PATHOPHYSIOLOGY AND MECHANISMS OF RADIOPHARMACEUTICAL LOCALIZATION

20140818 morning meeting 胡蓮欣

The Pathophysiological basis of Nuclear Medicine 2nd ed. Springer.

The mechanisms of radioisotope localization

1. Isotope dilution — In vivo, MUGA, RBC scan
2. Capillary blockade — MAA lung perfusion
3. Physicochemical adsorption — MDP bone scan
4. Cellular migration and sequestration — WBC scan, denatured RBC spleen scan
5. Membrane transport — Xe-133 ventilation
   - Simple diffusion — HMPAO/ECD brain perfusion scan
     - Diffusion and intracellular metabolism/binding — Tc-99m MIBI
     - Diffusion and mitochondrial binding
     - Diffusion and increased capillary and plasma membrane permeability — Gallium
   - Facilitated diffusion — FDG, IDA derivatives
   - Active transport — Radioiodine, pertecnetate, TlCl, Rb +
   - Phagocytosis — SC
   - Receptor-mediated endocytosis — Gallium
6. Metabolic Substrates and Precursors — FDG
   - Precursors: Radiolabeled Amino Acids — Amino acids
7. Tissue Hypoxia — F-MISO
8. Cell Proliferation
9. Specific Receptor Binding
   - Radiolabeled Peptides
   - Steroid Hormone Receptors
   - Adrenergic Presynaptic Receptors and Storage

Cell Proliferation

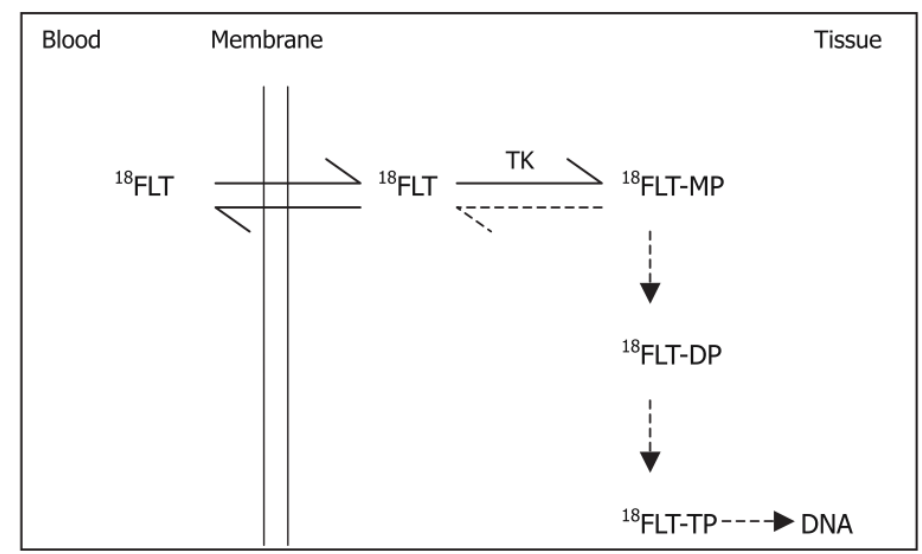
- Increased mitotic rate, cell proliferation, and lack of differentiation… main factors of malignant tissue
- Growth rate of tumors correlates with their level of differentiation
- Increased requirement of substrates (nucleotides) for DNA synthesis in tumors

8. Cell proliferation tracers

- H-3 TdR (H-3 thymidine)
  - in vitro use (thymidine labeling index)
  - Transported into cells by both passive diffusion & facilitated transport by Na+ dependant carriers
- C-11 TdR (C-11 thymidine)
  - PET tracer, used in head & neck tumors
  - But tumor uptake not optimal due to rapid metabolism in blood
- I-125 IudR (125 I-5-iodo-2'-deoxyuridine)
  - Analog of thymidine
  - Be phosphorylated and incorporated in DNA

Cell proliferation tracers

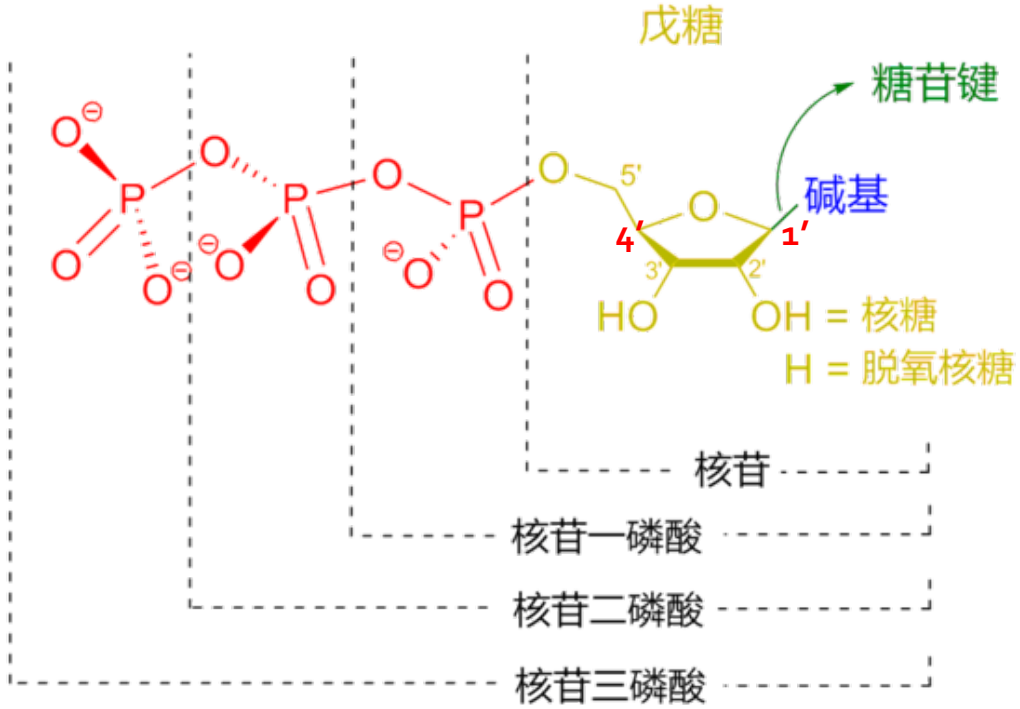
- F-18 FLT (18 F-Fluoro-3′-deoxy-3′-l-fluorothymidine)
  - passive diffusion & facilitated transport by Na+ dependant carriers
  - Then, phosphorylated by thymidine kinase 1 (TK1) into FLT-monophosphate→ trapped in the cells
  - Using H-3 FLT, it has been shown that FLT is not incorporated into DNA because it acts as a chain terminator (due to no 3′-OH group)



