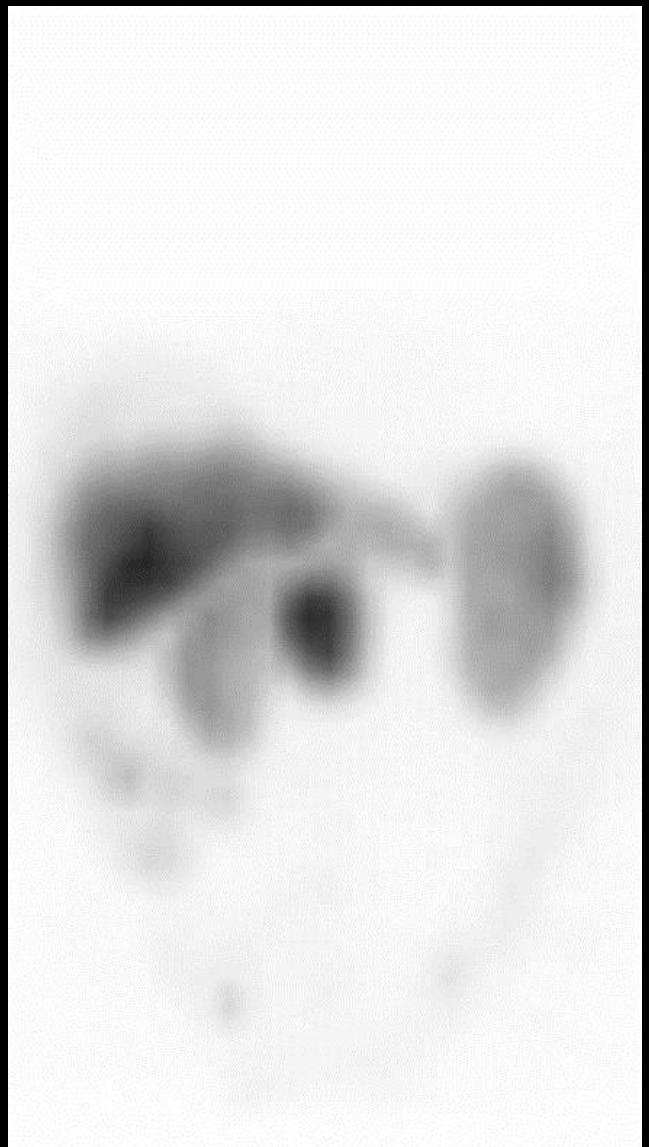
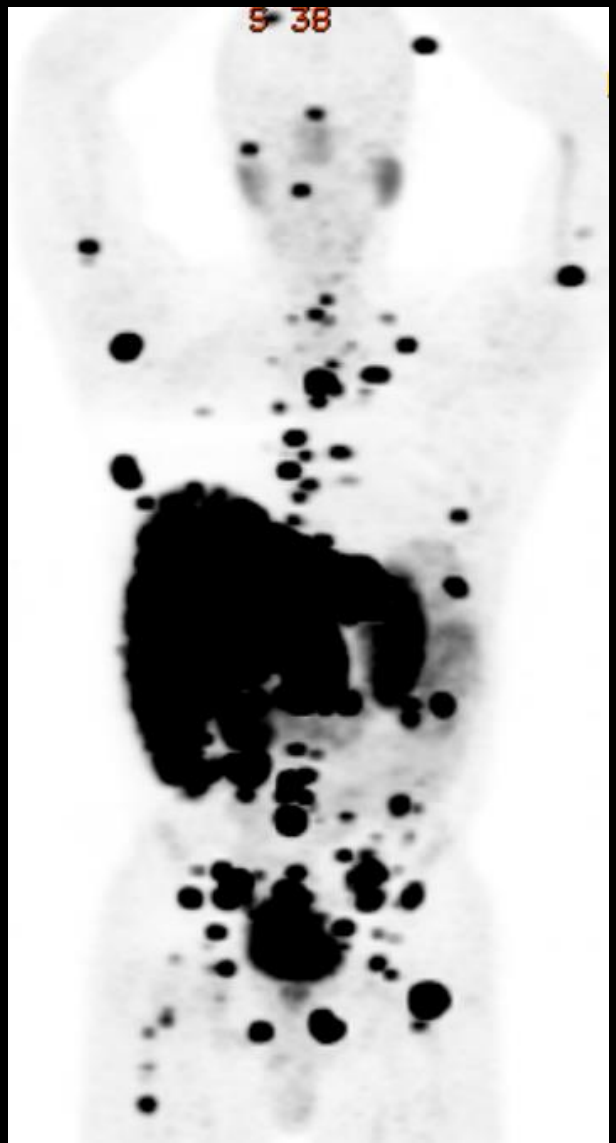
Everything you always wanted to know about PRRT, but didn't know whom to ask.

Eric H. Liu, M.D.
Vanderbilt University Medical Center
Department of Surgery
Nashville, TN
November 2, 2013

Let me tell you a story…

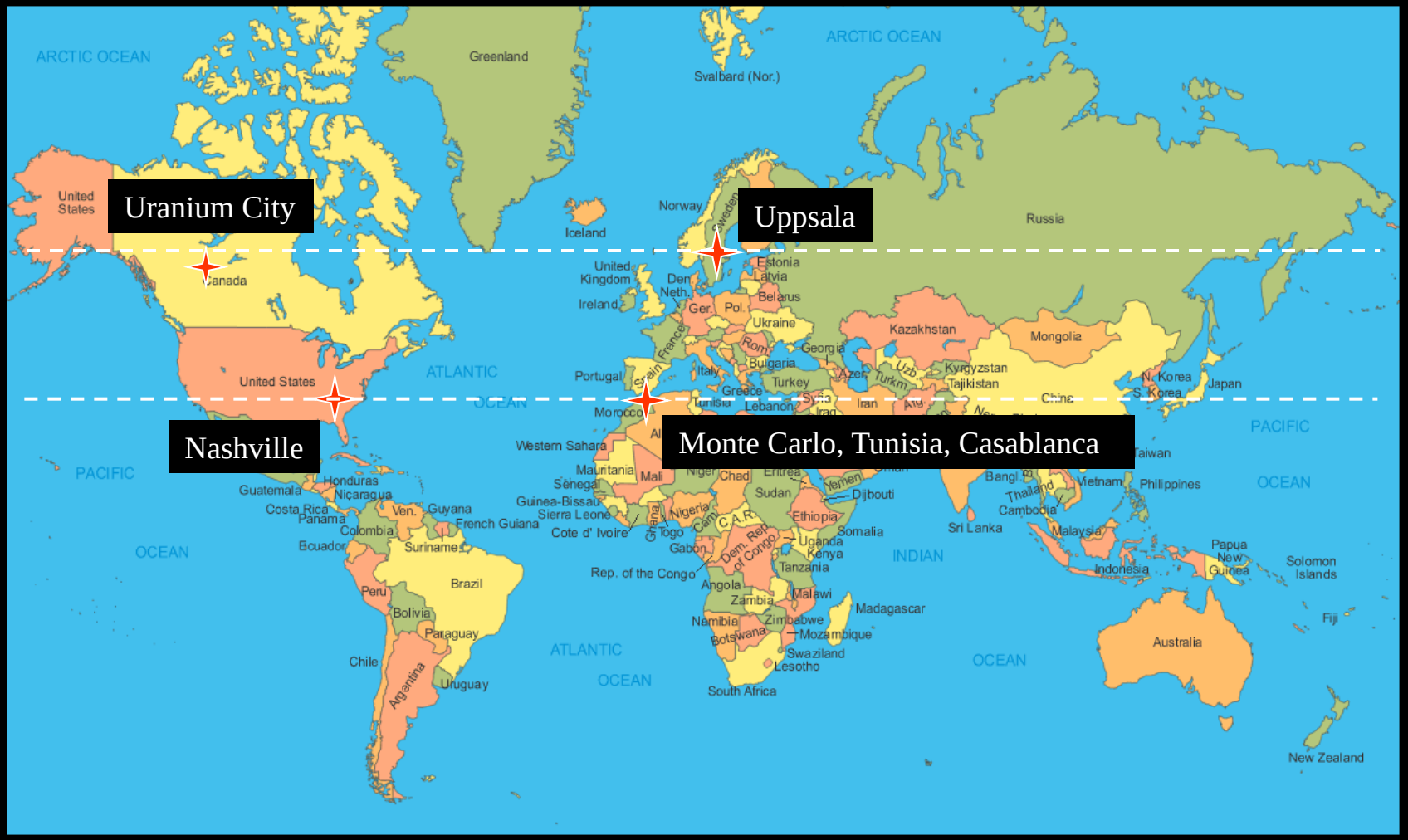




My Story

- Grew up in Maryland
- College in Boston
- Medical School in New York
- Trained in ISLET CELL TRANPLANTATION
- Trained in general surgery at New York-Presbyterian Hospital
- Trained in Diabetes Research at the National Institutes of Health
- Studied novel imaging for diabetes
- Training in Research, GI, Endocrine, Cancer, Surgery, Imaging, Nuclear Medicine

Uppsala, Sweden




F.Y.R.O.M. - The Former Yugoslav Republic of Macedonia
Greenland (DENMARK)
Jan Mayen (NORWAY)
Barents Sea
Hammerfest
Tromsø
Murmansk
Greenland Sea
Denmark Strait
Norwegian Sea
Kiruna
White Sea
Arkhangel'sk
Reykjavik
ICELAND
Arctic Circle
Luleå
Oulu
NORWAY
Umeå
FINLAND
Lake Onega
Trondheim
Tórshavn
Faroe Islands (DENMARK)
SWEDEN
Gulf of Bothnia
Tampere
Lake Ladoga
Gävle
Turku
Helsinki
St. Petersburg
SHETLAND ISLANDS
Bergen
Oslo
Stockholm
ÅLAND ISLANDS
Gulf of Finland
Tallinn
ESTONIA
RUSSIA
Rockall (U.K.)
ORKNEY ISLANDS
HEBRIDES
Stavanger
Moscow
North Atlantic Ocean
Aberdeen
Göteborg
Gotland
Riga
LATVIA
Glasgow
Edinburgh
UNITED
North Sea
Baltic Sea
Öland
LITHUANIA
Vitsyebsk
Smolensk
Belfast
DENMARK
Copenhagen
Malmö
Vilnius
Mahilyow
Minsk
Kaliningrad
RUSSIA
Bornholm
Dublin
Irish Sea
Isle of Man (U.K.)
Leeds
Manchester
Liverpool
IRELAND
KINGDOM
Gdańsk
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L'viv
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Jersey (U.K.)
Frankfurt am Main
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Brno
Kraków
Chernivtsi
Luxembourg
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Paris
SLOVAKIA
Mykolayiv
Chisinau
Stuttgart
Bratislava
Iaşi
Odesa
Strasbourg
Munich
Budapest
Cluj-Napoca
MOLDOVA
Nantes
Vienna
AUSTRIA
HUNGARY
LIECH.
Zürich
Bern
Vaduz
SWITZ.
Geneva
ROMANIA
Bay of Biscay
FRANCE
Lyon
Milan
Venice
SLOVENIA
Ljubljana
Zagreb
Bucharest
Constanța
Black Sea
Turin
A Coruña
Bordeaux
Genoa
CROATIA
BOSNIA AND HERZEGOVINA
Belgrade
Varna
Bilbao
SAN MARINO
SERBIA AND MONTENEGRO
Sarajevo
BULGARIA
Toulouse
MONACO
Sofia
Andorra la Vella
Marseille
Florence
Porto
Ligurian Sea
ITALY
Adriatic Sea
Skopje
Istanbul
ANDORRA
Zaragoza
Corsica
Rome
F.Y.R.O.M.
Thessaloniki
Bursa
Madrid
VATICAN CITY
Tirana
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PORTUGAL
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Naples
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Tyrrhenian Sea
Sardinia
Valencia
SPAIN
GREECE
Aegean Sea
İzmir
Athens
BALEARIC ISLANDS
Ionian Sea
Sevilla
Cagliari
Palermo
Mediterranean Sea
Sicily
Gibraltar (U.K.)
Málaga
Rhodes
Strait of Gibraltar
Ceuta (SPAIN)
Alborán Sea
Melilla (SPAIN)
Oran
Algiers
Tunis
Crete
Valletta
MALTA
Rabat
Casablanca
MOROCCO
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TUNISIA
Scale 1: 19,500,000
Lambert Conformal Conic Projection, standard parallels 40°N and 56°N
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Boundary representation is not necessarily authoritative.


SVERIGE
Uppsala
Stockholm
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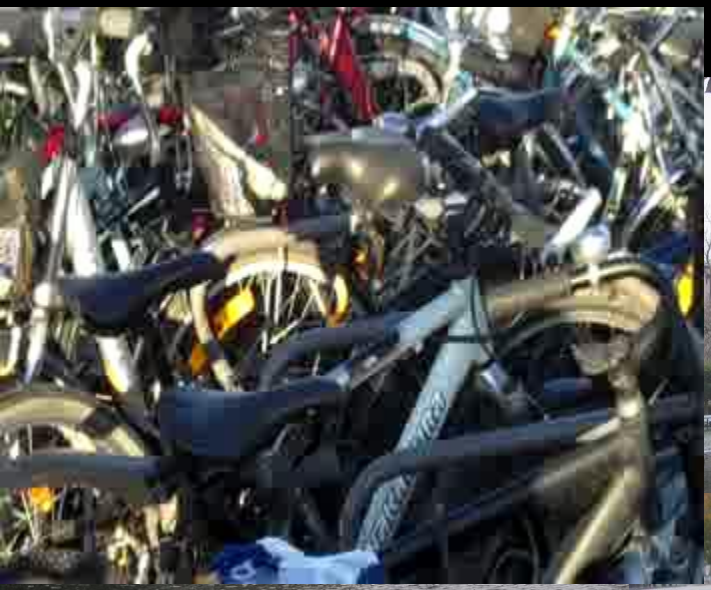
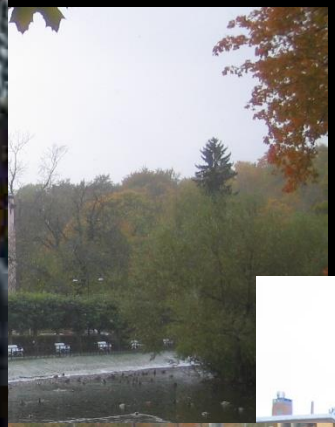
100 km

Uppsala, Sweden

Uppsala, Sweden





UPPSALA UNIVERSITET

Uppsala University

AKADEMISKA SJUKHUSET

UPPSALA UNIVERSITET

Uppsala University

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Uppsala University

AKADEMISKA SJUKHUSET

UPPSALA UNIVERSITET

Uppsala University

AKADEMISKA SJUKHUSET

Why Uppsala?

