Update in the Diagnosis & Management of Neuroendocrine Cancer

By
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Professor of Medicine
University of Iowa

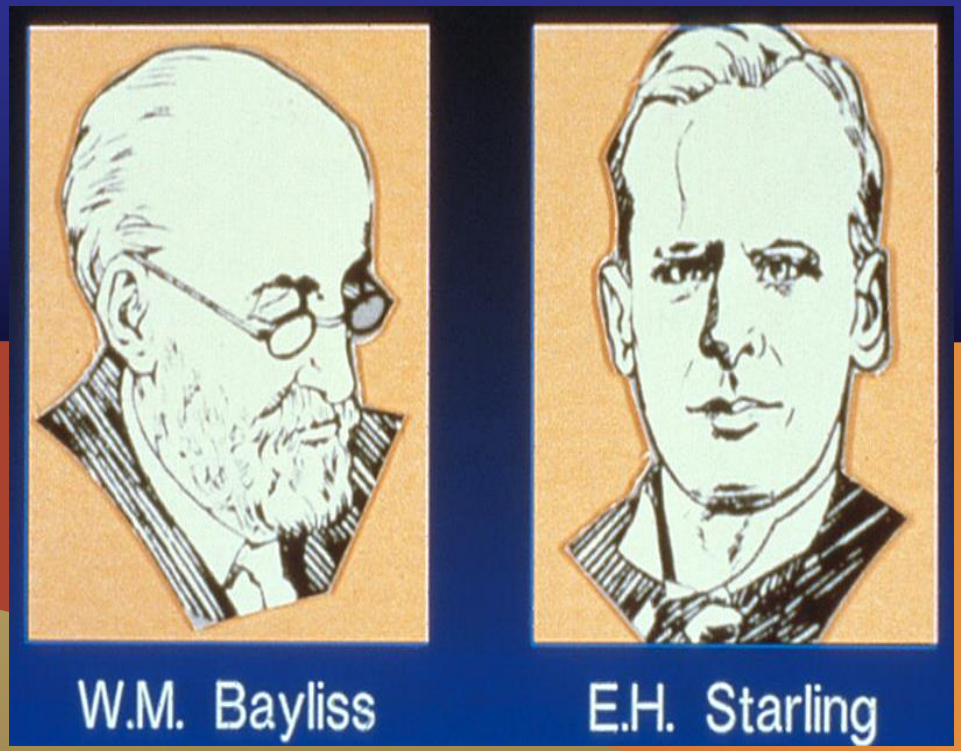
Presented at:

NJCCN Conference

Edison, New Jersey
October 3, 2015

UNIVERSITY OF IOWA HEALTH CARE

Secretin
1902



Evolution of Neuroendocrine Medical Therapy

Teresa Ruggle
Dawn Wray

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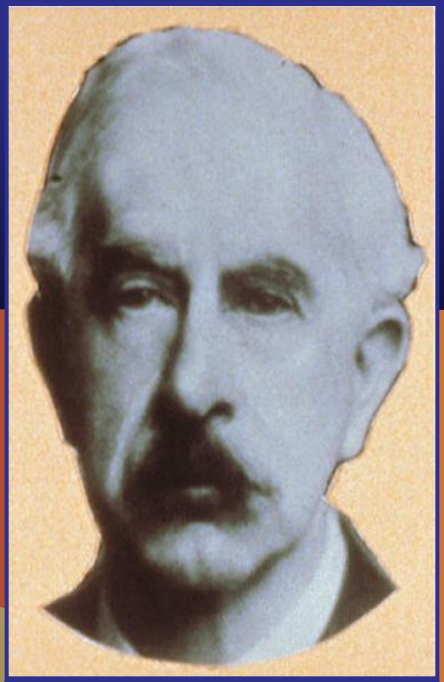
1902

Gastrin
1905



J.S. Edkins

Evolution of Neuroendocrine Medical Therapy

Teresa Ruggle
Dawn Wray

Secretin
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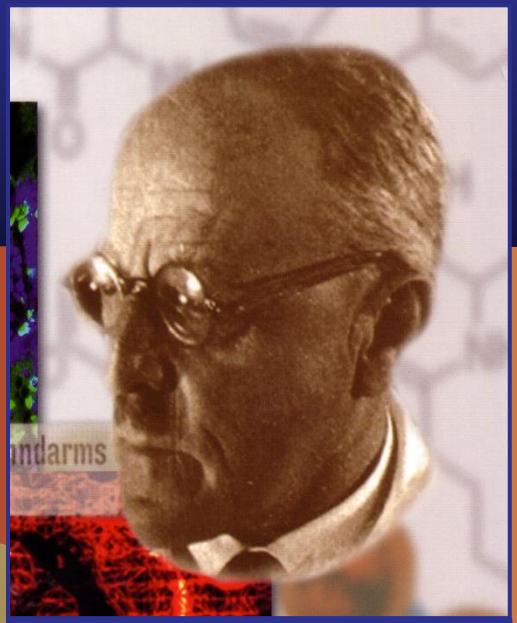
Gastrin
1905

“Karzinoide”
1907



Siegfried
Oberndorfer

Evolution of Neuroendocrine Medical Therapy

Teresa Ruggle
Dawn Wray

I-131 Therapy
1930

Secretin
1902

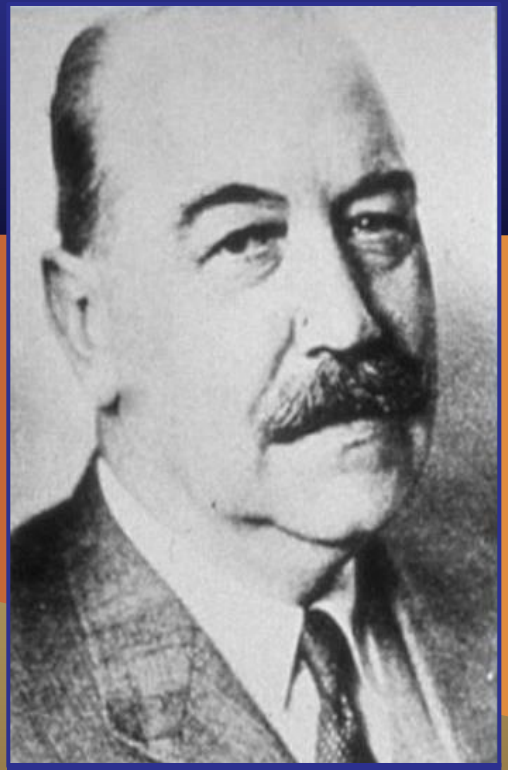
Insulin
1921

Gastrin
1905

CCK
1925

"Karzinoide"
1907

Endocrine Cell
(Helle Zellen)
1938



F. Feyrter

Evolution of Neuroendocrine Medical Therapy

Teresa Ruggle
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Zollinger-Ellison Syndrome 1955

I-131 Therapy 1930

Secretin 1902

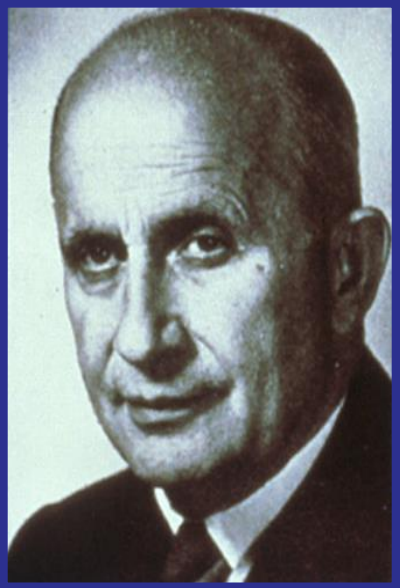
Insulin 1921

Gastrin 1905

CCK 1925

"Karzinoide" 1907

Endocrine Cell (Helle Zellen) 1938



R.M. Zollinger

E.H. Ellison

Gastrinoma

Evolution of Neuroendocrine Medical Therapy

Teresa Ruggle
Dawn Wray

Secretin 1902

Insulin 1921

I-131 Therapy 1930

Zollinger-Ellison Syndrome 1955

Gastrin Purified 1961

GIP 1971

Somatostatin 1973

Octreotide 1980

Gastr
190

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Evolution of Neuroendocrine Medical Therapy