Nucleotides(核苷酸): 構成nucleic acids的基本單元

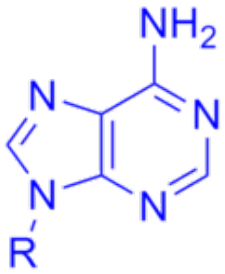
Structure of nucleotides

*注意5碳糖碳原子的編號

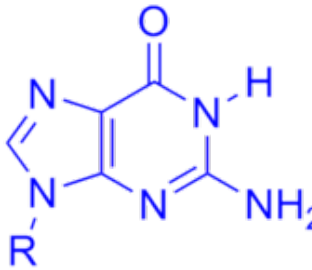


A G

嘌呤

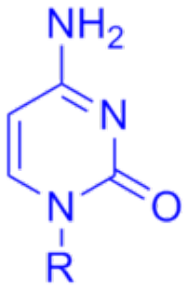


腺嘌呤

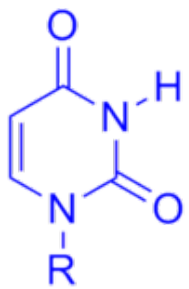


鸟嘌呤

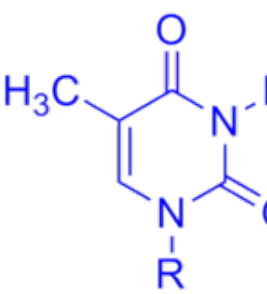
嘧啶



胞嘧啶



尿嘧啶



胸腺嘧啶

C U T

From Wikipedia, 核苷酸

Nucleic acid: include RNA & DNA

RNA (ribonucleic acid, 核醣核(苷)酸): GMP, TMP, AMP, CMP
→皆為核苷單磷酸，為30種**核苷酸**中的4種

		核醣+鹼基		單純鹼基	
Nucleotide **核苷酸**	Nucleoside **核苷**	Nucleobases 含氮鹽基	Adenosine 腺苷	Adenine (A) 腺嘌呤	purine
			Uridine 尿苷;尿嘧啶核苷	Uracil (U) 尿嘧啶	pyrimidine
			Cytidine 胞苷;胞嘧啶核苷	Cytosine (C) 胞嘧啶	pyrimidine
			Guanosine 鳥苷; 鳥嘌呤核苷	Guanine (G) 鳥糞嘌呤	purine
		五碳糖(核醣)			
	磷酸根	1 (M)			
		2 (D)			
		3 (T)			

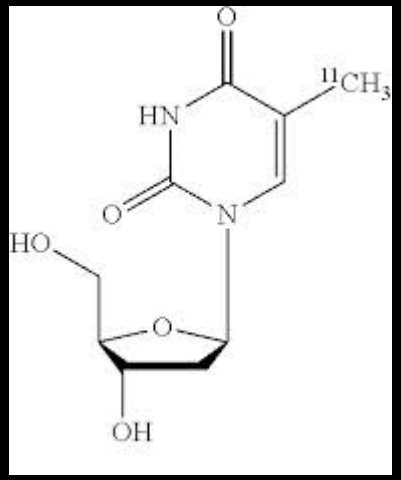
Nucleic acid: include RNA & DNA

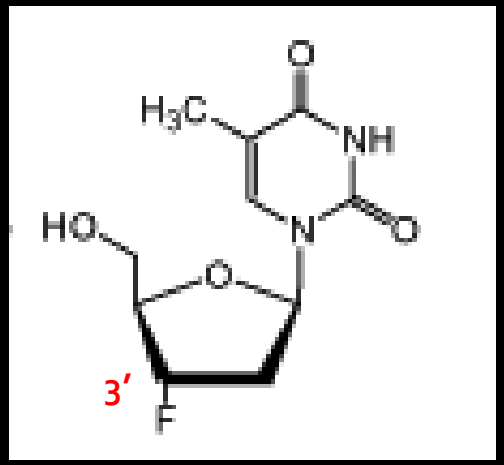
DNA (deoxyribonucleic acid, 去氧核醣核(苷)酸): dGMP, dTMP, dAMP, dCMP
皆為去氧核苷單磷酸,為30種**核苷酸**中的4種

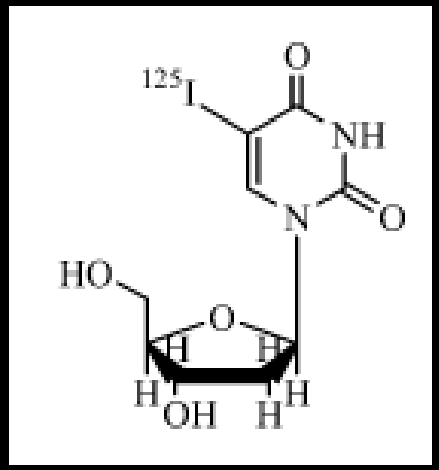
		核醣+鹼基		單純鹼基	
Nucleotide **(去氧)核苷酸**	Nucleoside **核苷**	Nucleobases 含氮鹽基	Adenosine 腺苷	Adenine (A) 腺嘌呤	purine
			Thymidine 胸苷;胸腺嘧啶核苷	Thymine (T) 胸腺嘧啶	pyrimidine
			Cytidine 胞苷;胞嘧啶核苷	Cytosine (C) 胞嘧啶	pyrimidine
			Guanosine 鳥苷; 鳥嘌呤核苷	Guanine (G) 鳥糞嘌呤	purine
		五碳糖(去氧核醣)			
	磷酸根	1 (M)			
		2 (D)			
		3 (T)			

A＝T（A 與T 配對→有二個氫鍵）
G≡C（G 與C 配對→有三個氫鍵）
二股間的寬度為2nm（$2x10^{-9}m$，20Å）

事實上不只核苷單磷酸…
還有核苷二磷酸、核苷三磷酸
還有去氧不去氧→ 共30種核苷酸!







