PET Tracer Development

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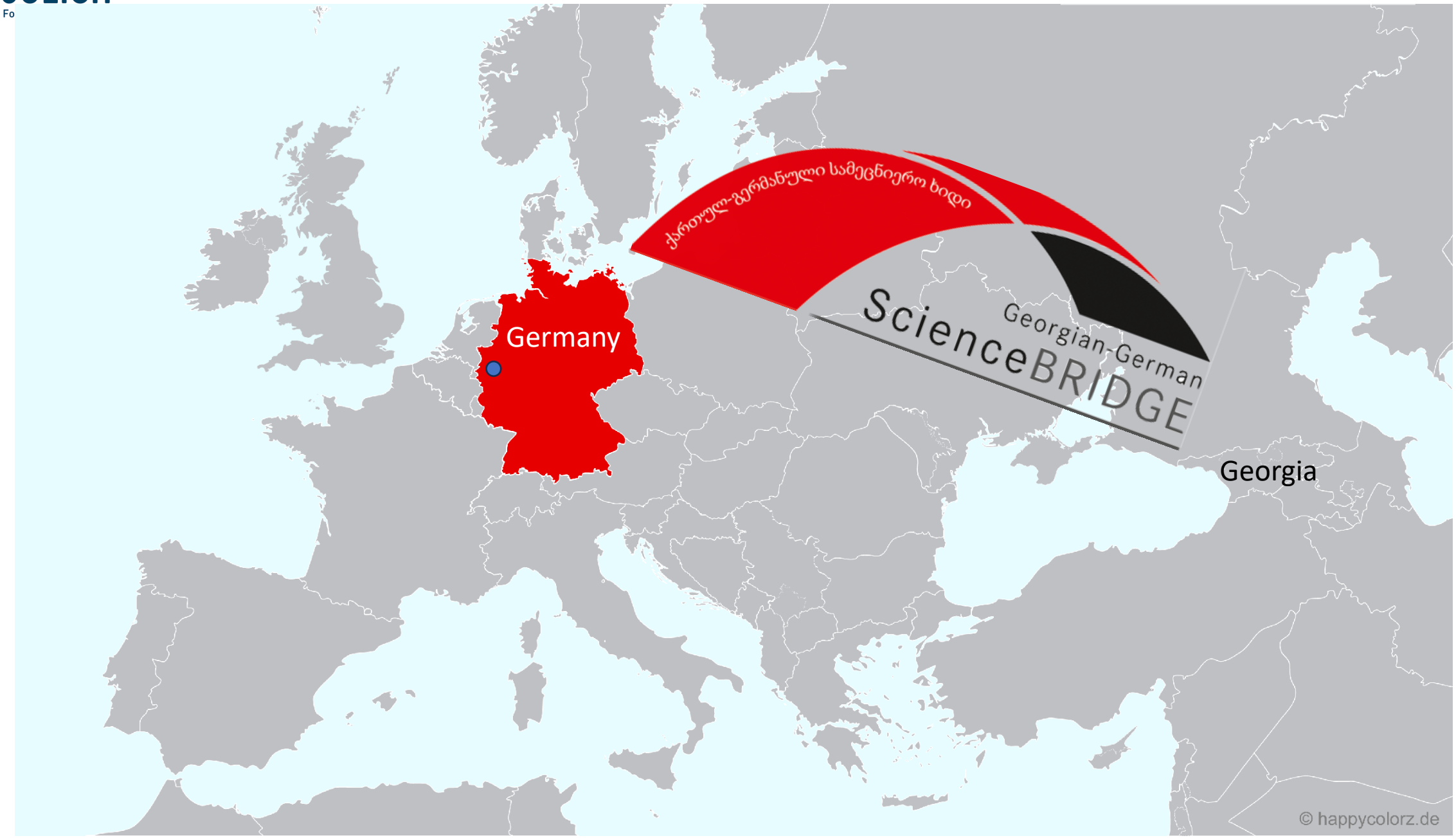
University Hospital Cologne

