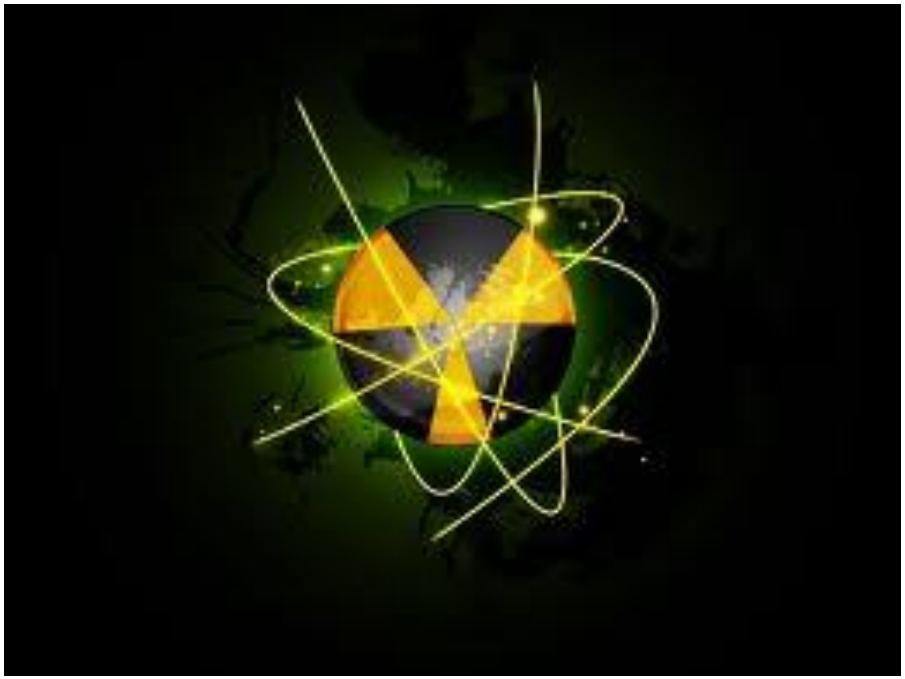
Lecture

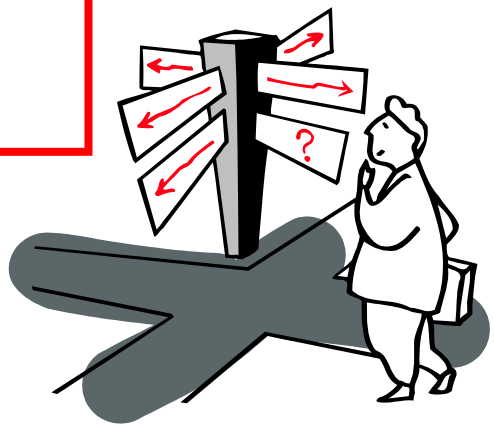
In vivo molecular neuroreceptor imaging



Matthias Bauwens - Radiochemist
Beeldvorming (NUTRIM) - MUMC

Outline of the presentation:

1) Introduction
- Neuro-imaging: why
- Targets: receptors/fysiological
- The best of nuclear medicine
- The worst of nuclear medicine



2) Which isotope?
- Karlsruhe chart
- Radiopharmaceutical = pharmaceutical

3) Some examples
- ^{18}F-FDG
- Alzheimer: amyloid / Tau
- Epilepsy
- Other tracers
- Radiomics

Why neuro-imaging?

- Fundamental research: to learn how the brain works
- Diagnosing neurological diseases non-invasively (*)
- Prognosing neurological diseases
- Follow-up of neurological diseases *(during therapy)*
- Guidance for treatment of … *(DBS)*

*Neurological diseases: Alzheimer, Parkinson, Epilepsy, Brain tumours, …

Tracer concept

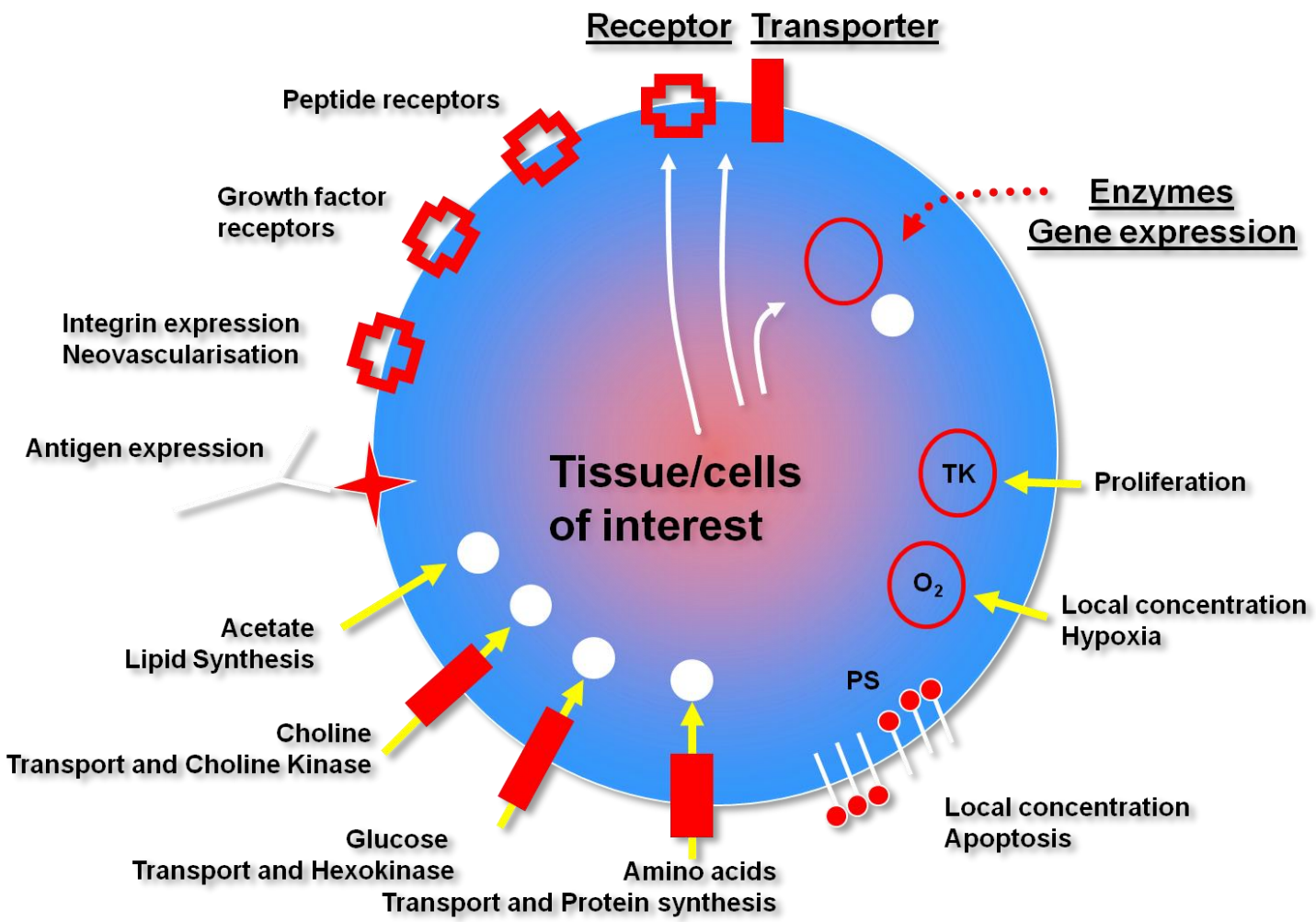
- Tracer: compound mimicking naturally occurring compounds

- (very) low concentration:
- Do not disturb physiological concentrations
- No pharmaceutical effect
- Generally: µmol – nmol tracer (tumor, infection, infarct, …)
- Target with low expression: nmol – pmol tracer

(alpha7 receptor: femtomol per cm^3)

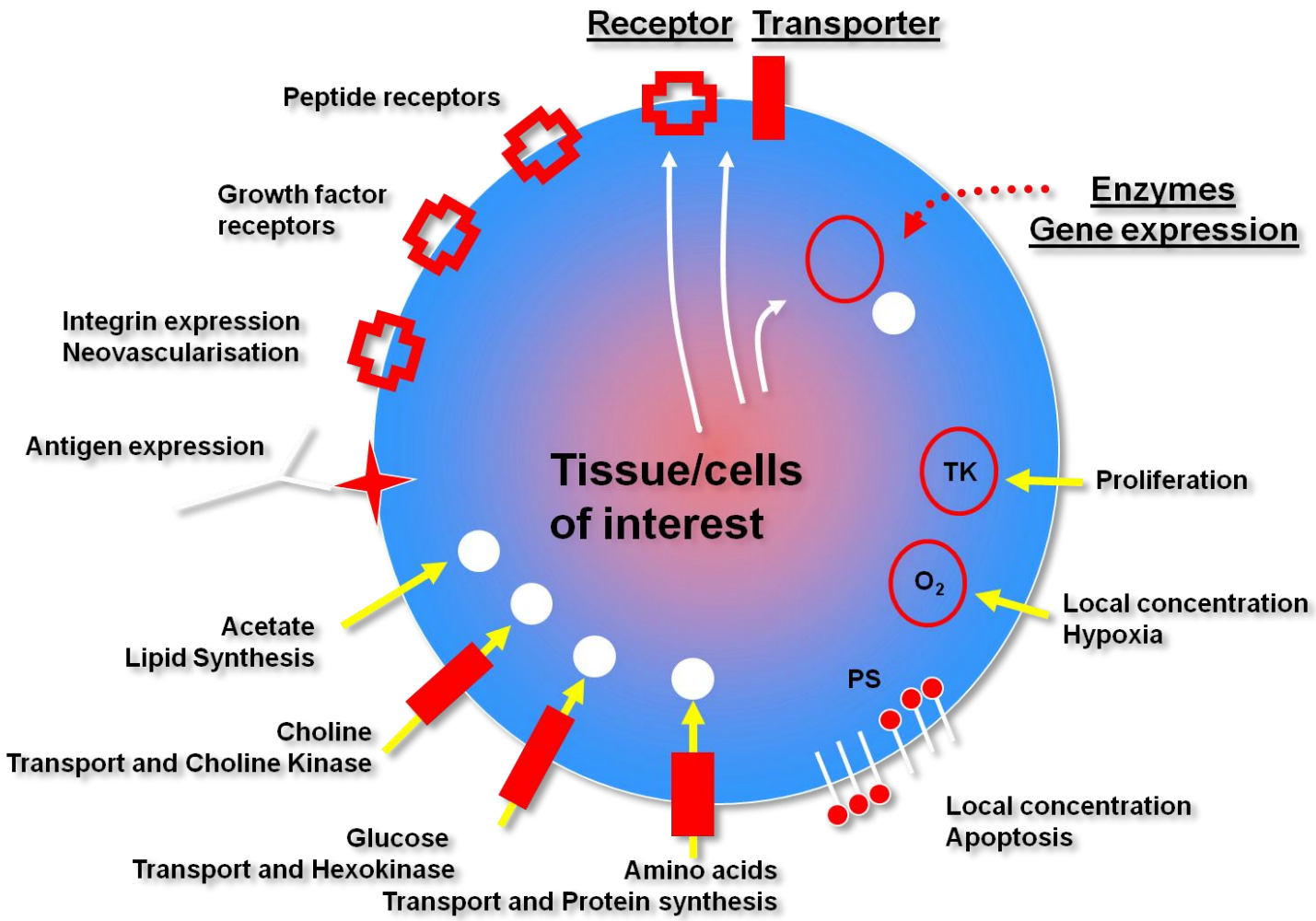
- Sufficient amount of radioactivity (or luminescence)
- Enough activity to get a signal
- More activity = better spatial and temporal resolution
- ALARA

Targets: receptors / physiological



Matrix proteins, vasculature-bound targets, immune cells, …

Targets: receptors / physiological



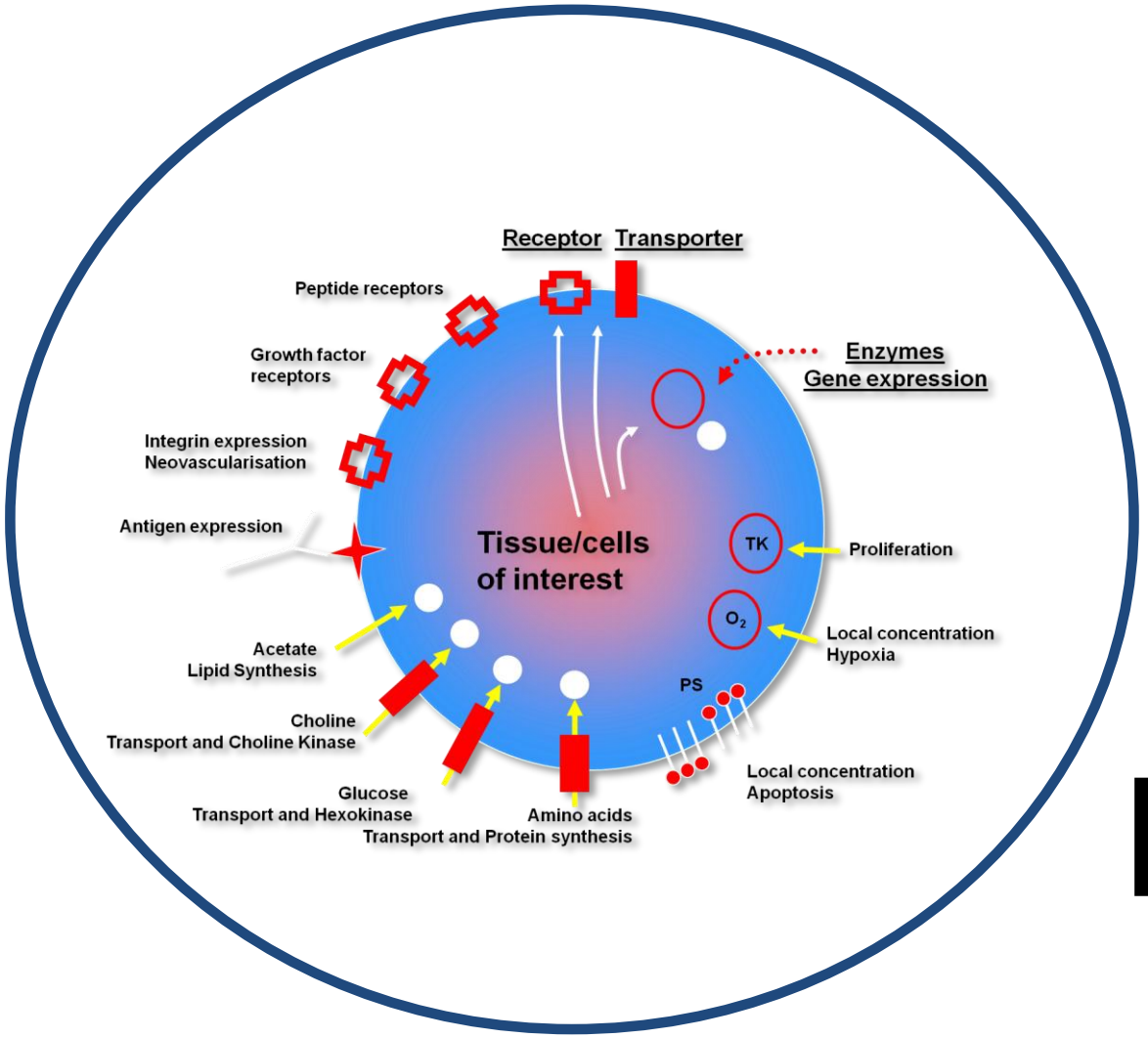
pH, perfusion, blood flow, vasculature (leaking), density, water and/or lipid content, …

The best of nuclear medicine

Imaging Method	Spatial resolution	Temporal resolution	Sensitivity
Ultrasound	50 µm	< 100 ms	10^{-3} mol
CT	50 µm	< 100 ms	10^{-3} mol
MRI	100 µm	< 50 ms	10^{-5} mol
fMRI	3-4 mm	< 2 s	10^{-5} mol
MRS	1-10 mm	< 10 s	10^{-5} mol
Bioluminescence, Fluorescence	1-3 mm (depth dependent)	< 5 s	10^{-8} mol
Nuclear (PET or SPECT)	2 mm	< 5 s	10^{-9}-10^{-12} mol

Take care: All numbers are strongly dependent on equipment/technique!

