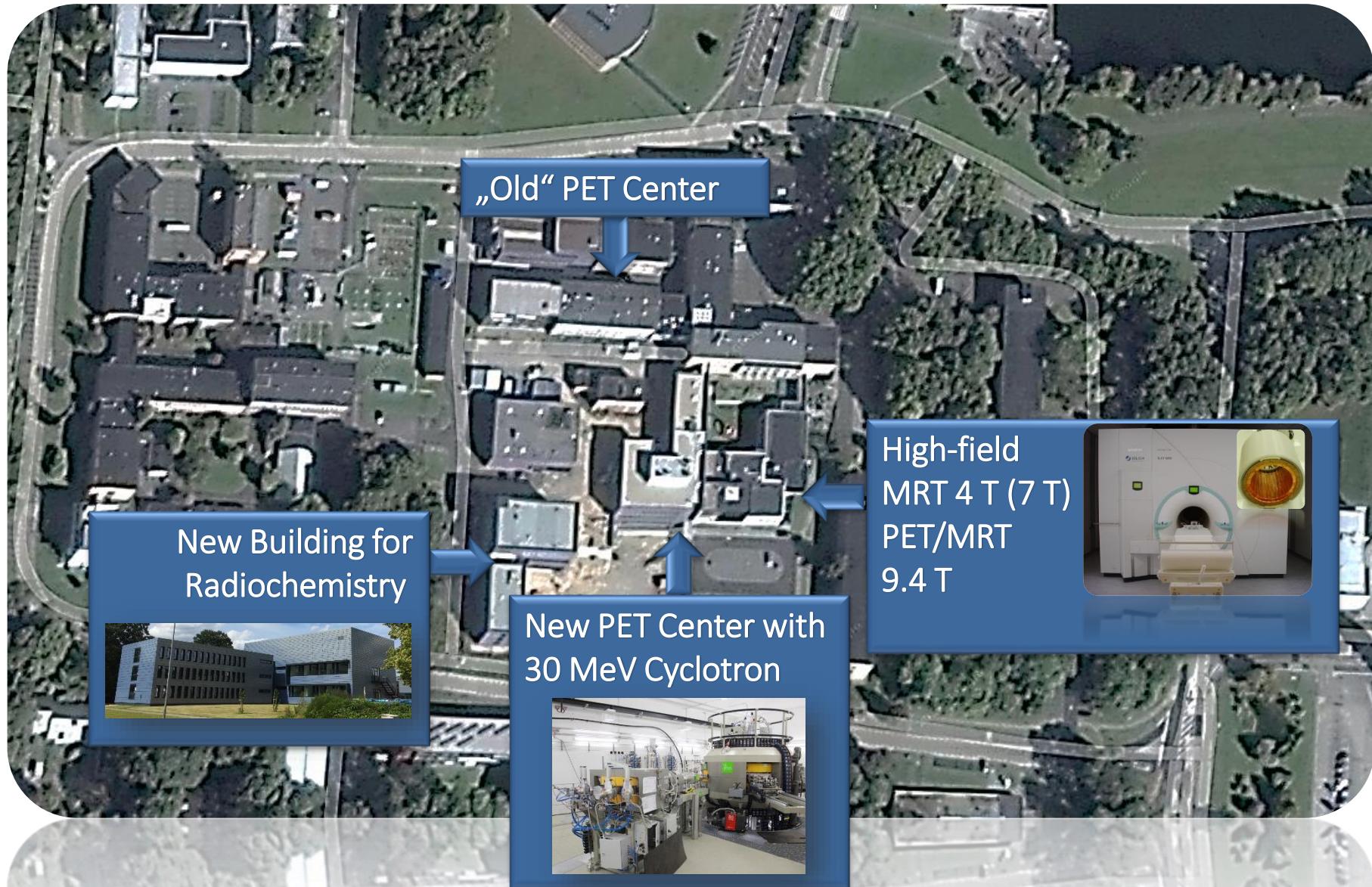




Institute of Neuroscience and Medicine (INM-5): Nuclear Chemistry

Kick-off meeting TSU
Selection Workshop

Infrastructure - Imaging Core Facility

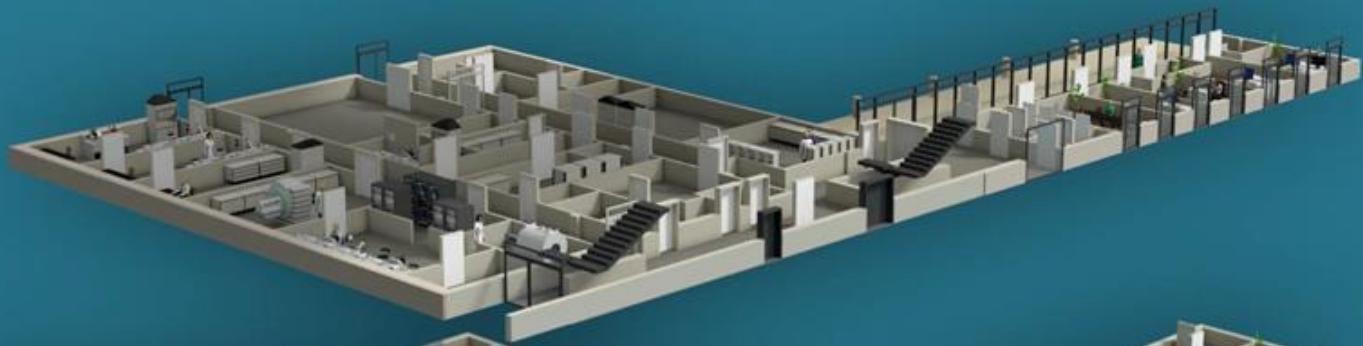


New PET-Center

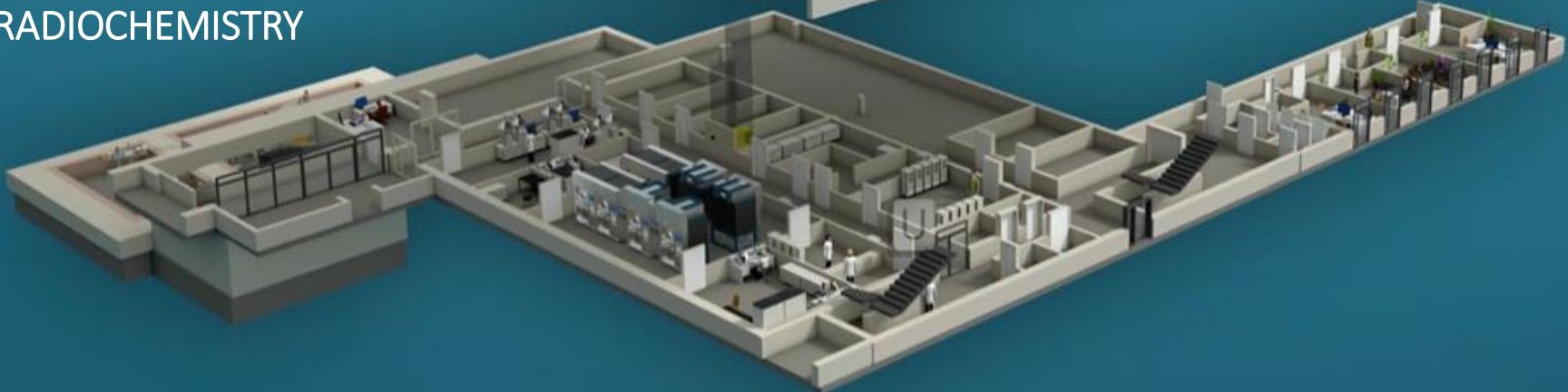
CLINICAL LEVEL



PRECLINICAL LEVEL



RADIOCHEMISTRY



Basement

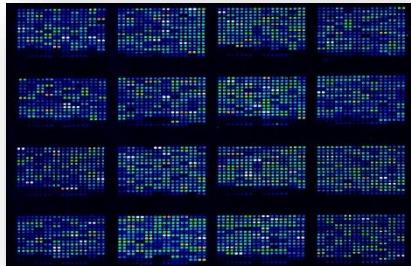
RADIOCHEMISTRY

Cyclotron

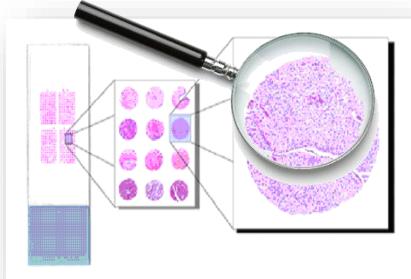
Hot cells for production of radiopharmaceuticals



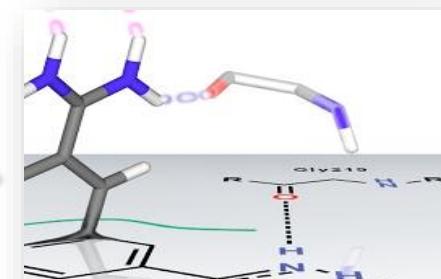
Development of molecular probes



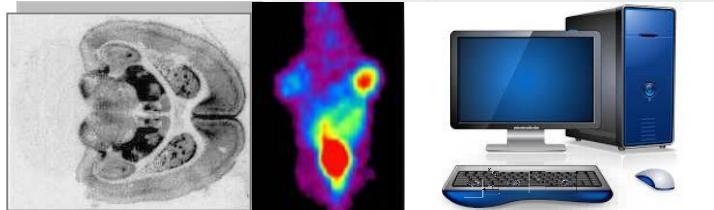
Molecular biological screening



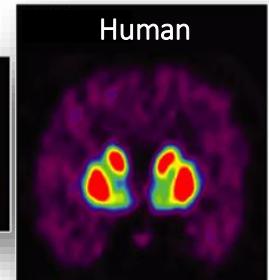
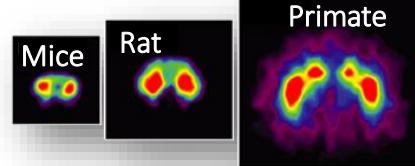
Selection of key processes and target lead structure identification



