APPLICATION OF RADIOACTIVE IMAGING AGENTS AS POWERFUL TOOLS IN CLINICAL PRACTICE

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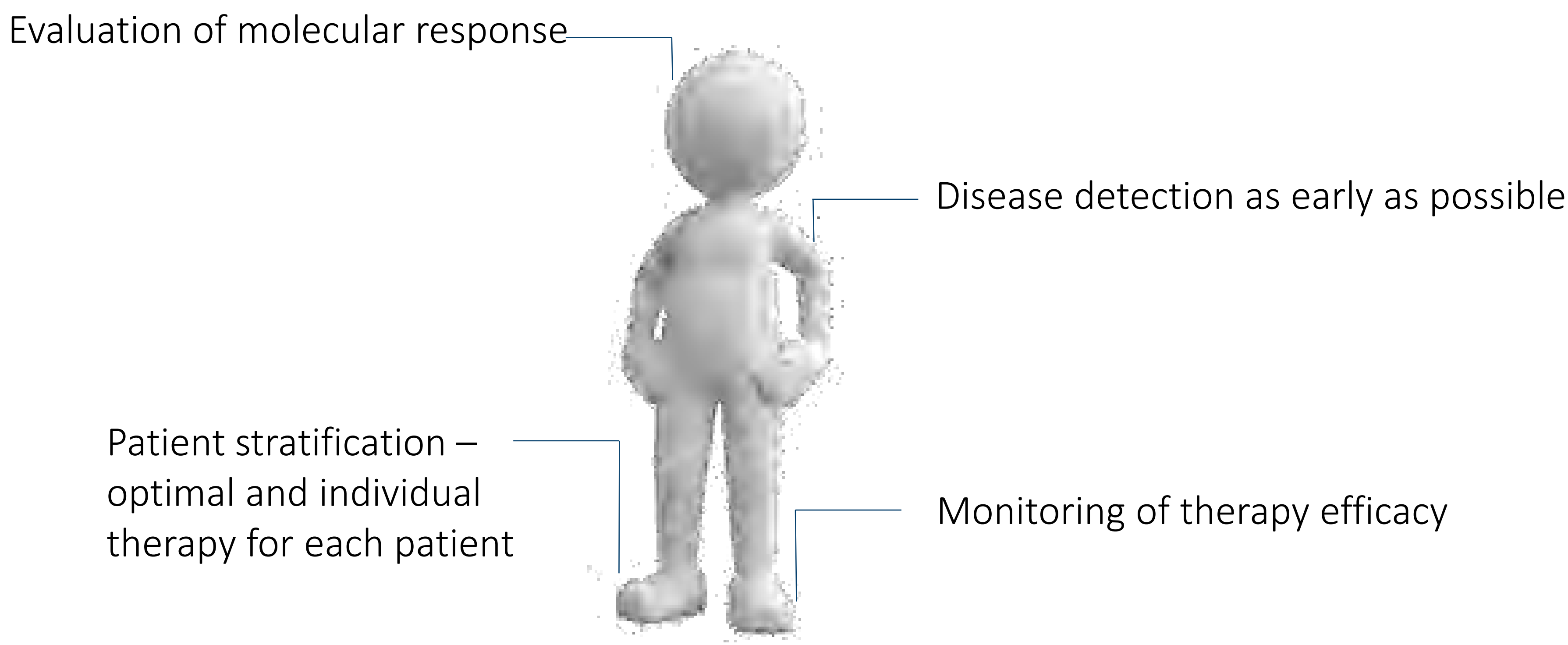
RADIOACTIVE IMAGING AGENTS- WHY?

Molecular Imaging: „In-vivo-characterization of biological processes at the molecular level"

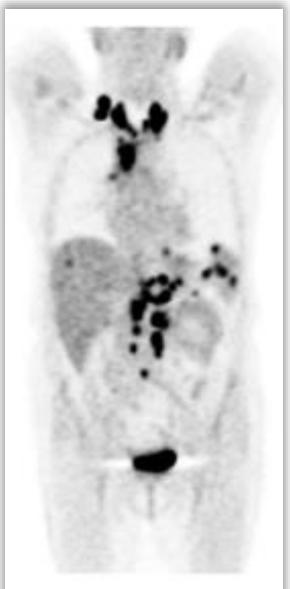
AIM:

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



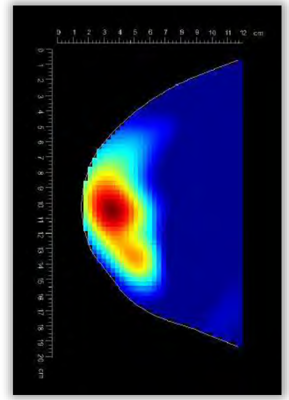
DIFFERENT METHODS OF MOLECULAR IMAGING

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



PET
Positron **E**mission **T**omography
(NHL;[^{18}F]FDG)

SPECT
Single **P**hoton **E**mission **C**omputed **T**omography
(NET; ^{111}In-DTPA-Octreotid)

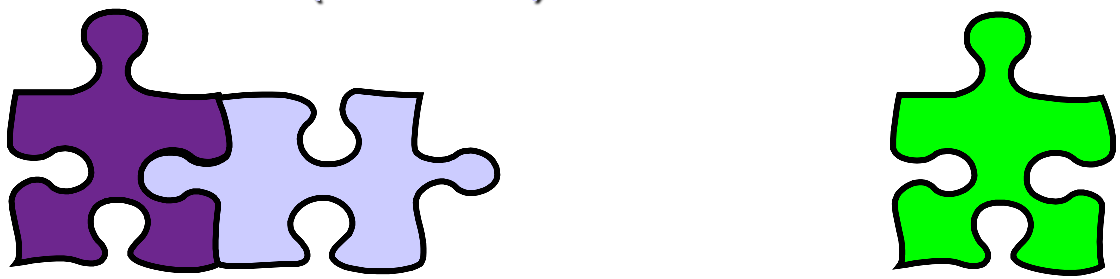


Softscan
NIR
Fluorescence Imager
(Breast cancer; DeoxyHb)

MR
Magnetic **R**esonance
(PCa, lymph node metastasis; Sinerem NT)

PRINCIPLE OF MOLECULAR IMAGING

Targeting molecule
(Vehicle)

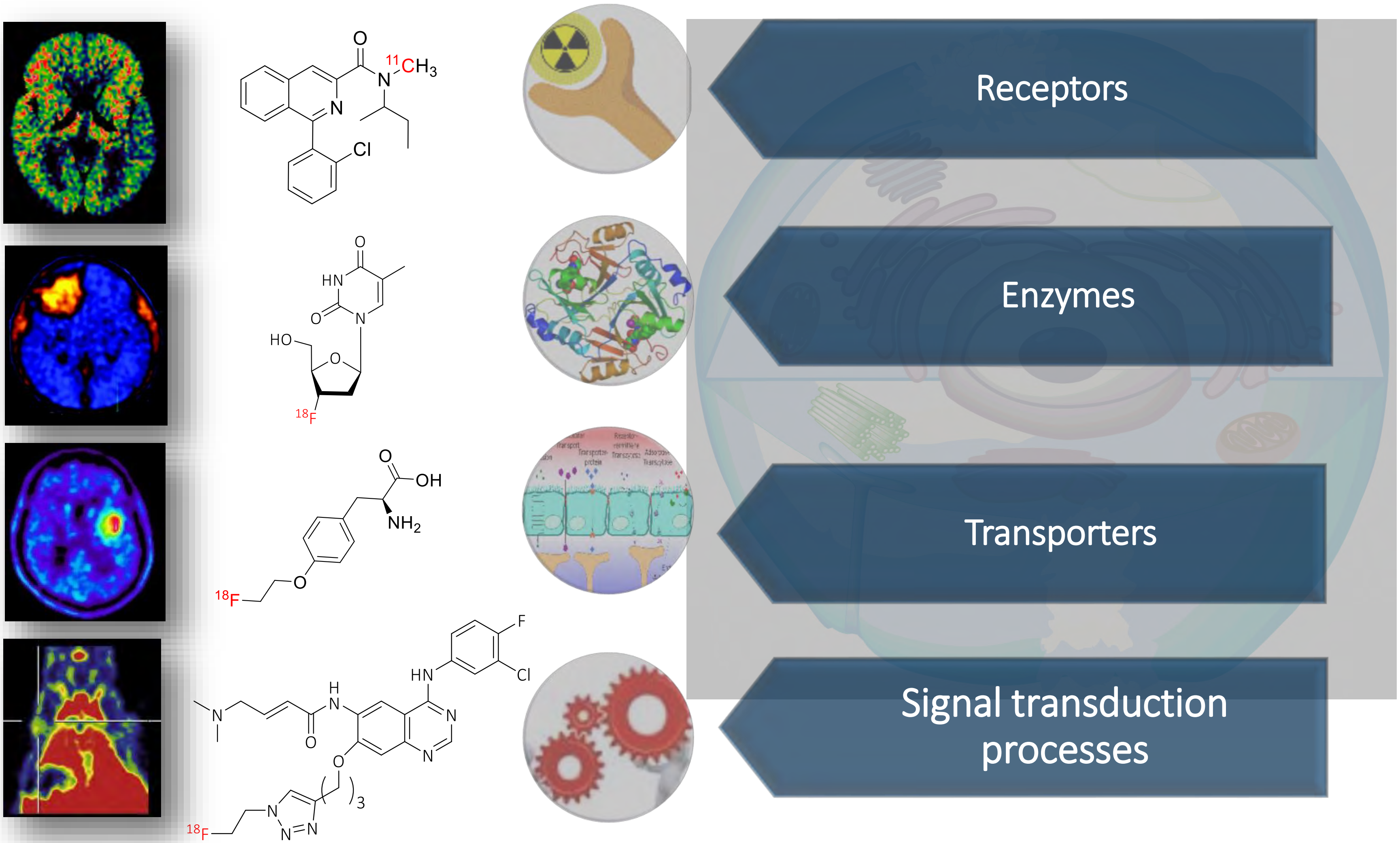


Reporter
(Radionuclide,
fluorescent dye or
magnetic label)

Biological targets

BIOLOGICAL TARGETS FOR DISEASE DETECTION

Visualization of molecular processes - measurement of molecular alterations UP- or DOWN regulation of



REPORTER SYSTEMS AND BIOLOGICAL PROBES FOR MOLECULAR IMAGING

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:

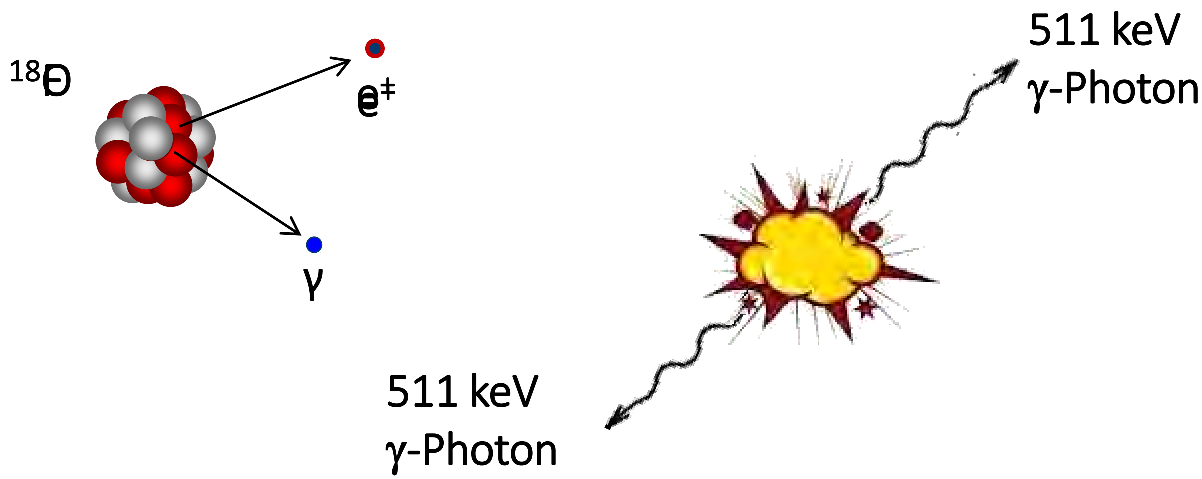
- Peptides
- Peptidomimetics
- Nucleosides
- Small molecules
- Antibodies
- Affibodies

Corresponding targets:

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

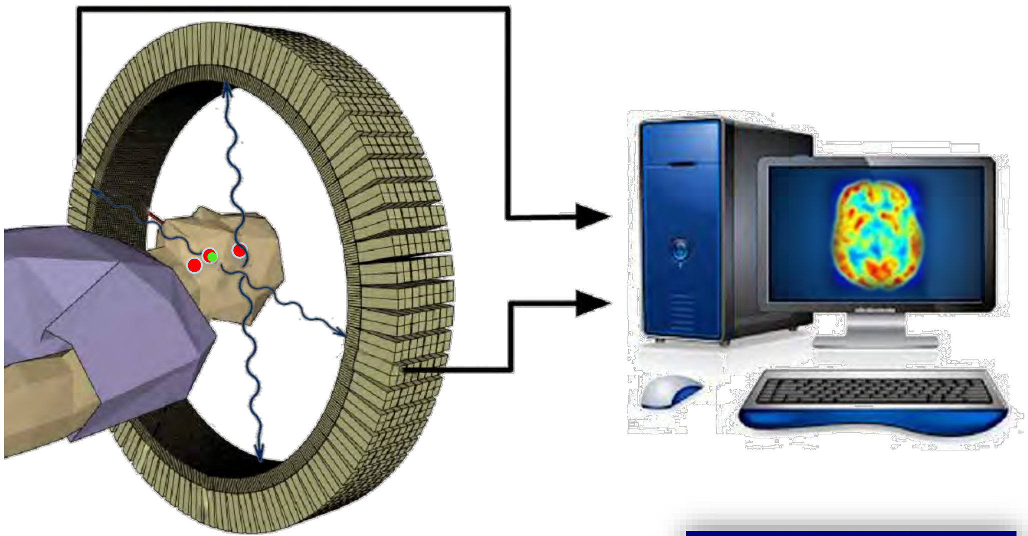
PET: PHYSICAL BACKGROUND

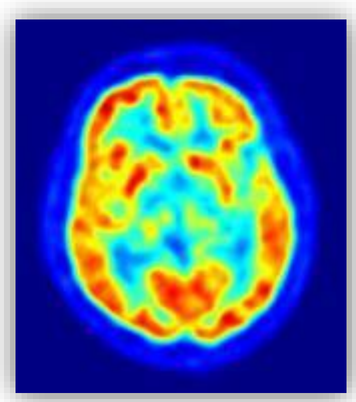
Positron decay and positron electron annihilation (e.g. for ^{18}F)



- Emission of an 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°)