Teresa Ruggle
Dawn Wray

Zollinger-Ellison

GIP

Gallium 68
RPR-PET
2000

I-131 Therapy
1930

Secretin
1902

Insulin
1921

R Guided
herapy
1994

Gastrin
1905

CCK
1925

THERANOSTICS
(R.P. Baum)
2011

"Karzinoide"
1907

M

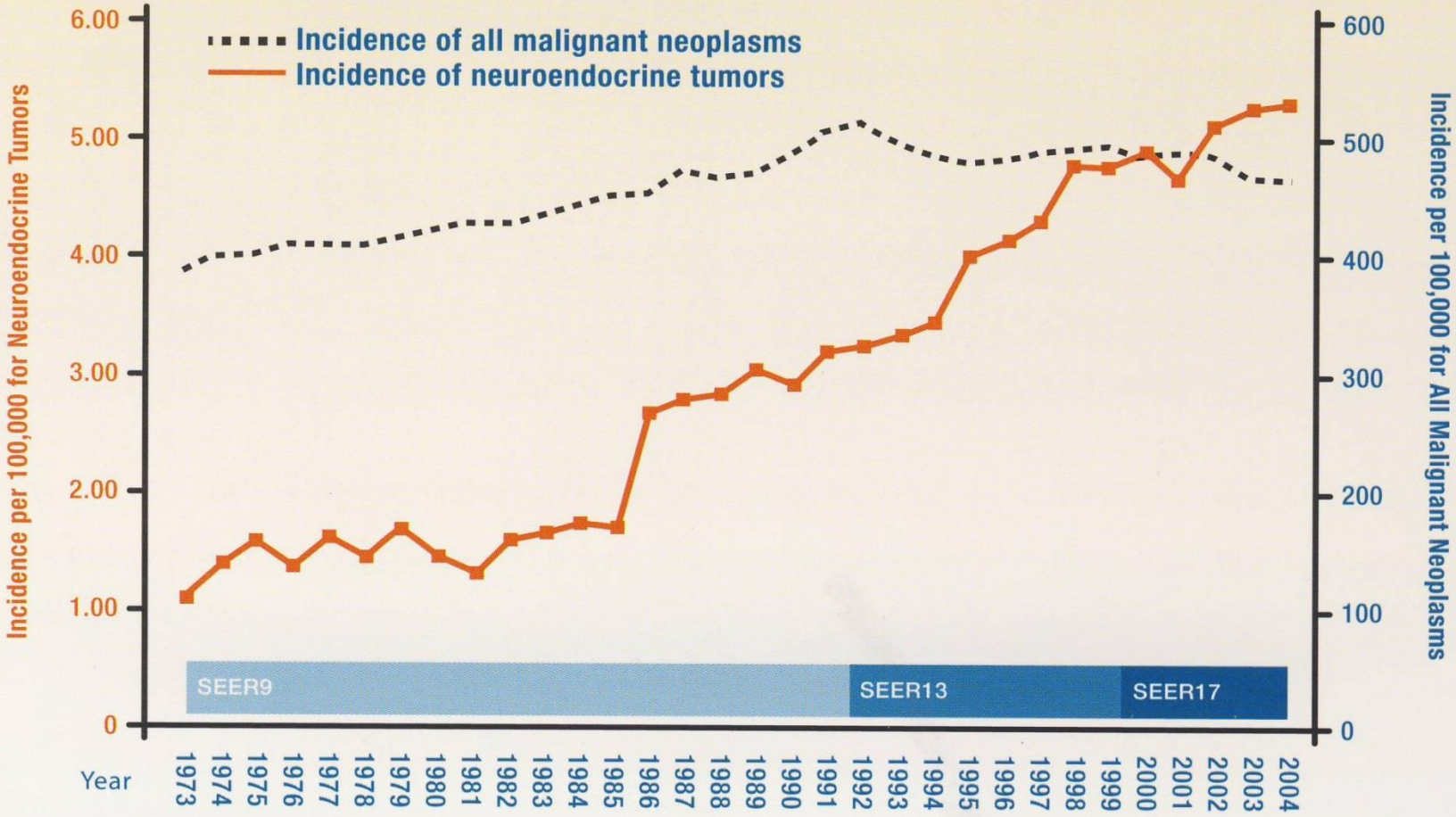
Endocrin
(Helle Z
193

RPR Guided
Surgery
1991

Evolution of Neuroendocrine Medical Therapy

Teresa Ruggle
Dawn Wray

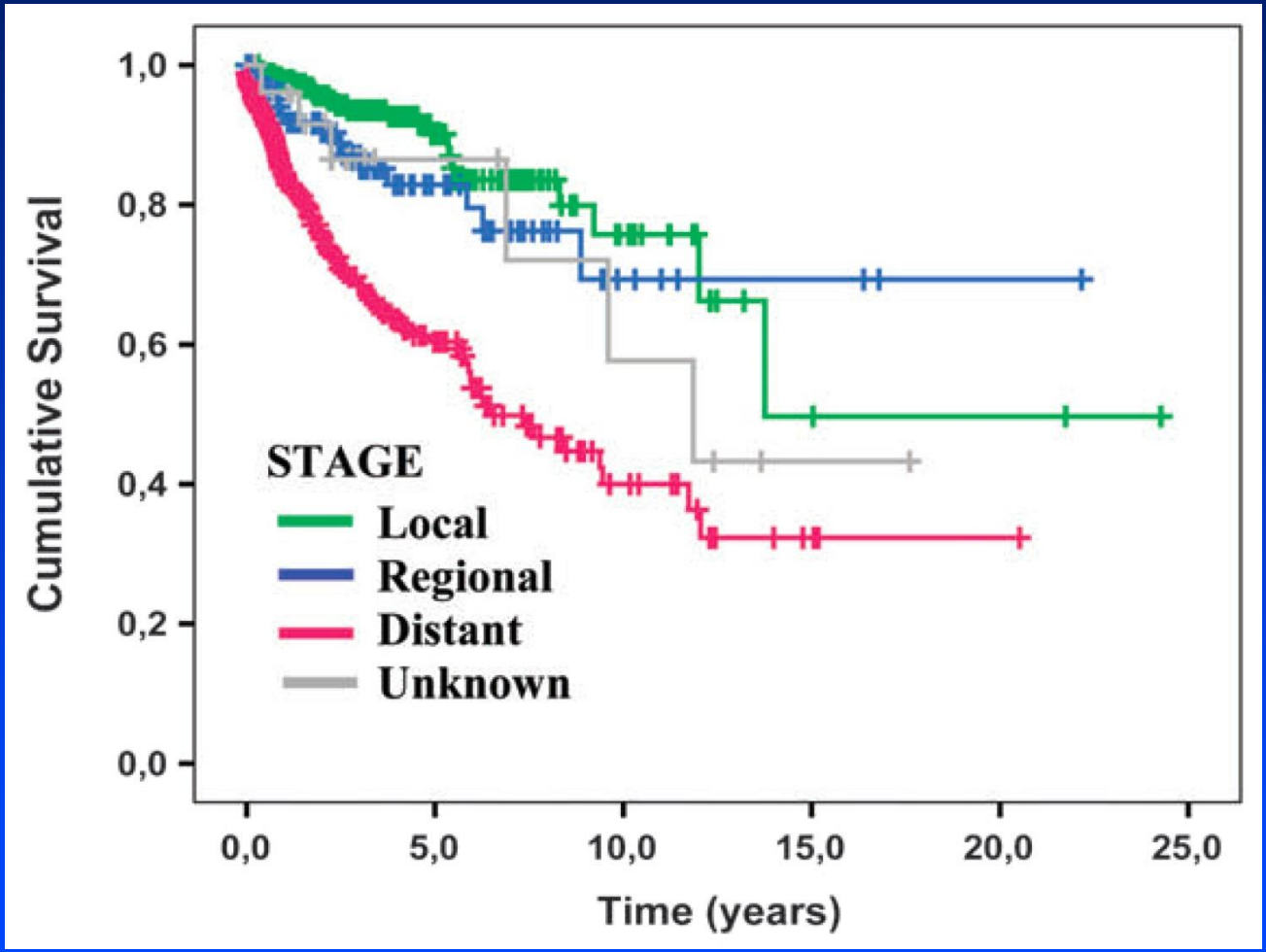
NET Incidence Increasing Faster Than Other Neoplasms[3]



Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

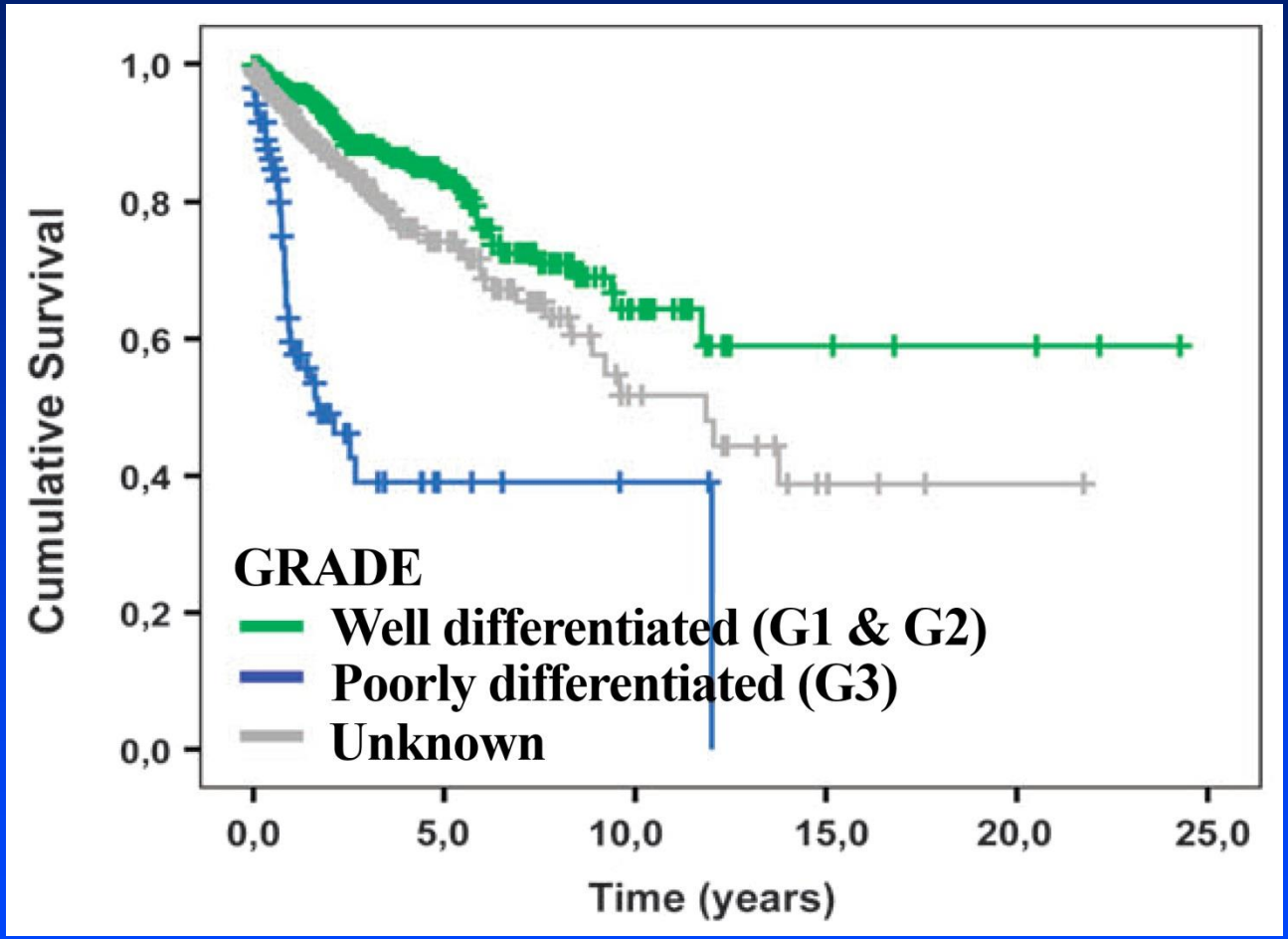
Adapted with permission from Yao JC et al. *J Clin Oncol*. 2008;26(18):3065.