Tracer design, development and production

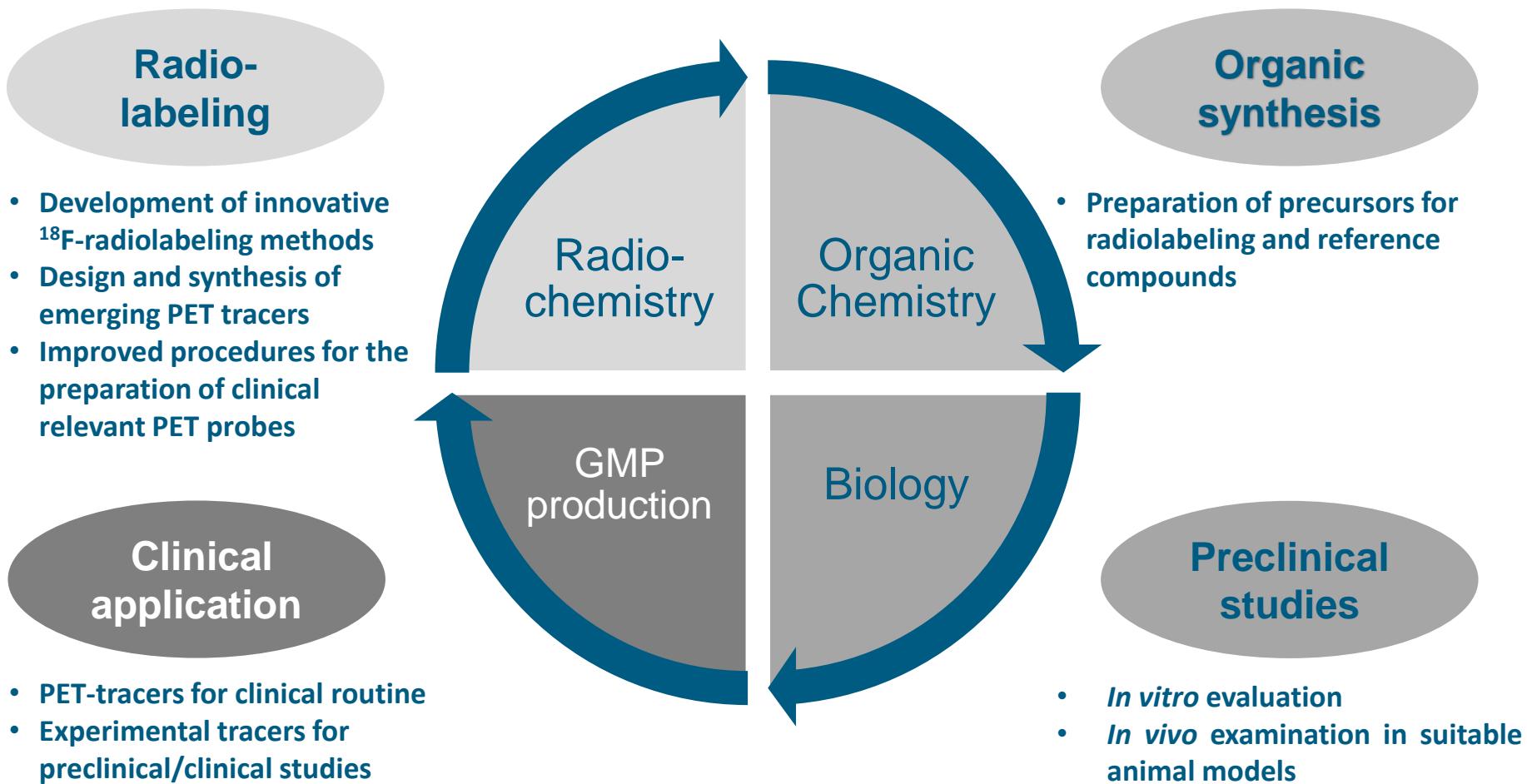


Preclinical evaluation, toxicity, metabolic stability, specificity, affinity, biodistribution



Translation into clinics
biodistribution, pharmacokinetics, pharmacodynamics, dosimetry, proof of efficacy in humans

Building blocks of the INM-5

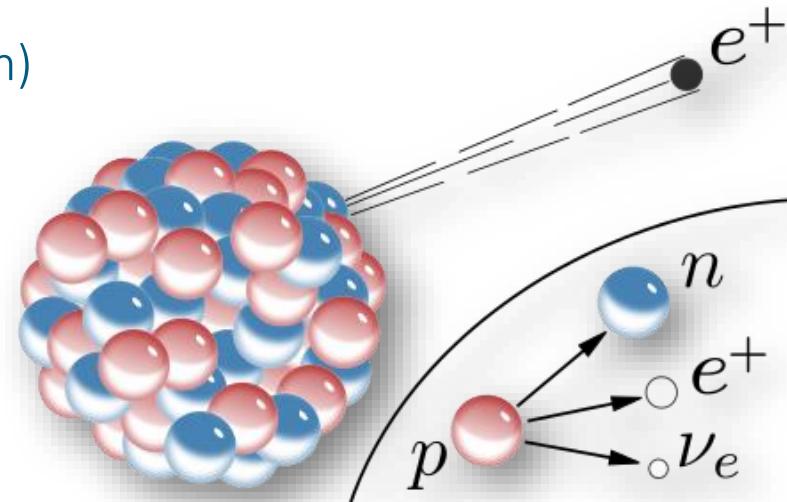


High performance cyclotron IBA Cyclone 30 XP

- High beam intensity (up to 300 mA)
 - Protons: 15–30 MeV
 - Deuterons: 7–15 MeV
 - α -particles: 30 MeV



- Short irradiation times (F-18: 10 min vs. 60 min)
- Dual beam mode (2 targets simultaneously)
- Production of non-standard radionuclides for diagnosis and therapy
(Cu-64, Br-77, I-124, At-211, Se-73)

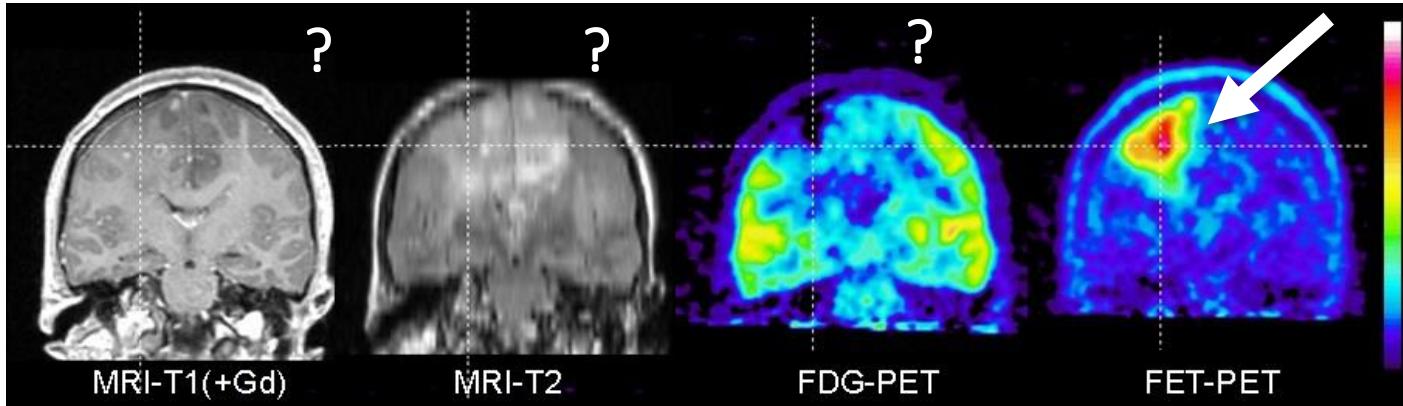
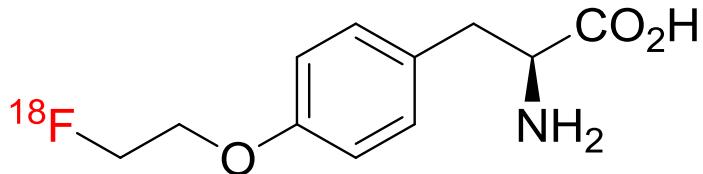


Nuclear Chemistry INM-5: *GMP-conform manufacturing of radiotracers*

TRACER	MOLECULAR TARGET
[¹⁵ O]H ₂ O	Perfusion
[¹⁸ F]Florbetaben	Amyloid
O-[¹⁸ F]Fluoroethyl-L-tyrosine	AA-transport
cis-2-[¹⁸ F]Fluoro-D-proline	AA-transport
[¹⁸ F]CPFPX	A ₁ -Rezeptor
[¹⁸ F]FP-CIT	DAT
[¹¹ C]Raclopride	D ₂ -Rezeptor
[¹¹ C]Flumazenil	Benzodiazepine
[¹¹ C]ABP-688	mGlu-5
[¹⁸ F]Altanserin	5-HT _{2A}
[¹⁸ F]T807	Neurofibrillary tangles
[¹⁸ F]DCFPyL	PSMA
[¹⁸ F]DPA-714	TSPO
[¹⁸ F]DAA1106	TSPO