The worst of nuclear medicine



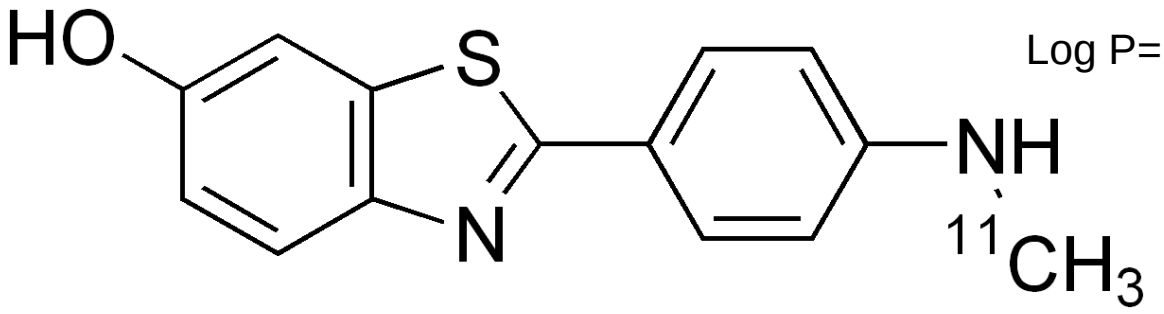
Immune-protected regions in the human body:

- Testes
- Eye
- Brain
- Placenta/foetus

BBB

The worst of nuclear medicine

Lipinski's rule of 5:
- No more than 5 hydrogen bond donors (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds)
- No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
- A molecular mass less than 500 daltons
- An octanol-water partition coefficient (log *P)* not greater than 5

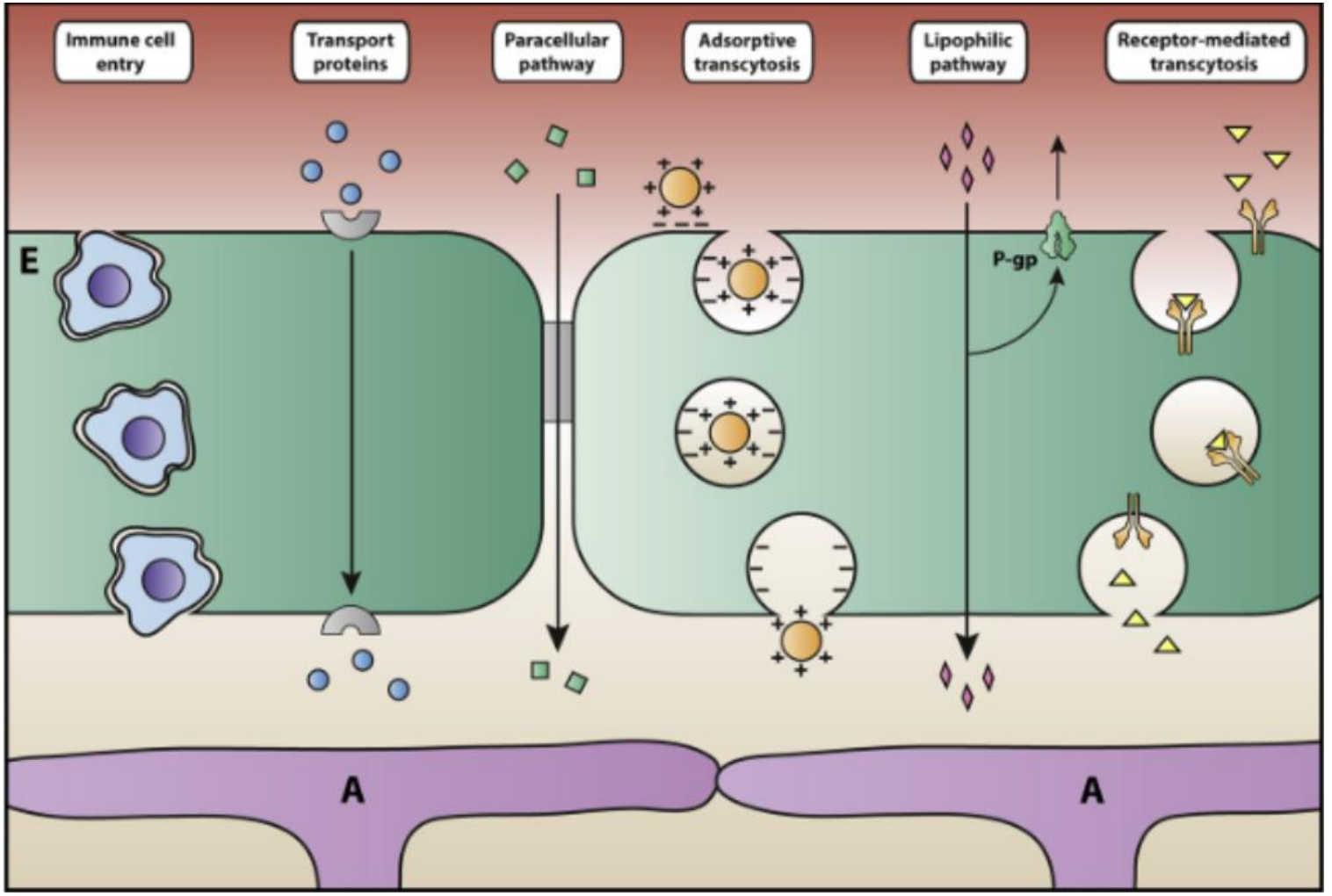


Log P= 1.2 ; MW = 256

Biggest exception so far: entire antibody passing BBB

Example: Therapeutic bispecific antibodies cross the blood-brain barrier in nonhuman primates. Sci Transl Med. 2014 Nov 5;6(261):261ra154

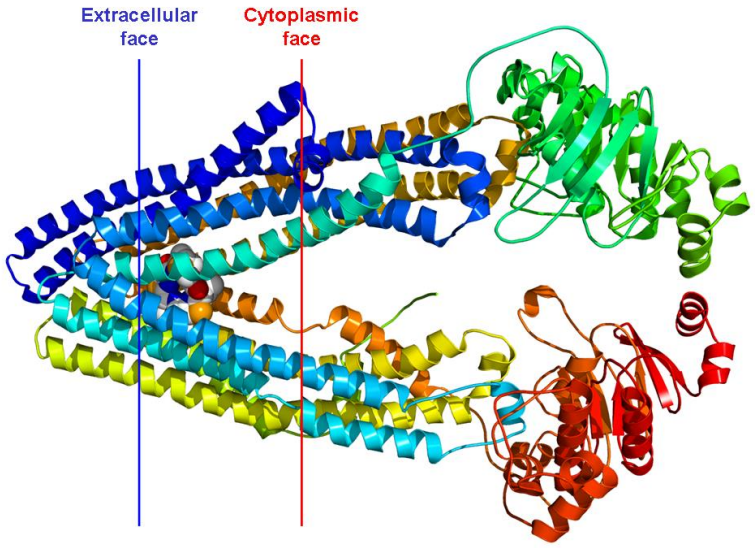
Can everything pass the BBB?



Suitable for tracer transport?	Not easy	No (only small and specific compounds)	Yes (if …)

In, but not out …

PgP
(P-glycoprotein, aka multidrug resistance protein)

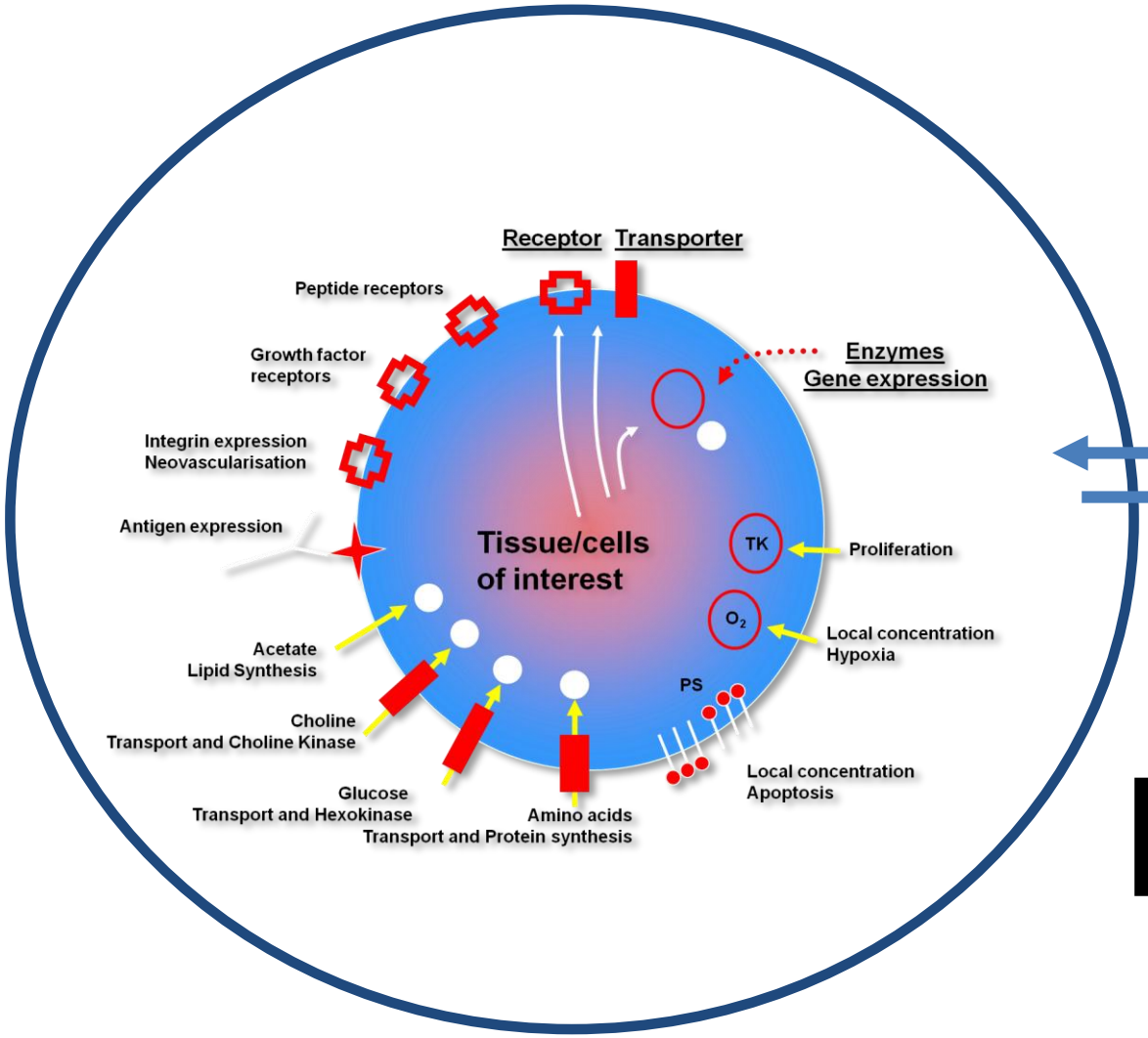


Pumps xenobiotics (drugs, toxins and tracers) back out to the blood

Avoid it by following a “rule of 4”

- MWt < 400 Da or > 800 Da
- with < 7 nitrogen plus oxygen atom HBAs
- basic pK_a of < 8

The worst of nuclear medicine



Very hard to predict in vivo pharmacokinetics !

High reward, high risk.

BBB

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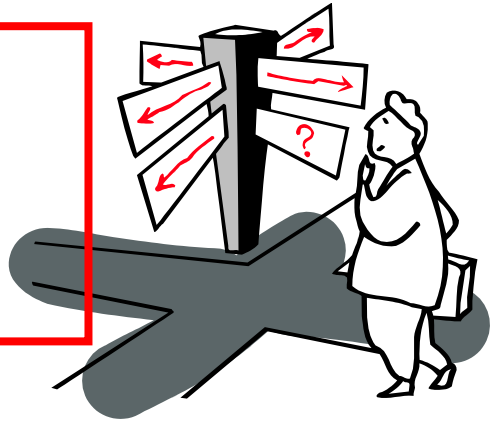

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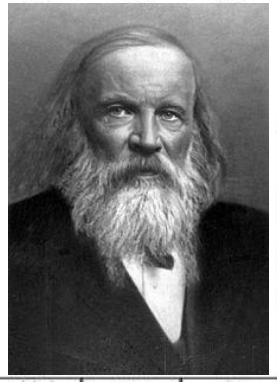
- Epilepsy
- Other tracers
- Radiomics