BY STAGE



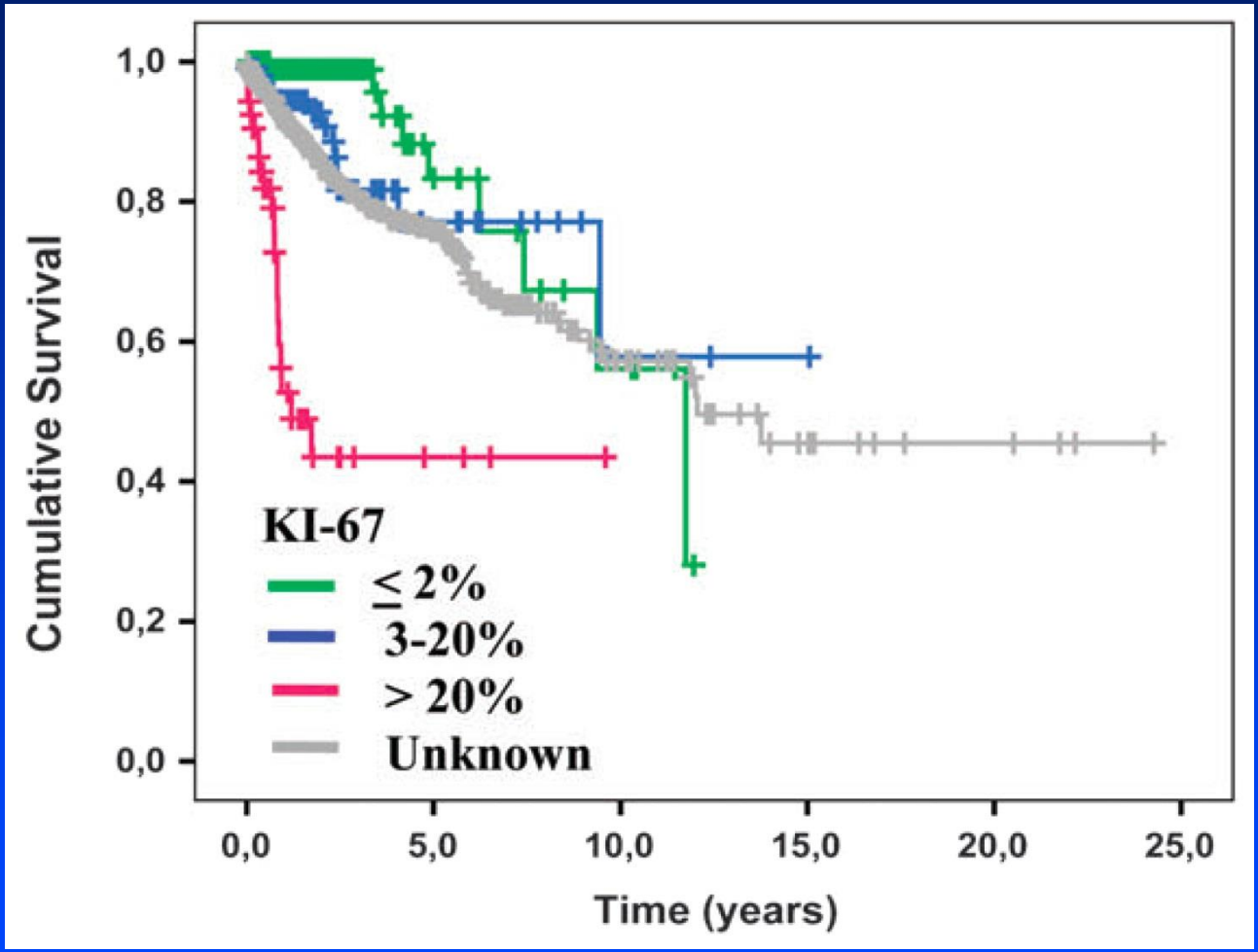
Adapted from: Garcia-Carbonero et al. Ann. Oncol. 2010; 21:1794

BY GRADE



Adapted from: Garcia-Carbonero et al. Ann. Oncol. 2010; 21:1794

BY KI-67

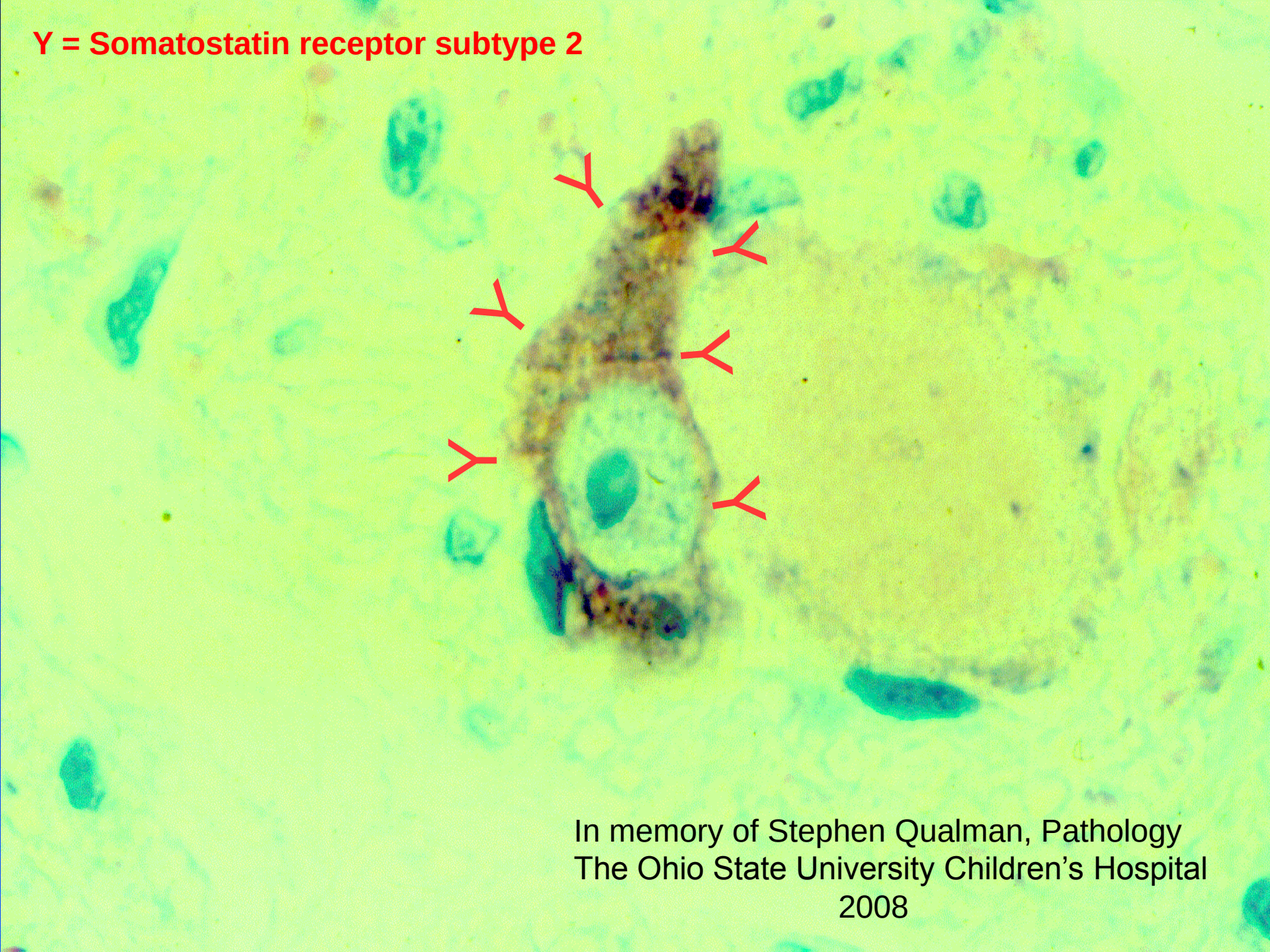


Adapted from: Garcia-Carbonero et al. Ann. Oncol. 2010; 21:1794

Neuroendocrine Cells
(Specific Characteristics)

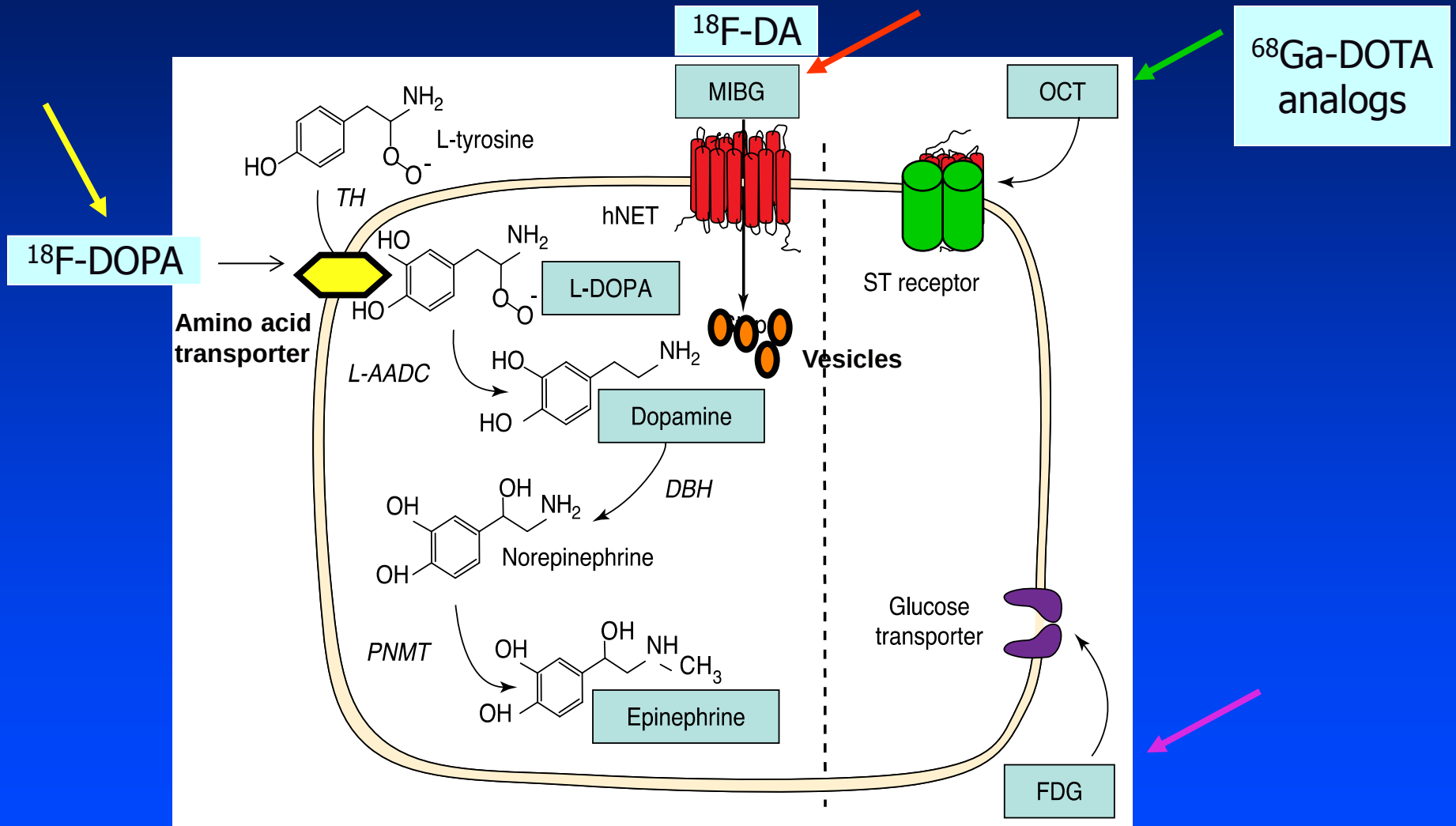
- Take up hormone precursors (Trytophan)
- Synthesize, store, release amines and neuropeptides (serotonin, insulin)
- Express specific receptors and transporters (sst2A receptors, norepinephrine transporter)
- Express specific genes – neuropeptides that can predict tumor activity and behavior (pancreastatin, Neurokinin A)
- CAN BE TUMOROGENIC