Kjell Öberg

>2500 patients >1000 current patients

>150 new patients/year (203 new patients 2008)

20-30% from abroad >90% from other parts of Sweden/abroad

Why Uppsala?

UPPSALA UNIVERSITET

AKADEMISKA SJUKHUSET

In-patients - 13 Beds

2800 hospital days
80% from other parts of Sweden
13% from abroad

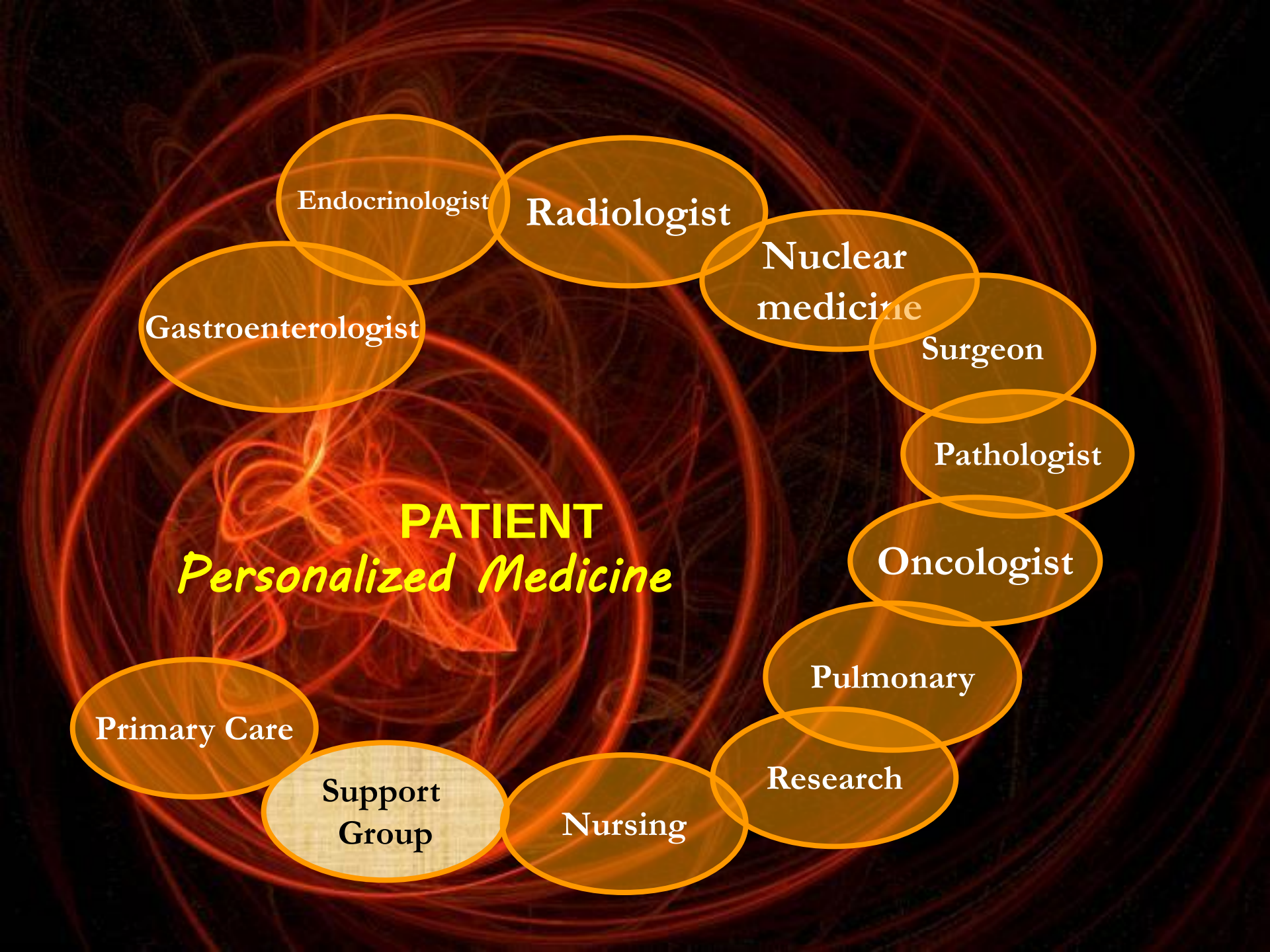
1100 visits/year
87% from other parts of Sweden
12% from abroad

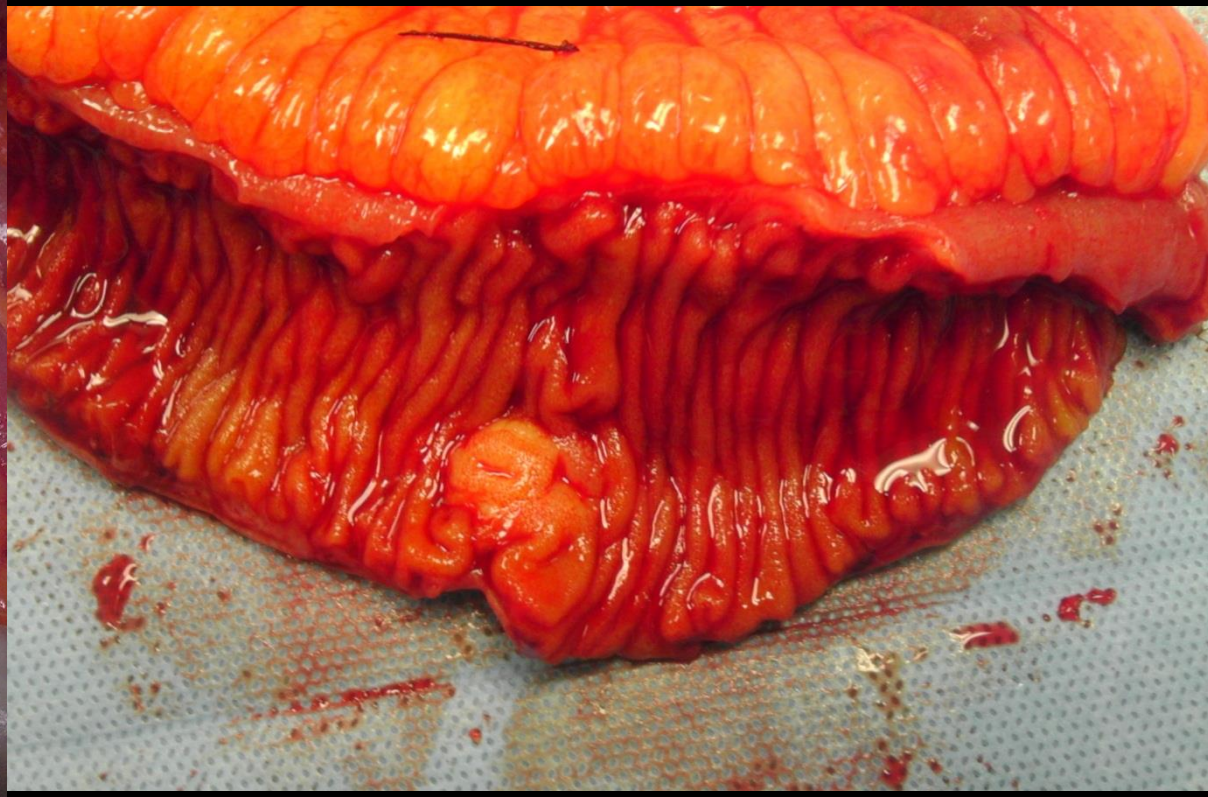
25–30 patients/week

Out-patient-clinic

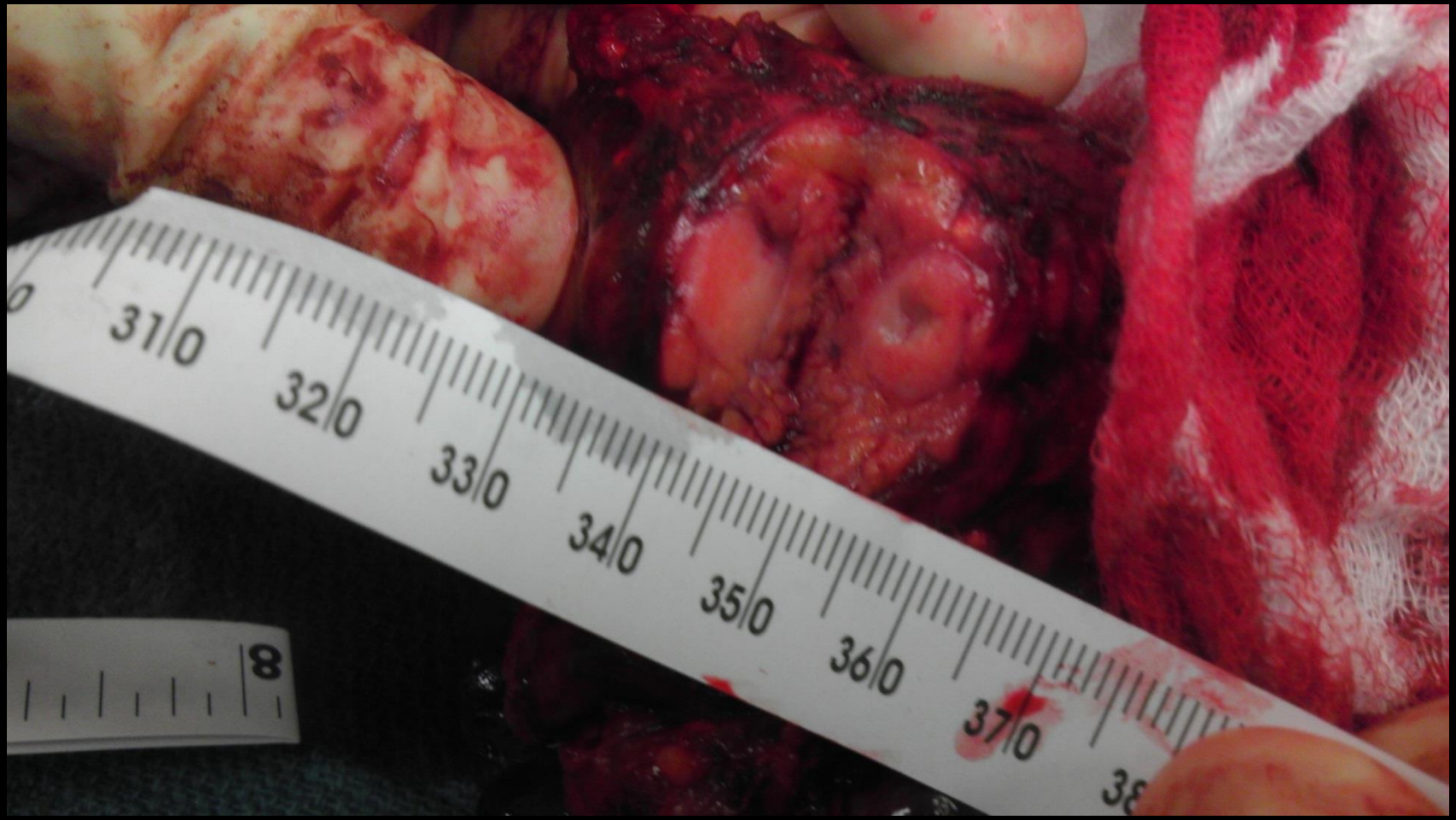
973 visits/year

76% from other parts of Sweden
11% from abroad


Endocrinologist
Radiologist
Nuclear medicine
Gastroenterologist
Surgeon
Pathologist
PATIENT
Personalized Medicine
Oncologist
Pulmonary
Primary Care
Research
Support Group
Nursing