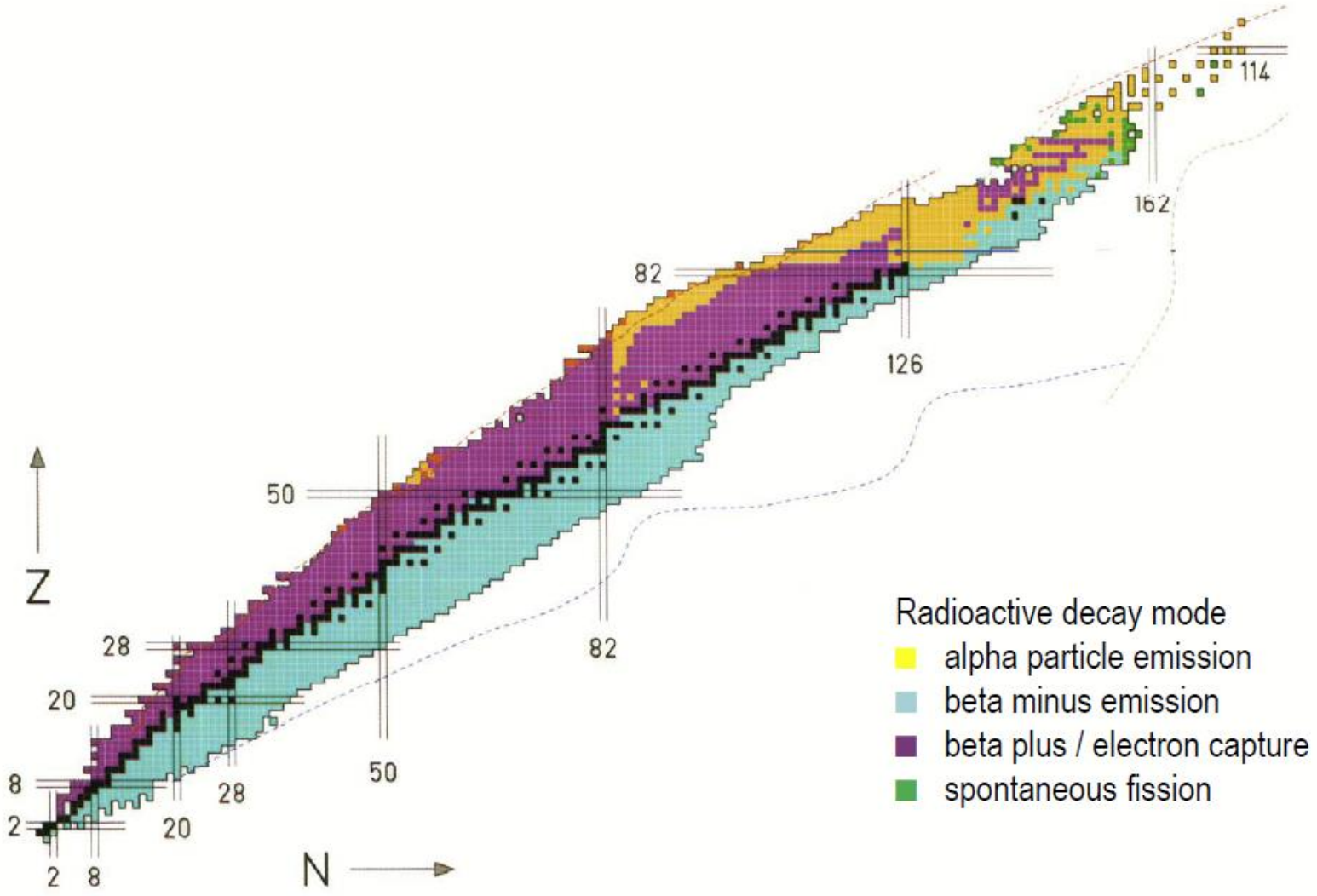
Table of Mendeljev



hydrogen 1 H 1.0079																	helium 2 He 4.0026
lithium 3 Li 6.941	beryllium 4 Be 9.0122											boron 5 B 10.811	carbon 6 C 12.011	nitrogen 7 N 14.007	oxygen 8 O 15.999	fluorine 9 F 18.998	neon 10 Ne 20.180
sodium 11 Na 22.990	magnesium 12 Mg 24.305											aluminium 13 Al 26.982	silicon 14 Si 28.086	phosphorus 15 P 30.974	sulfur 16 S 32.065	chlorine 17 Cl 35.453	argon 18 Ar 39.948
potassium 19 K 39.098	calcium 20 Ca 40.078	scandium 21 Sc 44.956	titanium 22 Ti 47.867	vanadium 23 V 50.942	chromium 24 Cr 51.996	manganese 25 Mn 54.938	iron 26 Fe 55.845	cobalt 27 Co 58.933	nickel 28 Ni 58.693	copper 29 Cu 63.546	zinc 30 Zn 65.39	gallium 31 Ga 69.723	germanium 32 Ge 72.61	arsenic 33 As 74.922	selenium 34 Se 78.96	bromine 35 Br 79.904	krypton 36 Kr 83.80
rubidium 37 Rb 85.468	strontium 38 Sr 87.62	yttrium 39 Y 88.906	zirconium 40 Zr 91.224	niobium 41 Nb 92.906	molybdenum 42 Mo 95.94	technetium 43 Tc [98]	ruthenium 44 Ru 101.07	rhodium 45 Rh 102.91	palladium 46 Pd 106.42	silver 47 Ag 107.87	cadmium 48 Cd 112.41	indium 49 In 114.82	tin 50 Sn 118.71	antimony 51 Sb 121.76	tellurium 52 Te 127.60	iodine 53 I 126.90	xenon 54 Xe 131.29
caesium 55 Cs 132.91	barium 56 Ba 137.33	57-70 *	lutetium 71 Lu 174.97	hafnium 72 Hf 178.49	tantalum 73 Ta 180.95	tungsten 74 W 183.84	rhenium 75 Re 186.21	osmium 76 Os 190.23	iridium 77 Ir 192.22	platinum 78 Pt 195.08	gold 79 Au 196.97	mercury 80 Hg 200.59	thallium 81 Tl 204.38	lead 82 Pb 207.2	bismuth 83 Bi 208.98	polonium 84 Po [209]	astatine 85 At [210]	radon 86 Rn [222]
francium 87 Fr [223]	radium 88 Ra [226]	89-102 **	lawrencium 103 Lr [262]	rutherfordium 104 Rf [261]	dubnium 105 Db [262]	seaborgium 106 Sg [266]	bohrium 107 Bh [264]	hassium 108 Hs [269]	meitnerium 109 Mt [268]	ununnilium 110 Uun [271]	unununium 111 Uuu [272]	ununbium 112 Uub [277]		ununquadium 114 Uuq [289]			

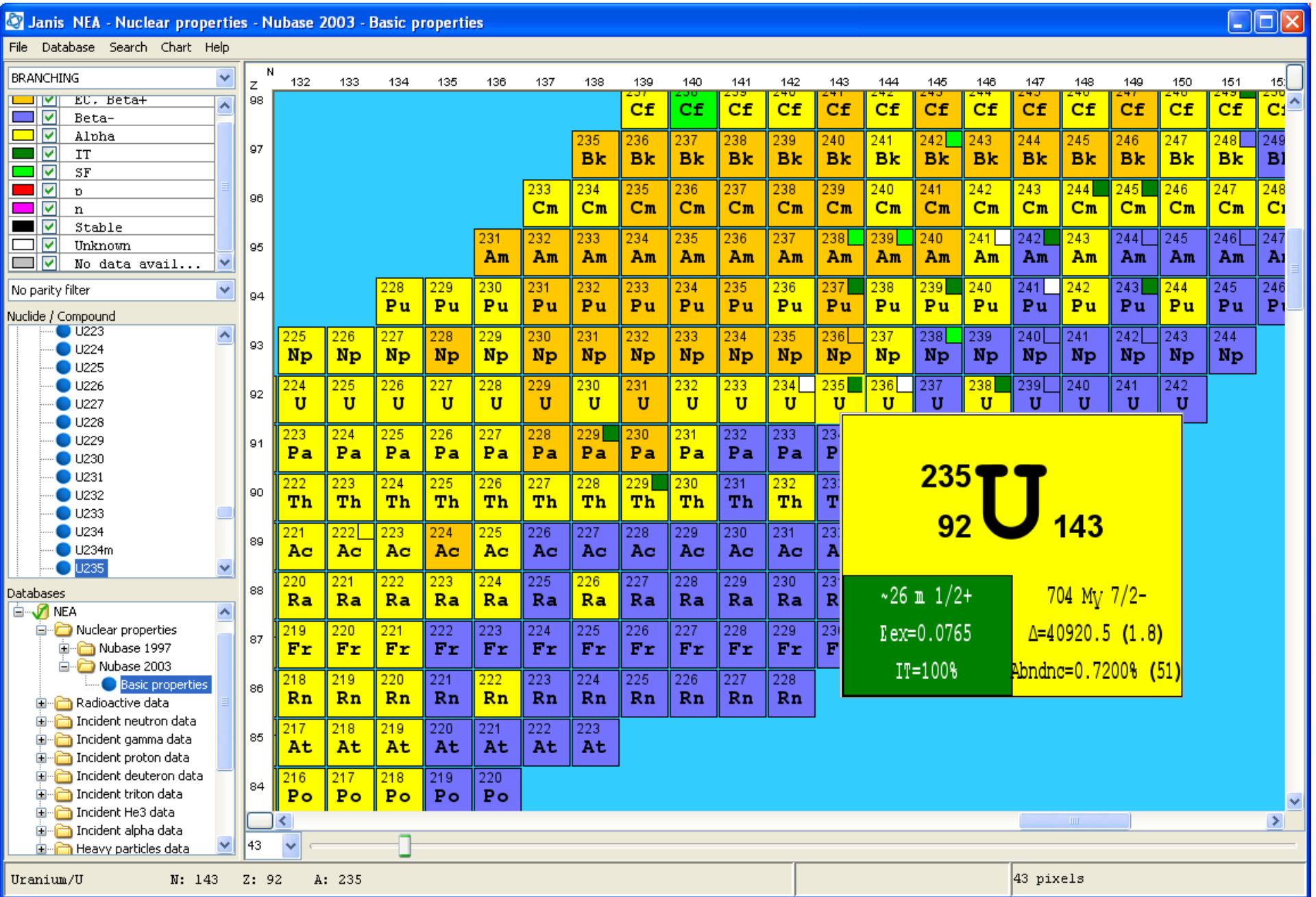
*Lanthanide series	lanthanum 57 La 138.91	cerium 58 Ce 140.12	praseodymium 59 Pr 140.91	neodymium 60 Nd 144.24	promethium 61 Pm [145]	samarium 62 Sm 150.36	europium 63 Eu 151.96	gadolinium 64 Gd 157.25	terbium 65 Tb 158.93	dysprosium 66 Dy 162.50	holmium 67 Ho 164.93	erbium 68 Er 167.26	thulium 69 Tm 168.93	ytterbium 70 Yb 173.04
**Actinide series	actinium 89 Ac [227]	thorium 90 Th 232.04	protactinium 91 Pa 231.04	uranium 92 U 238.03	neptunium 93 Np [237]	plutonium 94 Pu [244]	americium 95 Am [243]	curium 96 Cm [247]	berkelium 97 Bk [247]	californium 98 Cf [251]	einsteinium 99 Es [252]	fermium 100 Fm [257]	mendelevium 101 Md [258]	nobelium 102 No [259]

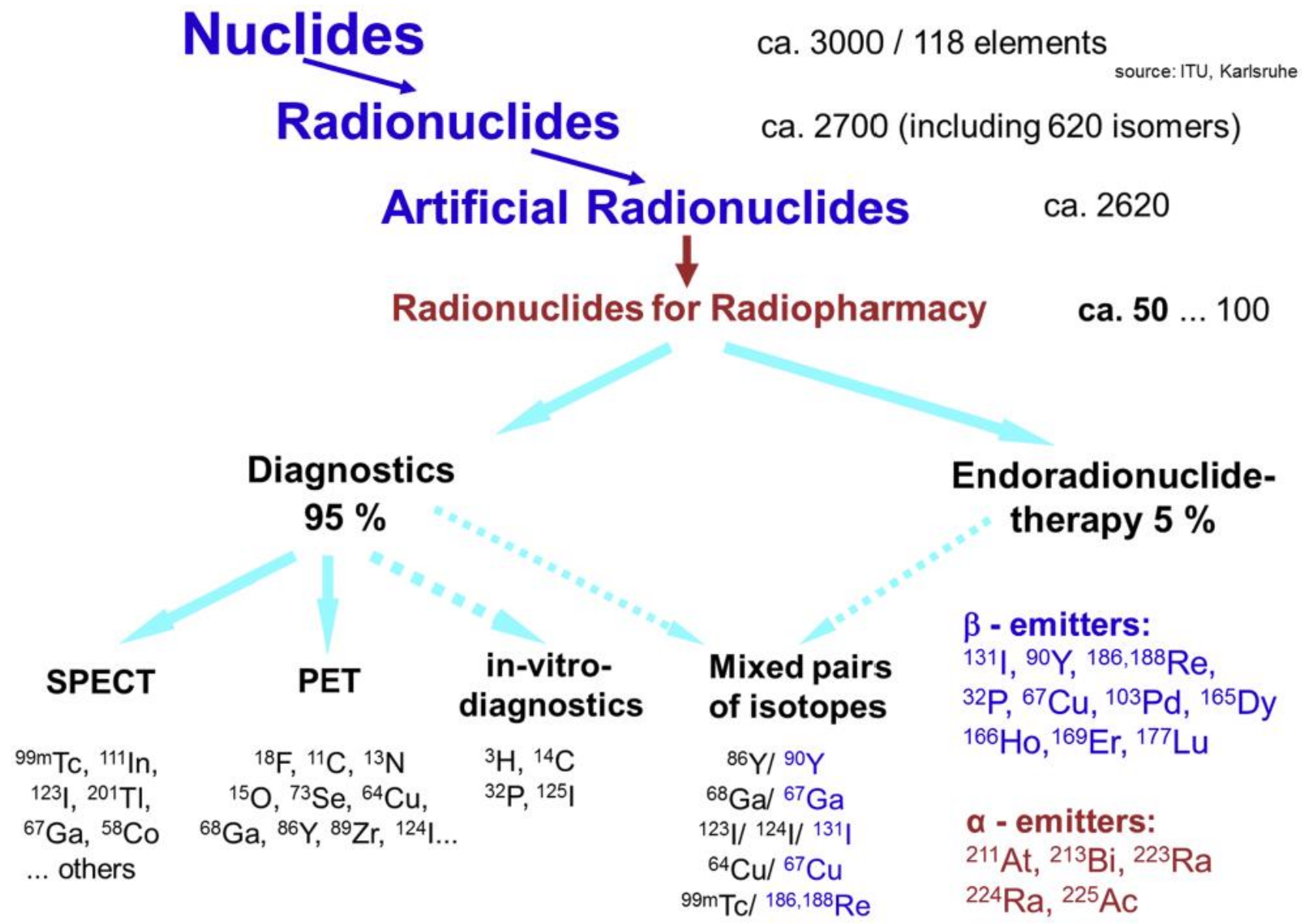
“Karlsruhe” chart of nuclides



Karlsruhe Chart

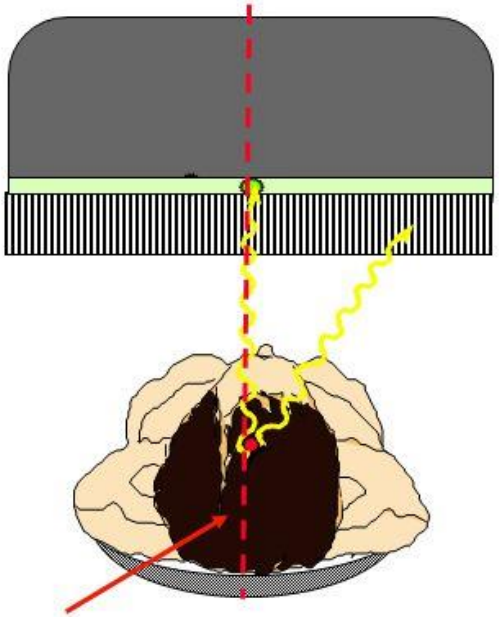
Karlsruhe Chart (zoomed in)




Nuclides
ca. 3000 / 118 elements
source: ITU, Karlsruhe
Radionuclides
ca. 2700 (including 620 isomers)
Artificial Radionuclides
ca. 2620
Radionuclides for Radiopharmacy
ca. 50 ... 100
Diagnostics
95 %
Endoradionuclide-
therapy 5 %
SPECT
PET
in-vitro-
diagnostics
Mixed pairs
of isotopes
β - emitters:
α - emitters:
99mTc, 111In,
123I, 201Tl,
67Ga, 58Co
... others
18F, 11C, 13N
15O, 73Se, 64Cu,
68Ga, 86Y, 89Zr, 124I...
3H, 14C
32P, 125I
86Y/ 90Y
68Ga/ 67Ga
123I/ 124I/ 131I
64Cu/ 67Cu
99mTc/ 186,188Re
131I, 90Y, 186,188Re,
32P, 67Cu, 103Pd, 165Dy
166Ho,169Er, 177Lu
211At, 213Bi, 223Ra
224Ra, 225Ac

SPECT

Only photons emitted perpendicularly to the detector plane can pass through collimator

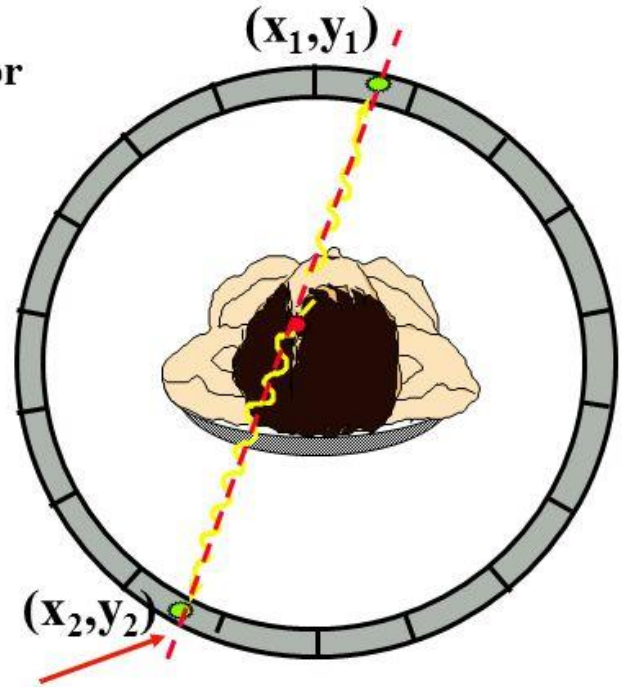


Collimator hole determines the line of photon emission

Collimated detector

Limit: 50 – 300 keV gamma or X-rays

PET



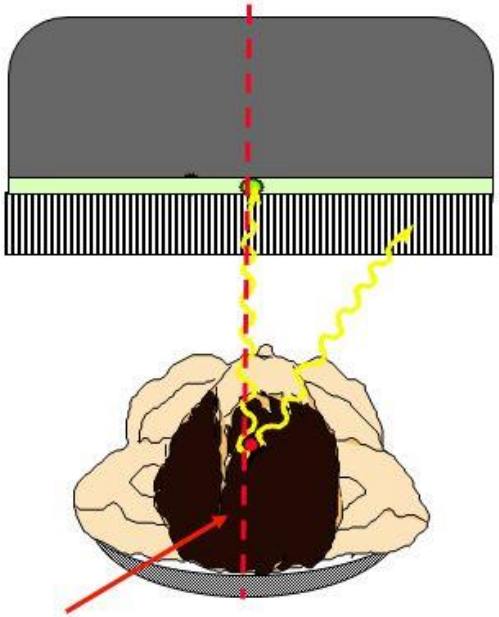
Coordinates of a two simultaneously detected photons determine the line of photon emission (line of response – LOR)

