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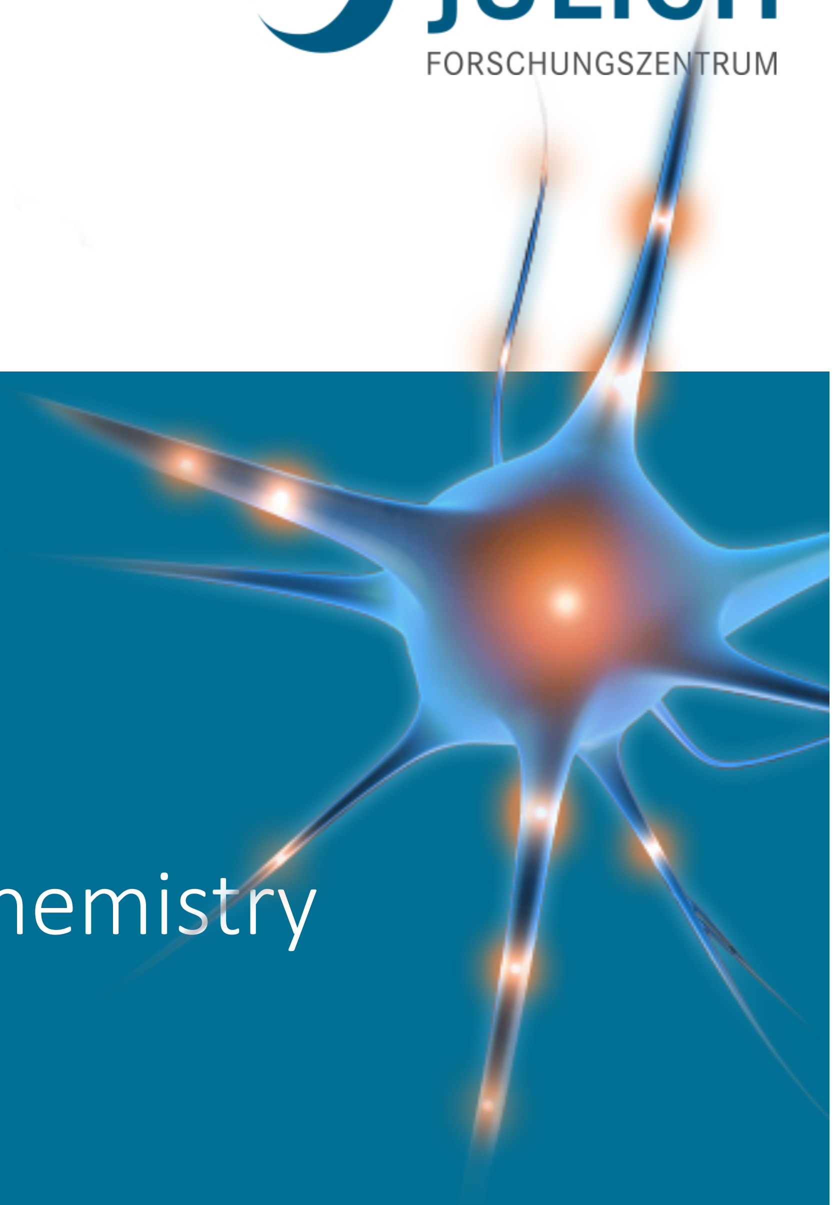


Introduction to Nuclear Chemistry

14.09.2017 | Prof. B. Neumaier

Molecular Imaging - Why?

AIM:

Non-invasive elucidation of disease specific biochemical-, molecular-, physiological- and pathological processes

Evaluation of molecular response

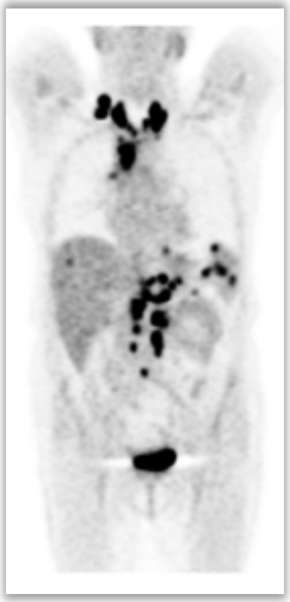
Disease detection as early as possible

Patient stratification – optimal and individual therapy for each patient

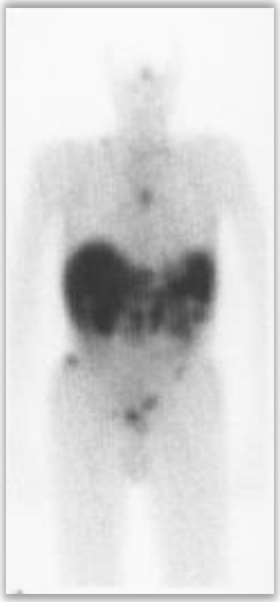
Monitoring of therapy efficacy

Molecular Imaging: Definition and Examples

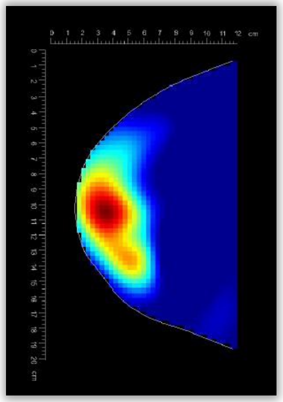
„*In-vivo*-characterization of biological processes at the molecular level“



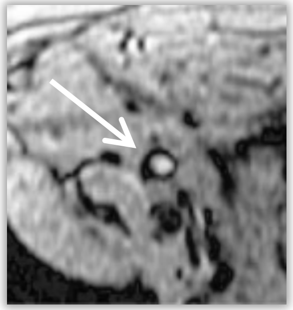
PET
Positron Emission Tomography
(NHL;[^{18}F]FDG)



SPECT
Single Photon Emission Computed Tomography
(NET; ^{111}In-DTPA-Octreotid)



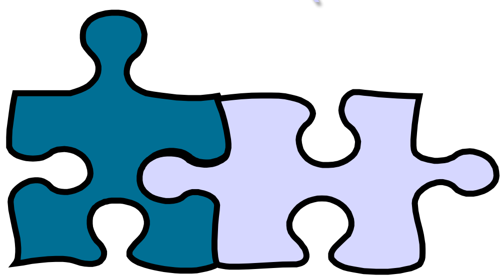
Softscan
NIR
Fluorescence Imager
(Breast cancer; DeoxyHb)

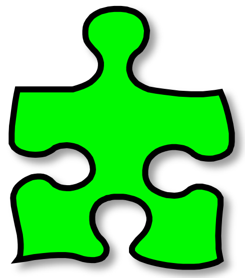


MR
Magnetic Resonance
(PCa, lymph node metastasis; Sinerem NT)

Principle of molecular imaging

Targeting molecule
(Vehicle)



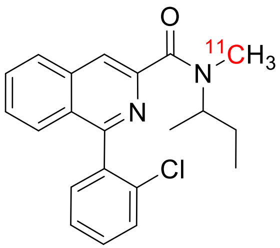


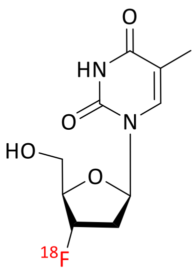
Reporter
(Radionuclide,
fluorescent dye or
magnetic label)

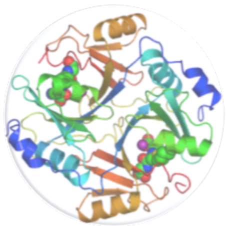
Biological targets

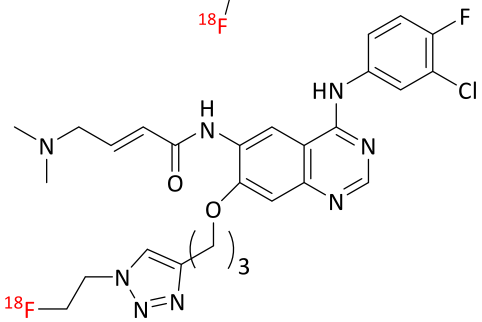
Disease detection

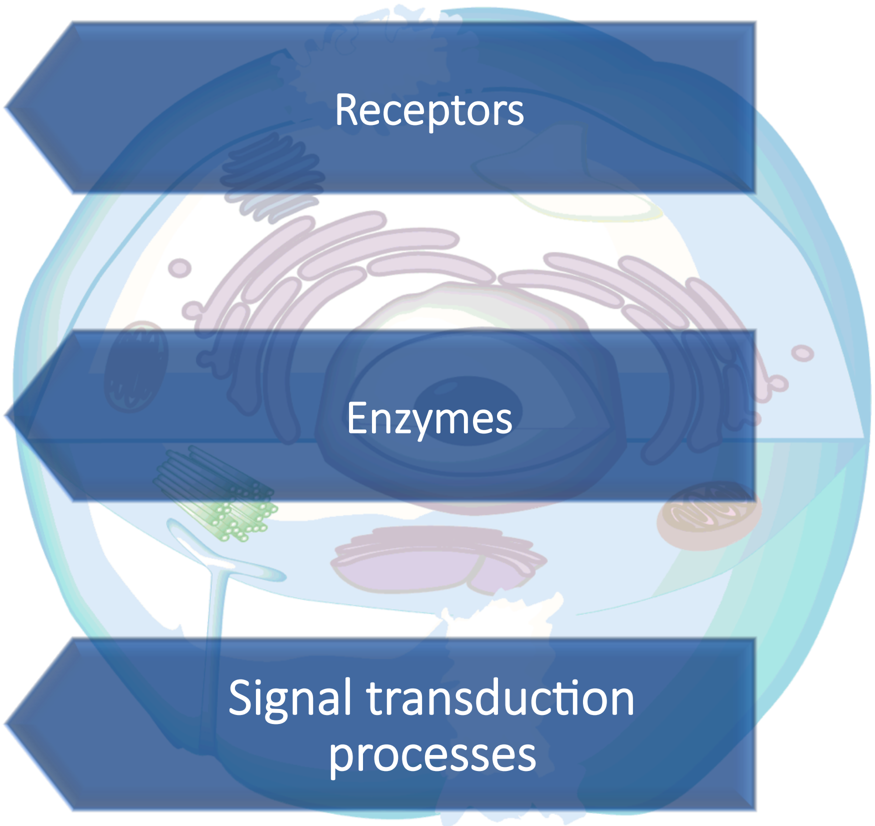
Visualization of molecular processes - measurement of molecular alterations
activation or inhibition of











Reporter systems and biological probes for molecular imaging

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Reporter systems:

PET

^{18}F (109 min), ^{11}C (20 min)
^{68}Ga (68 min), ^{13}N (10 min)
^{15}O (2 min), ^{124}I (4.2 d)

18F

SPECT

^{99m}Tc (6.0 h), ^{111}In (2.8 d)
^{123}I (13 h)

MR

Gd^{3+}, Fe_nO_m

Fluorescence:

Alexa Fluor, Cyanine dyes

Biological probes:

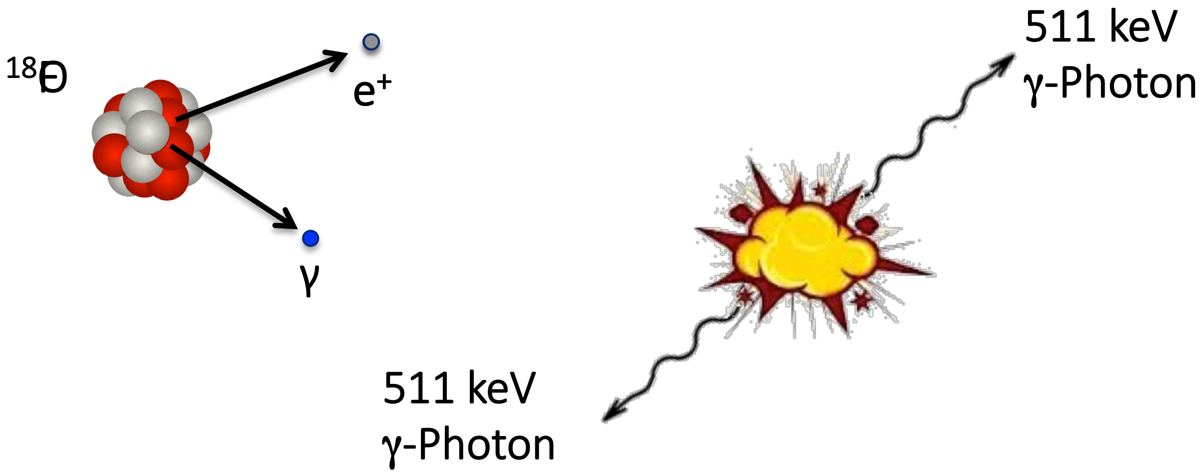
- Peptides
- Peptidomimetics
- Nucleosides
- Small molecules
- Antibodies
- Affibodies