H-3 thymidine

C-11 TdR

F-18 FLT

I-125 IudR

F-18 FLT 比起F-18 FDG sensitivity較差 (in malignant tumors)的可能原因:

1. Substitution in the 3′- position by F → decreased affinity for the pyrimidine transporter compared to thymidine
2. The affinity of FLT for TK is lower than that of thymidine

9. Specific Receptor Binding

Receptor binding radioisotopes,
各種會影響target tissue uptake的因素:

- blood clearance
- Specific activity
- affinity of the tracer
- Immunoreactivity or the relative biological potency
- in vivo stability
- nonspecific binding
- blood flow and perfusion of the tumor tissue

Specific Receptor Binding

- Radiolabeled Peptides
  - SST receptors
  - VIP receptors
- Steroid Hormone Receptors
- Adrenergic Presynaptic Receptors and Storage
- LDL Receptors
- Radiolabeled Antibodies

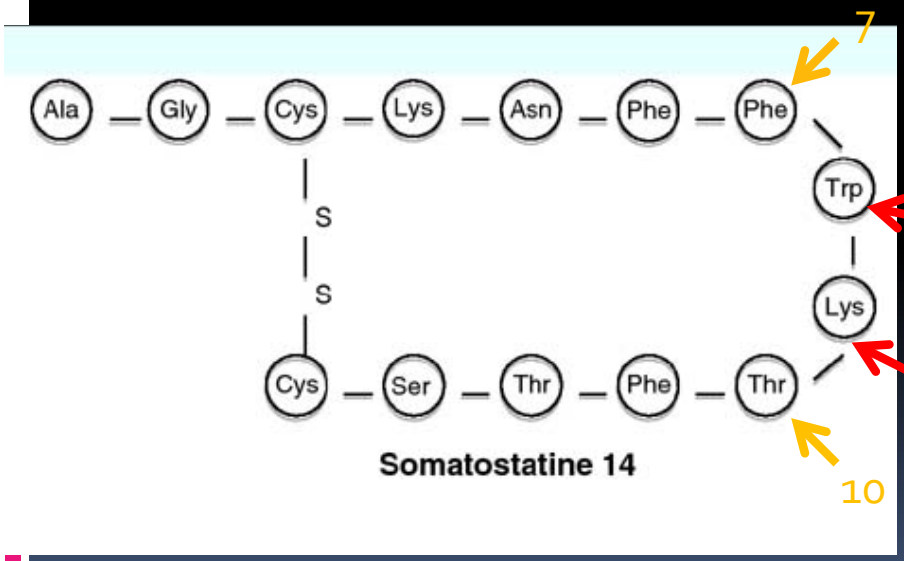
Specific Receptor Binding—Radiolabeled peptides

- Somatostatin receptors
  - Somatostatin
  - Somatostatin analogues
  - Radiolabeled SST analogs
- VIP Receptors
  - I-123 VIP

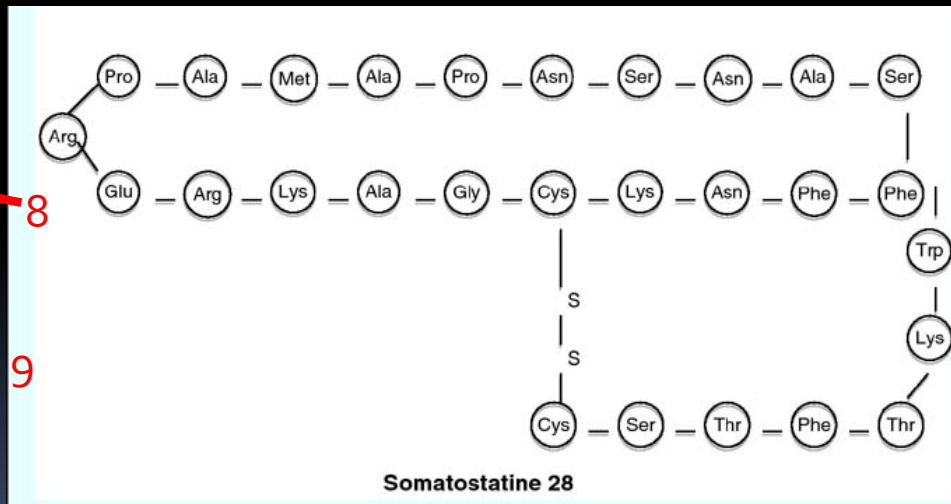
Specific Receptor Binding– Radiolabeled peptides

Somatostatin

- SST14 & SST28: two naturally occurring bioactive somatostatin products
- Phe 7 , Trp 8 , Lys 9 , Thr 10: are necessary for biological activity in SST 14
- Trp and Lys: essential; Phe and Thr: can undergo minor substitutions



Somatostatine 14



Somatostatine 28

Specific Receptor Binding– Radiolabeled peptides

Somatostatin

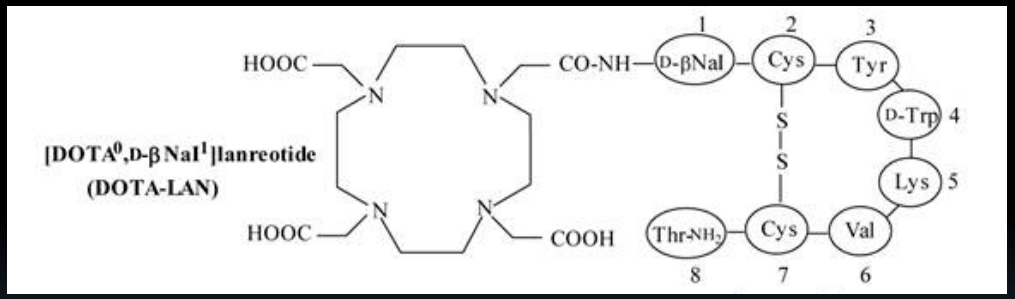
- Secretion: throughout the body
- Function: inhibition of secretion of GH, glucagon, insulin, gastrin, and other hormones by the pituitary and GI tract
- Receptors: G-protein-coupled receptors
  - 5 subtypes: SSTR1 to SSTR5
  - On cells of neuroendocrine origin as well as on lymphocytes
  - Neuroendocrine tumors (small cell lung cancers, and medullary thyroid carcinomas)

