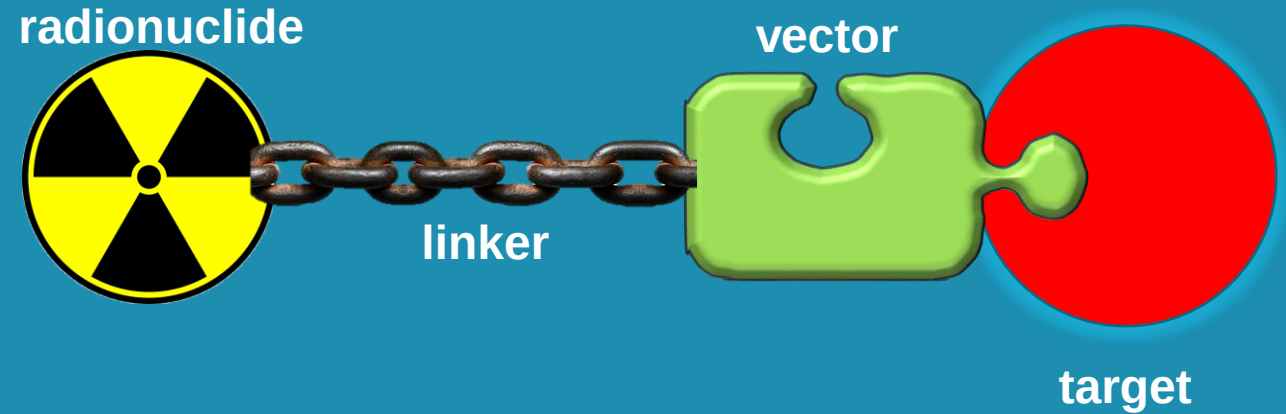




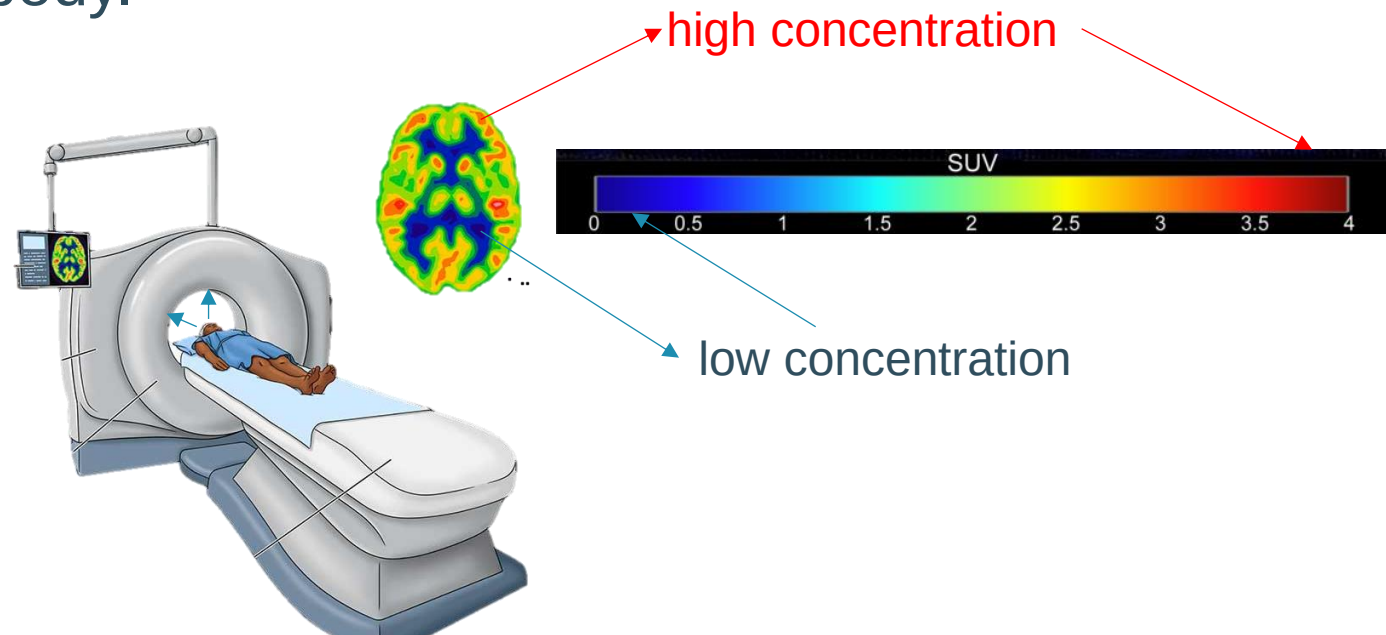
Radiopharmaceuticals: radionuclides and vectors

Guy Bormans

Lab Radiopharmaceutical Research

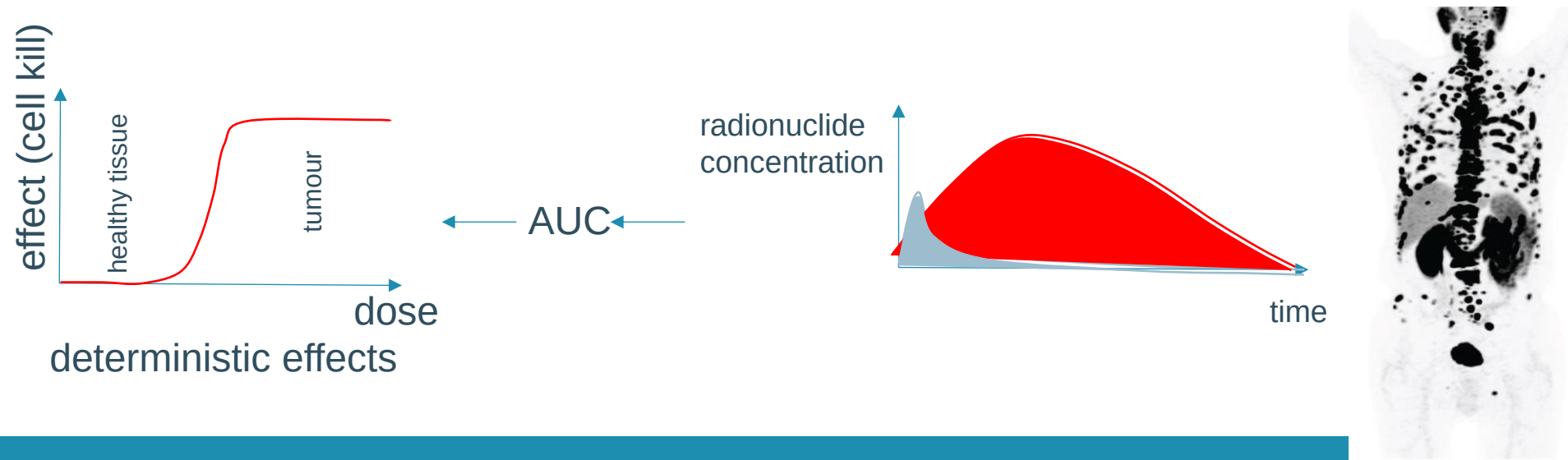
Diagnostic radiopharmaceutical

- Contains a **radionuclide** that upon decay will emit **electromagnetic radiation** (gamma or X-rays) that travel out of the body to be detected externally by a dedicated camera (SPECT or PET). This provides diagnostic images of which the **contrast** depends on the local concentration of the radionuclide in the body.



Therapeutic radiopharmaceutical

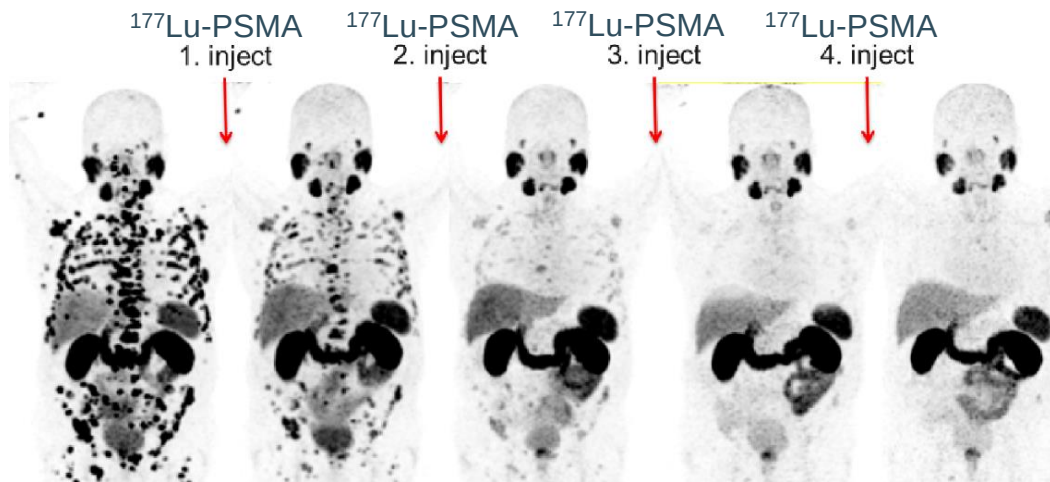
- Contains a **radionuclide** that upon decay will emit **particulate radiation** (beta, alpha rays) or low energy electromagnetic radiation generating Auger low energy electrons. This results in a lethal radiation dose to cells in the vicinity of the radionuclide. The **radiation dose** to the tissues in the body depends on the local concentration*residence time of the radionuclide in the tissues/cells.



Theranostics

combination of diagnostic imaging of a target for radionuclide therapy to select patients, calculate dosimetry and follow-up on treatment response.

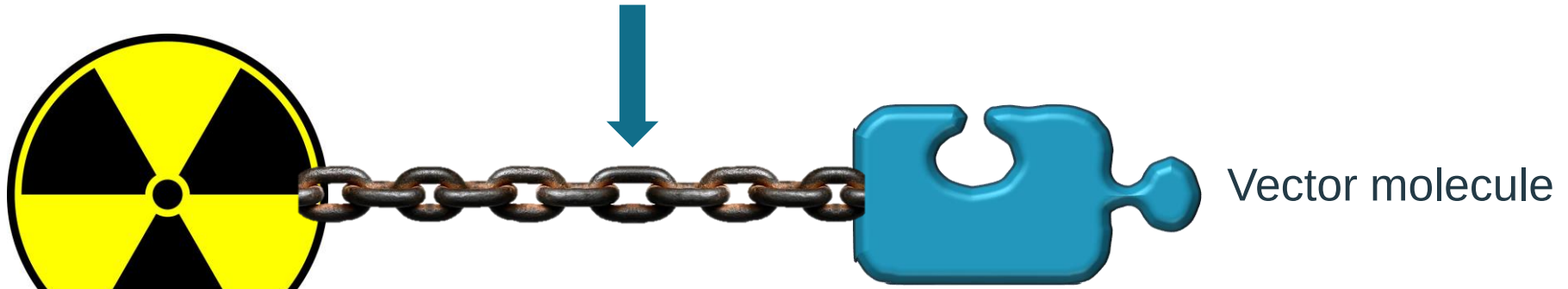
treat what you see- see what you treat



subsequent ^{68}Ga -PSMA PET scans in a patient with metastatic prostate cancer before and after 1-4 cycles of ^{177}Lu -PSMA radionuclide therapy

Radiopharmaceutical

linker: chemical connection between radionuclide and vectormolecule



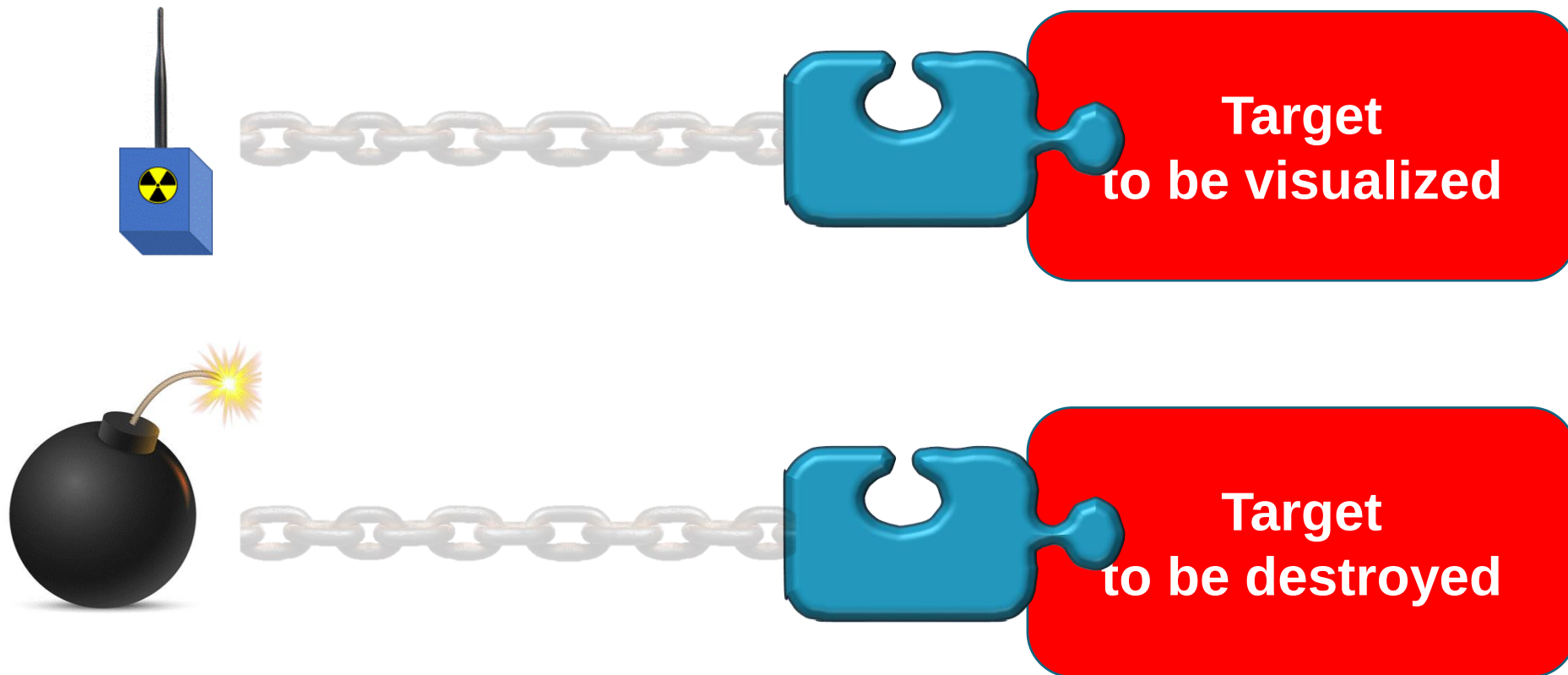
radionuclide
emits EM or particulate radiation

interaction with target in the body to increase
radionuclide concentration in target tissue:

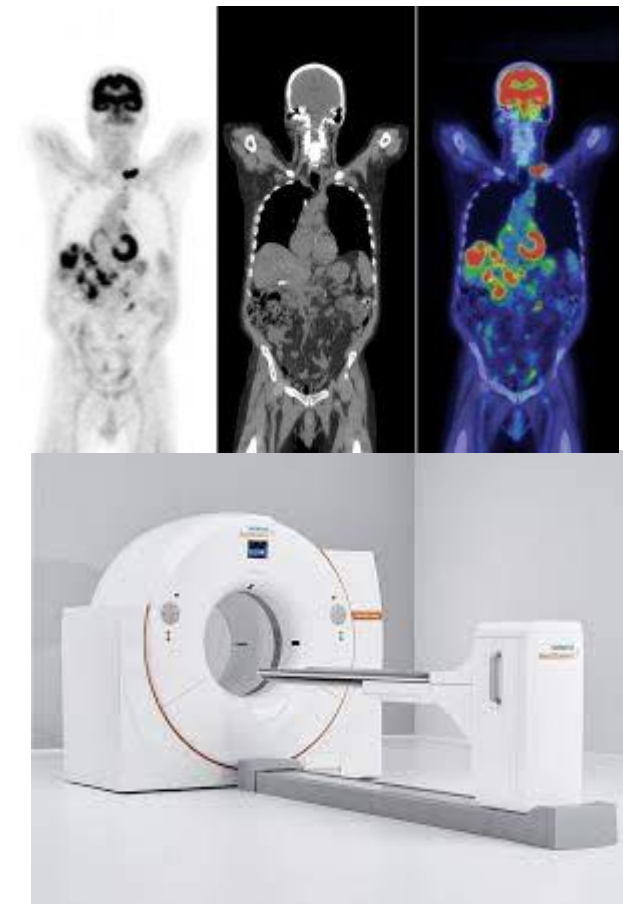
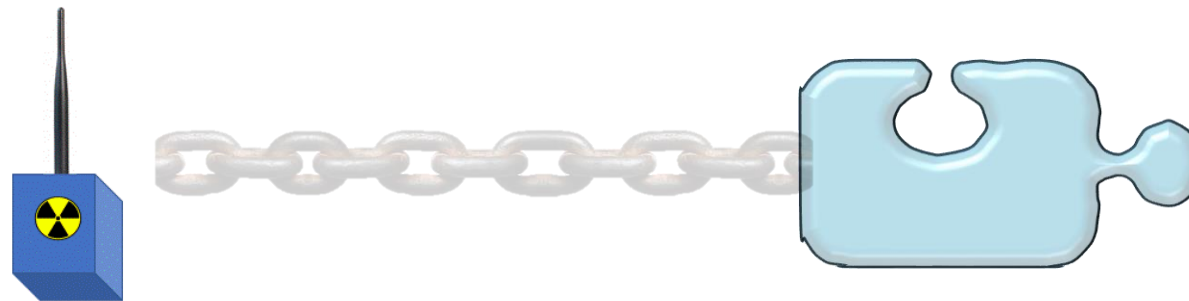
vectorisation

sensitive detection (diagnosis) /strong effects radiotherapy:
typically low mass amount of tracer needed (μg range), no pharmacological effects

concept radiopharmaceutical



Radionuclides for imaging



radionuclide for imaging:

emits radiation to be detected externally (PET or SPECT camera)

low radiation dose to the patient

high resolution images

ideal **physical** characteristics (decay, half-life, gamma ray energy, production,...)