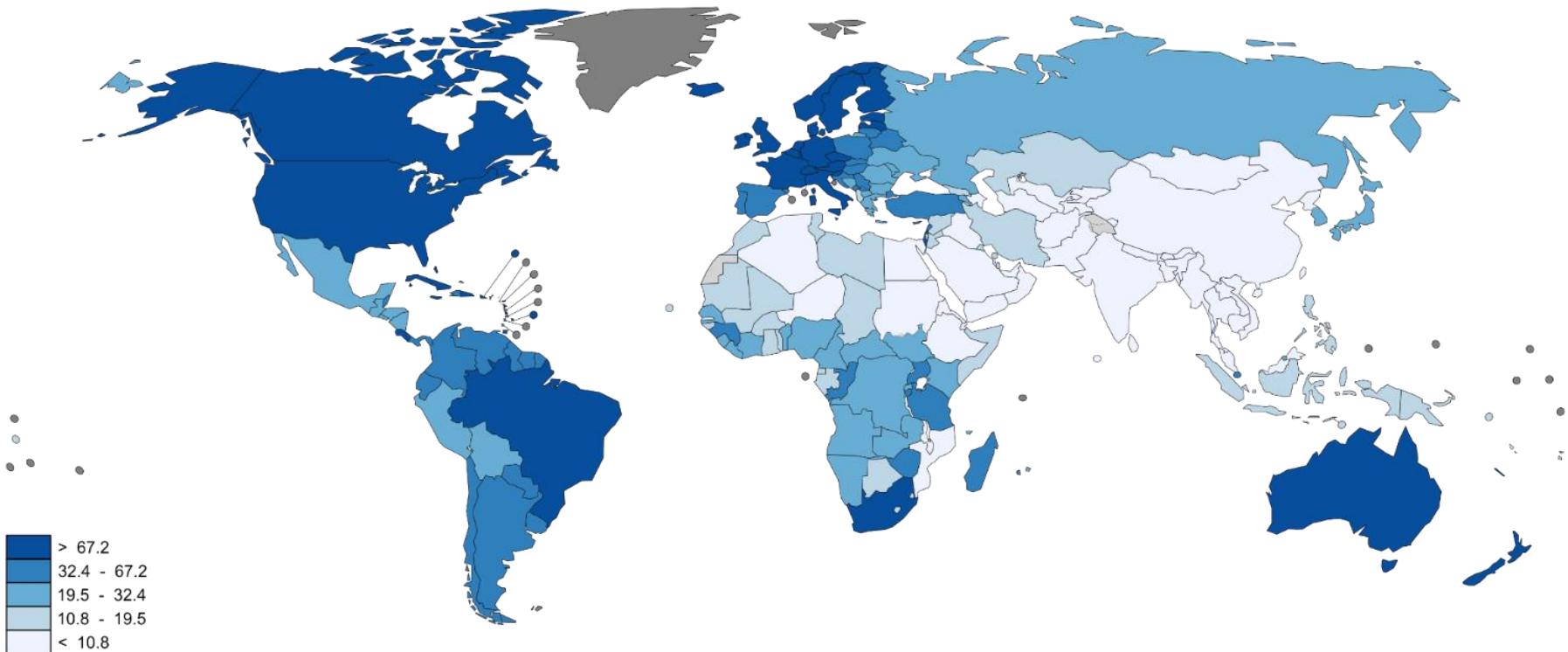
Imaging of brain tumors with [¹⁸F]FET



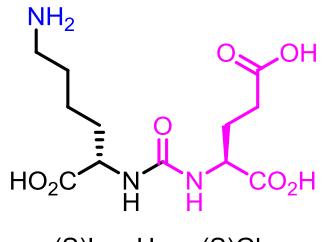
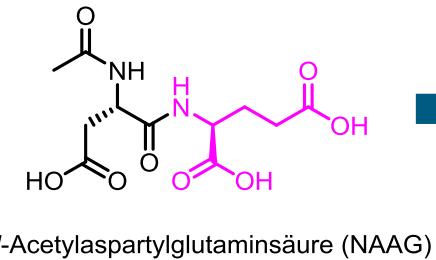
- Anaplastic Astrozytom Grade III:
- T1-and T2 weighted MRI do not allow differentiation of the tumor
- FDG PET indicates decreased glucose-metabolism in the region of the tumor
- In contrast FET PET allows precise differentiation of the solid tumor

Prostate carcinoma (PCa)

- second most frequently diagnosed cancer worldwide
- sixth leading cause of cancer death in males

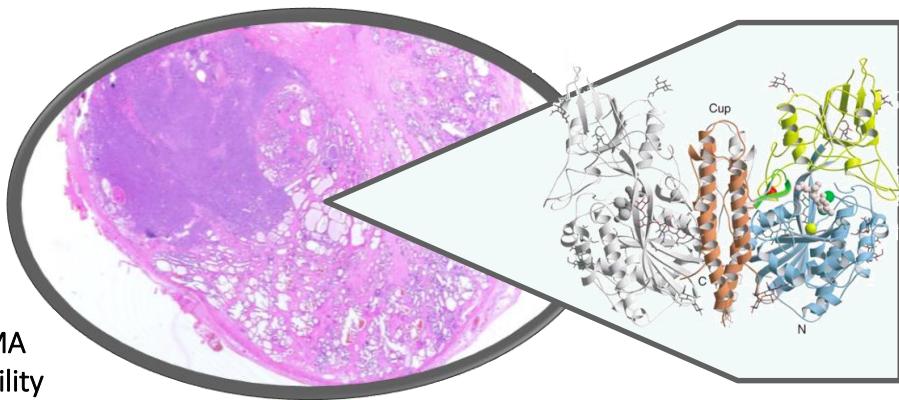


Prostate cancer detection by PSMA selective tracers

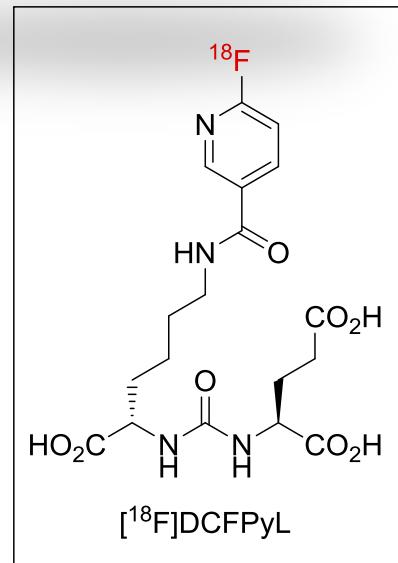
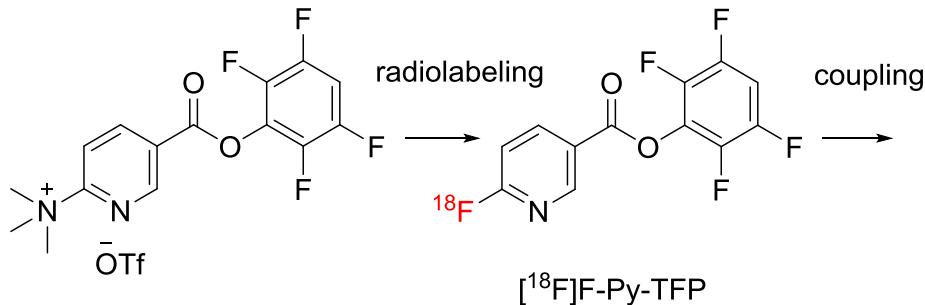


- Natural ligand of PSMA
- High affinity for PSMA
- High metabolic stability
- Amenable for labeling

