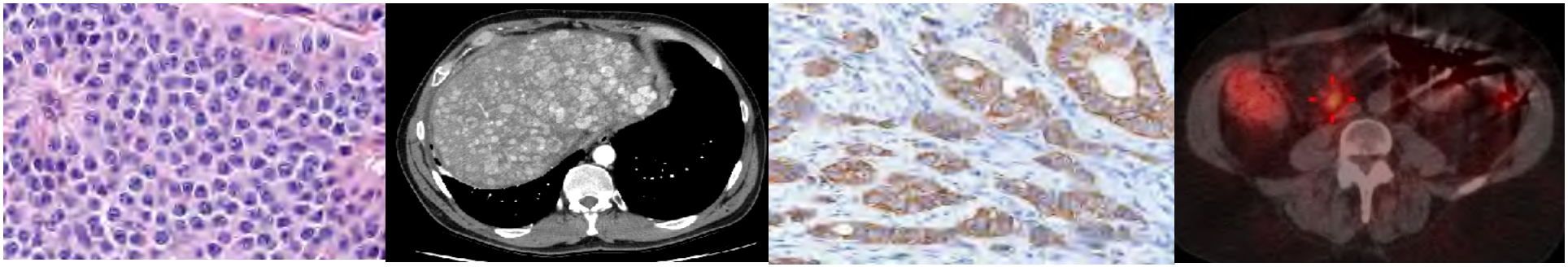
STANFORD
CANCER CENTER

Neuroendocrine Tumors 101
An Introductory Course

George Fisher, MD PhD



NET 101: disclaimer

- What I will **not** be discussing…

  Some types of lung cancer:

  Small cell neuroendocrine lung cancer

  Large cell neuroendocrine lung cancer

  Some types of colon cancer:

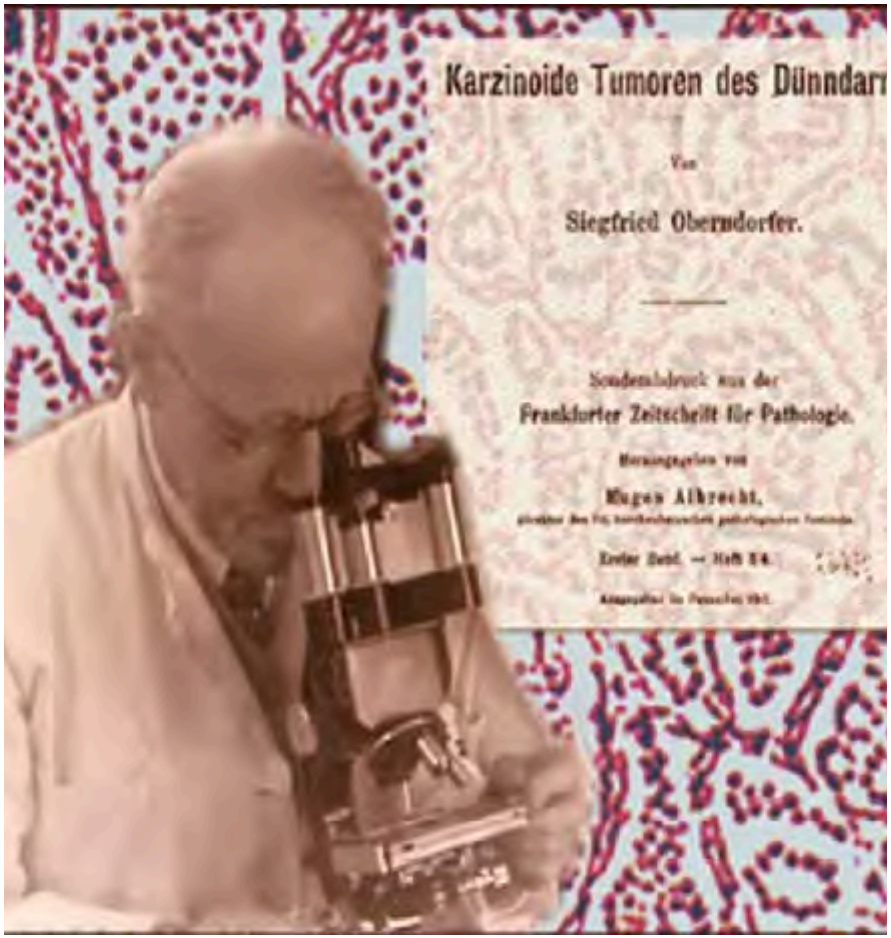
  Adenocarcinoma with “neuroendocrine features”

  Rare type of appendiceal cancer:

  Goblet cell “carcinoid”

NET History

- 1907 Sigfried Oberndorfer uses term “karzinoid” to describe morphologically distinct class of intestinal tumors with less aggressive behavior than carcinomas



NET Basics: “Rare-omas”

- Incidence is low

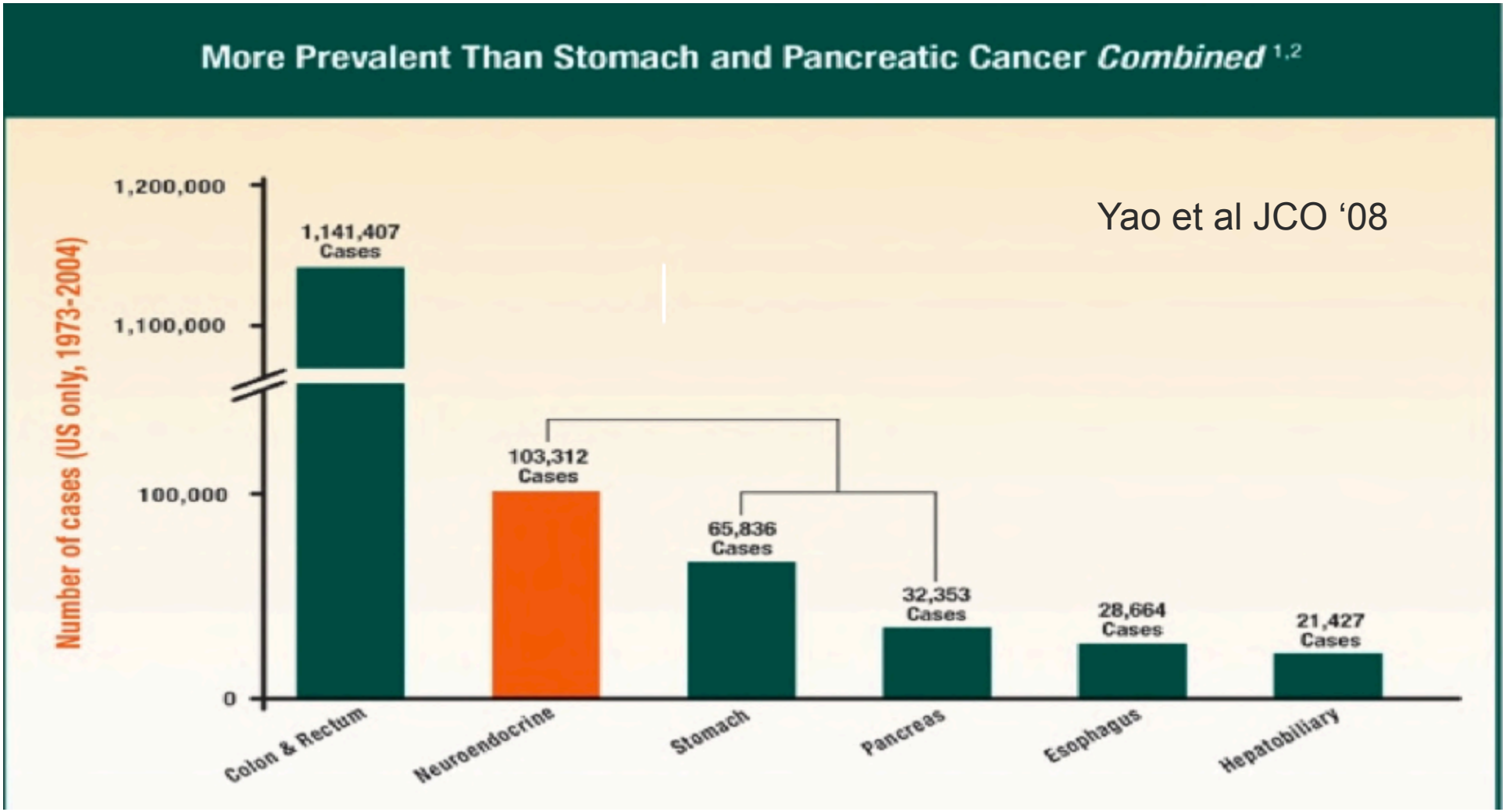
  # diagnosed per year per 100,000 people