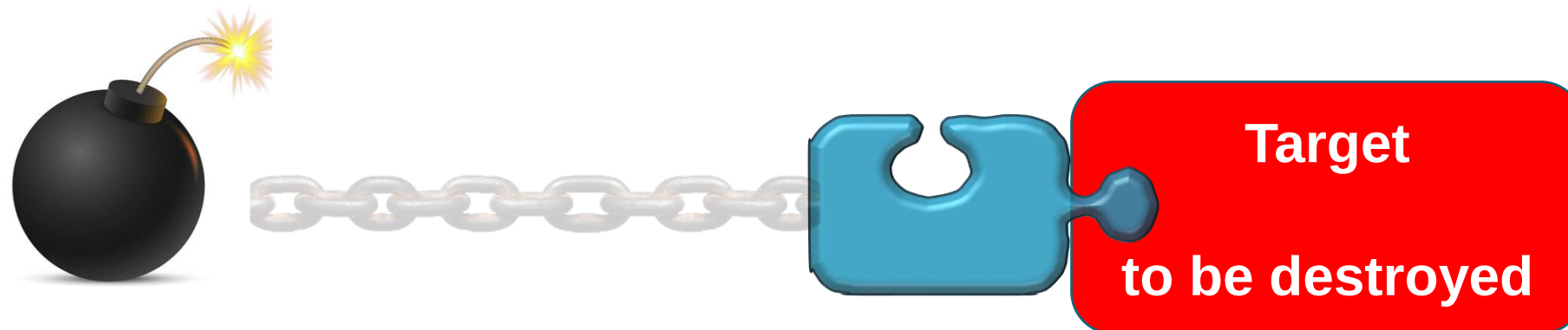
radionuclides for positron emission tomography (PET)

Radio-nuclide	Half-life	Mode of decay	β^+ $E_{\max}$ (keV) max range in H_2O (mm)	Chemistry	production
^{82}Rb	76 s	β^+ (95%) EC (5%)	3381 keV 18 mm	Only used as $^{81}Rb^+$	$^{82}Sr/^{82}Rb$ generator
^{15}O	122 s	β^+ (99.9%) EC (0.1%)	1732 8.4 mm	Only used as $H_2^{15}O$, $C^{15}O$	Cyclotron Gas target $^{14}N(d,n)$ or $^{15}N(p,n)$
^{13}N	9.97 min	β^+ (100%)	1199 keV 5.5 mm	Almost only used as $^{13}NH_3$ Very fast organic chemistry	Cyclotron Liquid target $^{16}O(p,\alpha)$
^{11}C	20.4 min	β^+ (100%)	960 keV 4.2 mm	Fast organic chemistry	Cyclotron Gas target $^{14}N(p,\alpha)$
^{68}Ga	68 min	β^+ (89%) EC (11%)	1899 keV 8.9 mm	Radiometal Chelation chemistry	Generator $^{68}Ge-^{68}Ga$ Cyclotron solid /liquid target $^{68}Zn(p,n)$
^{18}F	109.8 min	β^+ (97%) EC (3%)	634 keV 2.3 mm	Fast organic chemistry	Cyclotron Liquid target $^{18}O(p,n)$
^{64}Cu	12.7h	β^+ (18%) EC (44%) β^- (38%)	653 keV 2.5 mm	Radiometal Chelation chemistry	Cyclotron Solid target $^{64}Ni(p,n)$
^{89}Zr	78.4 h	β^+ (23%) EC (77%)	902 keV 3.8 mm	Radiometal Chelation chemistry	Cyclotron Solid target $^{89}Y(p,n)$

radionuclides for single photon emission computed tomography (SPECT)

Radio-nuclide	Half-life	Mode of decay	Gamma energy (keV)	Chemistry	production
^{81m}Kr	13 s	IT (100%)	190 (100%)	Only used as Kr gas	Generator $^{81}\text{Rb}-^{81m}\text{Kr}$
^{99m}Tc	6h	IT (100%)	140 (100%)	radiometal Chelation chemistry (reduction of Tc required)	generator
^{123}I	13 h	EC (100%)	159 (97%)	Organic chemistry	Cyclotron gas target $^{124}\text{Xe} (p,pn) ^{123}\text{Xe} \rightarrow ^{123}\text{I}$
^{111}In	67h	EC (100%)	245 (100%) 171 (100%)	Radiometal Chelation chemistry	Cyclotron solid target $^{112}\text{Cd}(p,2n) ^{111}\text{In}$
^{75}Se	119 d	EC(100%)	264 (59%) 136 (58%) 280 (25%)	Organic Chemistry	Cyclotron solid target $^{75}\text{As}(p,n)^{75}\text{Se}$ Nuclear reactor $^{74}\text{Se}(n,\gamma)^{75}\text{Se}$

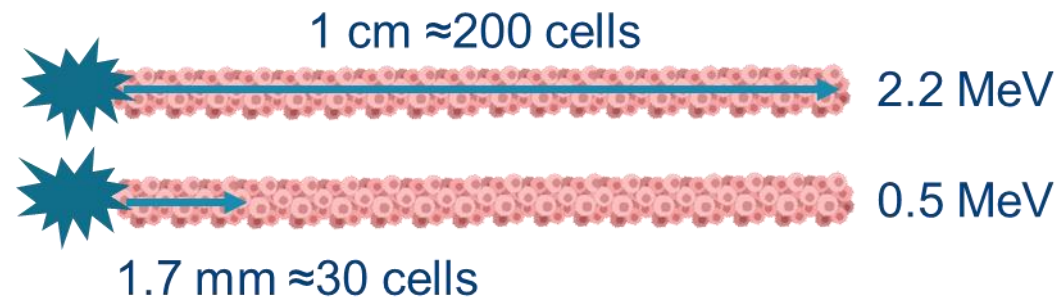
Radiopharmaceuticals for therapeutic applications



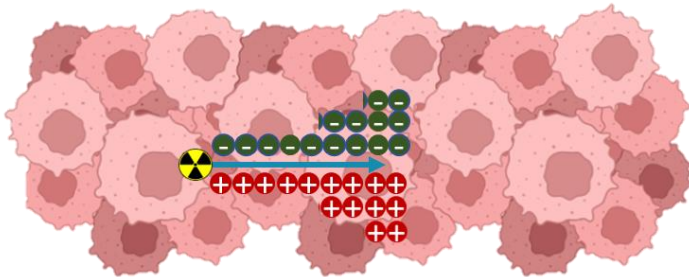
radionuclide for (tumor) therapy:
short range,
high LET
for selective killing of target cells

β^- emitters

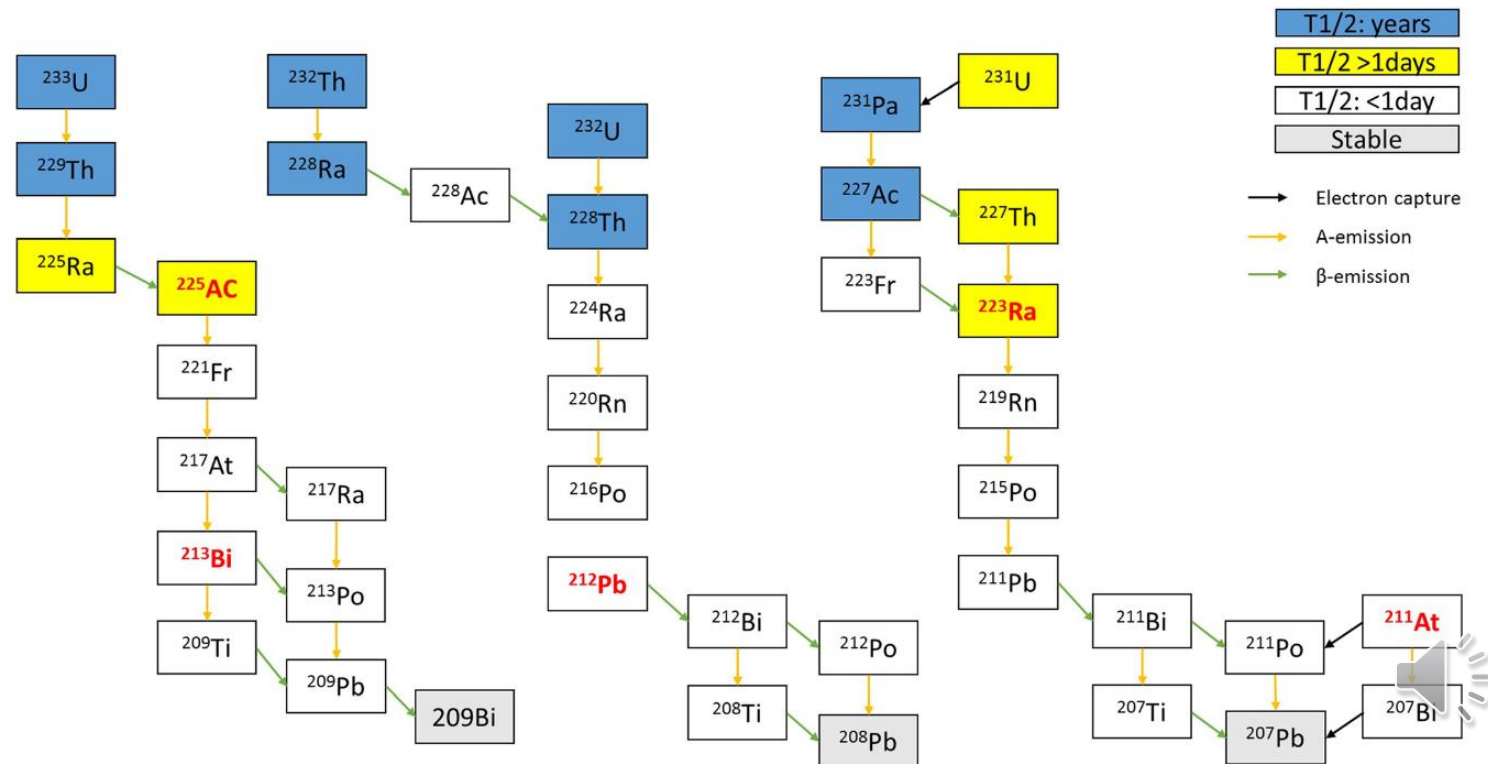
radionuclide	$T_{1/2}$	E_γ (keV) %intensity	E_β max (keV) max range (mm)	chemistry	production
^{90}Y	64 h		2280 keV 11 mm	Radiometal chelation chemistry	Nuclear reactor $^{89}\text{Y}(n,\gamma)^{90}\text{Y}$ Generator $^{90}\text{Sr}/^{90}\text{Y}$
^{131}I	8 d	364 keV 82%	606 keV 2.4 mm	Halogen Organic chemistry	Nuclear reactor ^{235}U fission $^{130}\text{Te}(n,\gamma)^{131}\text{Te} \rightarrow ^{131}\text{I}$
^{177}Lu	6.73 d	208 keV, 113 keV 11% 6%	498 keV 1.7 mm	Radiometal Chelation chemistry	Nuclear reactor $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb} \rightarrow ^{177}\text{Lu}$ $^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$ (low specific activity, contamination with $^{177\text{m}}\text{Lu}$ ($T_{1/2}$ 160 d))



radionuclide	T _{1/2}	#α energy	chemistry	production
²²⁵ Ac	10 d	4α 5 MeV	Radiometal Chelation chemistry	generator ²²⁹ Th→ ²²⁵ Ra→ ²²⁵ Ac
²¹¹ At	7.2 h	1α 5 MeV	Halogen Organic chemistry	Cyclotron (α accelerator) ²⁰⁹ Bi(α,2n) ²¹¹ At
²¹² Pb	10.64h		Radiometal Chelation chemistry	Generator (²²⁸ Th or ²²⁴ Ra)
²²³ Ra	11.4 d	4α 6 MeV	Radiometal Difficult to form stable chelates Used as RaCl ₂ (Xofigo)	generator ²²⁷ Ac→ ²²⁷ Th→ ²²³ Ra

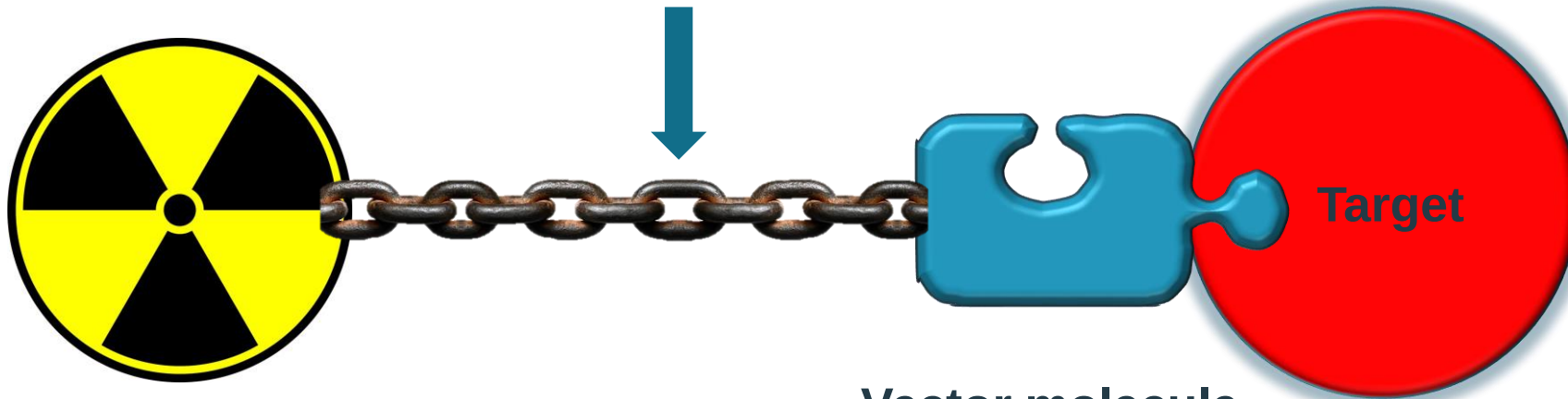


40-100 μm ~ 1-5 cells



Radiopharmaceutical

linker: chemical connection between radionuclide and vectormolecule



radionuclide

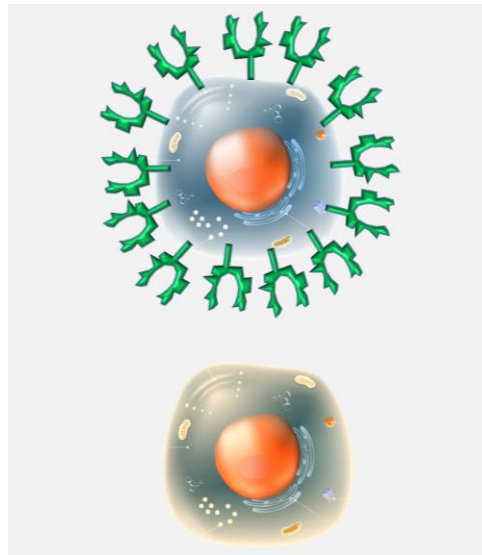
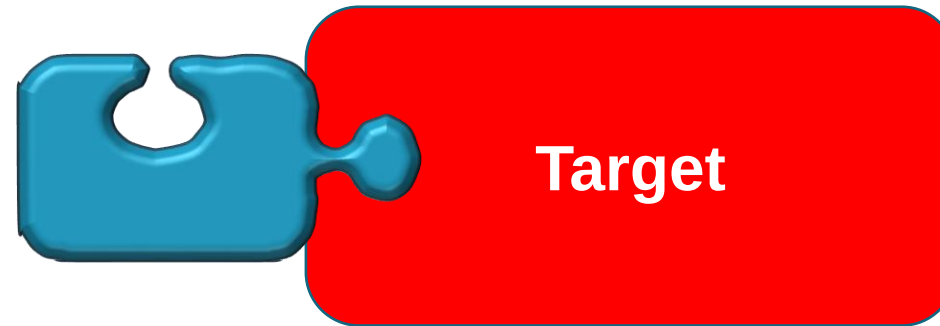
emits EM and/or particulate radiation

Vector molecule

interaction with target in the body to increase radionuclide concentration in target tissue:

vectorisation

vector targeting

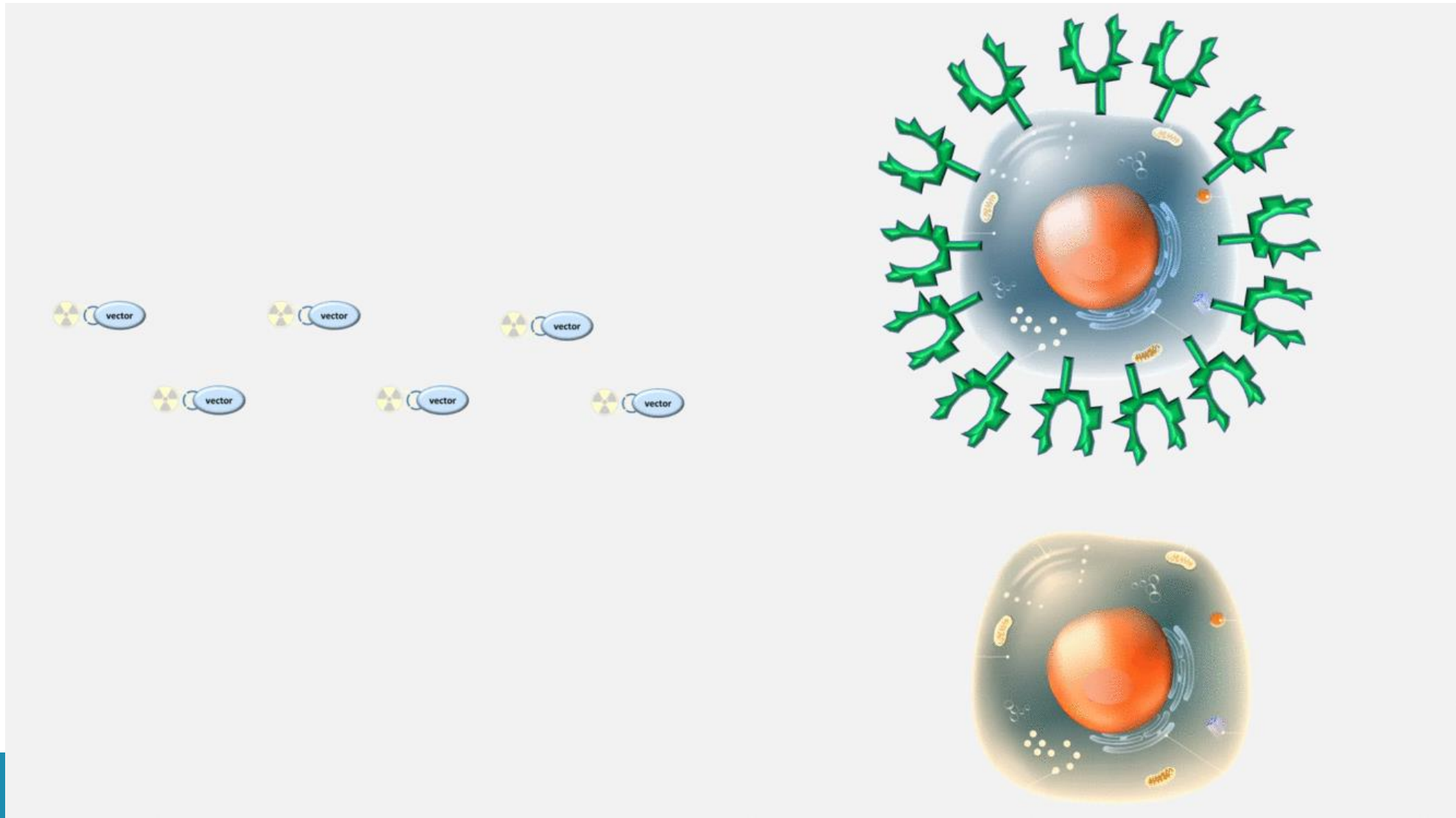


cell expressing the target

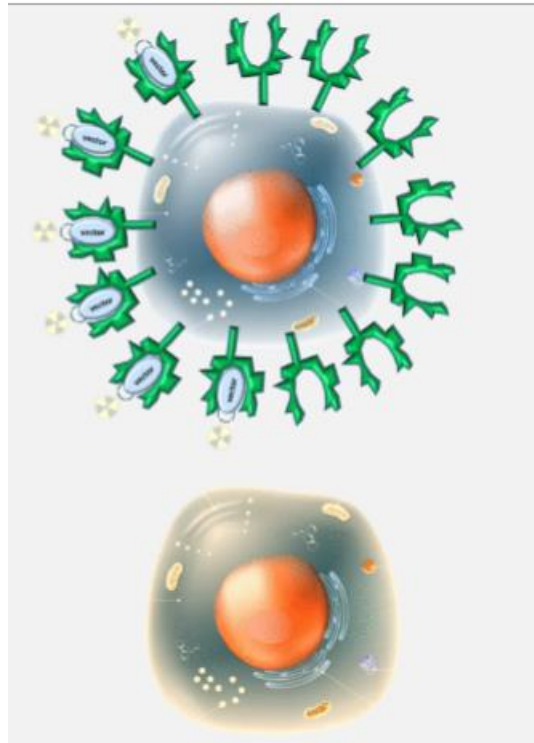


cell not expressing the target

vector targeting



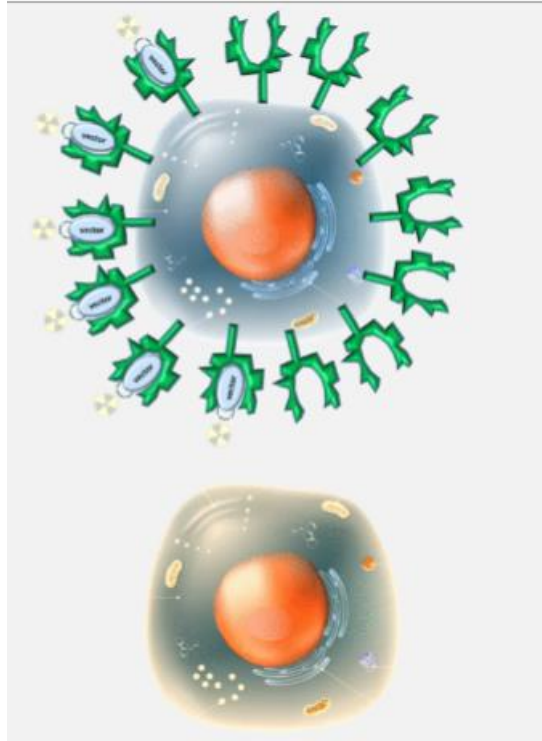
vector targeting



high concentration of radionuclide

low concentration of radionuclide

vector targeting

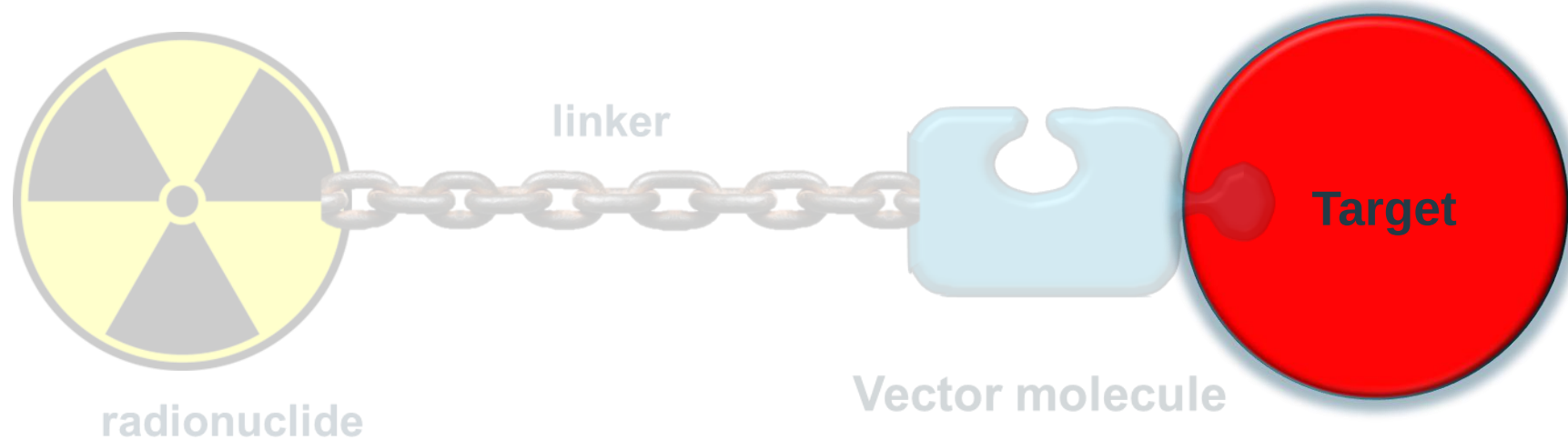


high expression of the target will result in high concentration of radionuclide

- high contrast (imaging)
- high radiation dose (therapy)

low concentration of radionuclide

Radiopharmaceutical target



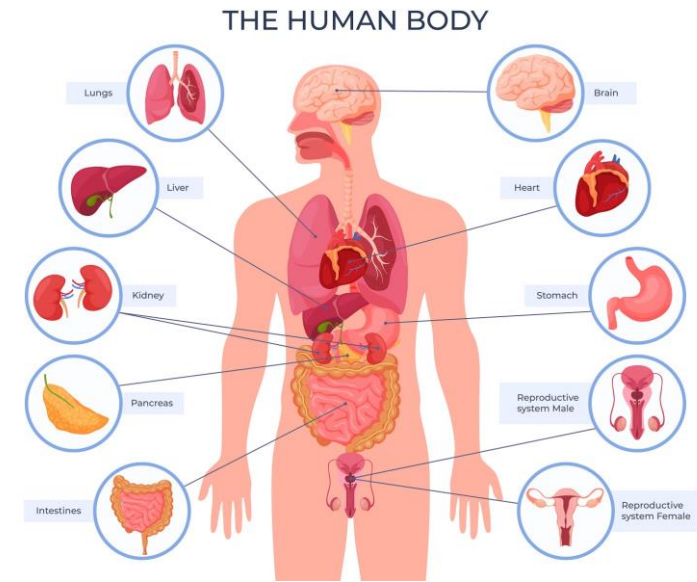
Target: what needs to be visualized?

Physiological function

- organ perfusion (=blood supply)
- bone formation
- stomach : gastric emptying rate
- hepatobiliary excretion (=liver function)
- renal function: glomerular filtration, tubular secretion, tubular reabsorption
- lymphatic flow

Specific cells/tissues

- tumor cells (imaging + therapy)
- inflammatory cells
- specific neurons in brain (eg dopaminergic neurons, neurotransmission)
- specific proteins (amyloid protein Alzheimer disease)



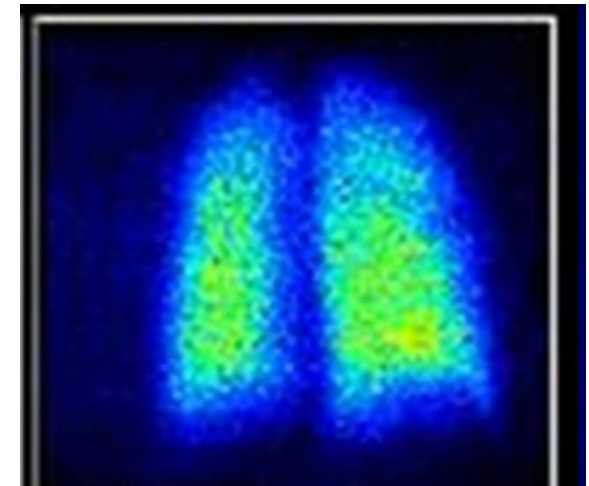
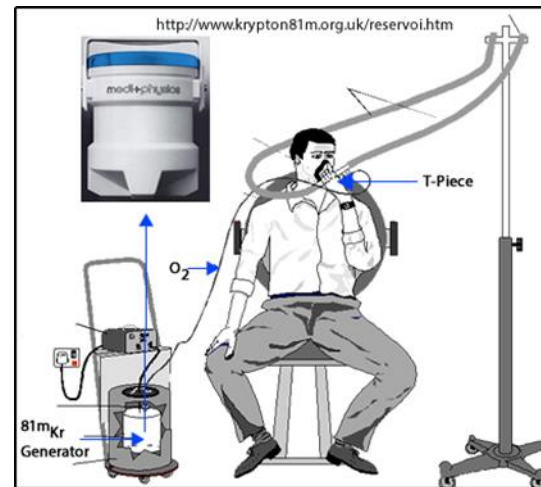
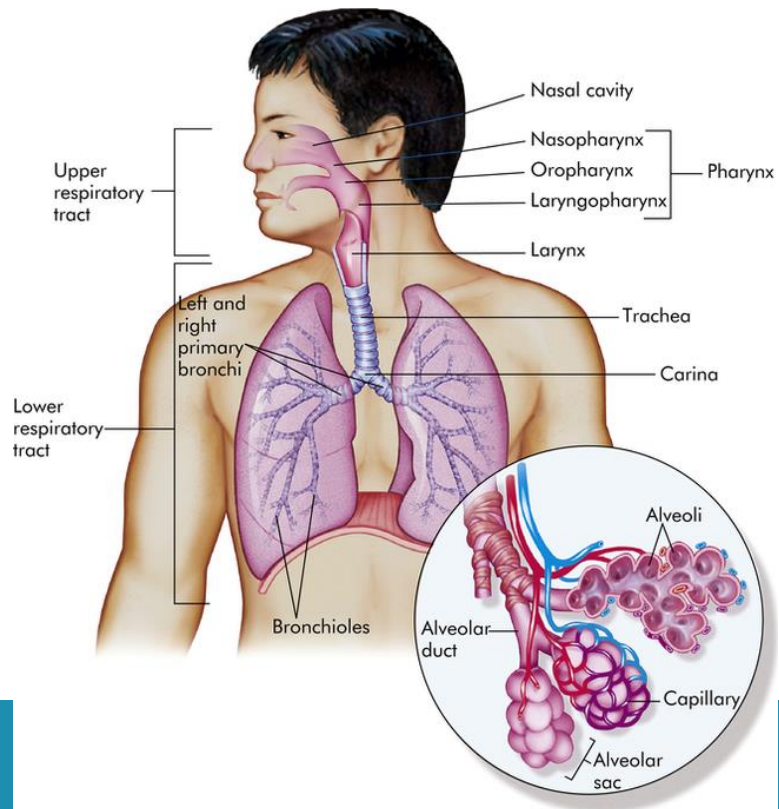
Access to the target?

- Direct administration in a specific body compartment

Access to the target?

- Direct administration in a specific body compartment
 - gas inhalation (lung ventilation, ^{99m}Tc -technegas, ^{81m}Kr gas)

vector=gas (like), transfer up to alveoli



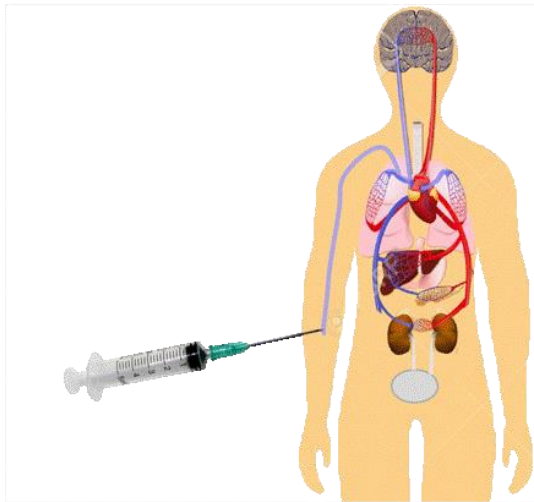
Access to the target?

- Direct administration in a specific body compartment
 - gas inhalation (lung ventilation, ^{99m}Tc -technegas, ^{81m}Kr gas)
 - Radioactive food/drink (stomach emptying ^{99m}Tc -colloid))
 - intravenous injection of radiolabelled compound that is restricted to blood circulation (^{99m}Tc -erythrocytes, ^{99m}Tc -albumin)
 - intra-articular injection (^{90}Y -colloid synovectomy)
 - intraarterial injection (SIRT particles)
 - subcutaneous injection (colloidal particles)
 - peritumoral injection

(almost) immediate contrast, possible to use short-lived radionuclide

Access to the target?

- Direct administration in a specific body compartment
- Use the bloodstream to provide acces: **intravenous administration**



radiopharmaceutical flows with the bloodstream reaching the whole body

Access to the target?

- Direct administration in a specific body compartment
- Use the bloodstream to provide acces: **intravenous administration**



Plasma clearance via excretory organs
kidneys (small hydrophilic compounds)
liver large molecules, lipophilic molecules

Access to the target?

- Direct administration in a specific body compartment
- Use the bloodstream to provide acces: **intravenous administration**

Plasma clearance via excretory organs

kidneys (small hydrophilic compounds)

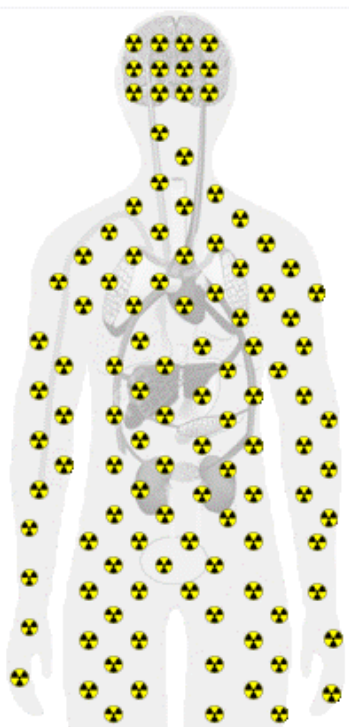
liver large molecules, lipophilic molecules



kidney and liver retention frequently observed
radionuclide therapy: high radiation dose to kidney/liver

Access to the target?

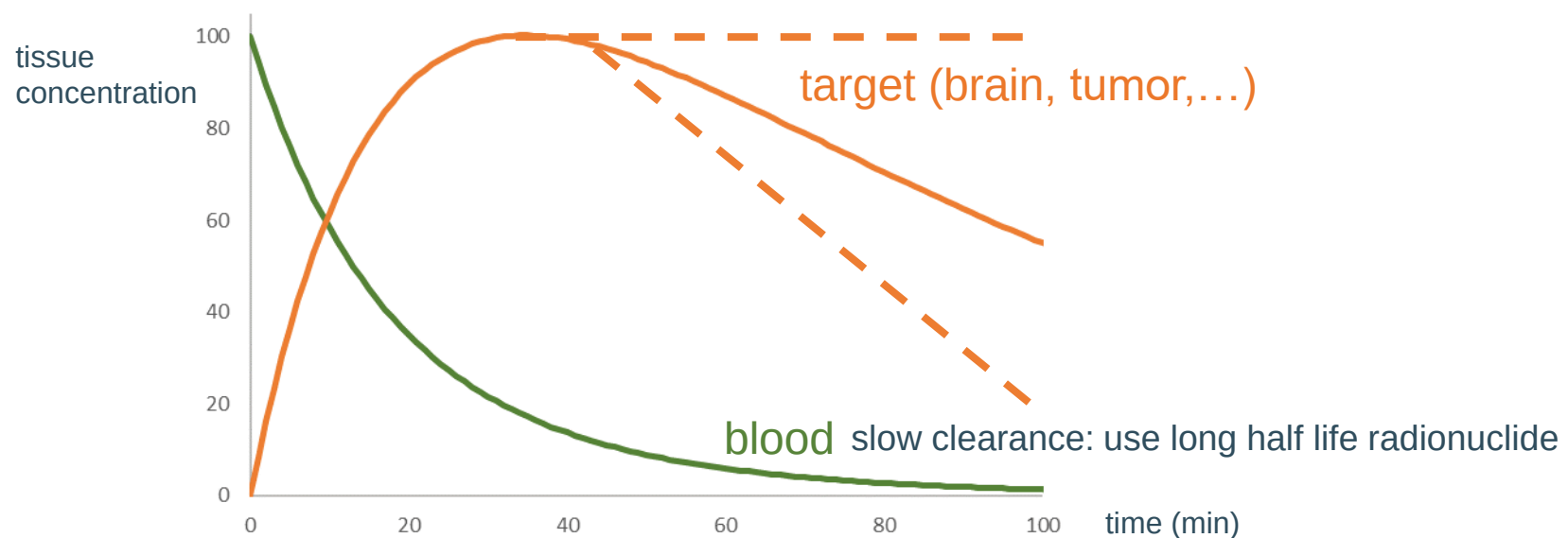
- Direct administration in a specific body compartment
- Use the bloodstream to provide access: **intravenous administration**



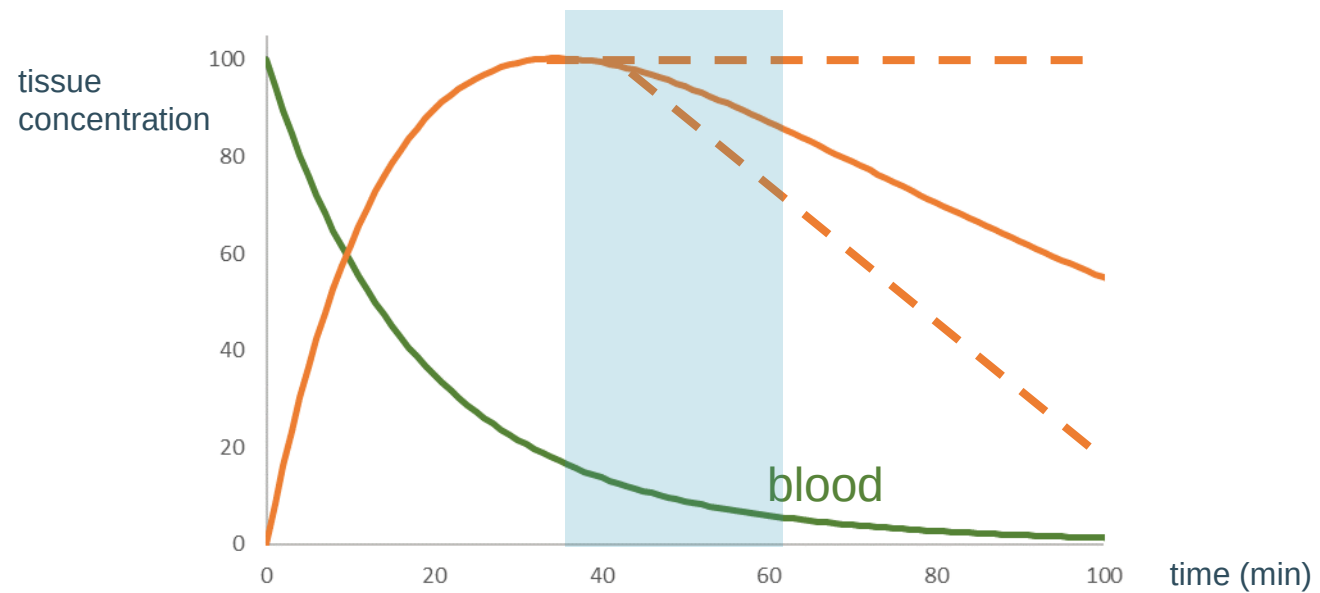
Plasma clearance via excretory organs

kidneys (small hydrophilic compounds)

liver large molecules, lipophilic molecules

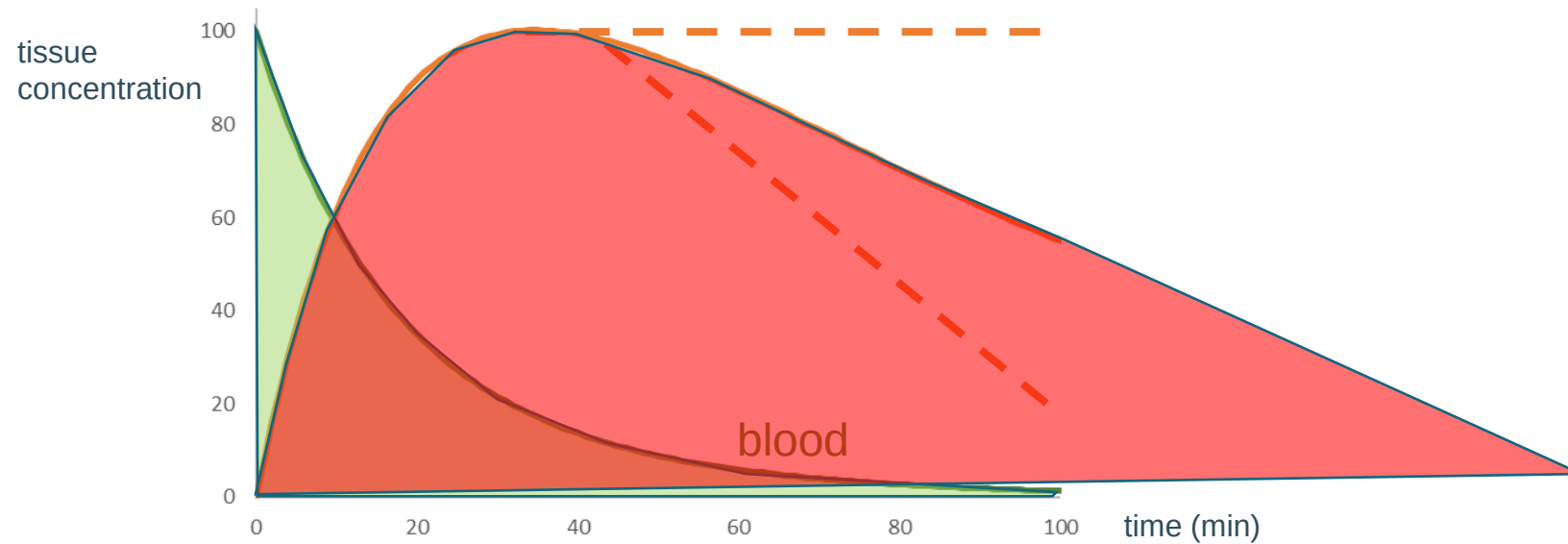


Access to the target?