Electronic collimation

Limit: < 5 MeV positrons
(gamma-energy is fixed)

SPECT

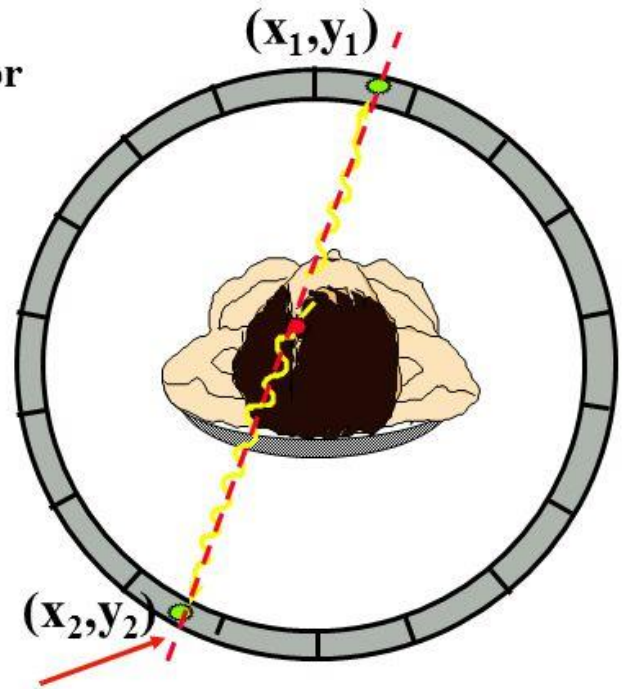
Only photons emitted perpendicularly to the detector plane can pass through collimator



Collimator hole determines the line of photon emission

Collimated detector

PET



Coordinates of a two simultaneously detected photons determine the line of photon emission (line of response – LOR)

Electronic collimation

Static image:
limited temporal resolution (>10min)

Dynamic image:
temporal resolution as of 0,1 min

Best isotopes for PET

Isotope	Half-life	Positron range in water	Chemistry
^{11}C	20 min	1.1 mm	Covalent bond
^{13}N	10 min	1.5 mm	Covalent bond
^{15}O	2 min	2.5 mm	Covalent bond
^{18}F	110 min	0.6 mm	Covalent bond
^{68}Ga	68 min	2.9 mm	Chelation
^{89}Zr	3.27 days	1.1 mm	Chelation
^{124}I	4.2 days	1.1 mm	Covalent bond

Why is half-life important?
Why is positron range important?
Does chemistry matter?

Radiopharmaceutical = pharmaceutical

Diagnosis with a (radio)pharmaceutical = same legislation as for treatment with a pharmaceutical

Molecular Imaging (with tracers)

- PET, SPECT, BLI, (photoaccoustic), (MRS)
- Licence for using tracers and equipment
- Manufacturing licence for syntheses
- Registration of tracer required before market application (>100 M euro)
- Yearly market value of <15 M euro per tracer

Morphological imaging (physiology)

- CT, (f)MRI, US, (photoaccoustic), (MRS)
- Licence for using equipment
- No synthesis required
- No tracer to register

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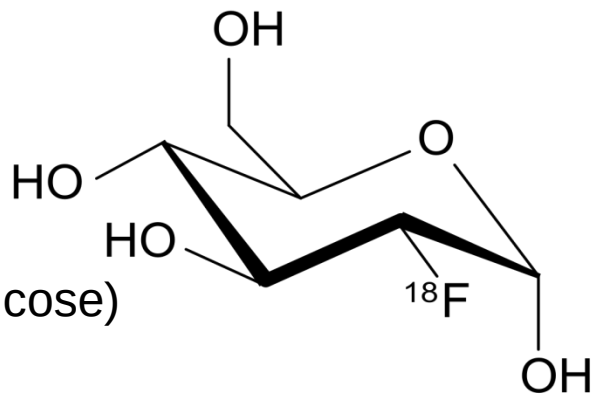
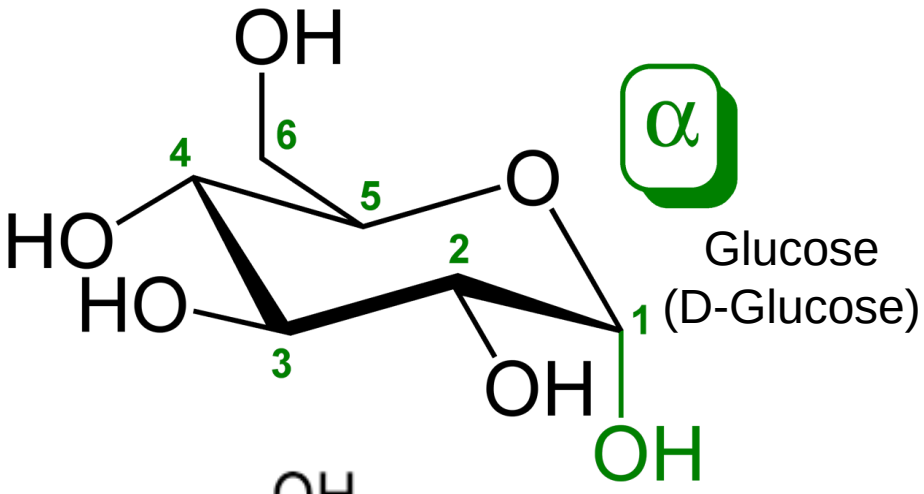
Some examples (1): ^{18}F-FDG

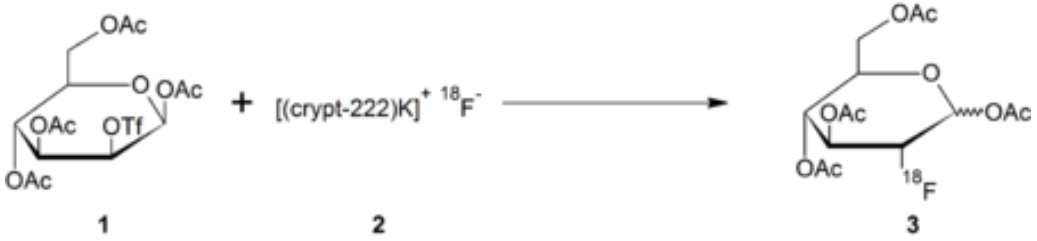
^{18}F-FDG =
^{18}F-labelled
2-fluorodeoxyglucose)





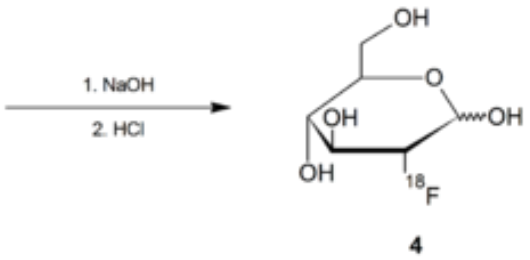
Glucose
(D-Glucose)

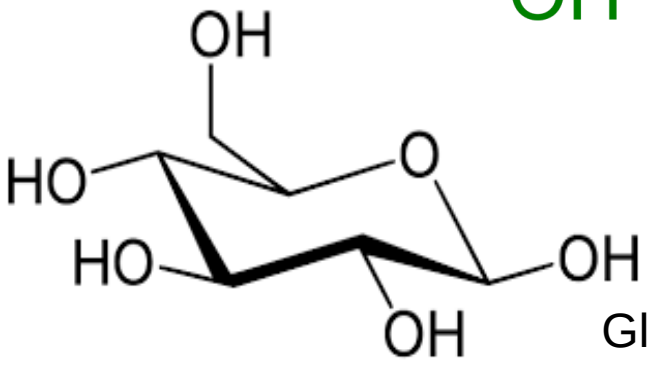
Synthesis:



Ac = CH_3CO

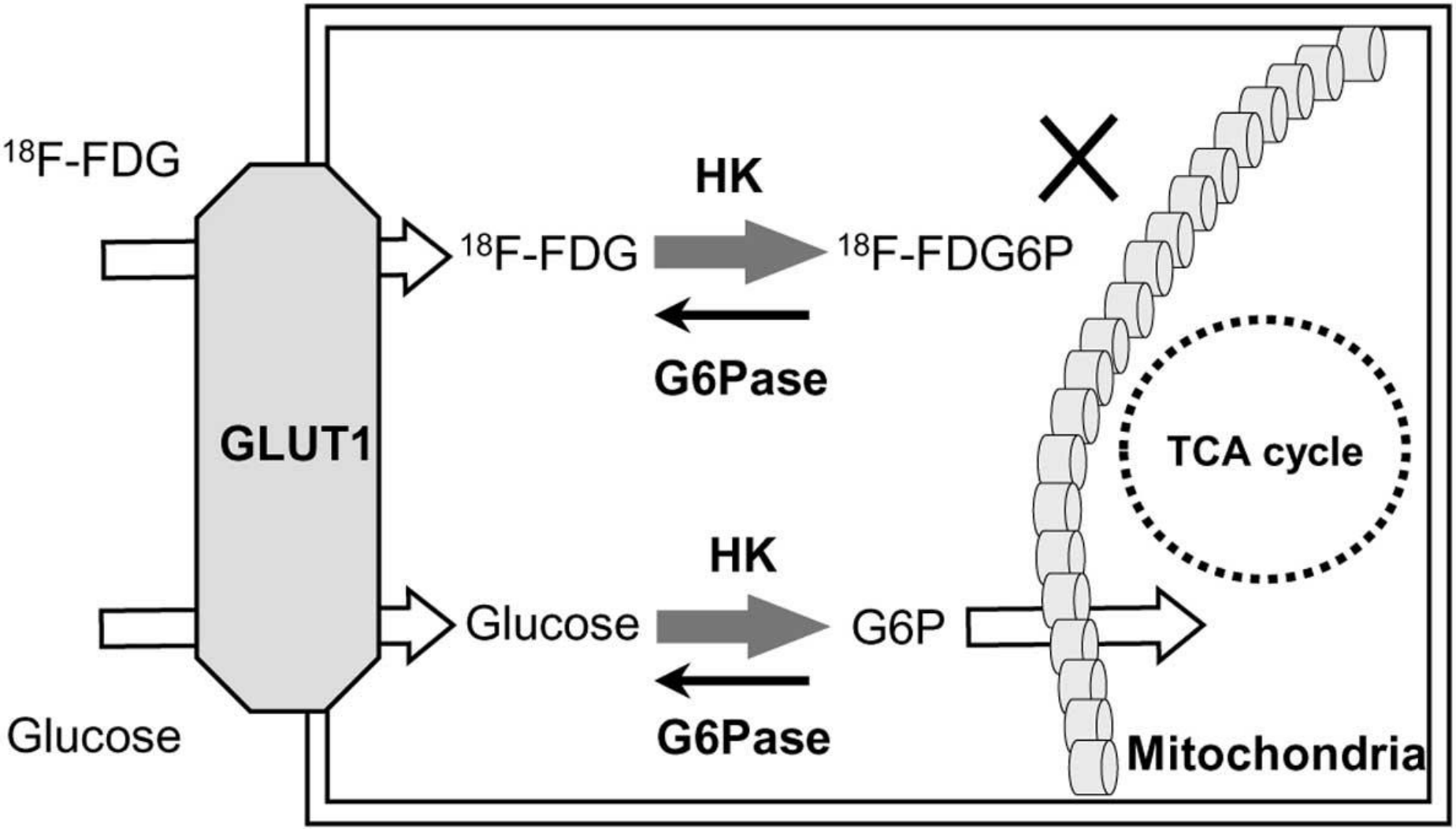
Tf = CF_3SO_2





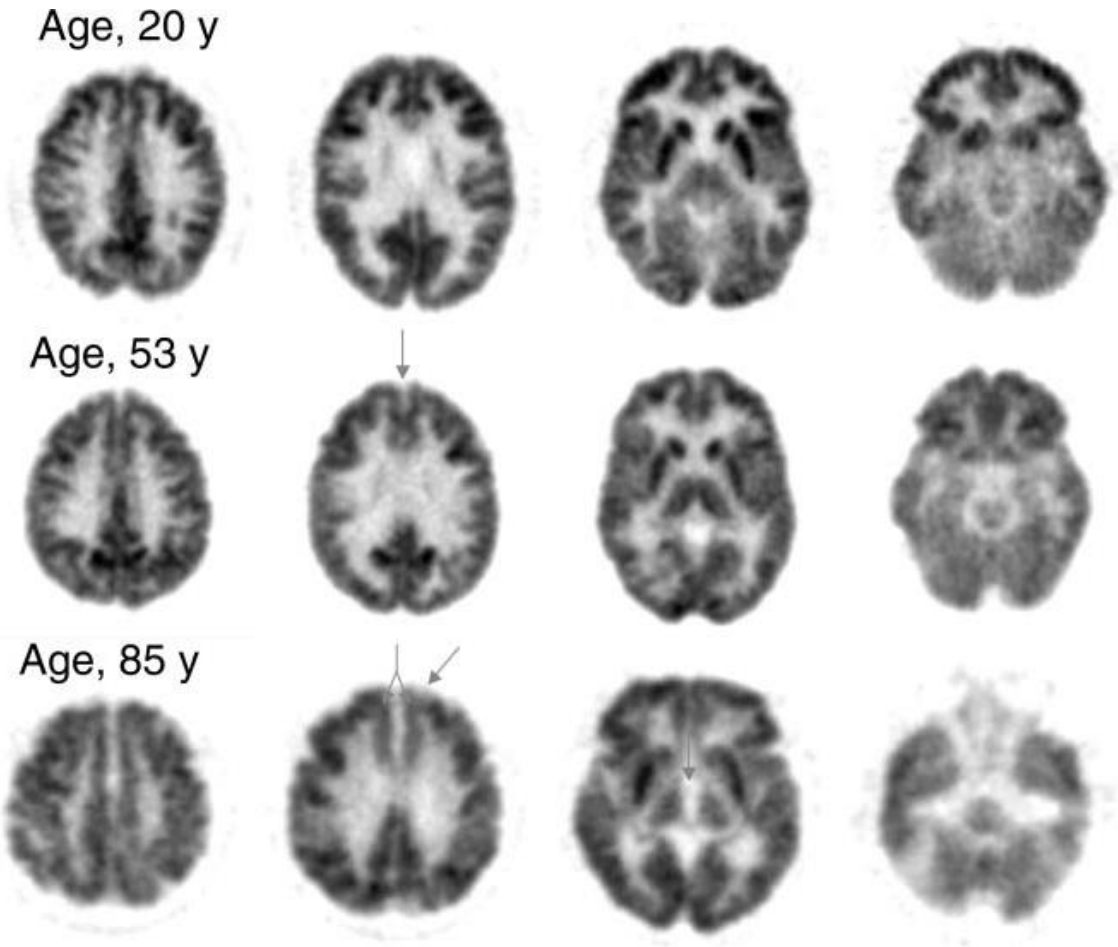
Glucose
(L-Glucose)

Some examples (1): ^{18}F-FDG



Be careful with interpretation: you are essentially visualising GLUT1, not mitochondrial activity (*although this is off course correlated*)

Some examples (1): ^{18}F-FDG



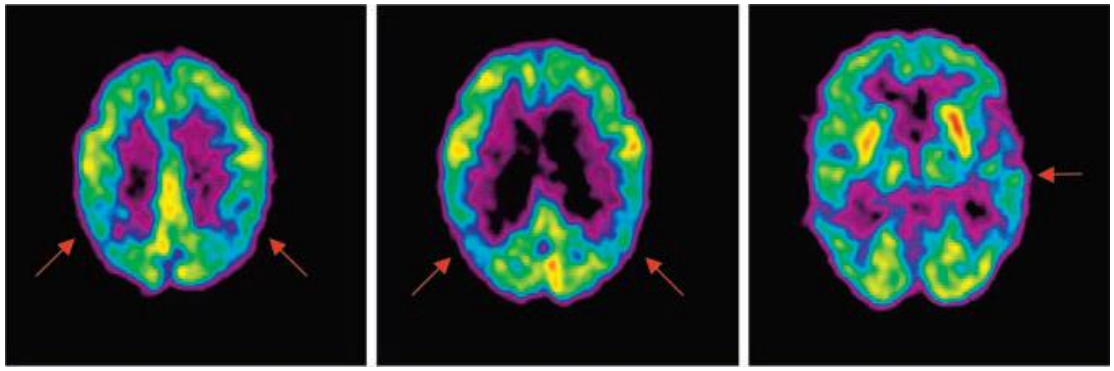
Normal adult pattern of cerebral glucose metabolism measured with 18F-FDG.