Site	Incidence (per 100,000)
Lung	1.35
Thymus	0.02
Stomach	0.30
Small intestine	0.86
Colon	0.36
Appendix	0.15
Rectum	0.86
Pancreas	0.32
Liver	0.04
Other / unknown	0.74
Total	**5.00**

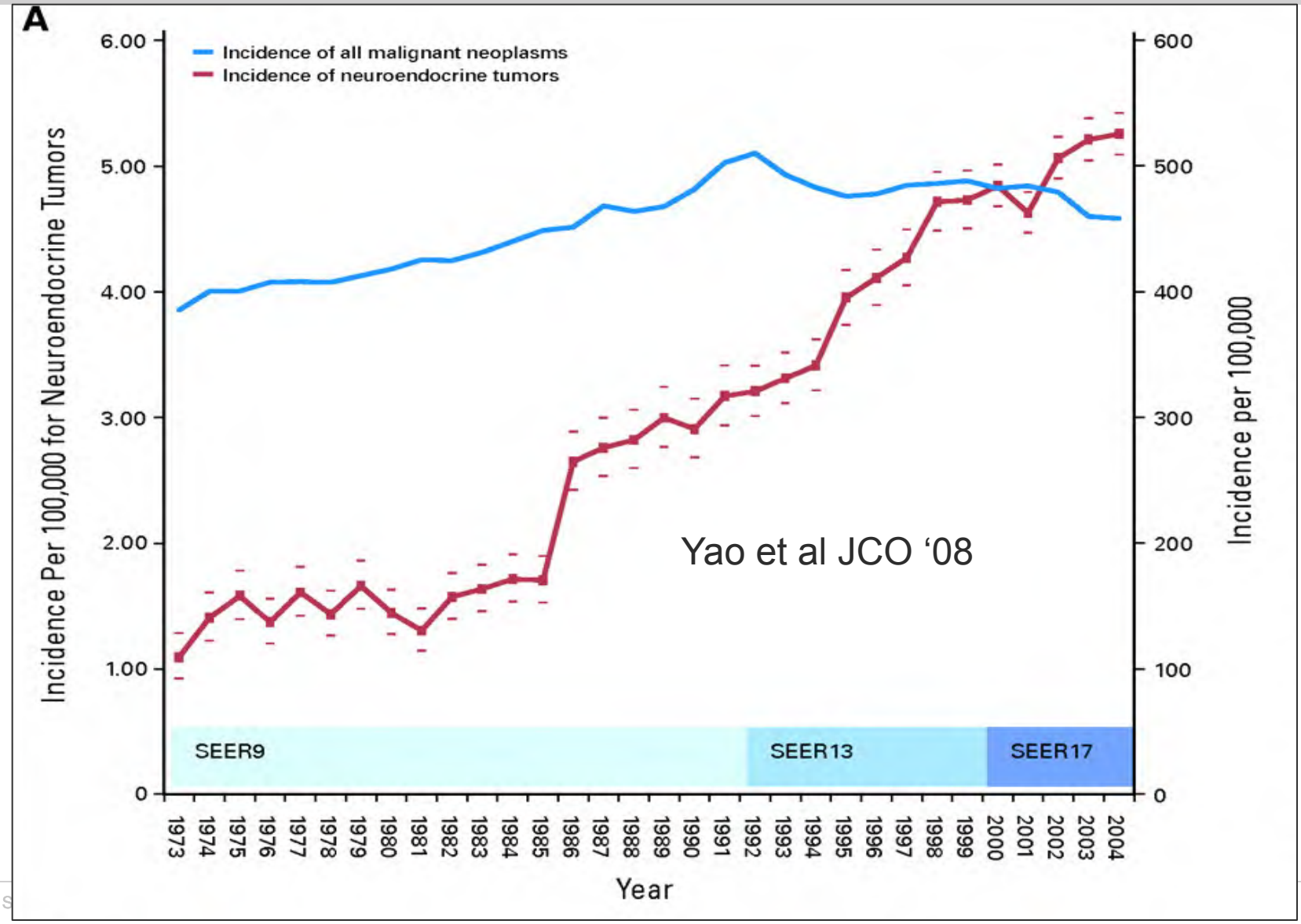
Yao et al JCO ‘08

NET Basics: Not really that “rare”

- Prevalence: # pts with the disease at any given time



NET Basics: Increasing Incidence



NET Basics: Historic nomenclature confusing

- APUDOMAS

  Amine precursor uptake and decarboxylation

- GEP NET

  gastro**e**ntero**p**ancreatic

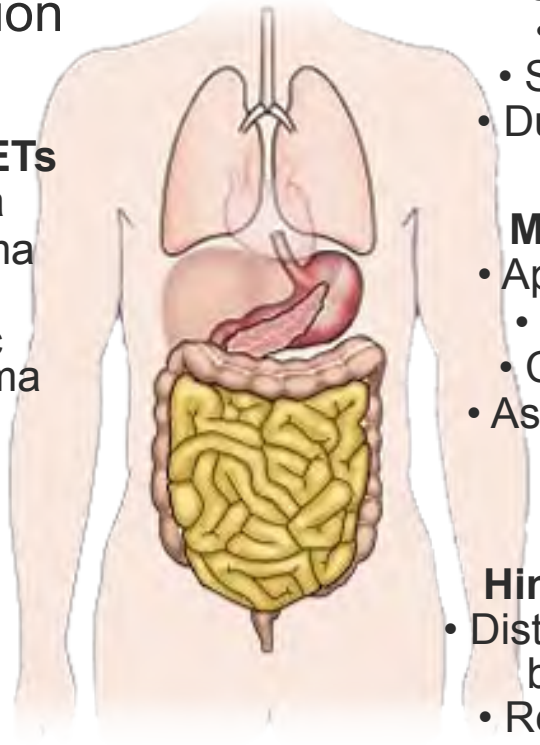
- ISLET CELL

- Carcinoid

- Bronchial: typical vs atypical

- Foregut / Midgut / Hindgut classification

Pancreatic NETs
- Insulinoma
- Glucagonoma
- VIPoma
- Pancreatic polypeptidoma



Foregut
- Thymus
- Esophagus
- Lung
- Stomach
- Duodenum

Midgut
- Appendix
- Ileum
- Cecum
- Ascending colon

Hindgut
- Distal large bowel
- Rectum

Modern NET Nomenclature

- **Organ of origin**
  - **e.g. ileal vs appendiceal vs pancreatic**

Modern NET Nomenclature

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- **Secreting or not secreting**

  e.g. glucagon vs insulin vs pancreatic polypeptide vs serotonin

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- **Syndrome vs no syndrome (functional or non-functional)**

  e.g. carcinoid syndrome from serotonin vs hypoglycemia from insulin

Modern NET Nomenclature

- Organ of origin

  e.g. ileal vs appendiceal vs pancreatic

- Secreting or not secreting

  e.g. glucagon vs insulin vs pancreatic polypeptide vs serotonin

- Syndrome or no syndrome (“functional” or “non-functional”)