optimal time window for high signal/background **imaging**

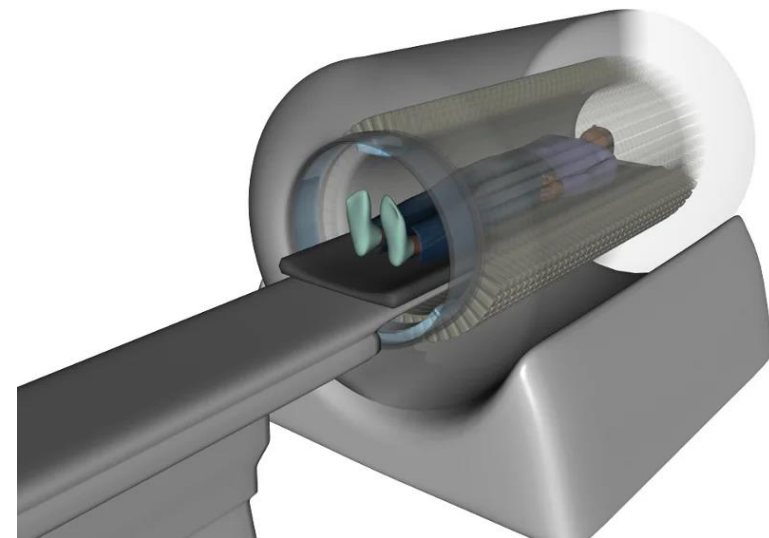
Access to the target?



for **radionuclide therapy**

- AUC is relevant
- radiation dose selectivity is higher for longer lived radionuclides

Access to the target?

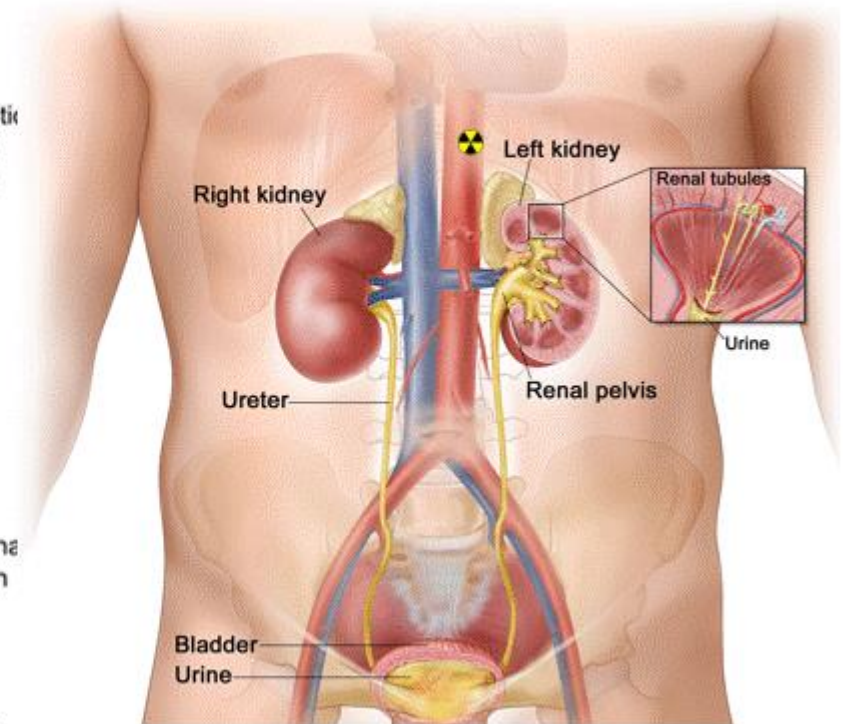
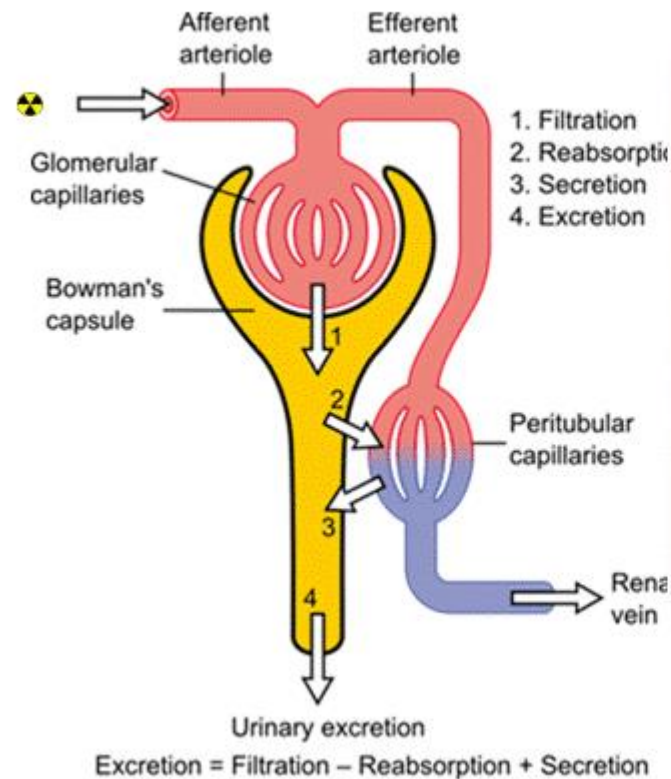


explorer total body PET camera
 ^{18}F -FDG

Targetting/retention strategies

- **Physiological function** (eg glomerular filtration kidney)

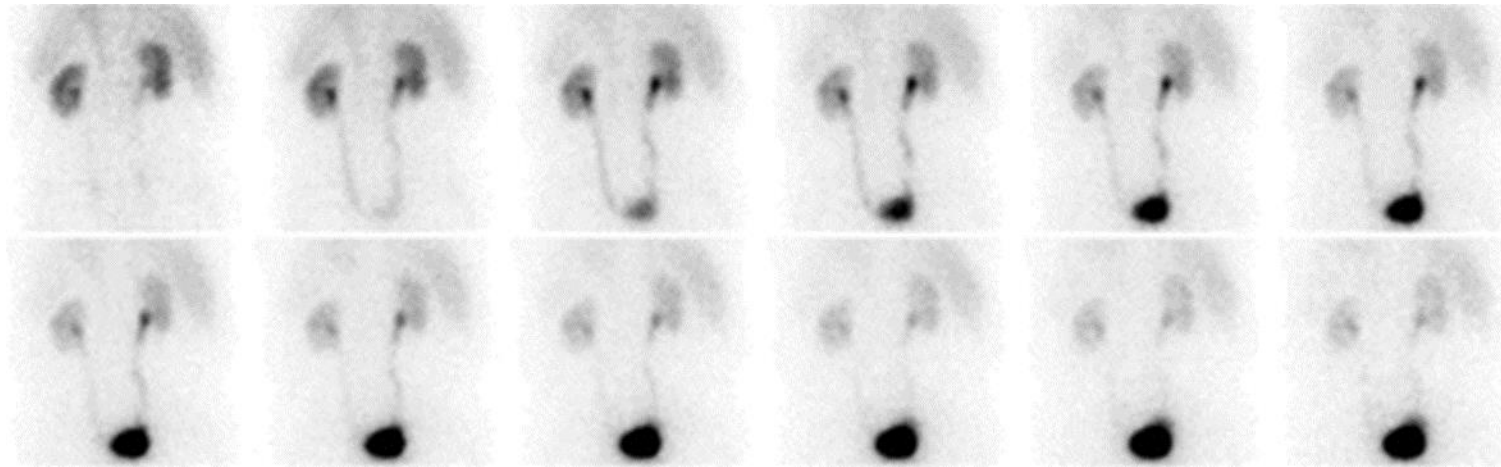
^{99m}Tc -DTPA targetting glomerular filtration system (kidney function)



Targetting/retention strategies

- **Physical transport** (eg glomerular filtration kidney)

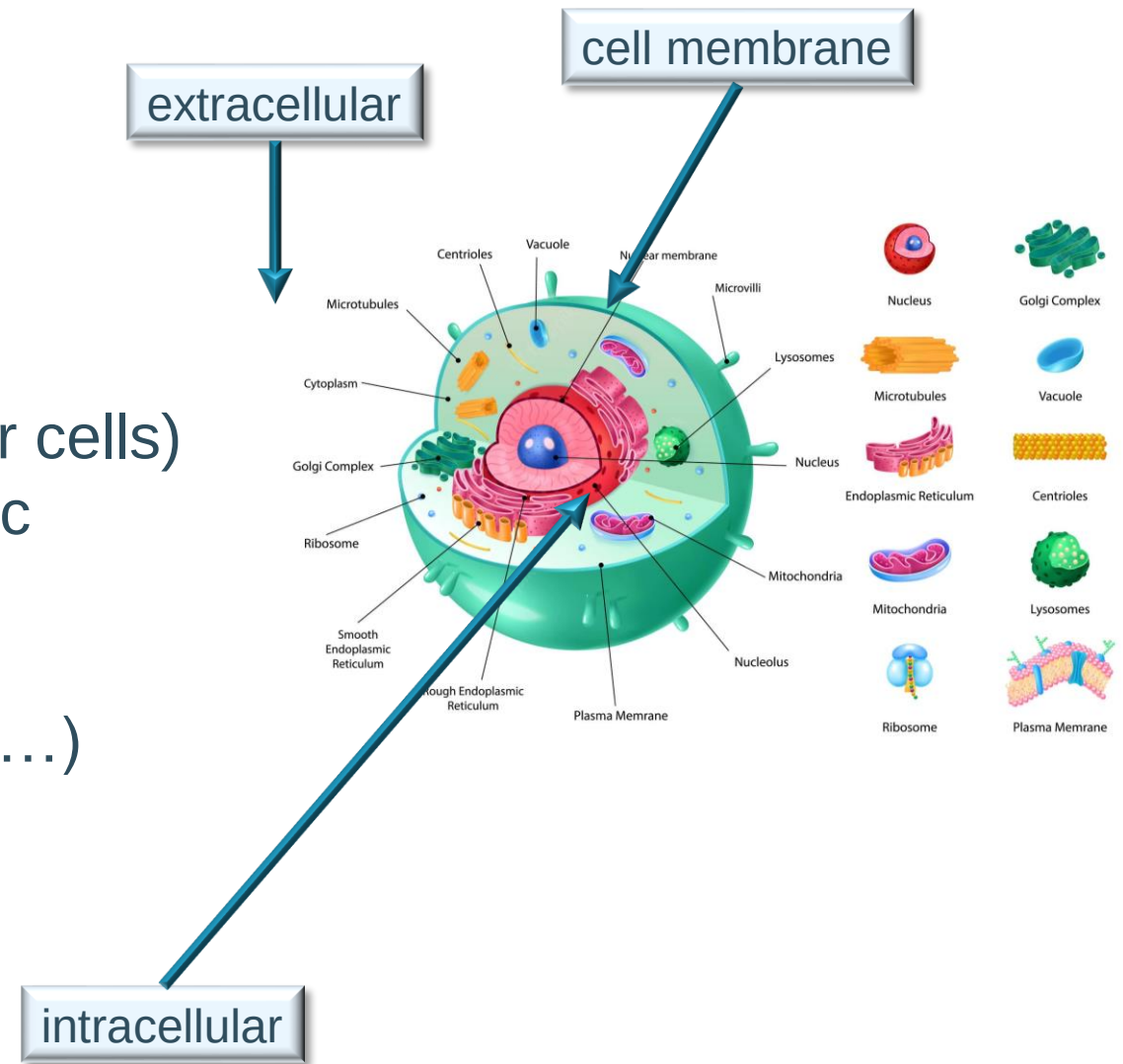
e.g. ^{99m}Tc -DTPA targetting glomerular filtration system (kidney function)



What is the target?

Physiological function Specific cells

- cells that express specific proteins
 - cell membrane receptors (tumour cells)
 - cell membrane receptors (specific neurons)
 - enzymes (eg hexokinase)
 - misfolded proteins (amyloid, tau,...)

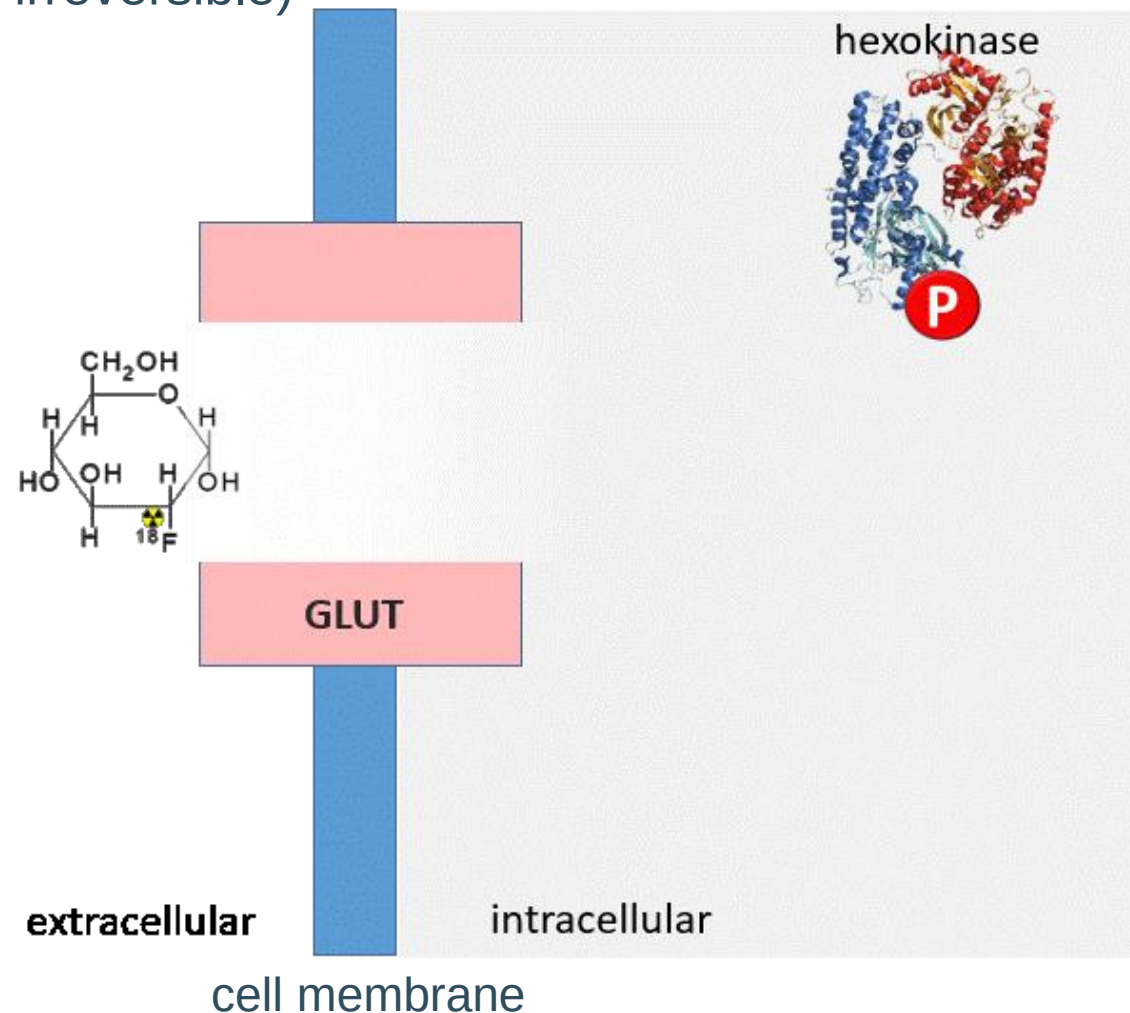
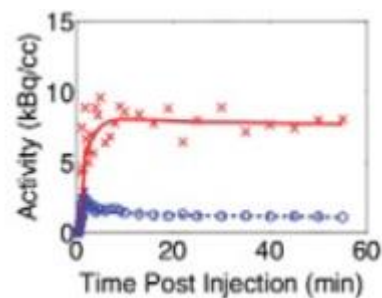
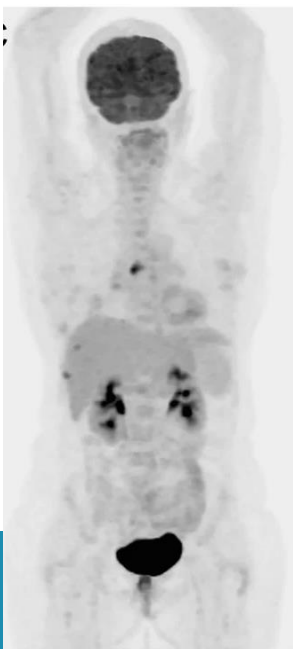


Binding to/by the target

Covalent binding: enzyme mediated ((pseudo) irreversible)

^{18}F FDG

FDG-6-phosphate retention
reflects GLUT and hexokinase
activity (**glucose metabolism**)