Modified from Karel Pacak, with permission



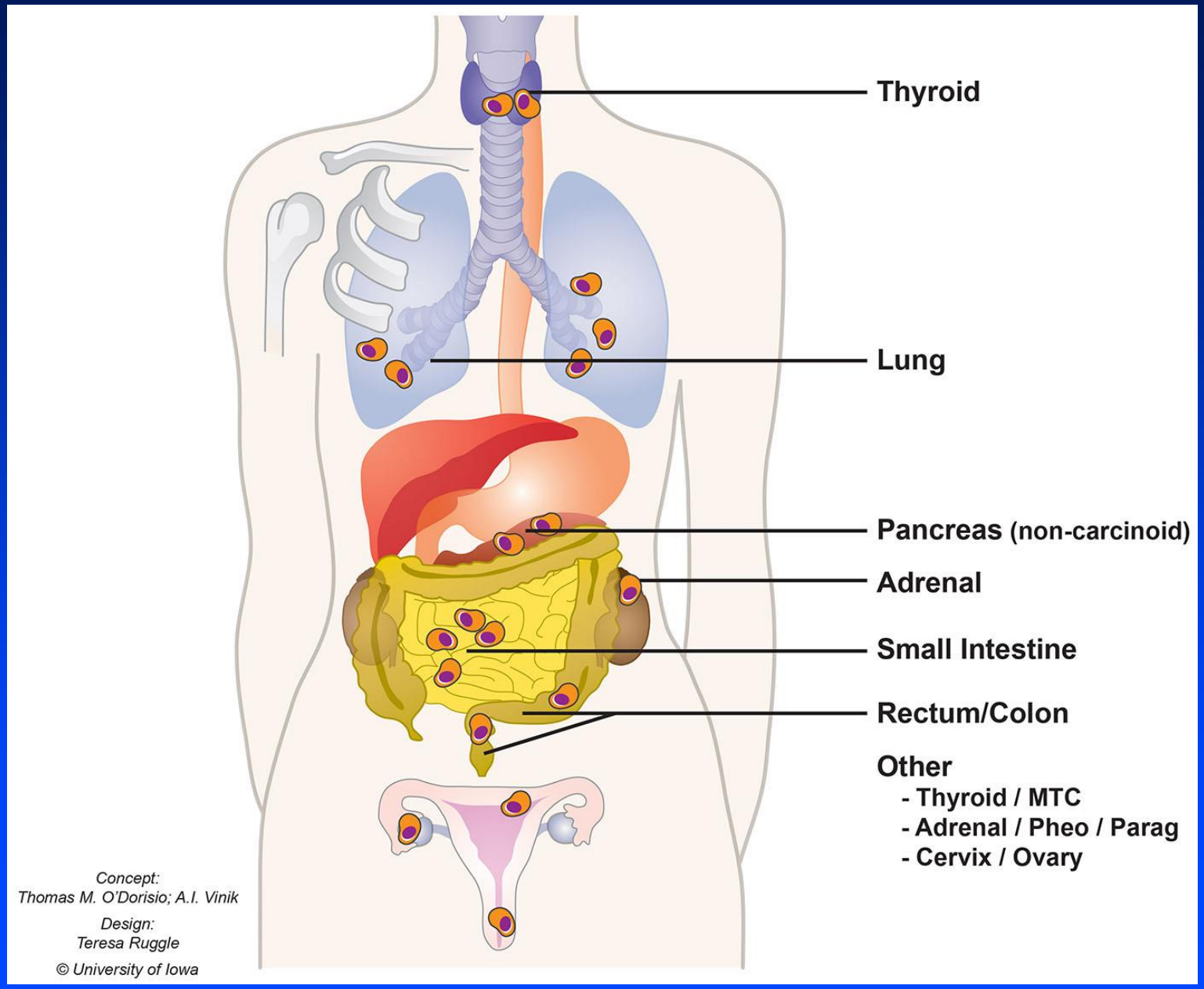
In memory of Stephen Qualman, Pathology
The Ohio State University Children's Hospital
2008