Specific Receptor Binding– Radiolabeled peptides

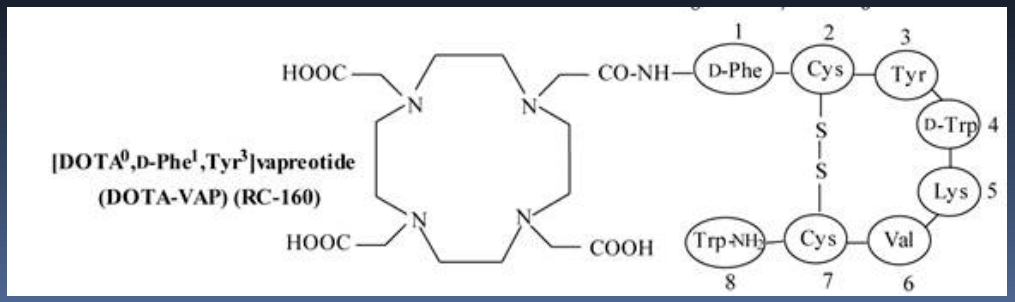
Somatostatin analogues

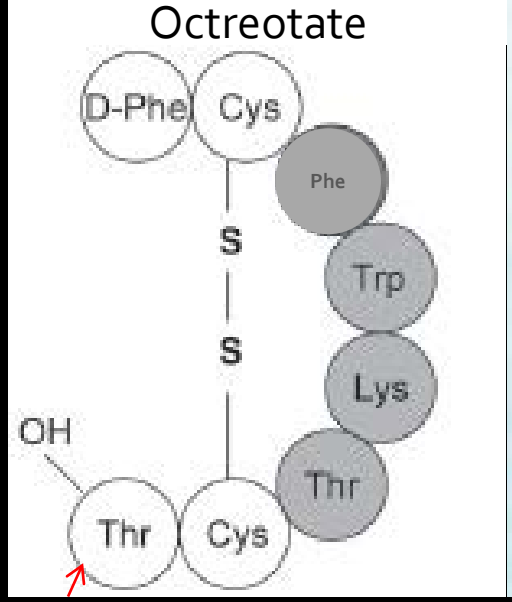
- have greater biological stability than SST 14
- consist of hexapeptide and octapeptide molecules, which incorporate the biologically active core of SST 14

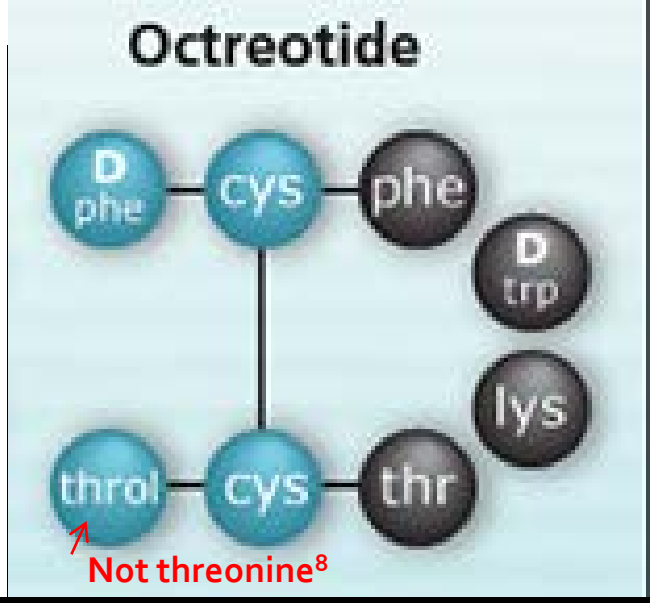
- Seglitide
- Octreotide
- Somatuline
- Lanreotide