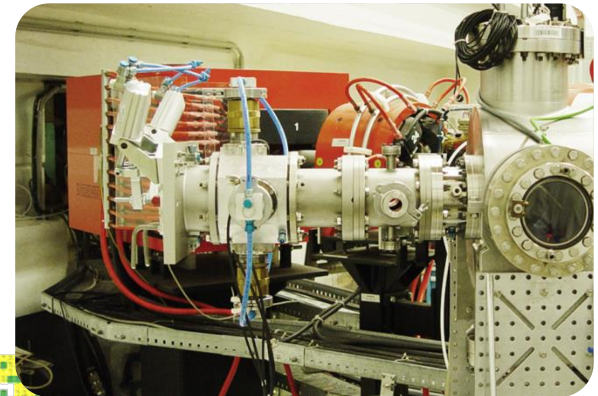
PET: PHYSICAL BACKGROUND

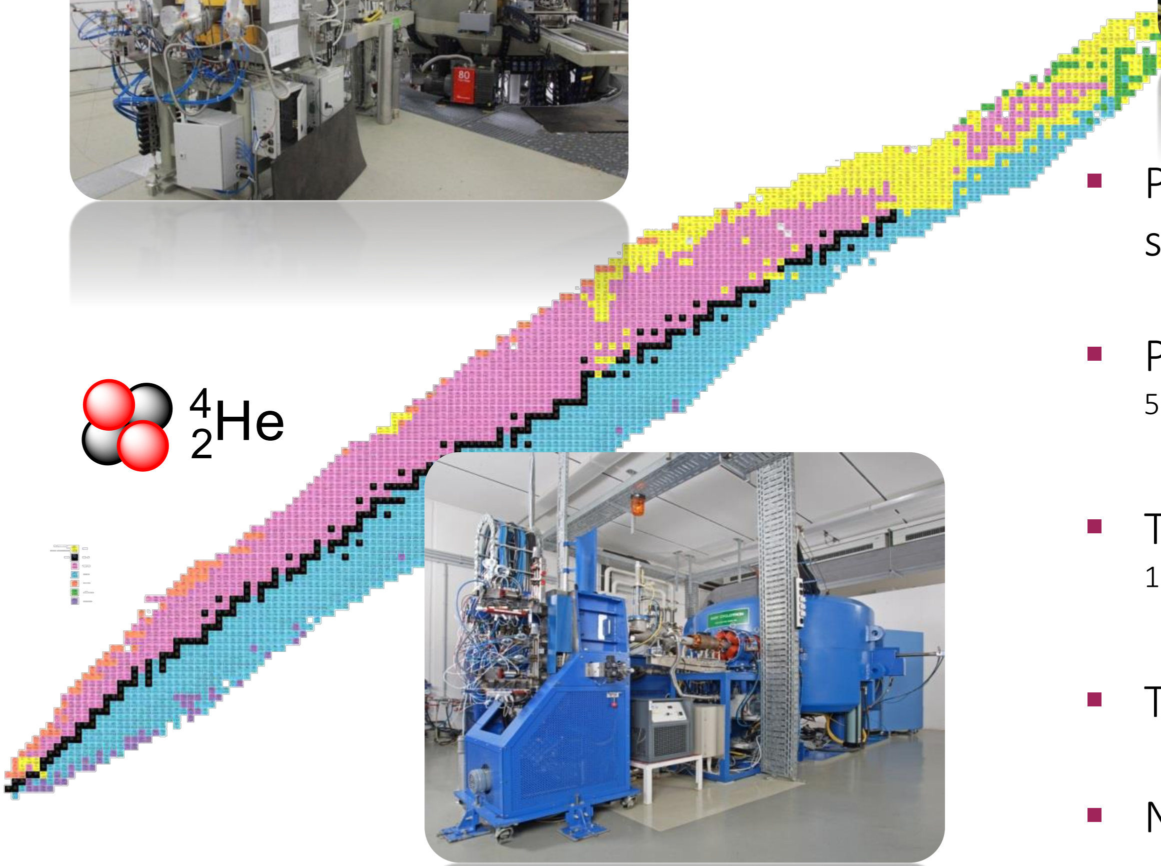




- Detection of coincident decay events
- Reconstruction of point of decay based on cross points of γ-photon trajectories
- Real-time reconstruction of 3D nuclide distribution by modern computer techniques

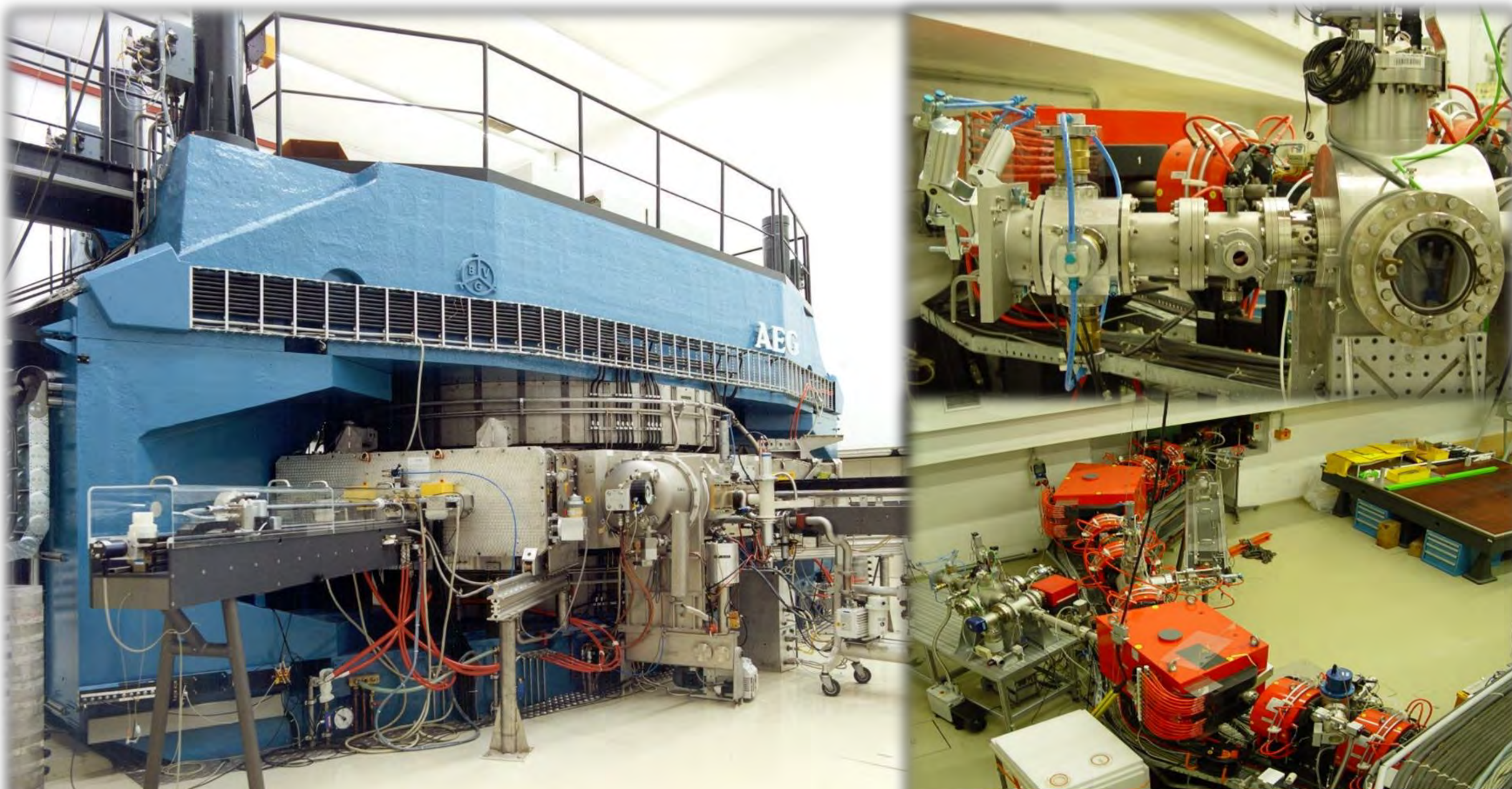
PRODUCTION OF RADIONUCLIDES





- 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



- p = 45 MeV
- d = 78 MeV

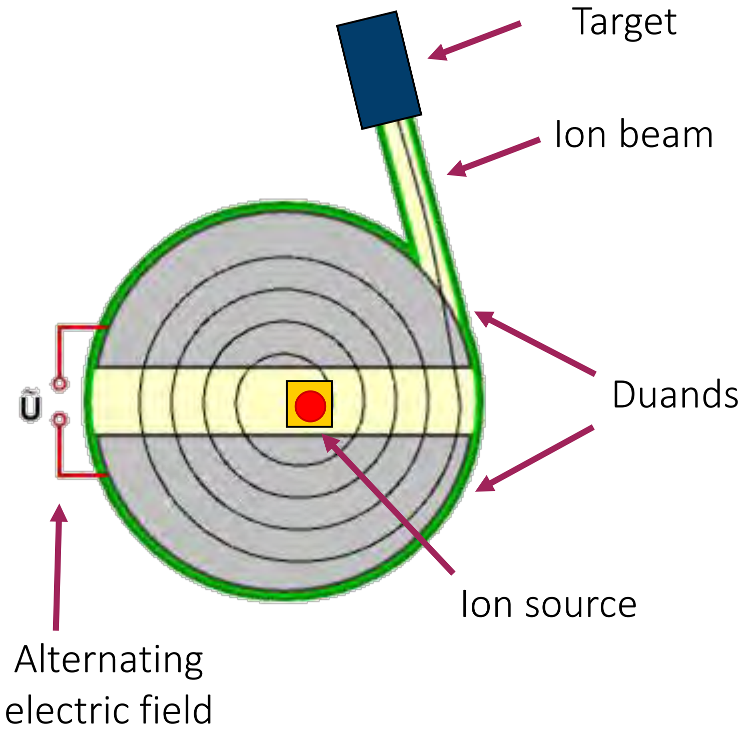
HIGH ENERGY NUCLEAR REACTIONS COSY

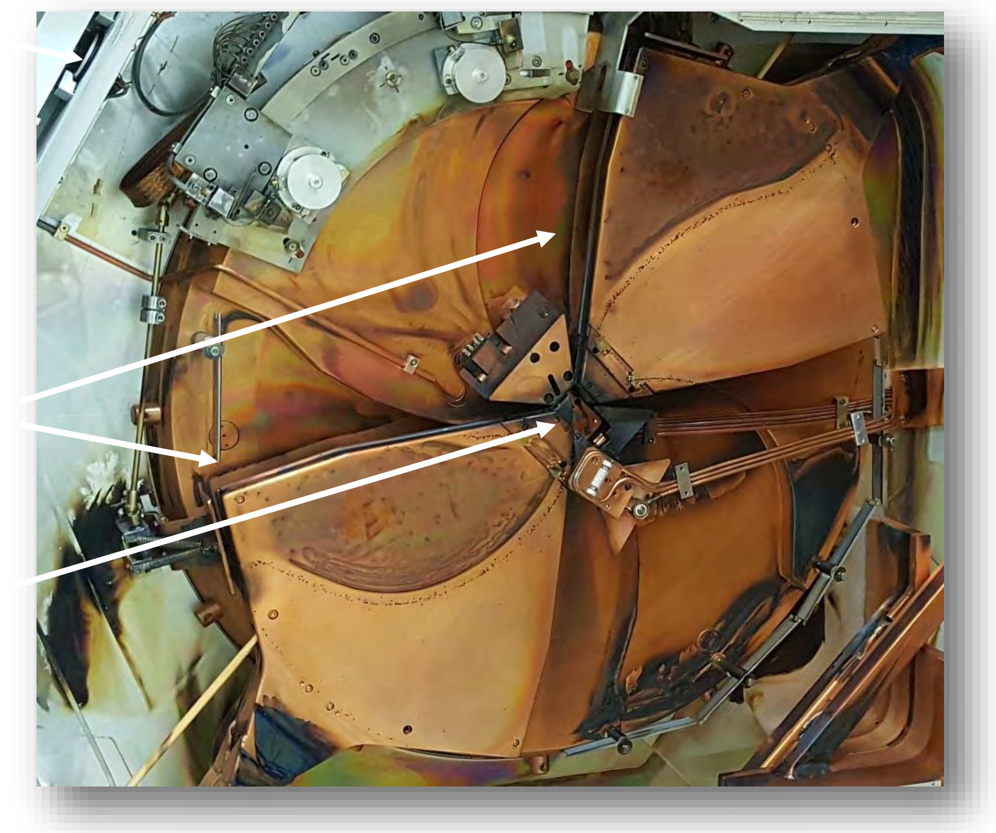
- 2.88 GeV Cooler Synchrotron
- 4 Quadrupole magnets
- p = 150 MeV

MEDICALLY RELEVANT RADIONUCLIDES VIA HIGH-ENERGY REACTIONS

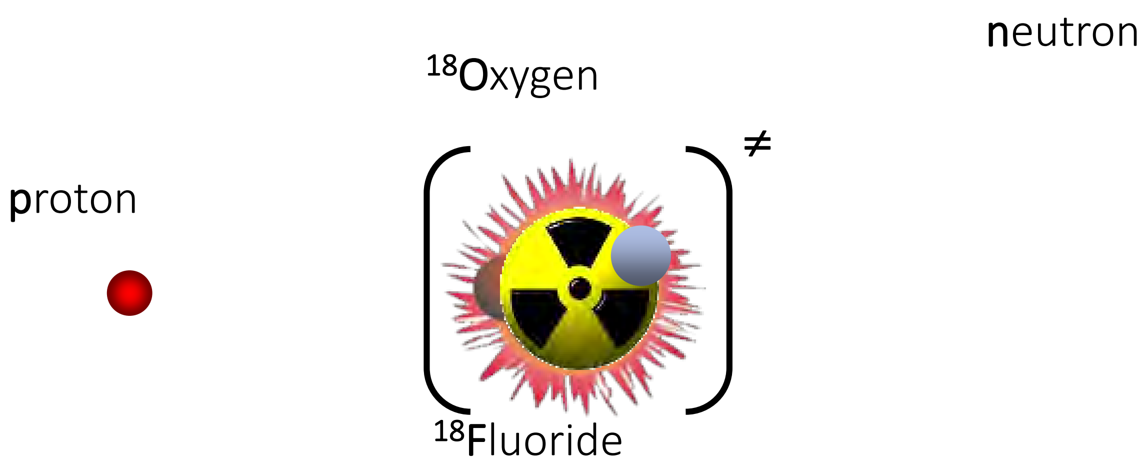
Target	Reaction	Radionuclide	Usage	Remarks
^{40}Ar, ^{nat}Ar	(p,α3n)	^{34m}Cl	PET	
^{39}K, ^{nat}K	(p,αpn) (p,α2n), decay	^{34m}Cl	PET	
^{nat}V	(p,αp)	^{47}Sc	Therapy	^{43}Sc/^{47}Sc theragnostic pair
^{55}Mn (nat.)	(p,4n)	^{52}Fe	PET	Multimodal imaging,
^{55}Mn (nat.)	(p,p3n)	^{52}Mn	PET	Multimodal 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