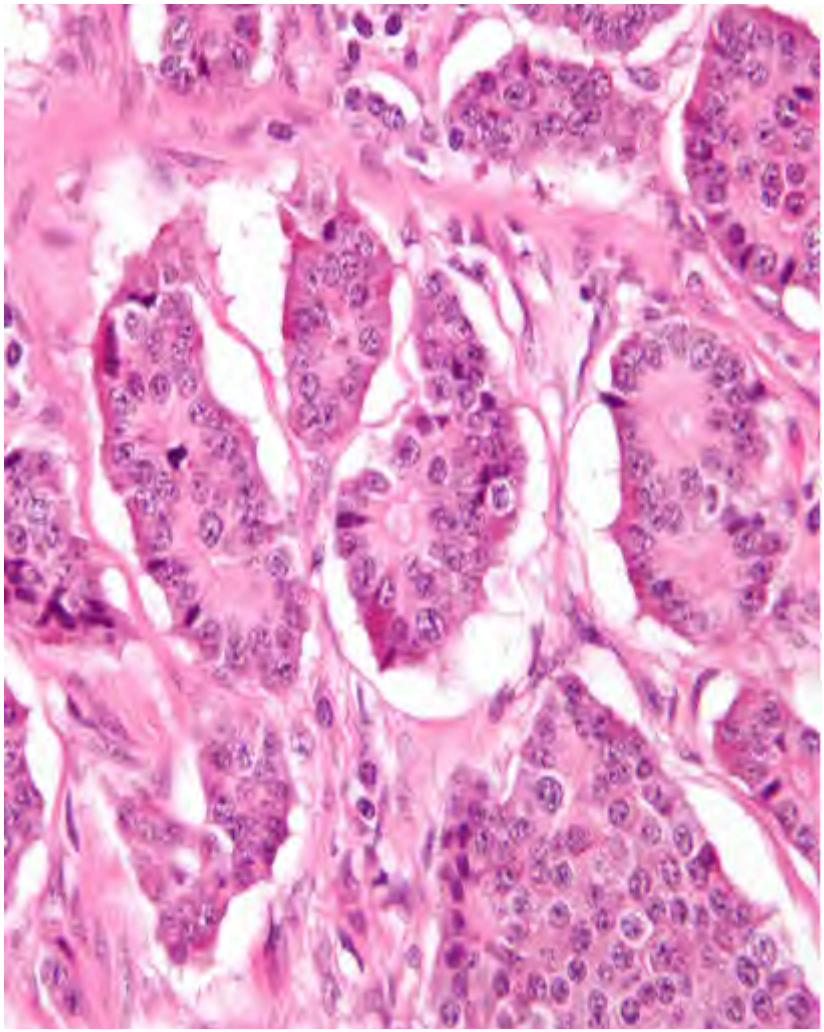
  e.g. carcinoid syndrome from serotonin vs hypoglycemia from insulin

- **Well differentiated or poorly differentiated**

  e.g. low grade (1 or 2) or high grade (3)

NET Biology

- Derived from neuroendocrine cells in the gut and elsewhere
  - -”endocrine” because they can release “hormones”
    - amines or small pieces of proteins called peptides
  - -”neuro” because they can be stimulated by nerves



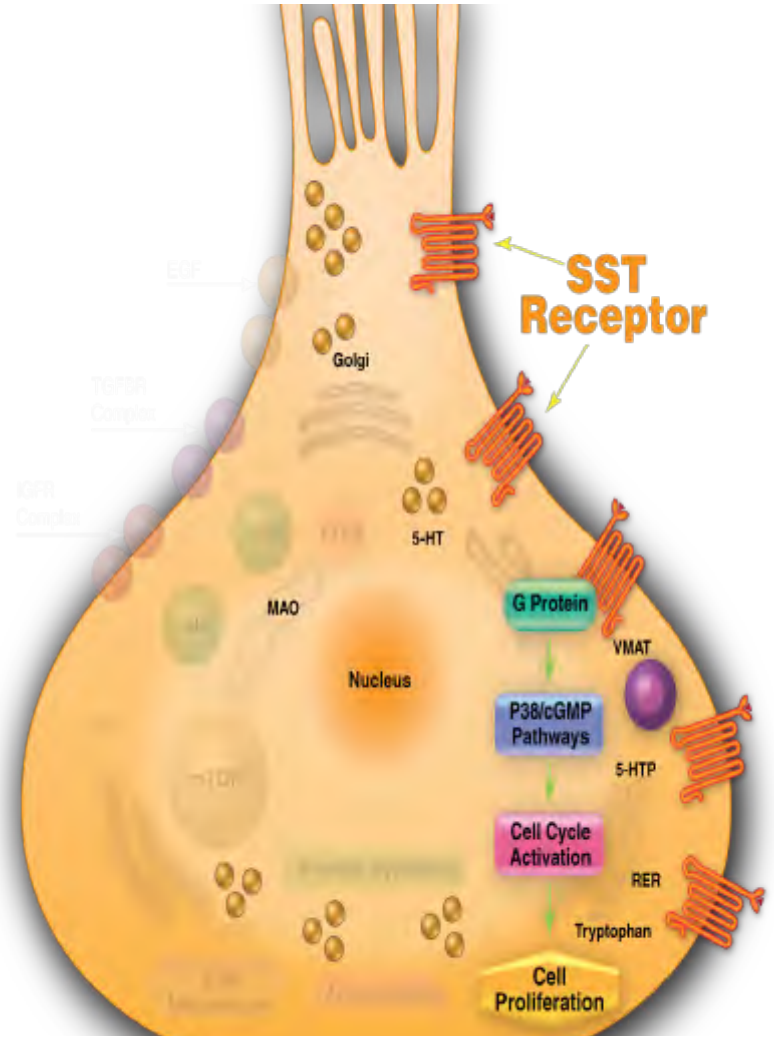
NET Biology

- Somatostatin receptors present on cell surface

  -5 somatostatin receptors (SSTR $_{1\text{-}5}$)

  -80% NETs over-express $SSTR_2$, followed by $SSTR_1$ and $SSTR_5$

  -Octreotide has high affinity for $SSTR_2$



NET Genetics

- Familial Genes
  - MEN-1 and MEN-2
  - Familial Paraganglioma
  - Carney Triad Syndrome
  - Von Hippel-Lindau disease
  - Neurofibromatosis Type 1
  - Tuberosclerosis
- Tumor Genes
  - Pancreatic NET
    - PTEN / TSC2
    - DAXX / ATRX
    - MEN-1
    - CDK 4/6 amplification
  - Midgut Carcinoid
    - ? Soon to be named

NET Clinical Tendencies

- **“slow growth” relative to all cancers**
  - **-hence the term “carcinoid” instead of carcinoma**
  - **-some grow so slowly that treatment is unnecessary**
  - **-exception: poorly differentiated NETs**

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- **Tumor cells release amines / peptides into blood**
  - **-hence can be used as "tumor markers"**
  - **-if causing symptoms then secretory syndromes or "functional"**

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- Tumor cells release of amines / peptides into blood
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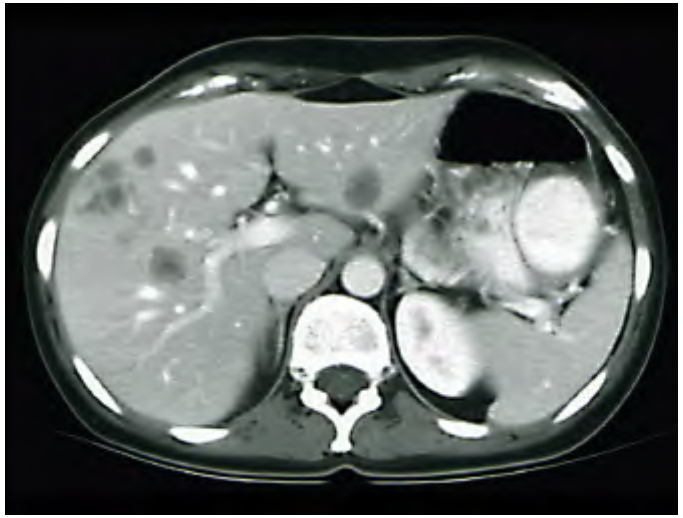
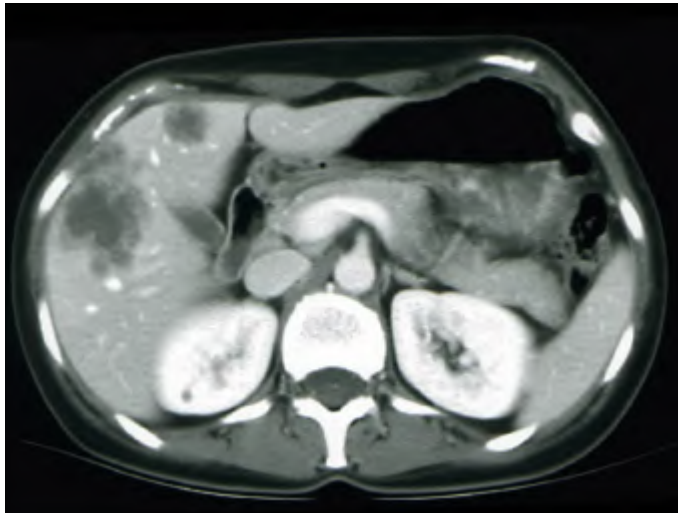
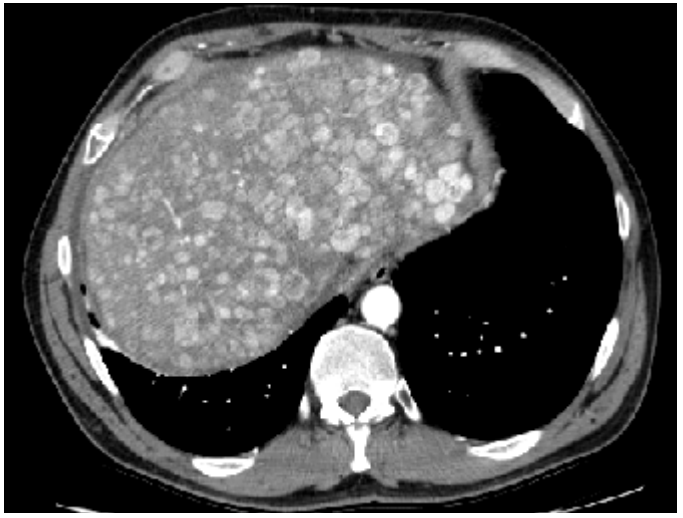
- **Hypervascular**
  - **-rich arterial blood supply compared with other cancers**