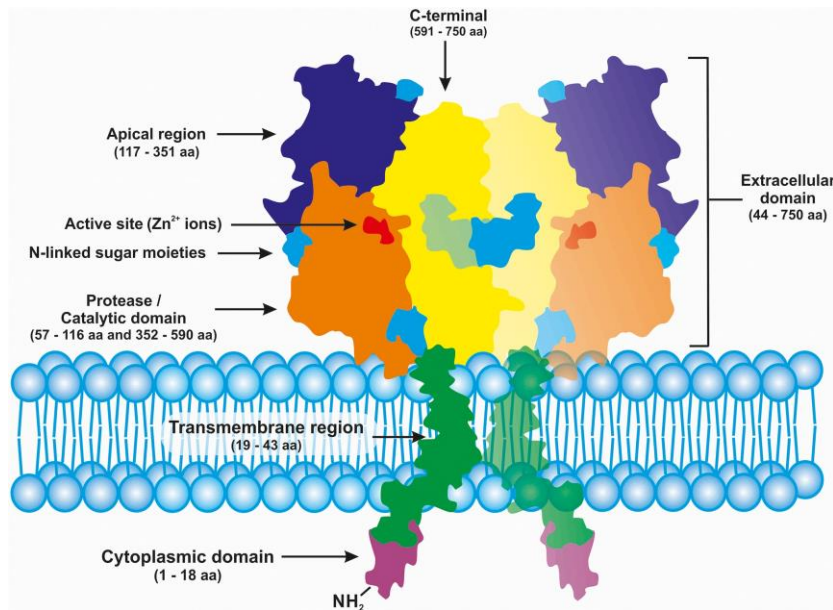


Binding to/by the target

Equilibrium binding

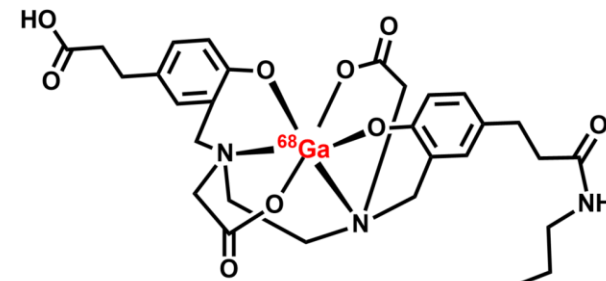
PSMA protein

expressed on cell membrane of prostate tumor cells

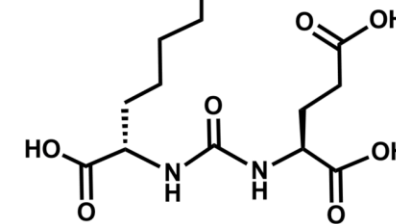


cell membrane

chelator/radiometal



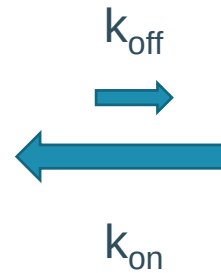
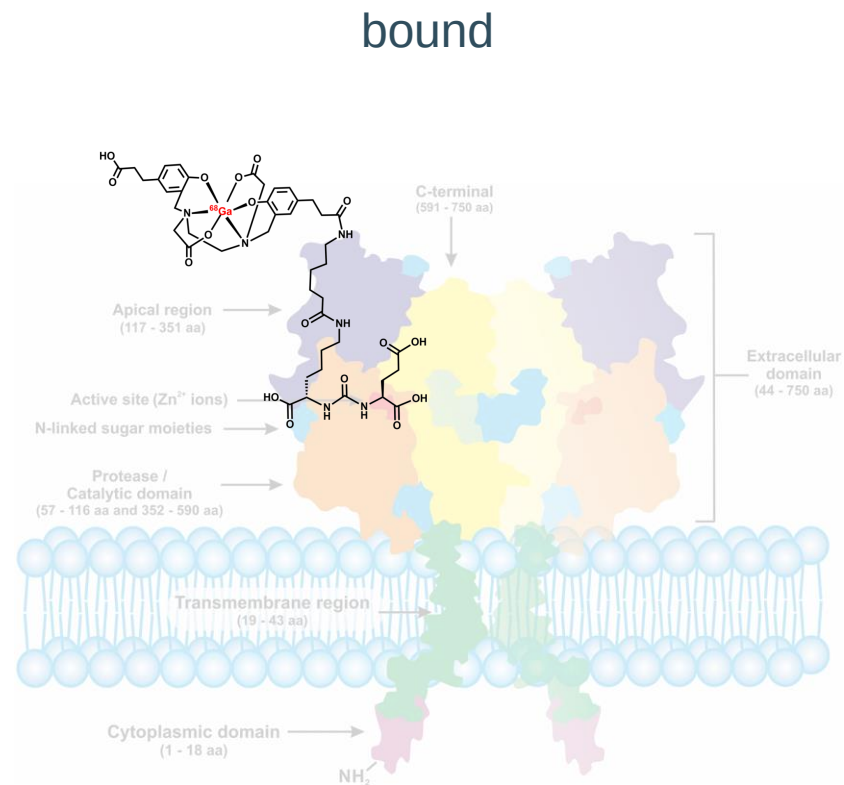
linker



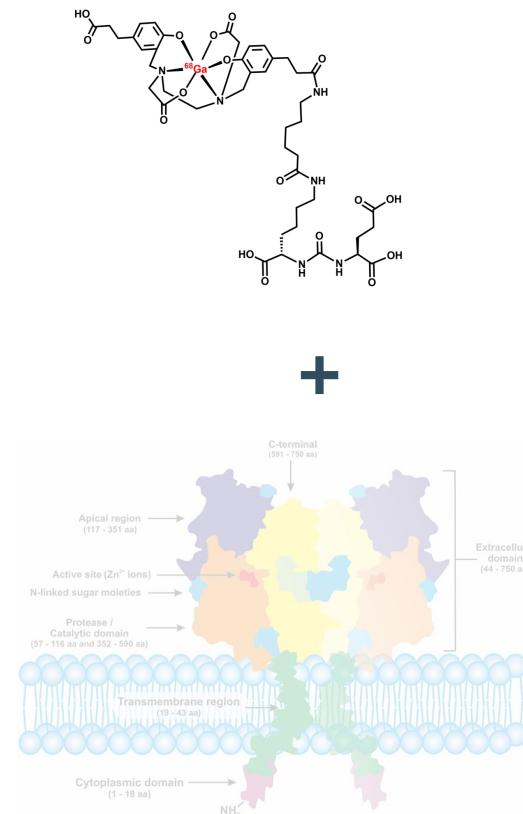
binding pseudopeptide

Binding to/by the target

Equilibrium binding



free

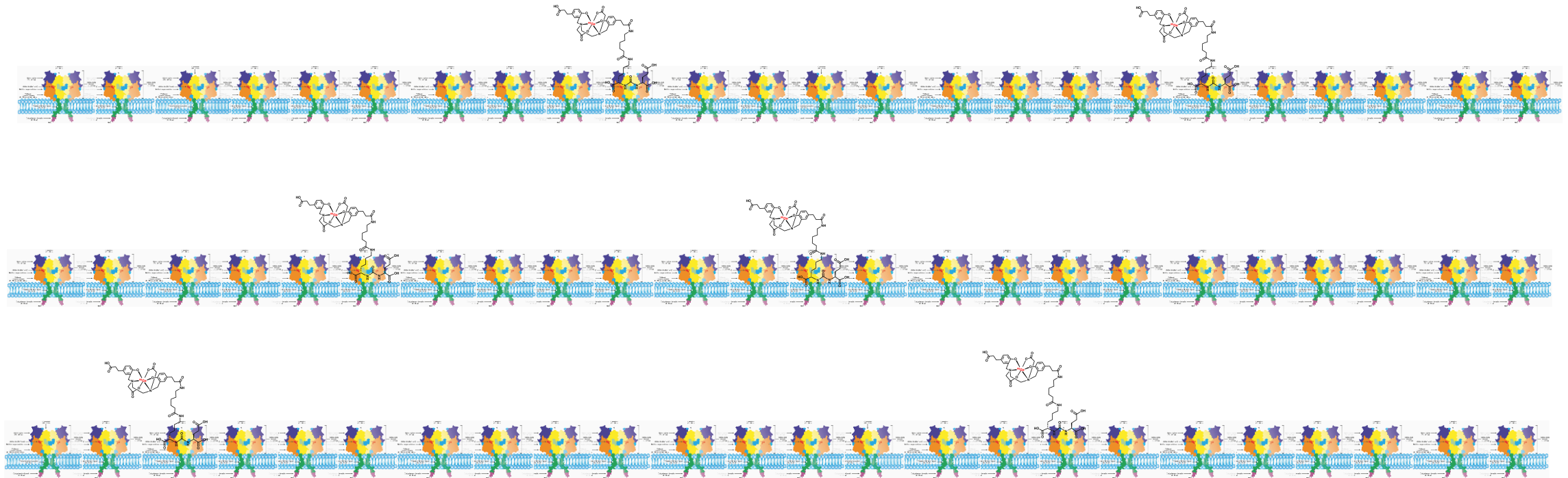


Binding to/by the target

Equilibrium binding



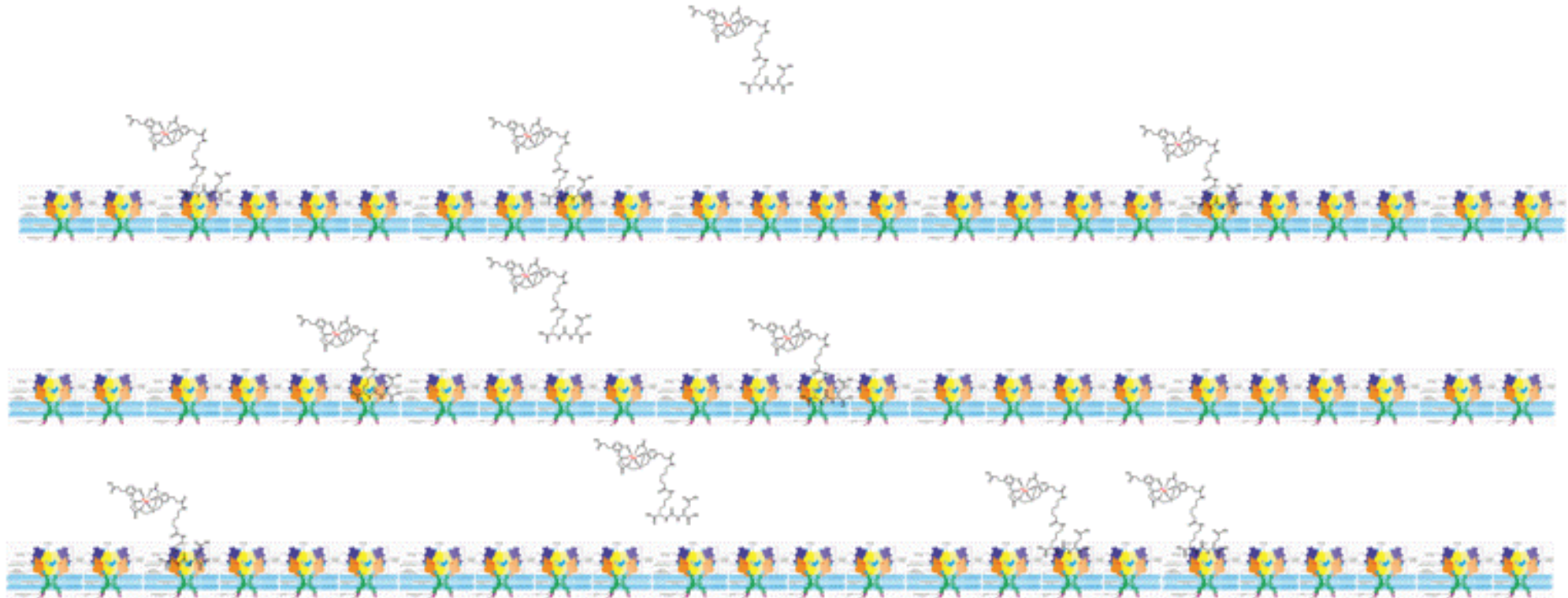
large excess of binding sites
large bound tracer fraction



Binding to/by the target

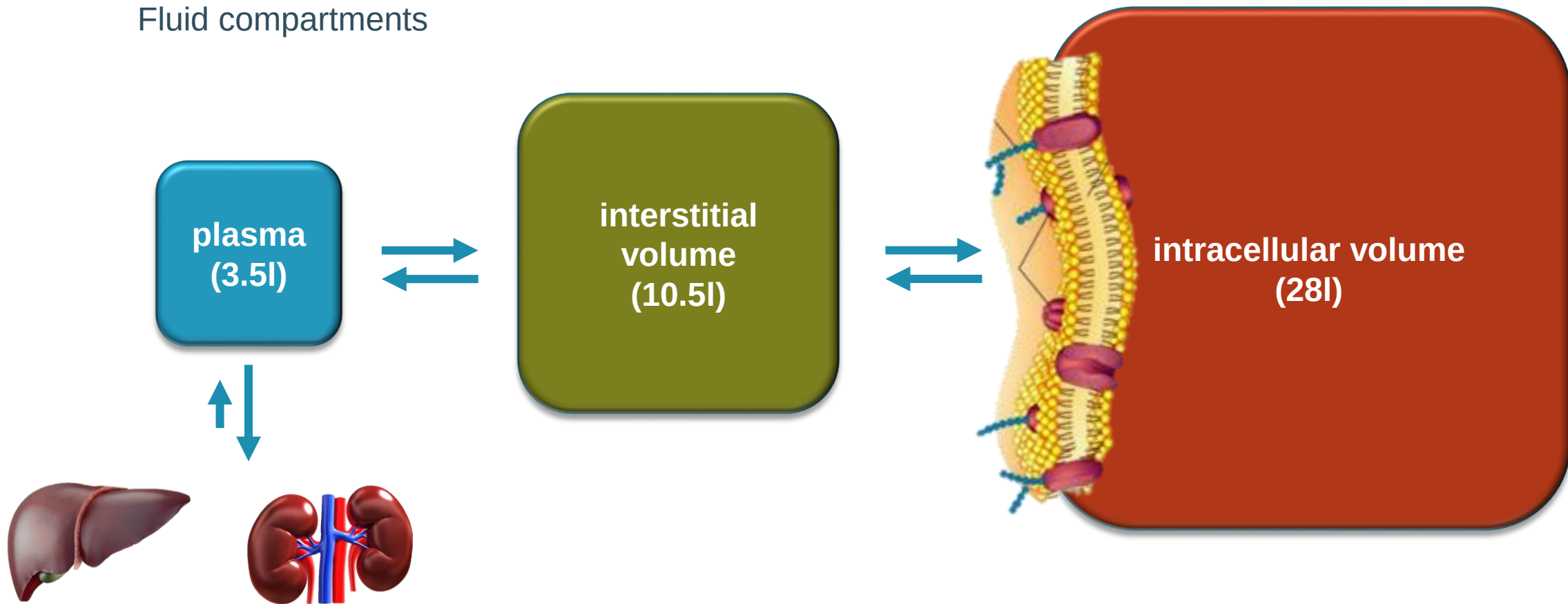
Equilibrium binding

dynamic process



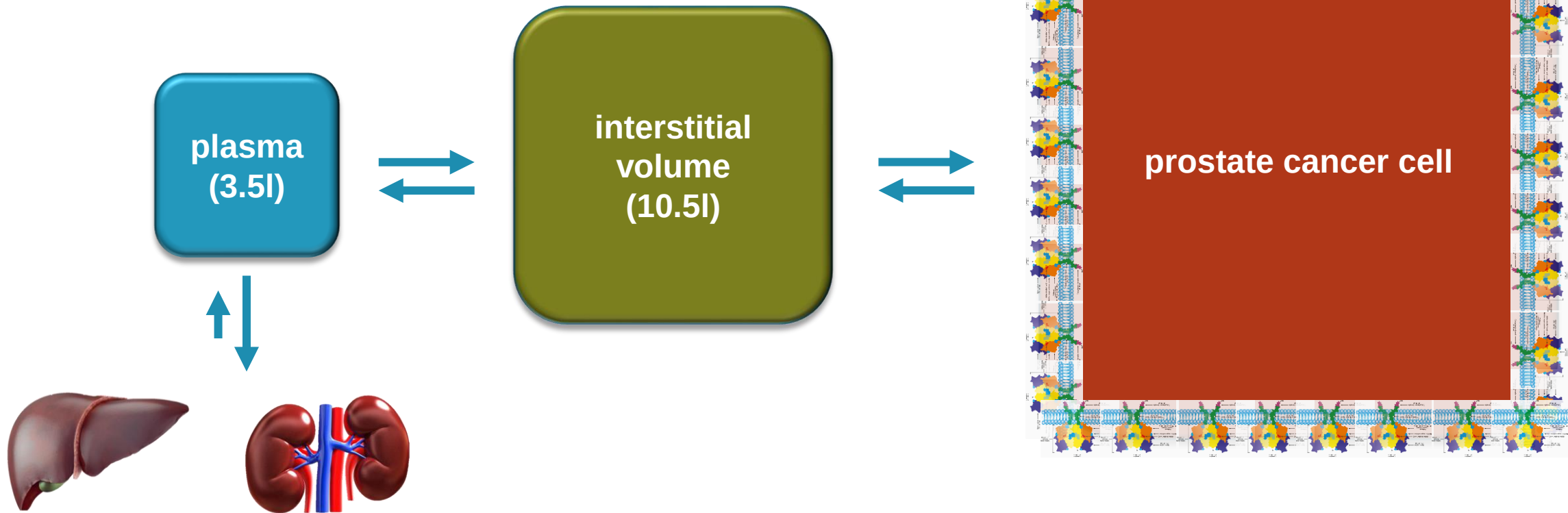
Equilibrium binding

Fluid compartments

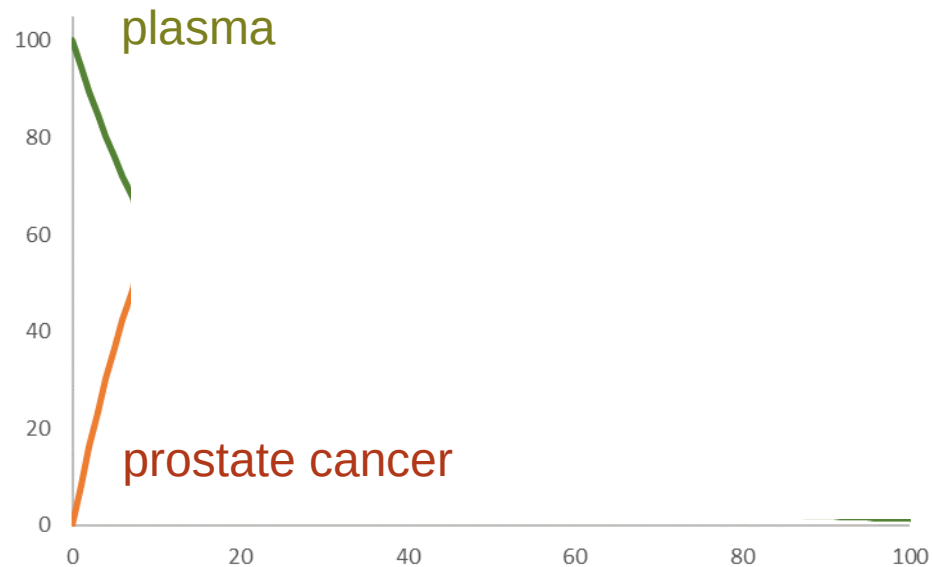


Equilibrium binding

Fluid compartments



Equilibrium binding

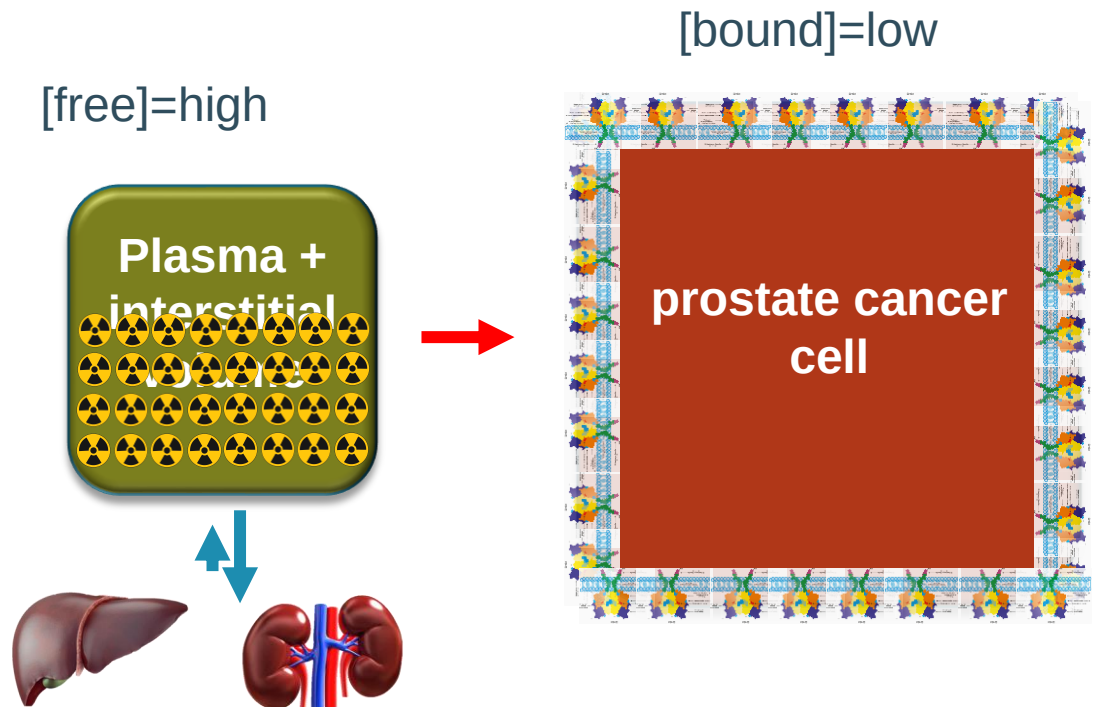


initial situation immediatly following IV injection:
bound tracer concentration is low