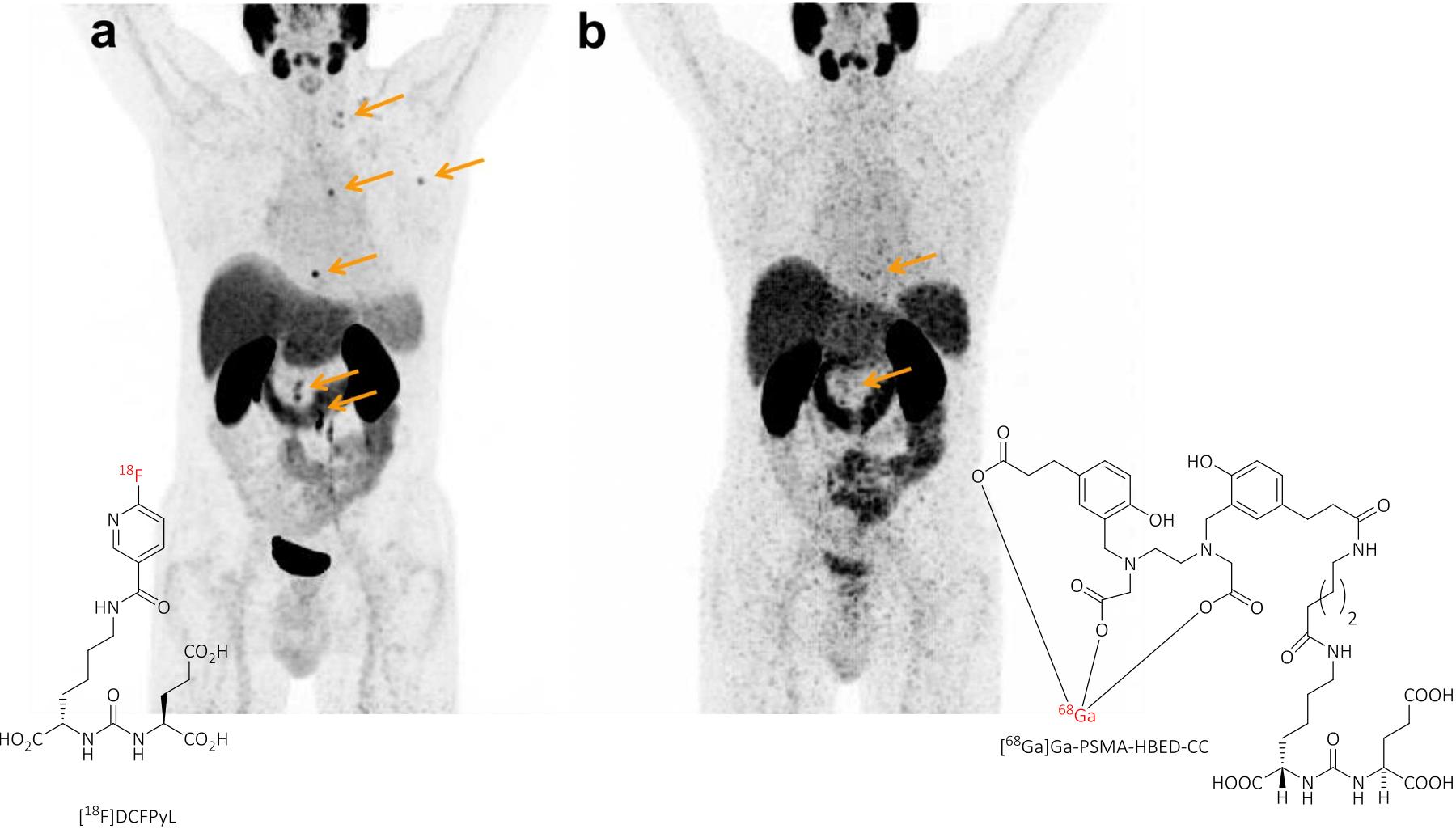
Prostate cancer



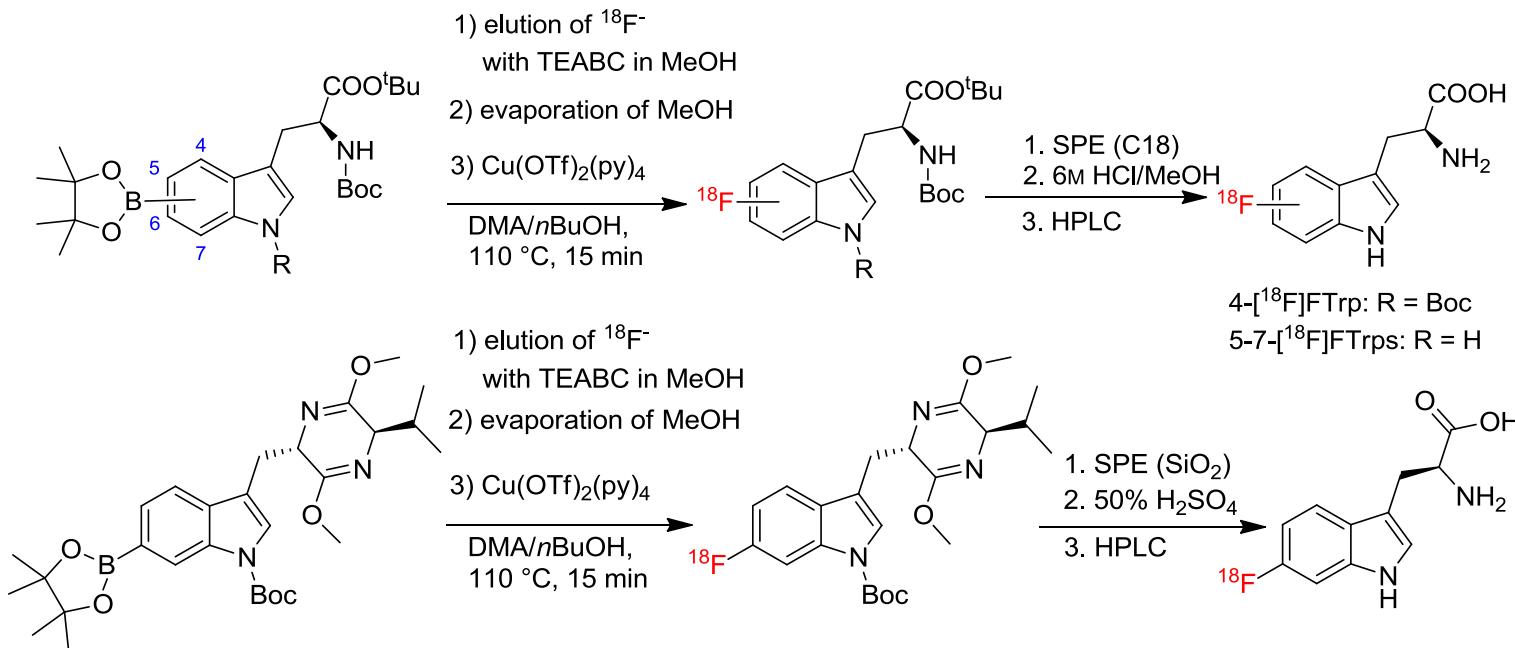
PSMA



[¹⁸F]DCFPyL superior to [⁶⁸Ga]PSMA-HBED-CC PET/CT



Preparation of [¹⁸F]Fluorotryptophans



Man. Synth. (RCY) Aut. Synth (RCY)

4-[¹⁸ F]FTrp	39±12 %	21±2 %
5-[¹⁸ F]FTrp	53±5 %	37±8 %
6-[¹⁸ F]FTrp ^(a)	30±3 %	30±5 %
6-[¹⁸ F]FTrp ^(b)	41±4 %	37±5 %
7- [¹⁸ F]FTrp	42±5 %	37±5 %

a) Bislactim precursor

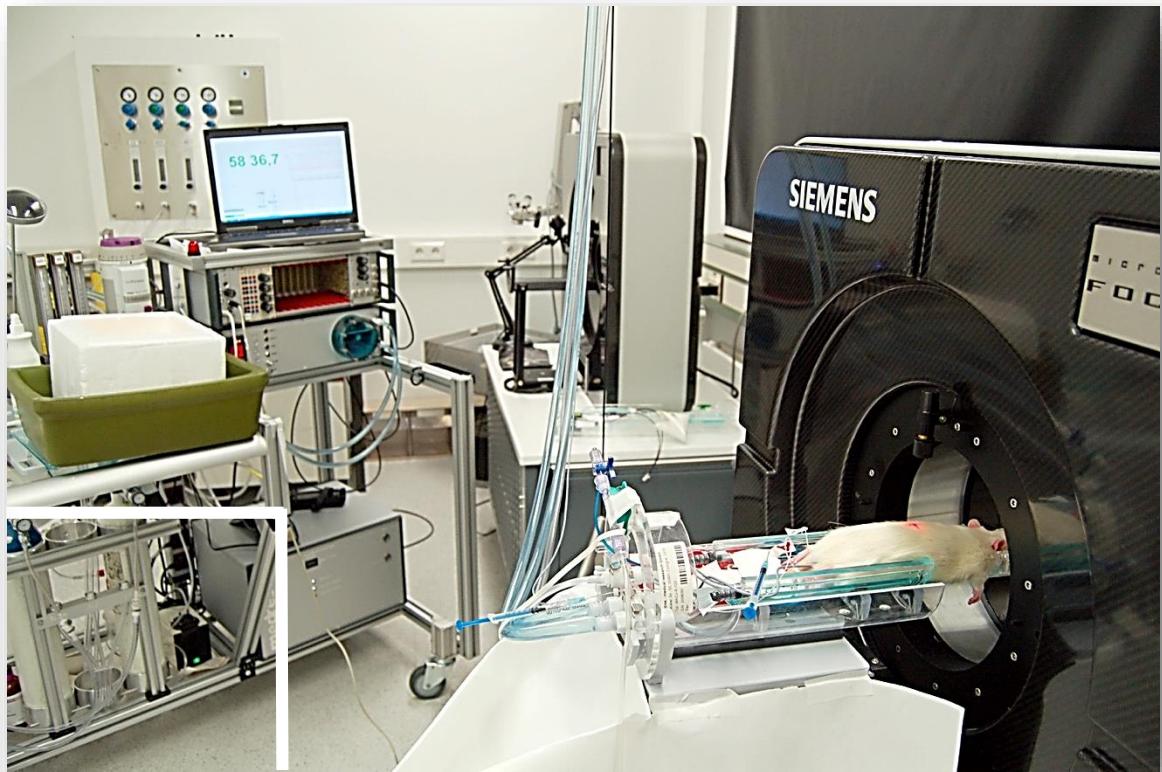
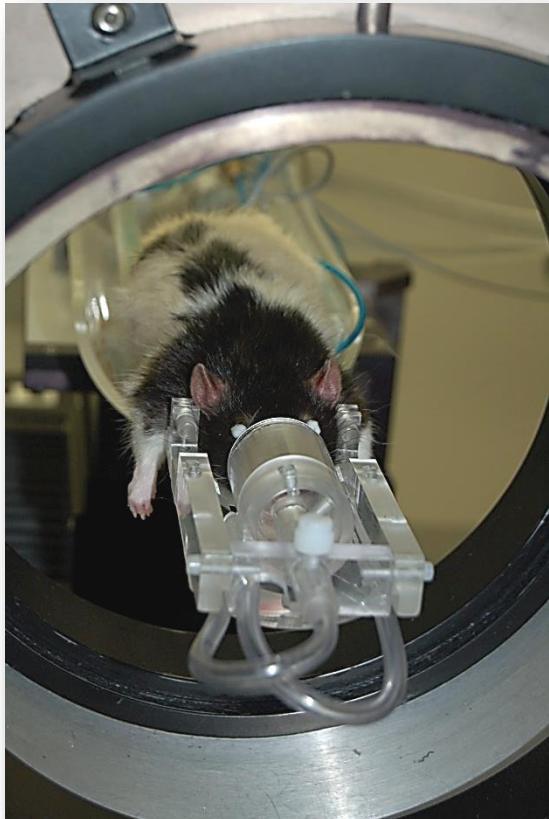
b) Boc-6-BpinTrp-OtBu precursor