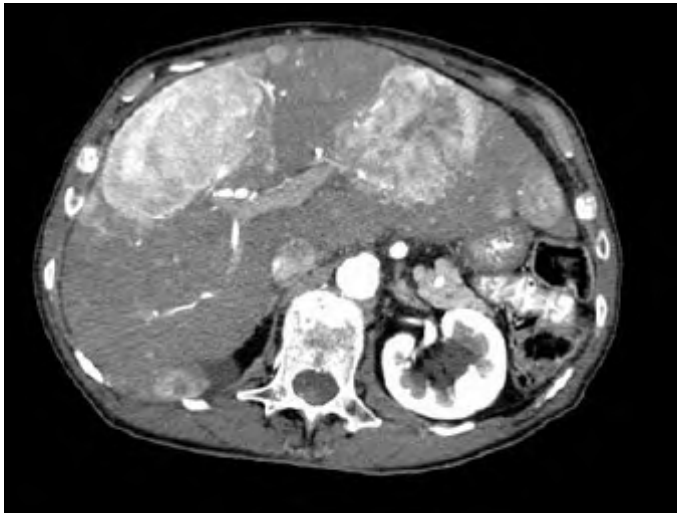
TYPICAL COLORECTAL CANCER METASTASES





TYPICAL NET METASTASES





NET: Staging and Grading

- **Stage**: defines the extent of disease at the time of diagnosis

  More importantly: where is it and can it be removed?

- **Grade**: defined by the pathologic characteristic of the tumor cells

  -how the cells look under the microscope

  -how many cells are in the process of dividing (i.e. growing)

  -% staining by Ki-67, a “proliferation” marker

Taking Advantage of NET Biology

- **Slow growth**
  - **Treat only those who need treatment**
    - **Tumor Grade and Ki-67**
    - **Extent of disease and symptoms**
    - **Rate of growth of disease**

Taking Advantage of NET Biology

- Slow growth

  Treat only those who need treatment

- **Somatostatin receptors on 80% of NETs**

  Somatostatin analogs: octreotide, lanreotide, pasireotide

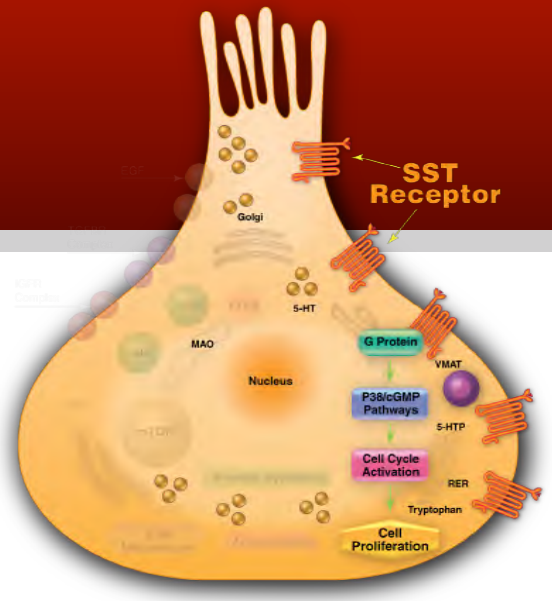
  -treats the syndrome by decreasing secretion of peptides

  -binds to receptors that might mediate growth

  -binds to the tumor so can be used as imaging agent

  -binds to the tumor so can be used as therapeutic delivery of high dose radiation (PRRT)

Somatostatin receptors as therapeutic targets

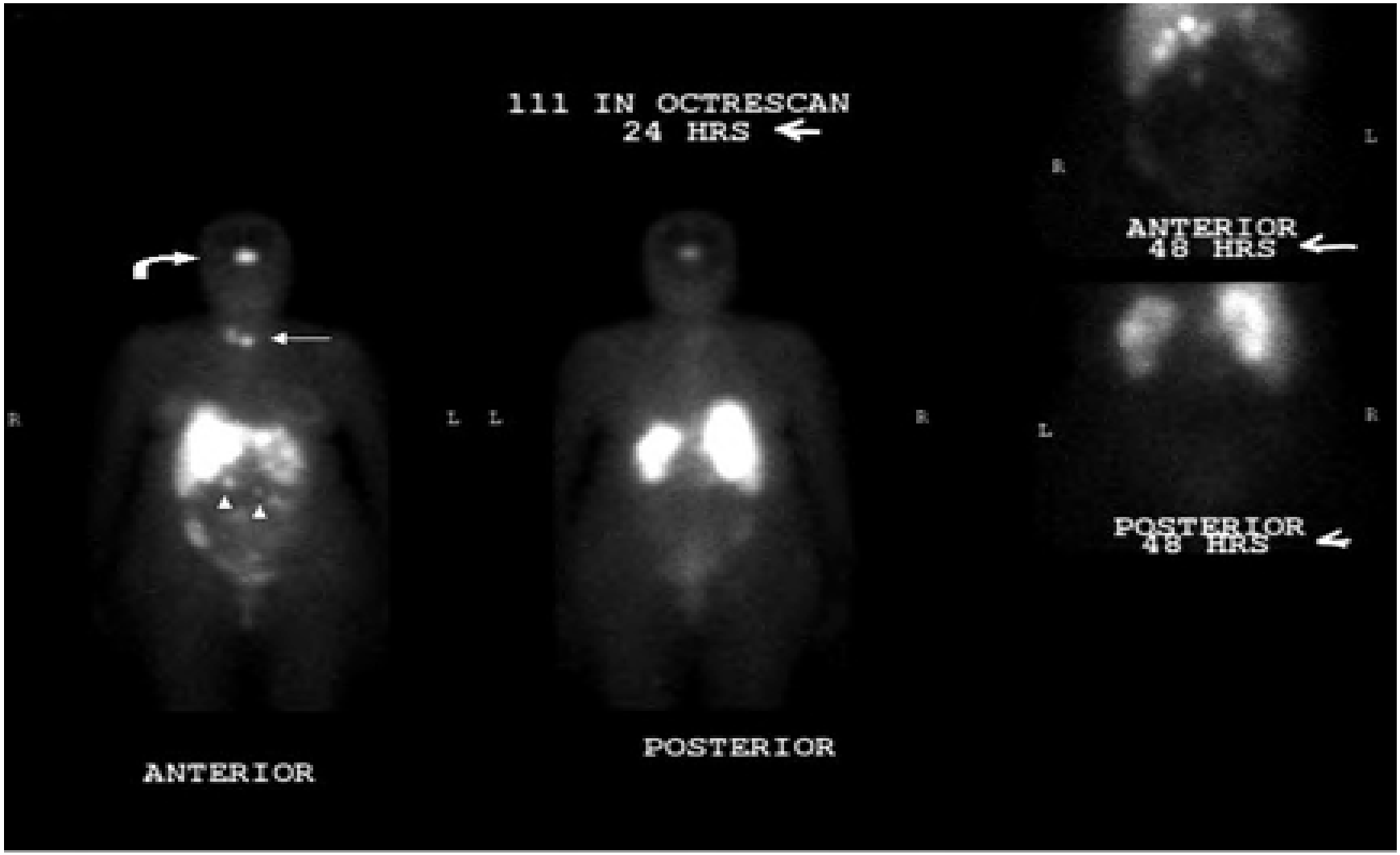


Function	SST_1	SST_2	SST_3	SST_4	SST_5
Antisecretory		➳	➳		➳
Anti-angiogenic		➳	➳		➳
Antiproliferative/ Inhibition of cell cycle	➳	➳	➳		➳
Induction of apoptosis	➳	➳	➳		