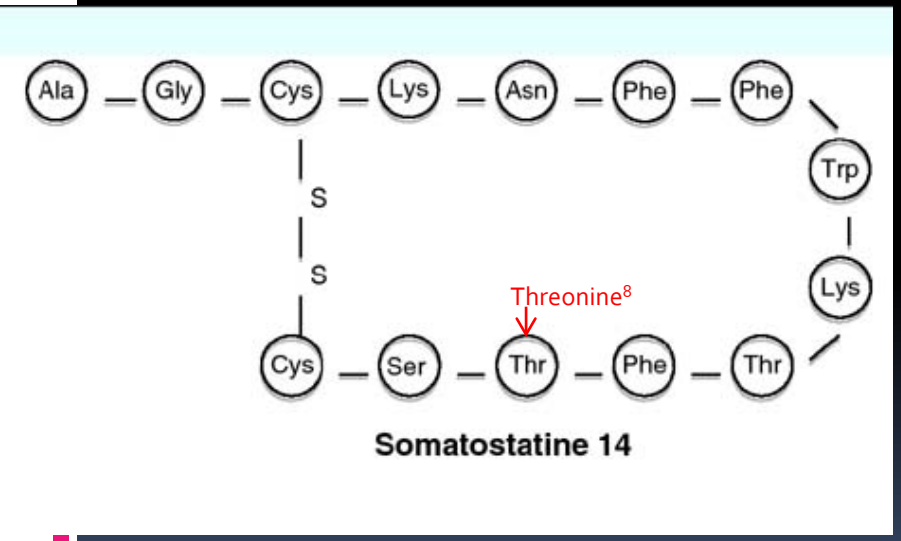


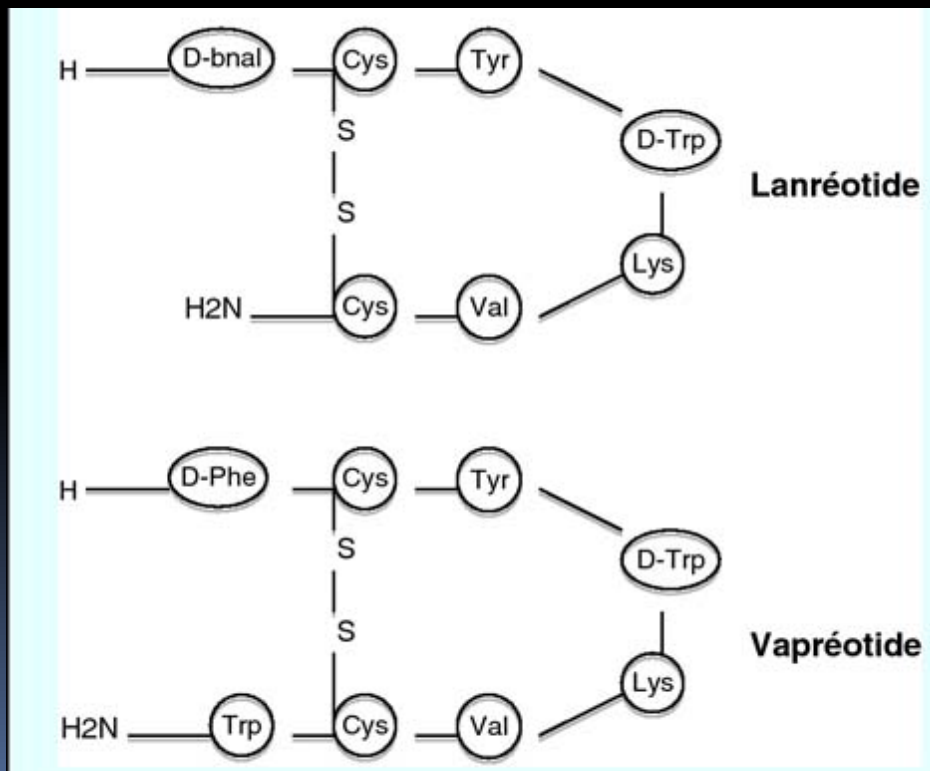
- RC-160



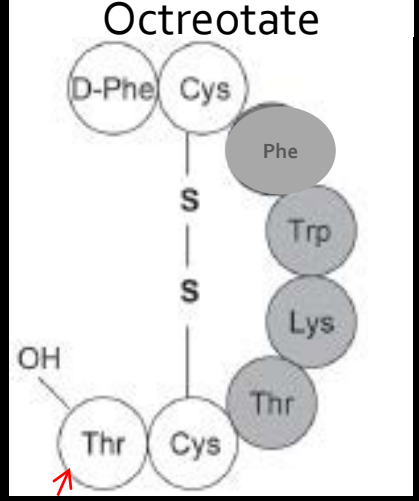

Octreotate
D-Phe
Cys
Phe
Trp
Lys
Thr
Cys
Thr
S
S
OH

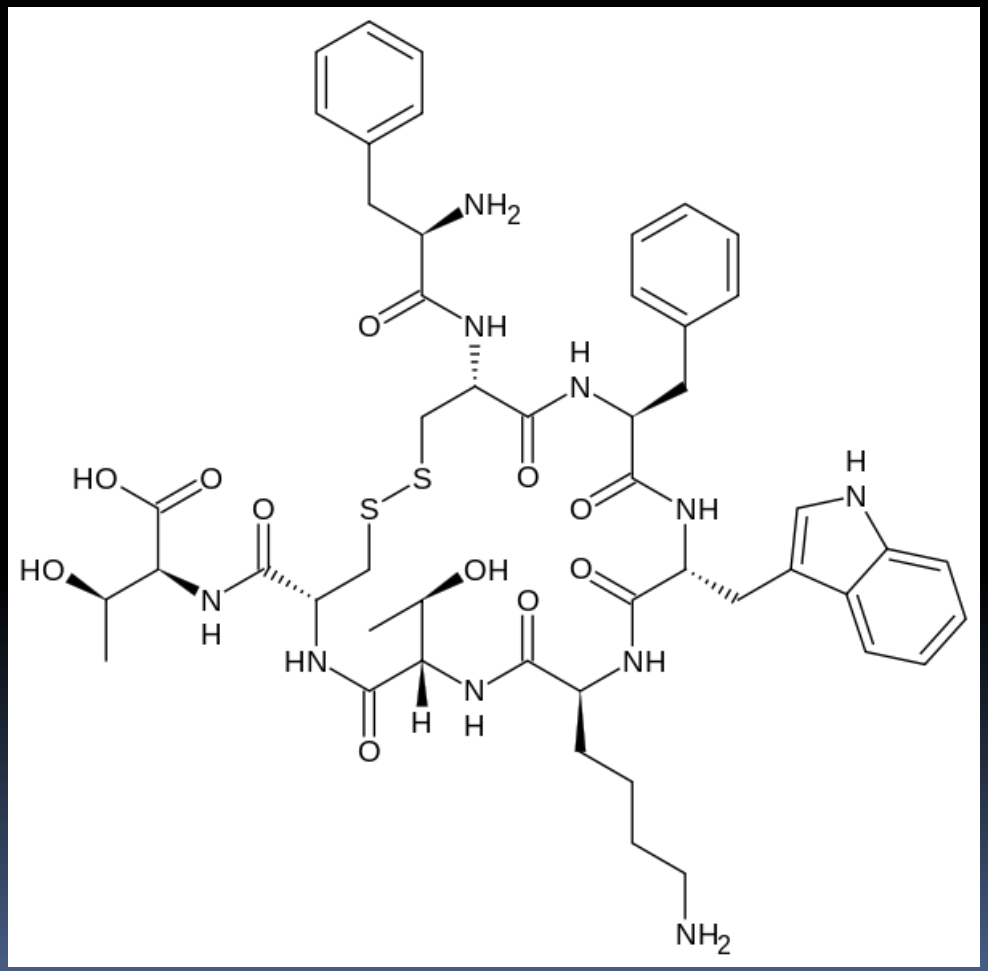

Octreotide
D phe
cys
phe
D trp
lys
throl
cys
thr
Not threonine8


Ala
Gly
Cys
Lys
Asn
Phe
Phe
Trp
Lys
Thr
Phe
Thr
Ser
Cys
S
S
Threonine8
Somatostatine 14


H
D-bnal
Cys
Tyr
D-Trp
Lanréotide
Lys
H2N
Cys
Val
S
S
H
D-Phe
Cys
Tyr
D-Trp
Vapréotide
Lys
H2N
Trp
Cys
Val
S
S