Small animal PET

Inhalation anesthesia:

2-3 % Isoflurane

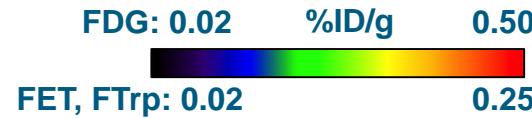
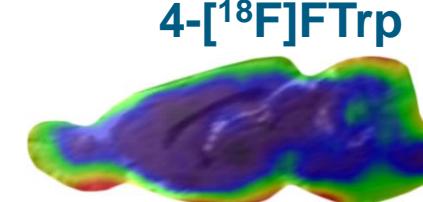
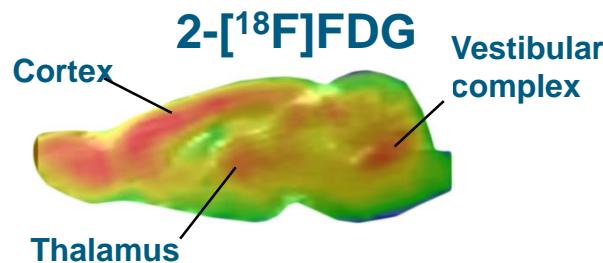
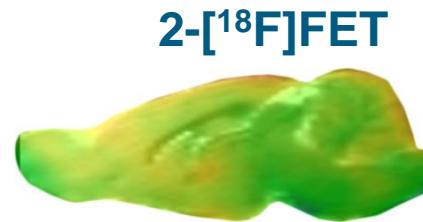
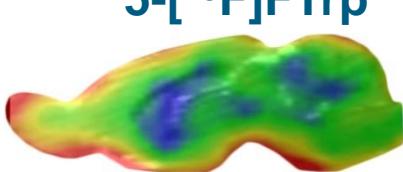
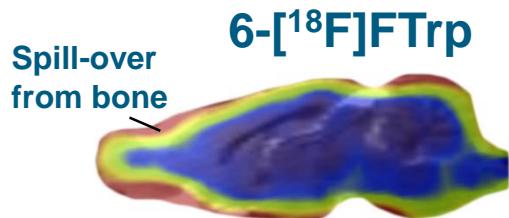
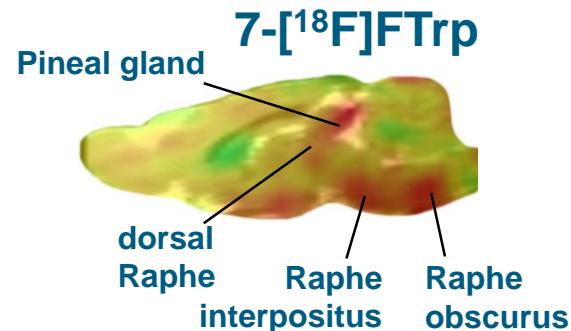
in 30 % O₂ + 70 % air



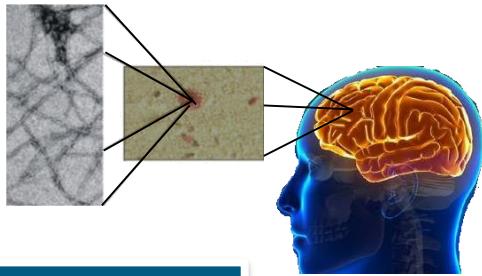
Monitoring and regulation of

- Body temperature (37 °C)**
- Breathing (40-50/min)**

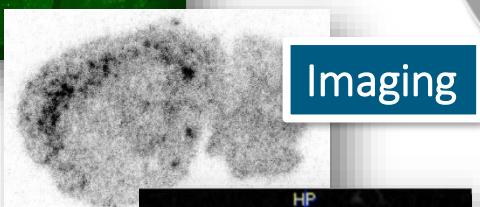
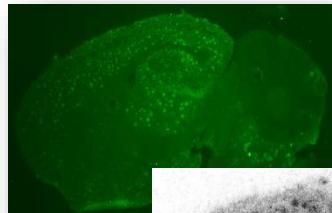
In vivo investigation of radiotracers



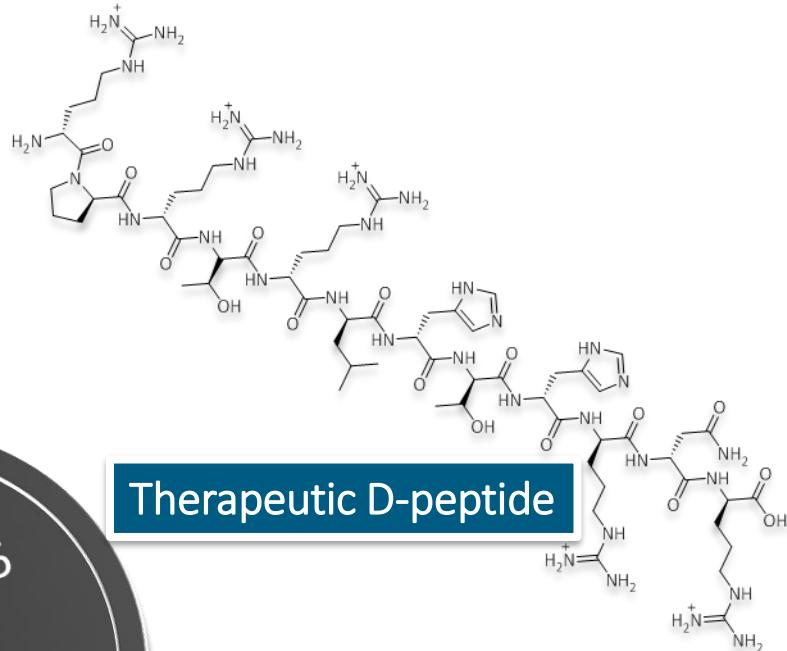
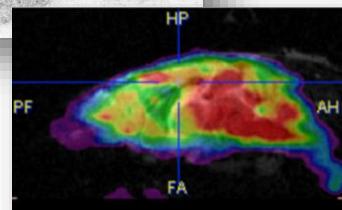
Collaboration project between ICS and INM: *Treatment of Alzheimer's Disease*



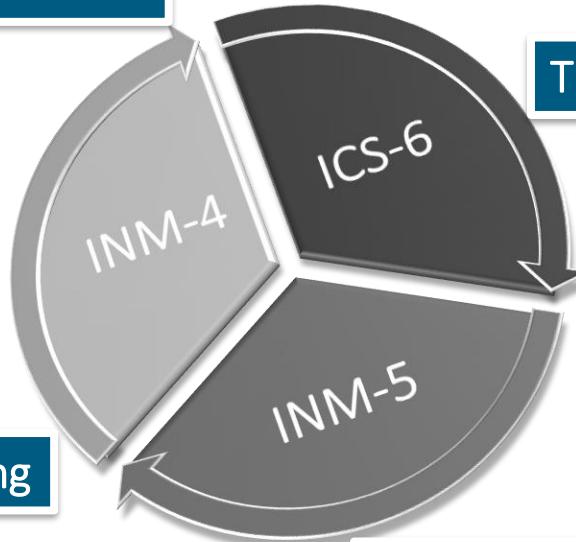
Behavioural Tests



Imaging



Therapeutic D-peptide



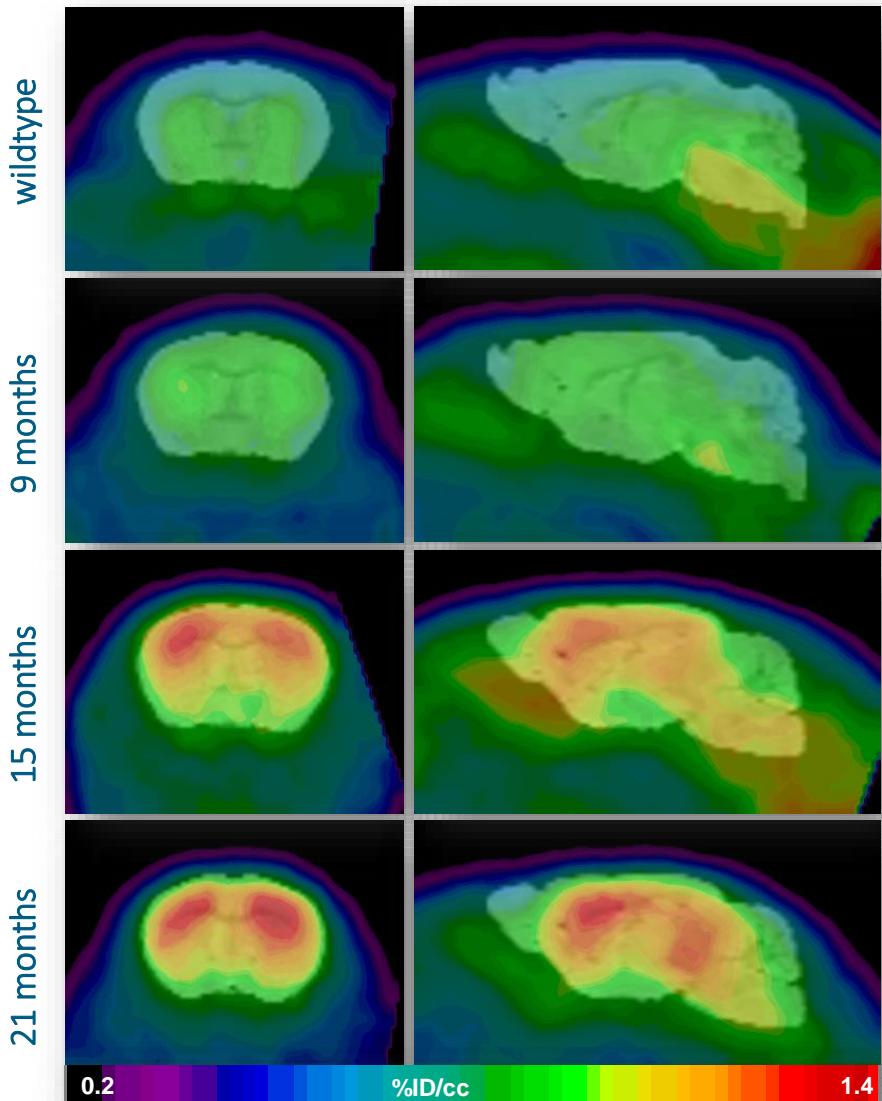
Amyloid Tracer



Preclinical imaging

[¹⁸F]Florbetaben PET in transgenic mice (ARTE10) overexpressing APP

- [¹⁸F]FBB retention (25-90 min p.i.)
 - Co-registered to a mouse brain MRI atlas
- Increasing FBB retention can be found especially in the cortex of ARTE10 mice upon aging but not in wildtype control mice.