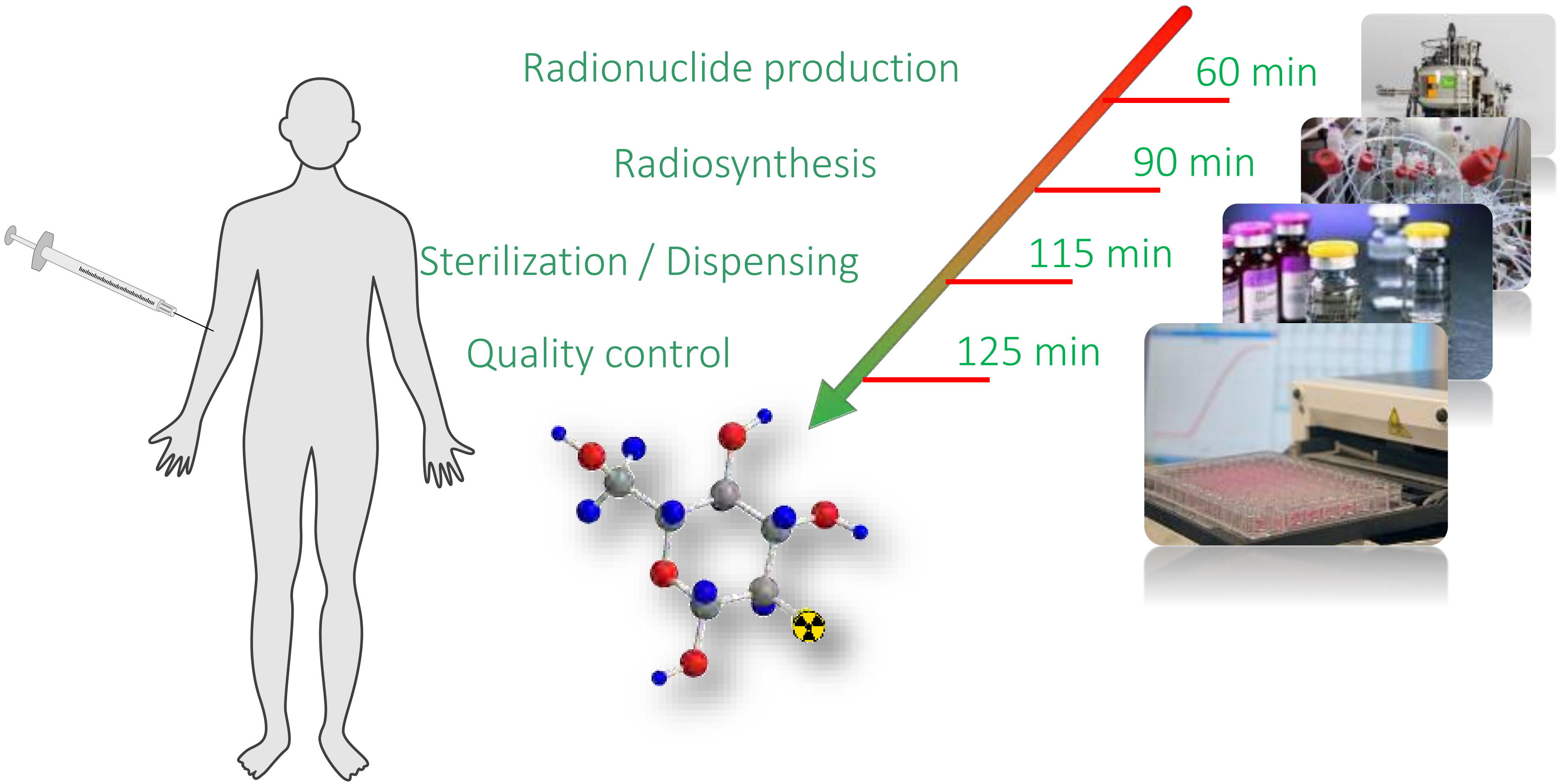


Compound nucleus [^{19}F]*

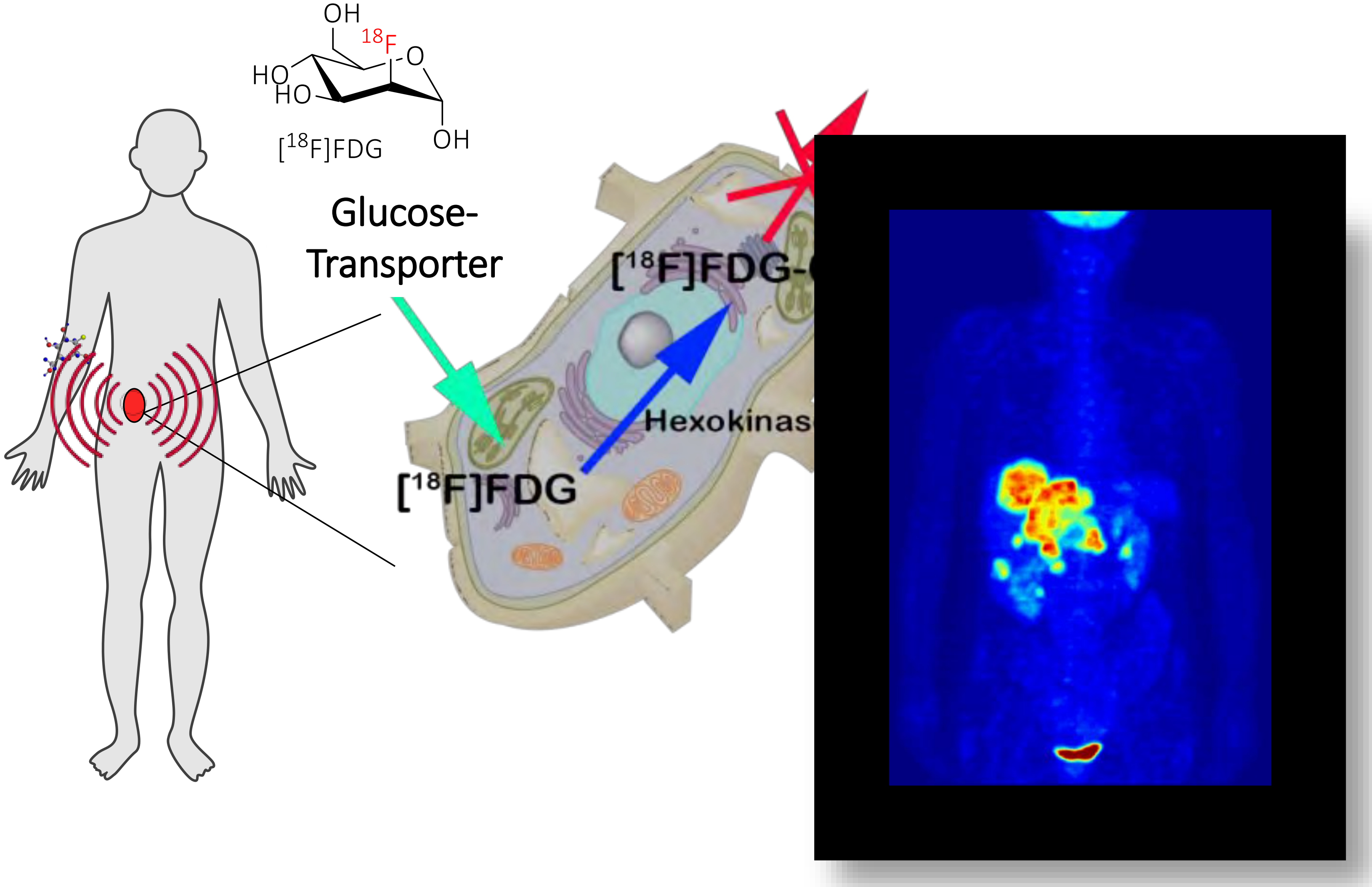
Reaction: $^{18}O(p,n)^{18}F$

^{18}F half life: 110 min

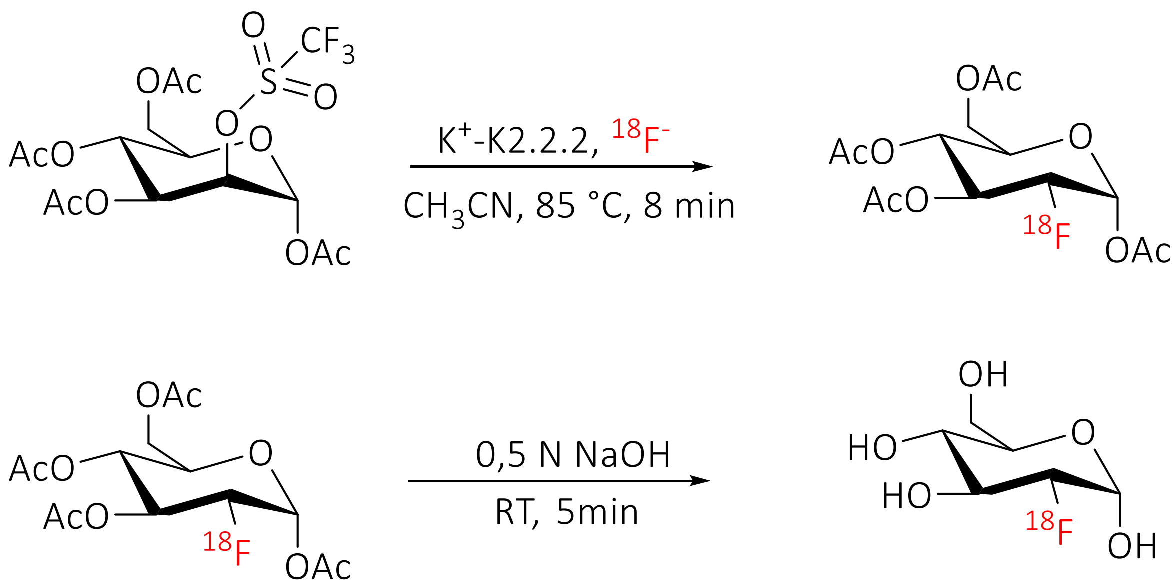
PRODUCTION OF RADIOPHARMACEUTICALS



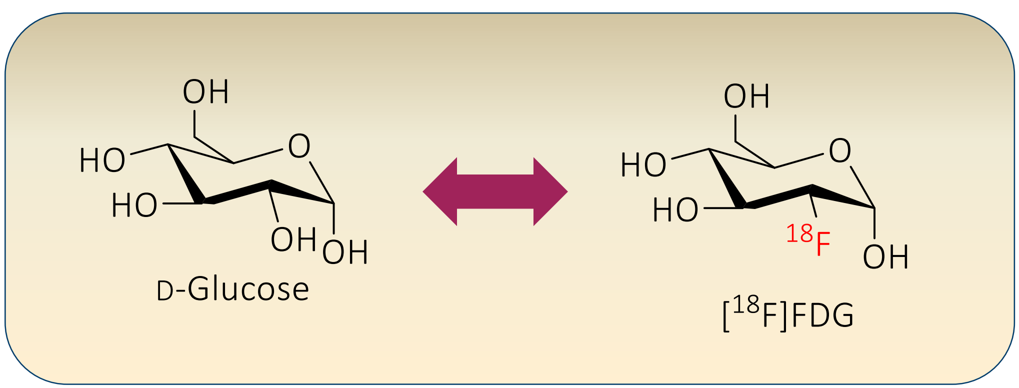
PET DIAGNOSTICS WITH [^{18}F]FDG



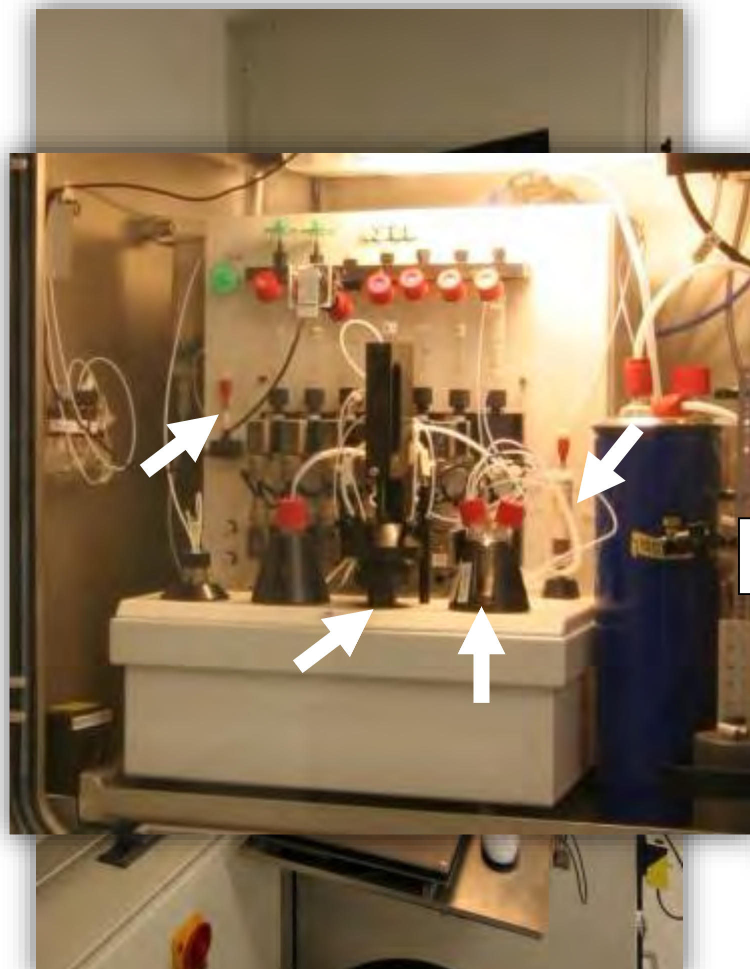
RADIOSYNTHESIS OF [^{18}F]FDG

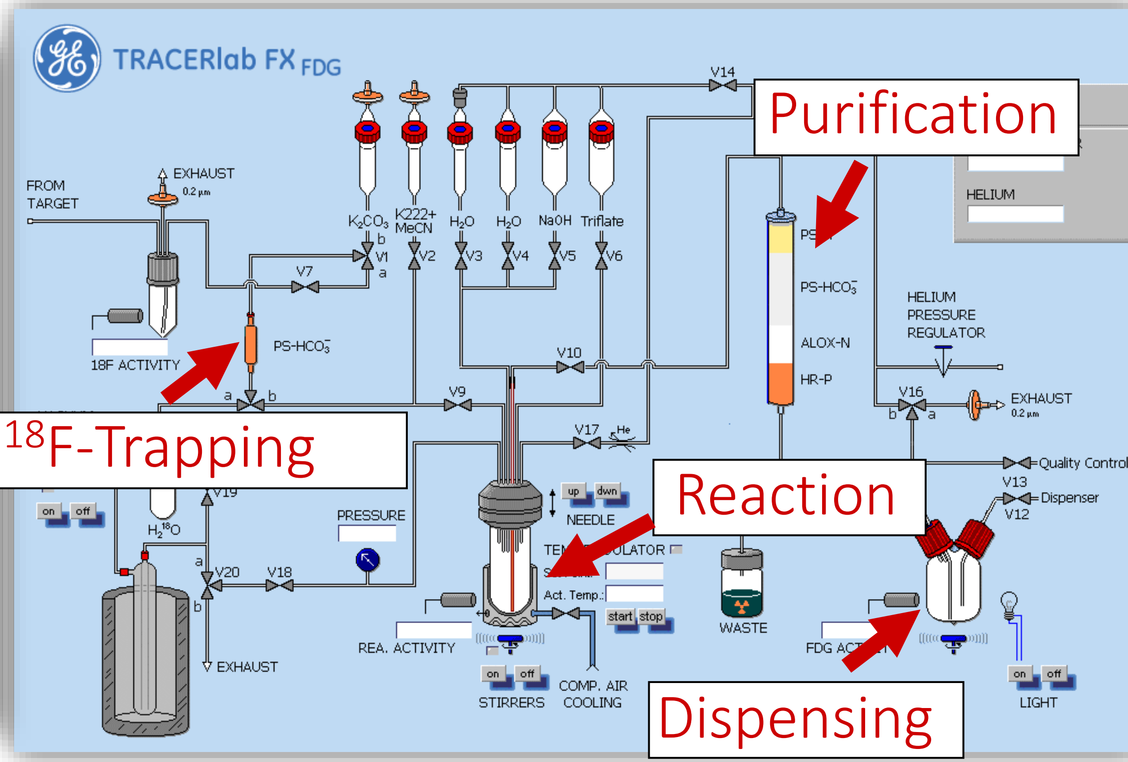


[^{18}F]FDG



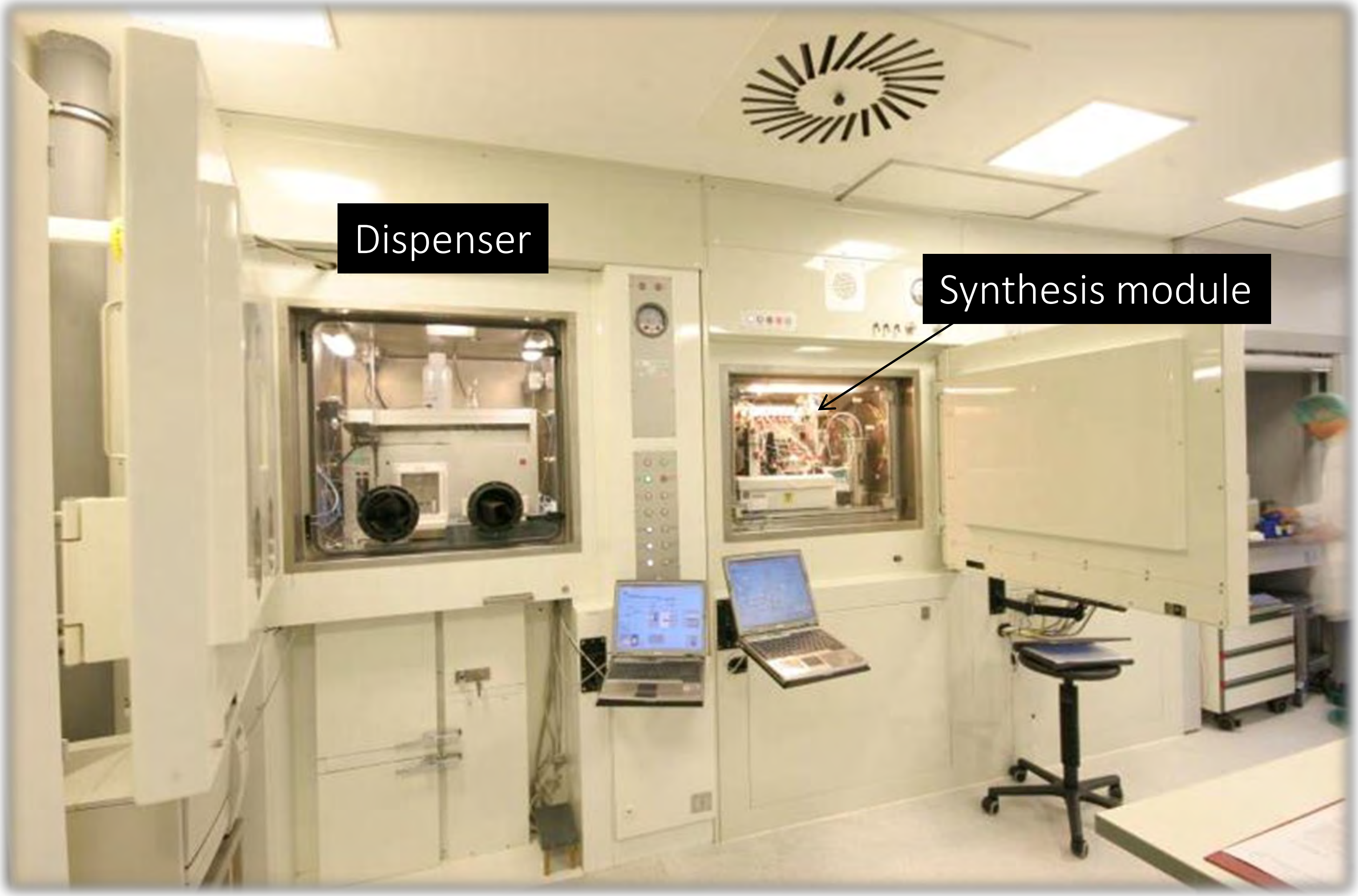
RADIOSYNTHESIS IN HOT CELLS





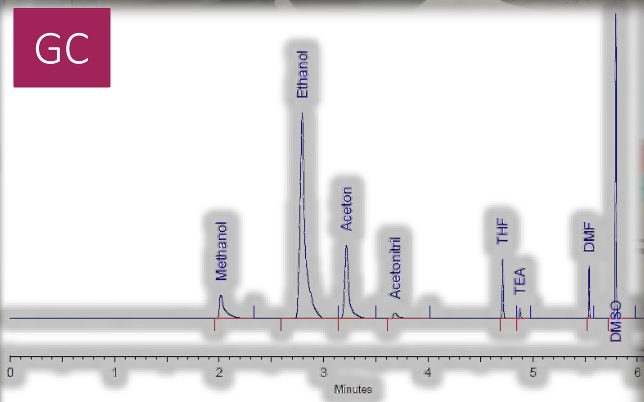
Automated and remotely controlled synthesis module

[^{18}F]FDG STERILISATION AND DISPENSING IN GMP FACILITY

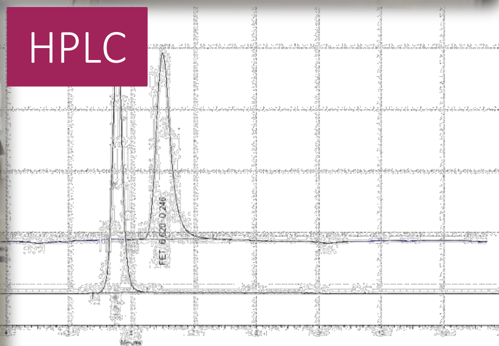


QUALITY CONTROL

GC



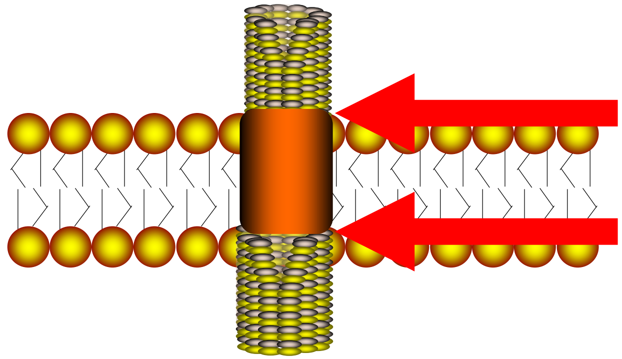
HPLC



also:
Endotoxins
pH...

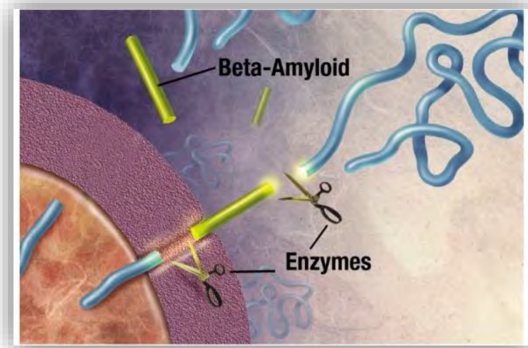