Corresponding targets:

- Cell surface receptors
- Transporters
- DNA/RNA
- Receptors
- Enzymes

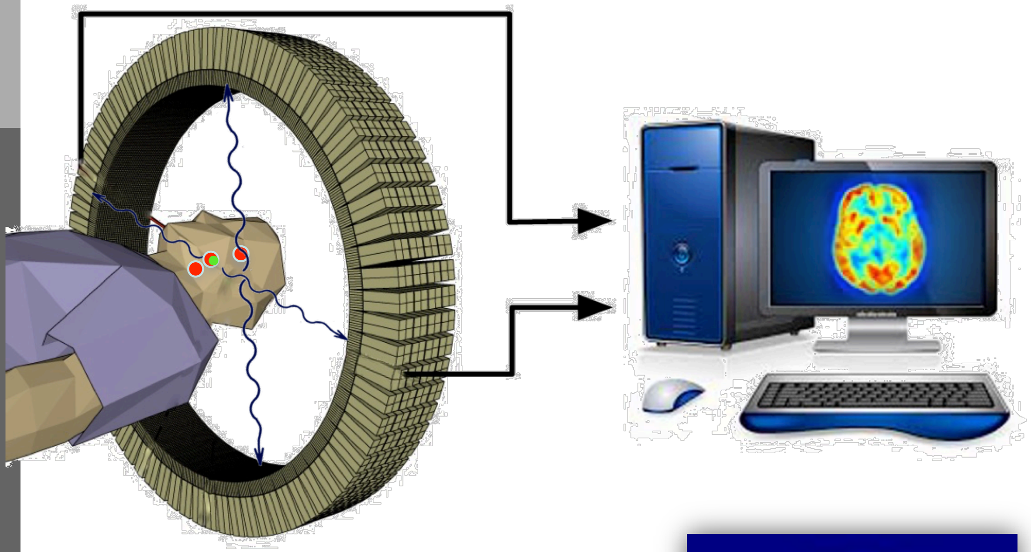
PET: Physical background

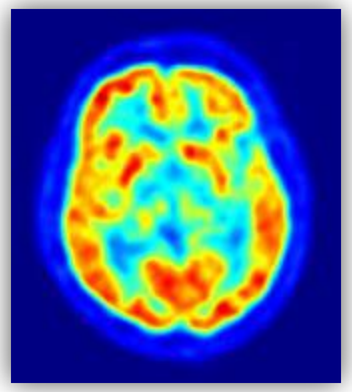
Positron decay and positron-electron-annihilation (e.g. for ^{18}F)



- Emission of a positron as a result of β^+ decay
- Positron is thermalized and undergoes recombination with electron
- Conversion of mass into energy by $E = m \cdot c^2$
- Emission of 2 γ-quants in opposite directions (180°)

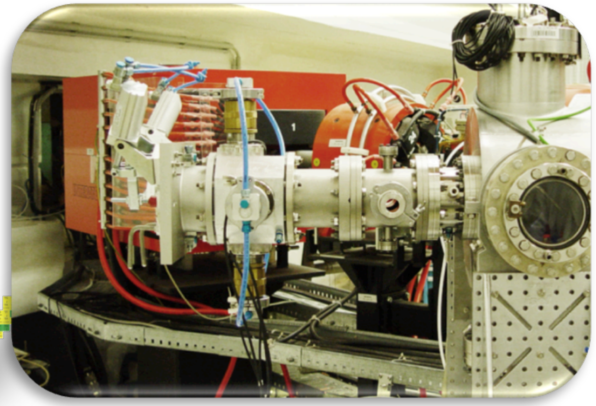
PET: Physical background





- Detection of coincident decay events
- Reconstruction of point of decay based on cross points of γ-photon trajectories
- Real-time reconstruction of 3D nuclide distribution by modern computer techniques

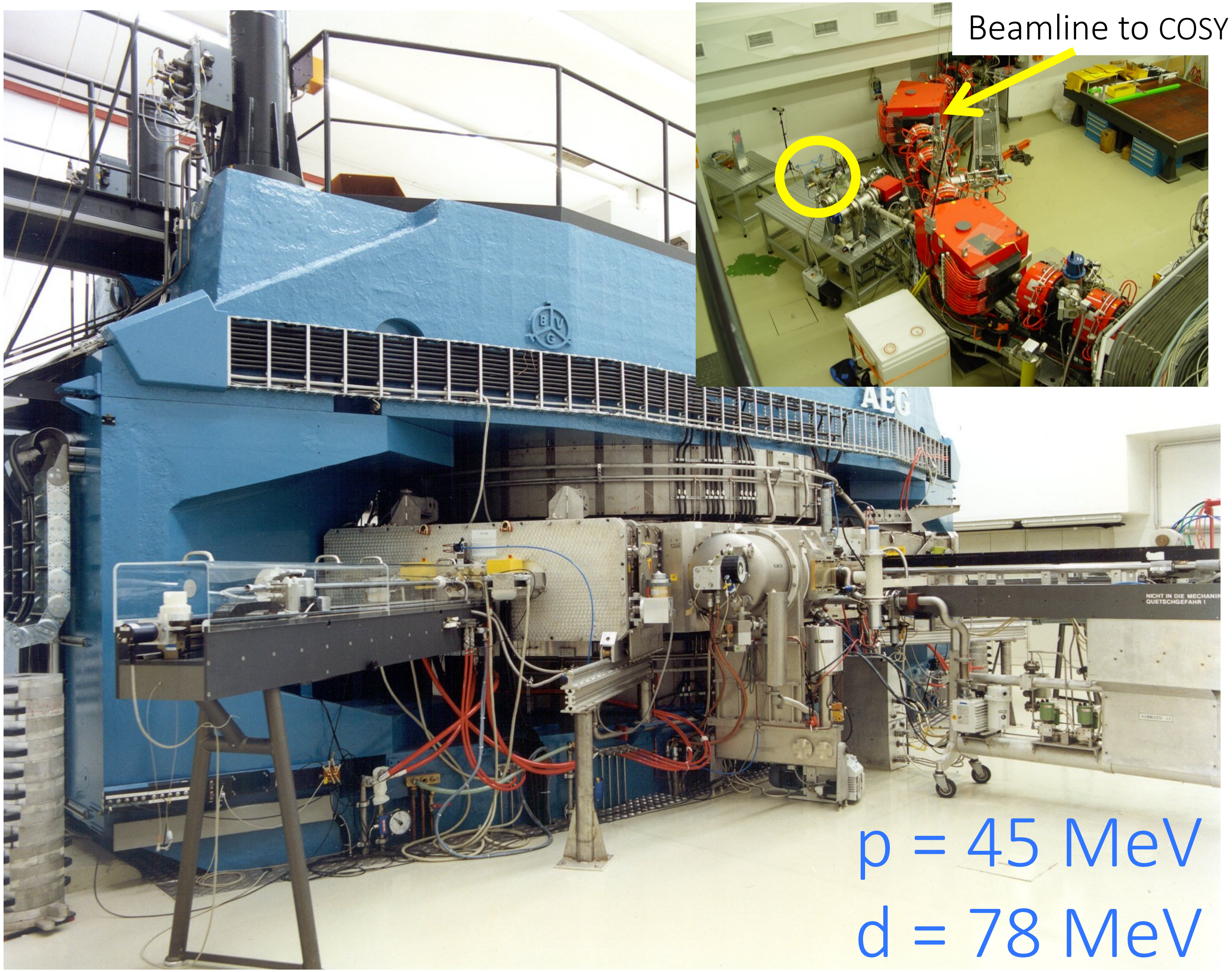
Production of Radionuclides



$^{4}_{2}He$

- Production of standard und non-standard radionuclides
- PET Nuclides (e.g. ^{34m}Cl, ^{38}K, ^{51}Mn, ^{55}Co, ^{72}As)
- Therapeutic Nuclides (e.g. ^{67}Cu, ^{103}Pd, ^{140}Nd, ^{167}Tm, ^{193m}Pt)
- Targetry
- Nuclear data

High energy cyclotron Julic



High energy nuclear reactions COSY

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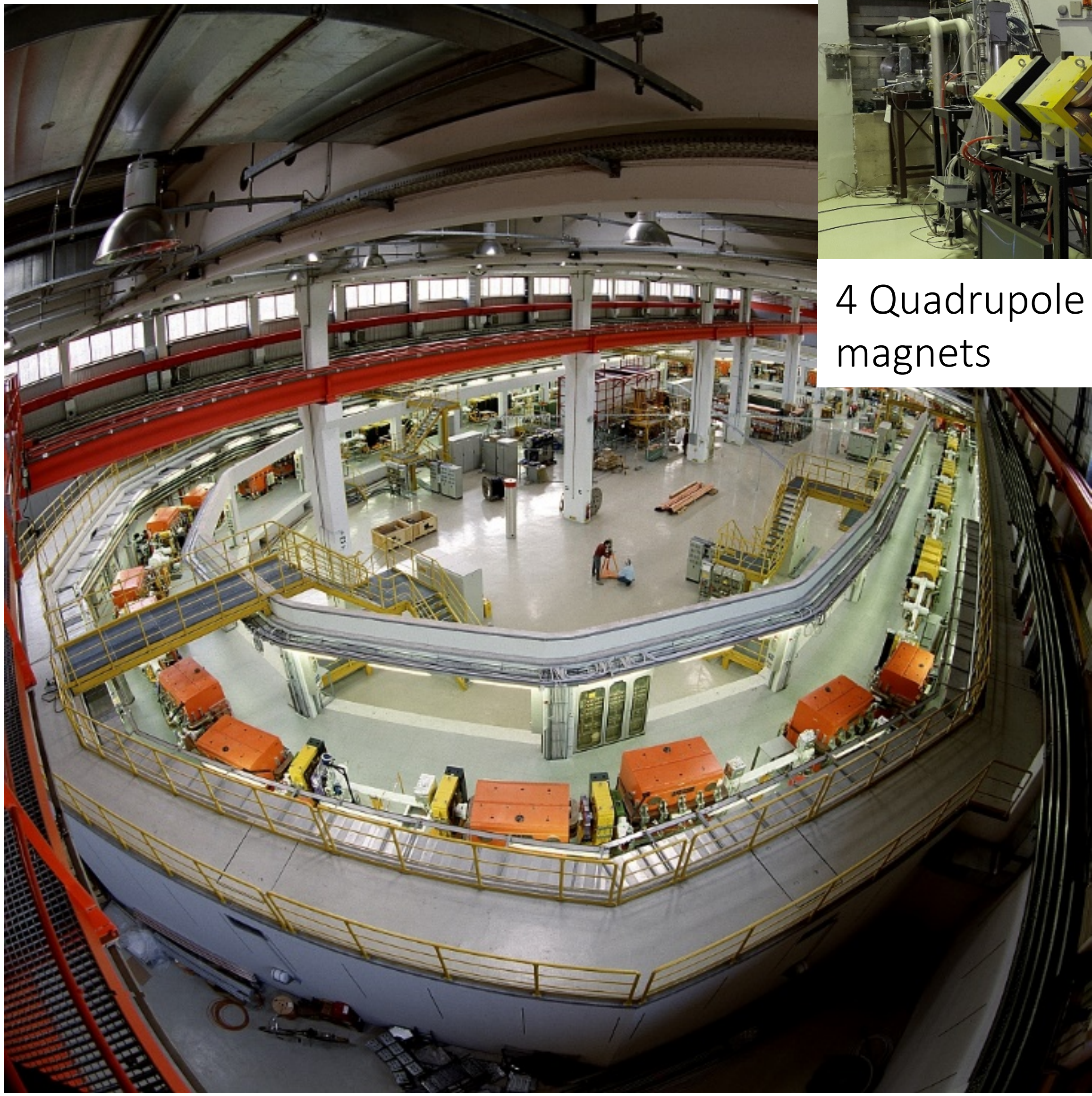
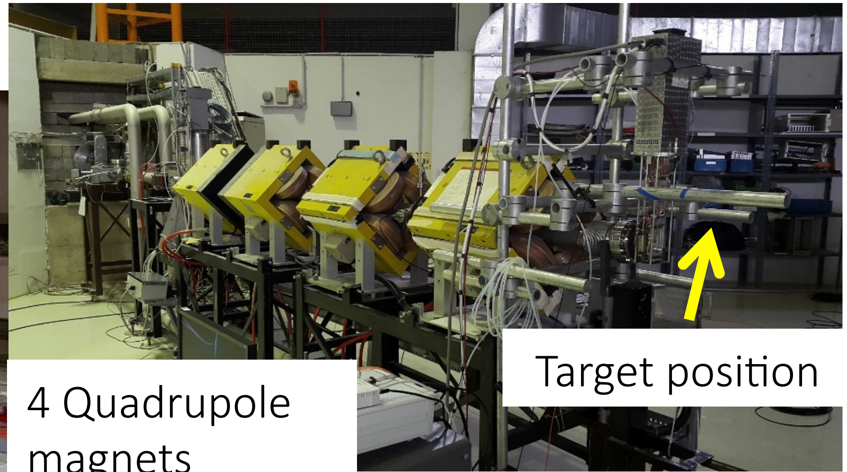
2.88 GeV Cooler Synchrotron