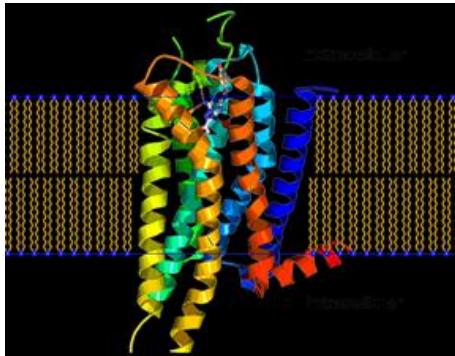




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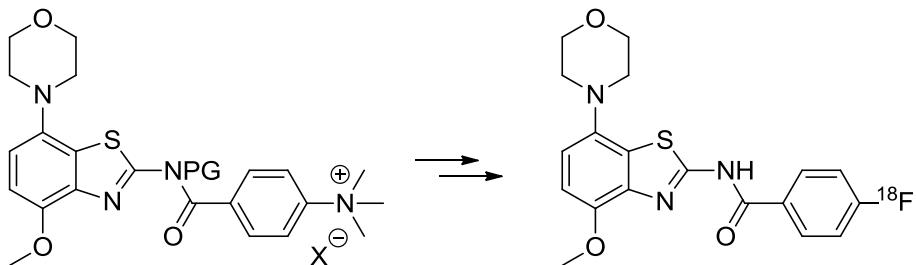
Ligands for the A_{2A}-Adenosine Receptor

Significance of the neuronal A_{2A} adenosine receptor



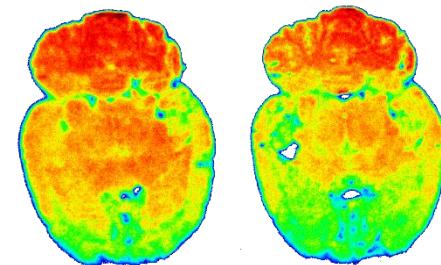
- neurodegeneration
- Parkinson's disease
- Huntington's disease
- migraine

Development of a A_{2A}AR radioligand



$K_i(A_{2A})$: 0,39 nM
 $K_i(A_1)$: 558 nM
 selectivity: 1430

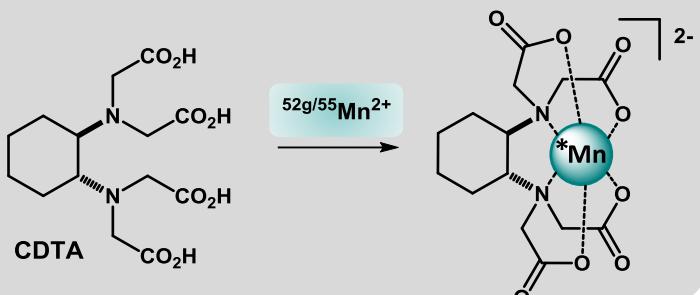
First autoradiographic results



Total binding
 Displacement with
 A_{2A}-AR-antagonist
 ZM241385 ($c = 1 \mu\text{M}$)

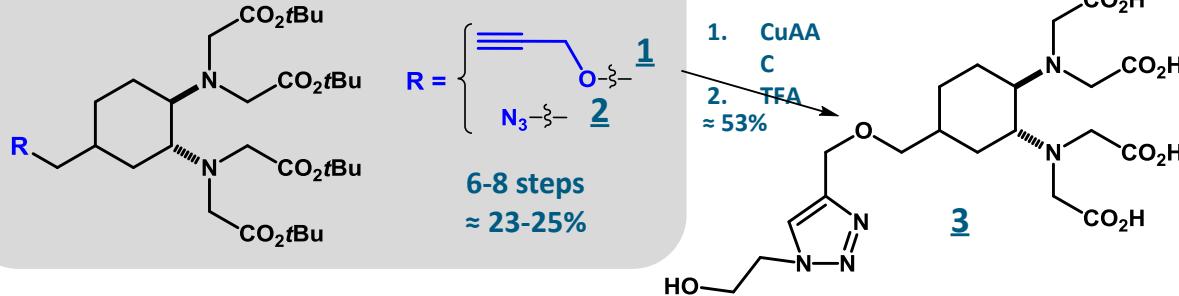
Manganese-based bimodal PET/MR tracers

First Mn-based PET/MR tracer

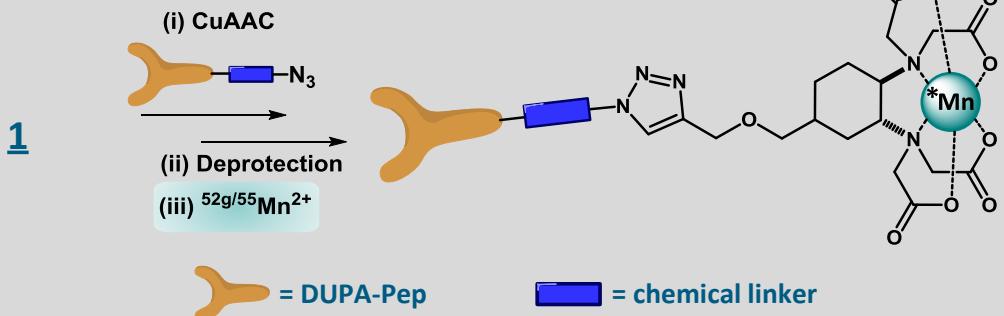


C. Vanasschen et al., *Dalton Transactions*, 2016, 45, 1315-21

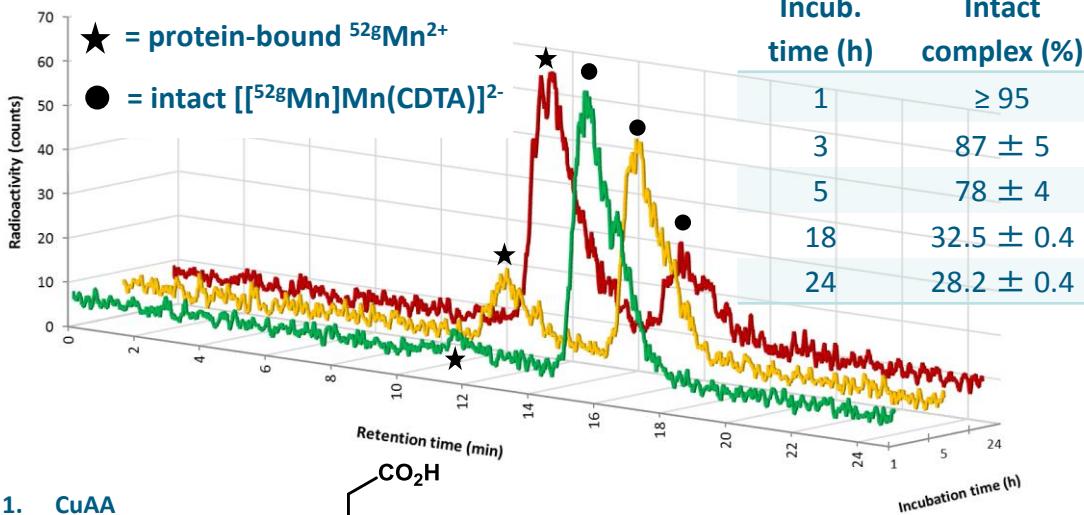
Synthesis of a bifunctional CDTA chelator



Design of a PSMA-targeted PET/MR tracer (ongoing)



Radiocomplex stability in HBS @ 37° C (SE-HPLC)