NET cell-specific characteristics currently used for their localization

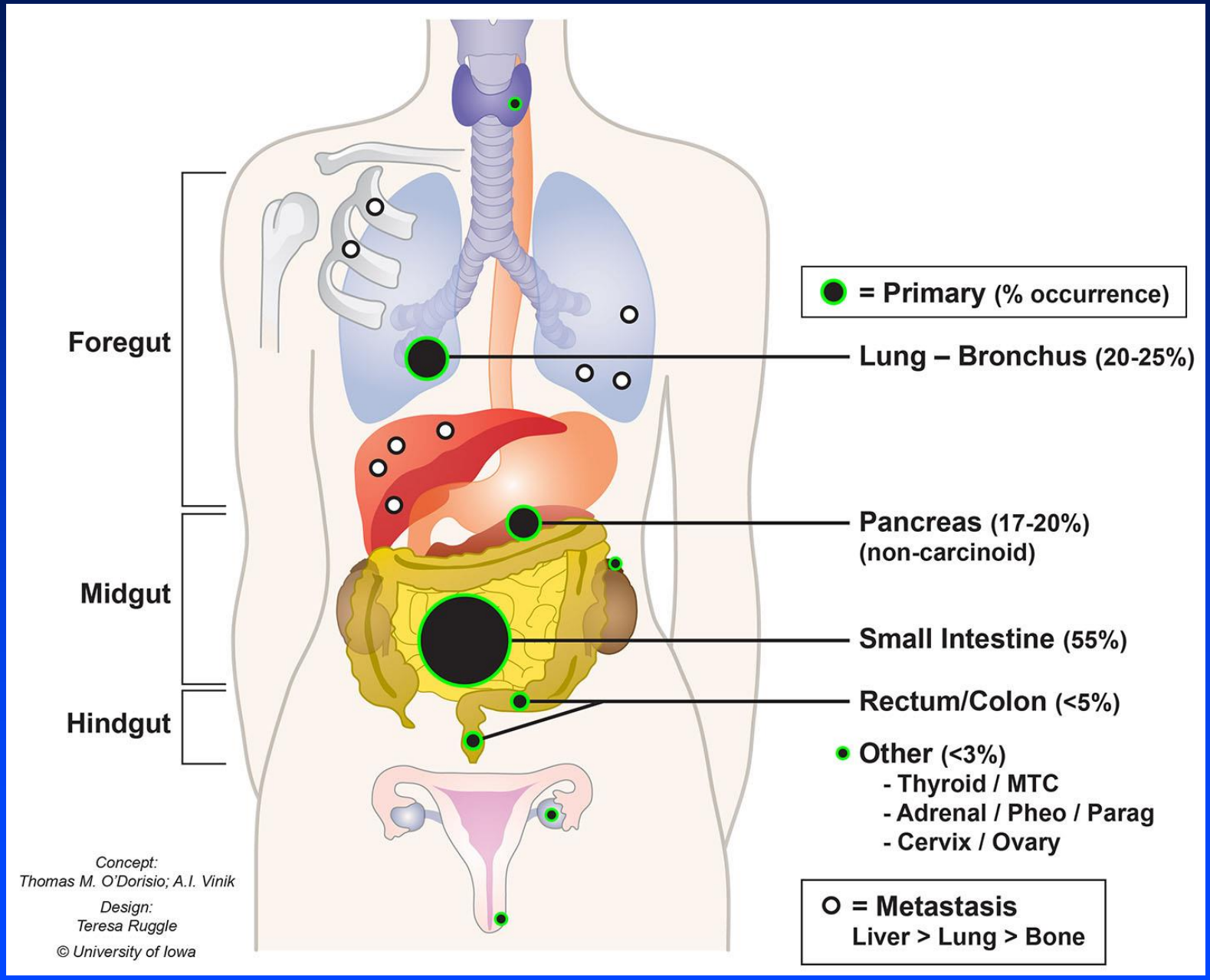


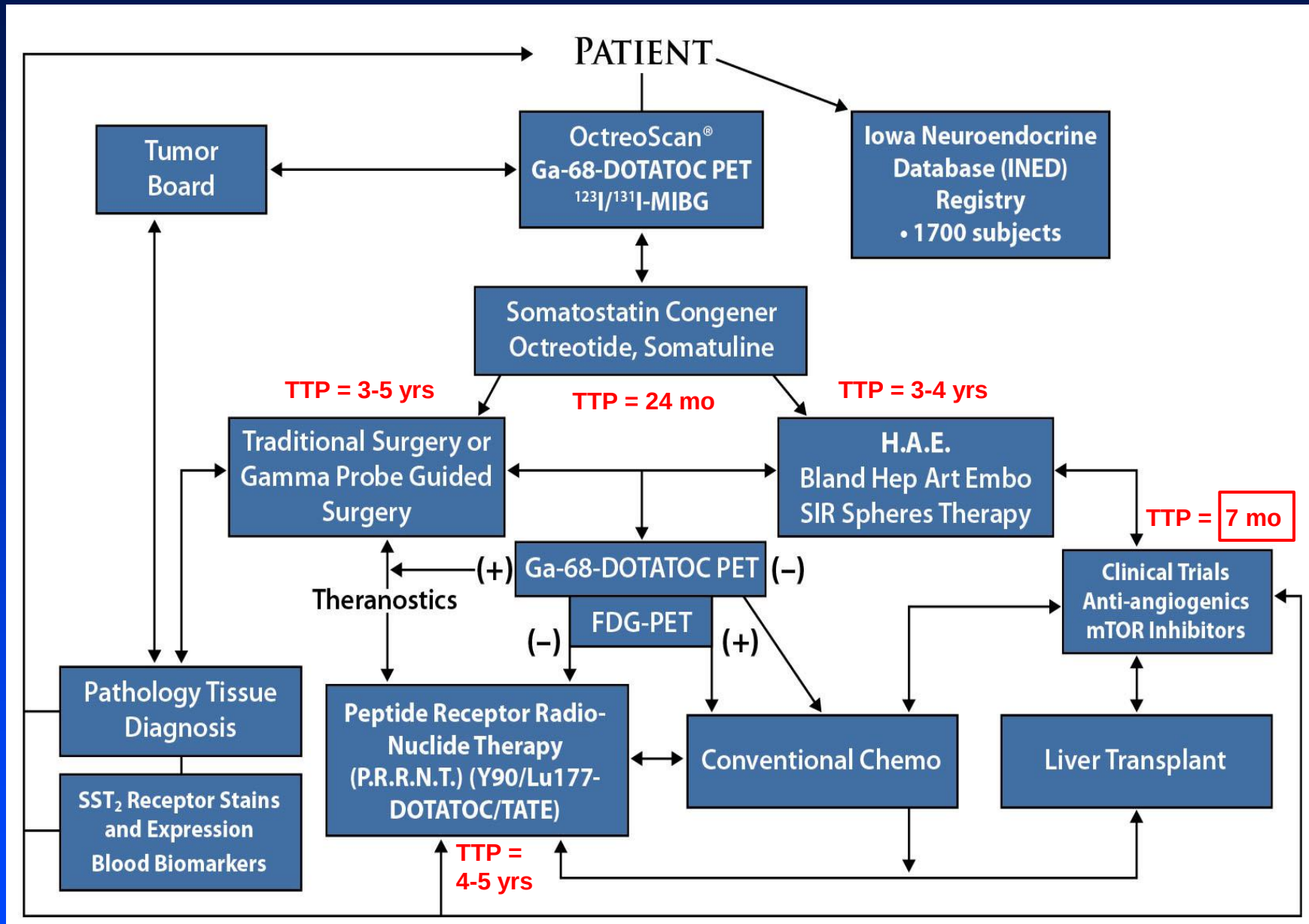
Ilias et al. Trends Endocrinol. Metab. 2005; 16:66
Adapted from co-author, Karel Pacak, with permission

Diffuse (Neuro)Endocrine System (DES)



Diffuse (Neuro)Endocrine System (DES)




PATIENT
Tumor Board
OctreoScan®
Ga-68-DOTATOC PET
123I/131I-MIBG
Iowa Neuroendocrine Database (INED) Registry
• 1700 subjects
Somatostatin Congener
Octreotide, Somatuline
TTP = 3-5 yrs
TTP = 24 mo
TTP = 3-4 yrs
Traditional Surgery or Gamma Probe Guided Surgery
H.A.E.
Bland Hep Art Embo
SIR Spheres Therapy
TTP = 7 mo
(+)
Ga-68-DOTATOC PET
(–)
Theranostics
FDG-PET
(–)
(+)
Clinical Trials
Anti-angiogenics
mTOR Inhibitors
Pathology Tissue Diagnosis
Peptide Receptor Radio-Nuclide Therapy (P.R.R.N.T.) (Y90/Lu177-DOTATOC/TATE)
Conventional Chemo
Liver Transplant
SST2 Receptor Stains and Expression
Blood Biomarkers
TTP = 4-5 yrs
TTP = Time to Progression
© University of Iowa

Detection of the Ki67 Antigen in Fixed and Wax-Embedded Sections with the Monoclonal Antibody MIBI

D. McCormick, H. Chong, C. Hobbs, et al.

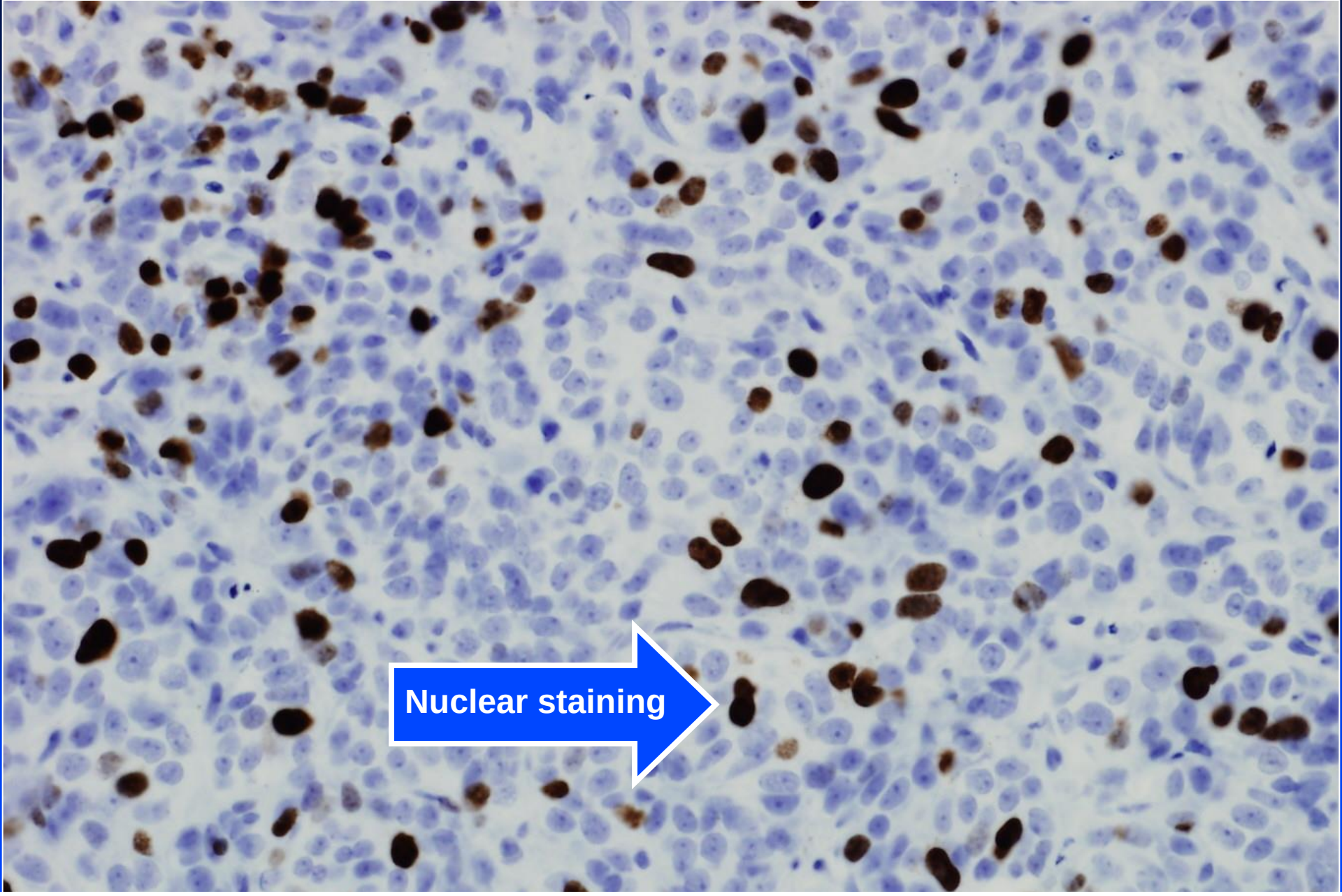
Histopathology 1993; 22:355-360

Demonstrated that MIBI (anti-Ki67 antibody) is an excellent “robust” marker of cell proliferation easily applicable to archival material.

Ki67

- An antibody that recognizes an antigen Mr, 345 and 395 kDa
  - Encoded by single gene (chromosome 10)
  - Expression tightly associated with cell cycle
  - Excellent indicator of tumor proliferation
- MIBI is a monoclonal antibody raised against a ki67 c DNA fragment and perpetuated in E. Coli
- Although, another antibody, it recognizes a different epitope of the ki-67 fragment than MIBI

Histopathology 1993; 22: 355-360.



MIB1 (Ki-67) – a marker of increased proliferation

Enrico Solcia

Professor of Pathology
University of Pavia, Pavia, Italy
2008

General WHO Neuroendocrine Tumor Categories

*1. Well-differentiated endocrine tumor (+) chromogranin A, synatophysin, earlier term, “carcinoid” (ki67 < 2%)

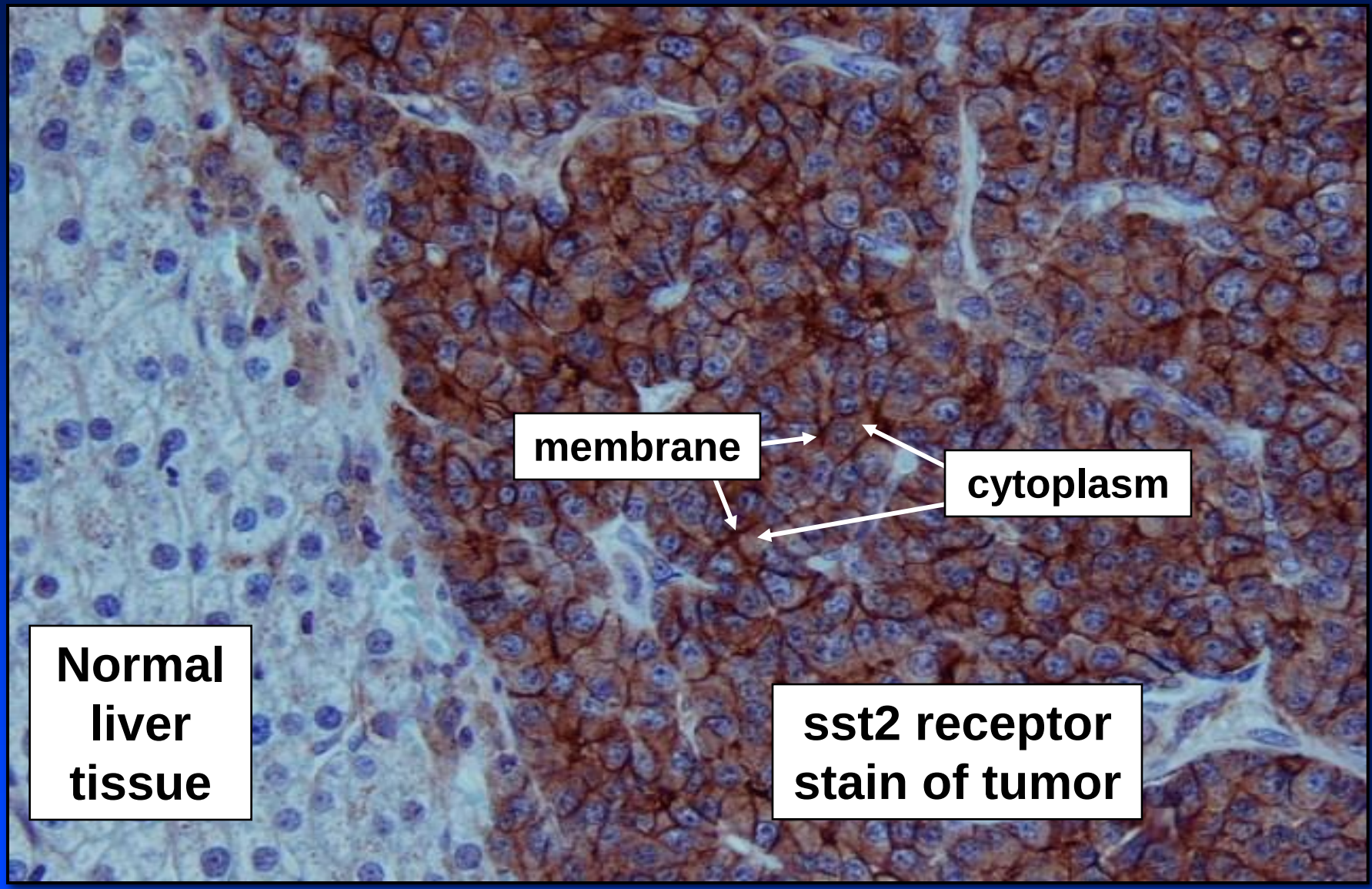
*2. Well-differentiated endocrine carcinoma
earlier term “atypical carcinoid” (ki67 2-20%)