Images are shown from the most superior (far left column) to most inferior (far right column) planes of the brain. Images are cross-sectional and are displayed with the anterior brain at the top of each image and the left side of the brain on the right of each image.

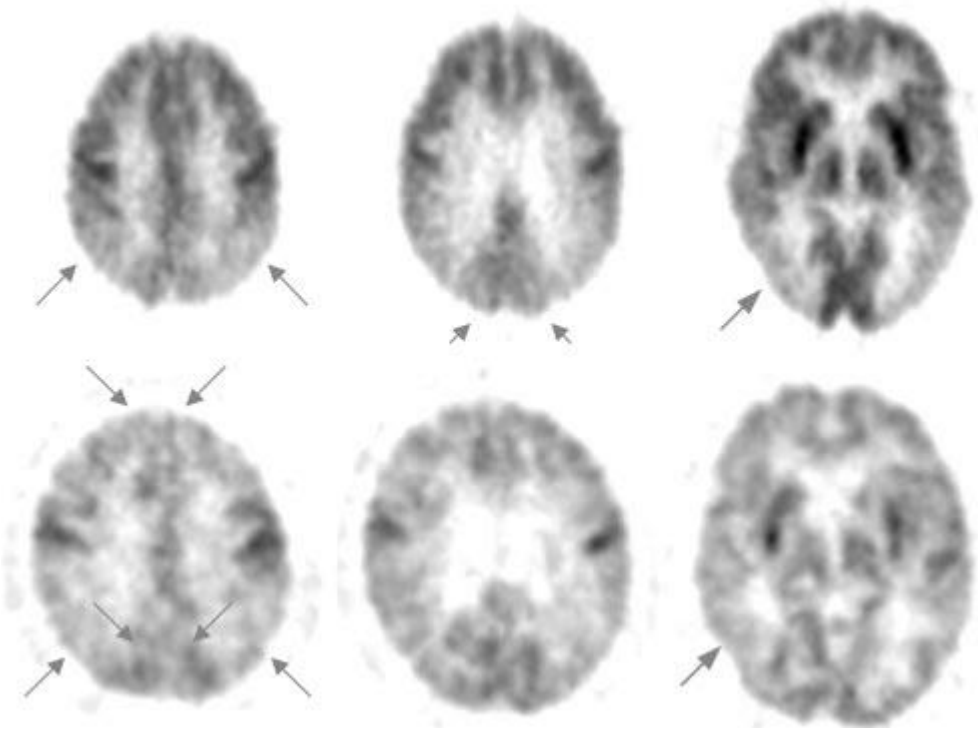
Normal aging is associated with some increased **generalized cortical atrophy**, as evidenced by moderate widening (arrow) of the interthalamic distances in the 85-y-old patient (middle right).

Additional arrows highlight the progression of **mild metabolic decline**, also attributable to normal aging, in the medial prefrontal cortex bilaterally (middle left, ages 53 and 85 y) and in the left anterior prefrontal cortex (middle left, age 85 y).
Otherwise, in healthy adults, the pattern of regional cerebral metabolism changes little throughout adulthood.

Some examples (1): ^{18}F-FDG

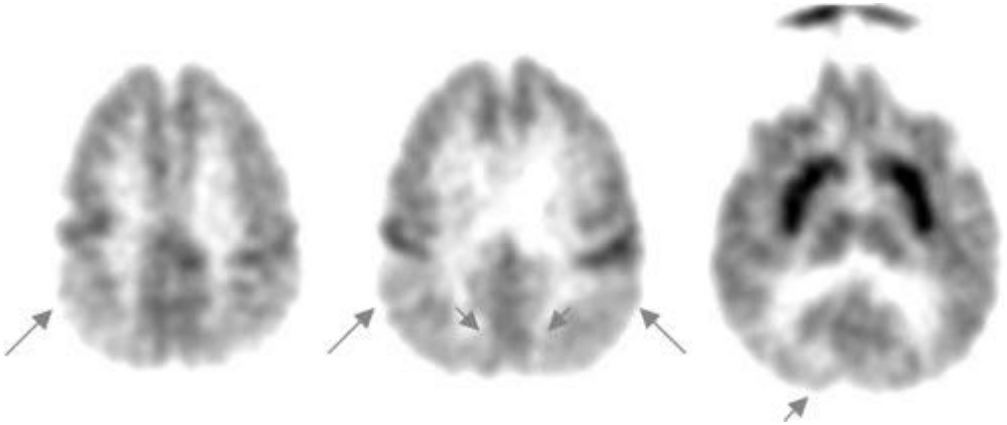


Early AD

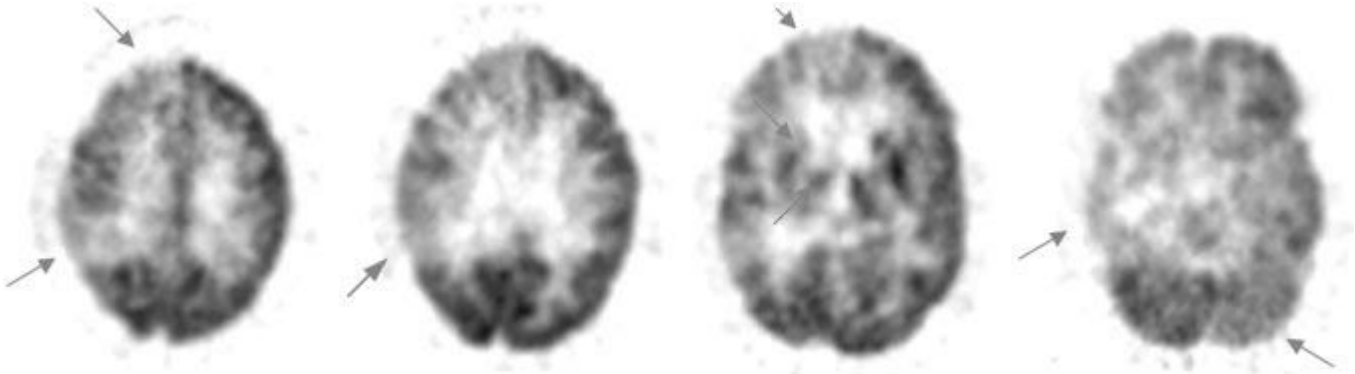


Lewy bodies

Some examples (1): ^{18}F-FDG



Parkinson



Vascular dementia

Hypometabolism

Non-invasive confirmation of “disease”, but not disease-specific

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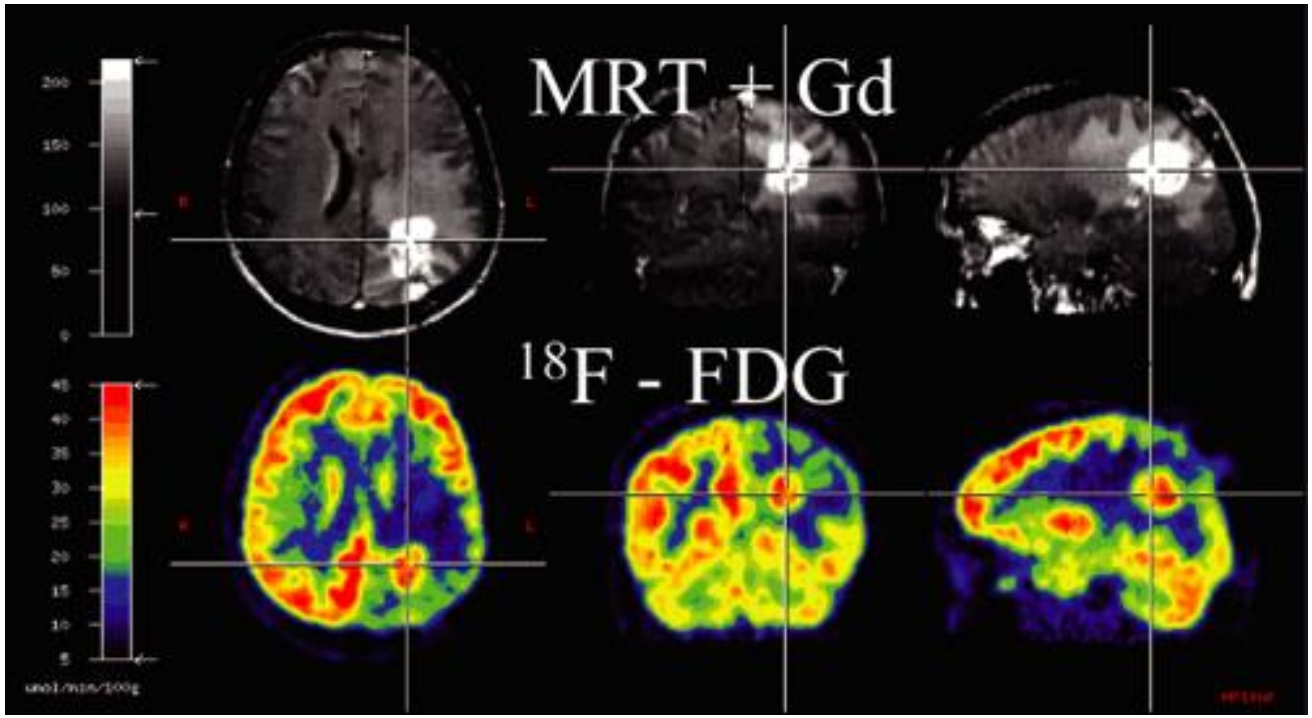
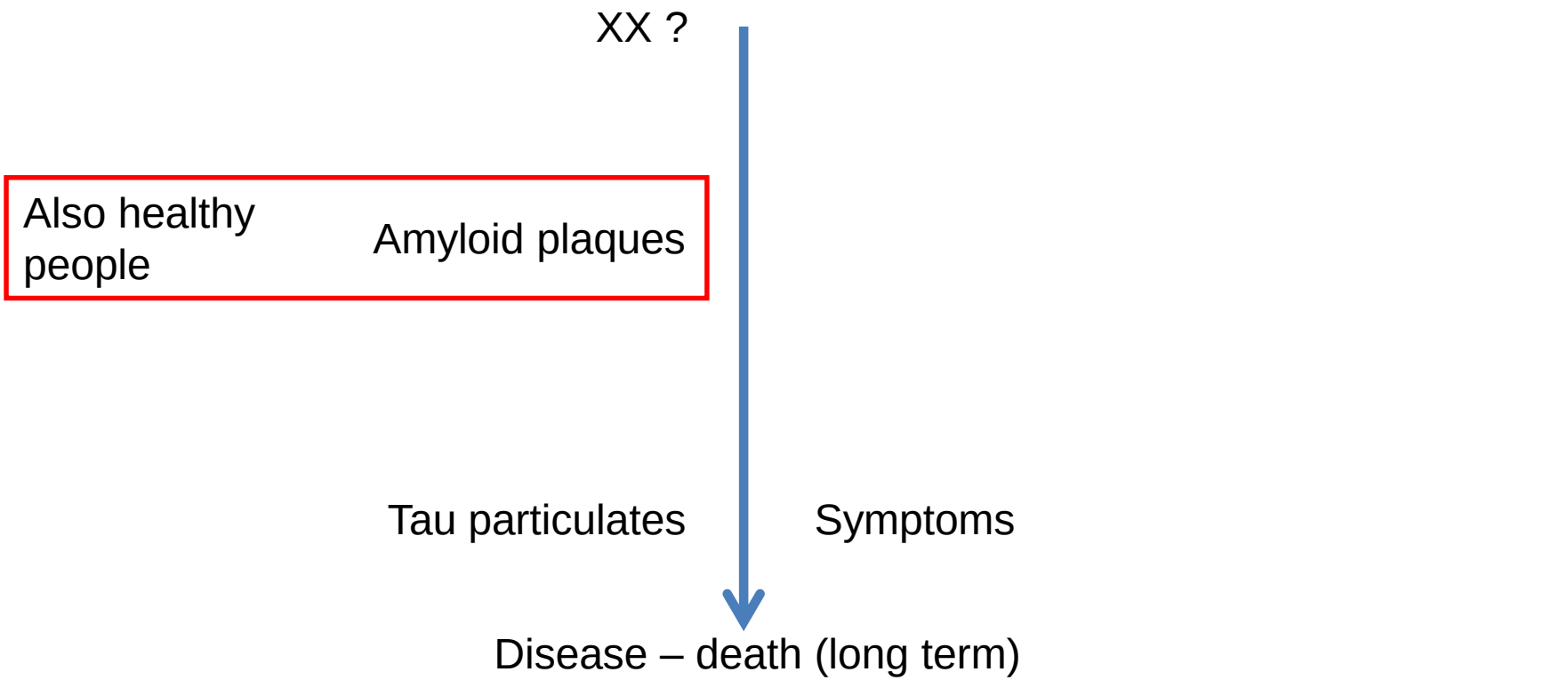
Some examples (1): ^{18}F-FDG



Typical pattern of a glioblastoma in ^{18}F-FDG-PET. Uptake is in the range of the normal unaffected cortex colocalized with the contrast enhancement in MRI. The area of high ^{18}F-FDG in the tumor is surrounded by decreased ^{18}F-FDG in the cortex.

Radiology Key, Kracht L. et al.

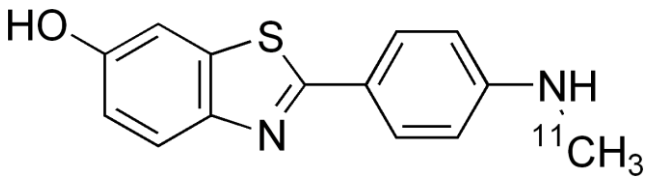
Some examples (2): Alzheimer: Amyloid / Tau



Therapy? *(simply dissolving amyloid plaques seems to worsen prognosis)*

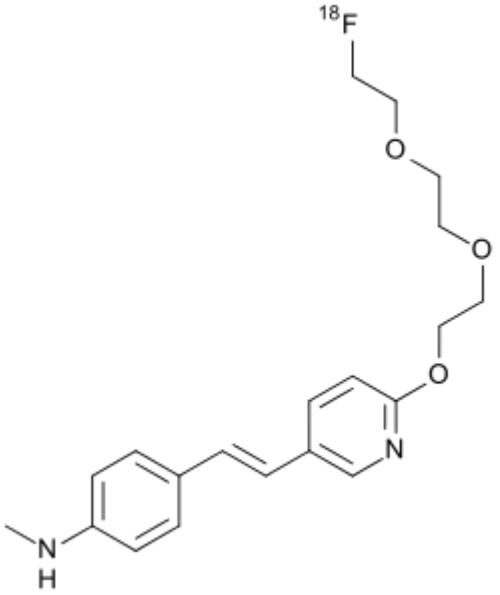
Lack of therapy ➔ diagnosis less usefull (reimbursement)

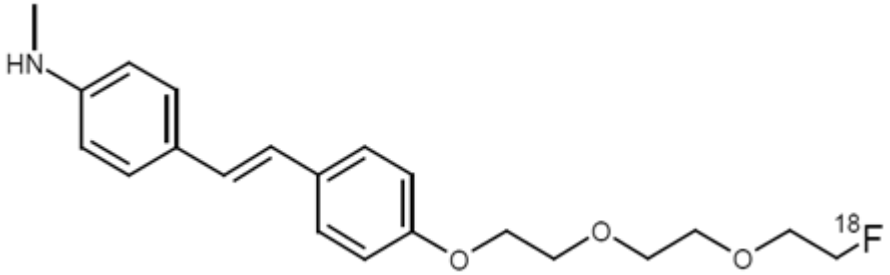
Some examples (2): Alzheimer: Amyloid / Tau



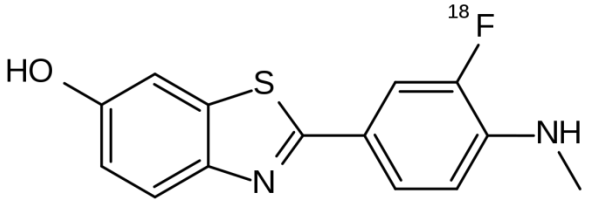
^{11}C-PIB: works, needs on-site cyclotron. Not commercially viable.