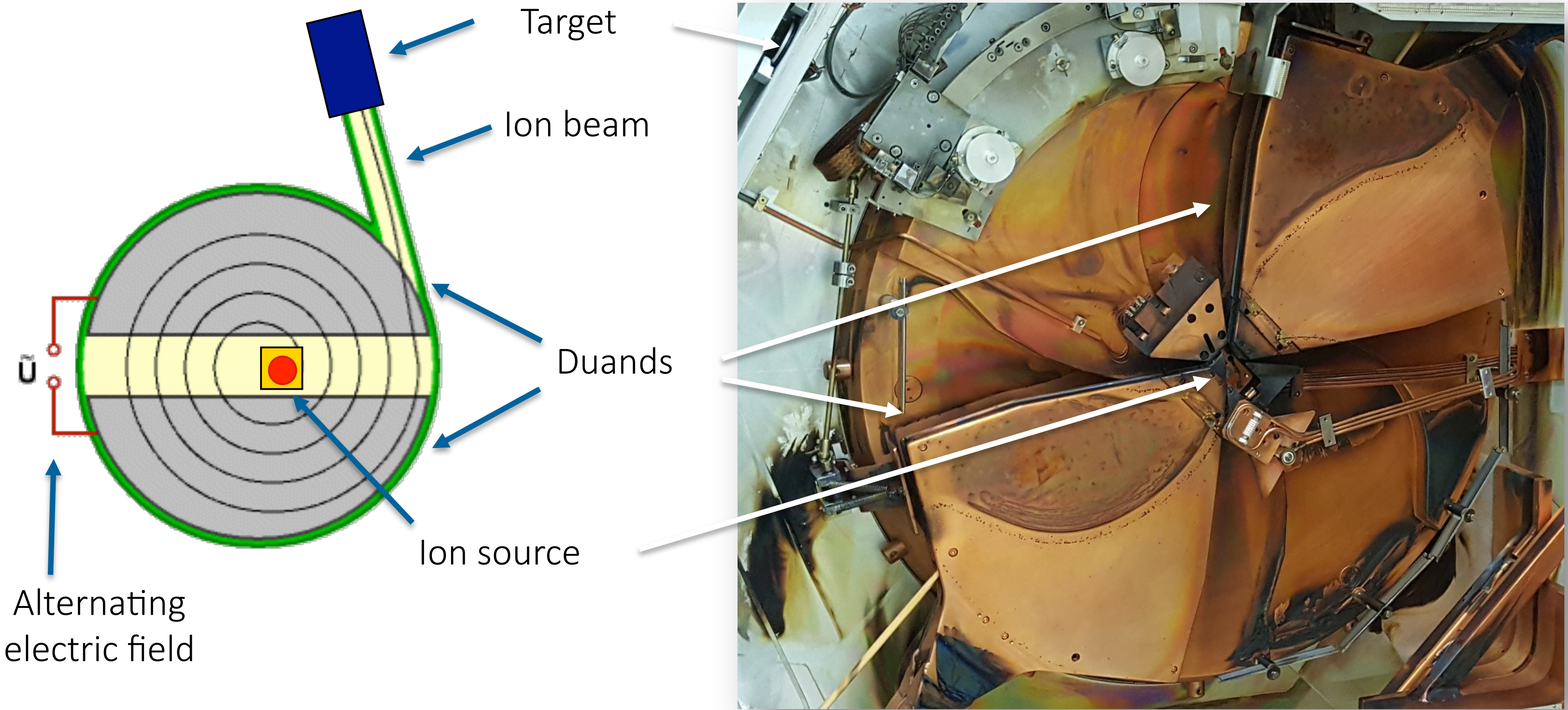


p = 150 MeV

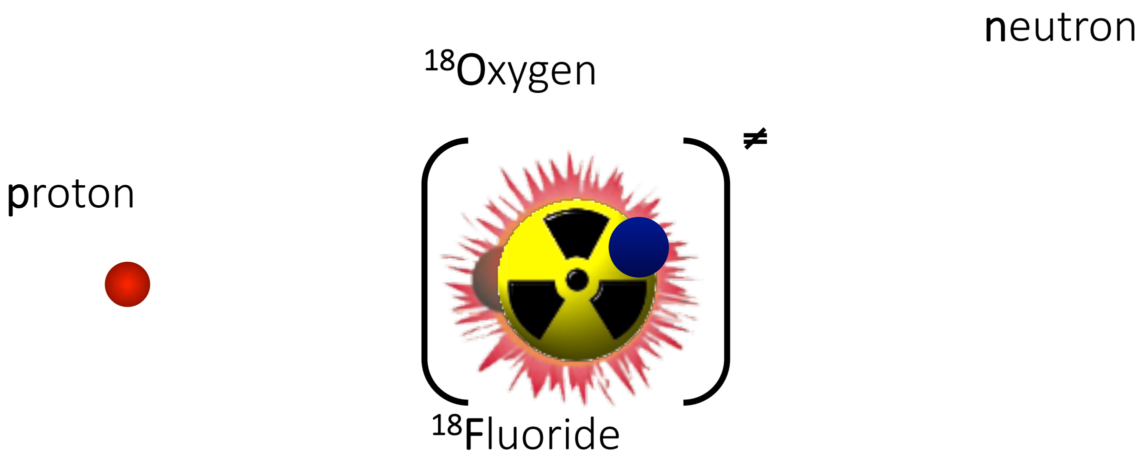
Medically relevant radionuclides via high-energy reactions

Target	Reaction	Radionuclide	Usage	Remarks
^{40}Ar, ^{nat}Ar	(p,α3n)	^{34m}Cl	PET	
^{39}K, ^{nat}K	(p,αpn) (p,α2n), decay	^{34m}Cl	PET	
^{nat}V	(p,αp)	^{47}Sc	Therapy	^{43}Sc/^{47}Sc theragnostic pair
^{55}Mn (nat.)	(p,4n)	^{52}Fe	PET	Multimodal imaging,
^{55}Mn (nat.)	(p,p3n)	^{52}Mn	PET	Multimodal imaging
^{68}Zn	(p,αn)	^{64}Cu	PET	
^{68}Zn	(p,2p)	^{67}Cu	Therapy	^{64}Cu/^{67}Cu theragnostic pair
^{nat}Rb, ^{85}Rb	(p,xn)	^{82}Sr/^{82}Rb	PET	Generator
^{88}Sr	(p,3n)	^{86}Y	PET	^{86}Y/^{90}Y theragnostic pair
^{107}Ag, ^{nat}Ag	(p,αn)	^{103}Pd	Therapy	
^{197}Au (nat.)	(p,αn)	^{193m}Pt	Therapy	Alternative to ^{192}Os(α,3n)

Production of radionuclides at a cyclotron



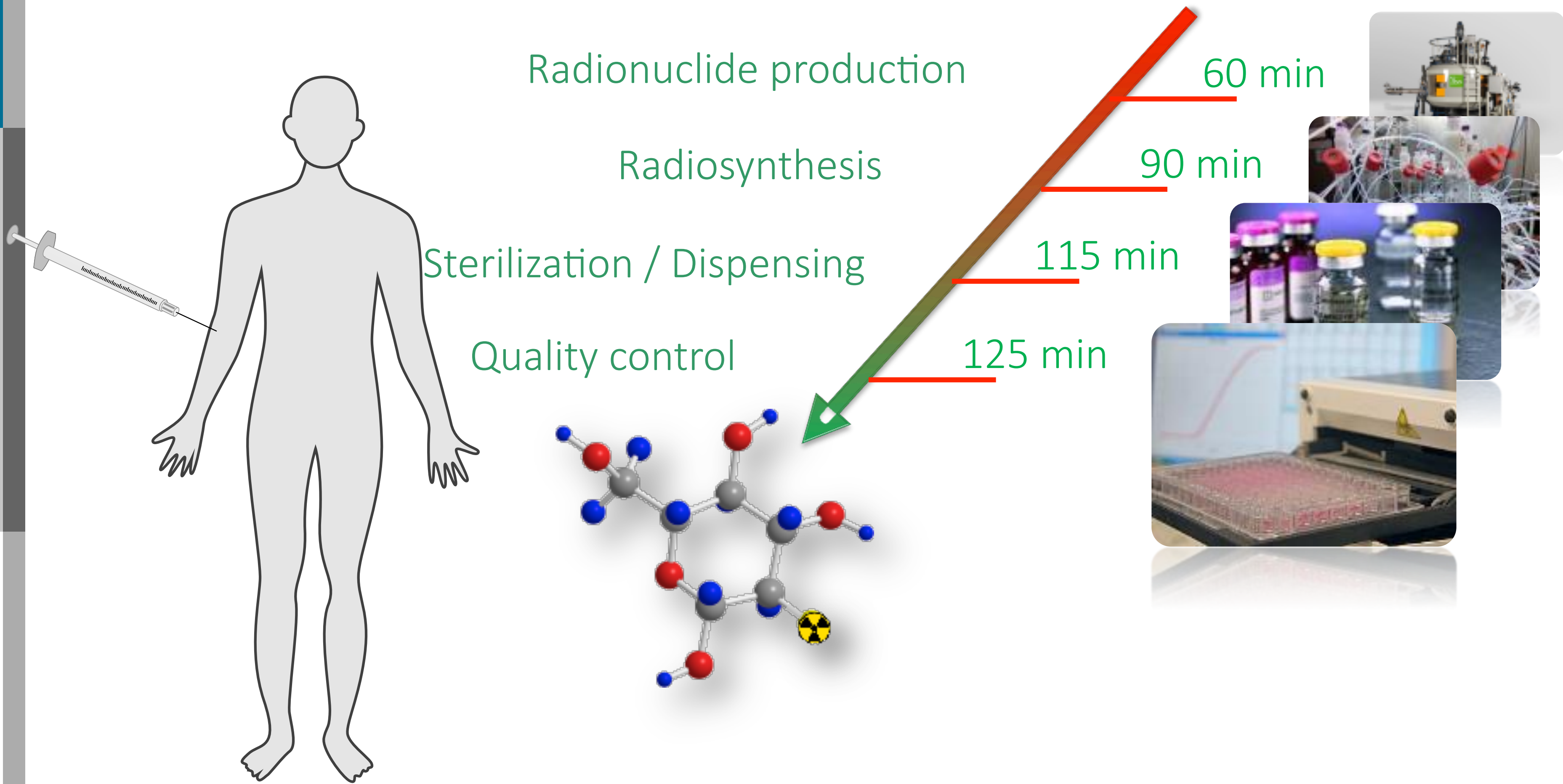
The cyclotron-produced radionuclide [^{18}F]fluoride