*3. Poorly-differentiated endocrine (small cell) carcinoma
scant CgA
high mitotic index (ki67 > 20%)

4. Mixed exocrine – endocrine tumor

5. Tumor-like lesions

E. Solcia, 2000, WHO Classification



Courtesy of B. DeYoung, M.D., MS O'Dorisio, MD, TM O'Dorisio, MD

Somatostatin Receptor Subtype 2A Immunohistochemistry Using a New Monoclonal Antibody Selects Tumors Suitable for In Vivo Somatostatin Receptor Targeting

M. Korner, B. Waser, A. Schonbrunn, A. Perren

J – C Reubi

AM J Surg Pathol 2012; 36(2): 242-252
(doi:10. 1097/PAS. 060 13 e 31823 do 7f3)

Methods

- A highly specific monoclonal antibody, UMB-1 was developed per an immunohistochemistry (IHC)

  Protocol for 89 neuroendocrine tumors
- All tumors' somatostatin receptor binding site levels were quantified with in vitro
- ^{125}[-Tyr^{3}]-octreotide autoradiograph

Am J Surg Pathol
2012;36(2):242

Results

SSt2A 1HC	Sensitivity	Specificity	(+) Pred Val	(-) Pred Val
>10% tumor cell	86%	95%	95%	84%
Stain Intensity 2^+ or 3^+	96%	80%	86%	94%
Any Tumor Cell	98%	67%	79%	96%

Am J Pathol 2012; 36(2):242

Results

- **The presence of more than 10% positive tumor cells (stained positive for sst2A Receptor Antibody) correctly predicted high sst2A receptor levels in 95% of the tumors studied.**

- **“For the first time, a reliable recommendation concerning eligibility of an individual patient for in vivo somatostatin receptor targeting based on sst2A receptor immunohistochemistry.”**

Am. J Surg Path
2012;36(2):242-252

Definition of Symptom

- Latin – Symptoma
- Greek - *συμπίπτω* – "I FALL"

"Subjective evidence of disease or physical disturbance observed by the PATIENT"

(Webster's Third New International Dictionary, 1993 Wikipedia)

Problems with Neuroendocrine Tumor Therapeutic Intervention(s)

- Decisions made primarily based on the "Gold Standard" CT, MR, Ultrasound demonstration of disease progression
- Both "symptomatic" and "asymptomatic" changes are subjective and clinical signs, like art, are often in the eye of the beholder
- Tumor-secreting amines and neuropeptides may be episodic initially & sustained later with tumor progression
- In U.S., calibrations between neuropeptide plasma markers are sorely lacking between commercial labs

Functioning Neuroendocrine Tumors

Basic Principles:

- **Syndromes and symptoms (e.g., hypoglycemia) are due to sudden or sustained elevations of circulating amines (e.g. serotonin, catecholamine, or neuropeptides (e.g., insulin, VIP).**

- **Documentation of elevated amines and neuropeptides should be done whenever possible.**

Neuroendocrine Tumors Symptoms and Biomarkers

Carcinoid, small intestine (Mid-Gut)	Diarrhea, flushing, sweats, fatigue, pain, obstruction, nocturnal perspiration	[Serotonin] 5-HIAA (urine or plasma) CgA, pancreastatin, NK A
Carcinoid, Lung (Fore Gut)	Cough, pneumonia	Serotonin (?) Substance P (?) CgA
N/E Pancreas Non-functional (70%)	Pain, nausea, Weight loss, jaundice	CgA and PP
Functional (30%)	Low sugar, ulcers, etc.	Insulin, Gastrin, etc.

Carcinoid Tumors

Small Bowel (mid gut)

- **Serotonin** EDTA (Plasma + ascorbic acid)
  - most sensitive, episodic
  - Collection critical for preservation
  - **Commercially available**
- **5-HIAA** (5-hydroxy-indoleacetic acid, urine) formed by metabolism of serotonin by monoamine oxidase
  - Almost **NEVER** elevated without liver METS ~~(usually 15-20% burden)~~
  - Plasma 5-HIAA correlates (R=0.8) with urine 5-HIAA

Pancreas 2013;42(6):937-4

Serotonin and Carcinoids

- Mid-gut carcinoids are rich in serotonin containing granules and are frequently associated with carcinoid syndrome
- Foregut carcinoids (Stomach, Lungs) have few serotonin granule
- Hind-gut carcinoids have very few serotonin granules
- Pancreatic NETs?

Modified: AC Deacon. Ann Clin Biochem 1994:31;215-232

Chromogranin A (CgA)

- Acidic, water soluble, secretory glycoprotein (ng/ml)
- Stored in matrix of secretory granules of nervous & neuroendocrine cells / tumors
- Cleared by prohormone convertase I (PC-1) to pancreastatin (pg/ml)
- An accurate “marker” of neurocrine tumor burden and metastasis

“Pearls” on Chromogranin A (CgA)

- Try and stay with the same lab (five in US)
- Is very helpful when you know you have a N/E tumor.
- May be elevated when there is no actual N/E tumor
    - Severe hypertension
    - Gastric acid suppression (PPI’s)
    - Check gastrin
    - Renal insufficiency

Purpose

- **To develop a pancreastatin radioimmuno assay (RIA) that is highly sensitive (pg/ml) and specific with negligible cross reactivity with CgA.**

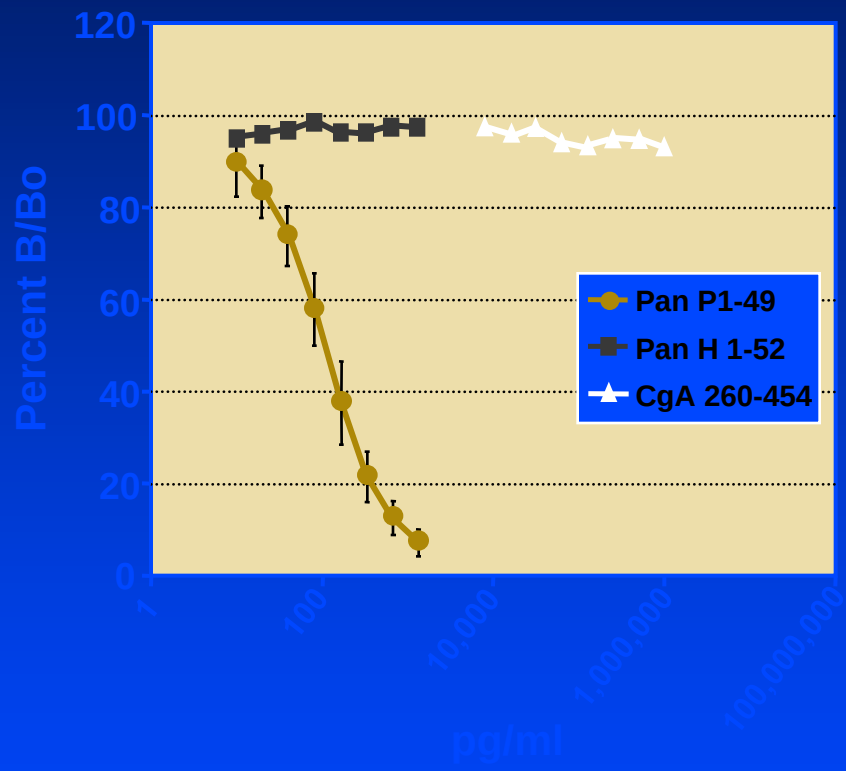
- **To compare with split-sample analysis, The Ohio State - University Reference Lab pancreastatin values with our assay.**

- **To demonstrate the utility of pancreastatin measurements as a sensitive marker of liver tumor activity.**