Florbetapir (Eli Lilly), florbetaben (Bayer, Avid, Piramal), and flutemetamol (GE)

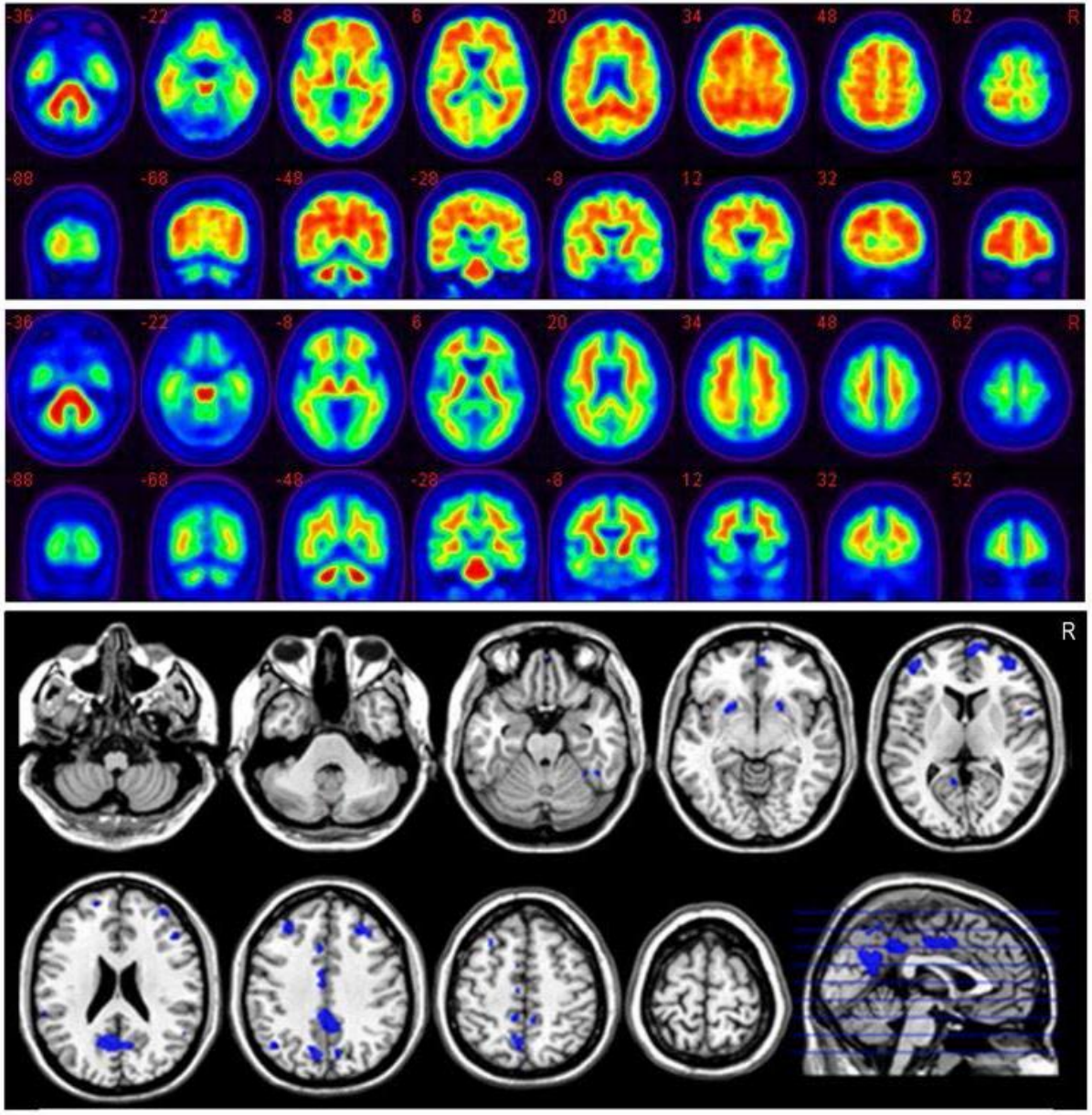




Same binding site
On amyloid plaque



Some examples (2): Alzheimer: Amyloid / Tau



18F-Flutemetamol

Presumed AD patient

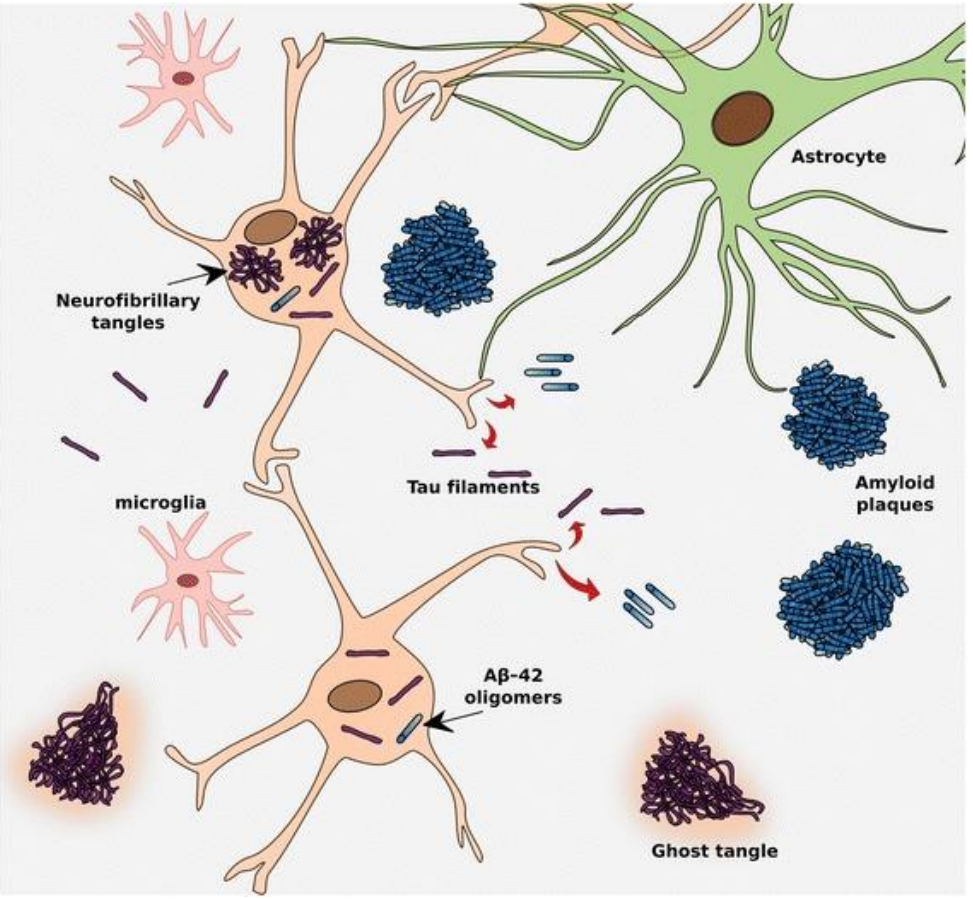
Presumed healthy volunteer

Areas of interest

Curr Opin Neurol 2013, 26:646655

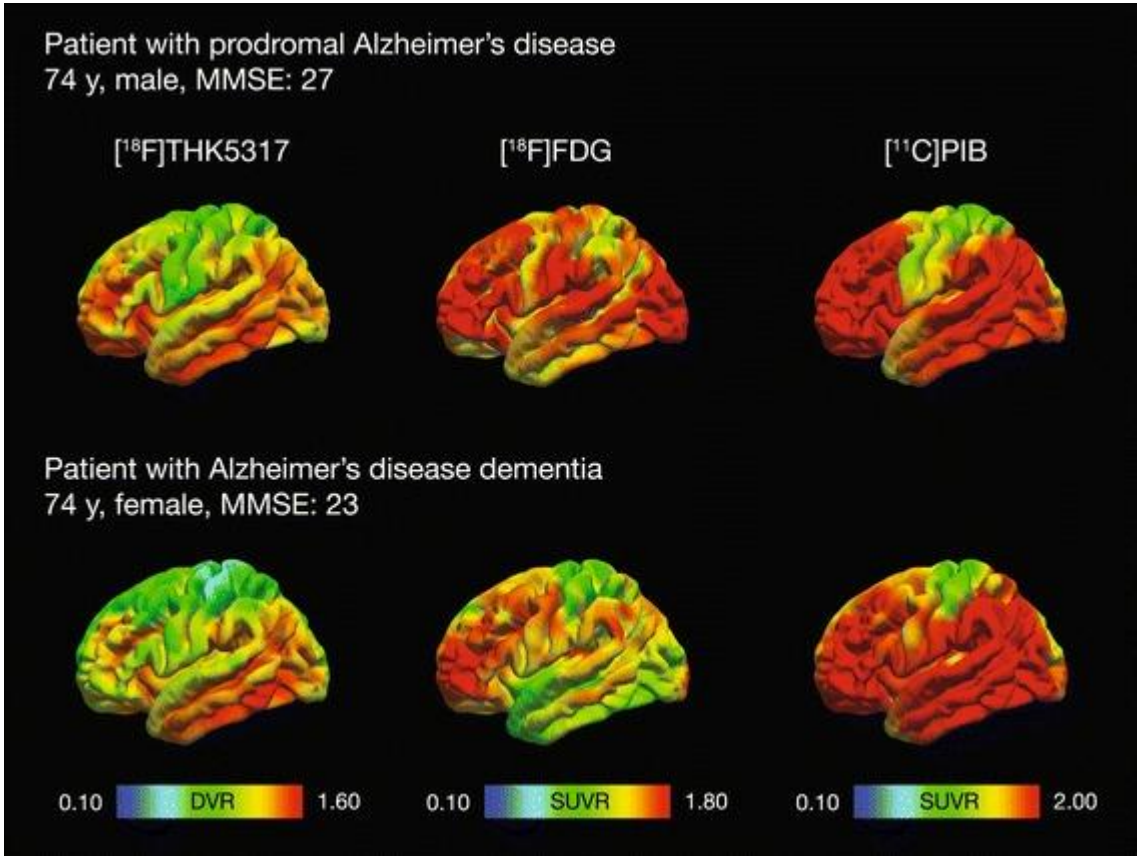
Some examples (2): Alzheimer: Amyloid / Tau

Tau = microtubuli-associated protein
Abnormal aggregation in “tauopathies”, including AD
6 different proteins
Intracellular aggregation (mostly)

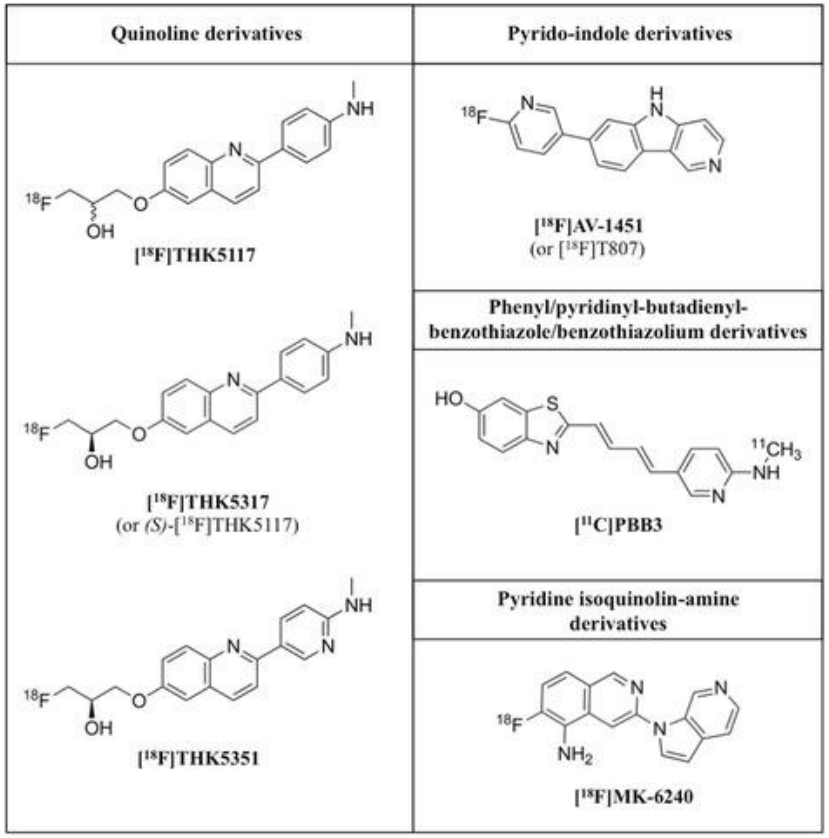


Mol Neurodegener. 2017; 12: 19.

Some examples (2): Alzheimer: Amyloid / Tau



Some examples (2): Alzheimer: Amyloid / Tau



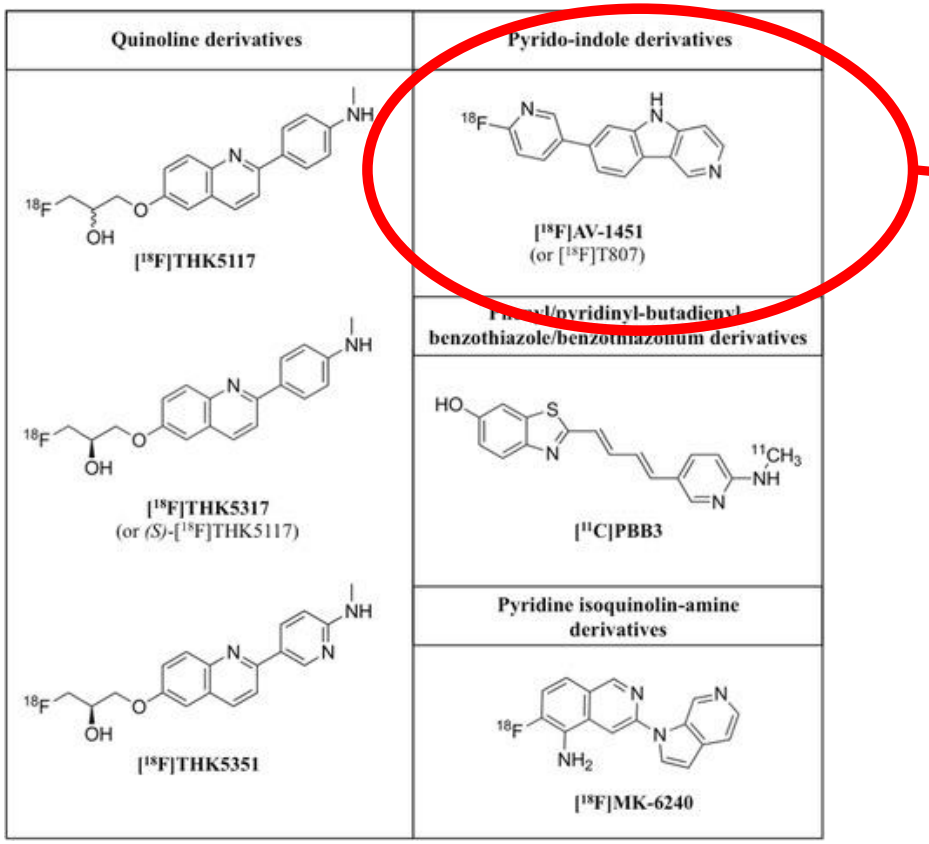
Binding sites

PBB3	THK5117	THK5351	AV-1451
			PHFs tau [18, 31, 37]; NFTs [23, 37] (both intracellular and extracellular [37], mature tangles [31] and ghost tangles [31, 33, 37]); neuritic plaques and primitive plaques [33] (to a limited extent); dense core amyloid plaques [33]; melanin-containing structures [31, 37]; lipofuscin-containing structures [31]; mineralized structures [31]; 3R + 4R tau deposits (much more than 3R or 4R [31]); MAO-A [23]
NFTs [28] (ghost tangles and non-ghost tangles [33]); neuropil threads [28, 33]; neuritic plaques [28, 33] and primitive plaques [33]; dense core amyloid plaques and diffuse amyloid-beta deposits [33]; Pick bodies [28]; astrocytic plaques [28]; tau inclusions in PiD, PSP and CBD [28]	PHFs tau [125]; NFTs[15, 24, 125](both intracellular and extracellular and ghost tangles [125]); neuritic plaques [125]; argyrophilic grains [125]; argyrophilic threads [125]; globose tangles [125]	NFTs [26]; thread-like structures in the white matter [35]; tufted astrocytes [36]	

Plethora of options and targets:
- Fundamental science: yes
- Clinical applications: not yet

Mol Neurodegener. 2017; 12: 19.

