical imaging**
- **Byron Hann: Pre-clincal therapeutics**
- **Emily Bergsland: Medical oncology**
- **Eric Nakakura: Surgical oncology**

Neuroendocrine Tumor Studies

Summary

- **We are motivated by the challenges to bring new treatments to our patients**
- **The mTOR pathway is an important target in NETs**
- **Rapid progress in NET studies would not be possible without the generous support of the CFCF and patients**

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Thank you, Caring for Carcinoid Foundation!

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