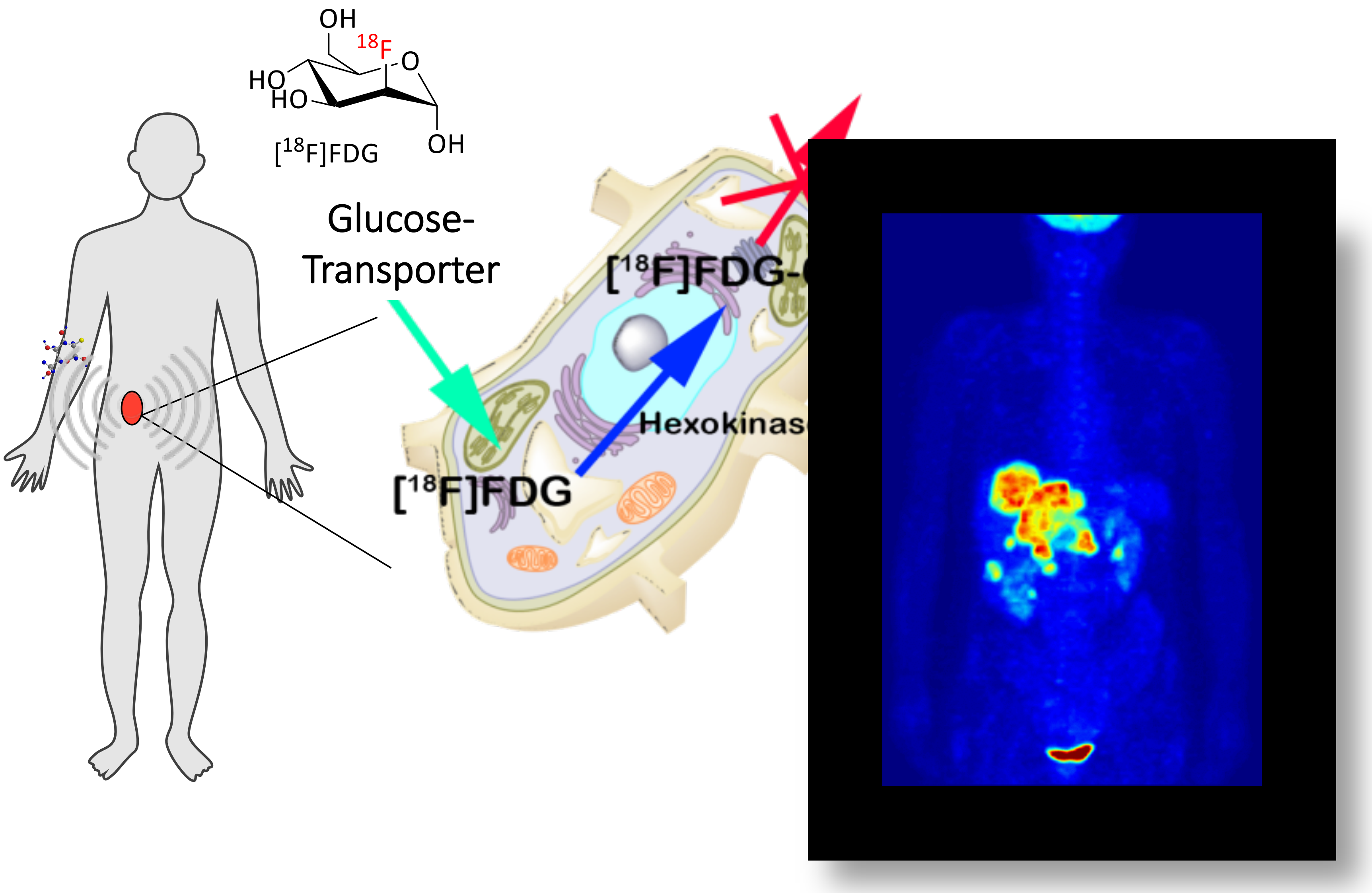
Compound nucleus [^{19}F]*

Reaction: $^{18}O(p,n)^{18}F$
^{18}F half life: 110 min

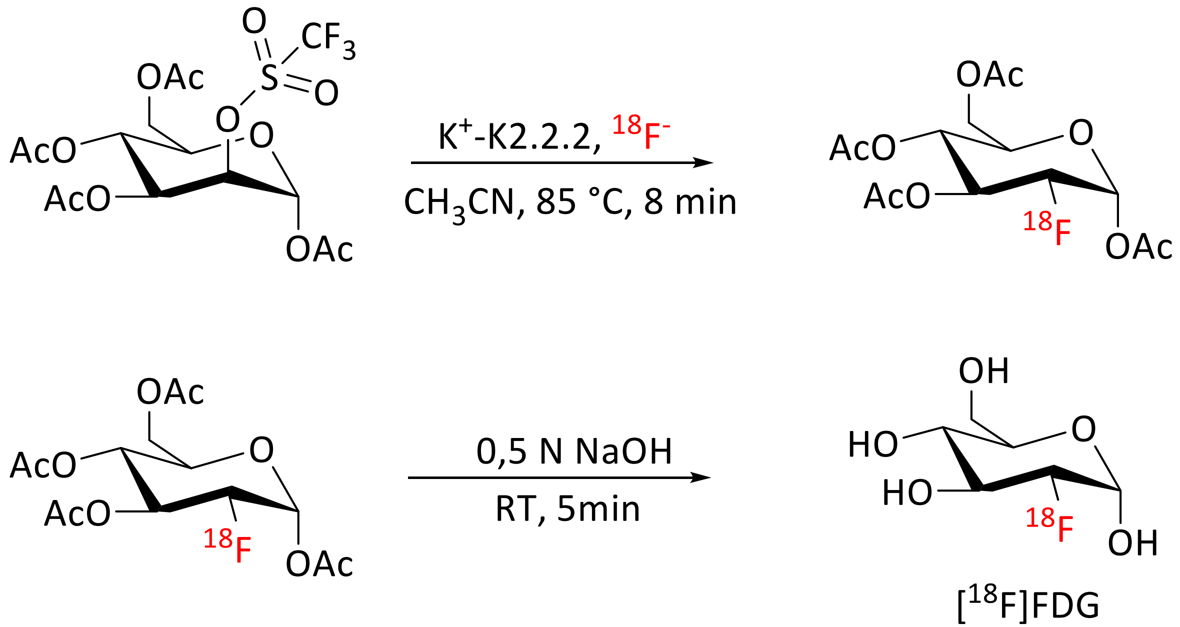
Production of radiopharmaceuticals

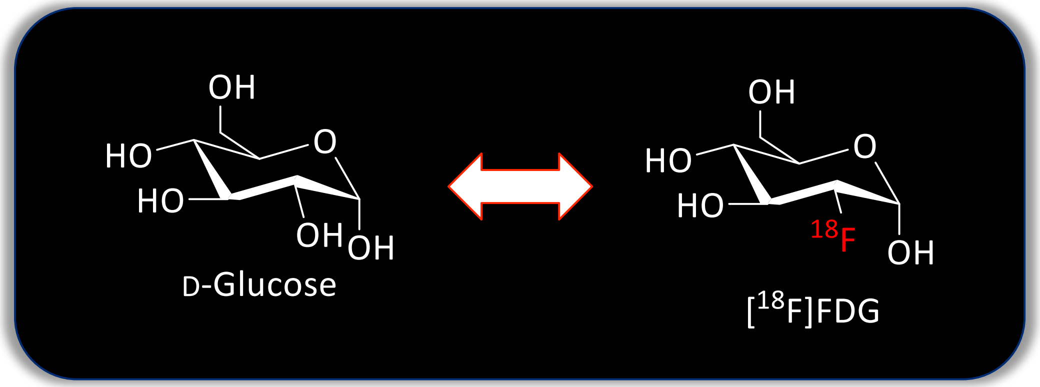


PET Diagnostics with [^{18}F]FDG

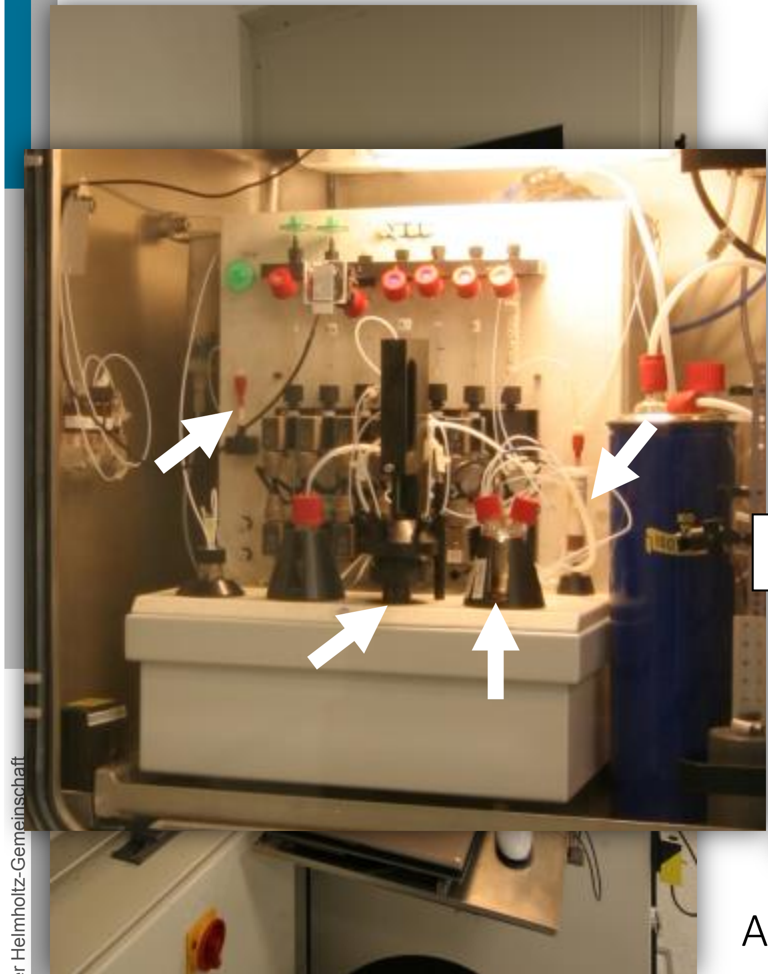


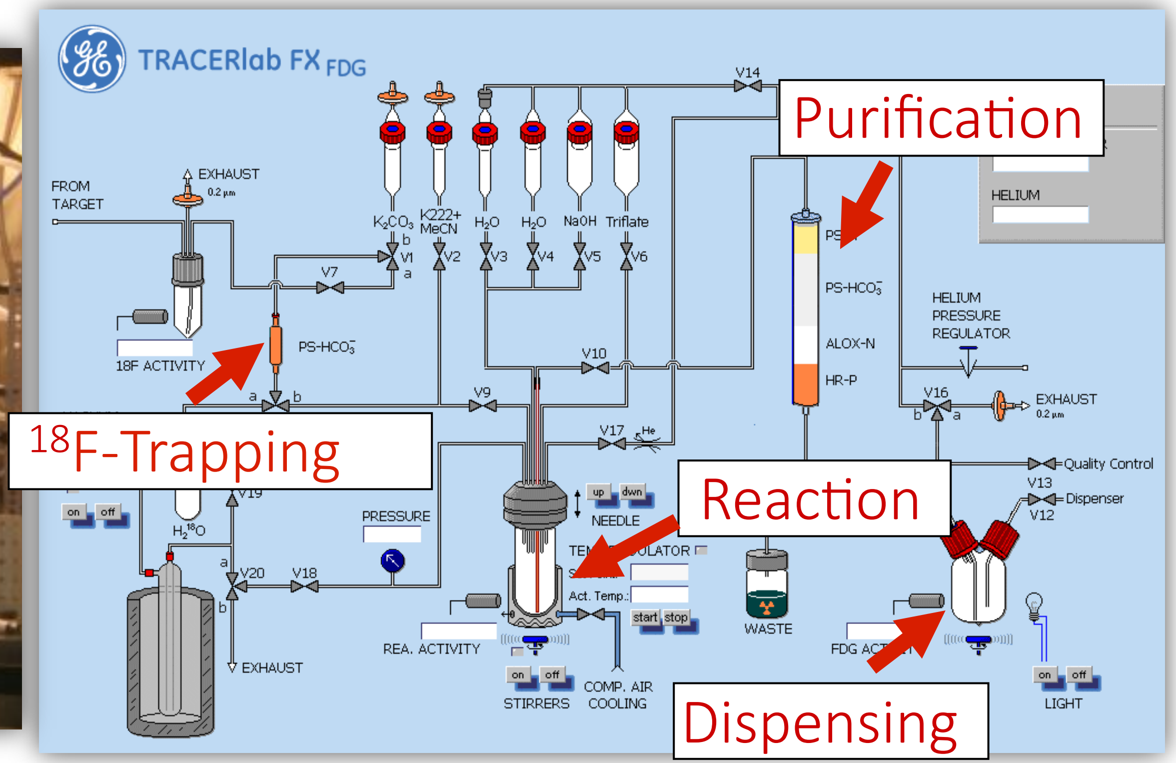
Production of [^{18}F]FDG





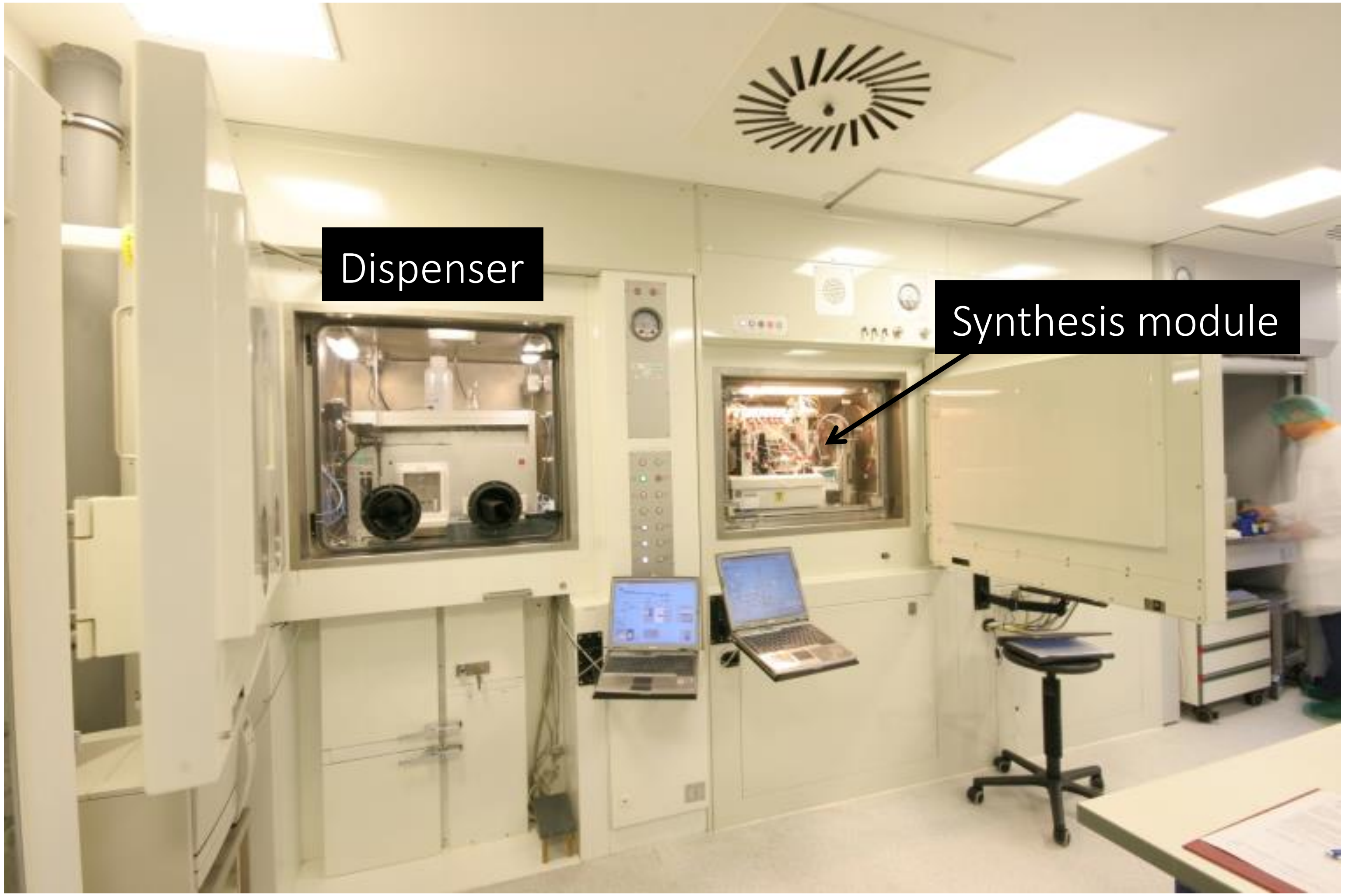
Radiosynthesis in hot cells





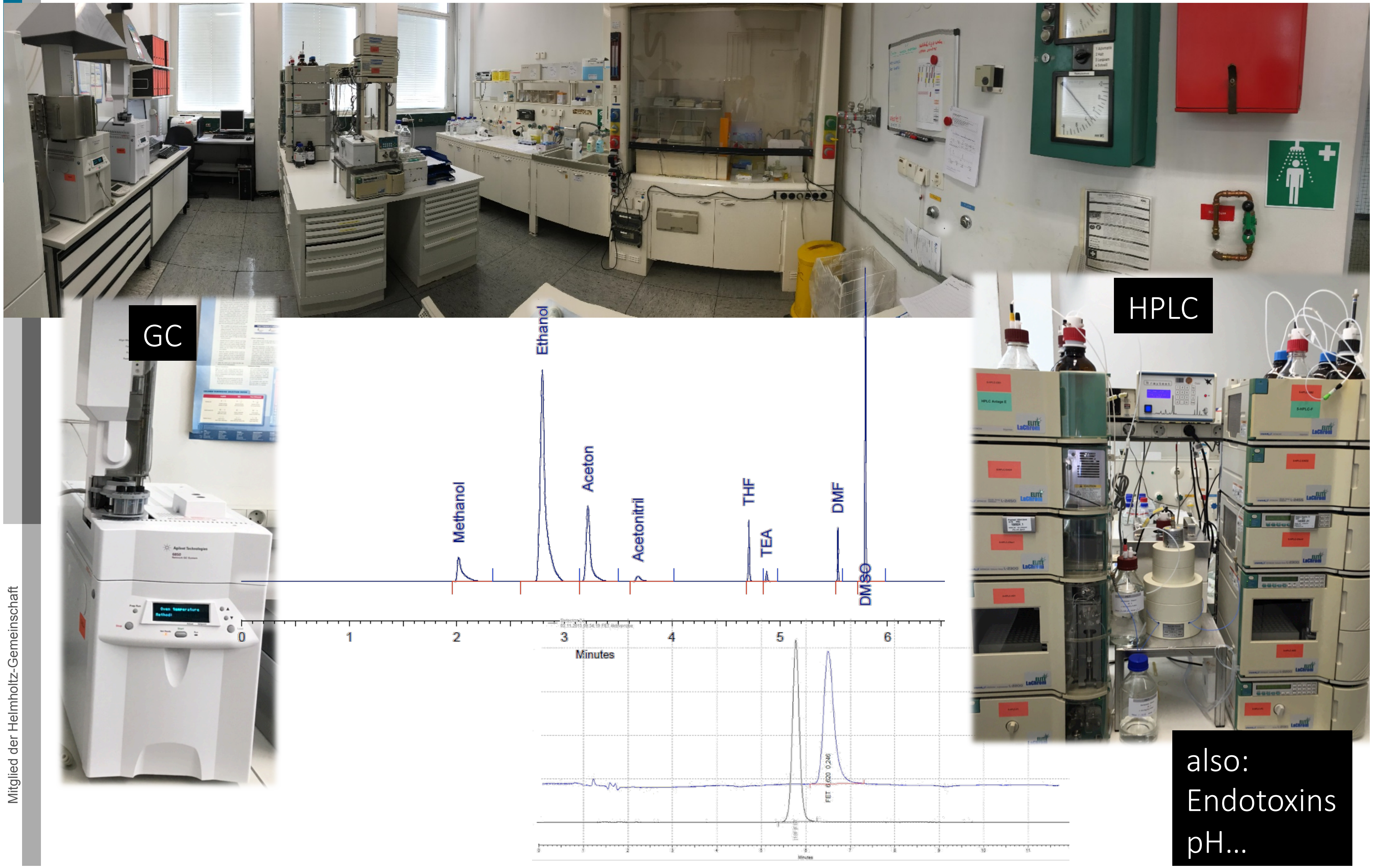
Automated and remotely controlled synthesis module

Sterilisation and dispensing



Mitglied der Helmholtz-Gemeinschaft

Quality control



Amyloid-Kaskaden-Hypothese