and Forschungszentrum Jülich GmbH, INM-5

Iv.Javakhishvili Tbilisi State University, Faculty of Exact and Natural Sciencies, Department of Biology, Morphology,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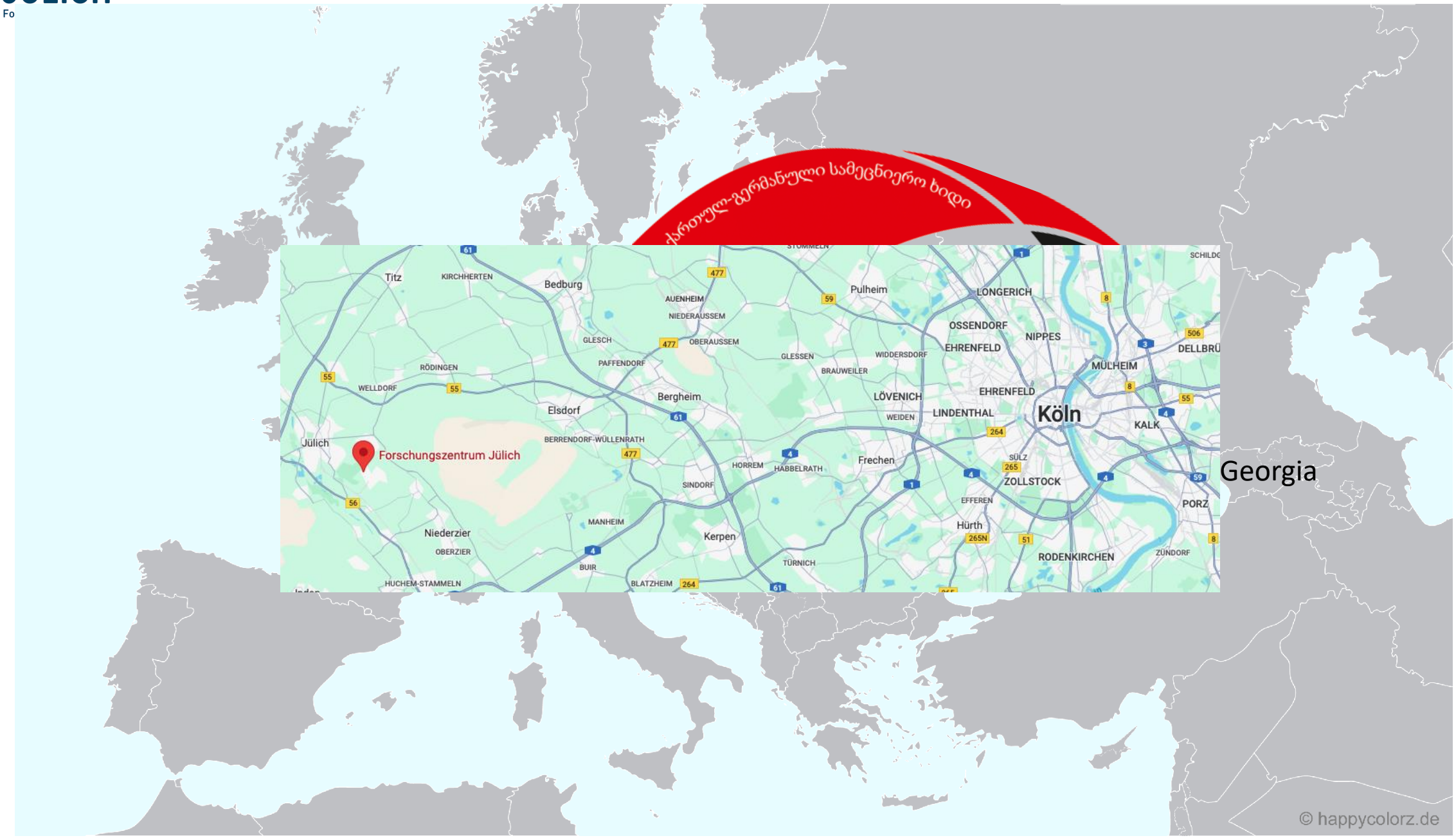
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KIRCHHERTEN
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Prof. Dr. Bernd Neumaier