PANCREAS 39(5):611-616, 2010

Results

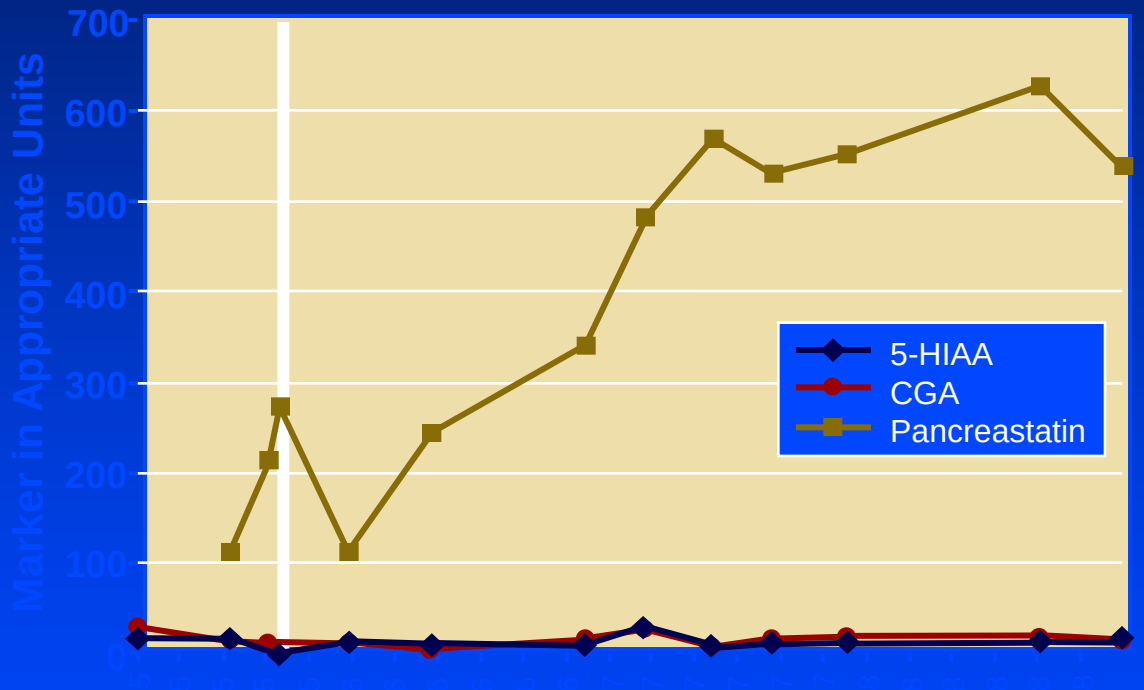
Cross-reaction of Anti P-Pan ISI-56 with human Pan 1-52 and CgA 260-454



	% B/Bo		
pg/ml	PanP 1-49	H 1-52	CgA260-454
10	89.1	95.9	
20	82.9	96.5	
40	73.2	96.6	
80	57.3	98.2	
160	37.5	96.3	
320	21.1	96.2	
640	11.9	97.5	
1280	6.7	96.6	
7800			97.5
15600			96.2
31200			97.1
62500			94.1
125000			93.5
250000			94.7
500000			94.6
1000000			93.1

Results

Sequential Marker Measurement



Neurokinin (NK) A Levels Predict Survival in Patients with Stage IV Well Differentiated Small Bowel Neuroendocrine Neoplasia

Diebold AE, Boudreaux JP, Wang Y-A, Mamikunian P,Mamikunian G, E.A.Woltering

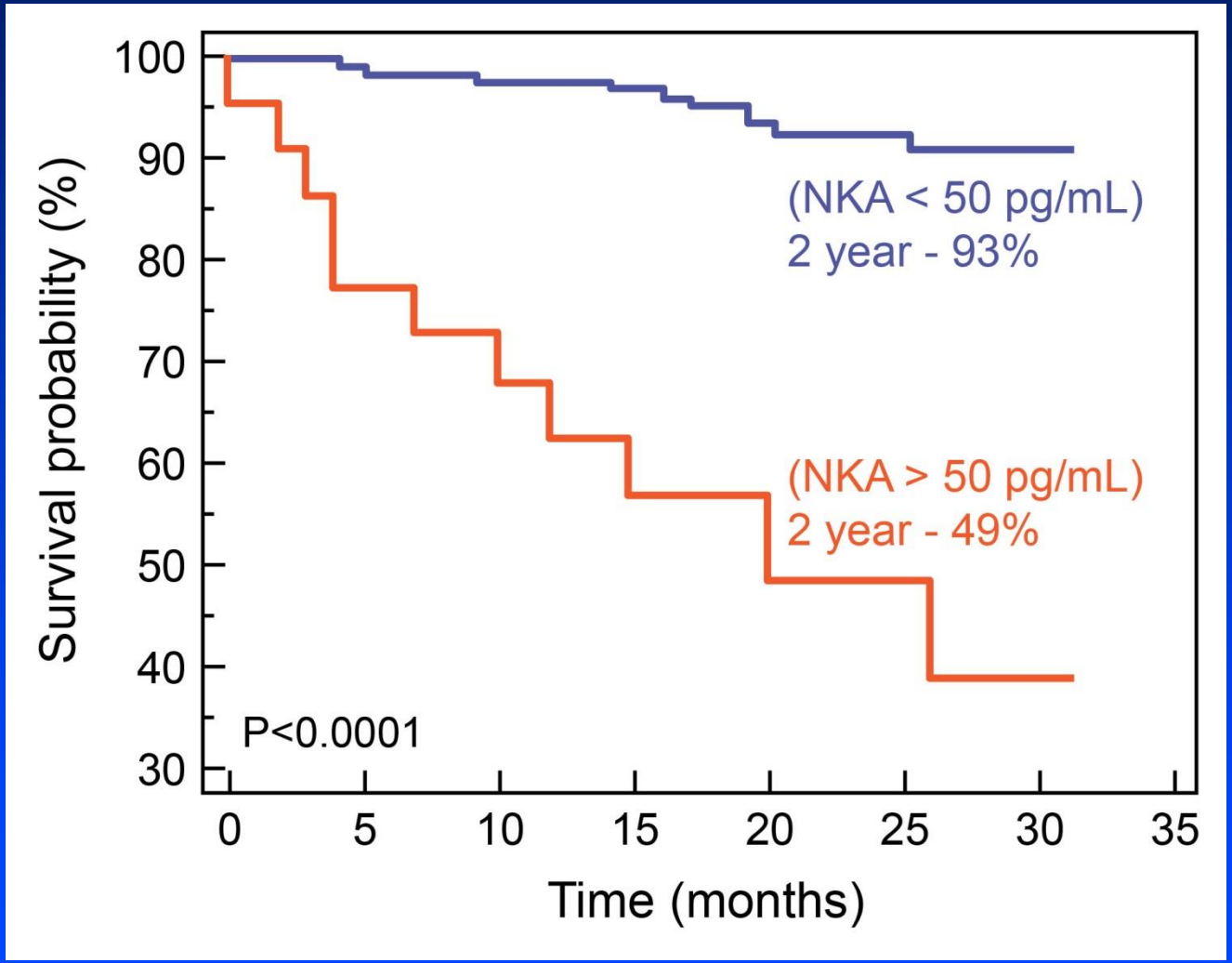
Surgery 2012; 152(6):1172-76

Patients and Methods
(Surgery 2012; 152(6):1172)

- 180 patients: retrospective – prospective
- Group 1: NK A persistently < 50 pg/ml
- Group 2: NK A elevated at least once – now < 50 pg/ml
- Group 3: NK A always > 50 pg/ml
- Median follow-up time: Kaplan-Meier Method

Results

(NKA > 50 pg/mL vs. NKA < 50 pg/mL)



Pancreastatin Predicts Survival in Neuroendocrine Tumors

Sherman SK, Maxwell JE, O'Dorisio MS, O'Dorisio TM, Howe JR

Ann Surg Oncol 2014; 21:29

Patients and Methods
(Ann Surg Oncol 2014; 21:2971-2980)

- 98 small bowel NETS:78 pancreatic NETS
- Event times were estimated by the Kaplan-Meier Method
- Pre and postoperative labs for correlation with outcomes
- A multivariant Cox model adjusted for confounders

Results (1)
(Ann Surg Oncol 2014; 21:2921)

- Preoperative serotonin levels significantly associated with progression free survival (PFS) ($p=0.02$)
- Postoperative reduction of serotonin by 88 ng/ml or more was significantly associated with PFS ($p=0.01$)
- Preoperative CgA and preoperative pancreastatin showed significant correlation with PFS and OS ($p<0.05$)

Results (2)
(Ann Surg Oncol 2014; 21:2921)

- Elevated preoperative PAN associated with shorter median PFS and OS vs normal PAN
- PFS 1.7 yrs vs 6.5 yrs vs median not reached
- 5 yr PFS 14.9% (high prePAN: 59% (normal PAN)
- Normalization of post-op pancreastatin significantly improved PFS and OS (3.9 yrs and 100%)
- Elevated post-op pancreastatin, 5 yr PFS dropped to 8.6% and OS decreased to 6.5 yrs

Conclusion

(Ann Surg Oncol 2014; 21:2921)

- Higher pancreastatin levels are significantly associated with worse PFS and OS in SBNETS and PNETS
- Independent of age, primary tumor site, and nodal or metastatic disease

“Pancreastatin provides valuable prognostic information and identifies surgical patients at high risk of recurrence who could benefit most from novel therapies”

Ann Surg Oncol 2014; 21:2921-2980

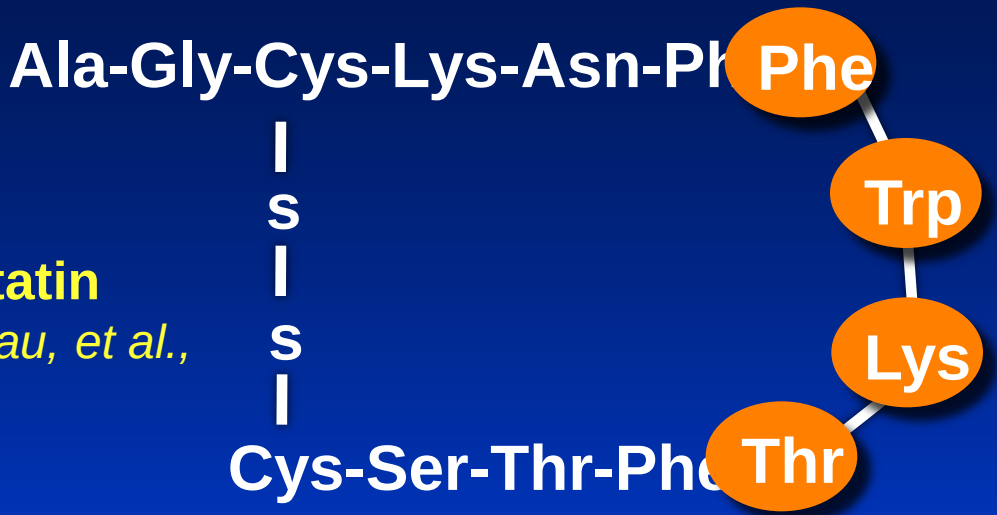
Thoughts Regarding Whole Blood Serotonin

- Several commercial, CLIA-approved and College of American Pathology (CAP) approved assays in US
- Positive predictive value of 89% and negative predictive value of 93% of midgut carcinoids (Meijer WG, et al. Clin Chem 2000; 46:1588)
- Elevated in 96% of mid-gut (ileal) carcinoids (Kema IP, et al. Clin Chem 1994; 40:86-95)