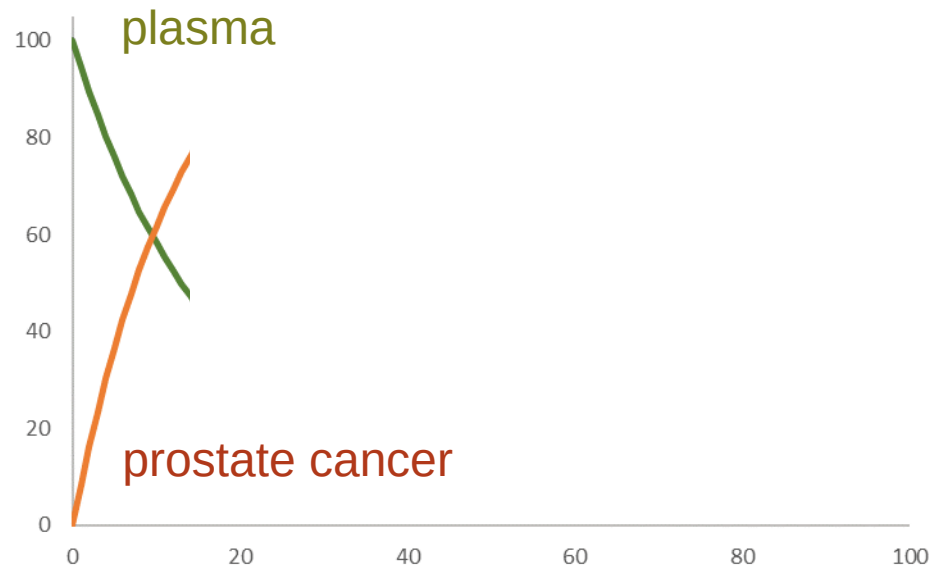
$$[\text{bound tracer}]/[\text{free tracer}] \ll B_{\text{max}}/K_d$$



association will be dominant, bound tracer concentration will increase



Equilibrium binding

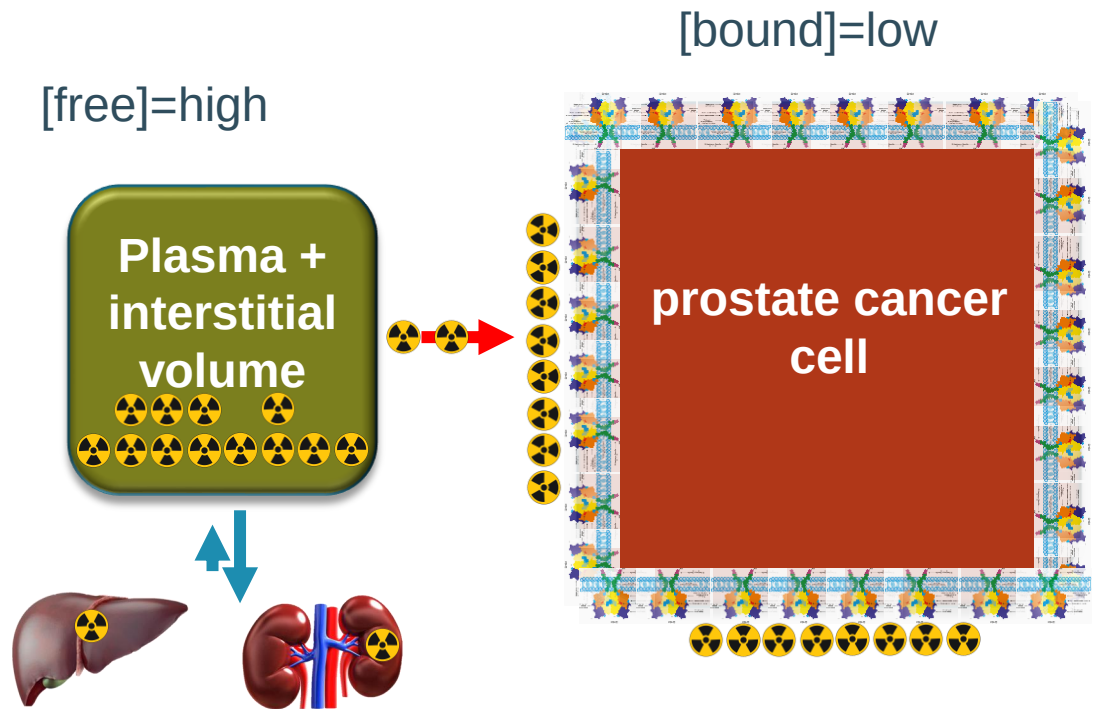


initial situation immediately following IV injection:
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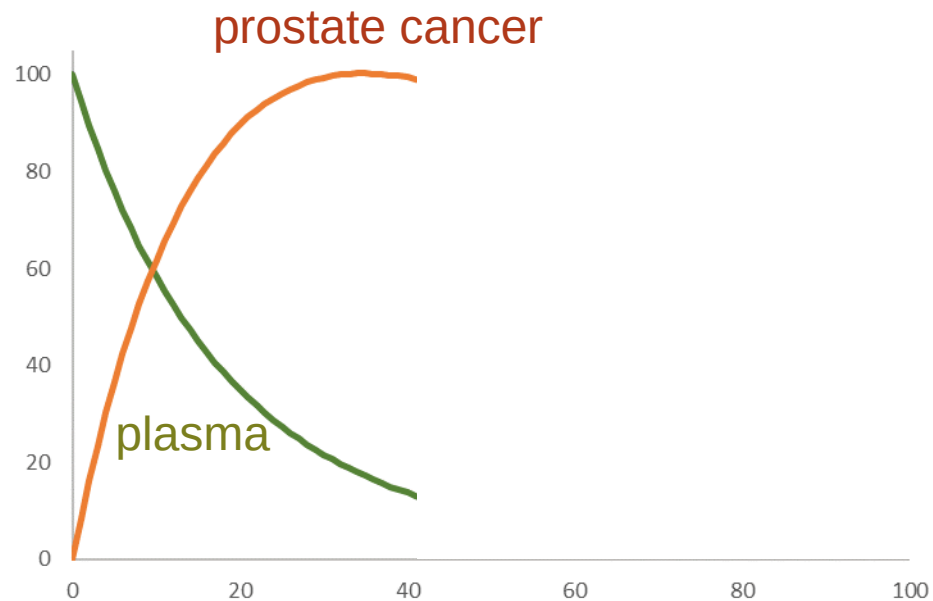
$$[\text{bound tracer}]/[\text{free tracer}] \ll B_{\text{max}}/K_d$$



association will be dominant, bound tracer concentration
will increase



Equilibrium binding

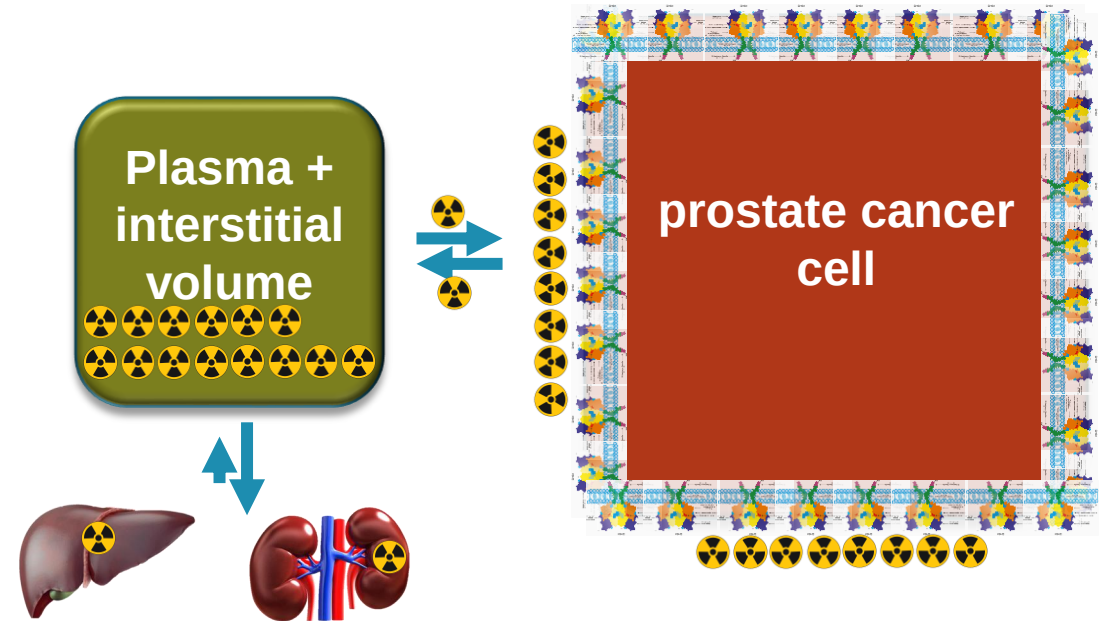


pseudoequilibrium:

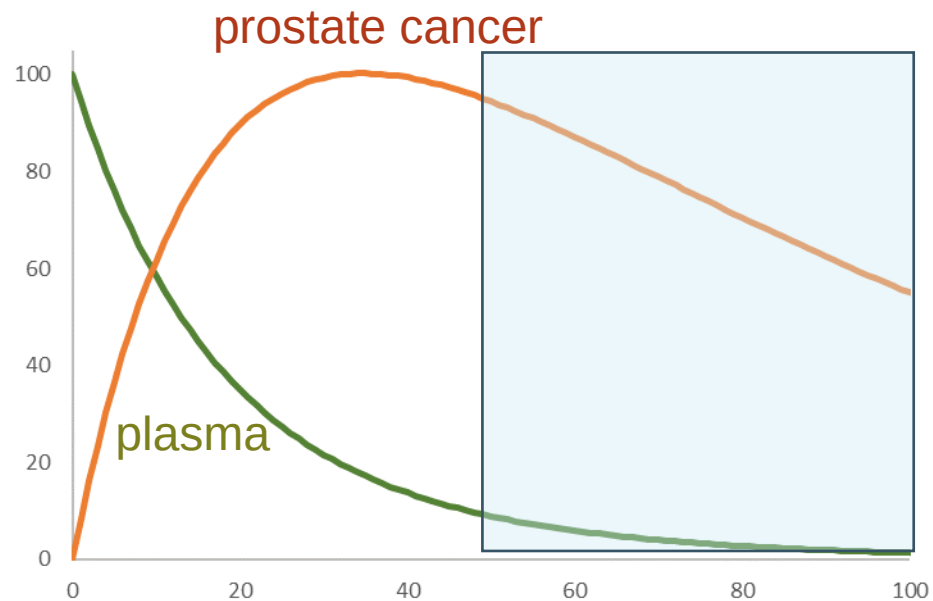
$$[\text{bound tracer}]/[\text{free tracer}] = B_{\text{max}}/K_d$$



association will be **equal** to dissociation
[bound tracer] will remain constant



Equilibrium binding

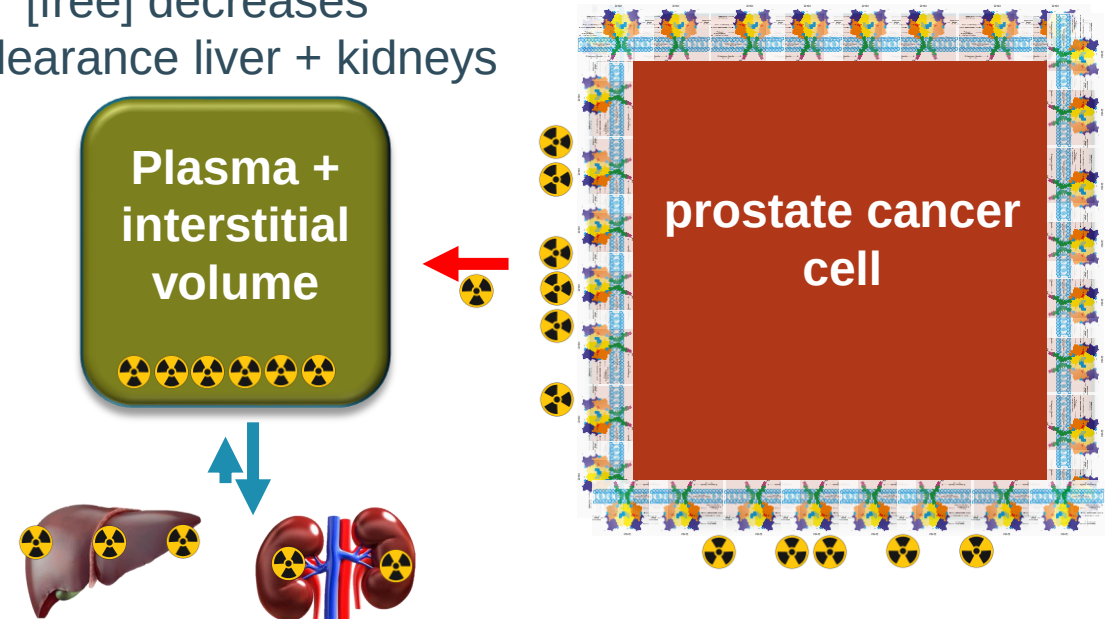


dissociation

$$[\text{bound tracer}]/[\text{free tracer}] > B_{\text{max}}/K_d$$

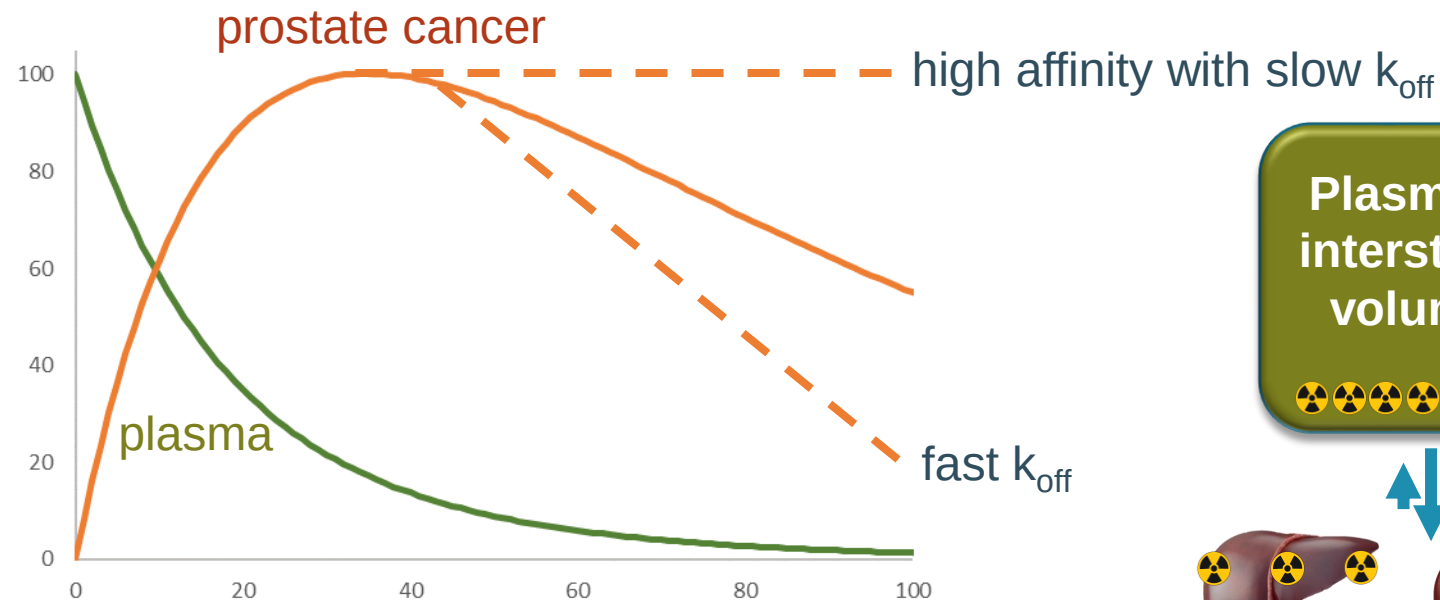


[free] decreases
clearance liver + kidneys



dissociation will be dominant
[bound tracer] will decrease

Equilibrium binding

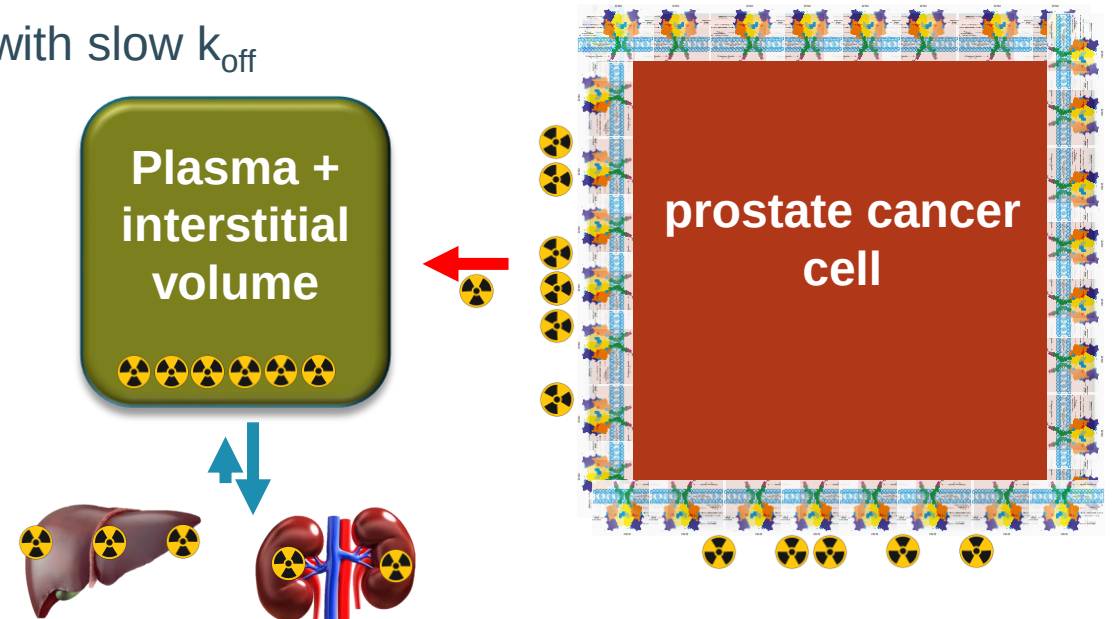


dissociation

$$[\text{bound tracer}]/[\text{free tracer}] > B_{\max}/K_d$$



dissociation will be dominant
[bound tracer] will decrease



Chemical structure of vector molecules

vector = radionuclide



$^{18}\text{F}^-$

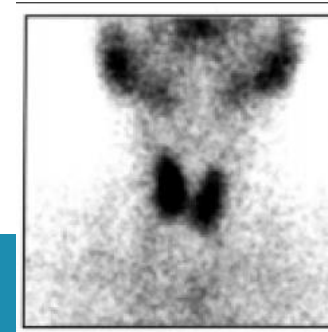


$^{223}\text{RaCl}_2$

$^{123/131}\text{I}^-$



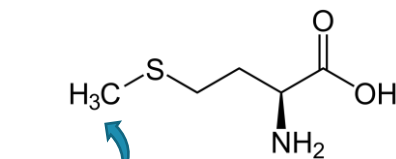
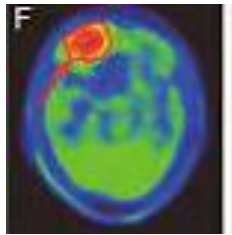
$^{99\text{m}}\text{TcO}_4^-$