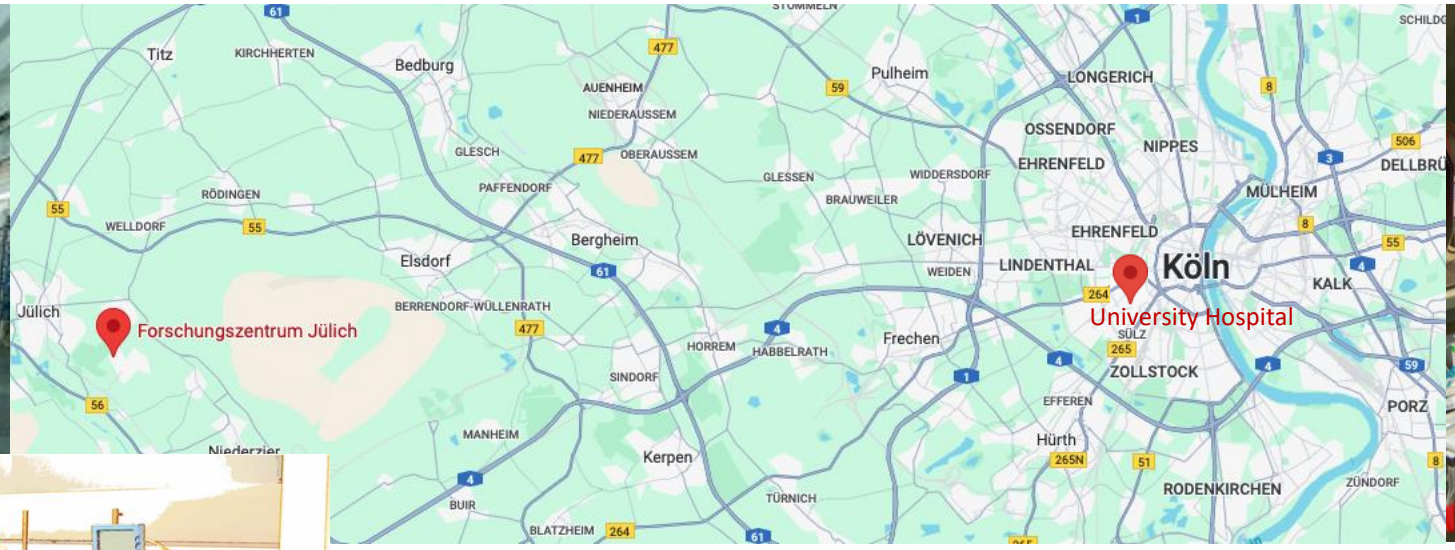
JÜLICH Forschungszentrum

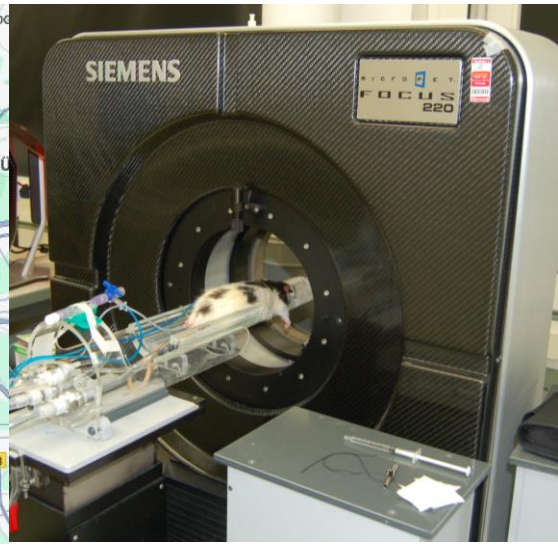
UNIKLINIK KÖLN

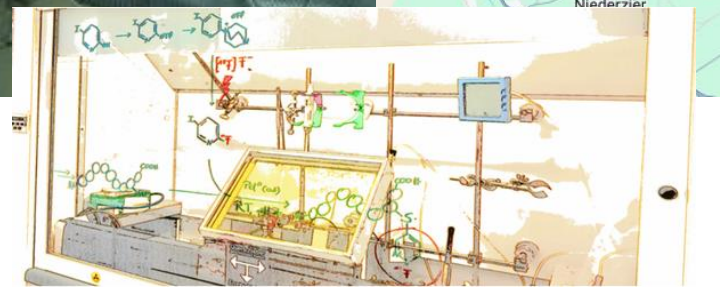
50 km

INM-5
Nuclear Chemistry

IREMB
Preclinical Imaging





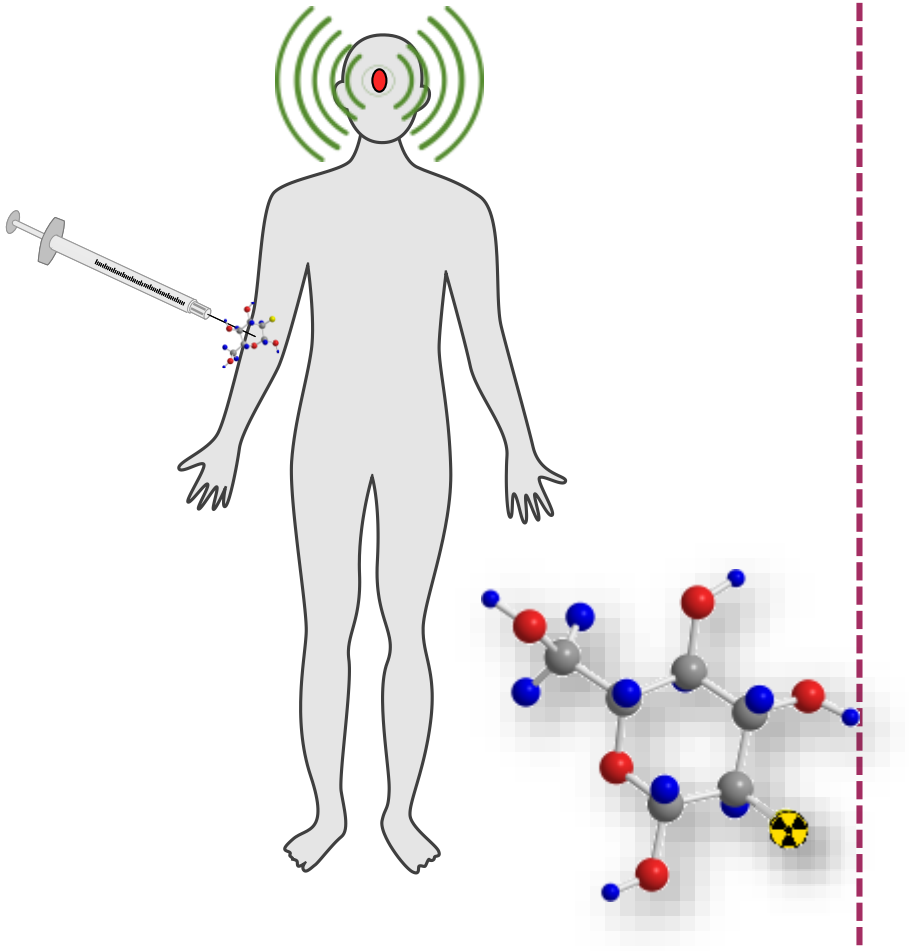


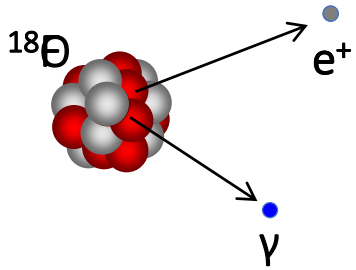
About me

- Scientific relations with Forschungszentrum Jülich since 2018;
- Internship in Molecular Imaging at University Cologne-2021;
- Iv. Javakhishvili TSU – Ph.D. Student – 2022
- Shota Rustaveli Foundation NG and Forschungszentrum Jülich joint grant – 2022
- Admission at the graduate school Interdisciplinary Program of Molecular Medicine at University of Cologne.
- Submitted grant application - **Partnerships for sustainable solutions with the countries of the South Caucasus and Central Asia 2024 - Development of bispecific radioligands for PET imaging and radioligand therapy metastatic prostate cancer.**

QUALI-Start-Up Lectures in Jülich (September, 2019)