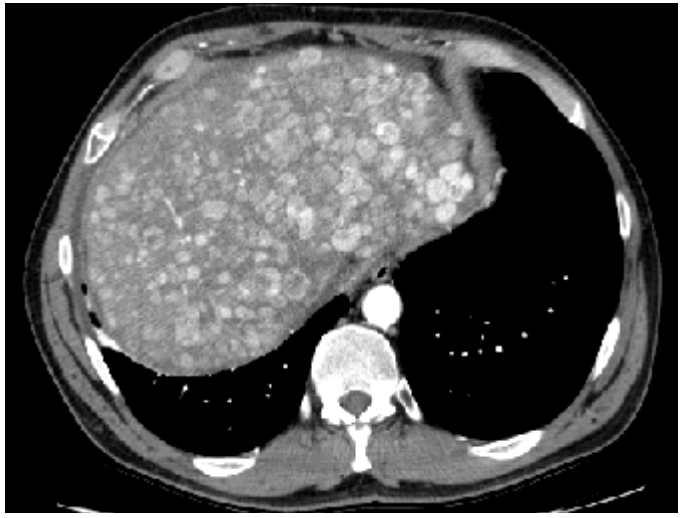
Adapted from Susini C, Buscail L and Weckbecker G, Lewis I, Albert R, et al.[1]

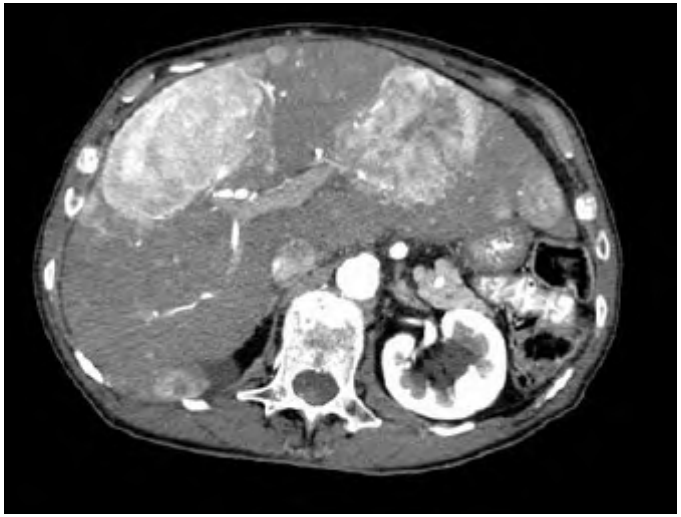
References: 1. Weckbecker G, Lewis I, Albert R, et al. *Nature Rev Drug Discov*. 2003, 2:999-1017. **2.** Öberg K, Kvols L, Caplin M, et al. *Ann Oncol*. 2004; 15:966-973. **3.** Susini C, Buscail L. *Ann Oncol*. 2006; 17:1733-1742.

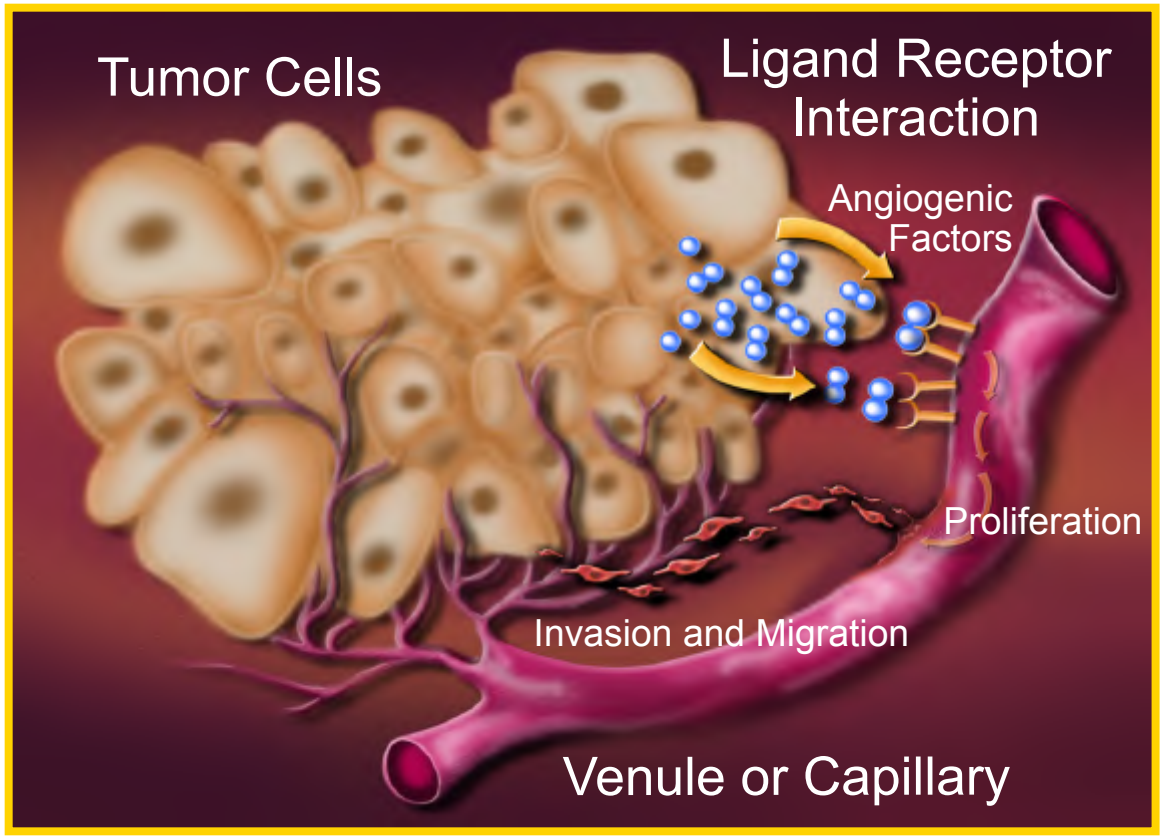
Somatostatin Receptors as Targets for Imaging (and treatment): patient with MEN-1



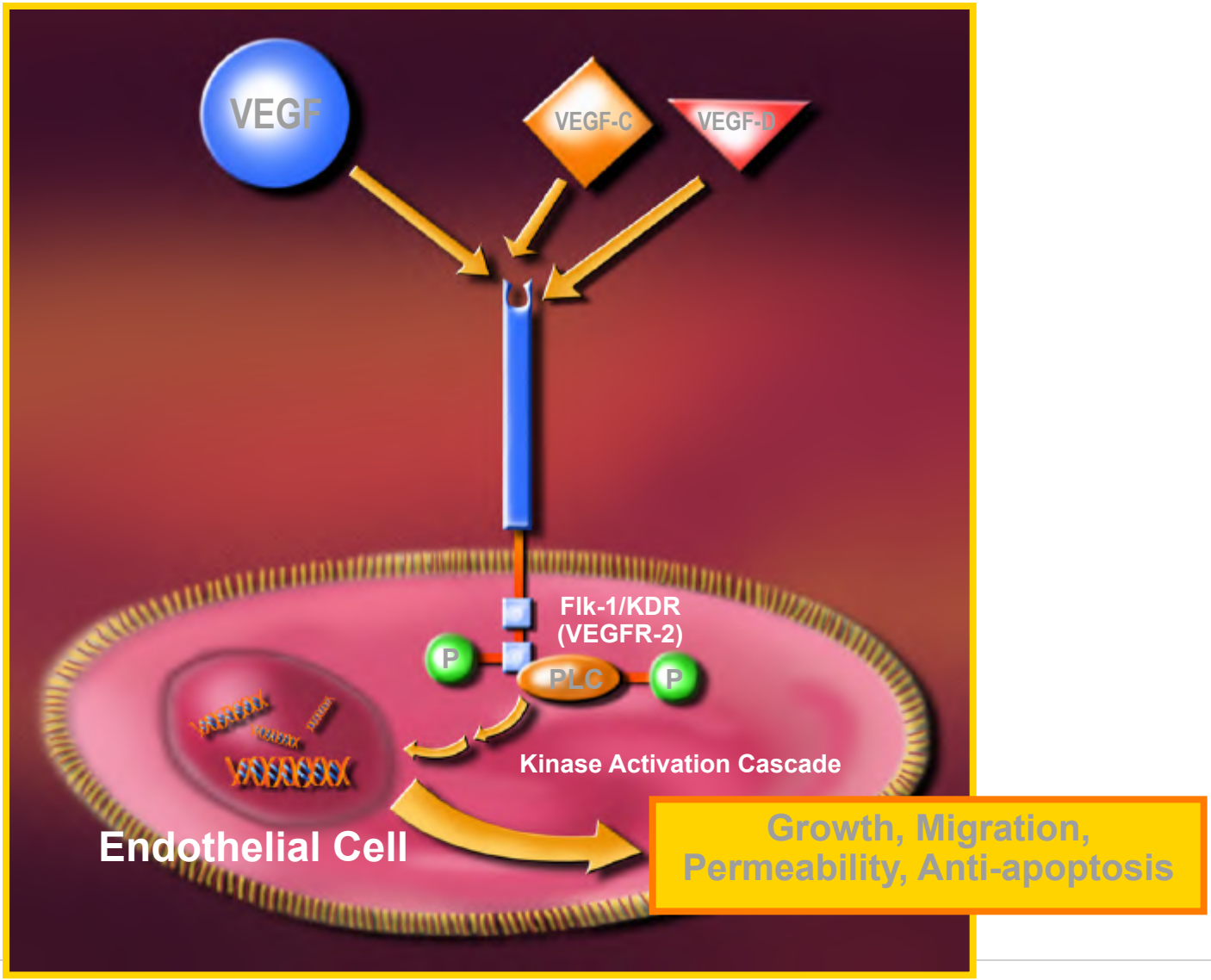
Taking Advantage of Hypervascular Features of NETs