Cardinal Health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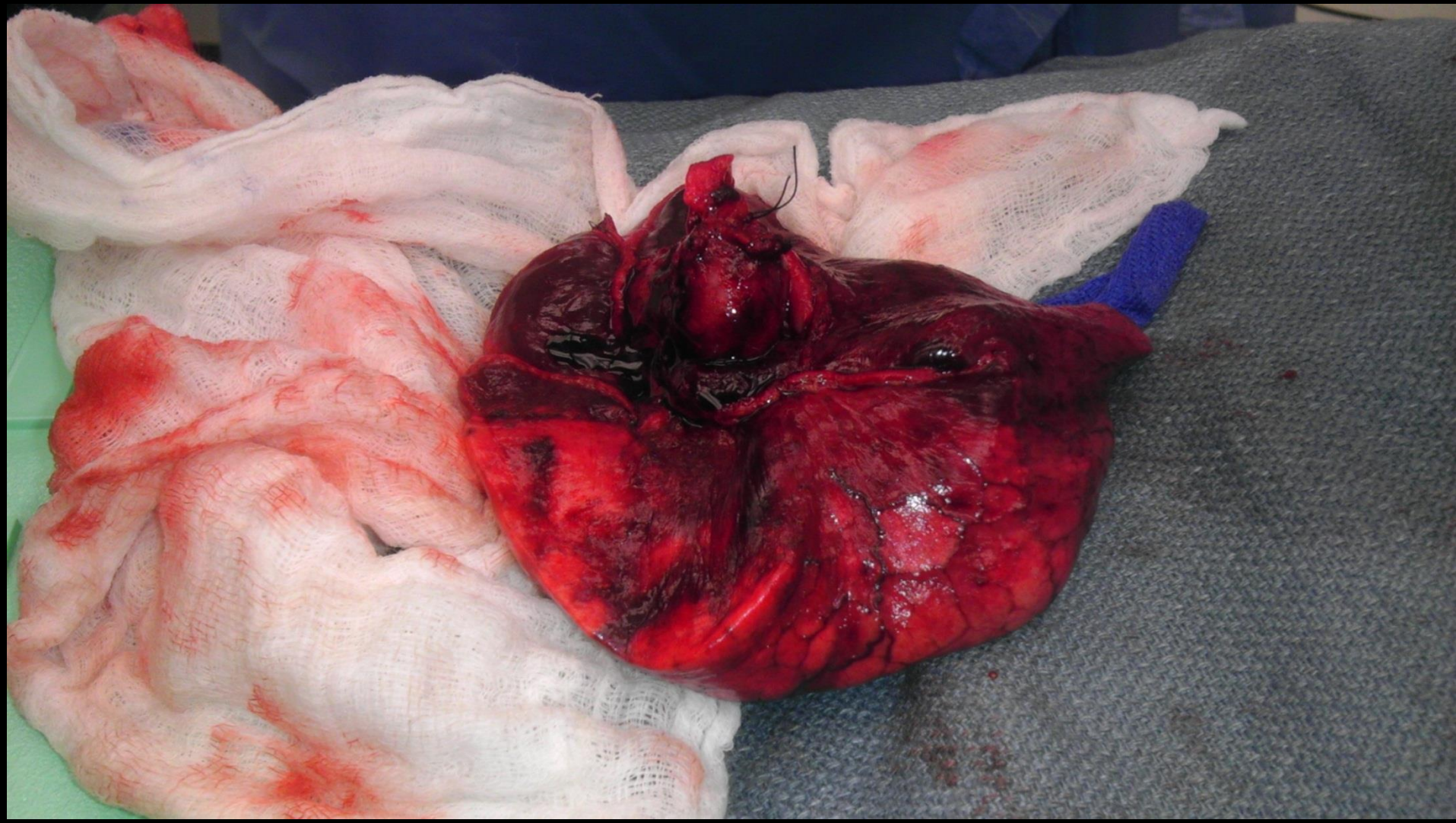
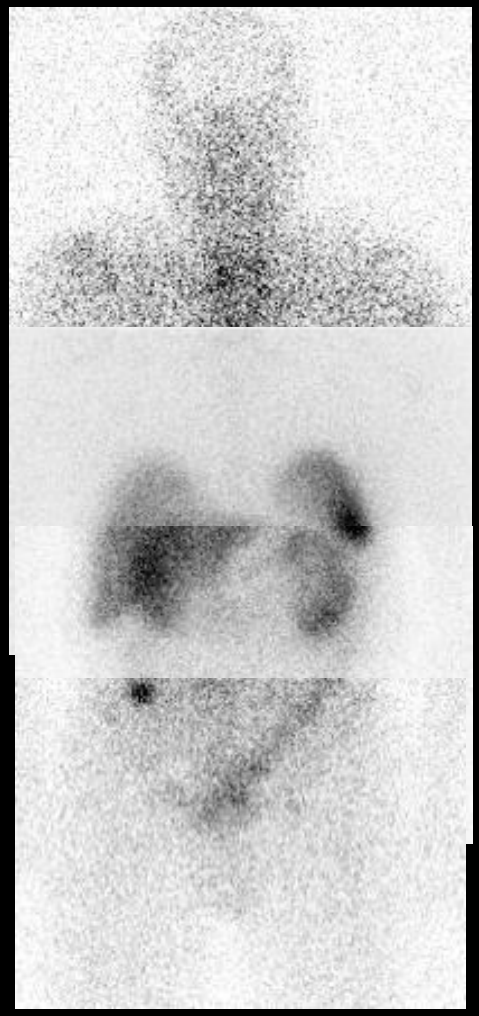
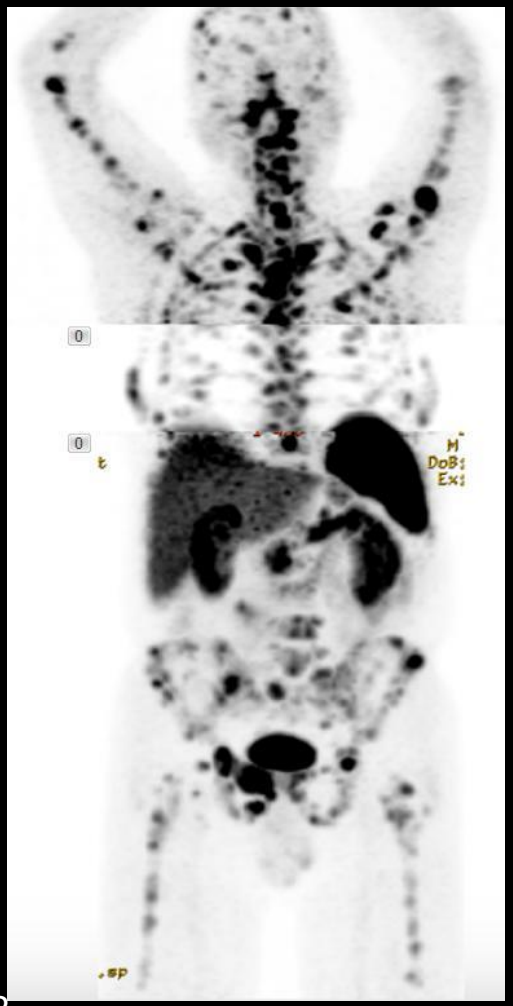
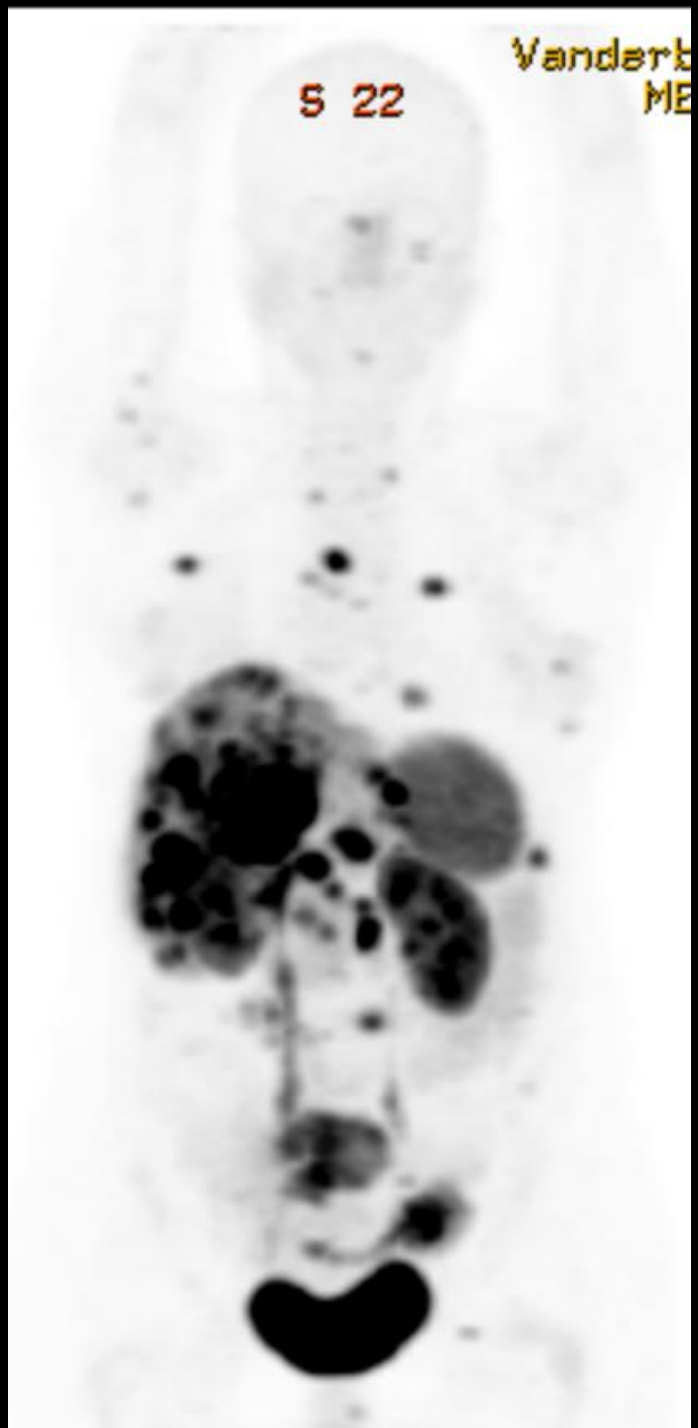


Another Story…







Another Story…

PRRT

Peptide Receptor Radionuclide Therapy
(a.k.a. PRRNT)

Outline

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- What can I hope for?
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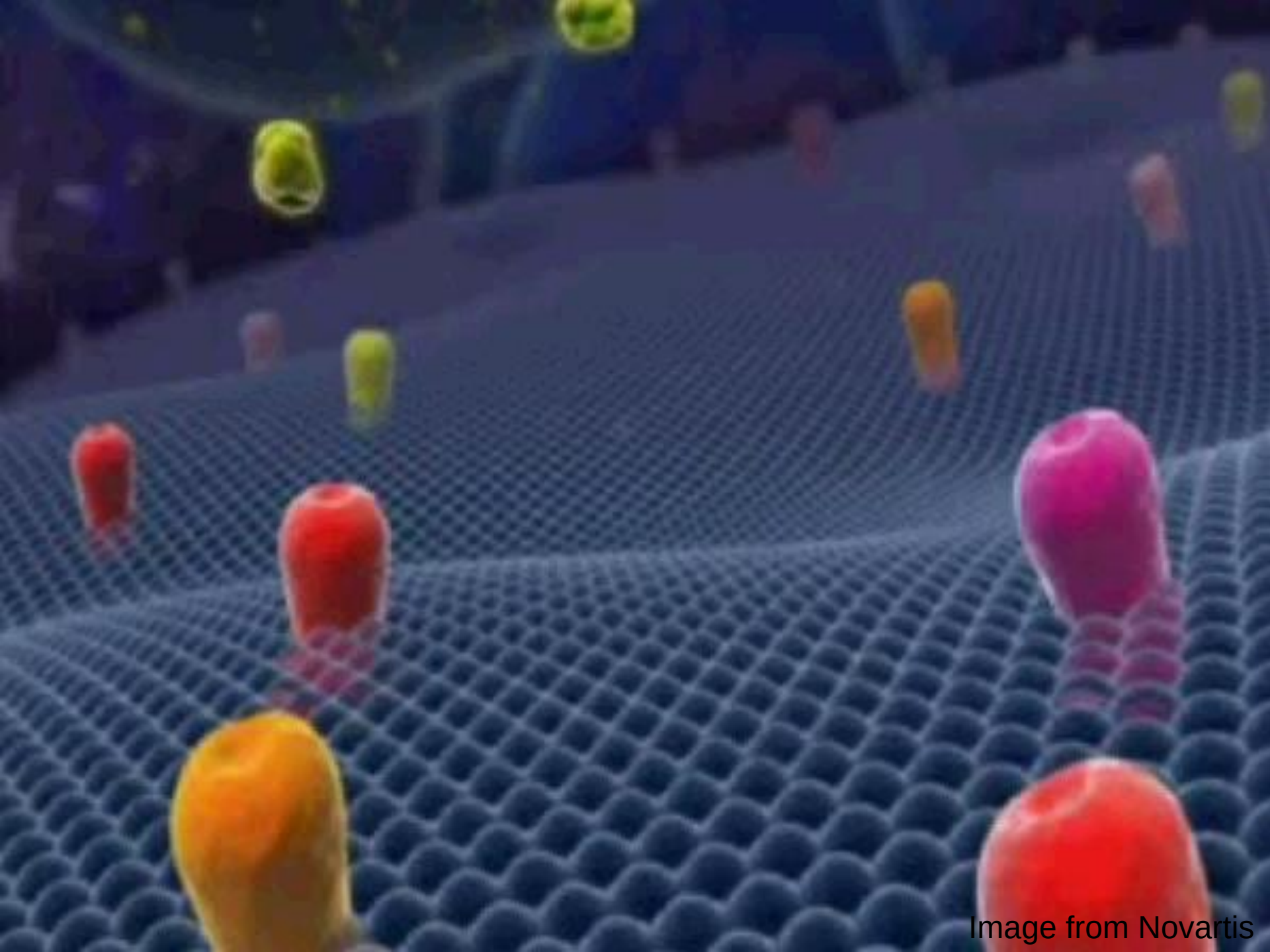