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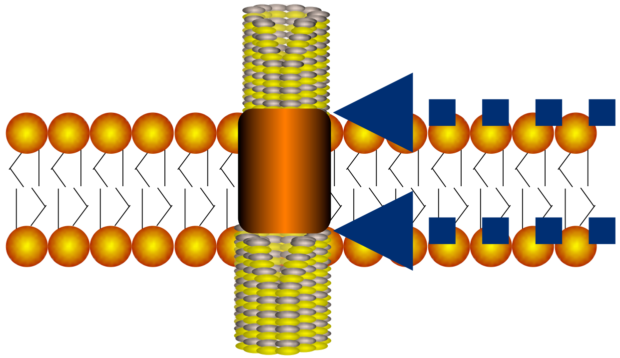
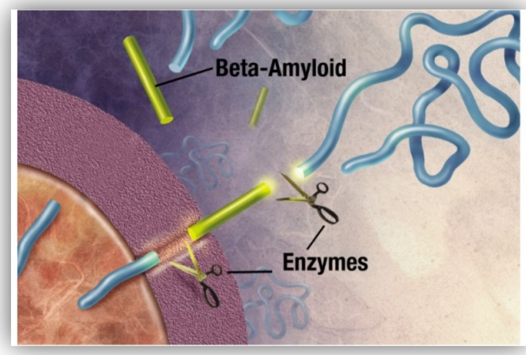


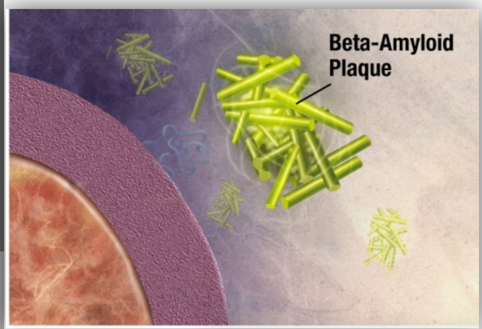
β-Sekretase

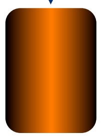
γ-Sekretase



APP Mutationen
Presenilin 1 Mutationen
Presenilin 2 Mutationen

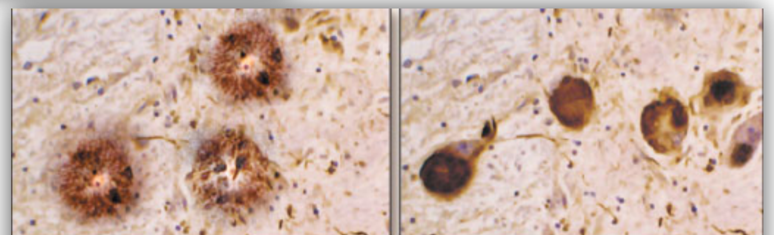
→ Erhöhte Aβ Produktion





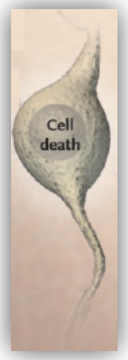
Lipoprotein ε4
LRP
Cholesterol
α2 Macroglobulin

→ Aggregation getriggert und Auswaschung reduziert



Senile plaque with microglial activation

Neurofibrillary tangles

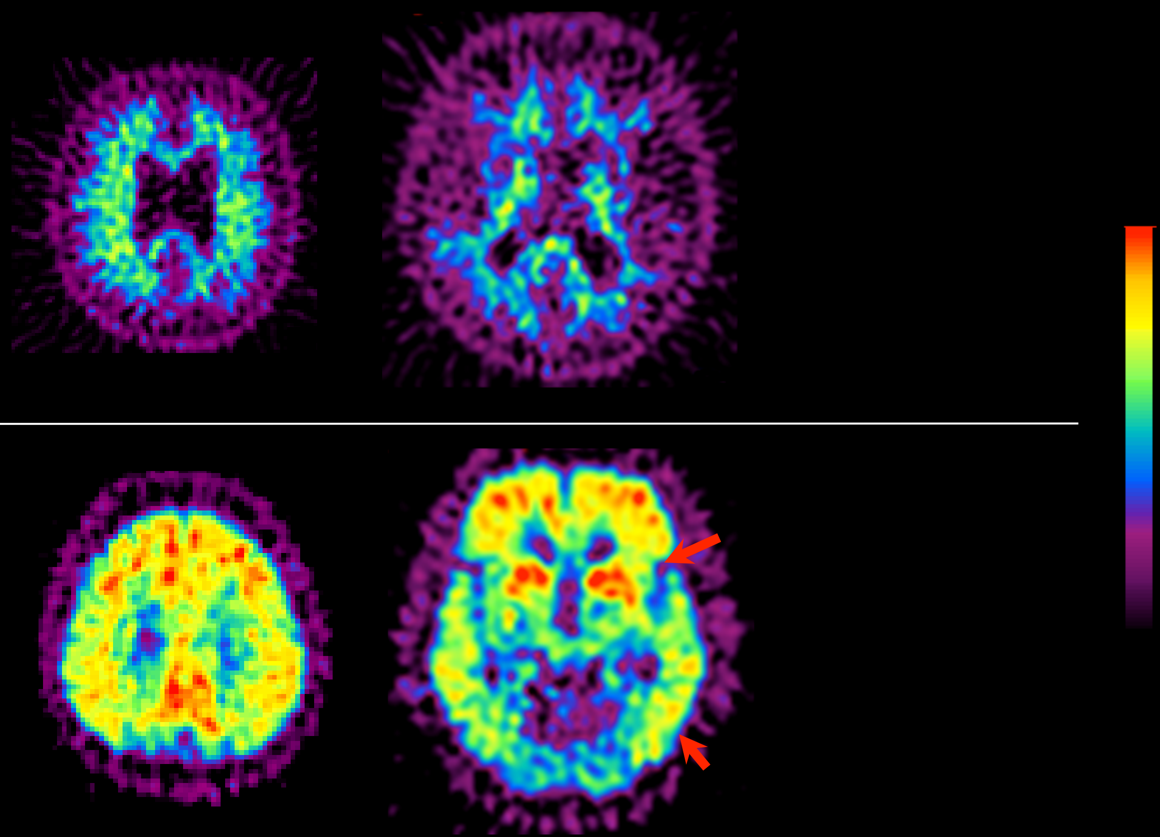


Amyloid imaging by [^{11}C]PIB-PET

Amyloid Plaque Imaging C-11 PIB
40-70 min p.i.