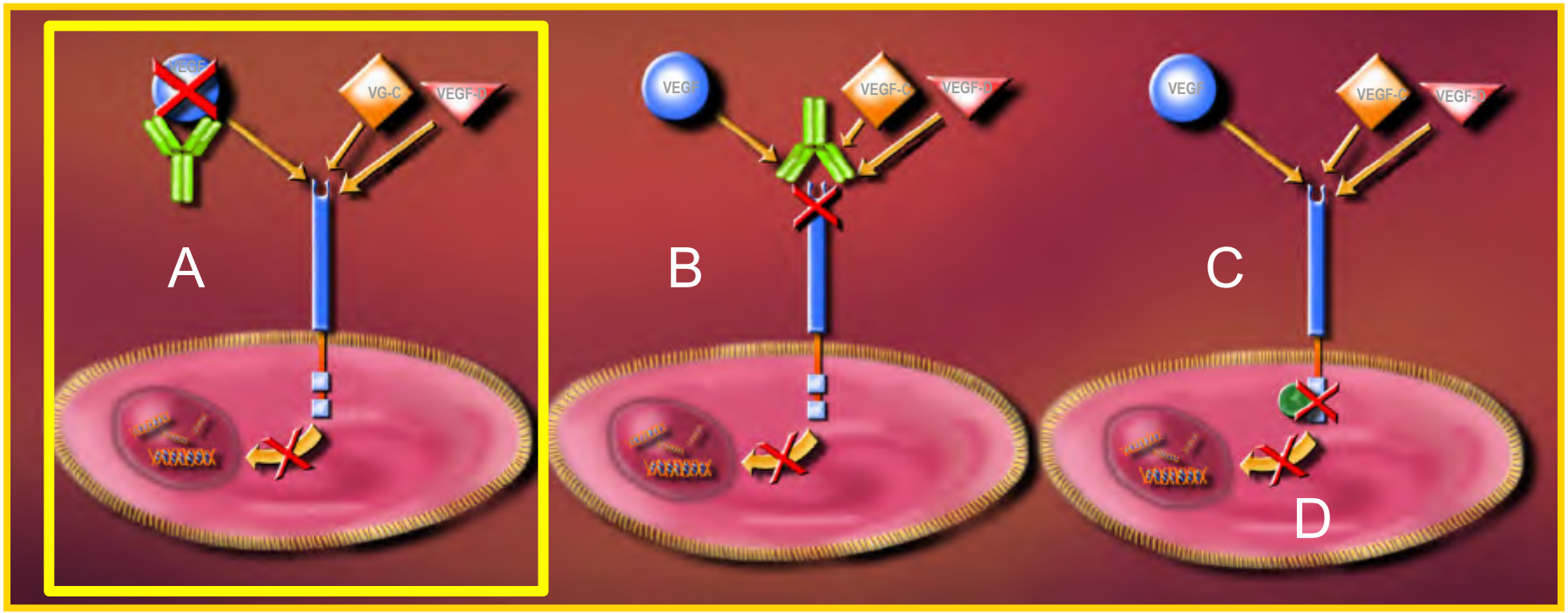




New blood vessels grow due to Receptor Mediated Signaling Pathway

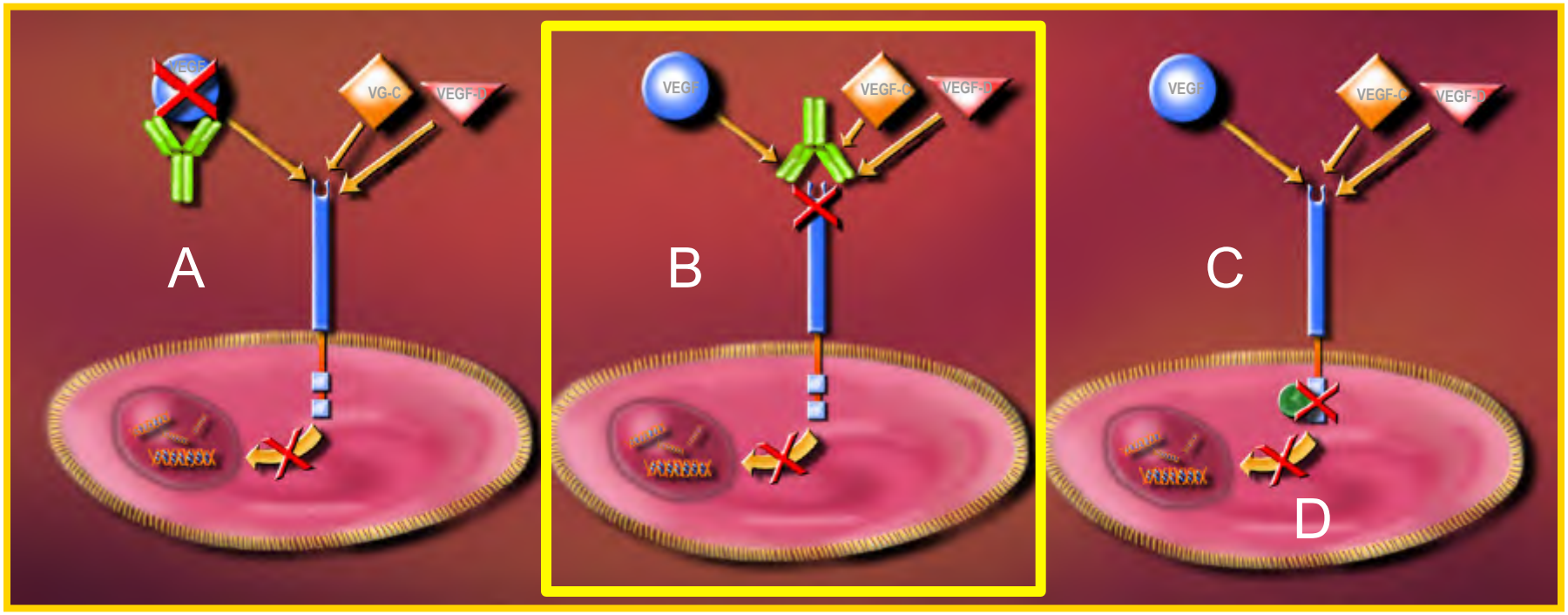


Four Strategies for Blocking Receptor-Ligand Mediated Signaling Pathways



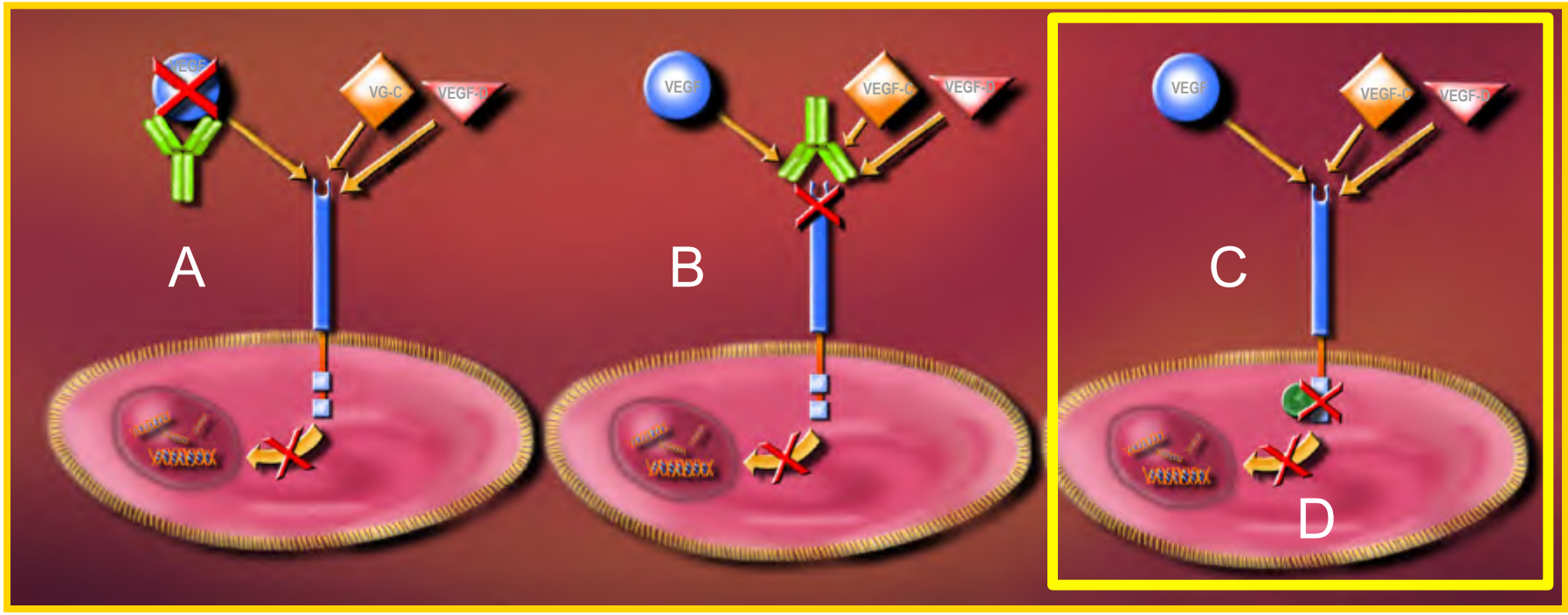
A. Attacking the Ligand (growth factor)
   Bevacizumab and VEGF A
   Aflibercept and VEGF A, C, Placenta GF (PlGF)

Strategies for Blocking Receptor-Ligand Mediated Signaling Pathways



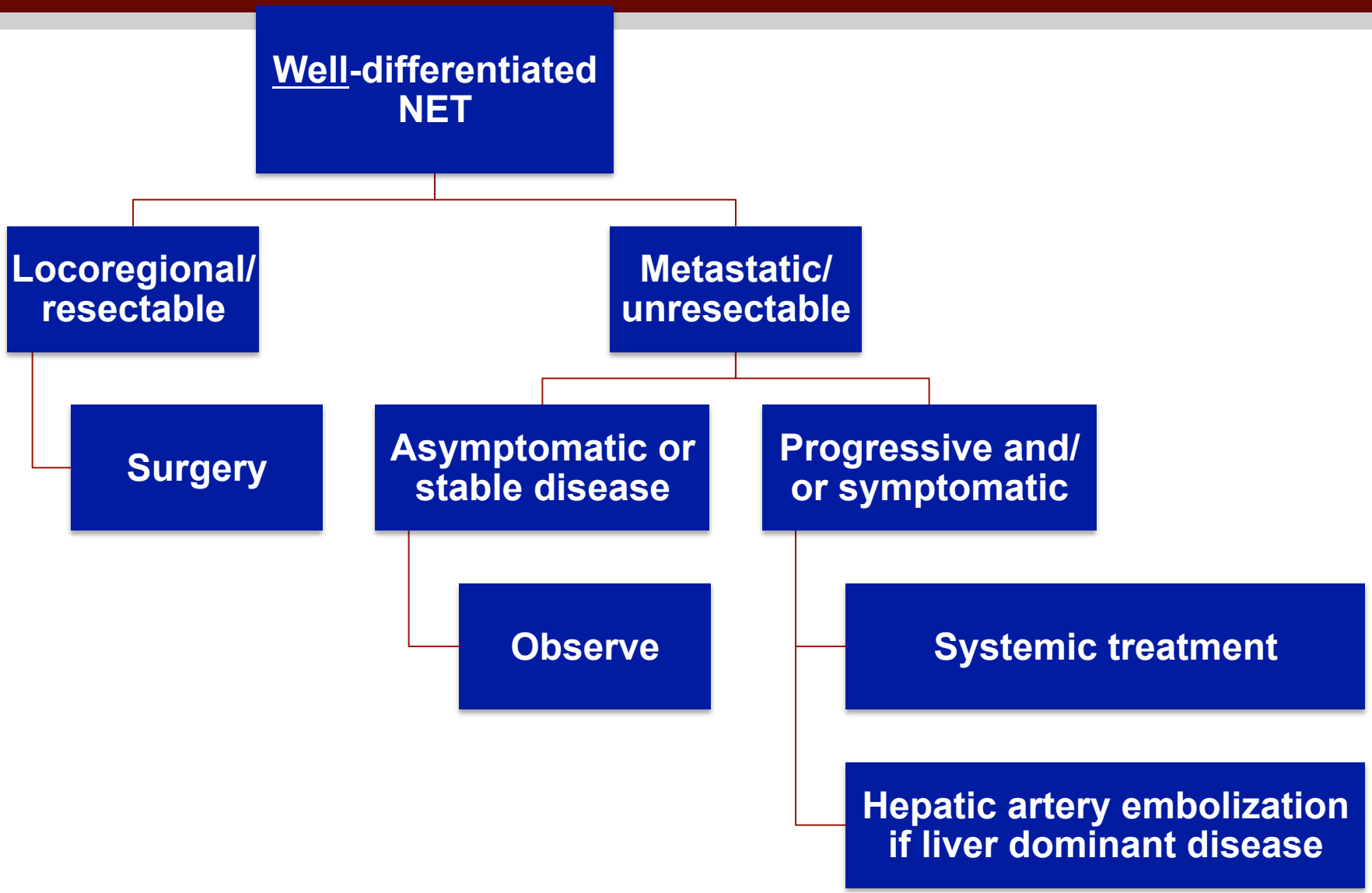
B. Attacking the Extracellular Domain of the Receptor
Ramicurumab (soon to be approved for gastric cancer)

Strategies for Blocking Receptor-Ligand Mediated Signaling Pathways



C. Attacking the Kinase Domain of the Receptor
   Sunitinib approved for pancreatic NETs
   sorafenib, pazopanib, axitinib all approved in kidney cancers

NET Treatment Algorithm



Impediments to Progress

- **Lack of adequate NET tumor models**
  - ***in vitro*** **(cells growing in petri dishes)**
  - ***in vivo*** **(tumors growing in animals)**
    - **mice that develop NETs**
    - **immune impaired mice for growth of human NETs**

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- **Lack of NET patient data base**
  - **EMR's don't talk to each other**
  - **Tissue scarce and often discarded**

Impediments to Progress

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    - immune impaired mice for growth of human NETs
- Lack of NET patient data base
  - EMR's don't talk to each other
  - Tissue scarce and often discarded
- **Lack of patients participating in clinical trials**

Clinical Trials: Converting Discovery to Care

- **Preclinical: Works in mouse tumors…**
  - **Ideally, strong biological rationale**