Image from Novartis

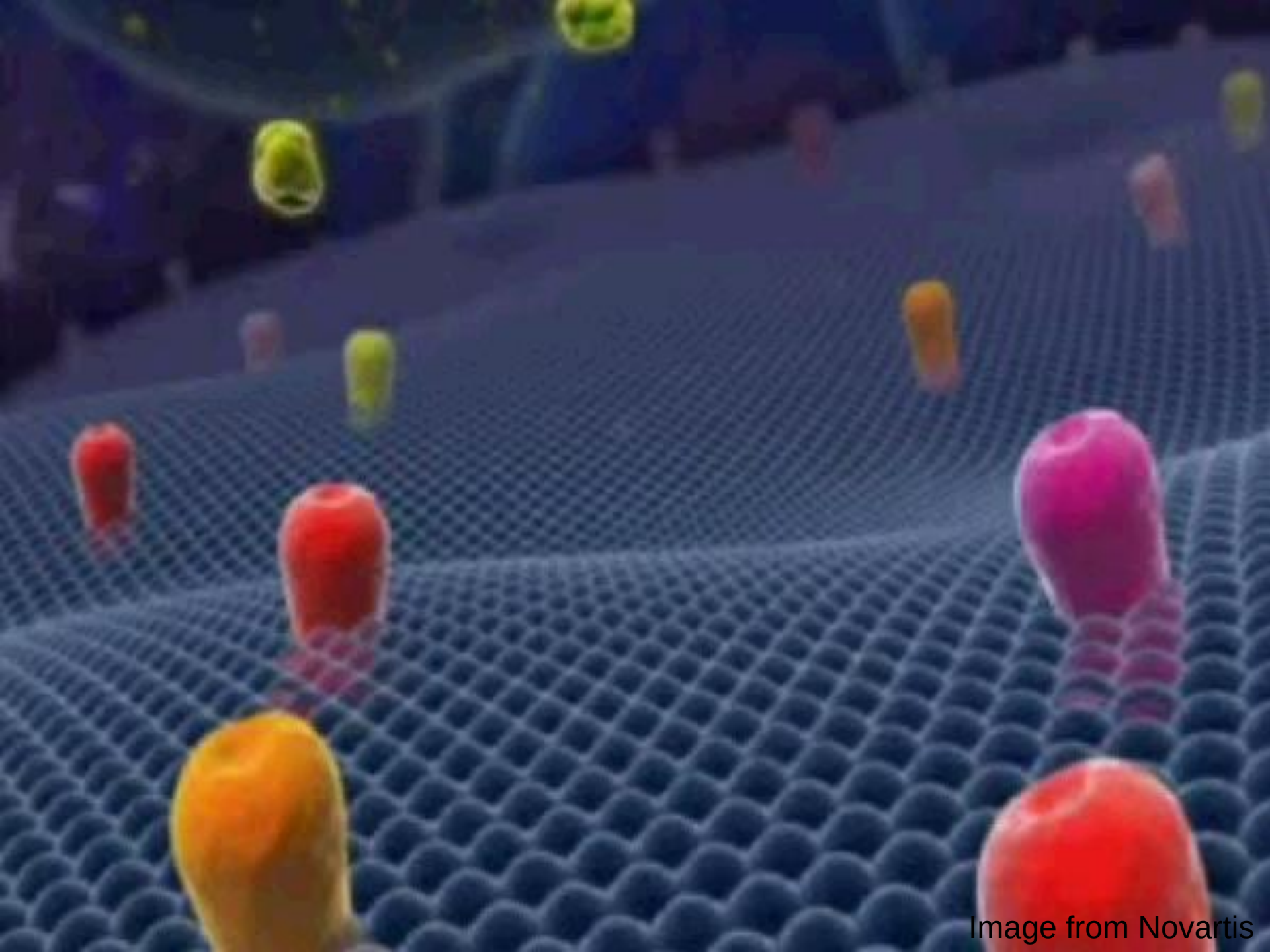
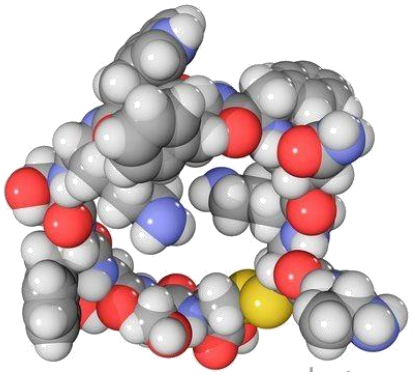


Image from Novartis

Roger Guillemin

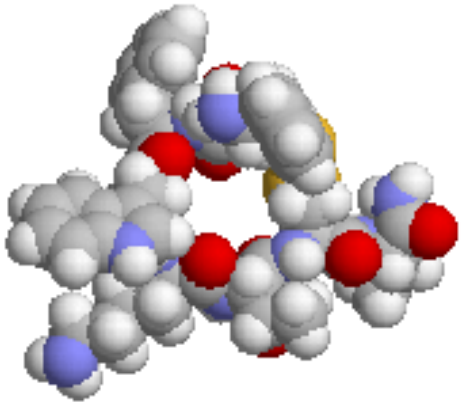
Andrew Schally

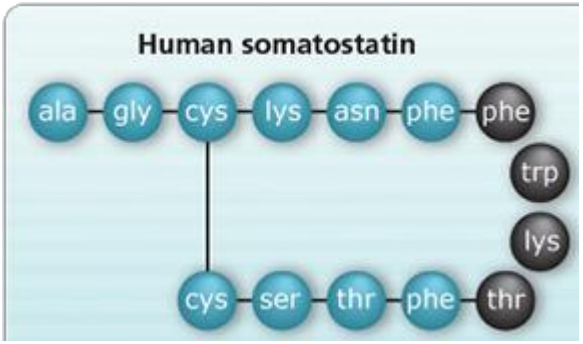
1977



Somatostatin

Somat = Body
Stat = Stop





Sandostatin LAR Depot Timeline

Sandoz forms Somatostatin project team, 1973

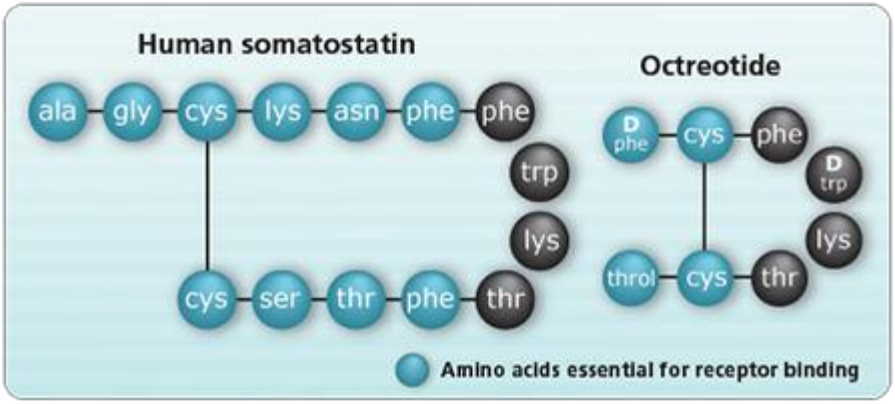
New analogue discovered, 1978

Biologic and Immunologic Activities and Applications of Somatostatin Analogs

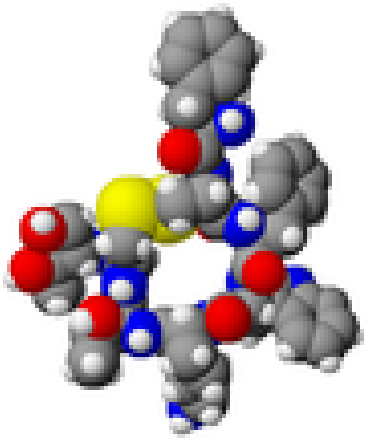
Wylie Vale, Jean Rivier, Nick Ling, and Marvin Brown

Sandoz abandons work and focuses on mini-SSAs, 1979

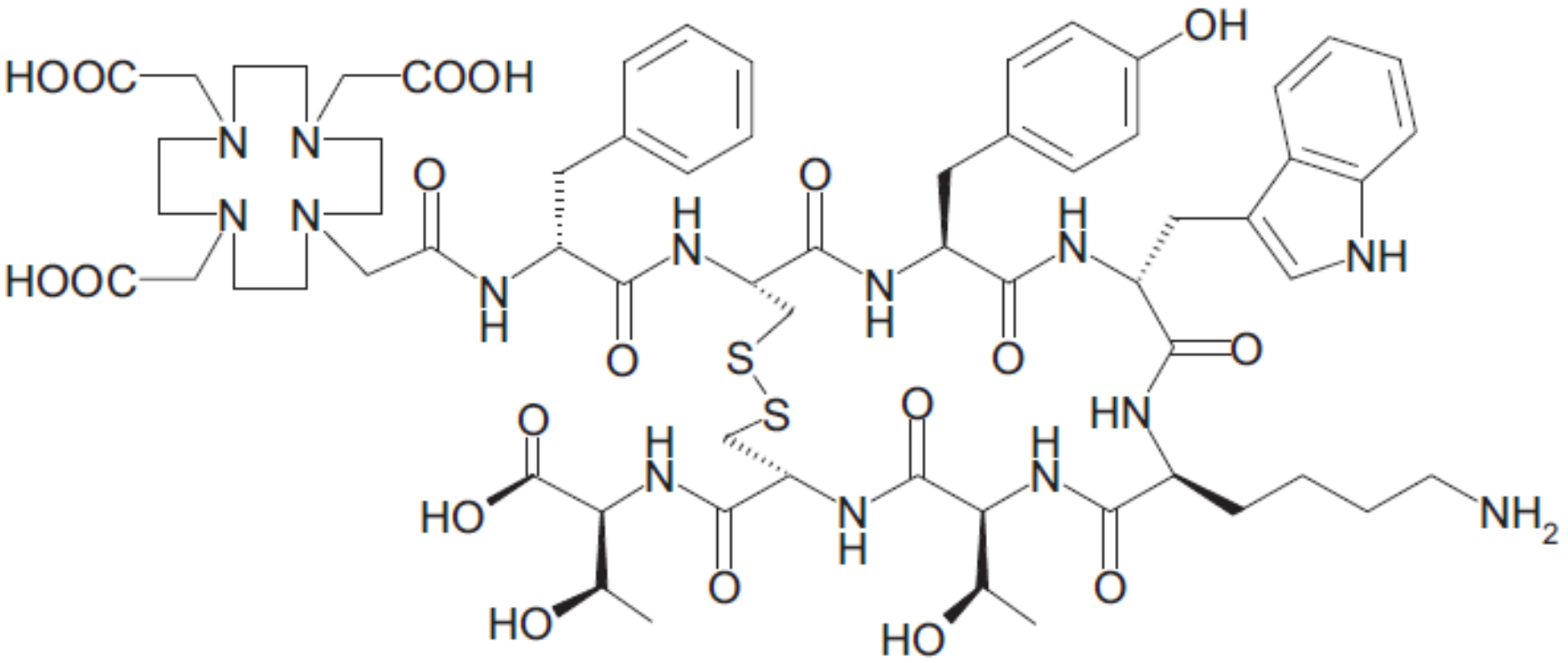
Wilfried Bauer synthesizes SMS 201-995, 1980



Amino acids essential for receptor binding



DOTATATE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Outline

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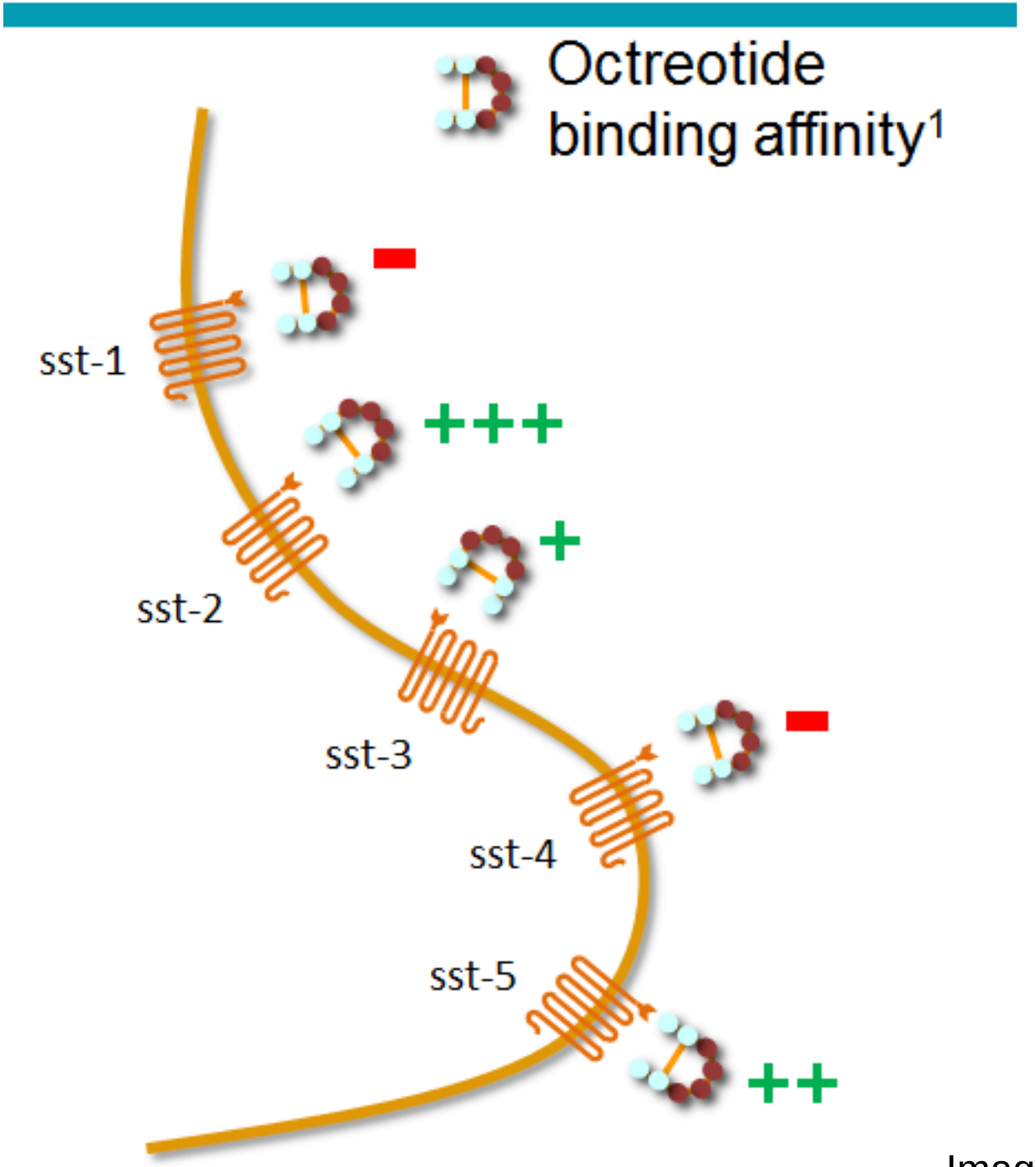
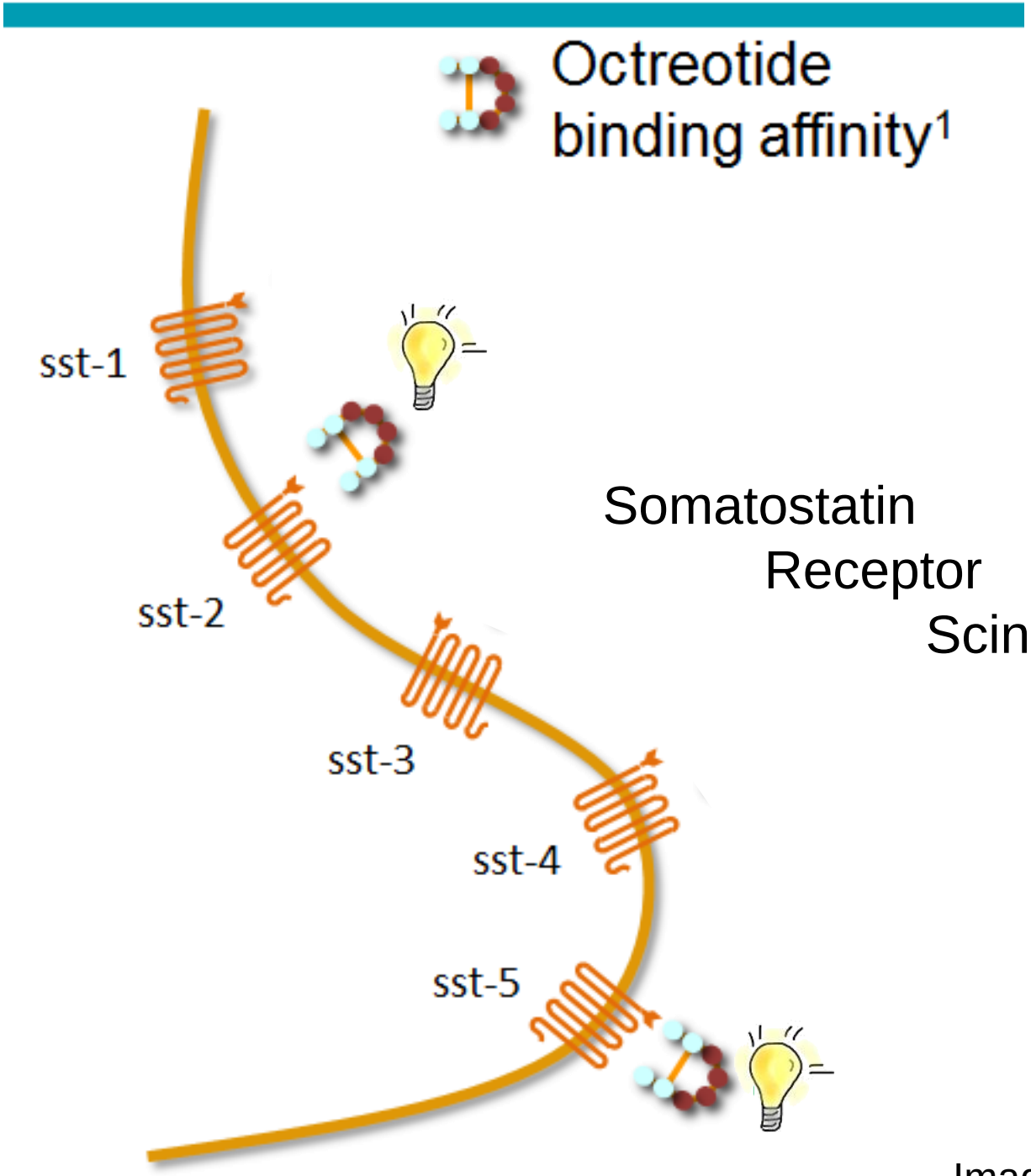