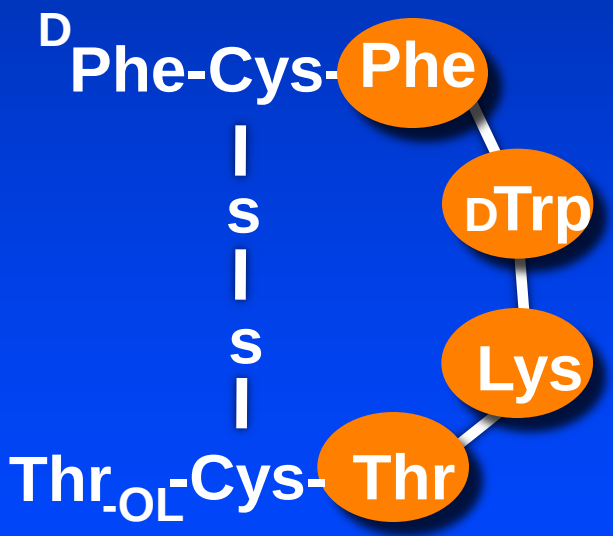
Biomarkers

- CgA levels can reflect total tumor burden (when metastatic) for both pancreatic and mid-gut (ileal) N/E tumors
- Neurokinin A is predictor for aggressive mid-gut (ileal) tumors
- Pancreastatin may be a very early marker for liver tumor activity and predicts both PFS and OS

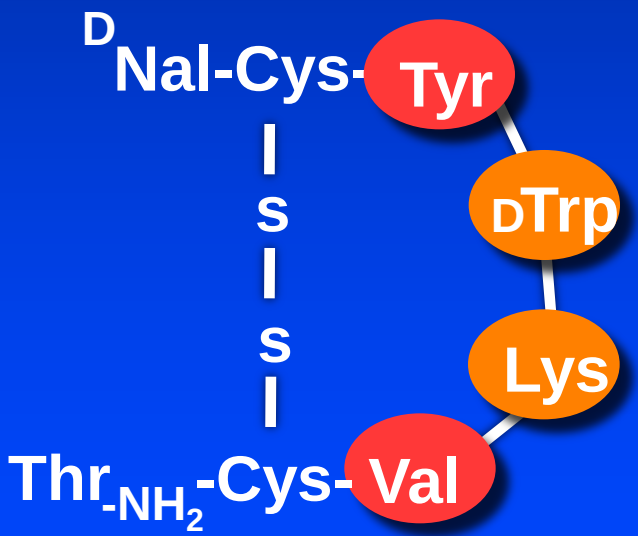
Somatostatin and its Congeners



Somatostatin
*(**GOD** & P. Brazeau, et al., Science 1973)*



Octreotide
(J. Pless, et al.)



Lanreotide
(D.H. Coy, et al.)

Dawn A. Wray & M. Pedersen

Placebo-Controlled, Double-blind, Prospective, Randomized study on the effect of Octreotide – LAR in the control in patients with metastatic neuroendocrine mid-gut tumors: A Report from the PROMID Study Group

Anja Rinkie, Hans-Helge Mueller….Rudolf Arnold

J.Clin Onc.;2009, 27(28): 4656-4663

- 85 patients (well-differentiated midguts);ki-67 < 2%
- Placebo versus Sandostatin-LAR 30 mg monthly
- Median time to tumor progression (TTP)

  6 months = placebo

  14.3 mo Octreotide-LAR (29.4 mo; Liver < 10%)

  (Non-Crossover)

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors (CLARINET Study Group)

M. E. Caplin, M. Pavel, J.B. Cwikta.... P. Ruszniewski

N.E.J.M., 2014; 371:224-233

- 107 Patients (well-differentiated midgut & hindgut) ki-67<10%
- Placebo versus Lanreotide Depot 120mg monthly
- Median time to progressive (TTP)

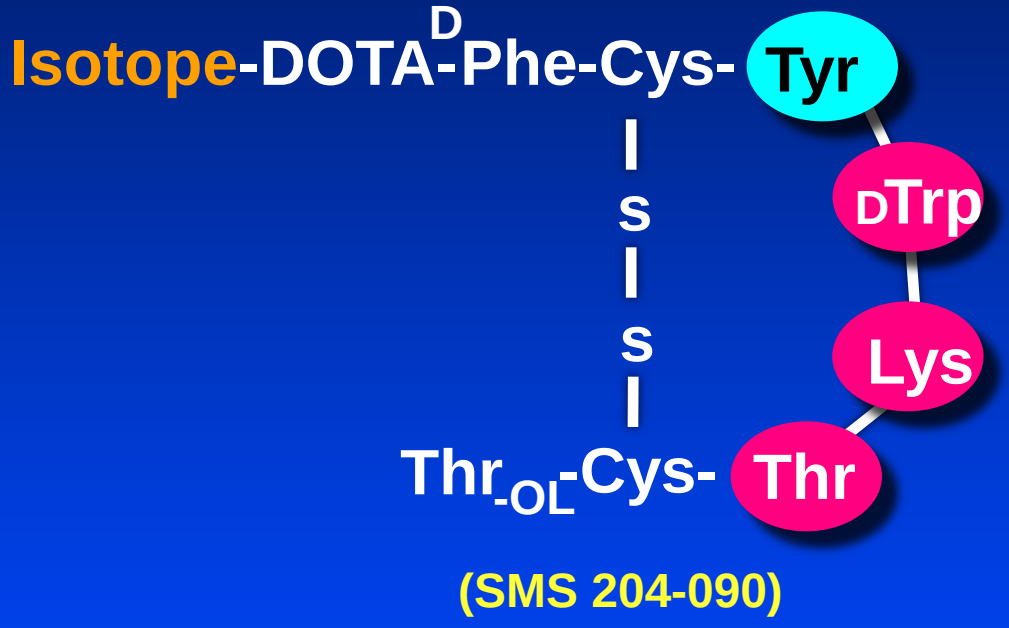
  18 months = Placebo

  LAN-DEP median not reached

  (Cross-over Study)

DOTA-DPhe^{1}-Tyr^{3}-Octreotide (DOTA-TOC)

Theranostic Application



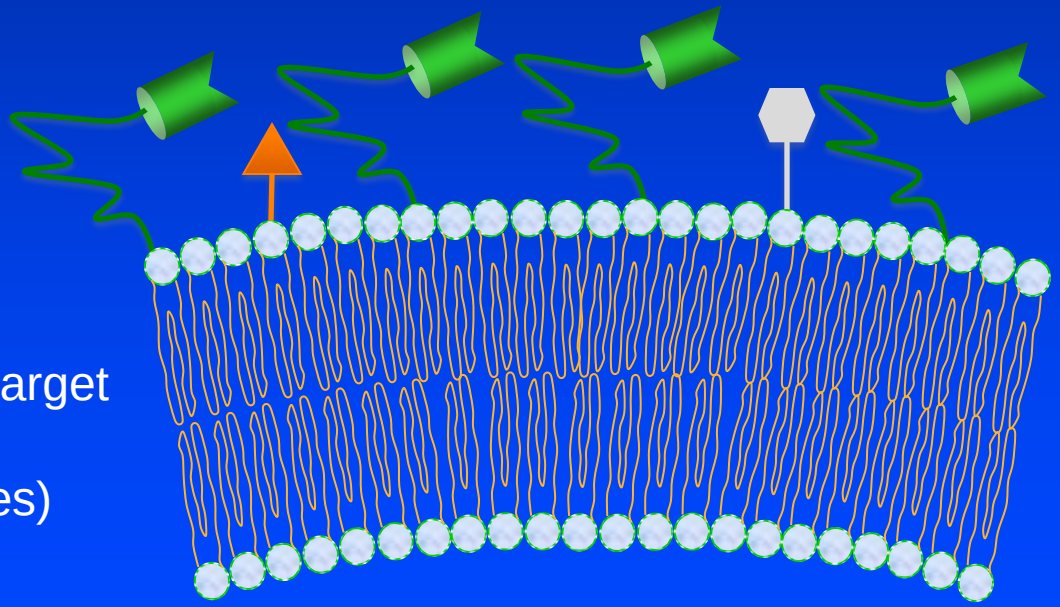
(SMS 204-090)

Isotope (Radiometal):

- Ga^{68}-DOTA-TOC-PET: sensitive; quantifiable
- Y^{90}-DOTA-TOC: hard beta; 7-9 mm range “kill”
- Lu^{177}-DOTA-TOC: soft beta; 3-5 mm range “kill”

Current Targeting Paradigm: One Receptor – One Ligand

- High receptor expression
- Native peptide sequence known
- High affinity/specificity/avidity for target
- Synthetically feasible (<50 residues)



Original: Helmut Maecke
Concept & design by M Schultz

Outcome of Peptide Receptor Radionuclide Therapy (PRRT) in Patients with Metastatic Low Grade Neuroendocrine Tumors

N. Sharma, E.S., B.G. Naraev Engelman, D.L. Bushnell, T.M. O'Dorisio, M. Sue O'Dorisio, T.R. Halfdanarson

PANCREAS 2012; 41(2):347 (Abs)

Methods

- **150 Metastatic Neuroendocrine tumors:**
  - **Small Bowel (Mid Gut, 44%)**
  - **Pancreas (PNET 28%)**
  - **Lung (Foregut 5%)**

- **Peptide Receptor Radio-Nuclide Therapy (PRRNT), 72% Basel, 26% Iowa**

- **86% y^{90}-DOTA-TOC and 13% Lu^{177} DOTATOC**

- **ALL followed up for 10 years in NETC**
- **ALL maintained on Octreotide**

B.G. Nareav, PANCREAS 2012

Site	OS from Diagnosis (years)	OS from PRRT #1 (months)	TTP from PRRT #1 (months)
All sites	9.9	40.6	39.6
SNETs	**13.7**	**96.7**	**60.3**
PNETs	**5.7**	**39.4**	**63.1**
Lung	2.7	22.7	4.5
Unknown Primary	4.1	20.7	24.1
Other	7.2	52.0	26.6
	P<0.0001	P=0.1	P<0.0001

OS: Median overall survival TP: Median Time to Progression

Conclusion

"PRRNT appears to be a valuable treatment option for mNETs, especially SBNETs, and its role earlier in the disease course warrants investigation"

B.G. Nareav, PANCREAS 2012

Reference Laboratories in the United States

- ARUP, Quest, MAYO, LabCorp, Viracor, Inter Science Institute (ISI), Cambridge Lab, OSU-URL

  ALL CLIA (Clinical Laboratory Improvement Act) accredited

  ALL CAP (College of American Pathologists) accredited

  Serotonin: ARUP, Quest, LabCorp
  CgA: ARUP, Quest, MAYO, LabCorp, ISI, Cambridge (?)
  Pancreastatin: ISI (published), URL (published), Cambridge (?)
  NkA: ISI (published), Cambridge (?)

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