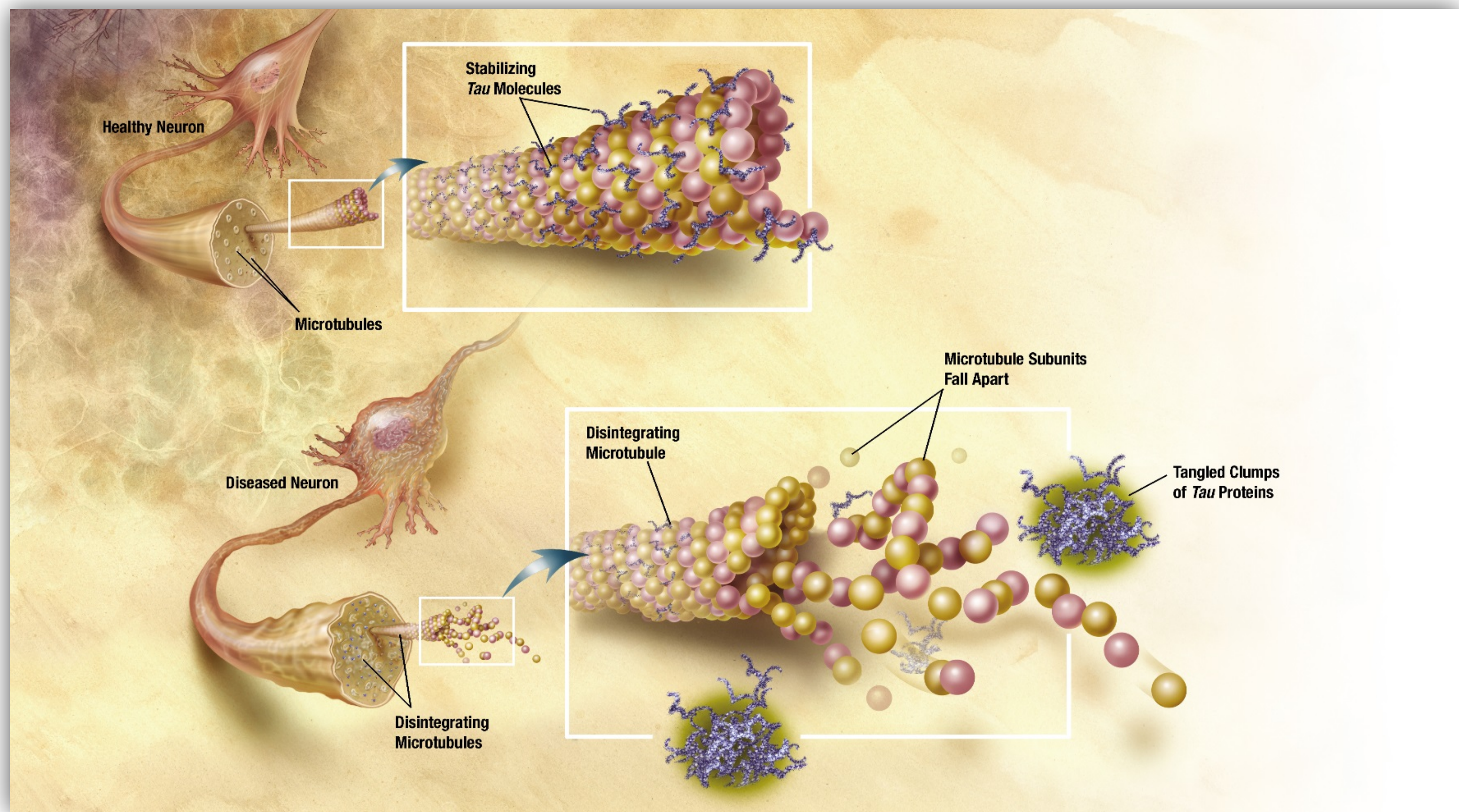
Control

Alzheimer's disease



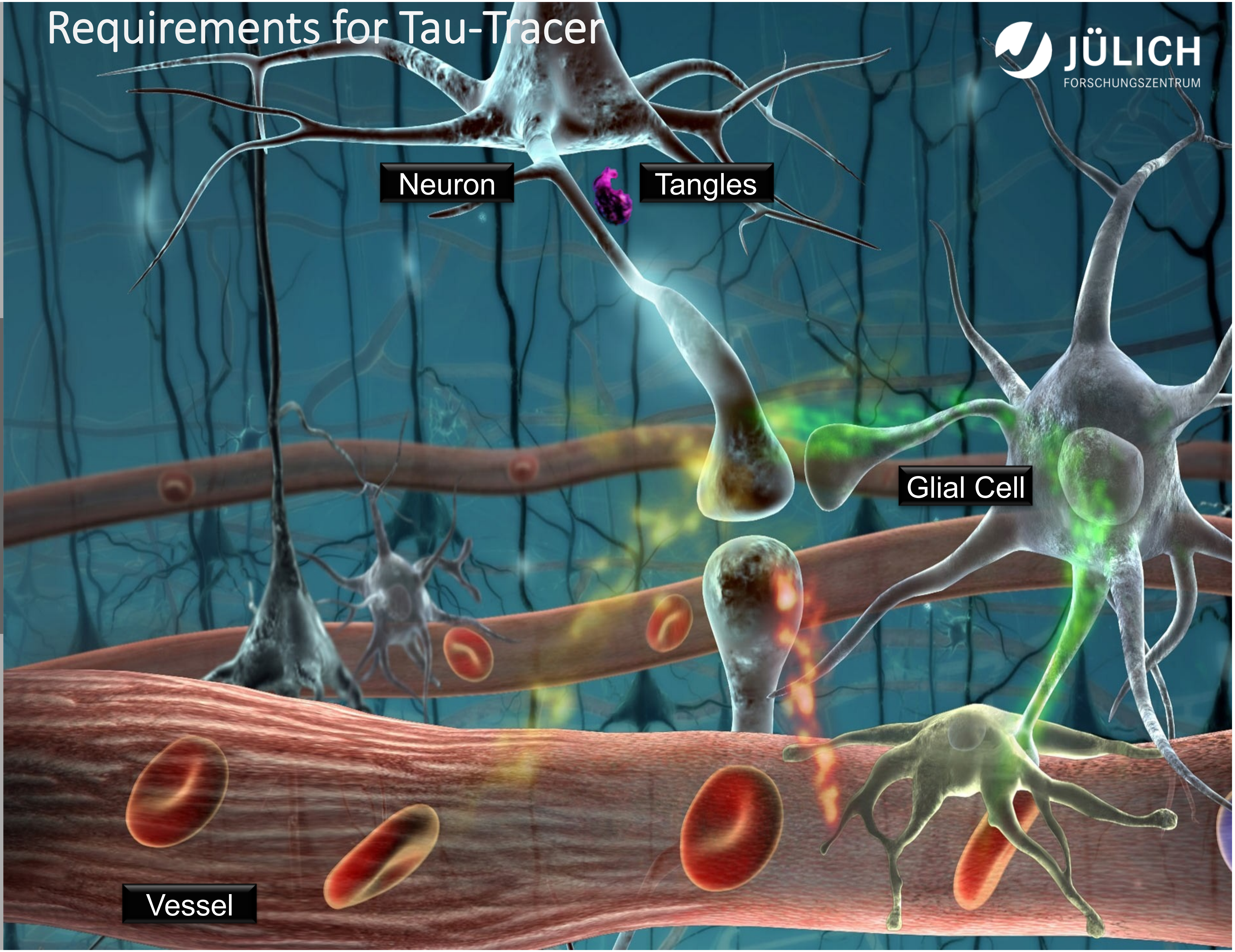
Axial slices
caudal aspects

Alzheimer's Disease: Tau-hypothesis



- Hyperphosphorylation of tau protein
- Disintegration of microtubules in brain cells
- Malfunctions and death of neurons
- AD pathogenesis development