Image from Novartis

What are SRS, PET and PRRT?

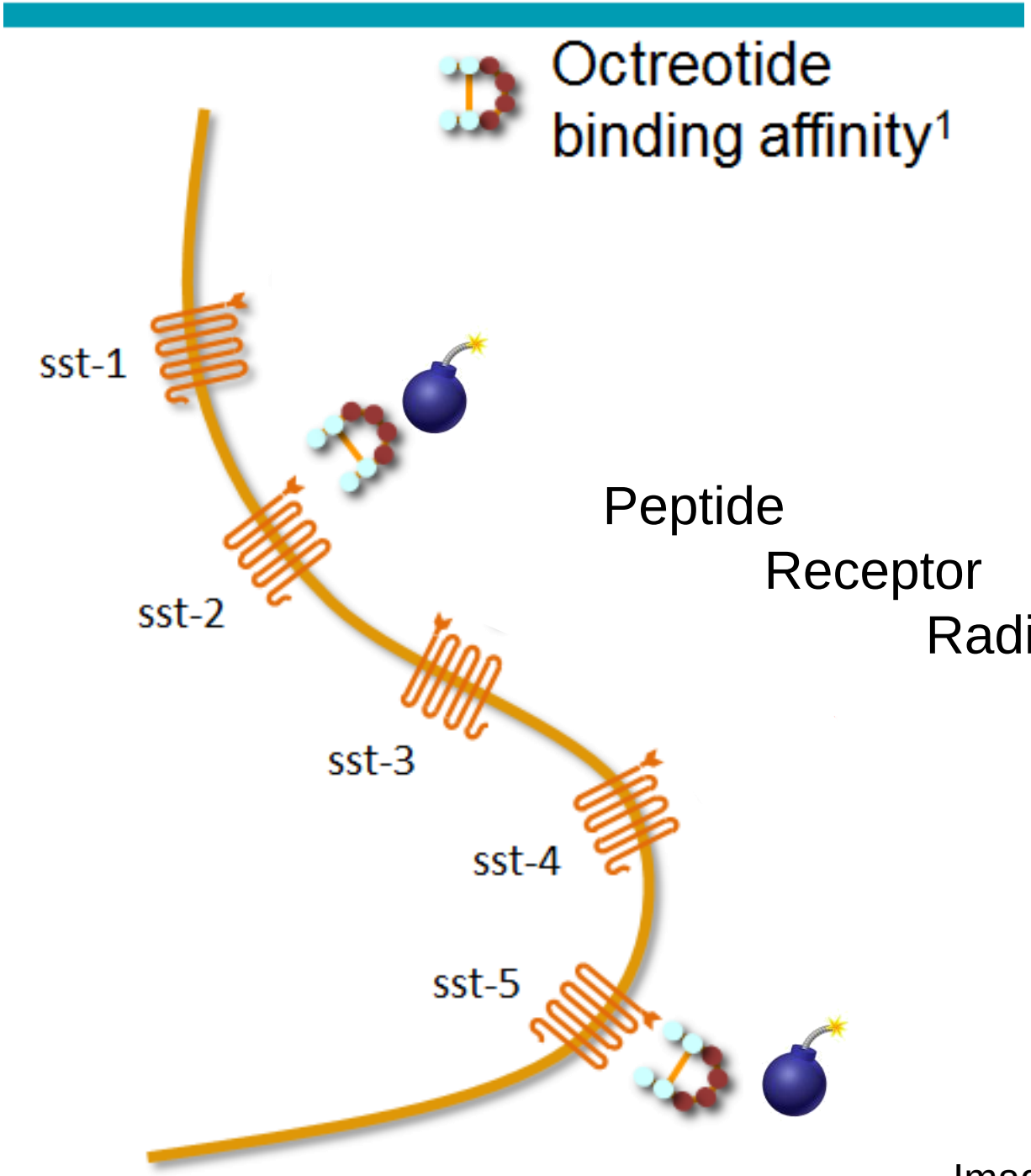
- SRS = Somatostatin Receptor Scintigraphy
- SPECT = Single Photon Emission Computed Tomography
- PET = Positron Emission Tomography
- PRRT = Peptide Receptor Radiotherapy
  - aka PRRNT (nuclide)

THERANOSTICS



Somatostatin
Receptor
Scintigraphy

Image from Novartis



Peptide
Receptor
Radionuclide
Therapy

Image from Novartis

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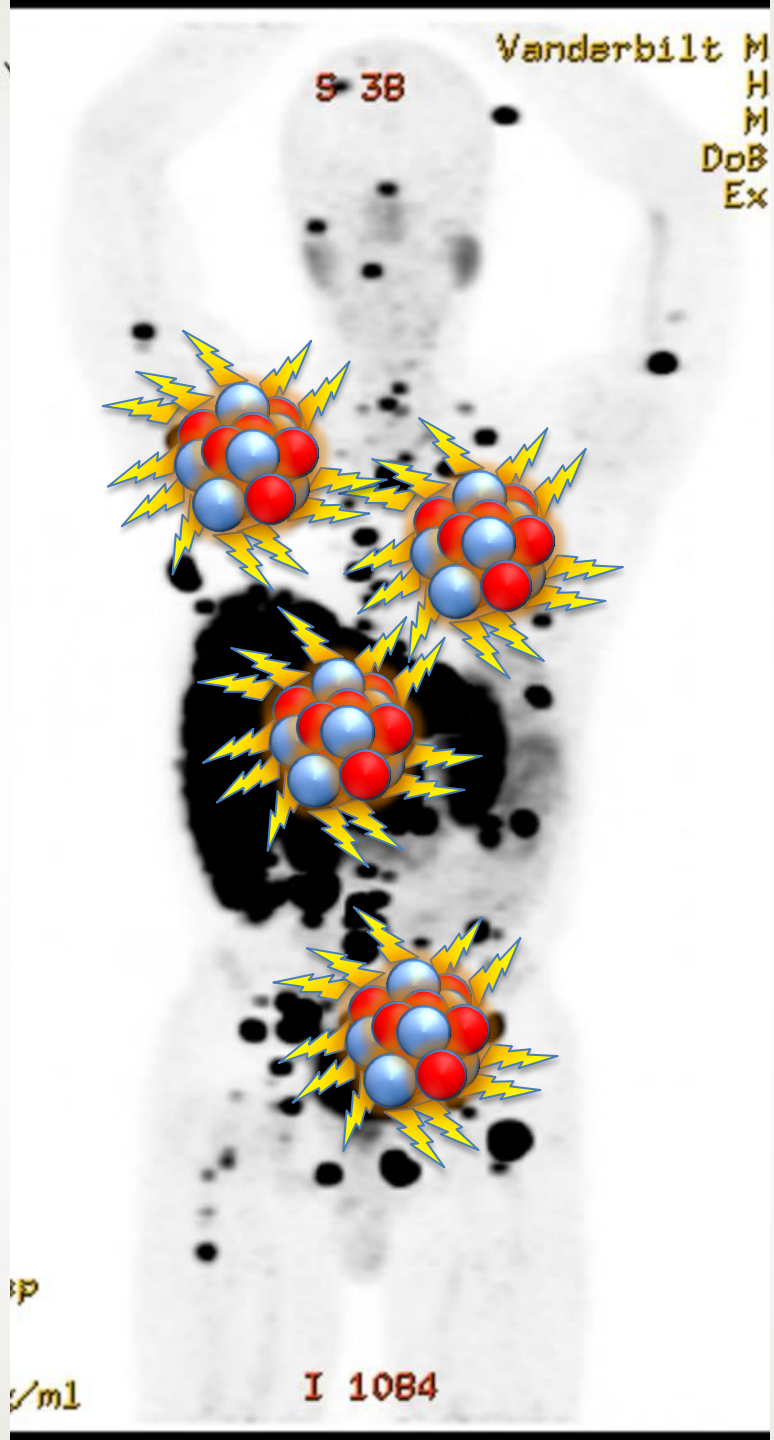
MEDICAL CENTER



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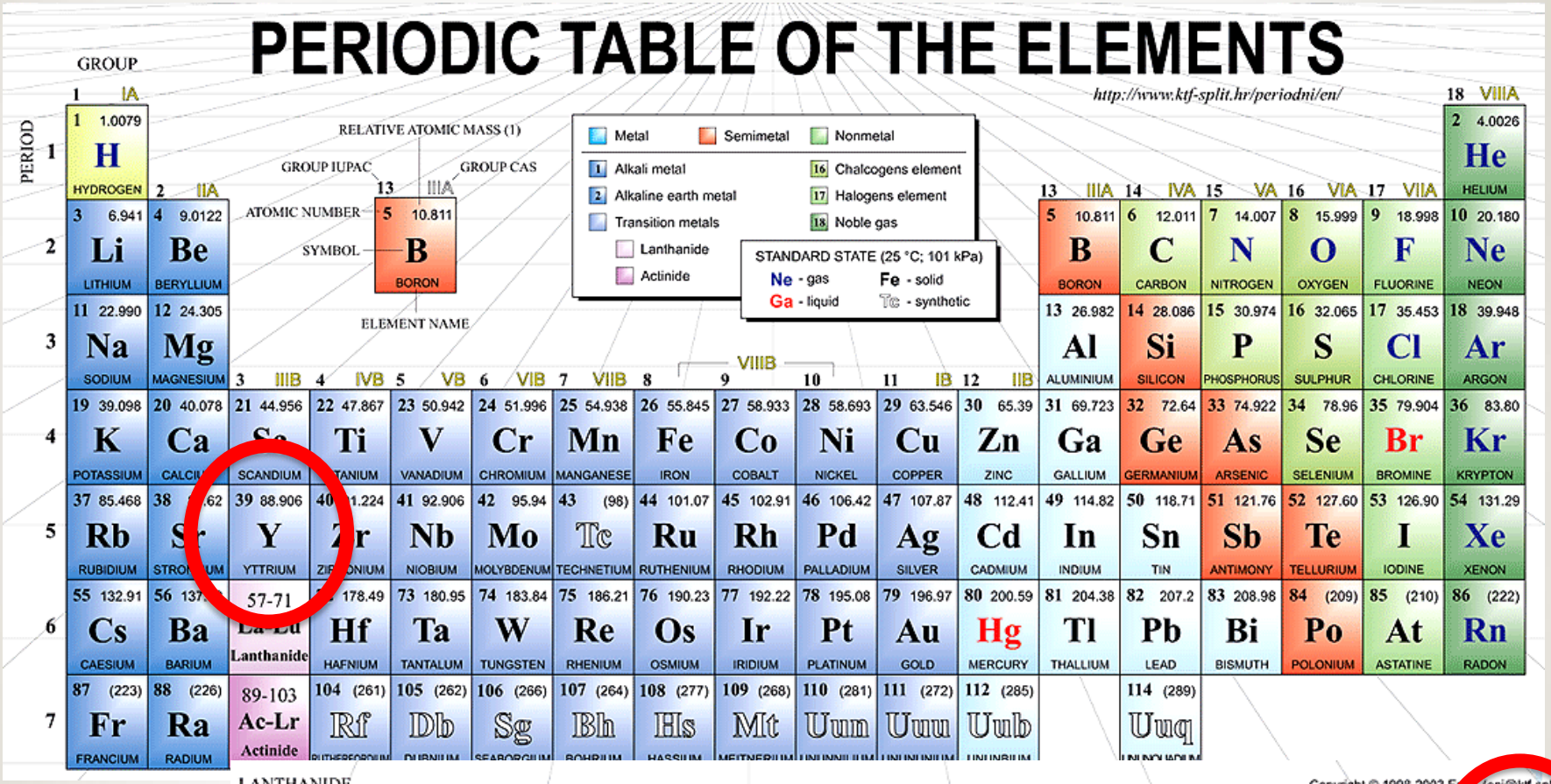
Types of PRRT