ALZHEIMER'S DISEASE:

Amyloid cascade hypothesis



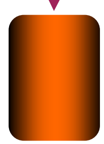
β-Secretase

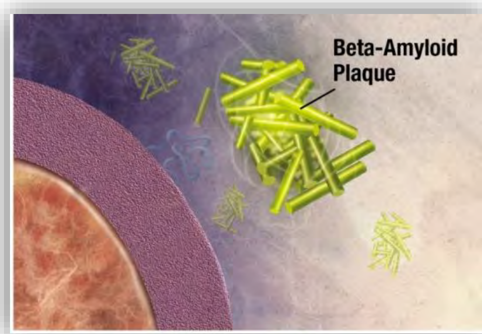
γ-Secretase



APP mutations
Presenilin 1 mutations
Presenilin 2 mutations

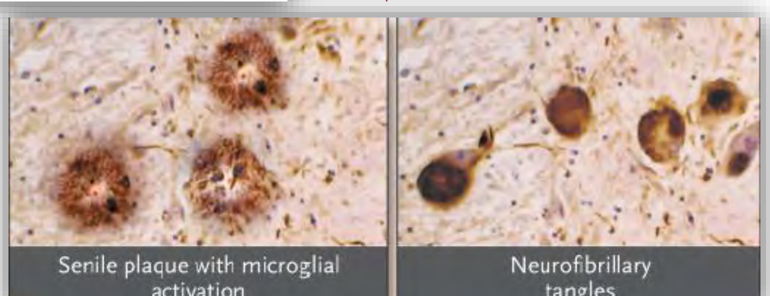
→ Increase of Aβ production





Lipoprotein ε4
LRP
Cholesterol
α2 Macroglobuline

→ Aggregation triggered and clearance reduced

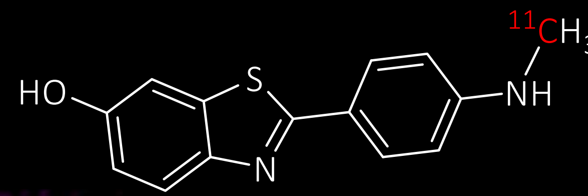


Senile plaque with microglial activation

Neurofibrillary tangles

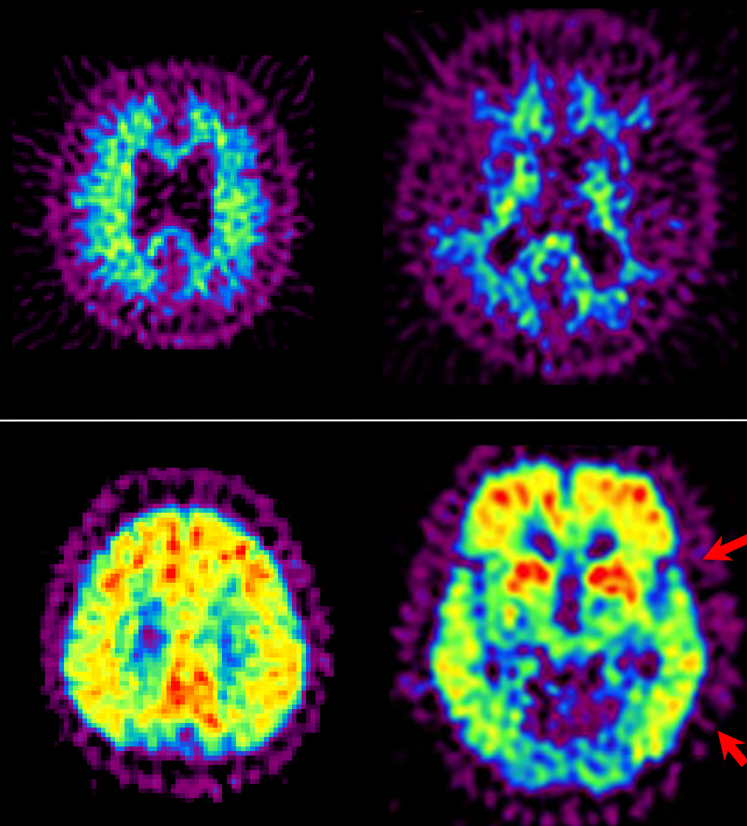
AMYLOID IMAGING BY [^{11}C]PIB-PET

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



Control

Alzheimer‘s disease



Axial slices
caudal aspects

SUMMER SCHOOL 2018

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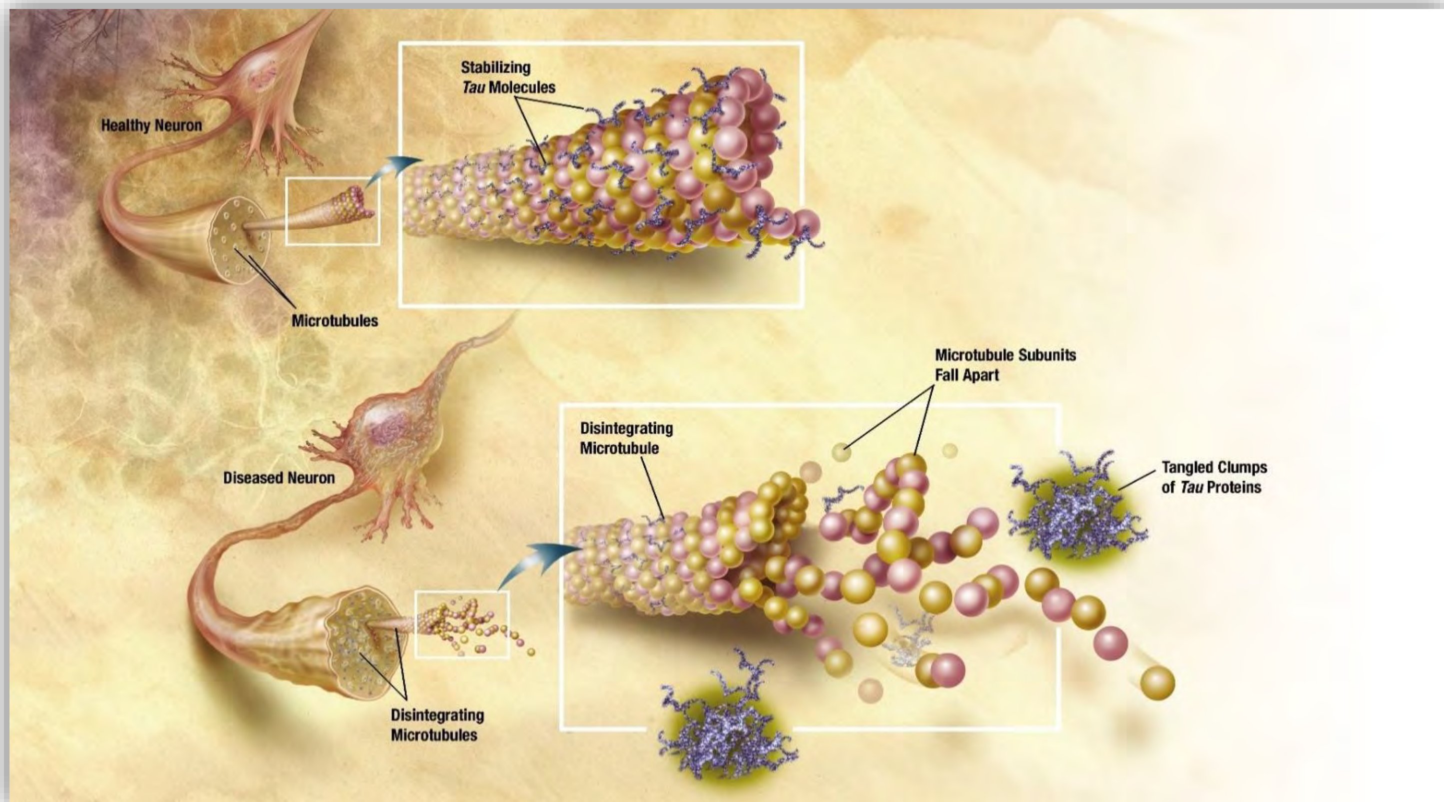
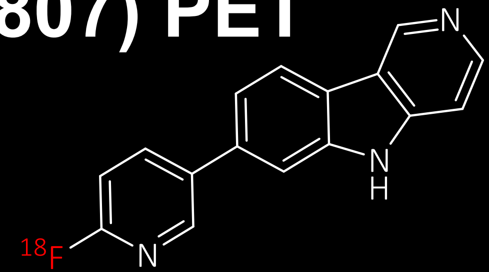
ALZHEIMER’S DISEASE:

Tau-hypothesis



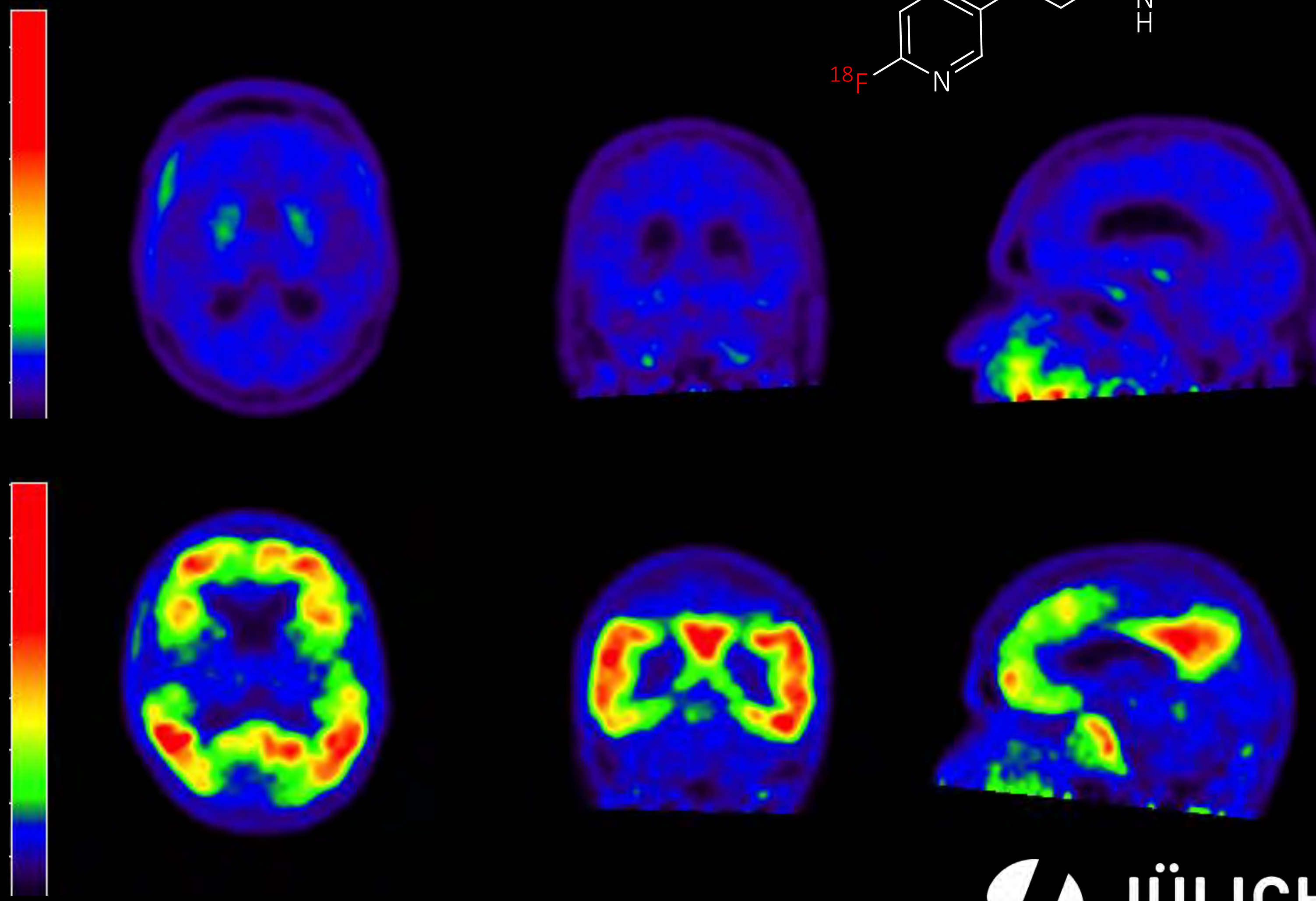
- Hyperphosphorylation of tau protein
- Disintegration of microtubules in brain cells
- Malfunctions and death of neurons
- AD pathogenesis development

TAU IMAGING BY [^{18}F]AV1451 (T807) PET



Healthy control person

Alzheimer‘s disease



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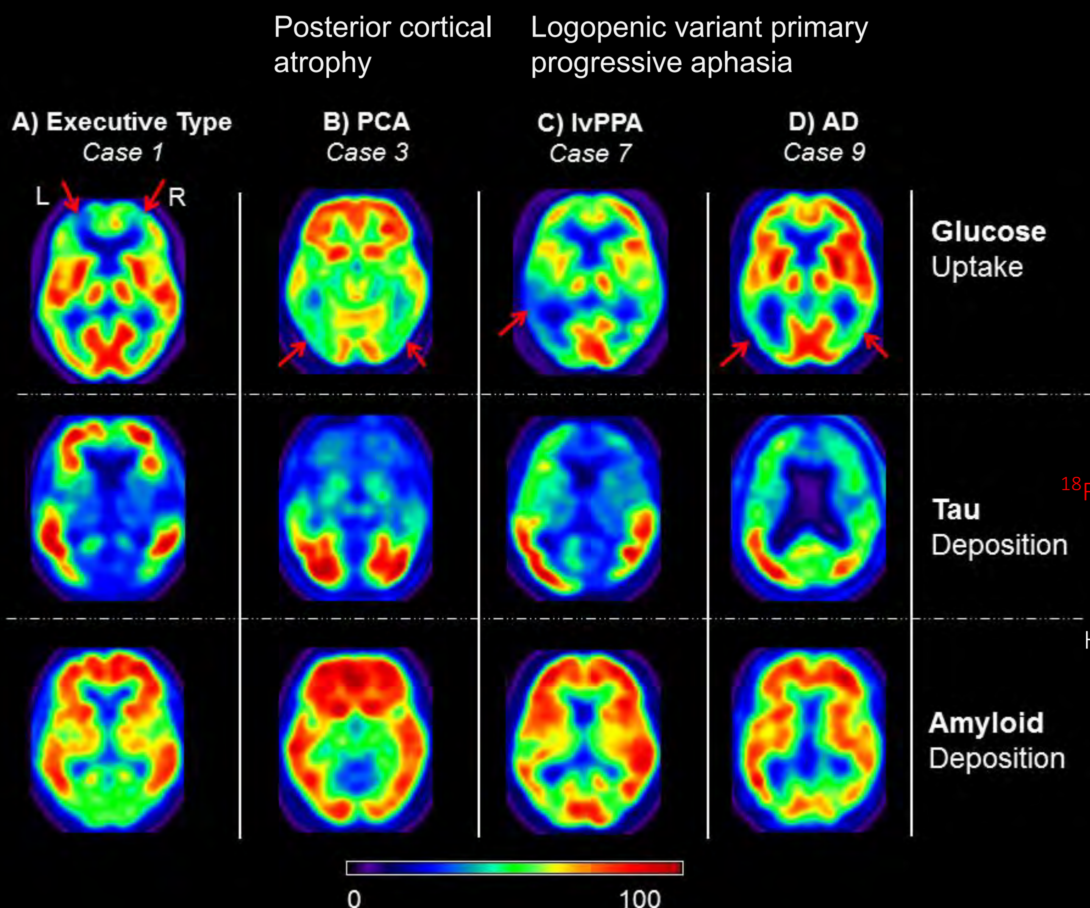
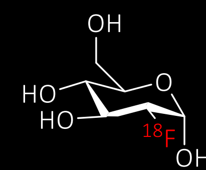
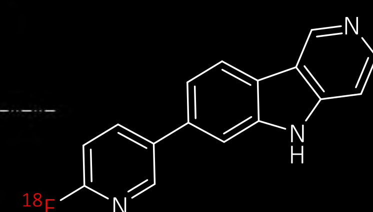
AMYLOID PLAQUE AND TAU IMAGING OF NEURO-DEGENERATIVE DISEASES USING [^{11}C]PIB AND [^{18}F]T807 PET

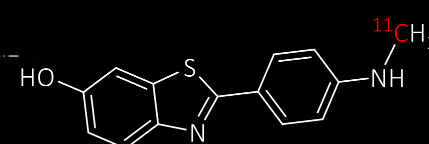




[^{18}F]FDG



[^{18}F]T807



[^{11}C]PiB

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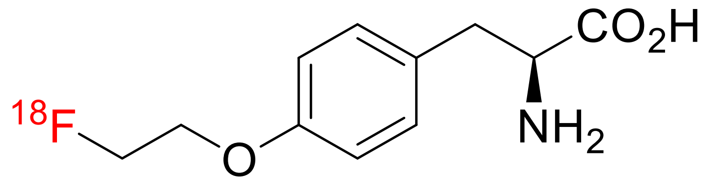
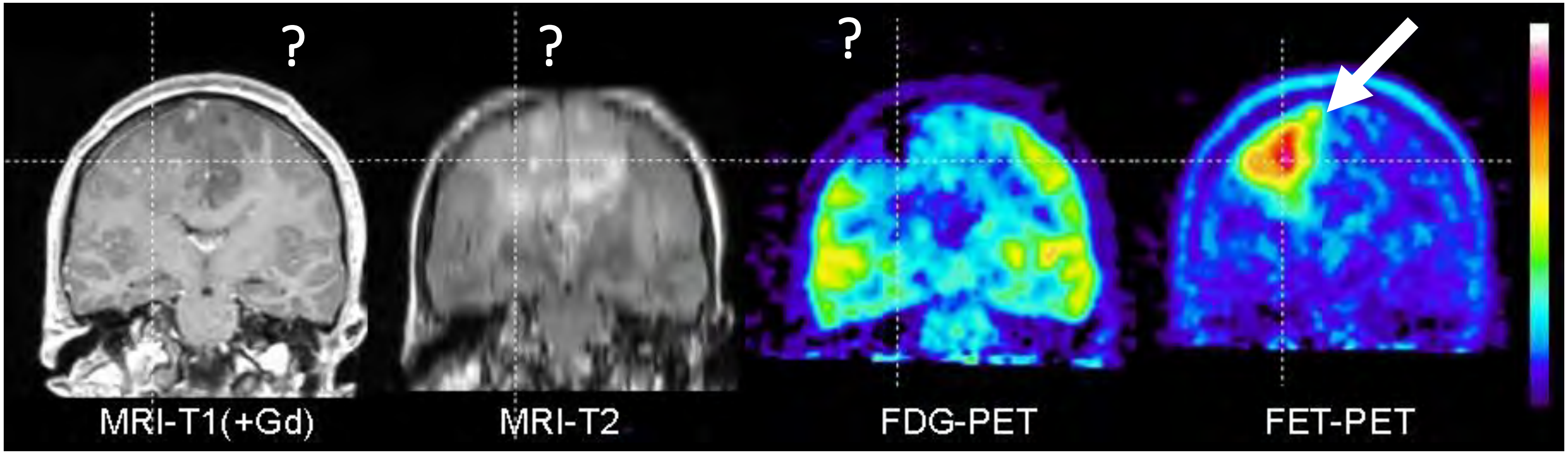
Dronse *et al*. J. Alzheimers Dis. 2017

IMAGING OF BRAIN TUMORS WITH [^{18}F]FET

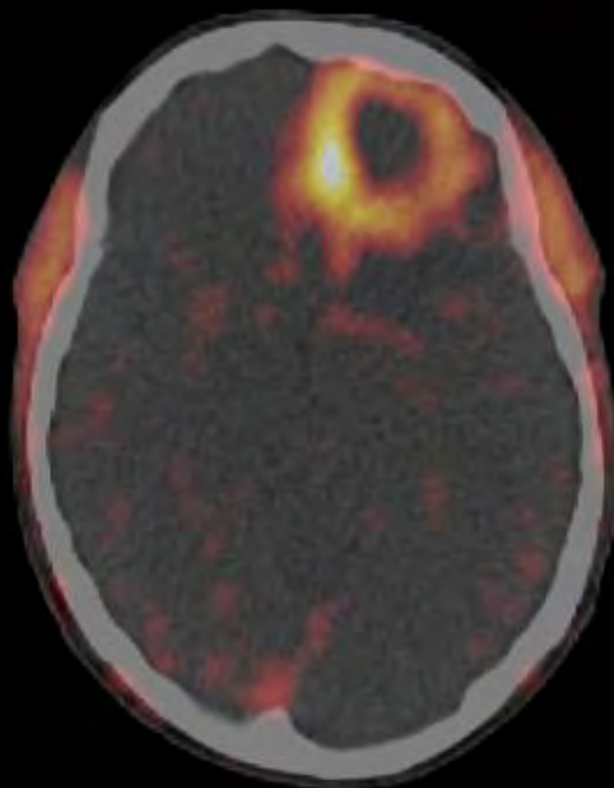




- Anaplastic Astrozytom Grade III:
- T1-and T2 weighted MRI do not allow differentiation of the tumor
- FDG PET indicates decreased glucose-metabolism in the region of the tumor
- In contrast FET PET allows precise differentation of the solid tumor

[illegible] ble.

[illegible] with high resolution



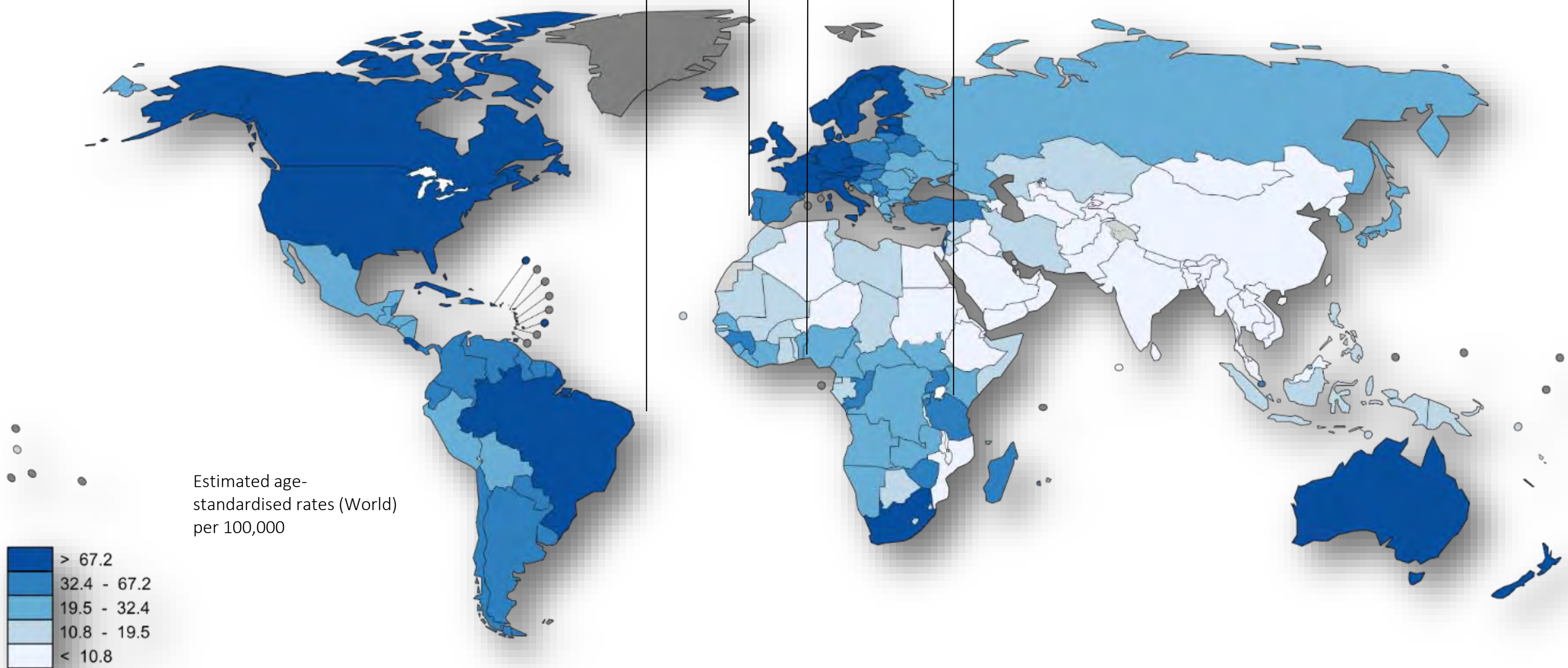
CLINICAL NEED: PROSTATE CARCINOMA (PCa)

second most frequently diagnosed cancer worldwide

incidence rates highest in developed countries

1,1 million men with PCa (2012)