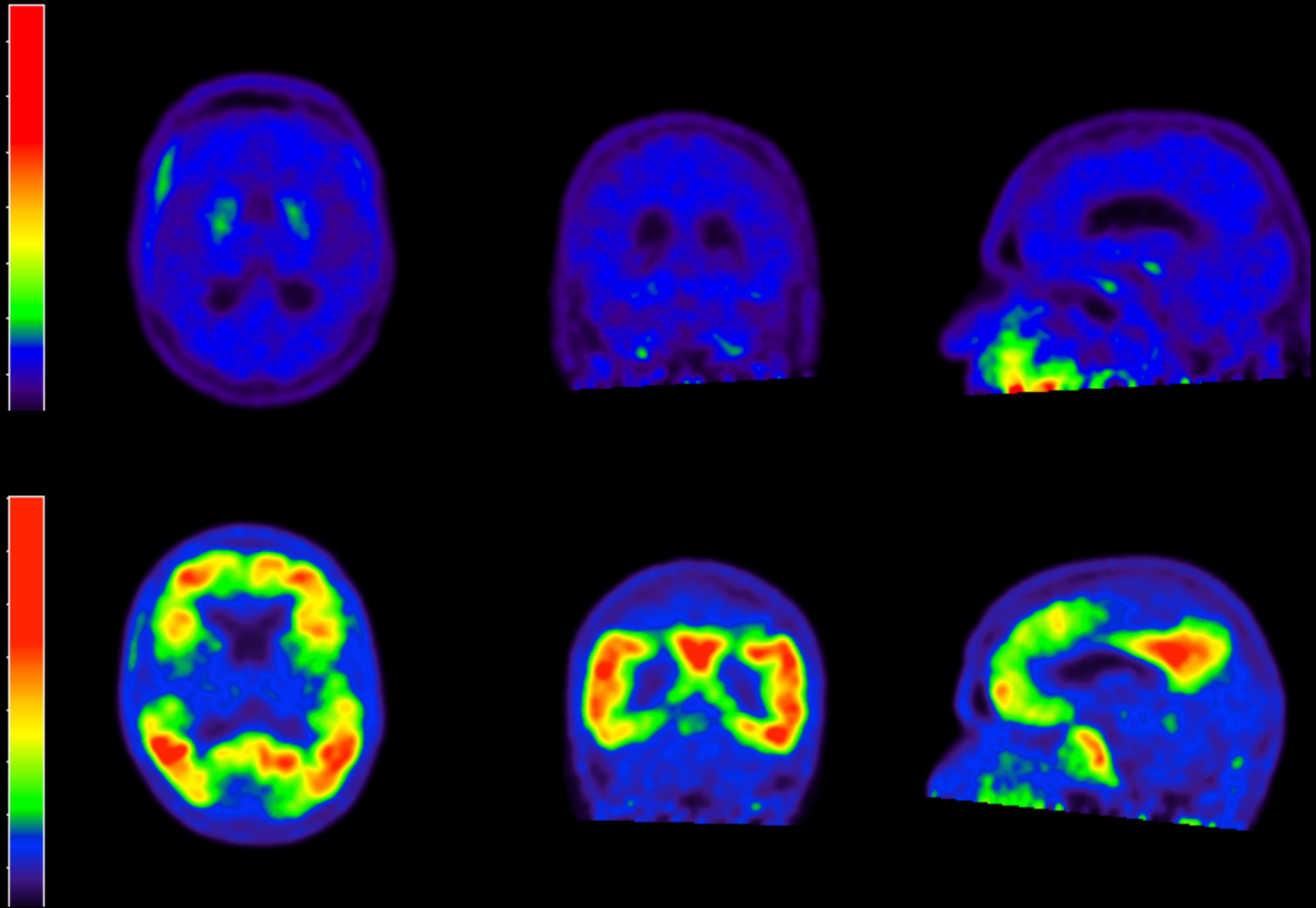
Requirements for Tau-Tracer



Tau imaging by [^{18}F]AV1451 (T807) PET

Healthy control person

Alzheimer's disease



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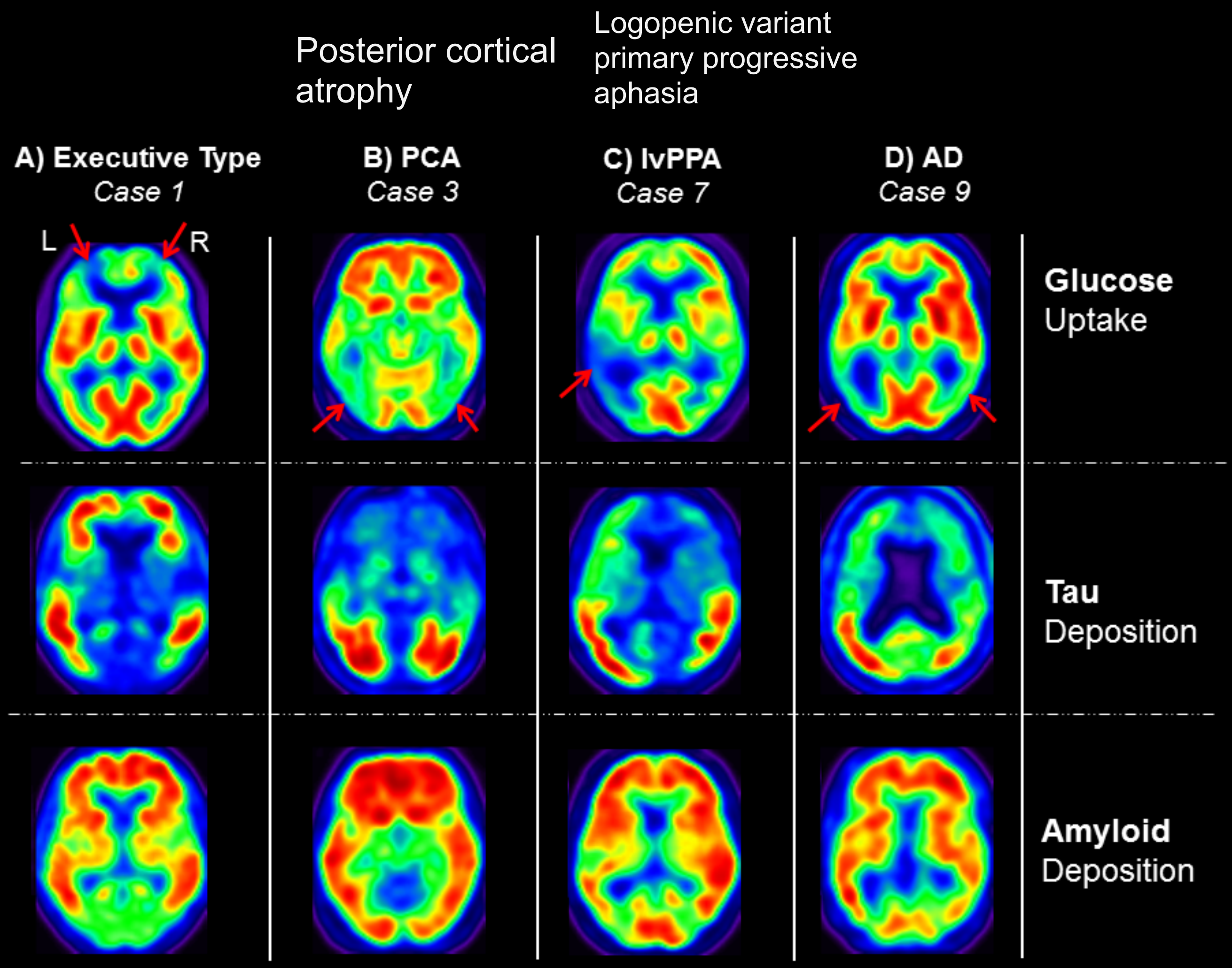
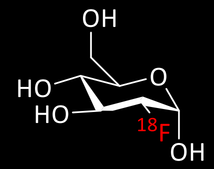
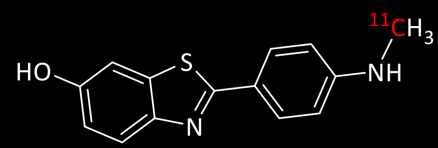
Amyloid plaque and tau imaging of neurodegenerative diseases using $[^{11}C]$PIB and $[^{18}F]$T807 PET





$[^{18}F]$FDG

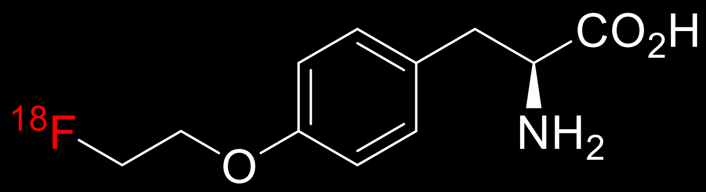
$[^{18}F]$T807



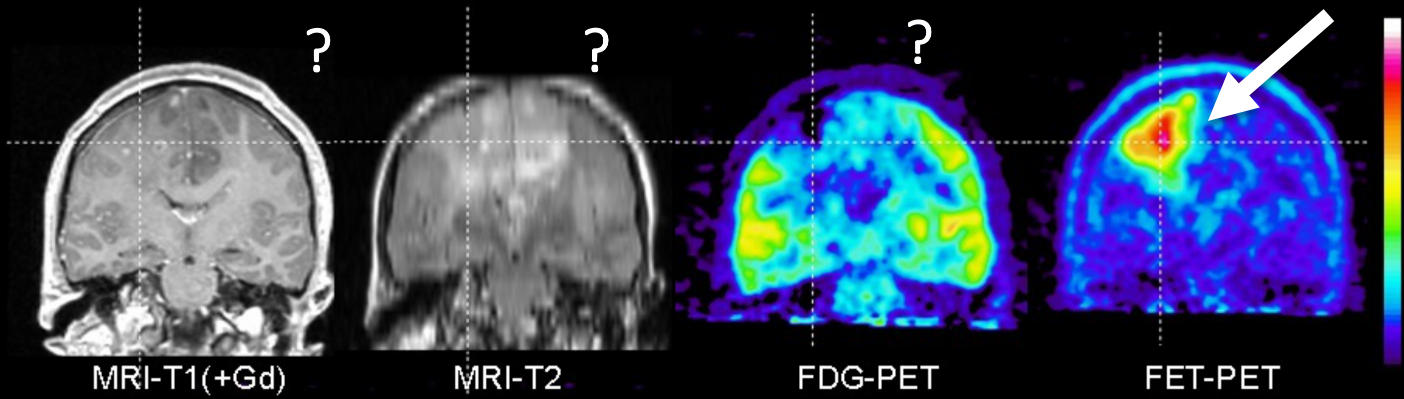
$[^{11}C]$PiB

Dronse *et al.* J. Alzheimers Dis. 2017

Imaging of brain tumors with [18F]FET

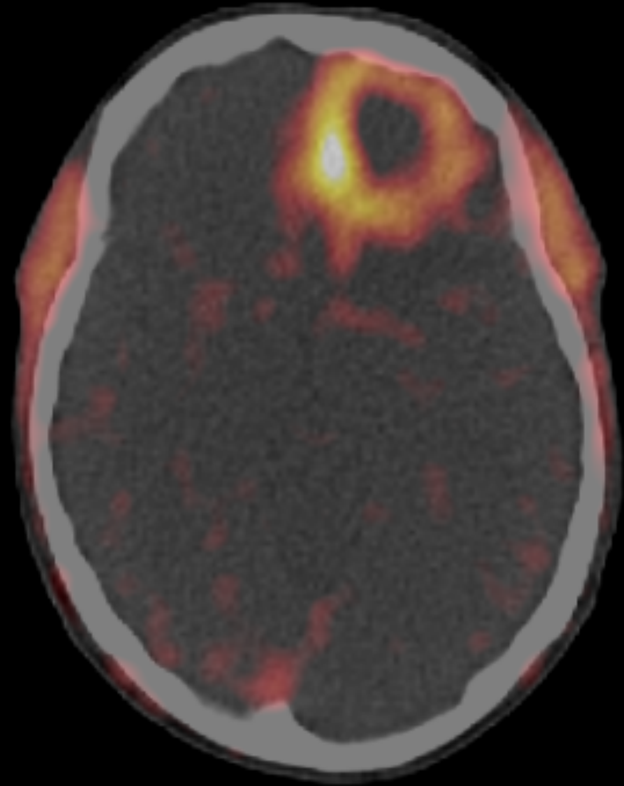


$[^{18}F]FET$



- Anaplastic Astrozytom Grade III:
- T1-and T2 weighted MRI do not allow differentiation of the tumor
- FDG PET indicates decreased glucose-metabolism in the region of the tumor
- In contrast FET PET allows precise differentation of the solid tumor

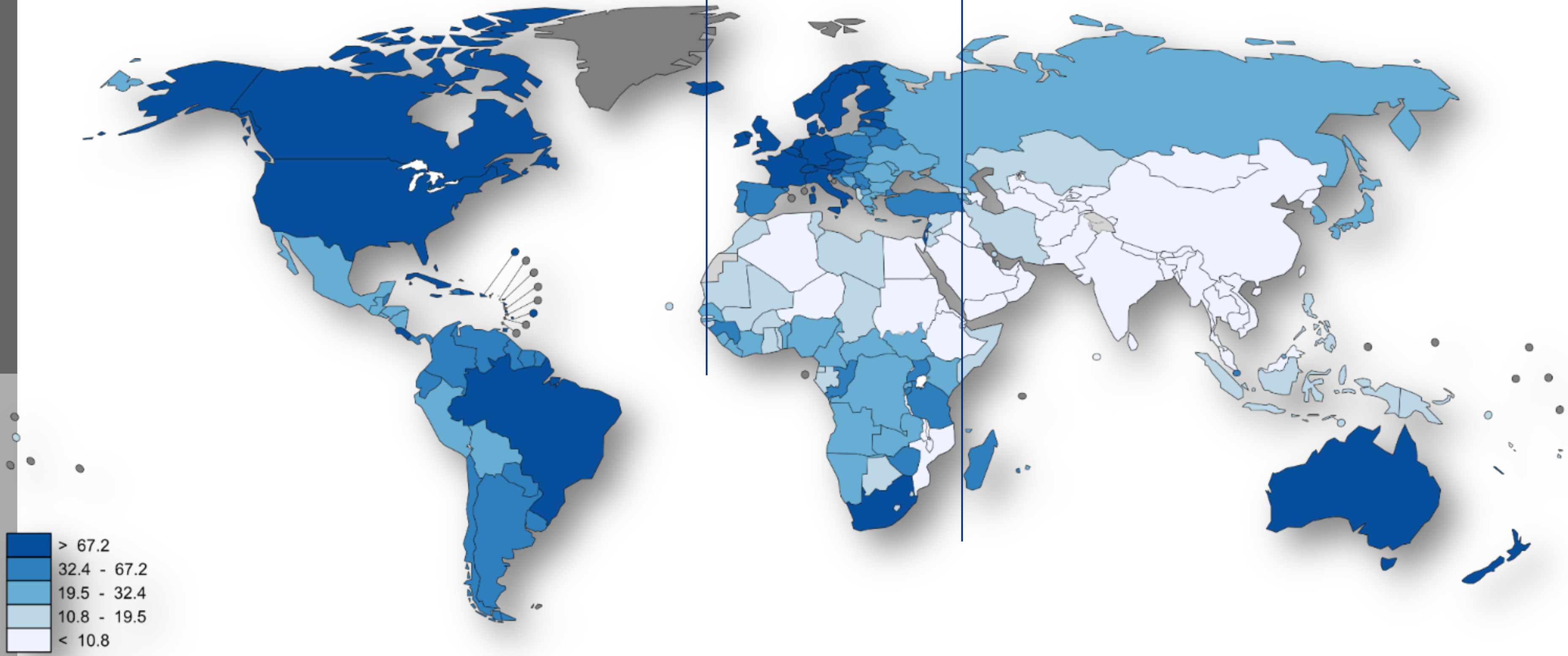
[illegible]



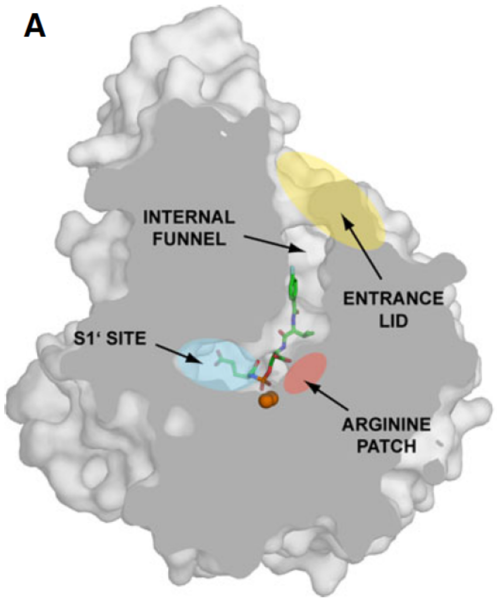
Prostate carcinoma (PCa)

second most frequently diagnosed cancer worldwide

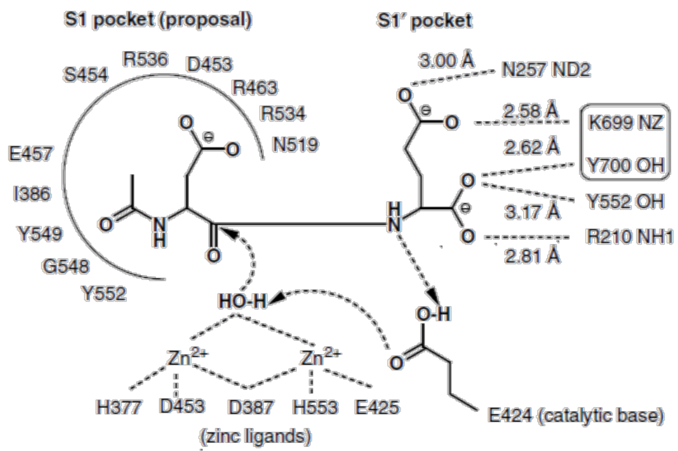
sixth leading cause of cancer death in males