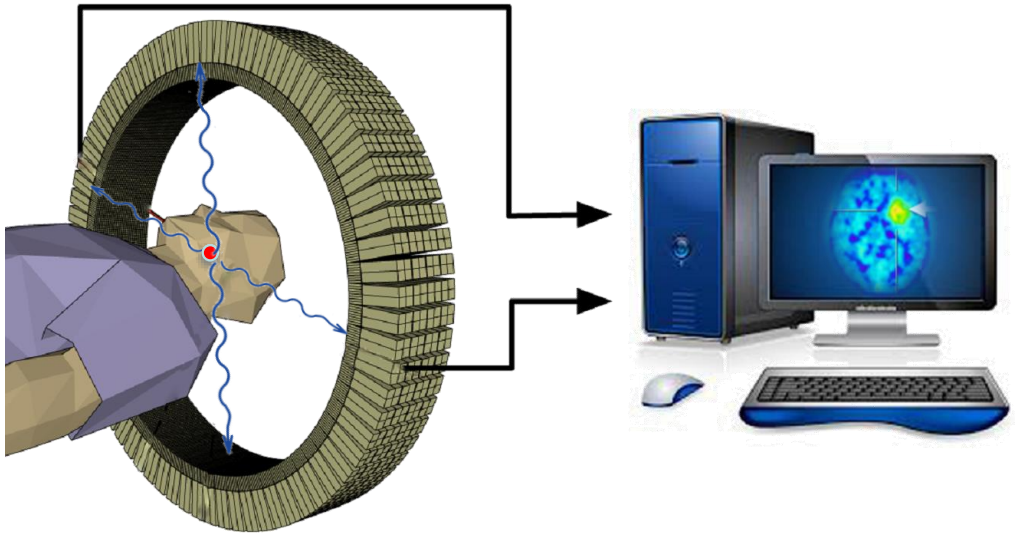
Detection of Molecular probes via PET





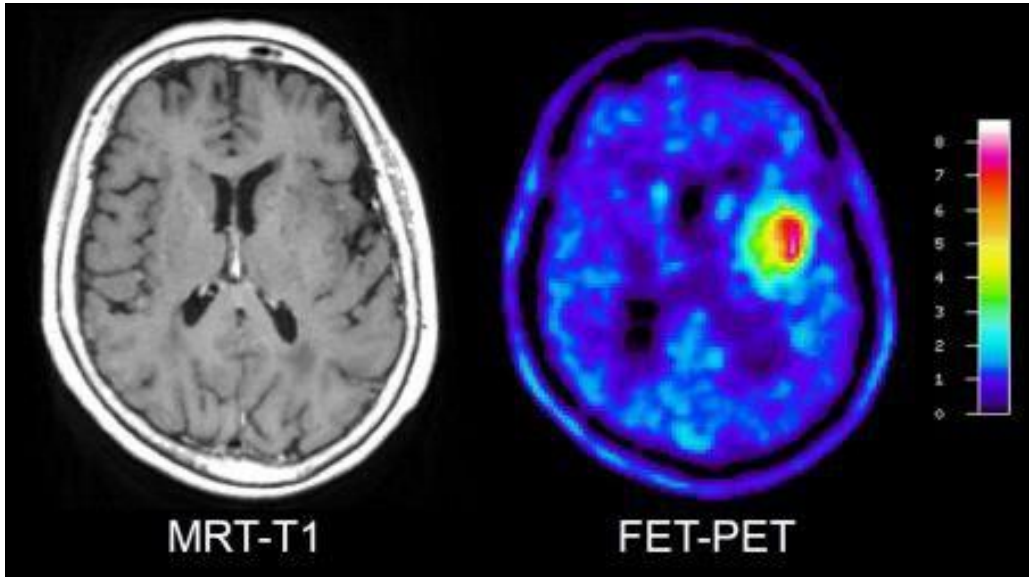
511 keV
γ-Photon

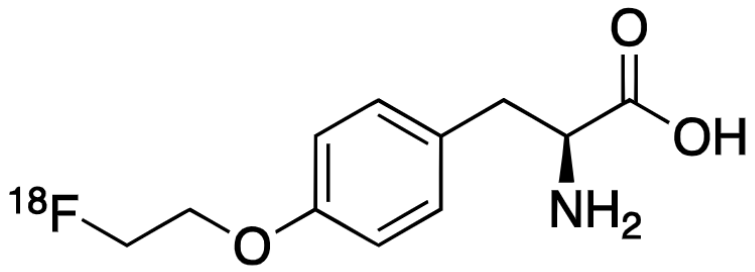
511 keV
γ-Photon



General aims of PET

- Early detection and localization of metastases and therapy monitoring.
- Molecular information about protein expression status, mutation status, vascularization, etc.
- Fusion of anatomic and metabolic images together (PET/MRT, PET/CT)
- Develop a theranostic approach for cancer diagnosis and treatment.