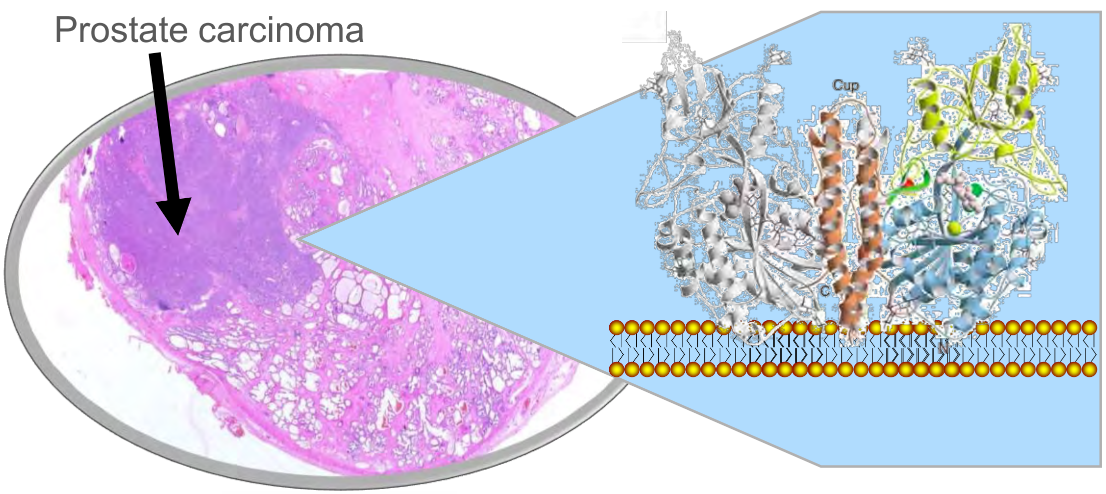
sixth leading cause of cancer death in males



…to enable best treatment options early detection of PCa and recurrent prostate cancer and/or metastases is required

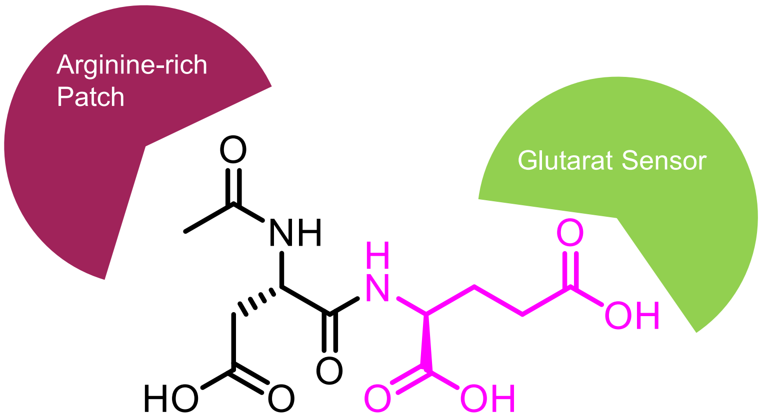
PSMA AS A MOLECULAR TARGET FOR PET

Prostate-**S**pecific-**M**embrane-**A**ntigen (aka GCPII)

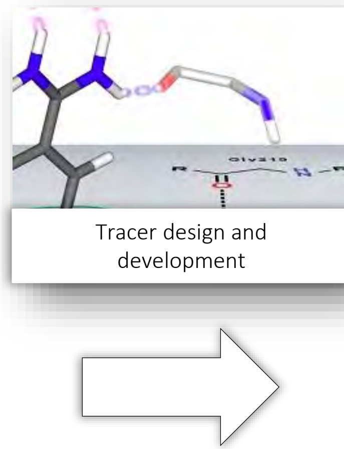


- Membrane-bound zinc metallopeptidase
- High expression in the ephithel cells of most PCa tumors
- Attractive Target for radiolabeled Ligands

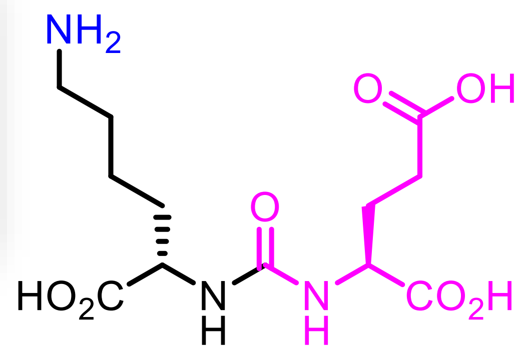
DEVELOPMENT OF SUITABLE PSMA-PET LIGAND



N-Acetylaspartylglutamic acid (NAAG)



Kozikowski *et al.* (2001)

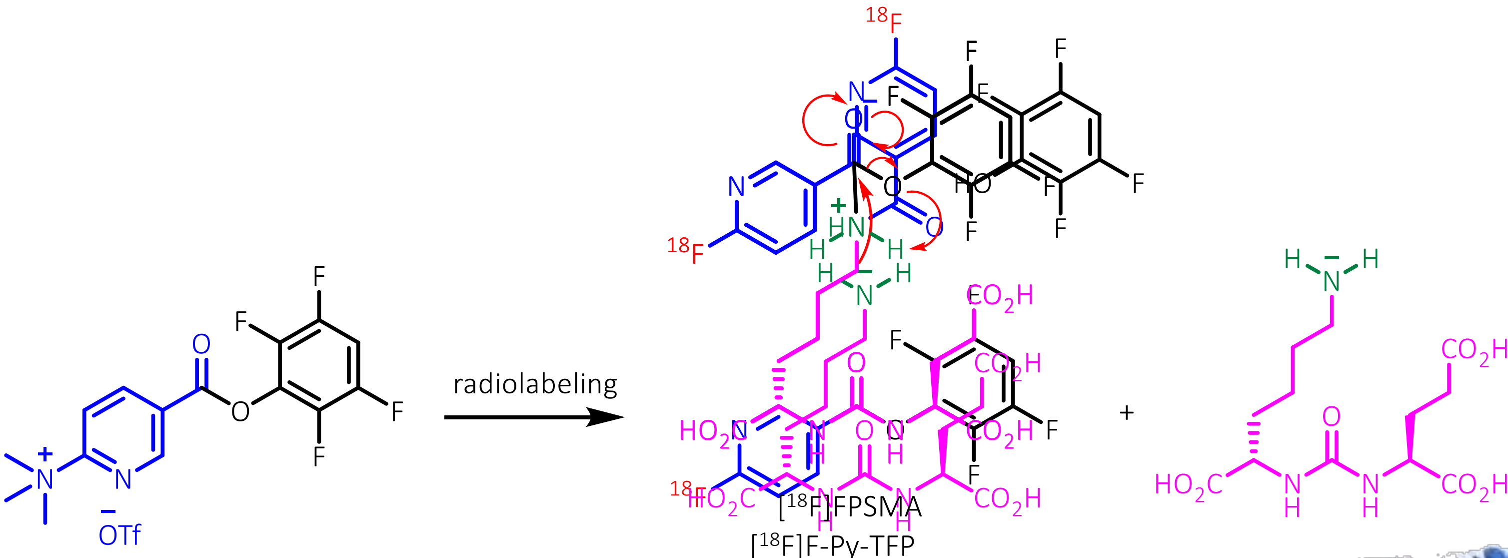


(*S*)-Lys-Urea-(*S*)-Glu

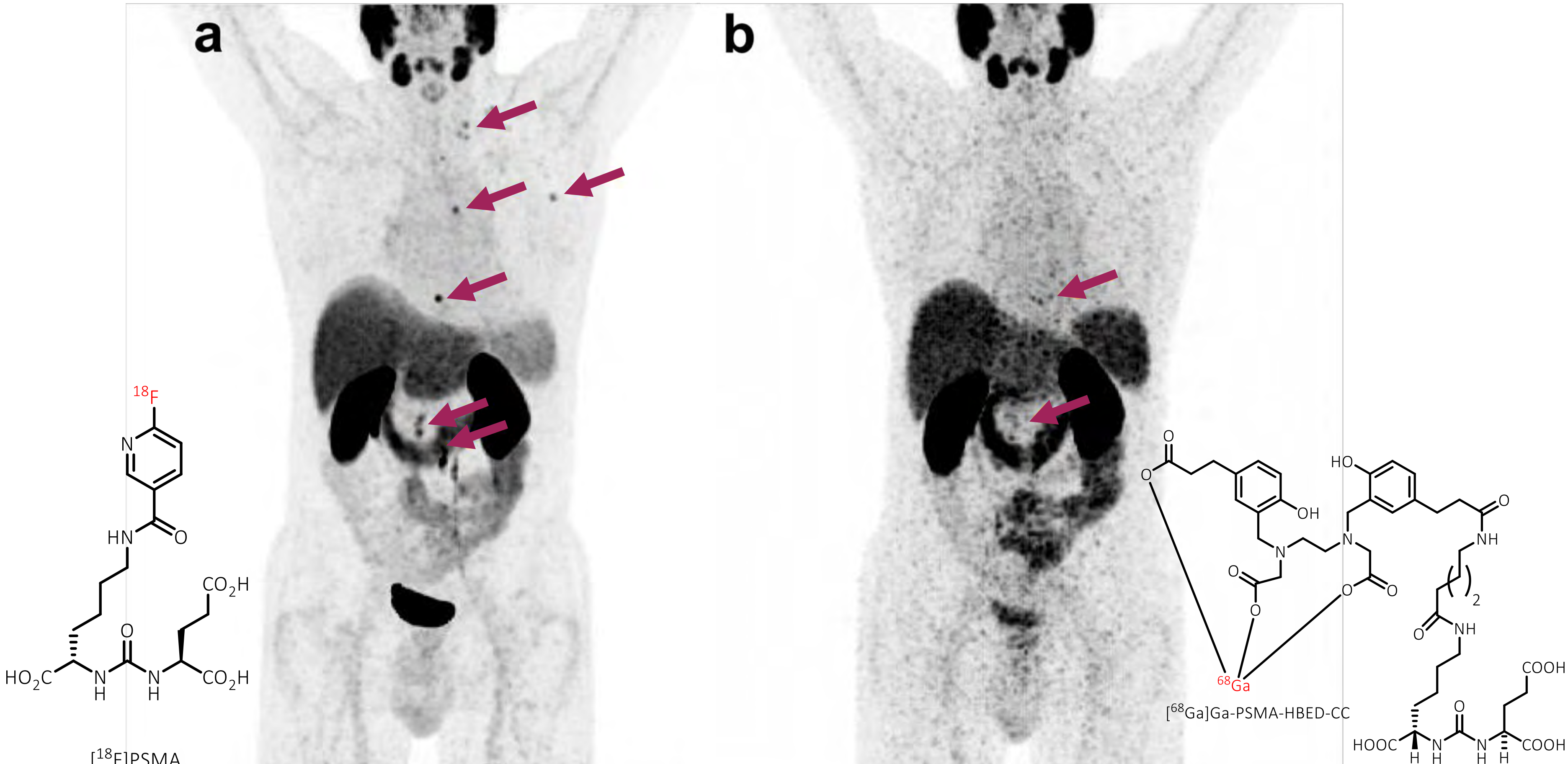
- Endogenous ligand of PSMA
- *in-vivo*: Cleavage to *N*-acetylaspartate and glutamate => short plasma half life
- Not suitable as PET probe

- Development of PSMA inhibitor
- High affinity for PSMA
- High metabolic stability
- Suitable for radiolabeling by prosthetic groups

RADIOSYNTHESIS OF [^{18}F]PSMA



[^{18}F]DCFPYL SUPERIOR TO [^{68}GA]PSMA-HBED-CC PET/CT



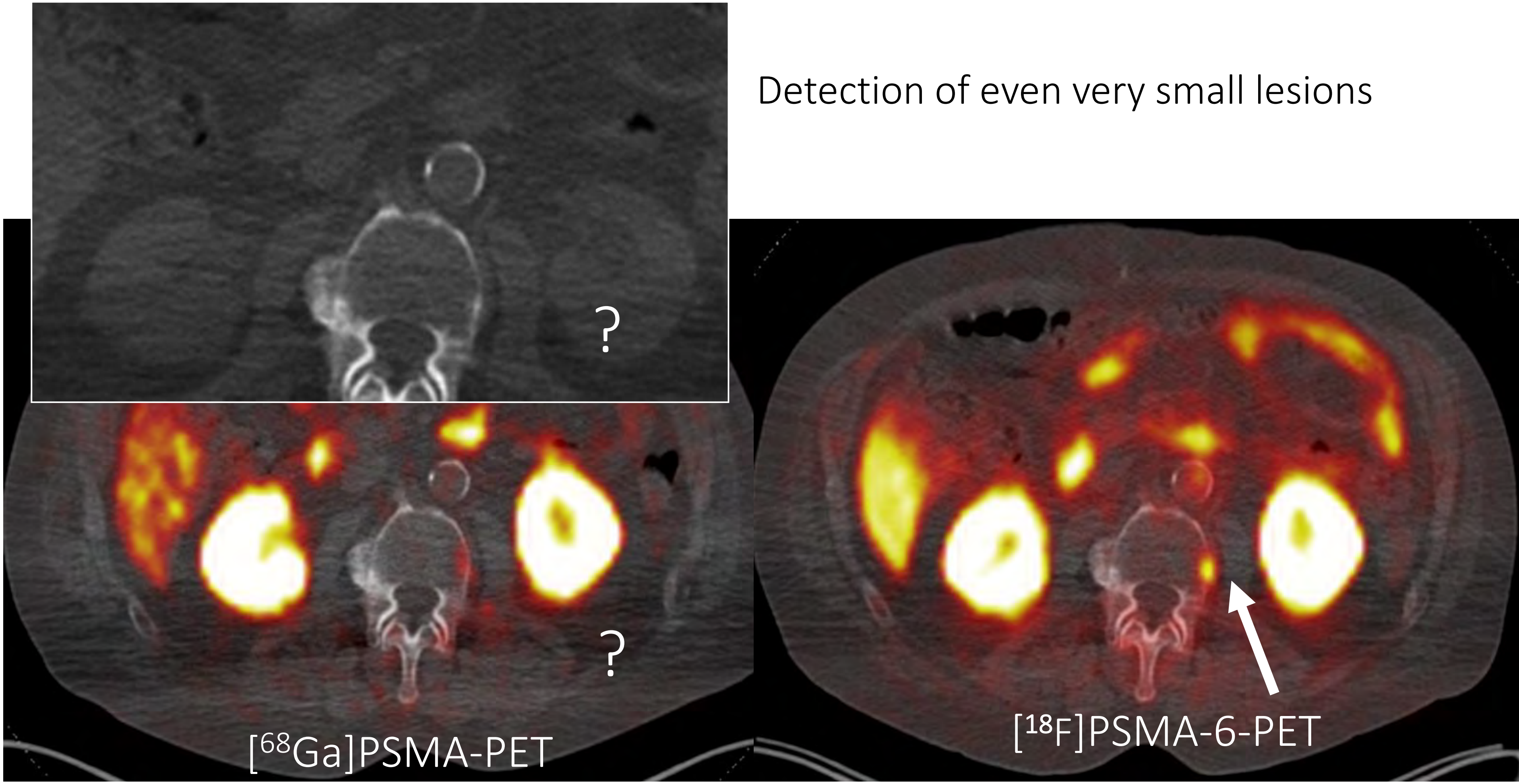
[^{18}F]PSMA

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

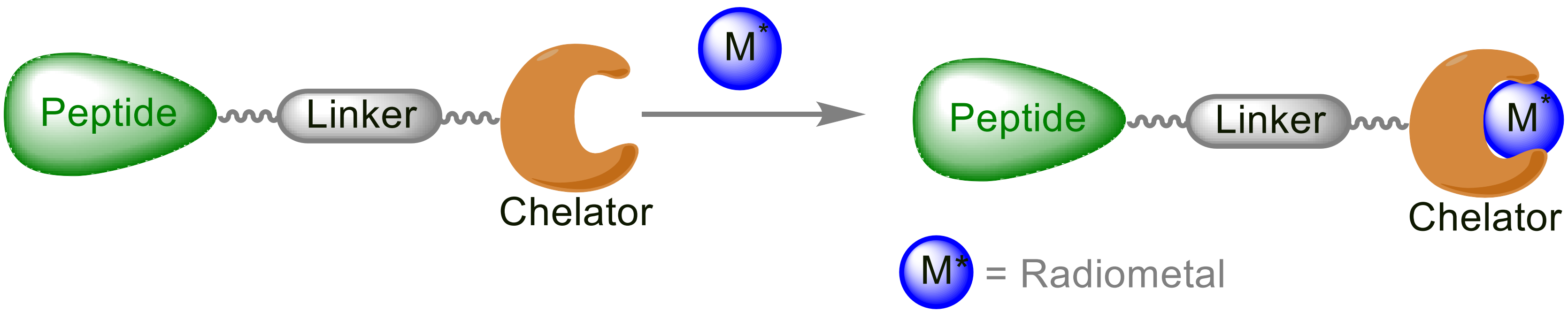
Courtesy of C. Kobe, M. Dietlein, Nuklearmedizin UKK