  - **Effective in cells in culture and in tumors in mice**
  - **Deemed "safe" in larger animals (looking for major side effects)**

Clinical Trials: Converting Discovery to Care

- Preclinical: Works in mouse tumors…
- **Phase I = tests safety (hope for efficacy)**
  - **Often any type of tumor eligible**
  - **Usually 15-25 patients; defines sides effects; "best" dose**

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  - **Limited to specific type of tumor**
  - **Usually 25-50 patients (sometimes randomized)**

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- Phase II = tests efficacy (still testing safety)
  - Limited to specific type of tumor
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- **Phase III = tests efficacy compared with "standard"**
  - **Sometimes placebo "control"**
  - **Essential to assess survival differences**
  - **Usually 200-500 patients**

Design and interpretation of clinical trials

- Eligibility Criteria
  - Pathologic confirmation?
    - -tissue available?
  - Measurable disease?
  - Which NETs?
    - - well vs poorly differentiated?
    - - site of origin?
  - Growing? (or stable)
  - Functioning? (or not)
  - Prior treatment? (or not)
- Measures of Success
  - Response Rate
    - - complete or partial
    - - stable disease
    - - progressive disease
  - Delay in growth of tumor
    - -time until tumor starts to grow
    - -"progression free survival"
  - Overall Survival
  - Quality of life

Addressing Lack of NET Data Base: NET Registry

- A NET Registry will allow researchers to identify connections between the molecular characteristics of tissue samples and the patient data associated with individual disease progression, and to test and validate correlation hypotheses.