[^{18}F]Fluoroethyl-L-Tyrosine

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General aims of PET

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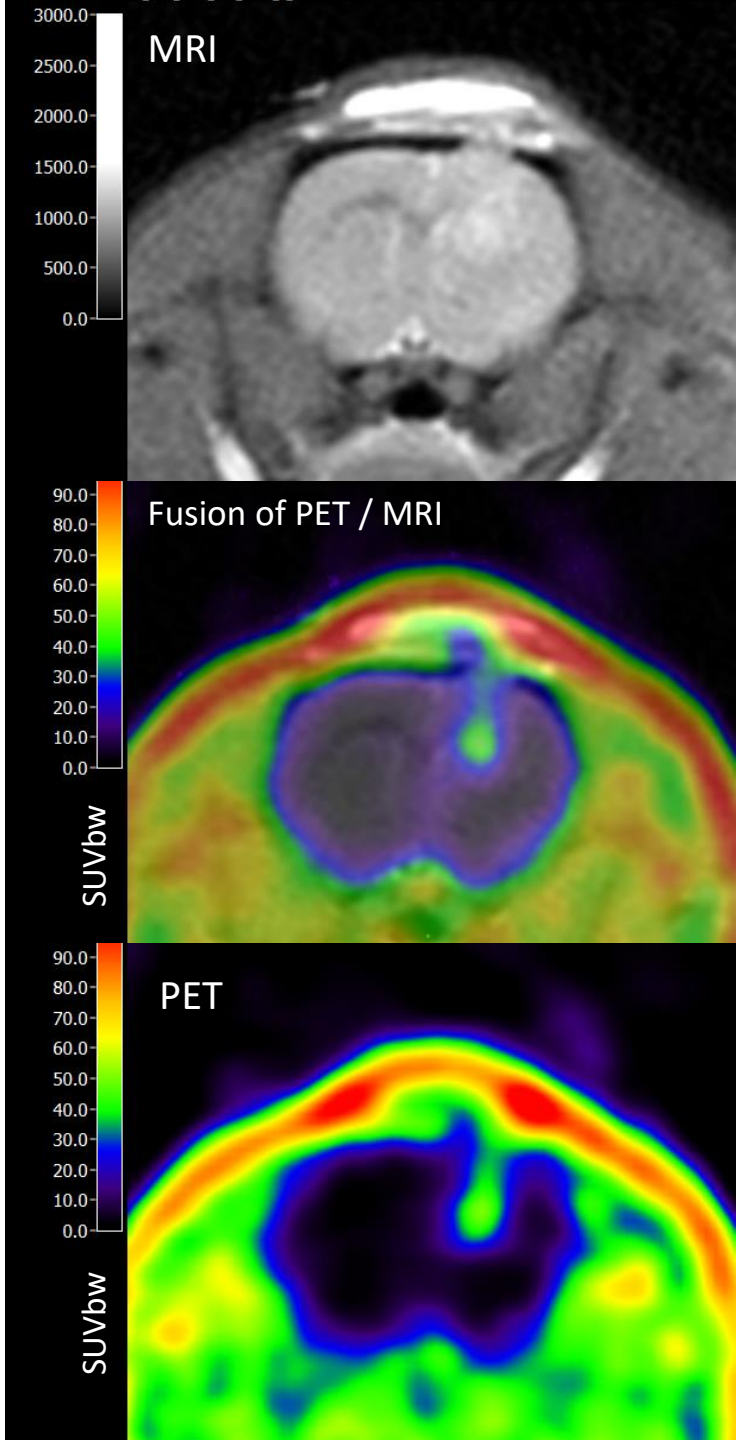
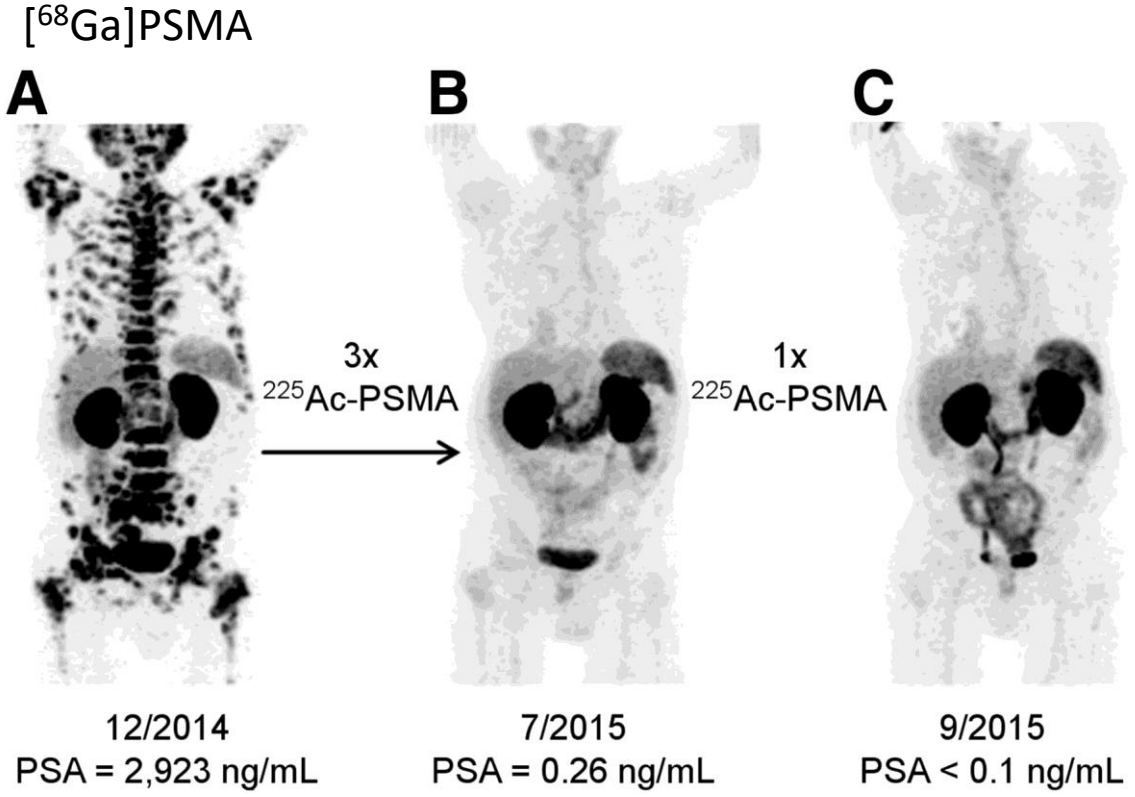