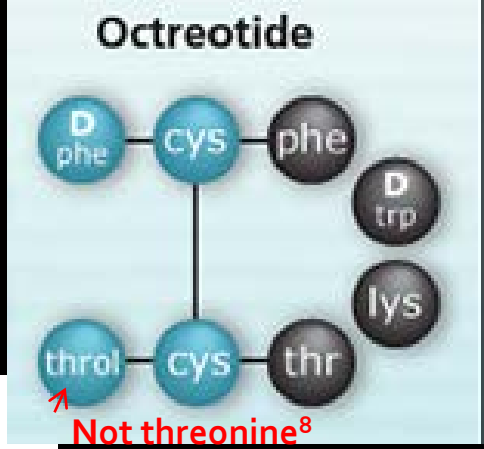
Octreotate





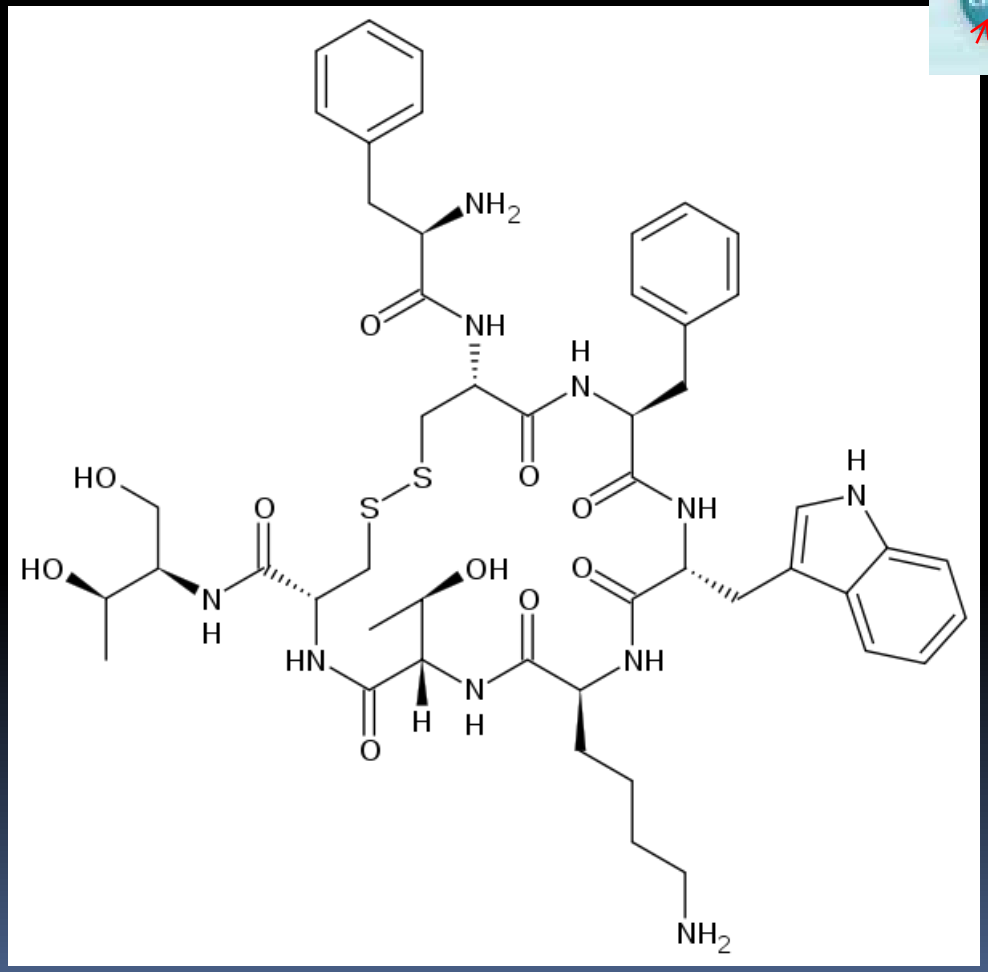
from: Wikipedia, octreotate

Octreotide

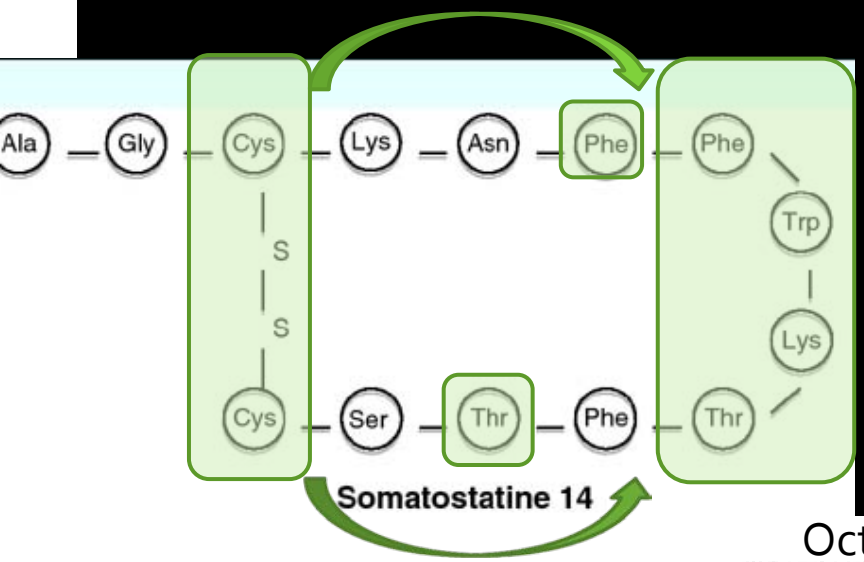


Not threonine[8]