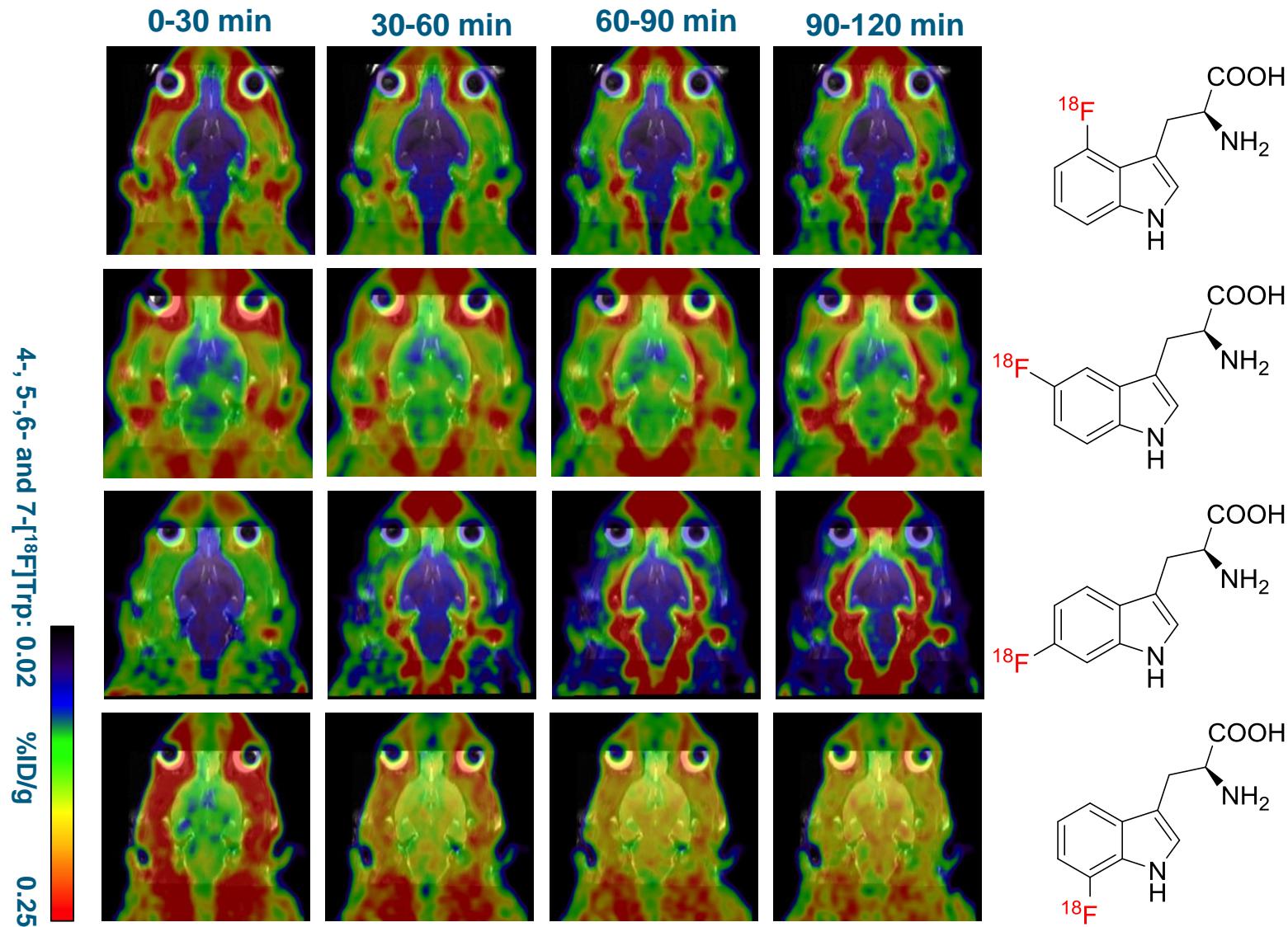
Incub. time (h)	Intact complex (%)
1	≥ 95
3	87 ± 5
5	78 ± 4
18	32.5 ± 0.4
24	28.2 ± 0.4

Stability and relaxivity assessment *

Mn-3	Mn-CDTA
$\log K_{\text{MnL}}$	13.80 14.32
Dissoc. $t_{1/2}$ (h)	16.23 12.00
Relaxivity, r_1 ($\text{mM}^{-1}\text{s}^{-1}$)	4.56 3.6

*collaboration with T. Gyula (University of Debrecen)

In vivo investigation of radiotracers



Preclinical Imaging



Inveon PET

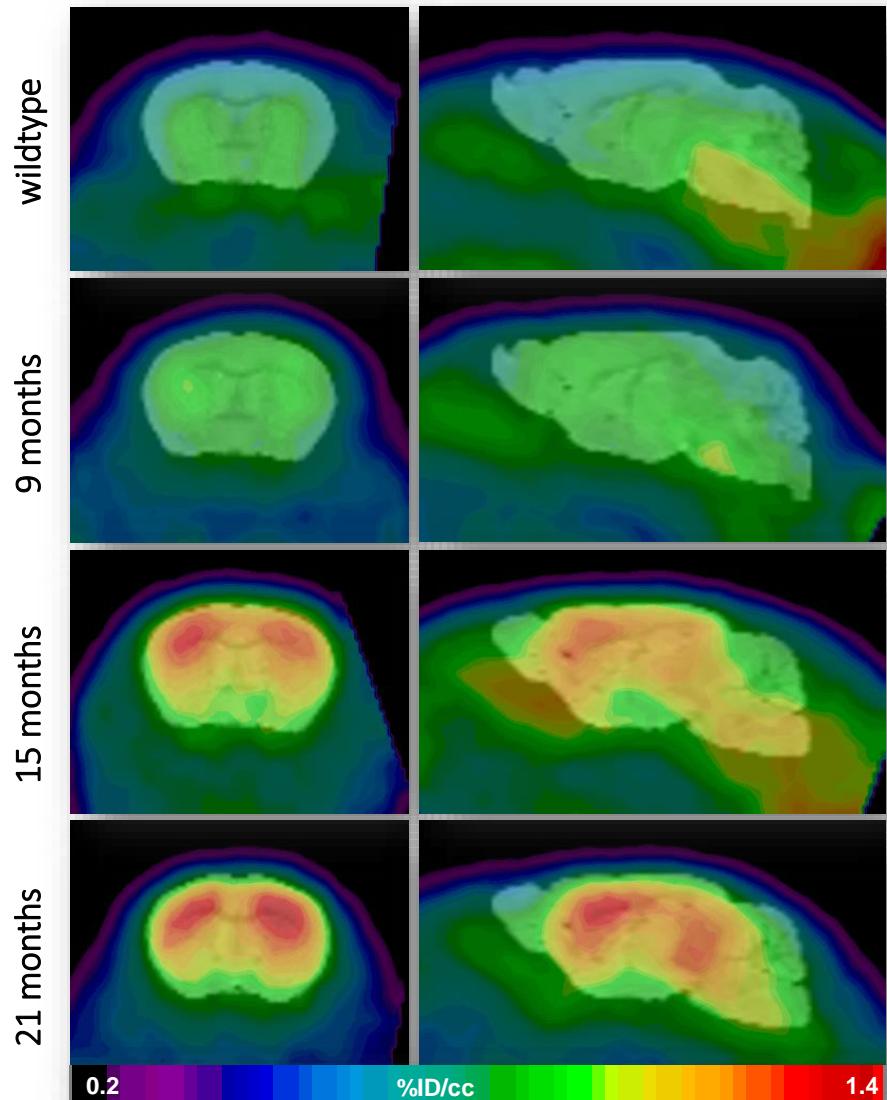


Bruker 7T Pharmascan

Results

[¹⁸F]Florbetaben PET in transgenic mice (ARTE10) overexpressing APP

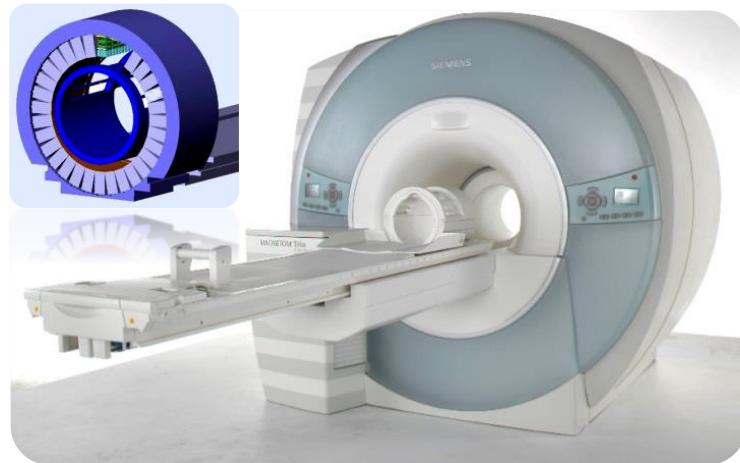
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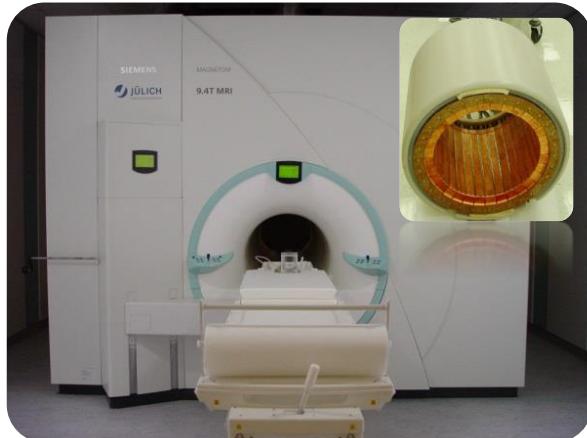
Clinical Imaging