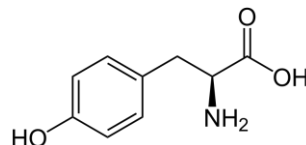
Chemical structure of vector molecules

Small molecules-biological molecules and derivatives

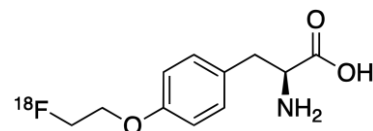
amino acids



L-methionine



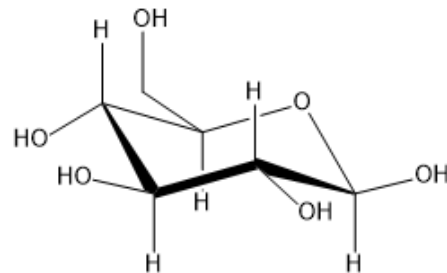
L-tyrosine



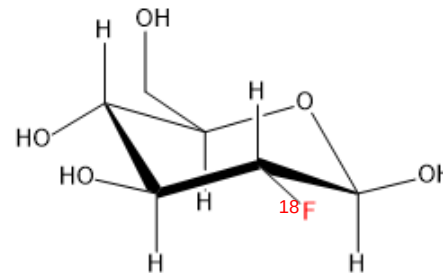
L-fluoroethyltyrosine

small	✓
charged	✓
lipophilic	-
Passes membranes	✓(transport) LAT

carbohydrates



D-glucose



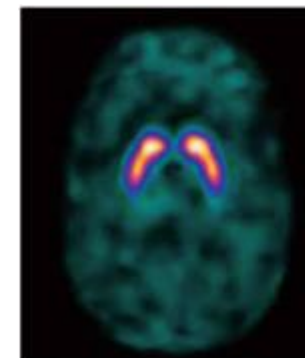
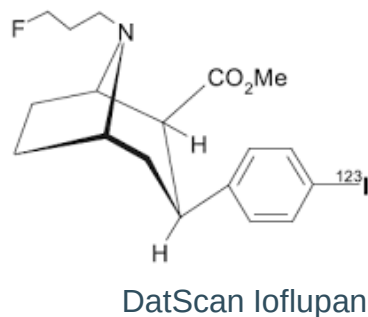
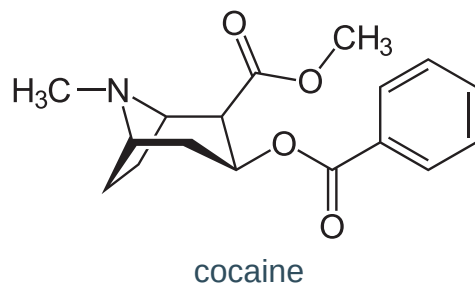
2-[¹⁸F]fluoro-2-deoxy-D-glucose
¹⁸FDG

small	✓
charged	-
lipophilic	-
Passes membranes	✓(transport) SGLT, GLUT

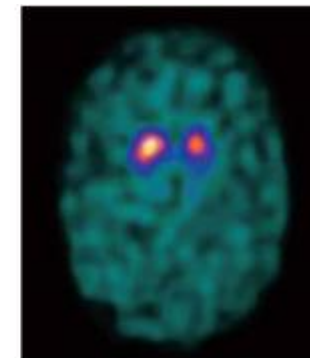
Chemical structure of vector molecules

Small molecules derived from medicinal compounds

dopamine transporter
neurotransmission



(a) Healthy Control



(b) Parkinson's Disease

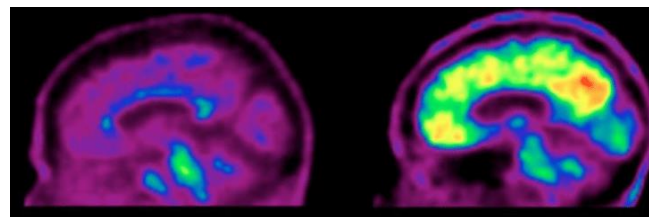
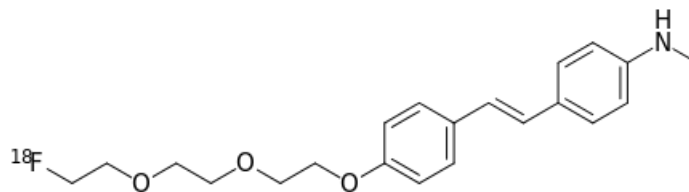
small	✓
charged	-
lipophilic	✓
Passes membranes	✓

Chemical structure of vector molecules

Small molecules developed as radiopharmaceuticals

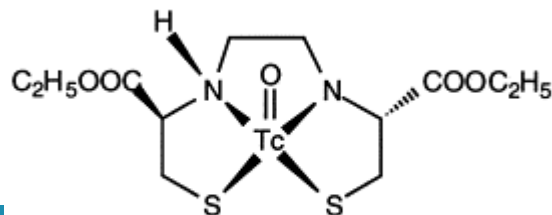
florbetaben (amyloid tracer)

Alzheimers disease

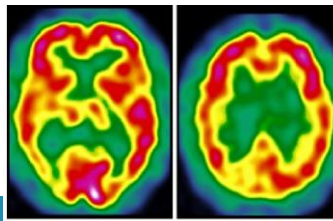


small	✓
charged	-
lipophilic	✓
Passes membranes	✓

^{99m}Tc complexes (^{99m}Tc -MIBI, ^{99m}Tc -HMPAO, ^{99m}Tc -ECD, ^{99m}Tc -MAG3...)



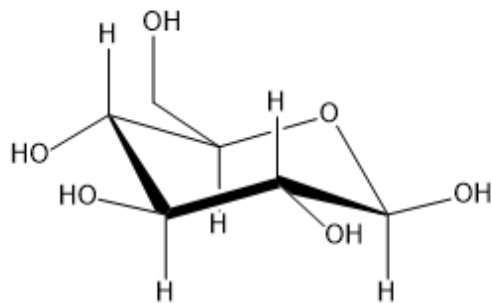
$[^{99m}\text{Tc}]$ ECD (Neurolite®)



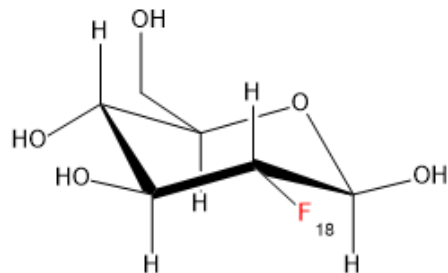
small	✓
charged	-
lipophilic	✓
Passes membranes	✓

Chemical structure of vector molecules

Small molecules as vector for radiopharmaceuticals



D-glucose
 $M_r=180$



2-deoxy-2-(^{18}F) fluoro-D-glucose
 $M_r=181$

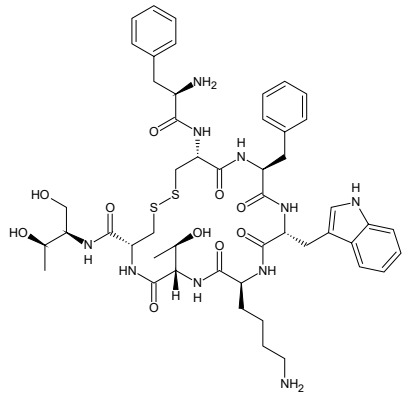


$M_r=472$

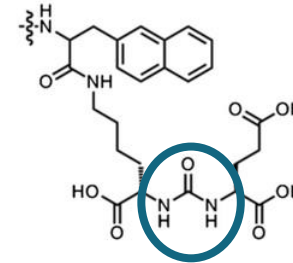
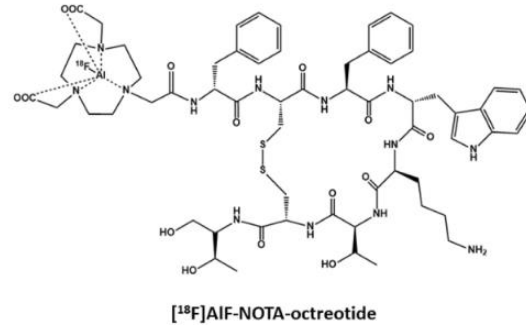
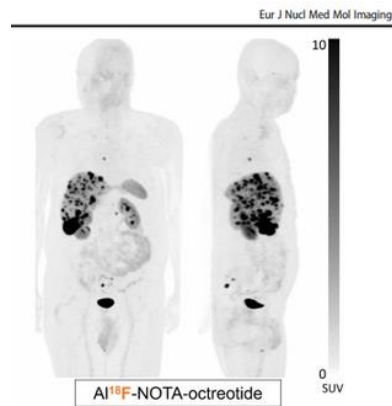
- **polar** chelator/radiometal **size** large compared to vector molecule
- derivatisation with chelator/radiometal will likely result in decrease of affinity or loss of potential to pass biological membranes
- labelling of small molecules is generally restricted to **non-radiometal radionuclides**

^{11}C , ^{18}F , $^{123,124,125,131}\text{I}$, ^{211}At

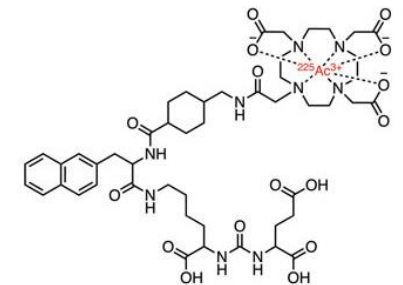
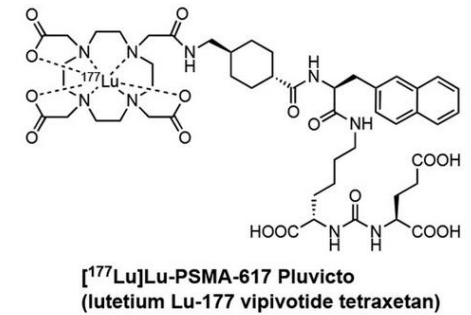
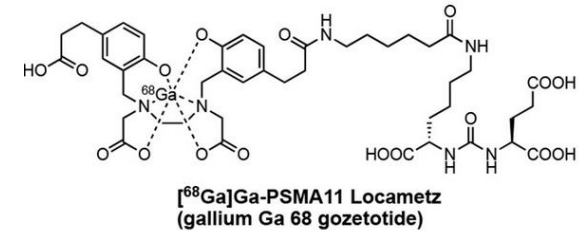
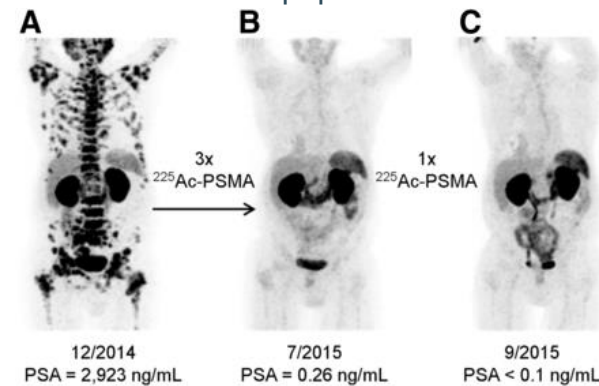
Chemical structure of vector molecules



somatostatine
affinity for the somatostatin receptor



pseudopeptide (affinity for PSMA)
“ureide” bond instead of peptide bond

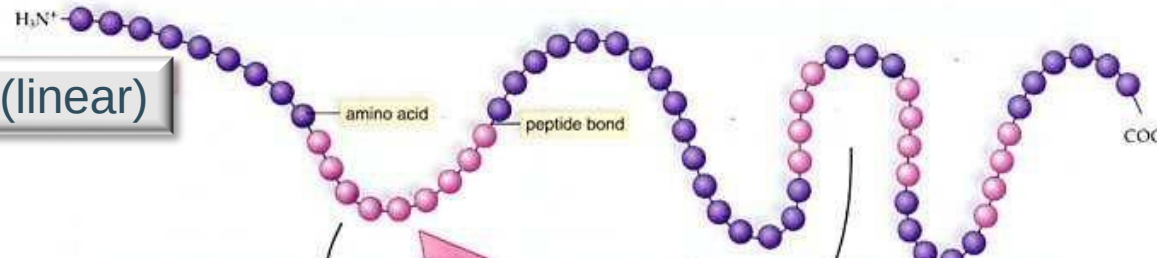


peptides
2-50 amino acids
thermostable

Chemical structure of vector molecules

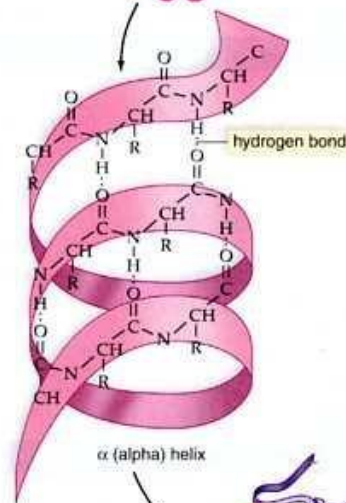
protein >>50 amino acids

primary structure (linear)