But a reduced amino alcohol



from: Wikipedia, octreotide



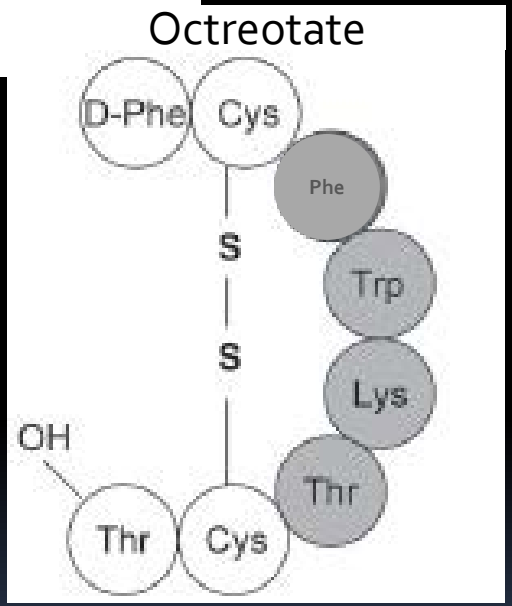
Somatostatin14 →Octreotate→ DOTATATE

重新組裝

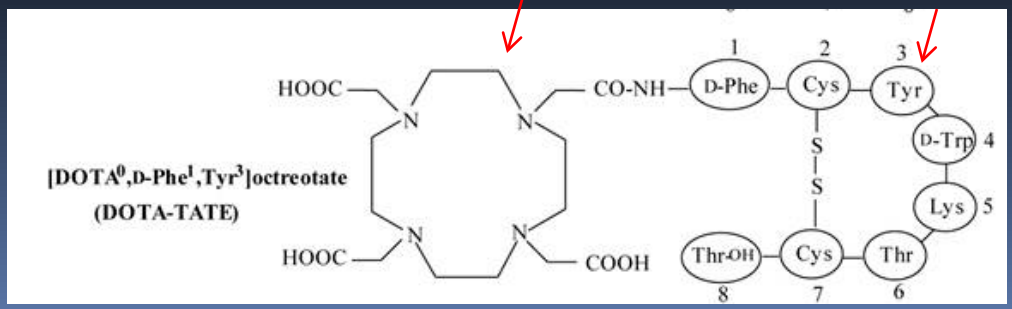
Phe³→ Tyr³
並加上DOTA

DOTATATE
= DOTA-(Tyr³)-octreotate

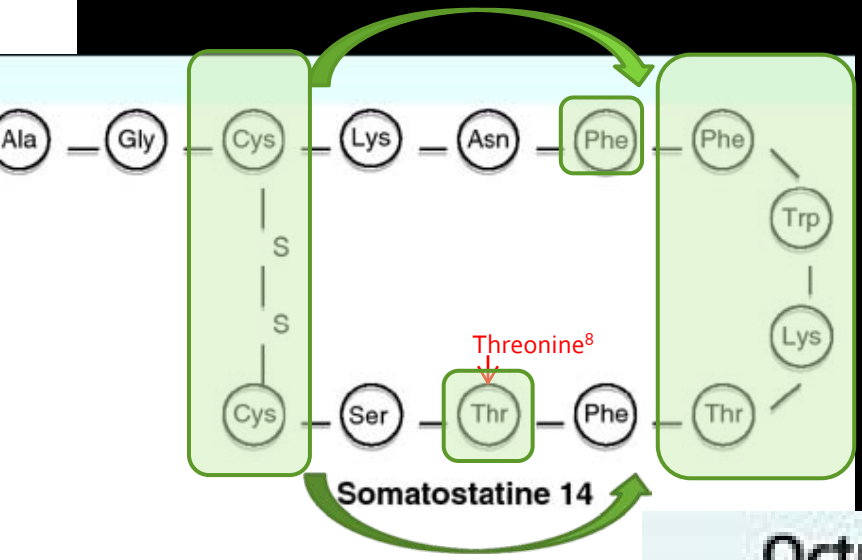
Octreotate



DOTATATE



Theranostics 2012; 2(5):481-501
http://www.thno.org/vo2po481.htm

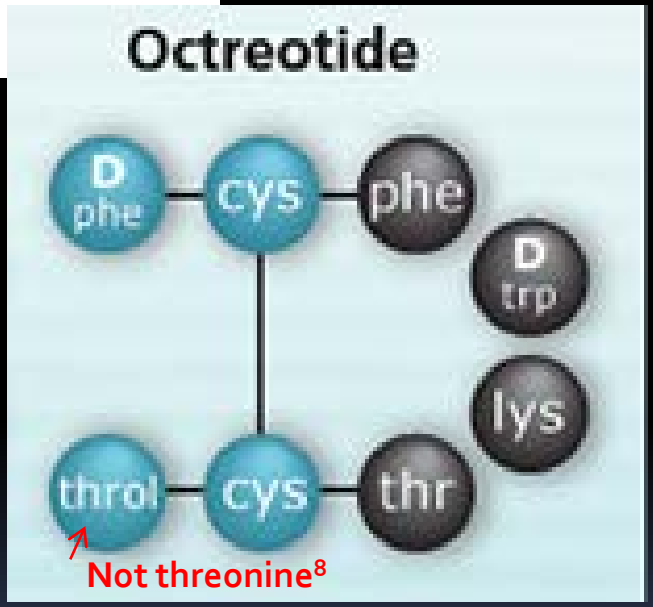


Somatostatin14 →Octreotide→ DOTATOC

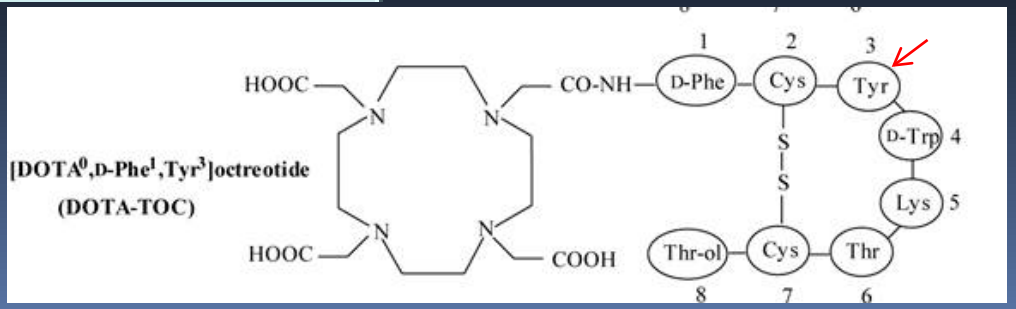
重新組裝&thr→throl

Phe³→ tyr³
並加上DOTA

DOTATOC
= (DOTA⁰-Phe¹-Tyr³)octreotide
= **Edotreotide** (USAN, codenamed **SMT487**)