ECAT HR+ PET



3T-Trio MR/PET

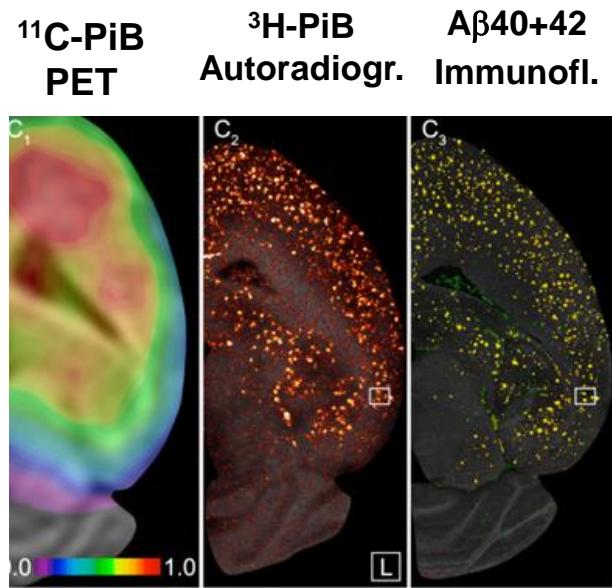
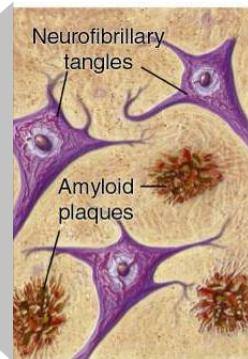
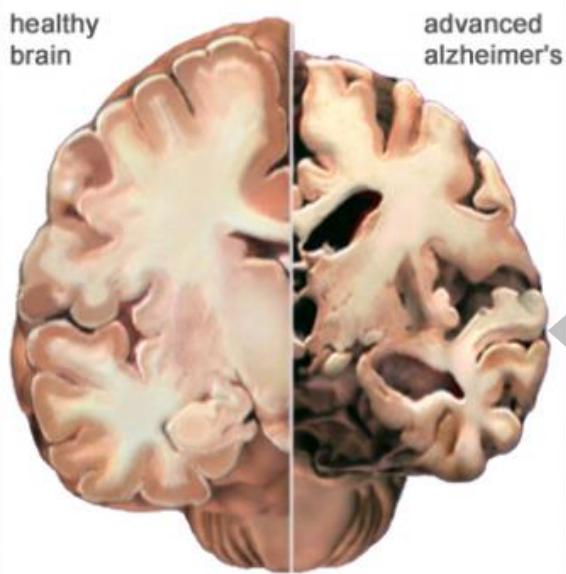


9.4 T MR/PET



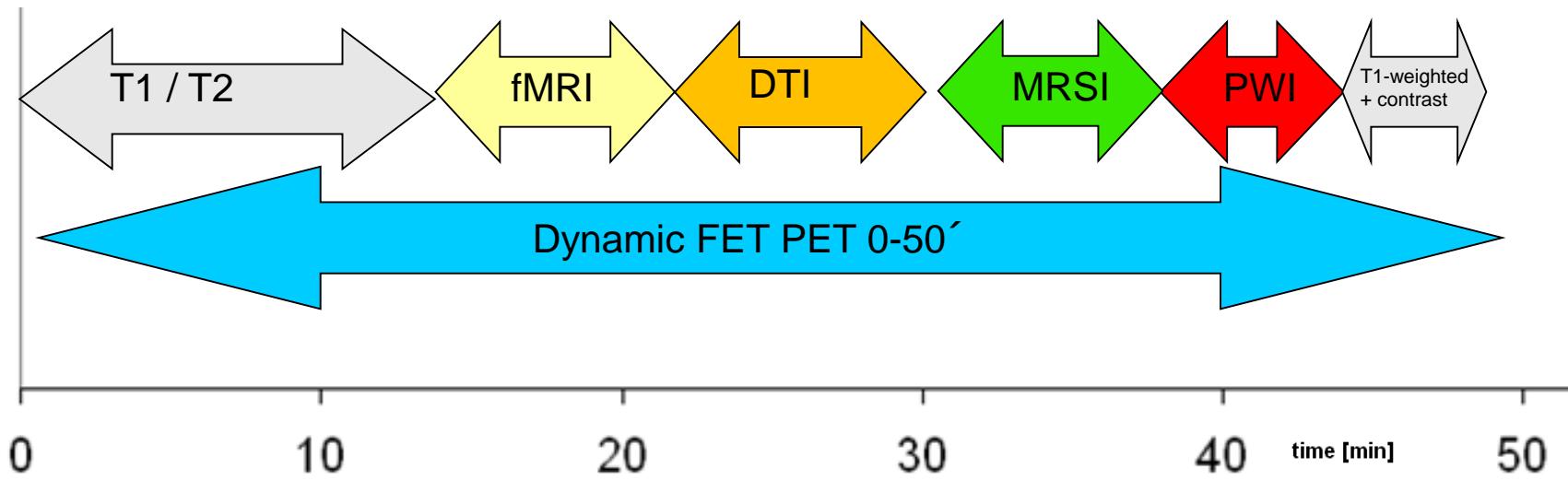
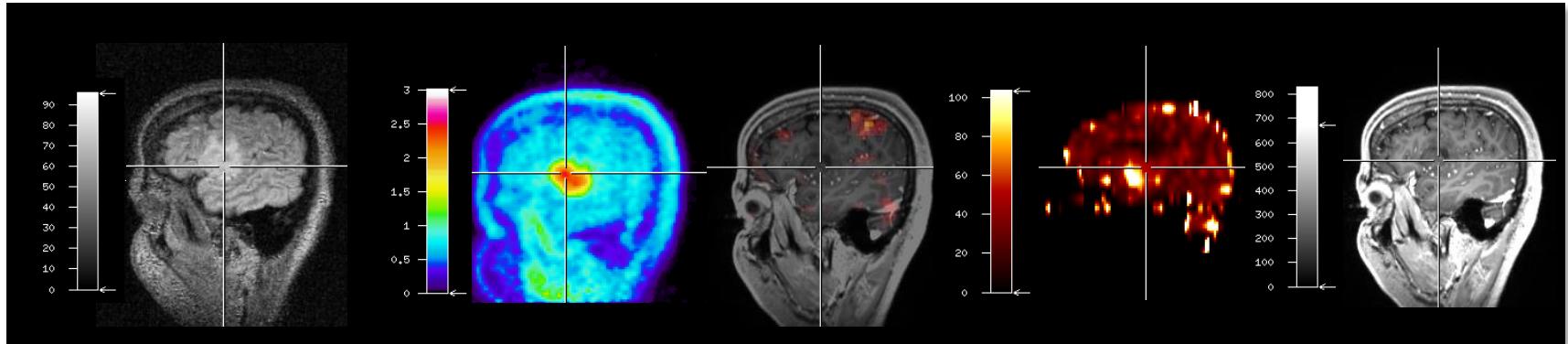
Biograph mCT

Therapie mit Amyloid-senkenden D-Peptiden

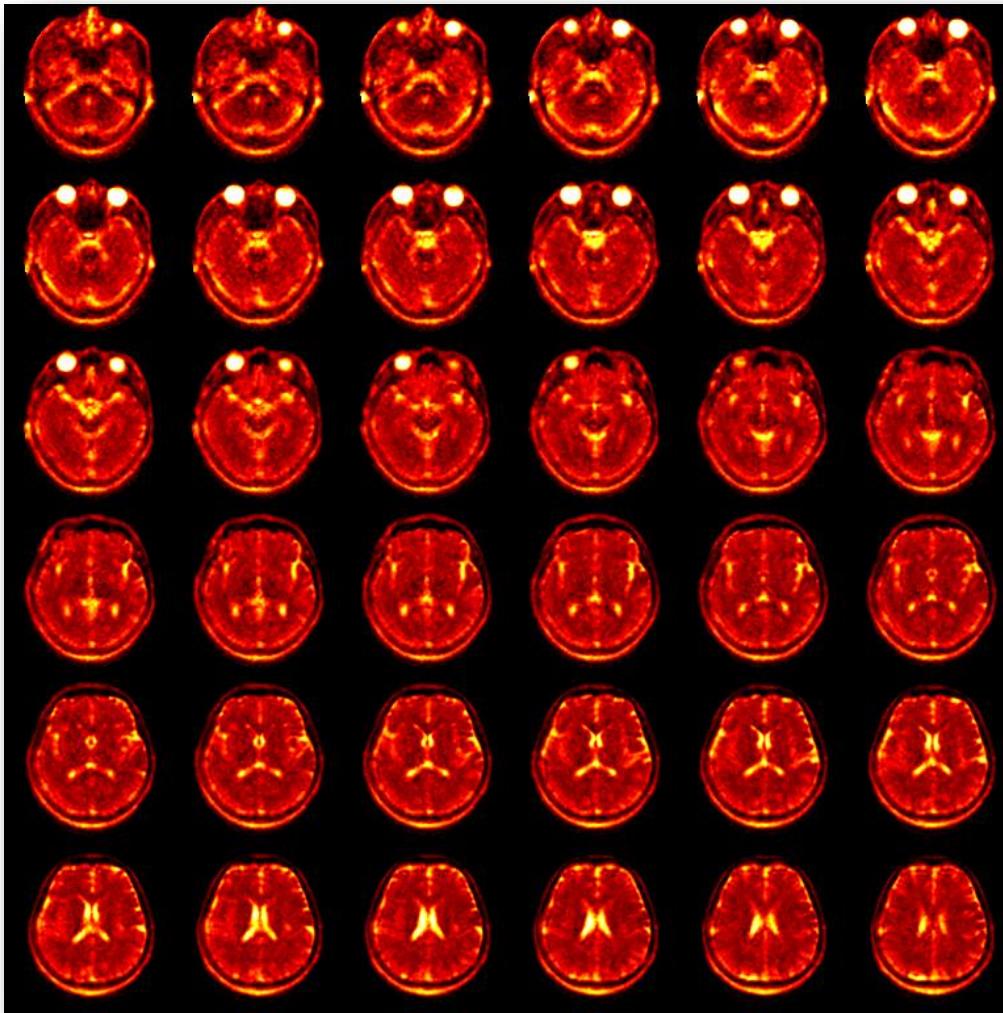


Willuweit (INM-4), Langen (INM-4), Willbold (ICS-6)

PET – MR hybrid imaging



^{23}Na *in vivo* 9.4 T



Natrium – 9.4T
TPI
2 mm isotrop
15 min Akq.-zeit