Prostate Specific Membrane Antigen (PSMA)

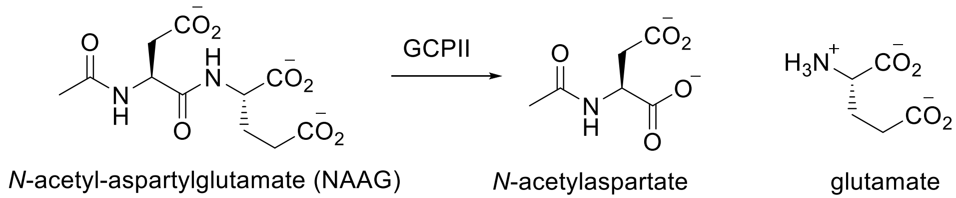


Navakova Z. *et al.* FEBS Journal, 2016



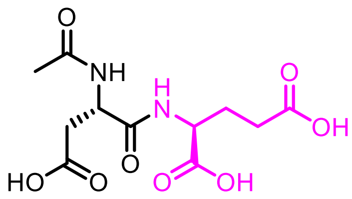
Mesters J.R. *et al.* EMBO Journal, 2006

In-vivo:



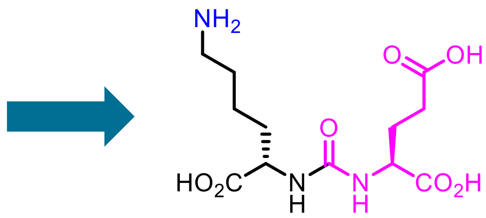
- 750 amino acids, ~84 kDa
- PSMA - zinc metalloenzyme that resides in membranes
- catalyzes hydrolysis of *N*-acetylaspartylglutamate (NAAG) to glutamate and *N*-acetylaspartate (NAA)
- up-regulated in prostate cancer cells

[^{18}F]DCFPyL, the novel [^{18}F]PSMA-PET



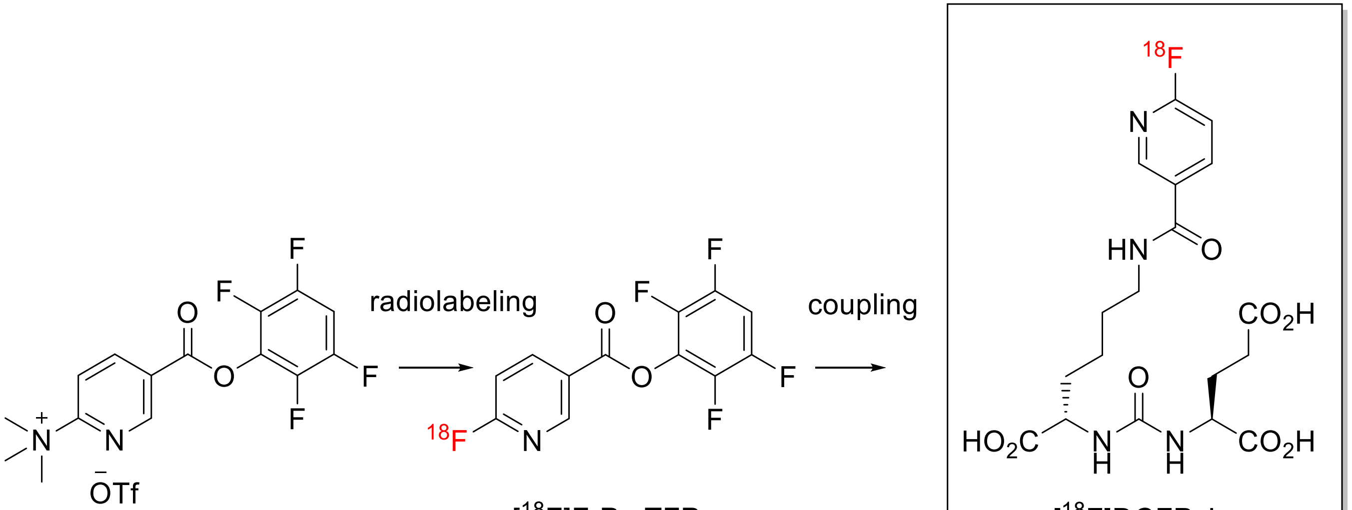
N-Acetylaspartylglutaminsäure (NAAG)

- Natural ligand of PSMA



(S)Lys-Urea-(S)Glu

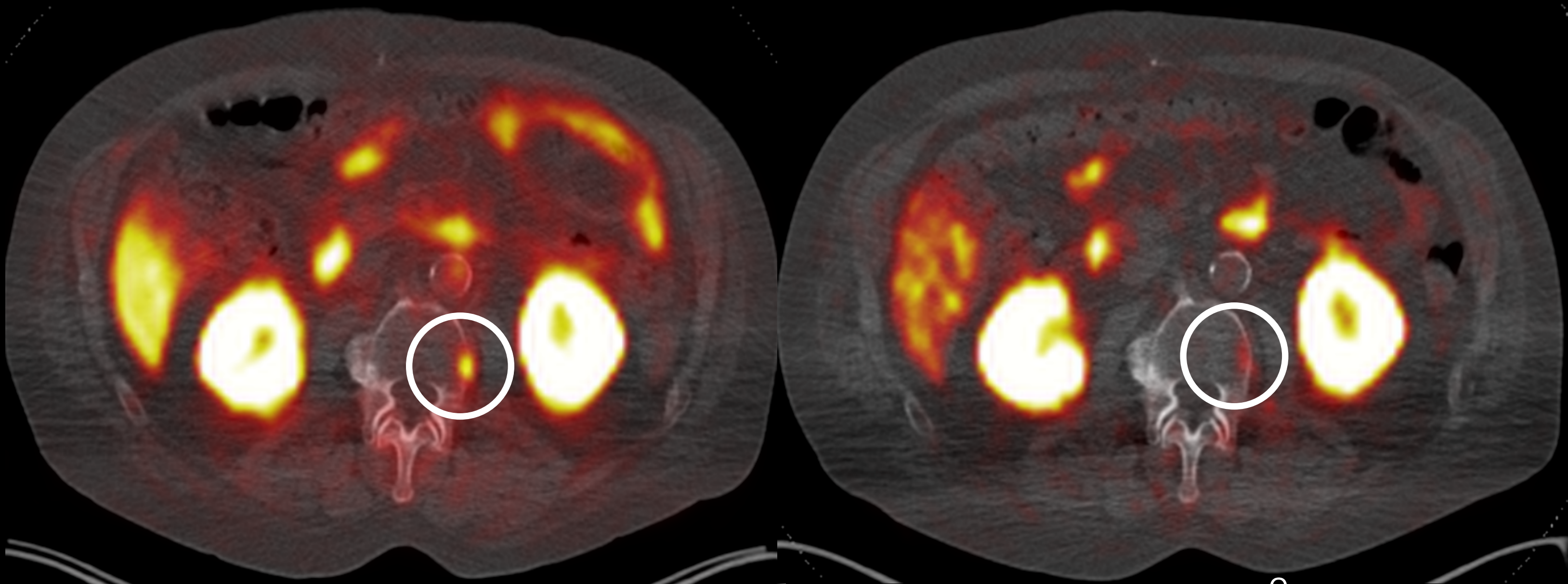
- High affinity for PSMA
- High metabolic stability
- Amenable for labeling

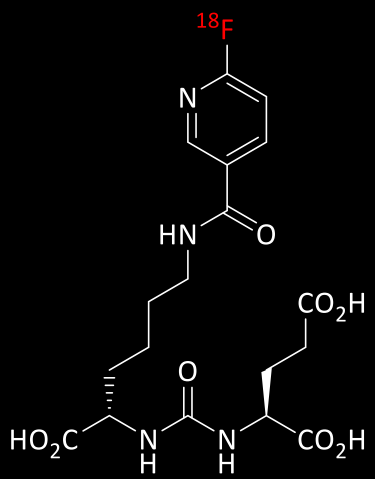


[^{18}F]F-Py-TFP

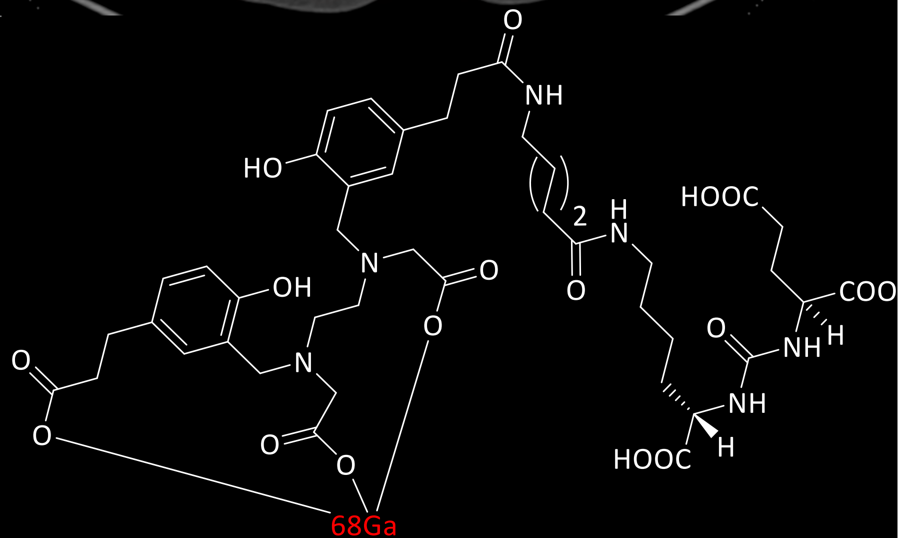
[^{18}F]DCFPyL

$[^{18}F]$DCFPyL Superior to $[^{68}Ga]$PSMA-HBED-CC / Imaging of Lymph node metastasis by $[^{18}F]$PSMA-6 PET/CT





$[^{18}F]$PSMA-6



$[^{68}Ga]$Ga-PSMA-HBED-CC

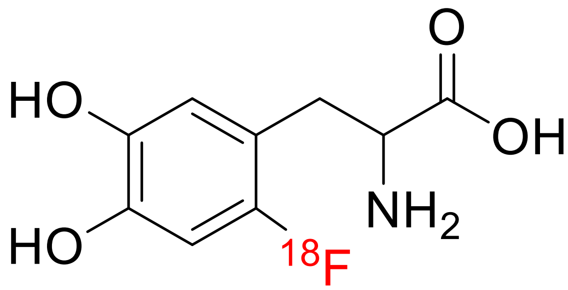
THANK YOU!

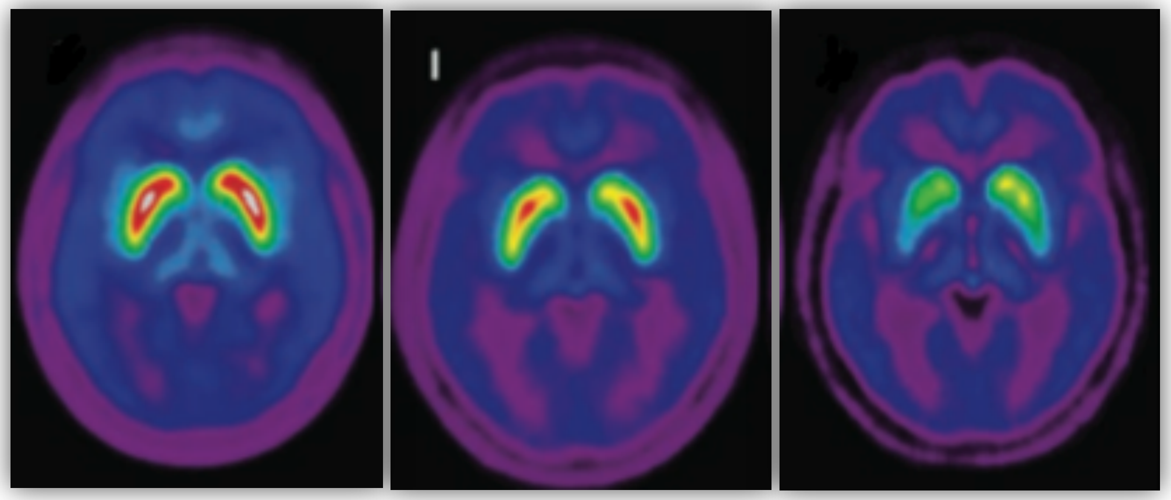
03.07.2017 | B. Neumaier

Imaging of Parkinson's Disease with [^{18}F]FDOPA

non-invasive assessment of the binding capacity of the cerebral D2 dopamine receptor

Early ilustration of PD by Sir William Richard Gowers in *A Manual of Diseases of the Nervous System* 1886.





healthy young person

healthy aged person

Parkinson's disease