DOTATOC



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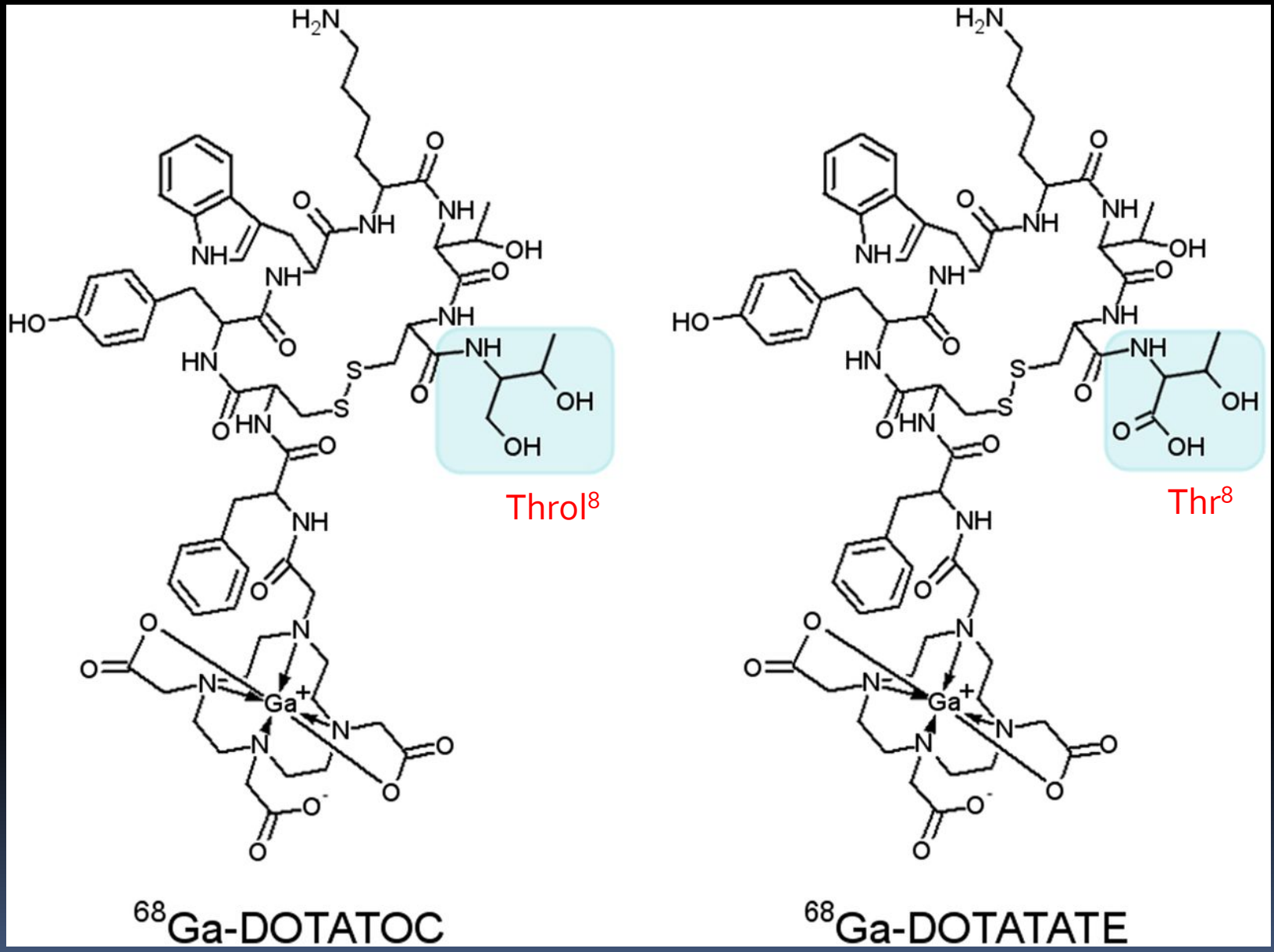


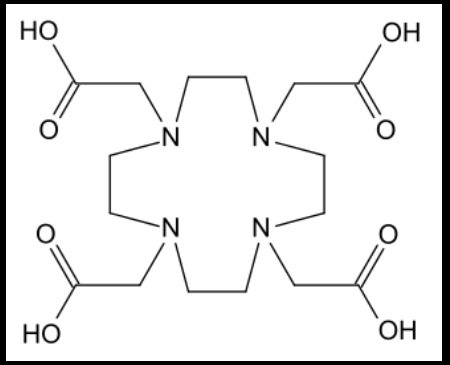
J Nucl Med February 1, 2014 vol. 55 no. 2 204-210

The relationship between…

- Somatostatin: SST14 or SST28
- Octreotate: 8 amino acid
- Octreotide: 8 amino acid, thre→ throl
- DOTA-TATE: octreotate phe→ tyr + DOTA
- DOTA-TOC: octreotide phe→tyr + DOTA
- Pentreotide: octreotide + DTPA
- DOTA-LAN: lanreotide + DOTA
- Y90-DOTA-Tyr^3-octreotide: DOTATOC+ Y90

- DOTA

DOTA (chelator)



- 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, formula $(CH_2CH_2NCH_2CO_2H)_4$
- The molecule consists of a central 12-membered tetraaza (i.e., containing four nitrogen atoms) ring
- DOTA is used as a complexing agent (錯合劑、複合劑), especially for lanthanide(鑭系元素) ions
- Its complexes have medical applications as contrast agents and cancer treatments.

圖文from: Wikipedia, DOTA

Specific Receptor Binding–Radiolabeled peptides

Radiolabeled SST Analogs

1. [^{123}I-Tyr^{3}]-octreotide
   - The 1st radiotracer introduced for imaging SSTR-positive tumors
   - in vivo dehalogenation (脫鹵) and biliary excretion→ accumulation of activity in the intestines and bladder→ interpretation difficulty
2. [^{111}In-DTPA-d-Phe^{1}]-octreotide
   - In-111 pentetreotide, Octreoscan®
   - High specific activity (5-6 mCi of In-111/10 ug octreotide)
   - Filtrated by glomerulus, and reabsorbed in renal tubules partially → prolonged residence time of renal activity
   - Rapidly cleared from kidneys (50% within 5h)→ less intestinal activity than [123 I-Tyr 3]-octreotide

Specific Receptor Binding– Radiolabeled peptides

Radiolabeled SST Analogs

3. $^{90}Y/^{111}In$-DOTA-lanreotide
   - $^{90}Y/^{111}In$-DOTA-LAN
   - SSTR1: low affinity (Kd 200 nM)
   - SSTR2-5: high affinity (Kd 1-10 nM)
   - ^{90}Y-DOTA-LAN: Tx potential under investigation
4. $^{90}Y/^{111}In$-DOTA-TOC
   - ^{90}Y-DOTA-TOC: Tx potential under investigation
5. ^{99m}Tc-P829
   - NeoTect®, Amersham Inc
   - approved by the FDA for imaging lung tumors

Specific Receptor Binding– Radiolabeled peptides

- Somatostatin receptors
  - Somatostatin
  - Somatostatin analogues
  - Radiolabeled SST analogs
- VIP Receptors
  - I-123 VIP

Specific Receptor Binding– Radiolabeled peptides

Vasoactive intestinal peptide (VIP) & VIP receptors

- 28-amino-acid neuroendocrine mediator
- broad range of biological activity in diverse cells and tissues:
  - Vasodilator
  - promotes the growth and proliferation of normal and malignant cells.
- VIP receptors
  - Cell membrane of GI tract: widely distributed
  - various other cell types
- Icreased VIP receptor expression:
  - Adenocarcinomas
  - breast cancers
  - Melanomas
  - Neuroblastomas
  - pancreatic carcinomas

Specific Receptor Binding–Radiolabeled peptides

I-123 VIP

- High-specific-activity 123 I-VIP (150–200 MBq/μg)
- Specific uptake:
  - primary tumors
  - metastases (in liver, lung, and LNs) of pancreatic adenocarcinoma, colon adenocarcinoma, or GI neuroendocrine tumors
- Interaction between VIP and SST on various cell types
  - high-affinity binding of 123 I-VIP to SSTR 3 suggests that the SSTR 3 receptor subtype might be the site of cross-competition between VIP and SST