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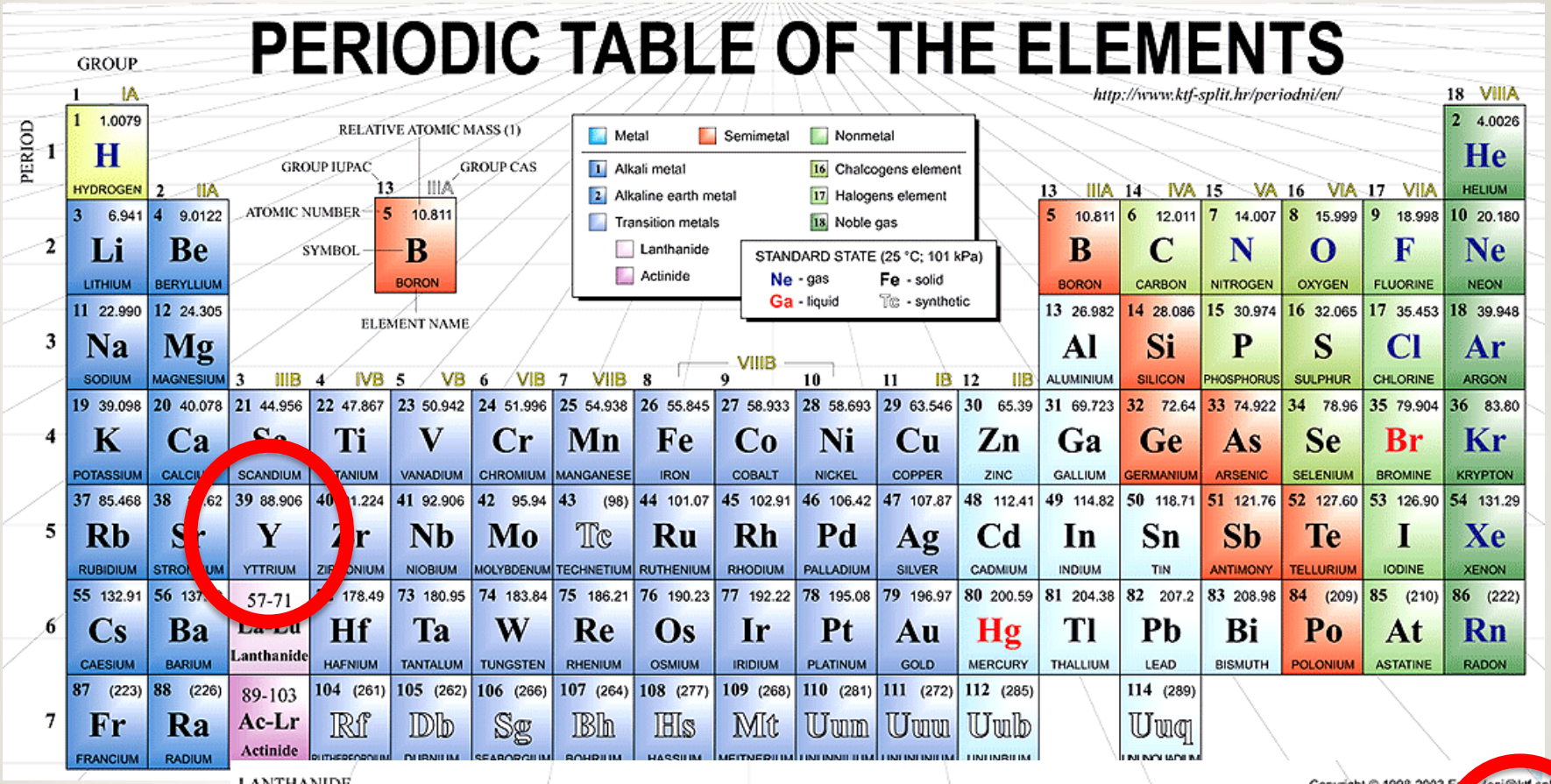
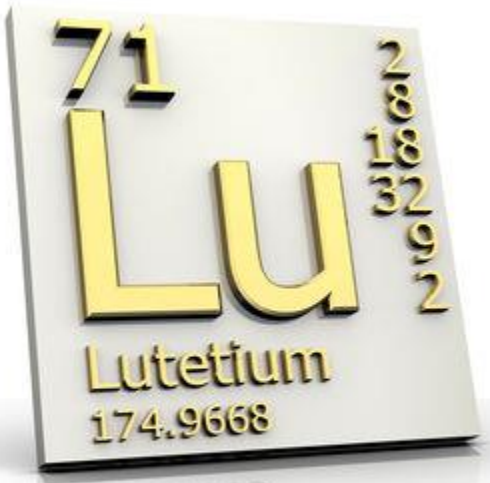
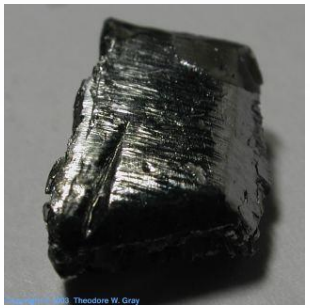
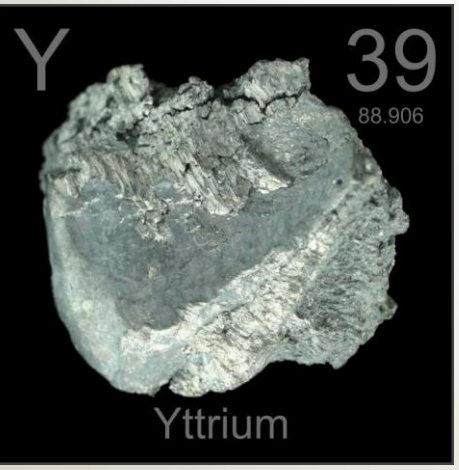
Types of PRRT



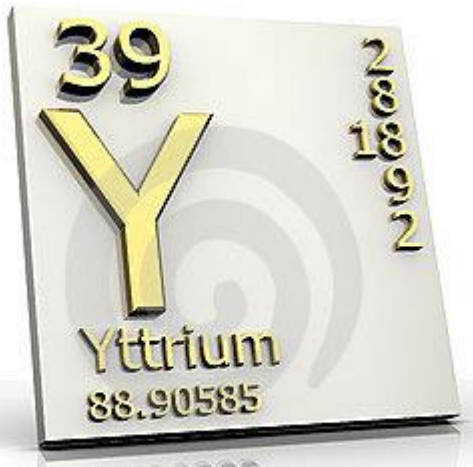


Beta and Gamma emitter
T1/2 6.73 days
Path length 0.04-1.8 mm
Toxicity: renal, bone marrow, liver





Beta emitter
T1/2 64 hr
Path length 2.7 mm
Toxicity: renal, bone marrow



Pagel et al, Principles of Cancer Biotherapy, Oldham and Dillman, 2009

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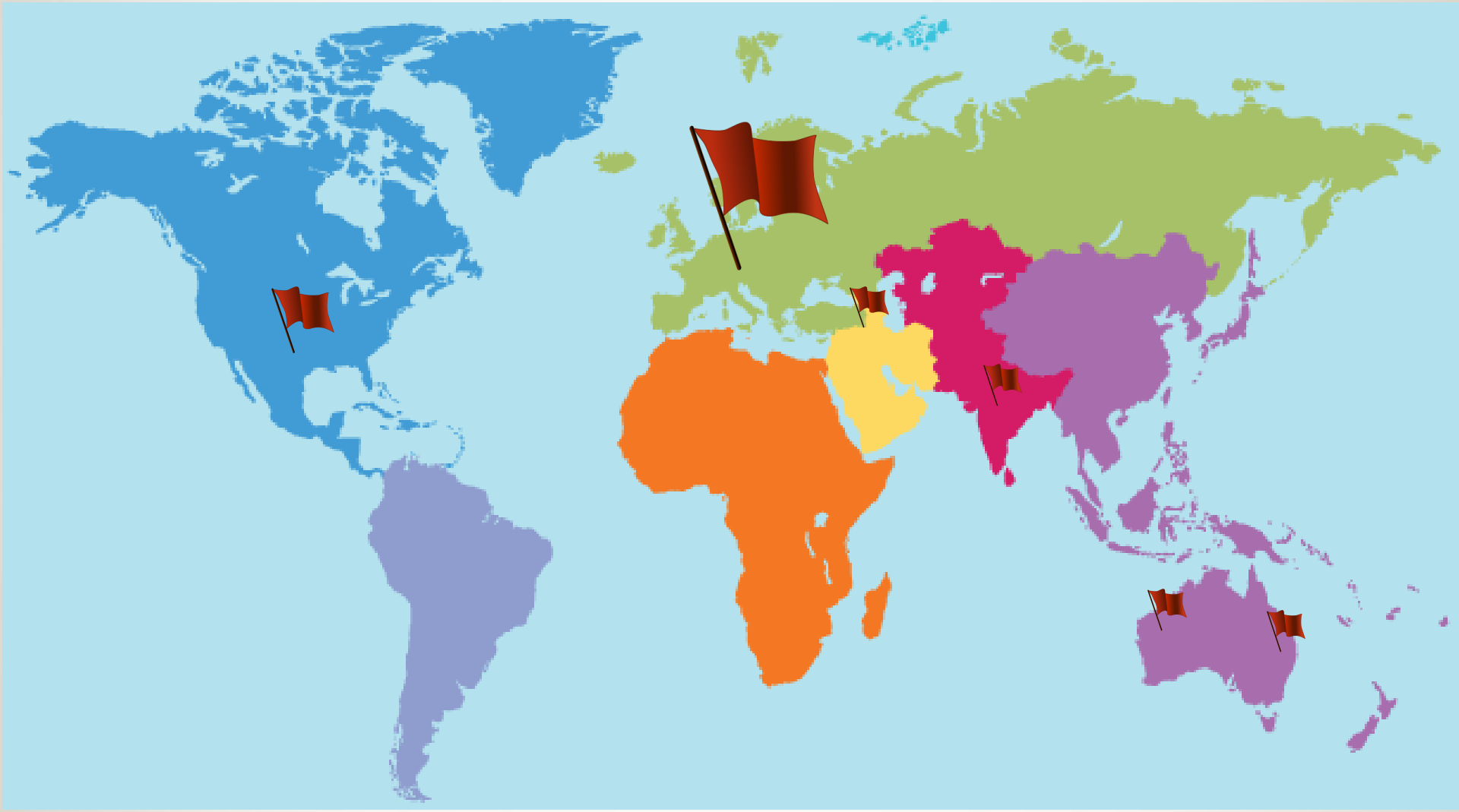
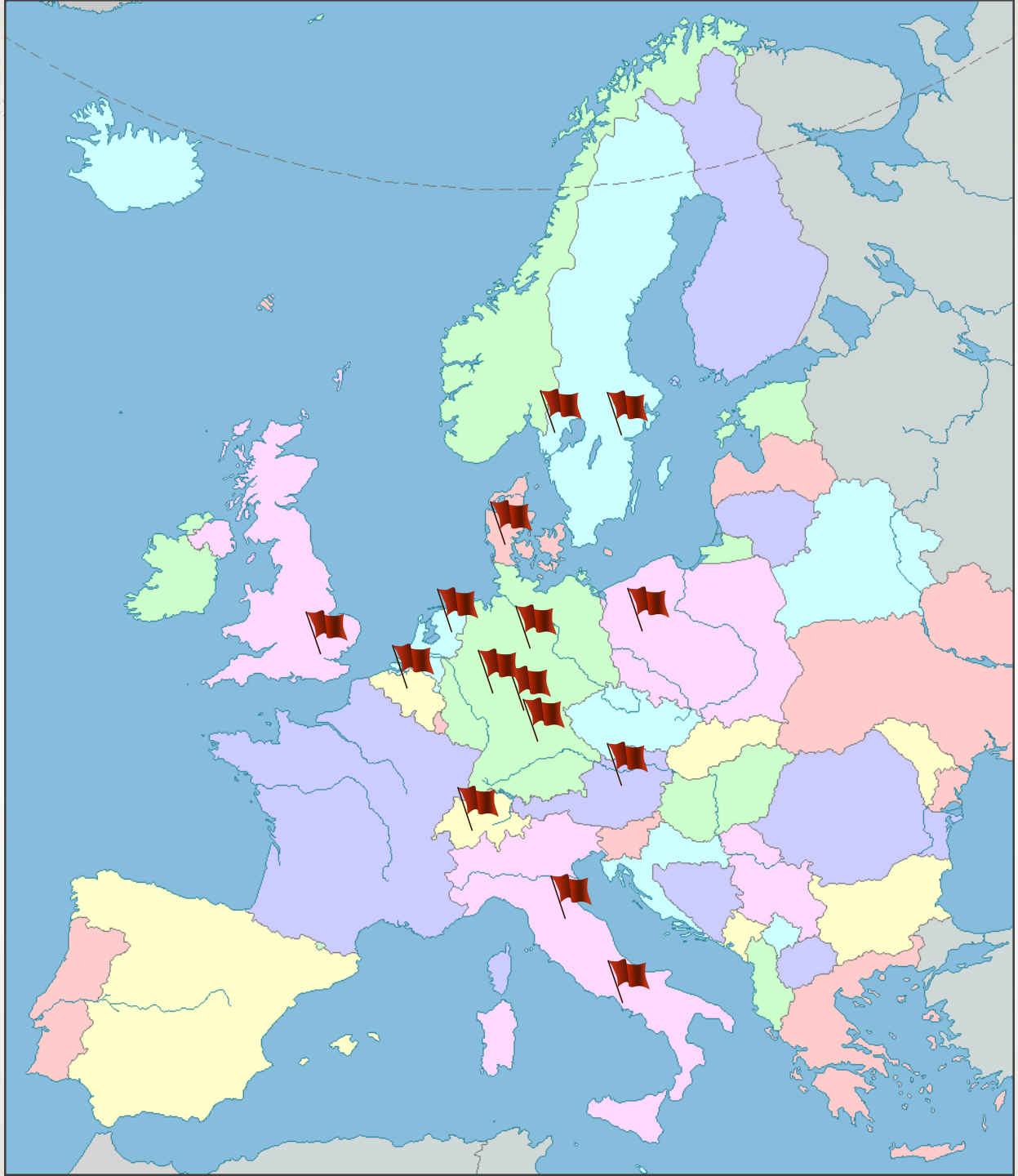
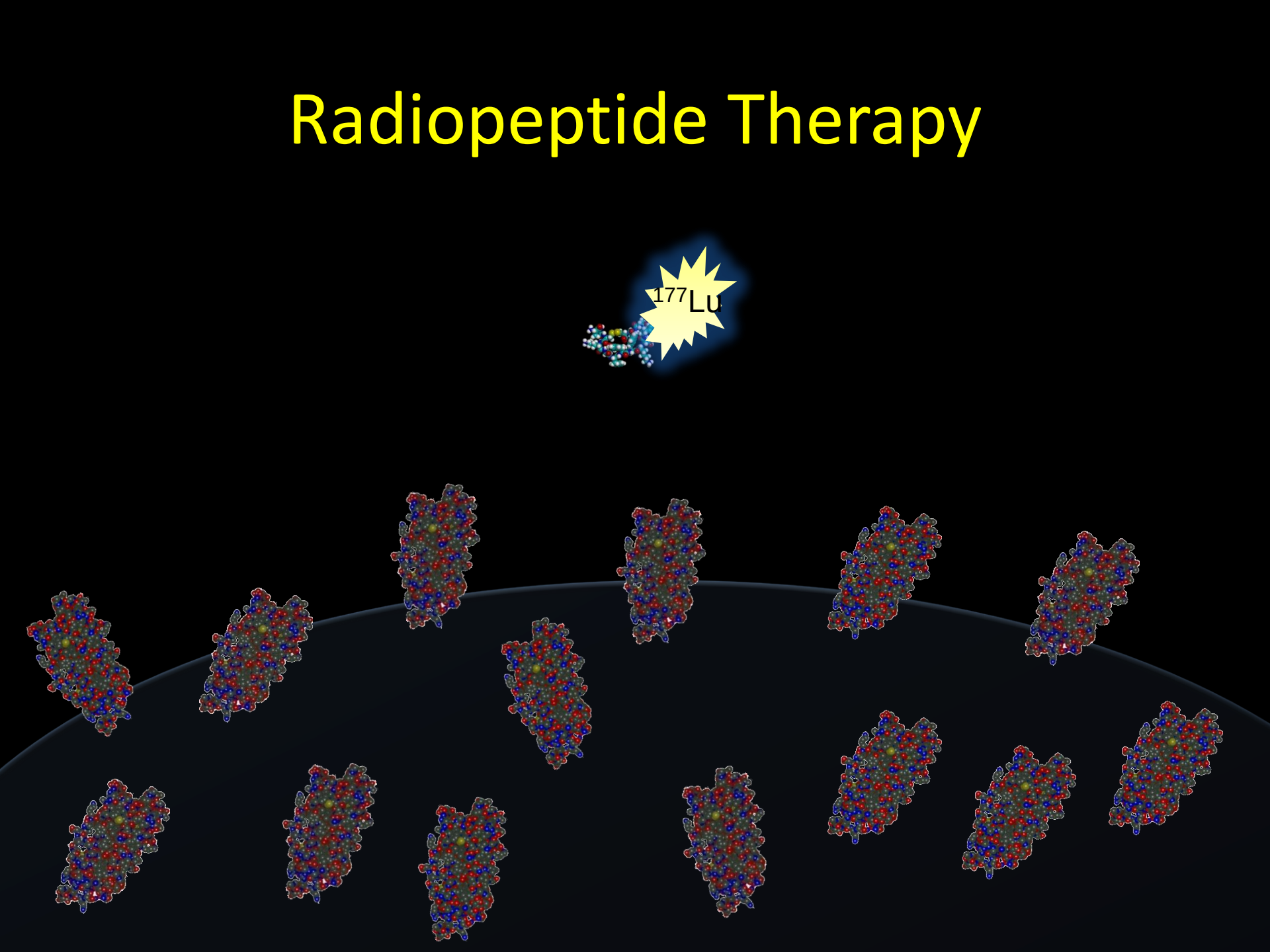