NET Database Eligibility

- Possible participants must meet three criteria to be eligible for the Registry:

  Current or past diagnosis of NET

  18 years of age or older

  Adequate English proficiency to complete online consent and questionnaire or the ability to understand and the willingness to sign a written informed consent document in native language.

  Note: You do not need to be a Stanford patient to participate

NET Database: logistics

Patient contacted to schedule meeting with research assistant prior to regular clinic visit


STANFORD UNIVERSITY – RESEARCH CONSENT FORM

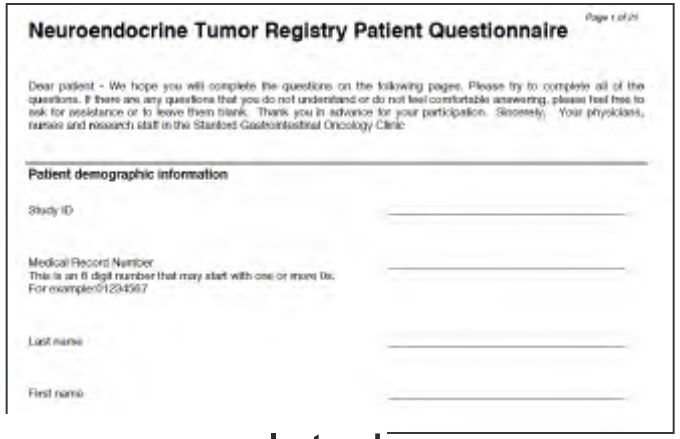
Are you participating in any other research studies? _____ yes _____ no

INTRODUCTION TO RESEARCH STUDIES

A research study is designed to answer specific questions, sometimes about a

Consent form reviewed and signed


Blood drawn


Neuroendocrine Tumor Registry Patient Questionnaire

Dear patient - We hope you will complete the questions on the following pages. Please try to complete all of the questions. If there are any questions that you do not understand or do not feel comfortable answering, please feel free to ask for assistance or to leave them blank. Thank you in advance for your participation. Sincerely, Your physicians, nurses and research staff in the Stanford Gastrointestinal Oncology Clinic

Patient demographic information

Study ID

Medical Record Number

Last name

First name

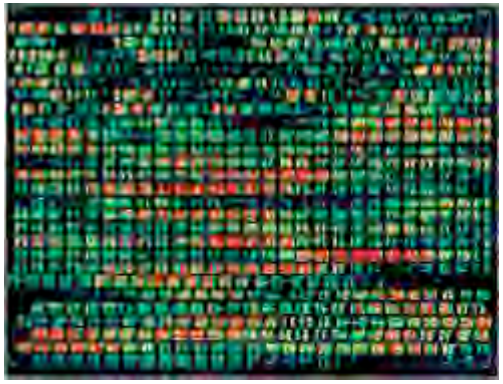
Survey completed

Timeline

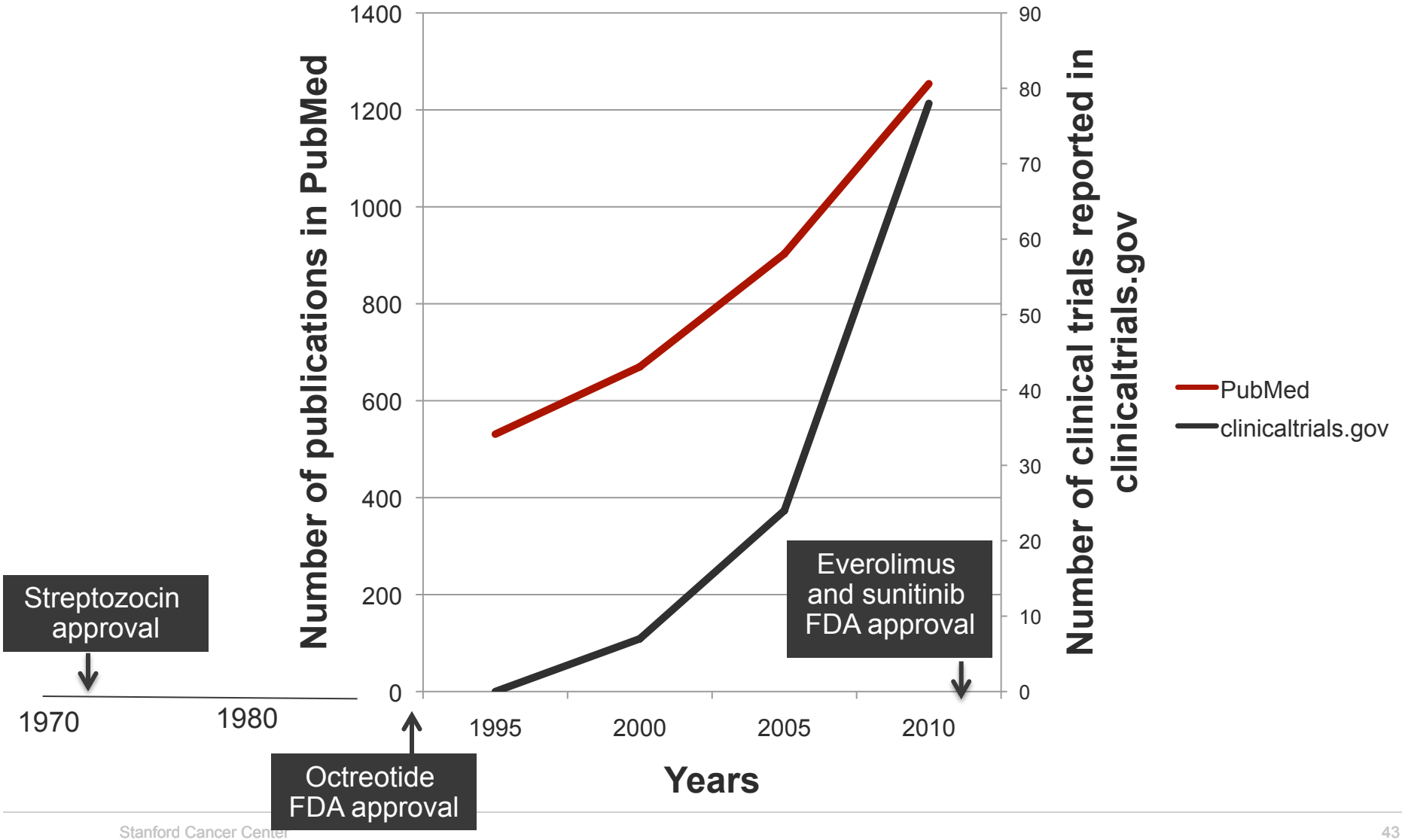
- September 2009: Institutions granted funds from Caring for Carcinoid Foundation
- Sept 2009-Sept 2010: Database development and optimization of data collection
- July 2011: First data export and analysis

Future directions

- The NET Registry will connect the tumor tissue bank, databases containing clinical and epidemiologic data, clinical outcome data, and archived blood specimens.
- Will enable the rapid examination of future hypotheses and allow studies using tissue and clinical data
- The NET Registry is a tool that will lead to improved understanding of neuroendocrine tumor prevention, pathogenesis, and treatment.



Explosive growth of NET research



Take home points

- There is a renaissance of research in the field of NETs
- There are numerous active and developing clinical trials
- Thank you to all clinical trial participants! Participation in clinical trials is essential to advance the field