Update on Alzheimer: Amyloid / Tau



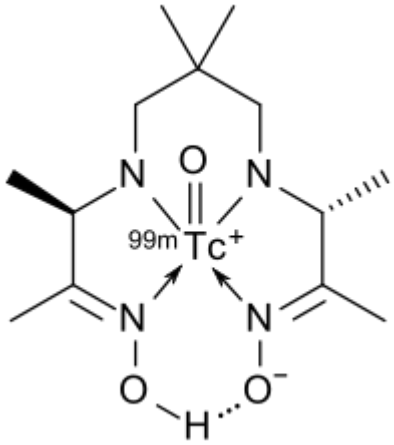
This one made it!

Flortaucipir / Tauvid

FDA approved since may 2020. It is indicated for positron emission tomography (PET) imaging of the brain to estimate the density and distribution of aggregated tau neurofibrillary tangles (NFTs), a primary marker of Alzheimer's disease.

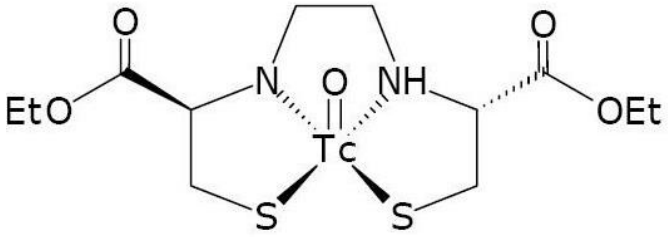
How did they prove the link to Alzheimer?

Some examples (3): Epilepsy



^{99m}Tc-HMPAO (exametazime, ceretec)

➔ 3 or 4-compartment analysis of brain tissue
➔ Trapping of hydrophilic form to glutathion (intracellular)



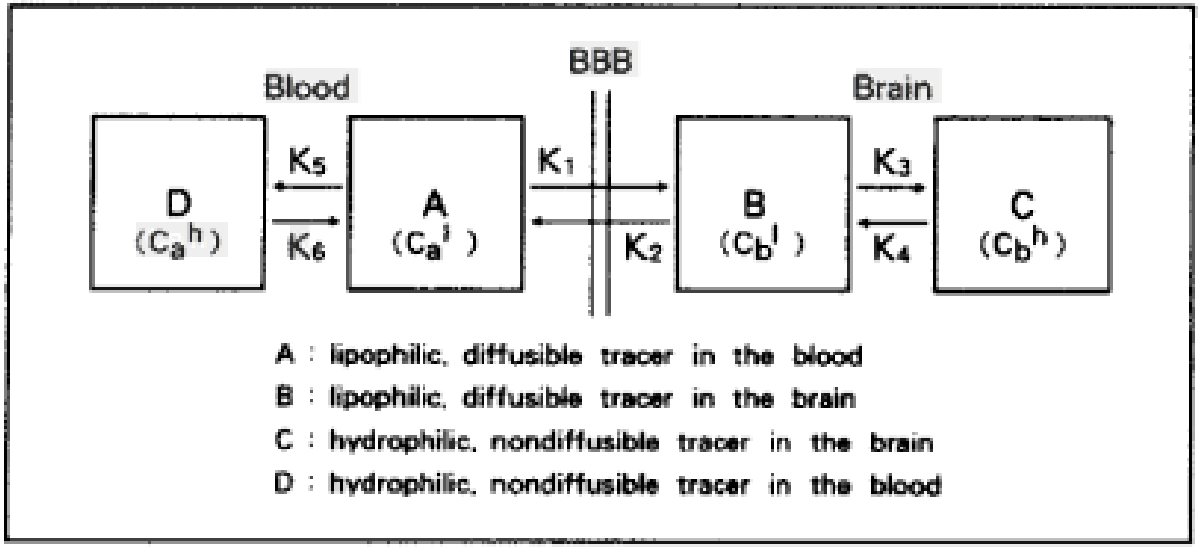
Tc-99m-L,L-ECD

^{99m}Tc-ECD (ethyl cysteinate dimer)

➔ 3 or 4-compartment analysis of brain tissue
➔ Trapping of metabolised polar form (intracellular)

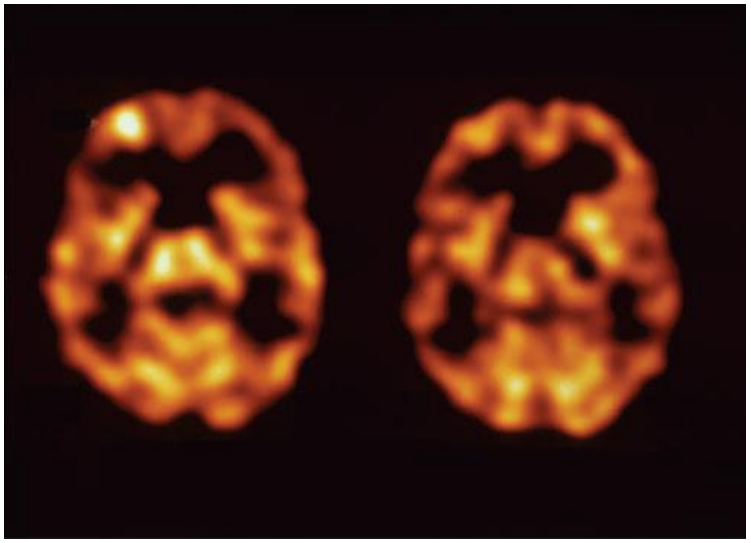
Some examples (3): Epilepsy

4-compartmental analysis

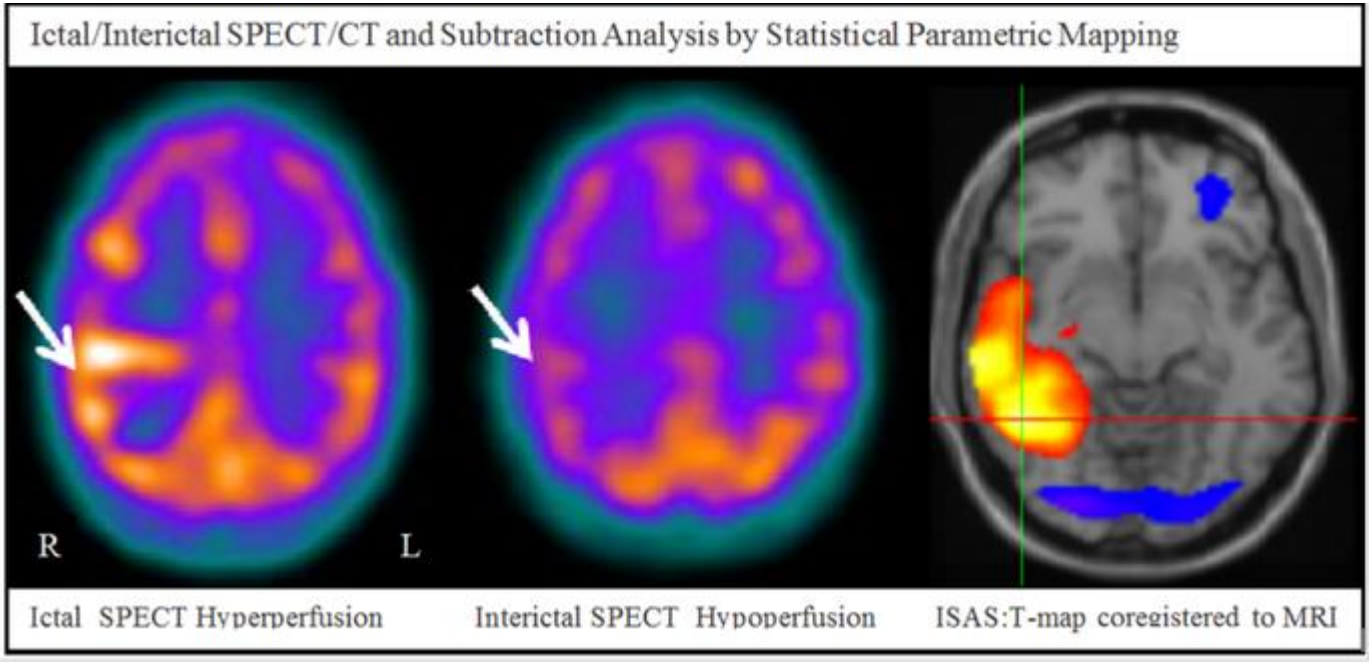


- K4 and K6 assumed to be zero (negligible)
- Known blood values + imaging data ➔ cerebral blood flow

Some examples (3): Epilepsy

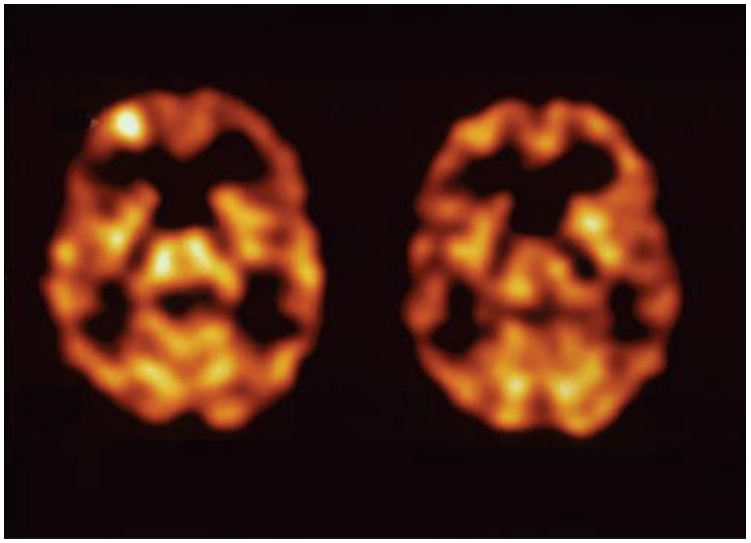


Ictal Interictal



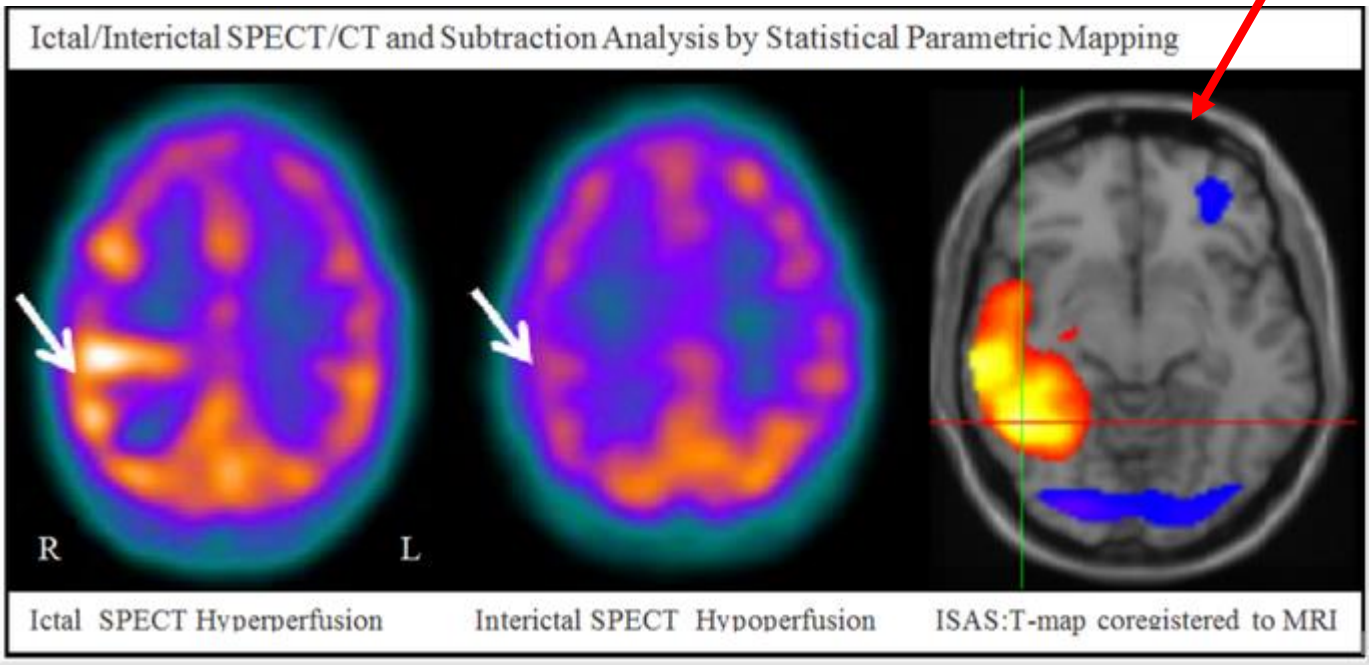
- Manual substraction
- Parametric mapping

Some examples (3): Epilepsy



Ictal Interictal

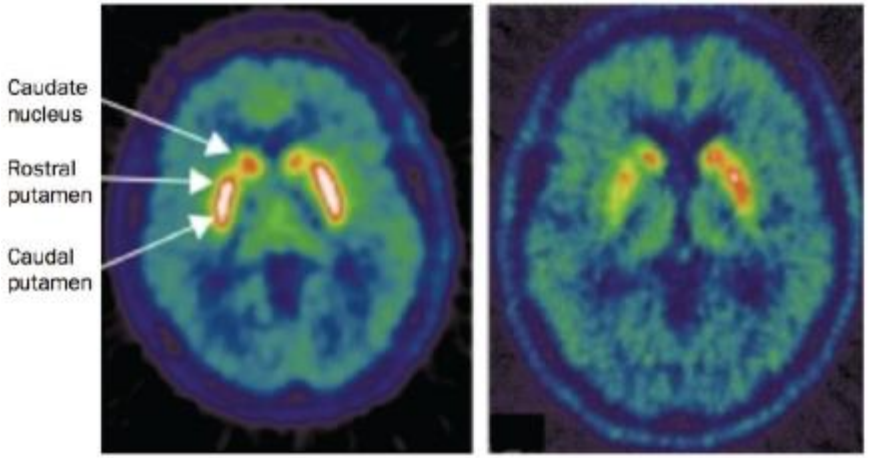
How can this image be improved?