VANDERBILT

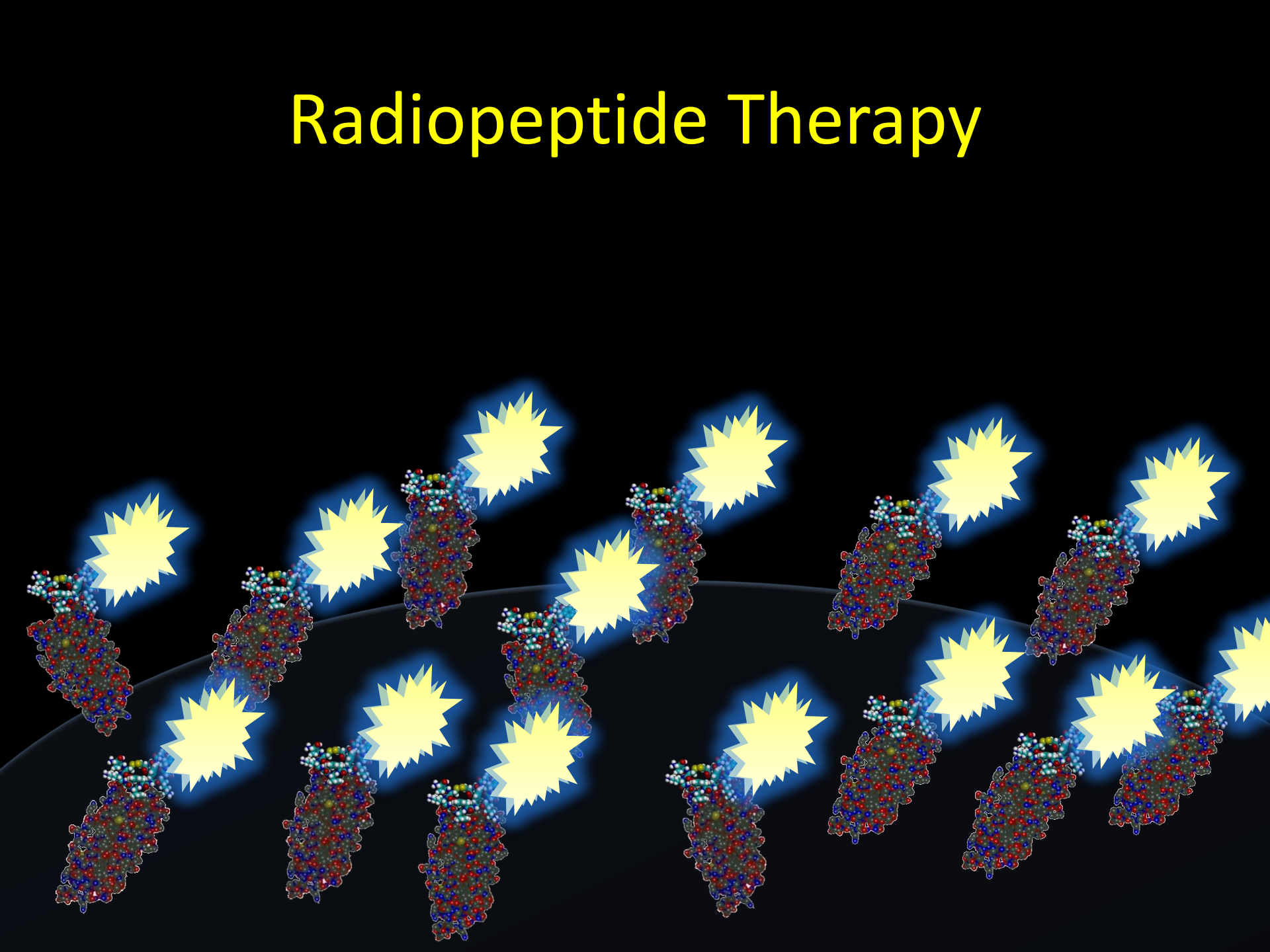
MEDICAL C



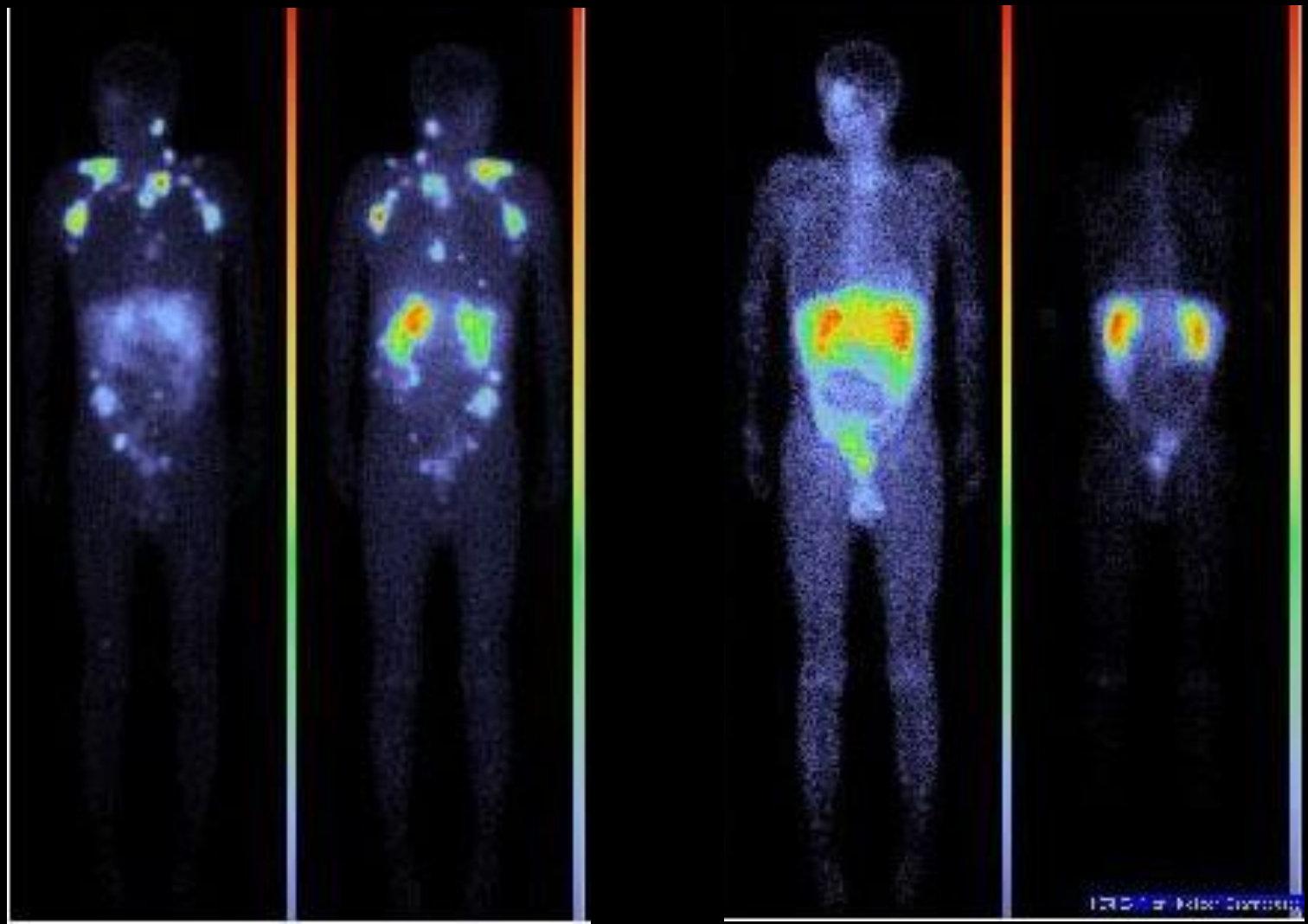
Radiopeptide Therapy



Radiopeptide Therapy



Metastatic Insulinoma Treated with ^{177}Lu-DOTA-Octreotate



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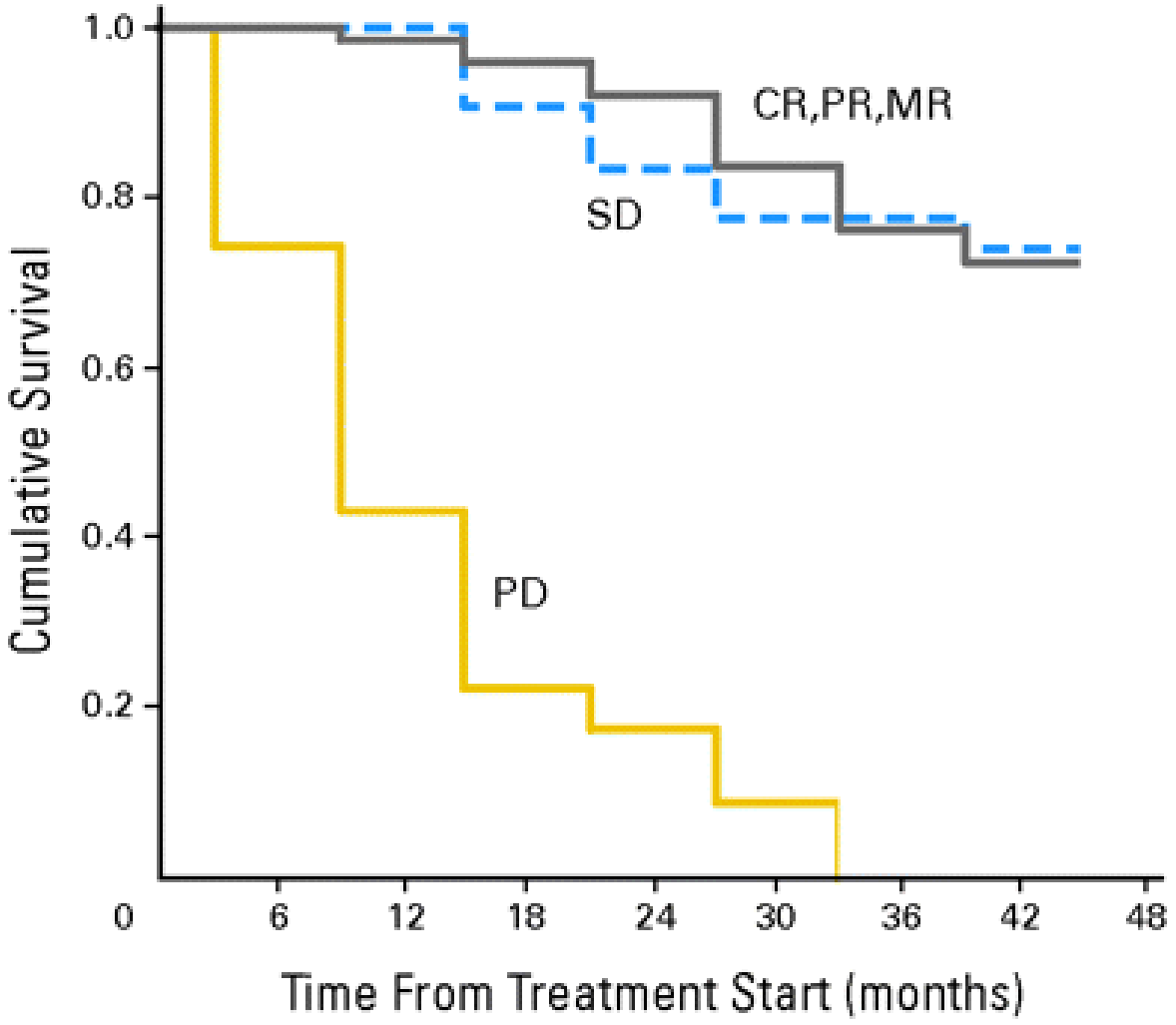
Survival With PRRT - Dutch



Predictors:
Disease Stabilization
Less Liver Involvement
Good Performance
No weight loss
No Bone Mets
Not gastrinoma/

insulinoma/VIPoma

Kwekkeboom et al, JCO, 2009

Dutch

- 504 patients
- PFS 40 mo
- Median OS from Tx 46 mo
- Median OS from Dx 128 mo

Tumor Type	Response										
	CR		PR		MR		SD		PD		Total No. of Patients
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Carcinoid	1	1	41	22	31	17	78	42	37	20	188
Nonfunctioning pancreatic	4	6	26	36	13	18	19	26	10	14	72
Unknown origin			10	32	3	10	7	23	11	36	31
Gastrinoma			5	42	4	33	2	17	1	8	12
Insulinoma			3	60			1	20	1	20	5
VIPoma			1	50					1	50	2
Total	5	2	86	28	51	16	107	35	61	20	310

Kwekkeboom et al, JCO, 2009

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Side Effects

- Bone marrow suppression
  - WBC (immune cells)
  - RBC (anemia)
  - Platelets (clotting)
- Kidney function
  - Lost 1-3% per year
- Nausea
  - Amino Acid Infusion
- LIMITED NUMBER OF TREATMENTS

Outline

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Candidates

- ✓STRONG SSTR2 SIGNAL
  - Octreoscan
  - 68Ga-DOTA-SSA PET/CT
- ✓Strong kidneys
- ✓Strong bone marrow
- ✓Good nutrition

Outline

- What is it?
- How does it work?
- What are the results?
- What are the side effects?
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- What's it like?
- What can I hope for?
- When is it going to be here in the U.S.?

NETTER – 1

- http://netter-1.com/
- “A multicenter, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumors”

USA

- Nashville, TN (Eric Liu)