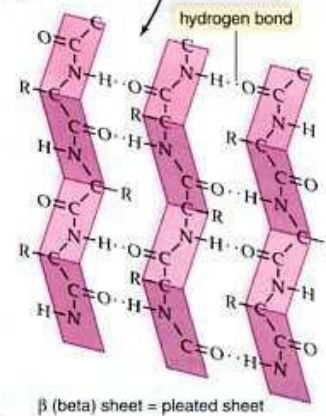


secondary structure

α -helix

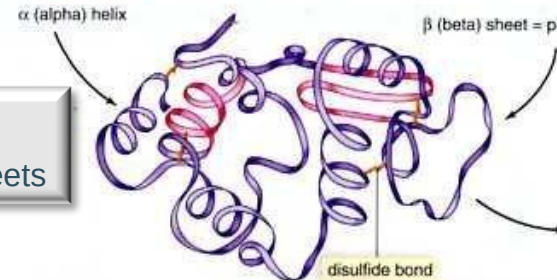


β -sheet



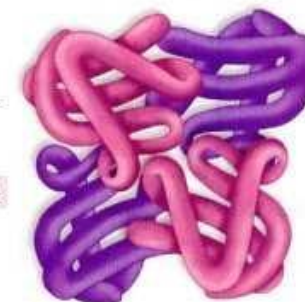
tertiary structure

combination of linear, α -helices and β -sheets

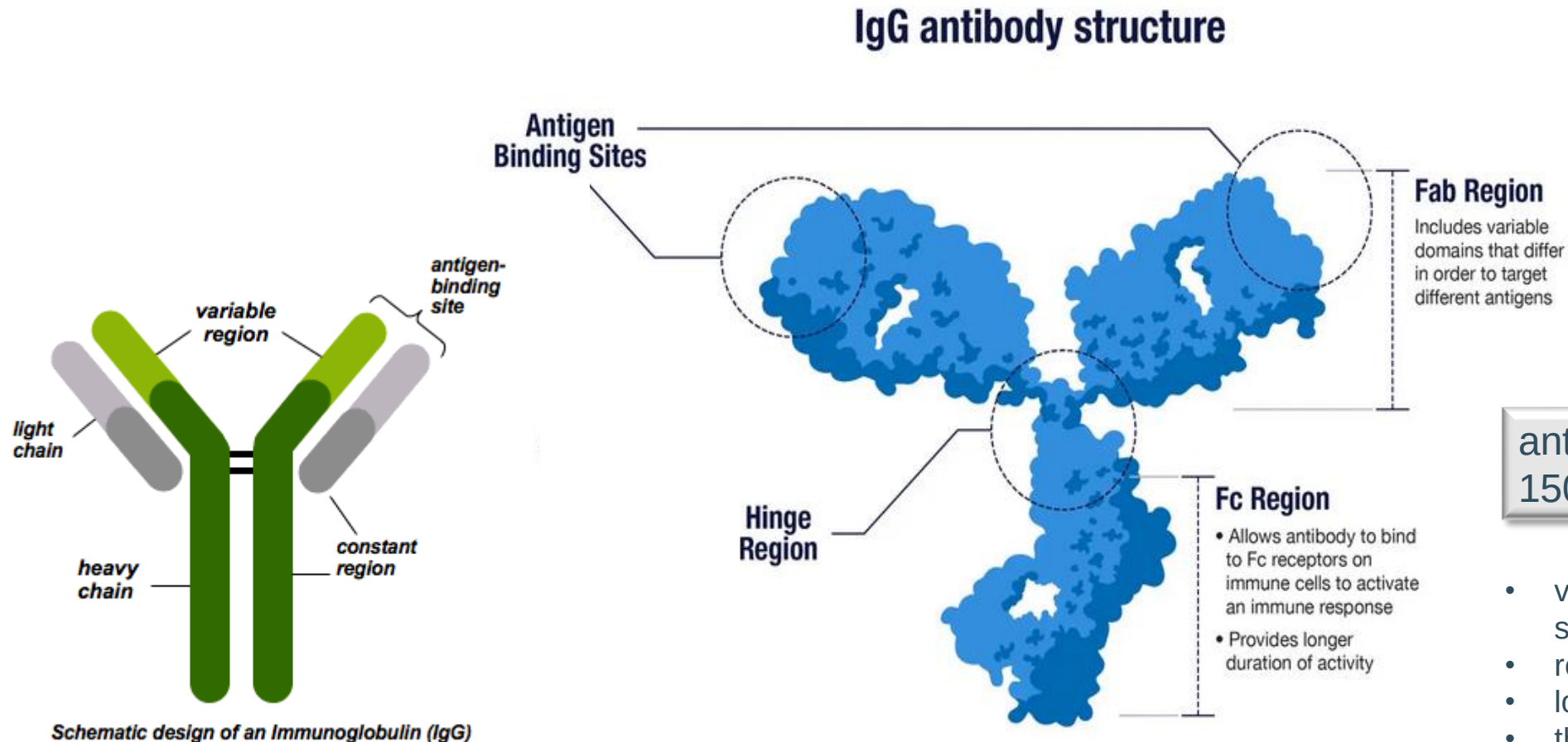


quaternary structure

combination of different tertiary chains



Chemical structure of vector molecules

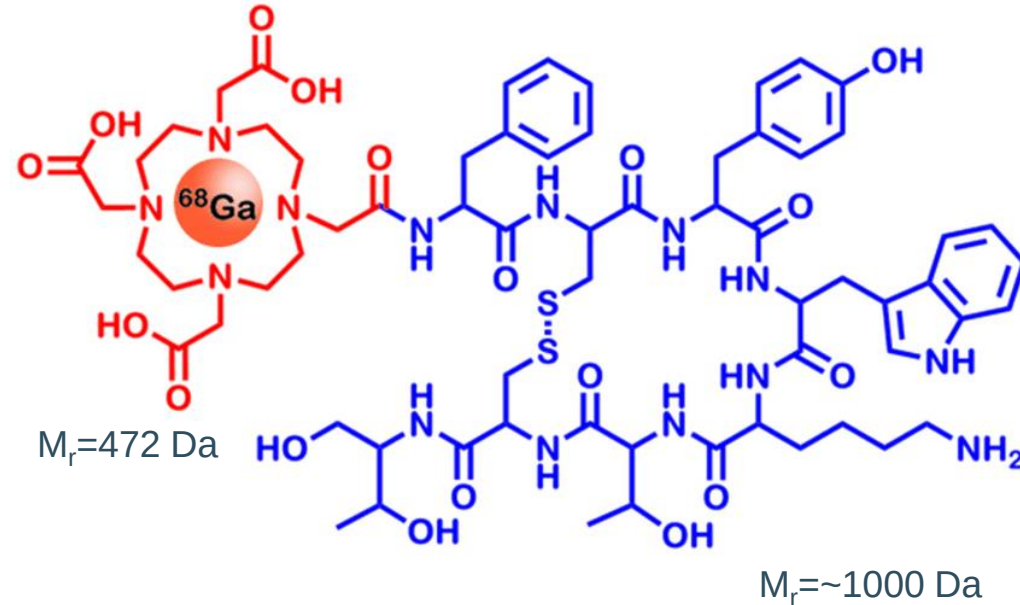
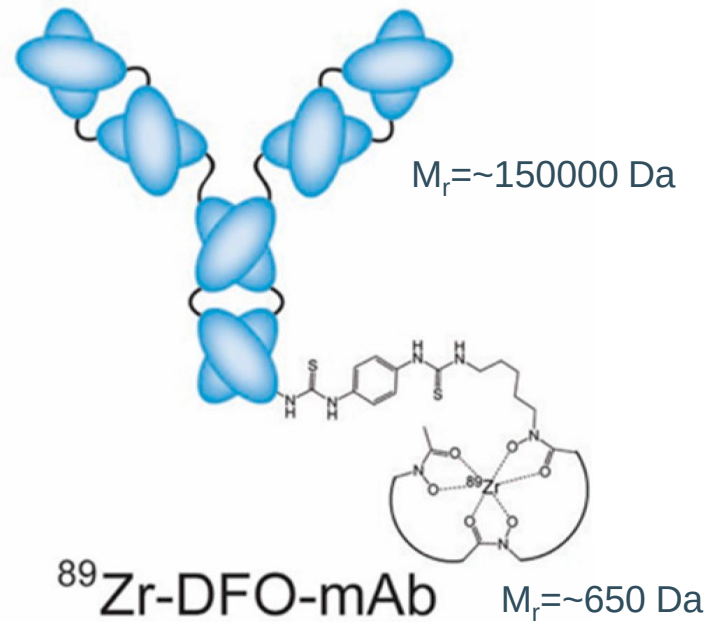


antibodies
150 kDa ~1330 amino acids

- versatile tunable affinity/selectivity spectrum
- recombinant production lines
- long plasma half-life (days-weeks)
- thermolabile, sensitive to organic solvents

protein >>50 amino acids

Chemical structure of vector molecules



- **large vector**, potential to derivatise with **chelator** without compromising the affinity for the target
- **radiometal labelling** fast, efficient and in aqueous solution (no organic solvents required)
- antibody: slow plasma clearance requires radionuclide long half life

proteins
>50 amino acids
thermolabile

peptides
2-50 amino acids
thermostable

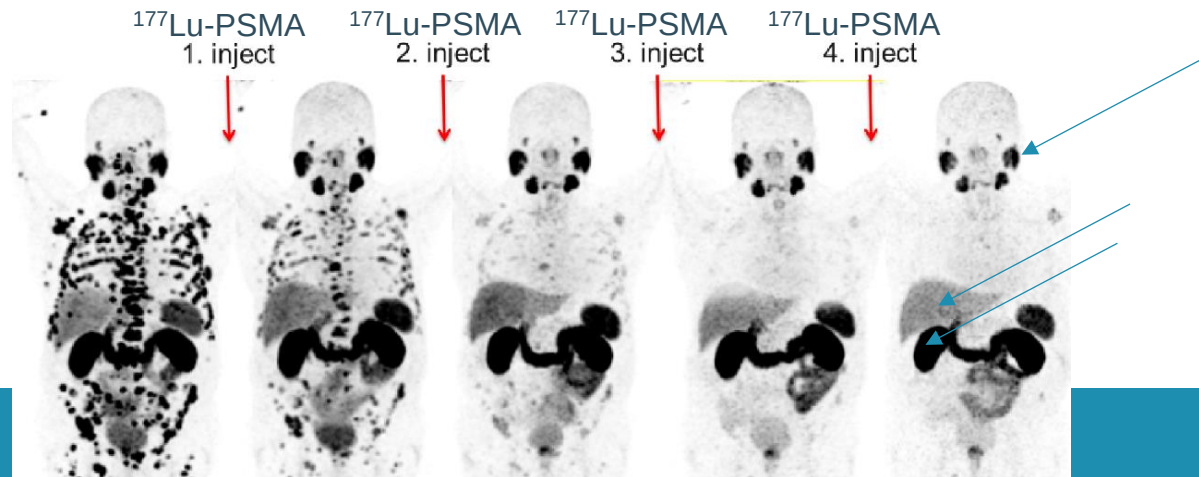
Vector type: chemical structure

feature	Small molecule	Biologic agent
example	^{18}F FDG	Peptide-affibody- nanobody-antibody
entity	chemical	amino-acid sequence
labeling	^{11}C , ^{18}F , radio-iodine	Radiometal (chelator); long half-life (antibody)
production	Organic synthesis	Peptide synthesis (peptide) biotechnological (protein)
structure	Small, simple well characterized, robust	Large complex heterogeneous Temperature sensitive
application	Extracellular and intracellular targets	Extracellular targets;

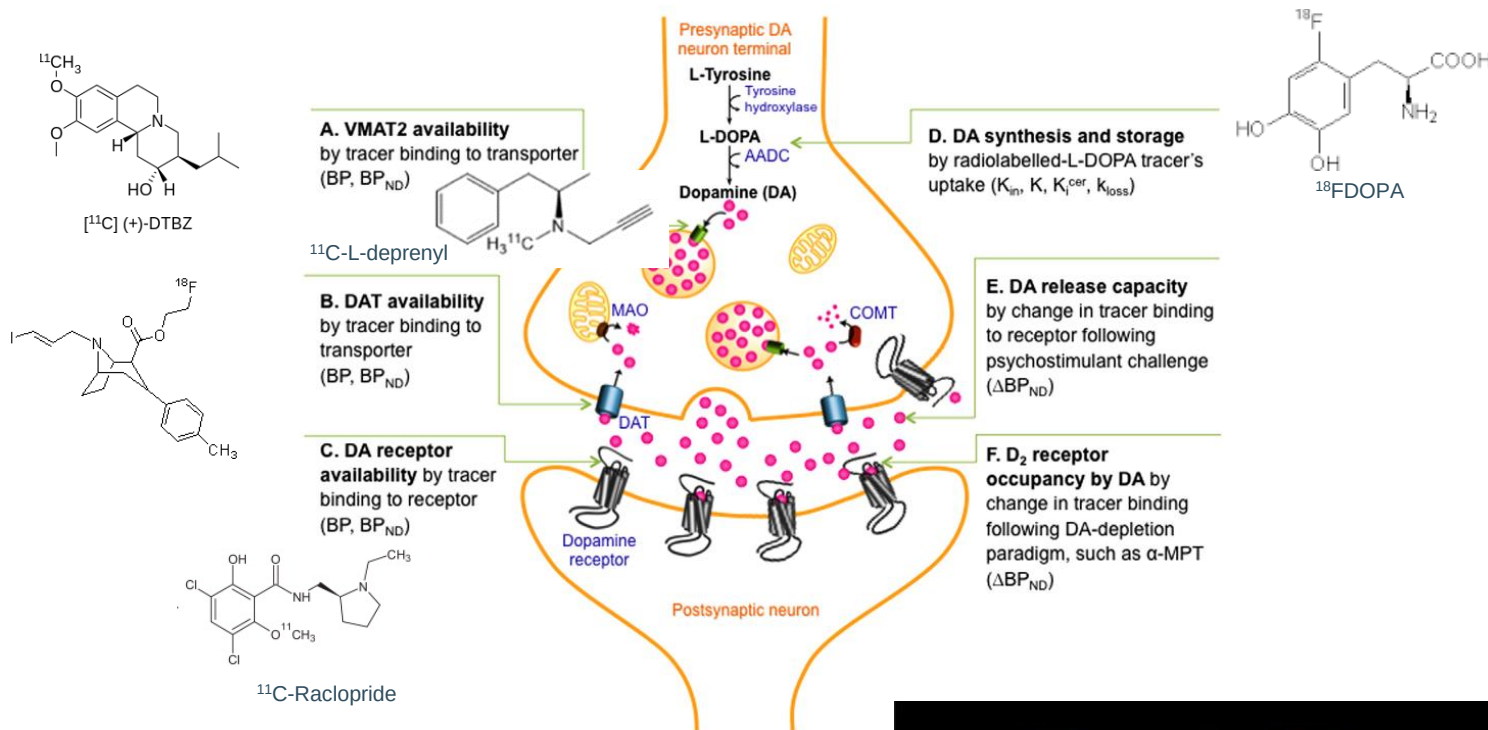
Off target binding

accumulation of the radionuclide in non-target cells/tissues

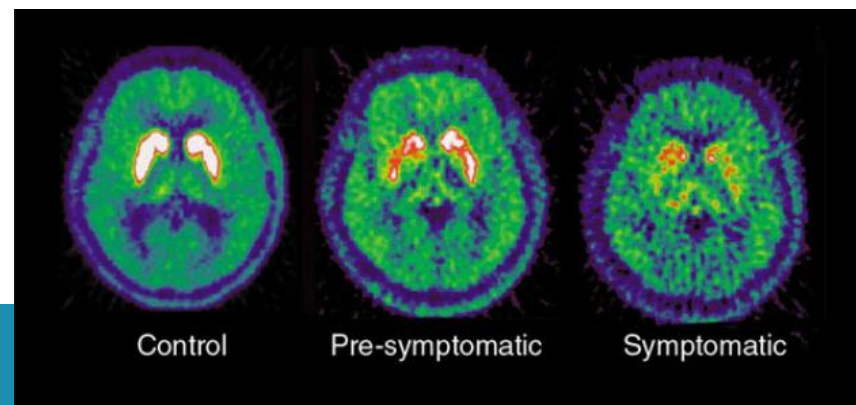
- due to excretion (kidneys/liver)
- due to instability (demetallation, recoil effect,...) and metabolism of the radiopharmaceutical
- due to off target uptake in healthy tissues (salivary glands)



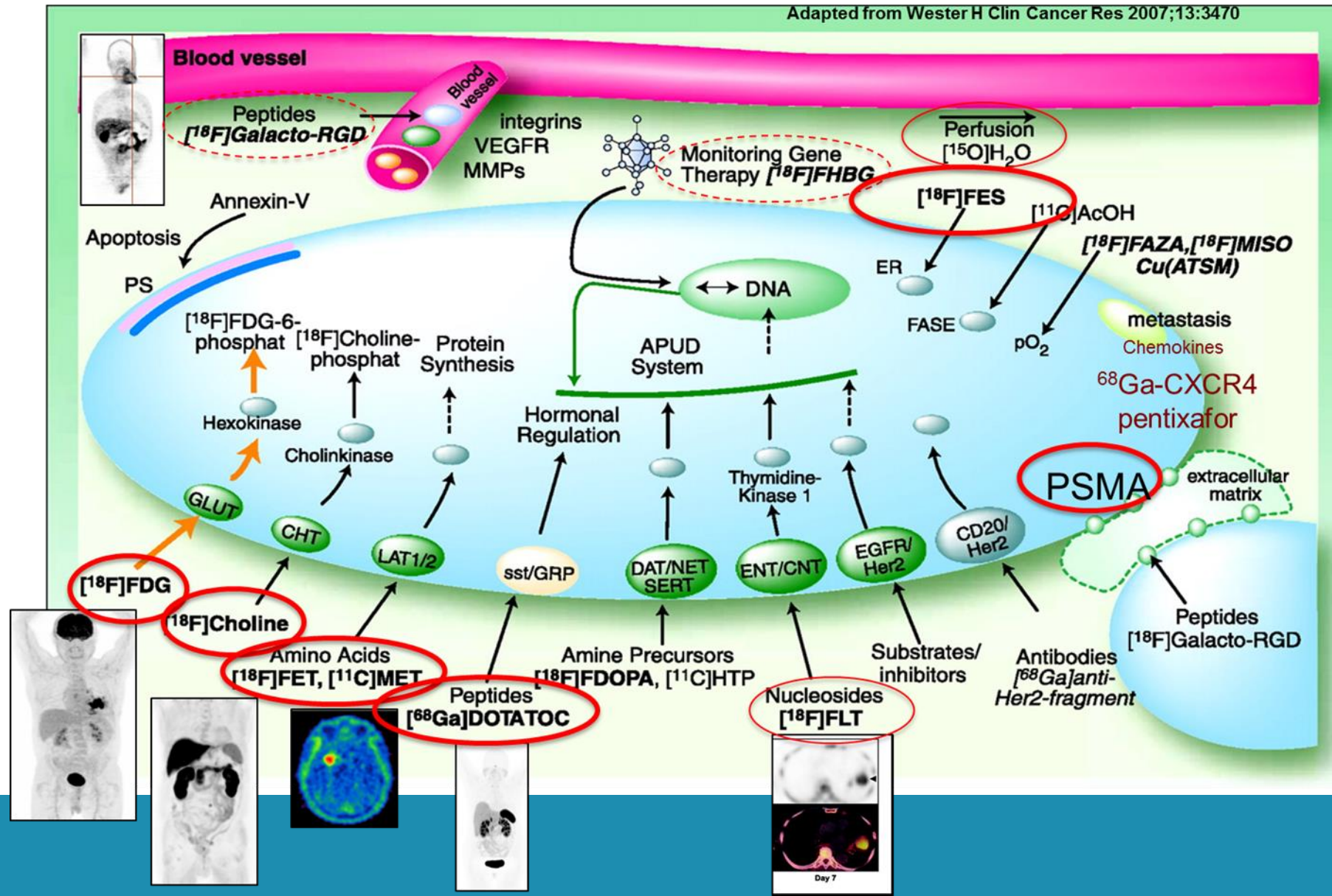
CNS: ^{11}C en ^{18}F tracers: the sky is the limit



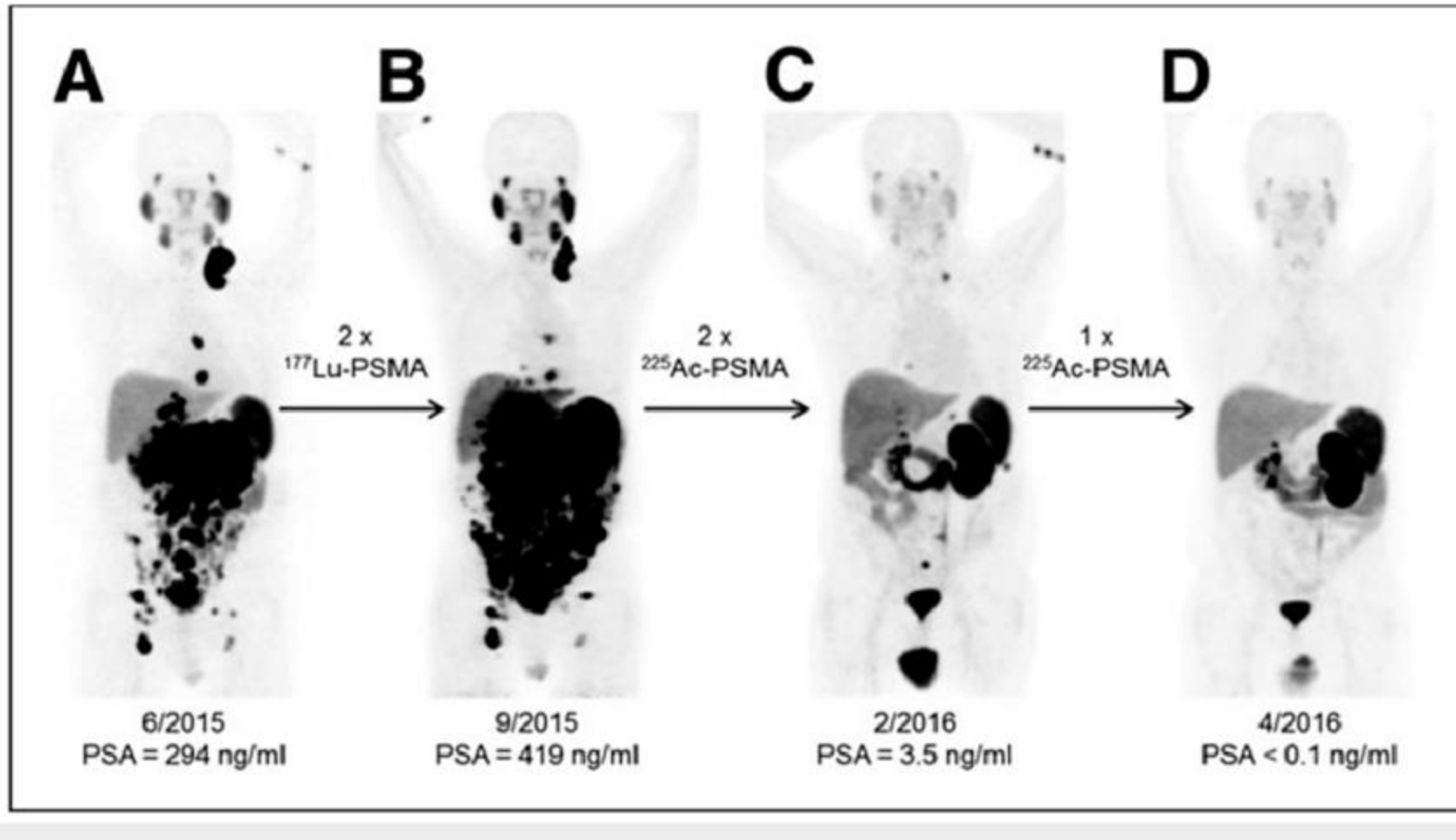
loss of dopaminergic neurons in Parkinson's disease



Oncology targets: the sky is the limit



The alpha therapy revolution



The alpha therapy revolution

Bayer starts Phase I study with novel targeted radionuclide therapy ^{225}Ac -PSMA-Trillium in advanced metastatic prostate cancer

^{225}Ac -PSMA-Trillium (BAY 3563254) is an investigational next-generation PSMA-targeted alpha therapy with potential to treat patients with advanced metastatic prostate cancer / Prostate cancer is the second most commonly diagnosed cancer in men¹, with less than three years median survival among metastatic patients, who have developed castration-resistance² / Bayer remains committed to advancing medical innovations for patients across all stages of prostate cancer



AstraZeneca to acquire Fusion to accelerate the development of next-generation radioconjugates to treat cancer



Thanks for your attention!