IMAGING OF PCA BONE METASTASIS BY [^{18}F]PSMA-6-PET

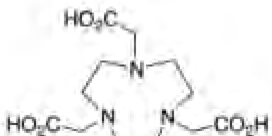
Detection of even very small lesions

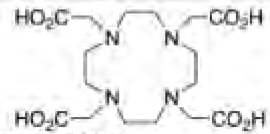


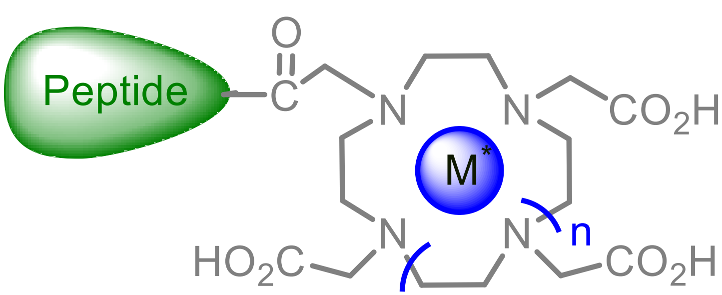
LABELING WITH RADIOMETALS



APPLICATION OF RADIOMETALS WITH SUITABLE CHELATORS

Chelator and common bifunctional derivatives	Radiometal ion	a	Radiolabeling conditions
 NOTA, 1,4,7-triazacyclononane-1,4,7-triacetic acid, CN = 6, N_3O_3	$^{64}Cu^{2+}$	✓	25 °C, 30–60 min, pH 5.5–6.5
	$^{67/68}Ga^{3+}$	✓	25 °C, 30–60 min, pH 4.0–5.5
	$^{44/47}Sc^{3+}$	–	95 °C, 20–30 min, pH 4.0
	$^{111}In^{3+}$	–	60–95 °C, 20–30 min, pH 4.0–5.0

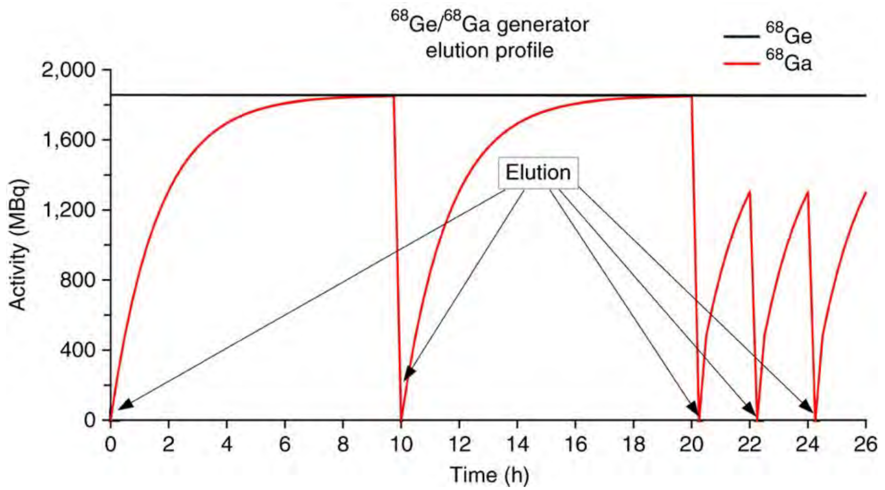
Chelator and common bifunctional derivatives	Radiometal ion	a	Radiolabeling conditions
 DOTA, 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid, maximum CN = 8, donor set N_4O_4	$^{64}Cu^{2+}$	–	25–90 °C, 30–60 min, pH 5.5–6.5
	$^{67/68}Ga^{3+}$	–	37–90 °C, 10–30 min, pH 4.0–5.5
	$^{44/47}Sc^{3+}$	✓	95 °C, 20–30 min, pH 4.0
	$^{111}In^{3+}$	✓	37–100 °C, 15–60 min, pH 4.0–6.0
	$^{177}Lu^{3+}$	✓	25–100 °C, 15–90 min, pH 4.0–6.0
	$^{86/90}Y^{3+}$	✓	25–100 °C, 15–90 min, pH 4.0–6.0
	$^{213}Bi^{3+}$	–	95–100 °C,[103] 5 min, pH 6.0–8.7
	$^{212}Pb^{2+}$	–	25–75 °C, 30–60 min, pH 4.0–5.5
	$^{225}Ac^{3+}$	✓	37–60 °C, 30–120 min, pH 6.0

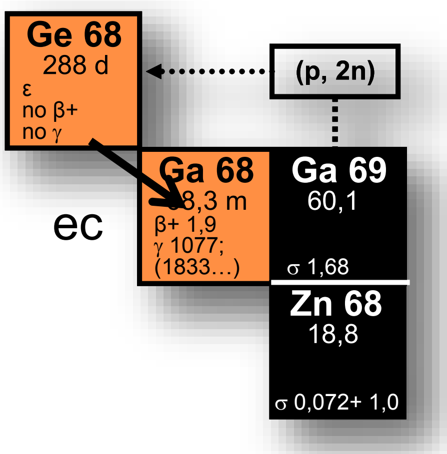


n=0,1,2 size of ring determines radiometals for chelation

Macrocyclic chelators offer enhanced metabolic stability

^{68}GA: GENERATOR RADIONUCLIDE





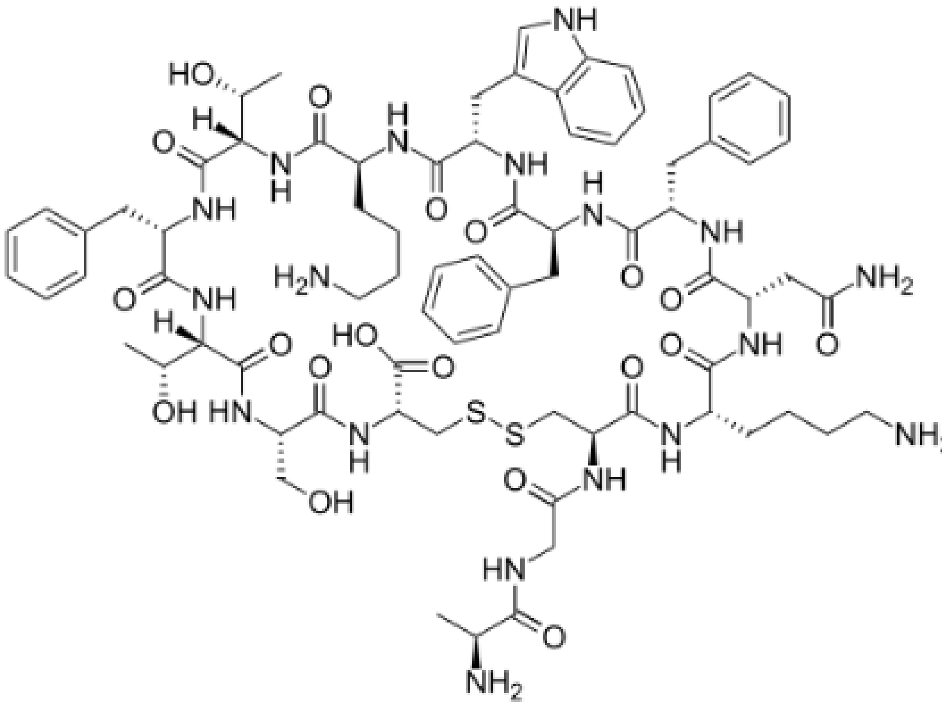
PEPTIDES FOR MOLECULAR IMAGING

F e a t u r e s   o f   r a d i o p e p t i d e s

- Small in size
- **Easy to synthesize**
- **Easy to radiolabel**
- Feasibility of kit formulation
- Amenable to chemical/molecular modifications
- Ability to attach a chelating agent at the C- or N-terminus of the peptide
- **High receptor binding affinity**
- High tumor penetration
- **Favorable pharmacokinetics**
- **Attain high concentration in target tissues**
- **Rapid clearance from the blood and non-target tissues**
- Rate and way of excretion can be modified
- Few side effects
- **Not immunogenic**
- Many possible targets

SOMATOSTATIN FOR TUMOR LABELING

- ✓ Overexpression of somatostatin receptors in most neuroendocrine tumors
- ✓ Most tumors express more than one receptor type

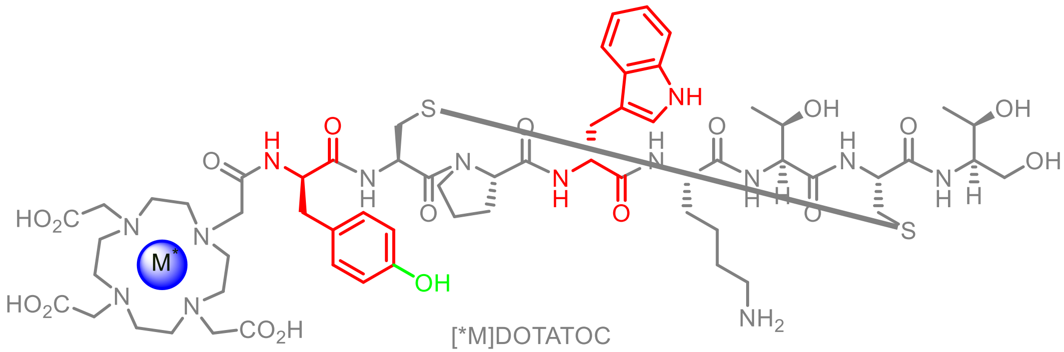


- – Somatostatin itself unsuitable for in vivo use (plasma half-life: 3 min)
- – Development of somatostatin analogs resistant to enzymatic degradation by different modifications of the natural molecule

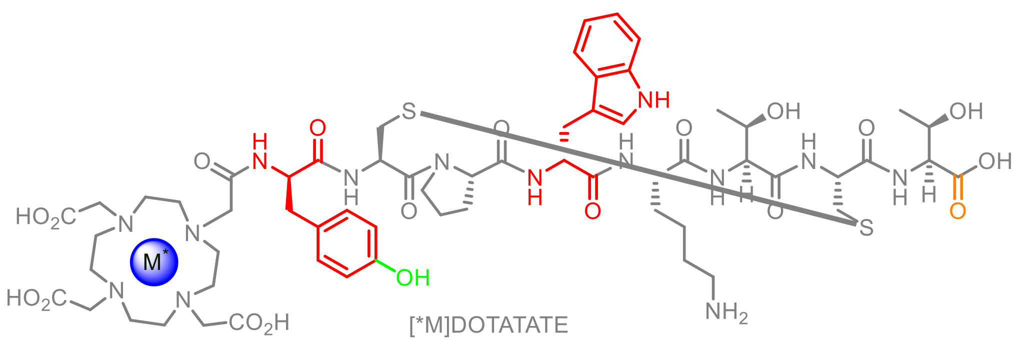
DOTATOC AND DOTATATE:

second generation ligands for somatostatin receptor imaging

- Tyrosine instead of phenylalanine: fair sst2 affinity

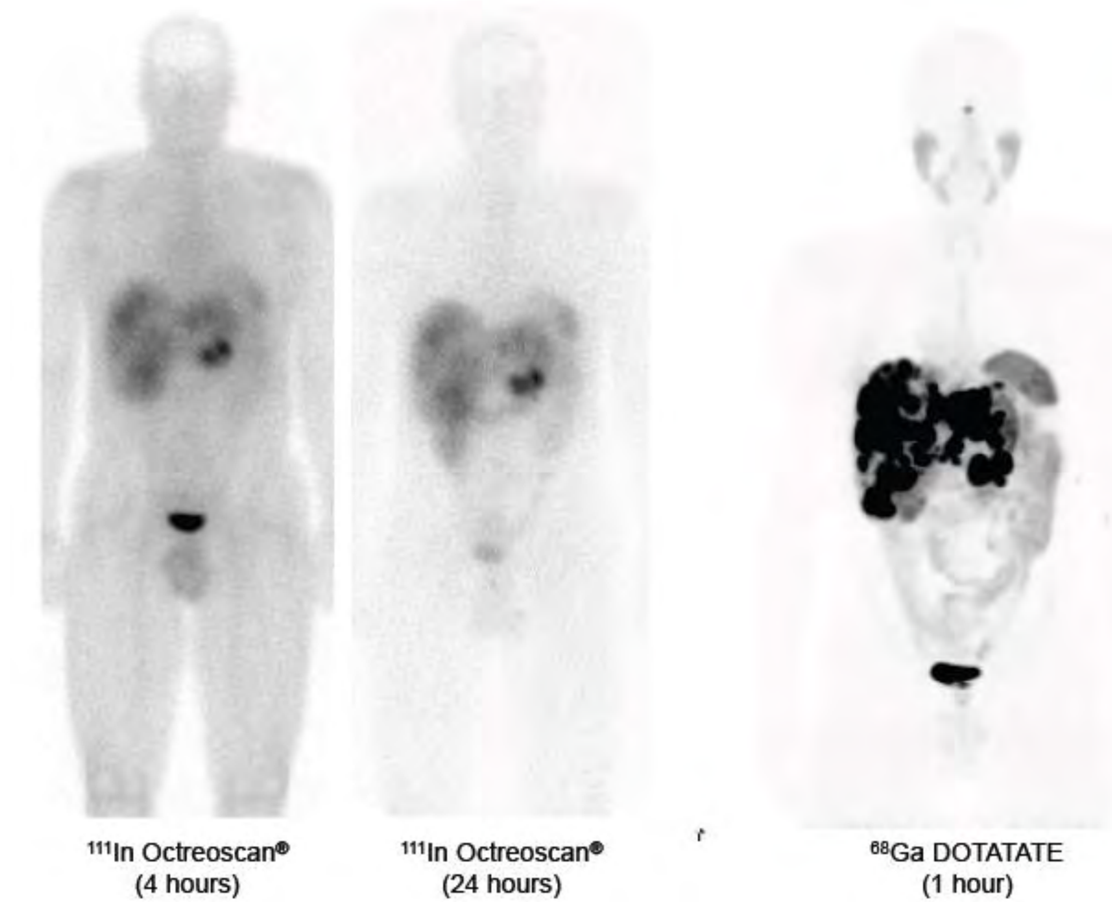


- Thr (threonine)(TATE) for Thr(ol) (TOC): enhanced sst2 affinity



OCTREOTATE VS. DOTATATE:

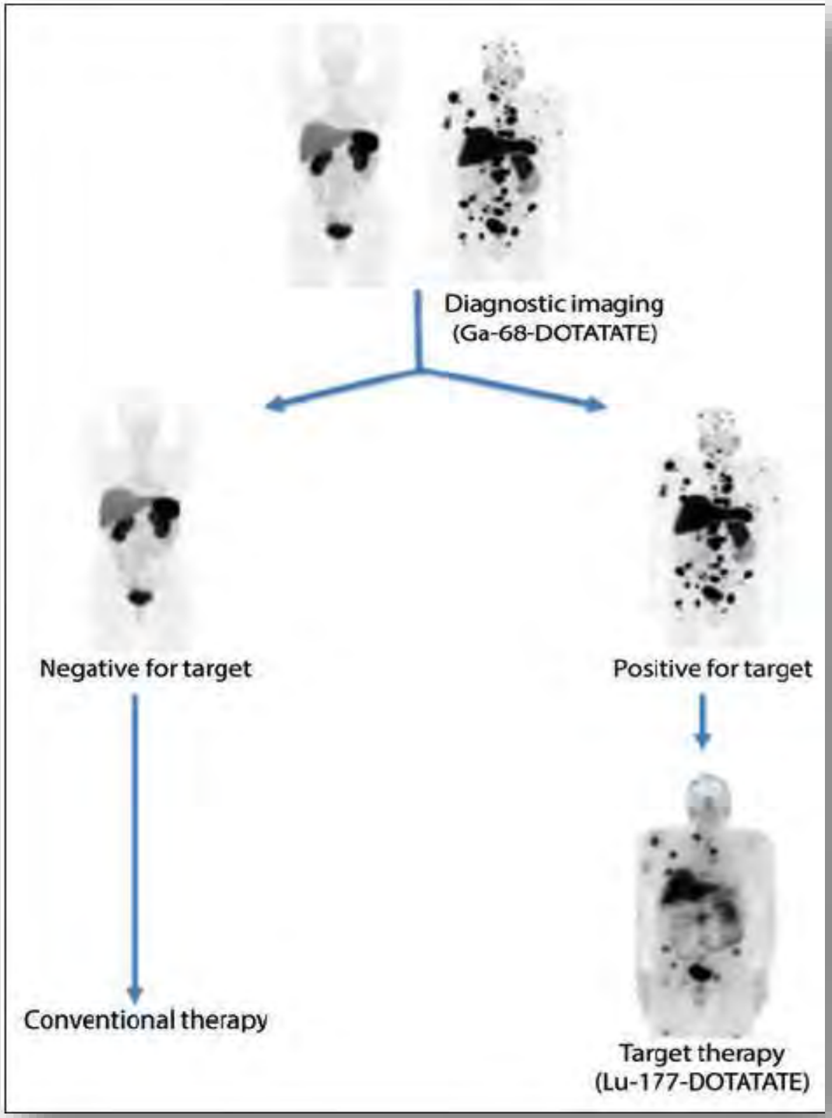
imaging of neuroendocrine tumors



^{68}Ga DOTATATE: faster, less radiation exposure for patients, higher resolution

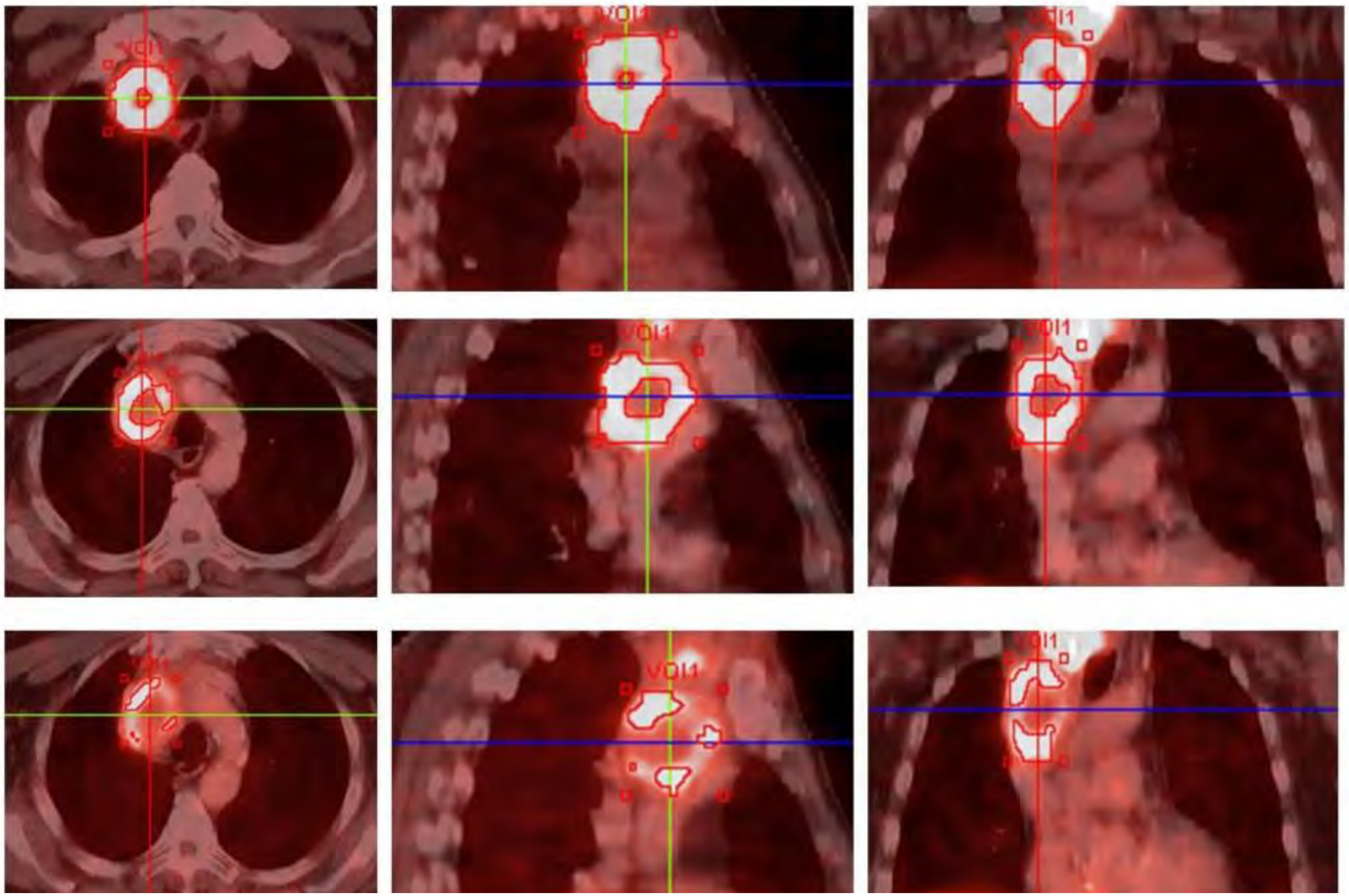
THERAPY AND DIAGNOSTICS IN ONE:

Theranostics



THERANOSTICS:

PRRT with 177Lu, PET/CT with 68Ga



Before PRRNT:

MTV = 63.5 ml
SUV = 8.6
MTI = 546.1

4 months after 1st PRRNT:

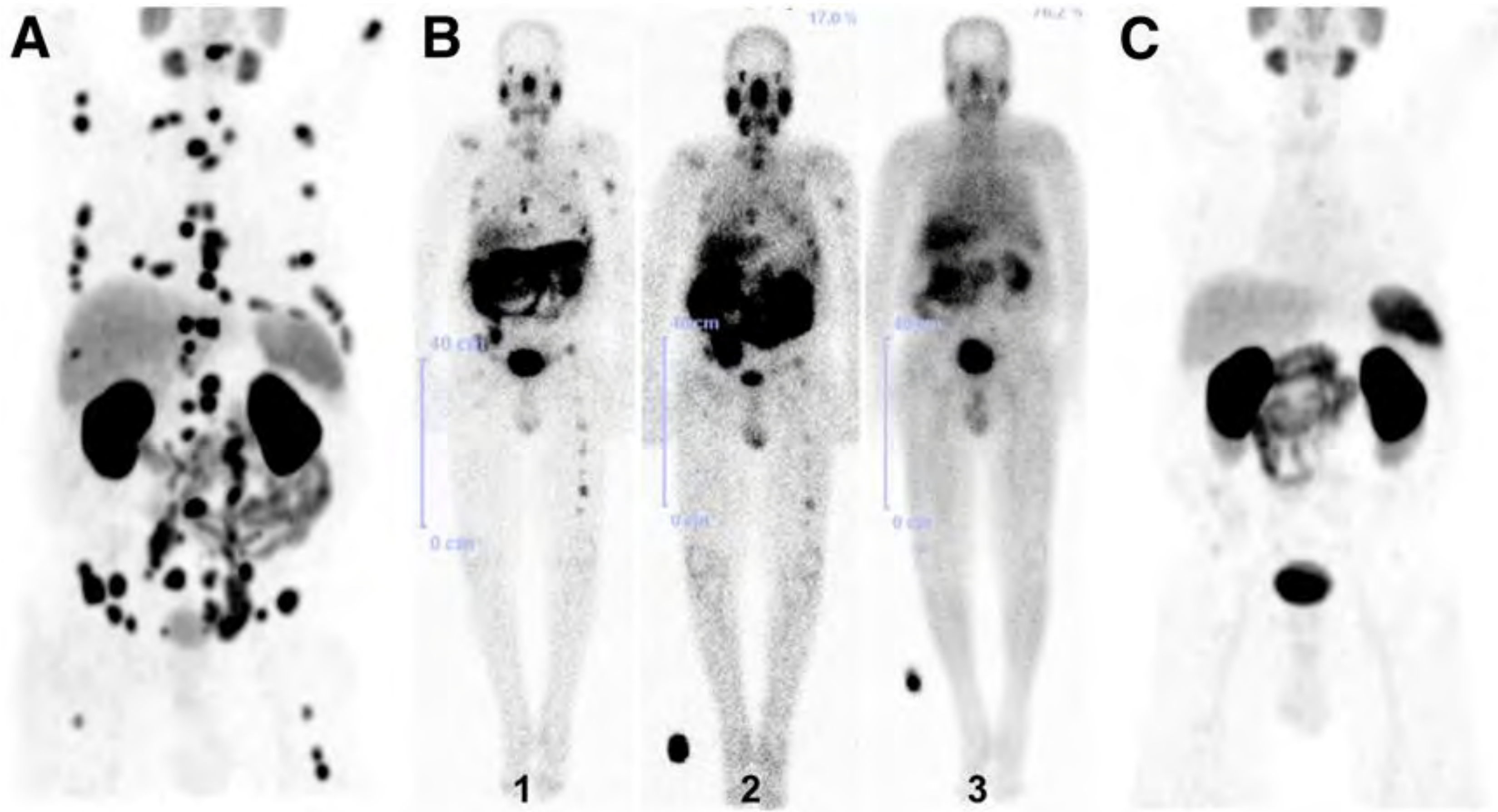
MTV = 49.4 ml
SUV = 7.4
MTI = 365.6

3 months after 2nd PRRNT:

MTV = 28.2 ml
SUV = 6.3
MTI = 177.7

THERANOSTICS:

PRRT with 177Lu, PET/CT with 68Ga (Prostate Cancer)



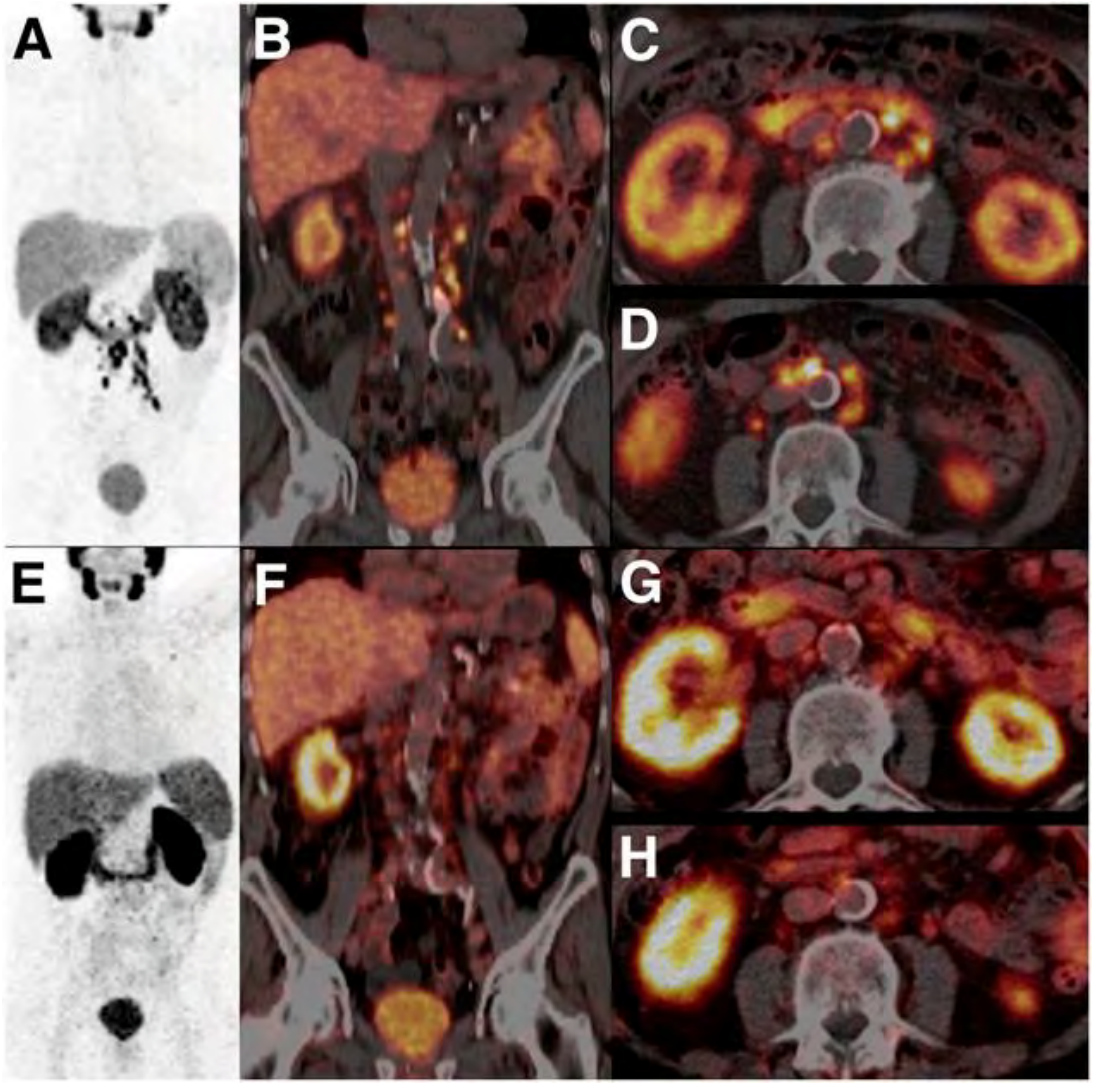
^{68}Ga-PSMA-PET ^{177}Lu PSMA-Therapy ^{68}Ga-PSMA-PET

THERANOSTICS:

PRRT with 177Lu, PET/CT with 68Ga (Prostate Cancer)

^{68}Ga-PSMA PET before therapy with ^{177}Lu-PSMA

^{68}Ga-PSMA PET after therapy with ^{177}Lu-PSMA



SUMMARY

- Molecular imaging using PET plays a leading role in many diagnostic algorithms in oncology
- Differential diagnosis of neurodegenerative diseases
- Theragnostic approaches will change therapy management in several oncological diseases
- Important contribution to individualized medicine