- Los Angeles, CA (Ed Wolin)
- Palo Alto, CA (Erick Mittra)
- Tampa, FL (Jon Strosberg)
- Chicago, IL (Al Benson)
- Iowa (Dave Bushnell)
- Houston, TX (James Yao, Ebrahim Delpassand)
- New Orleans, LA (Richard Campeau)
- Boston, MA (Matt Kulke)*
- Rochester, MN (Anthony Hobday)
- New York, NY (Stan Goldsmith)
- Durham, NC (Michael Morse)*
- Philadelphia, PA (Dave Metz)

* NOT RECRUITING

Eligibility

- 18 y/o or greater
- MIDGUT carcinoid (lower duodenum through right colon)
- PROGRESSING through a stable dose of Sandostatin LAR 20 or 30 mg
- Off other systemic therapies for 4 weeks
- No procedures for 12 weeks
- RANDOMIZED 1:1 PRRT vs. Sandostatin LAR 60mg monthly

Outline

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A day in the life of PRRT…

- Land in Europe
- Evaluation (tests, ultrasound, kidney tests)
- IV – hydration and amino acids
- PRRT Infusion
- Nauseated overnight
- Mildly tired for about a week
- Fly home
- Repeat every 8 weeks, 4x

Outline

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Hope…

- Stop the disease growth
- Slow the disease growth
- Improve the symptoms (hormones, pain, fatigue)
- Shrink the tumors
- Lasting effect

Outline

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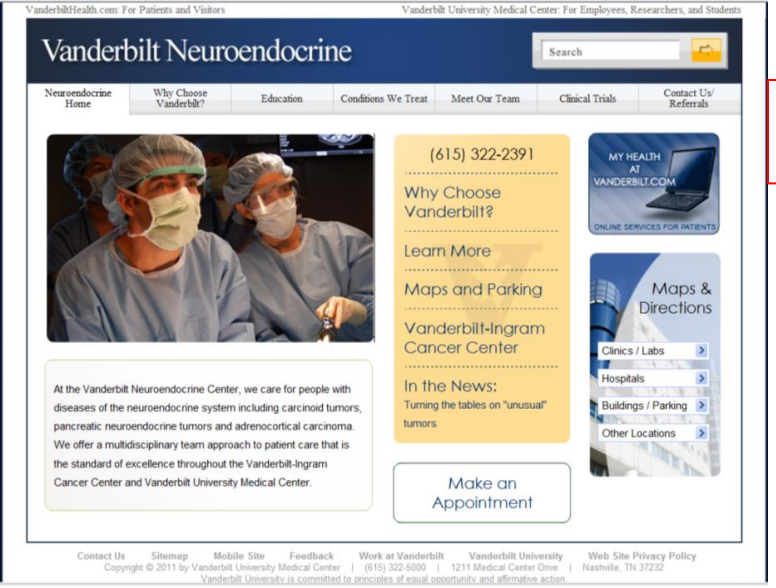
The history of the FDA…

- NETTER-1: 3-5 years
- FDA review
- Other small trials

- NEXT GENERATION OF PRRT
- COMBINATION THERAPY


derbilt Heart Institute
719 Thompson Lane
Suite # 22100
Nashville, TN 37204
MONROE CARELL JR.
Radioactive
Lutetium-177
LotNo.
Lu-11-020-03
Order No.
110674
Radioactive
Lutetium-177



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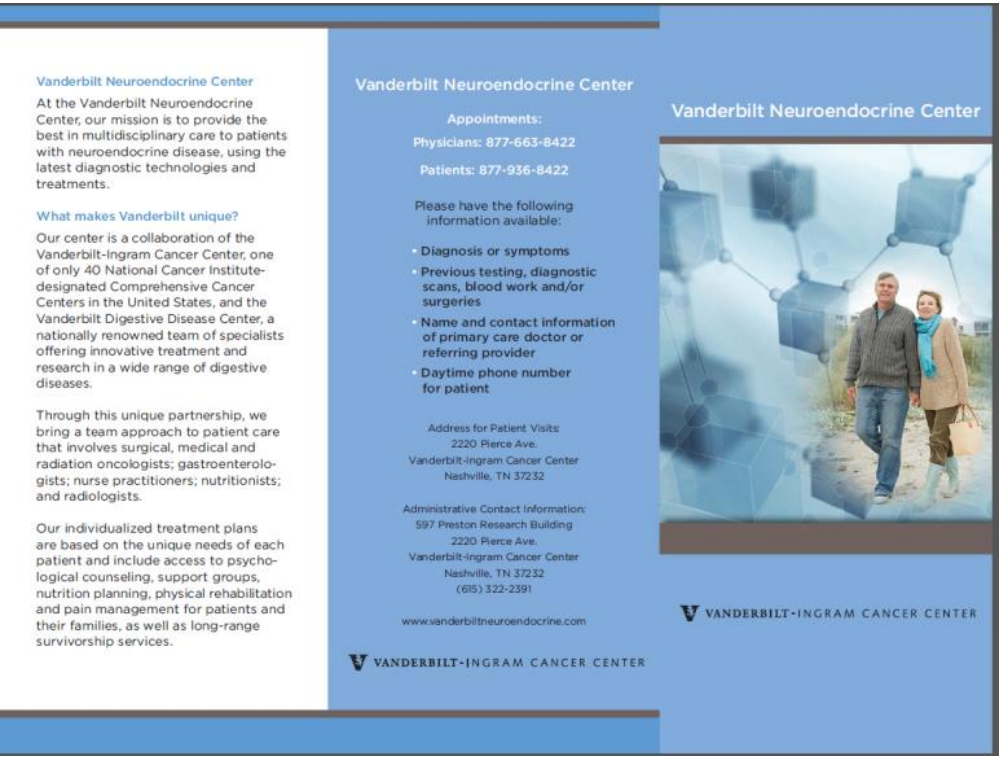
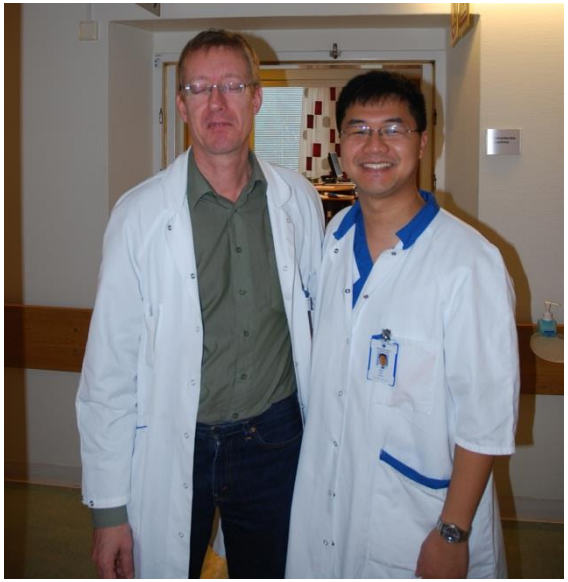
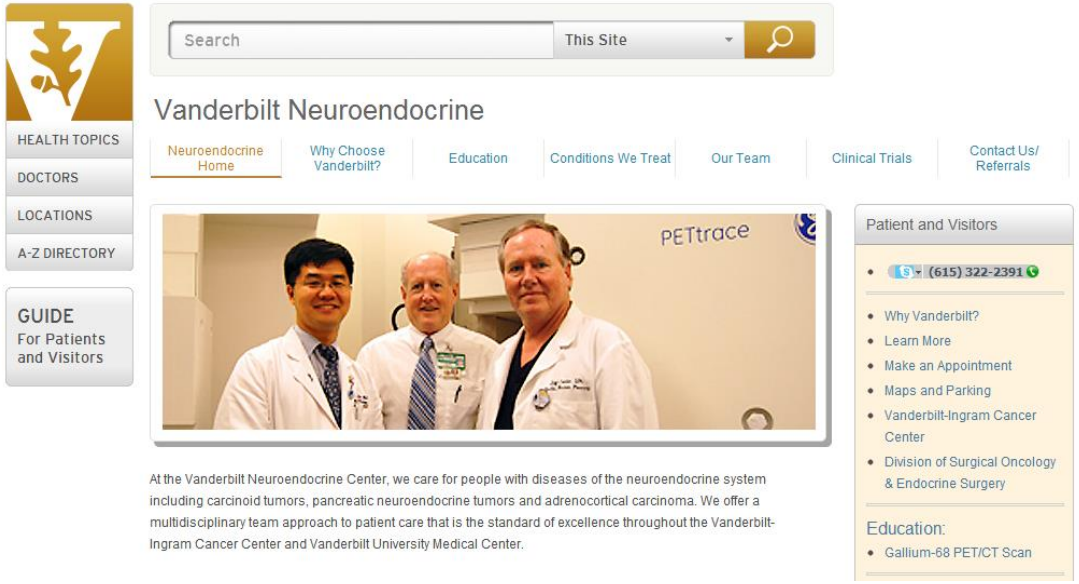


Thank You





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