- Manual substraction
- Parametric mapping

Some examples (4): Parkinson

^{18}F-DOPA



Healthy subject

Patient with idiopatic PD

Uptake correlated to aromatic amino acid decarboxylase, reflecting dopaminergic functionality.
(AADC converts DOPA to Dopamine)

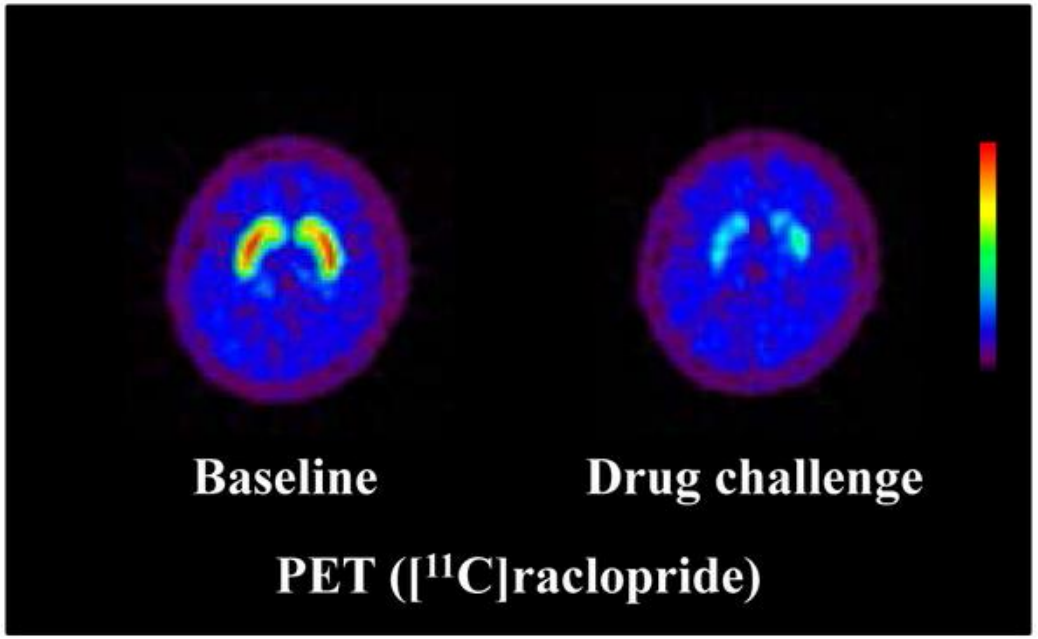
Striatal ^{18}F-DOPA uptake correlates to motor function and inversely correlates with rigidity, but does not correlate with tremor or depression.

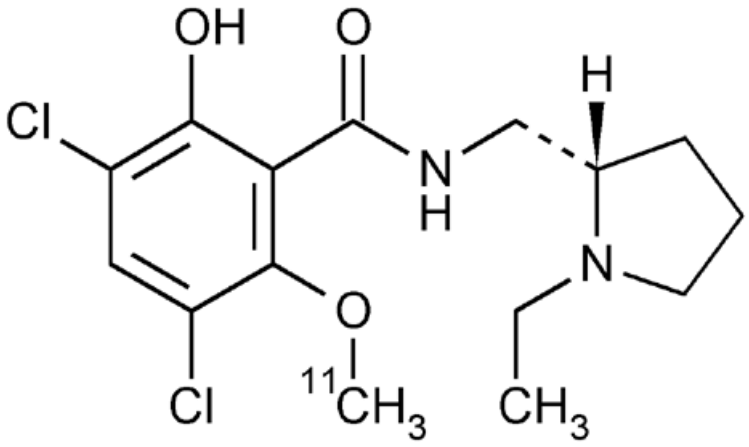
Note the assymetry in PD.

- Serotonergic system: ^{11}C-DASB and ^{11}C-McN5652
  striatal serotonergic denervation is relatively moderate compared to striatal DA denervation
- ^{11}C-diprenorphine (visualising μ, κ and δ opioid sites)
  Related to PA, but no clinical applications

Some examples (4): Parkinson

^{11}C-Raclopride





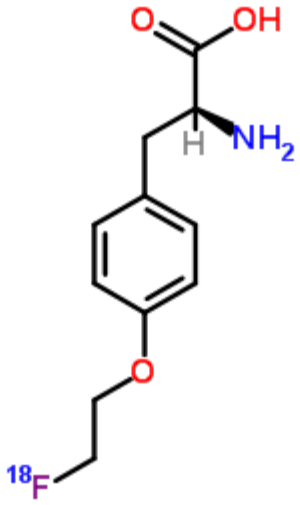
Drug = antipsychotic aripiprazole , an antagonist for dopamine D_2 receptors

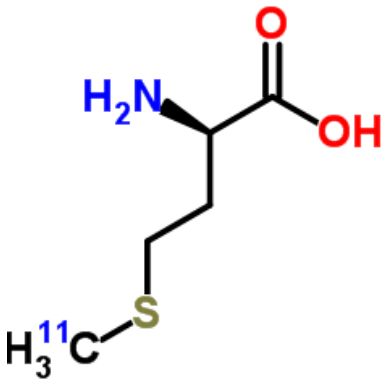
^{11}C-Raclopride:

- Diagnosis of huntington disease
- Personality disorders (schizophrenia, …)

https://doi.org/10.1371/journal.pone.0046488

Some examples (6): 18F-FET / 11C-Methionine





Radiolabelled amino acids

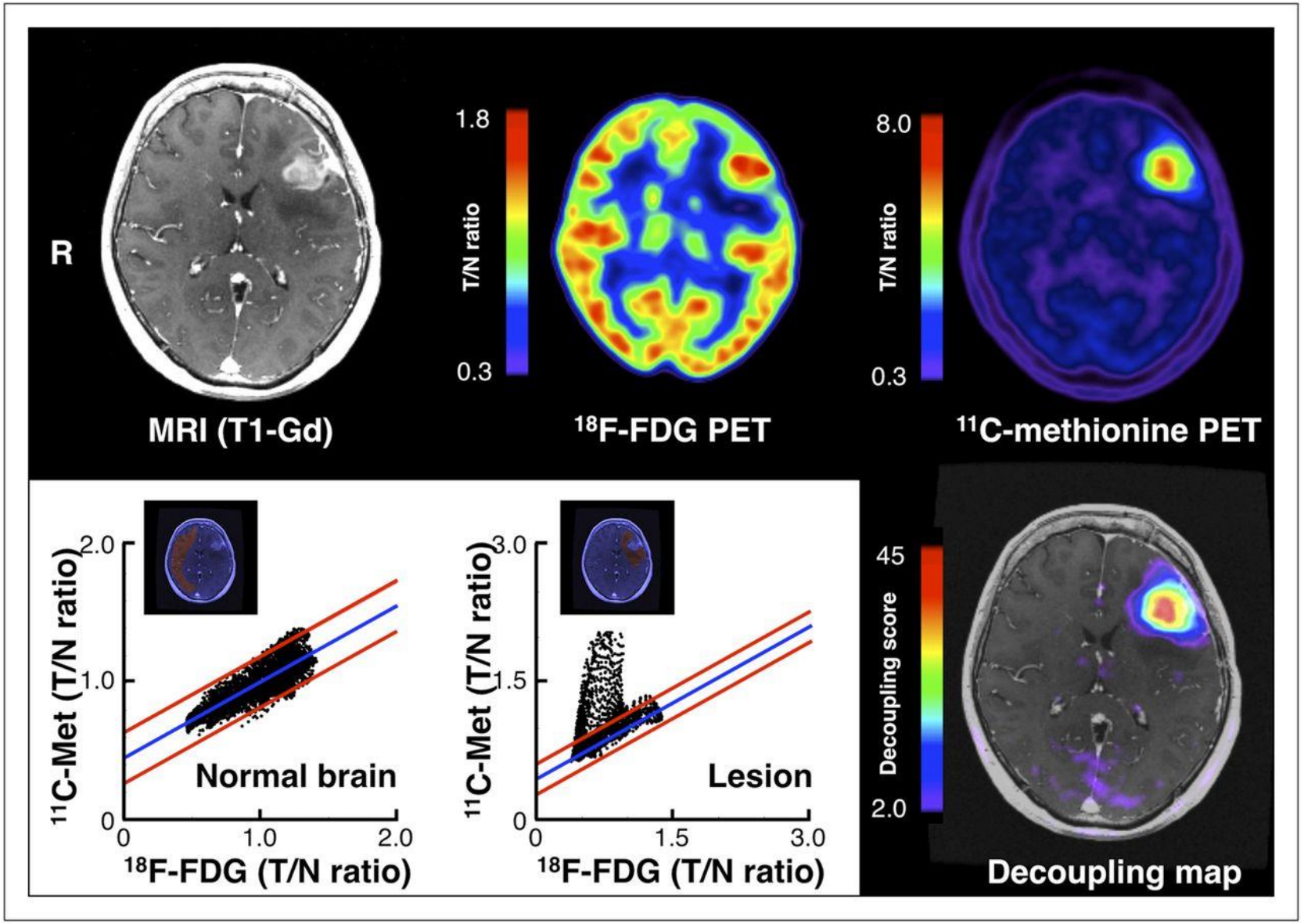
Correlate to transport system expression, do not necessarily reflect intracellular metabolism.

Both tracers: uptake via LAT1 transport system.

LAT1 = L-type Amino acid Transport system

LAT1 correlates strongly with glioma grading

Some examples (6): 18F-FET / 11C-Methionine

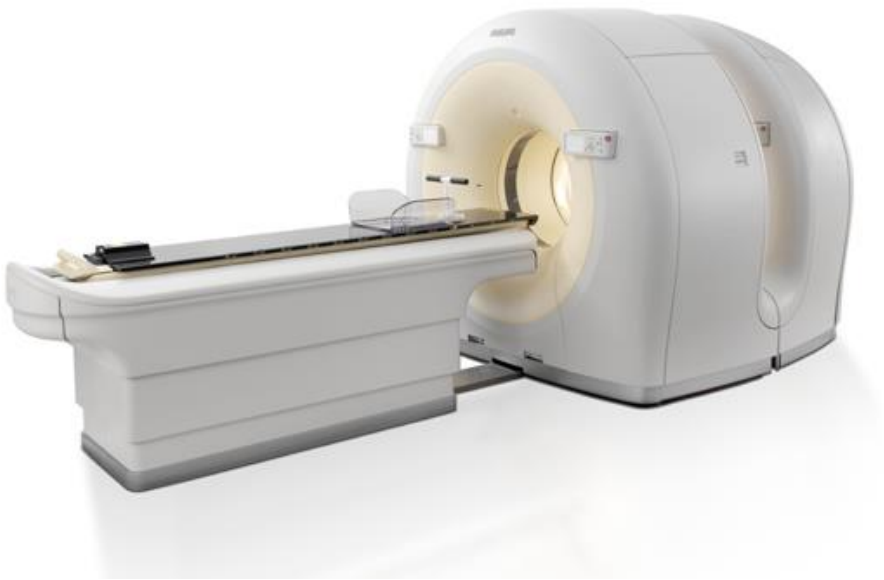


J Nucl Med November 1, 2012 vol. 53 no. 11 1701-1708

Outline of the presentation:

4) What's available in-house?

- SPECT/CT (clinical and preclinical)
- PET/CT (clinical and preclinical)
- PET/MR (clinical)
- (MR, CT, US, …)
- Proton therapy
- Radiopharmacy (clinical and preclinical)

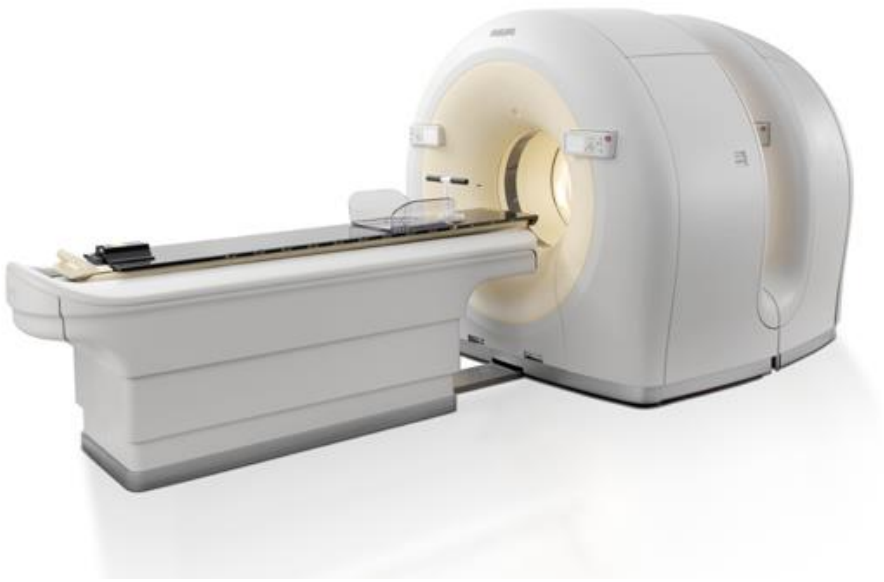


SPECT/CT

- ✓ Spatial resolution: 1.5 cm
- ✓ Temporal resolution: >20 min
- ✓ 4D imaging (total-body)
- ✓ no quantitative imaging
- ✓ Multi-isotope (new models)

PET/CT

- ✓ Spatial resolution: 0.8 cm
- ✓ Temporal resolution: < 10 sec
- ✓ 4D imaging (total-body)
- ✓ Quantitative imaging
- ✓ No multi-isotope



PET/MRI

- ✓ Spatial resolution: 0.4 cm
- ✓ Temporal resolution: < 10 sec
- ✓ 4D imaging (total-body)
- ✓ Quantitative imaging
- ✓ No multi-isotope

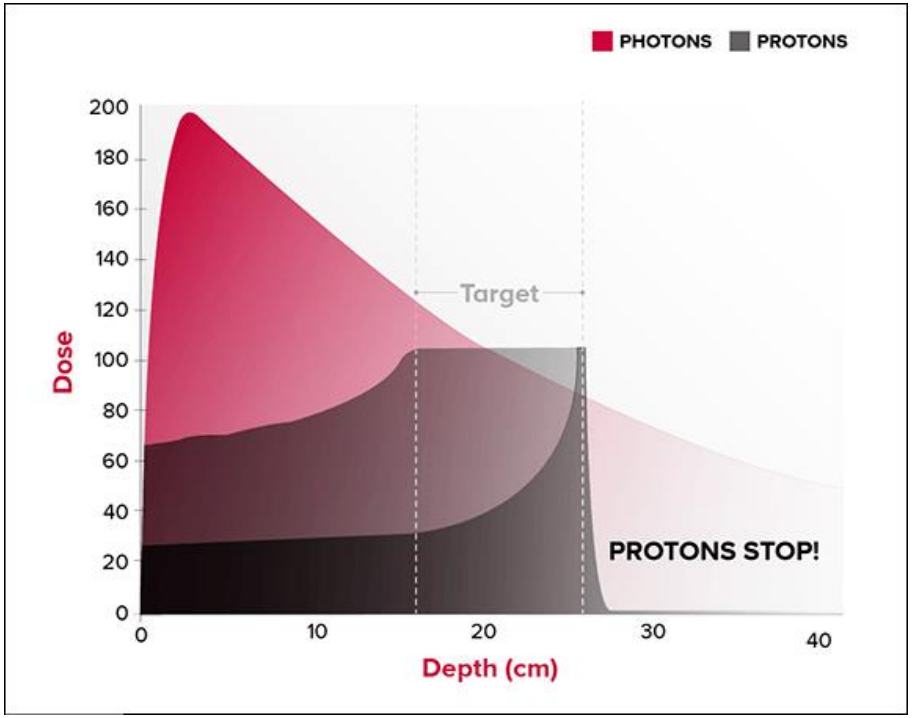
PET/CT

- ✓ Spatial resolution: 0.8 cm
- ✓ Temporal resolution: < 10 sec
- ✓ 4D imaging (total-body)
- ✓ Quantitative imaging
- ✓ No multi-isotope

microPET/CT: soon available (again)?

- ✓ Spatial resolution: 0.1 cm
- ✓ Temporal resolution: < 5 sec
- ✓ 4D imaging (total-body)
- ✓ Quantitative imaging
- ✓ No multi-isotope

Proton therapy in Maastricht



Photons: exponentially less dose
Protons: Bragg peak


"That's all Folks!"™