Fusion of PET (6-[^{18}F]F-FAPI) and MRT (T2w) images; U87 Glioblastoma model

General aims of PET

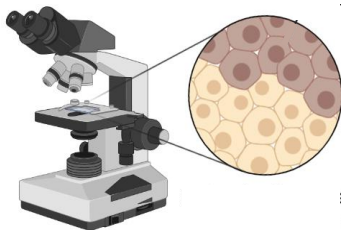
- Early detection and localization of metastases and therapy monitoring.
- Molecular information about protein expression status, mutation status, vascularization, etc.
- Fusion of anatomic and metabolic images together (PET/MRT, PET/CT)
- Develop a theranostic approach for cancer diagnosis and treatment. (Same ligand could be labeled with both diagnostic or therapeutic nuclide)



Kratochwil *et al.* Journal of Nuclear Medicine December 2016, 57 (12) 1941-1944; DOI: https://doi.org/10.2967/jnumed.116.178673

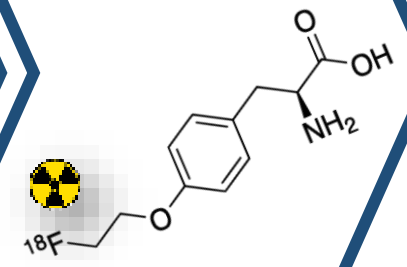
Workflow of Molecular Probe Development

Identification of appropriate molecular targets

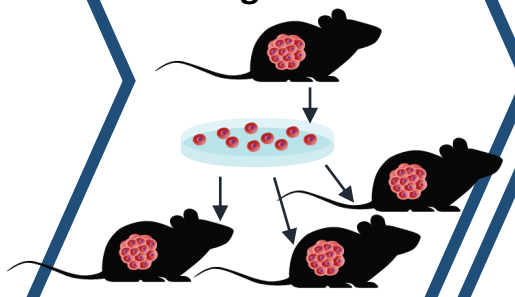


Selection of ligand precursor

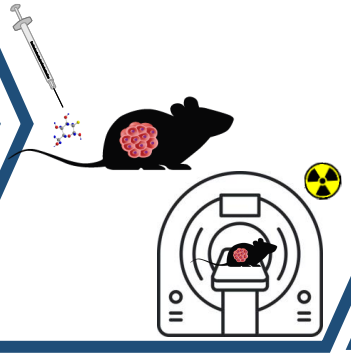
Development of labelling strategies



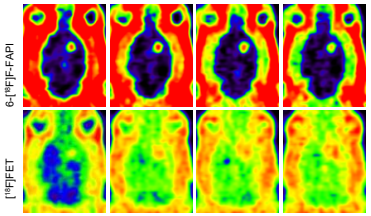
Pre-clinical model for testing



Pre-clinical evaluation



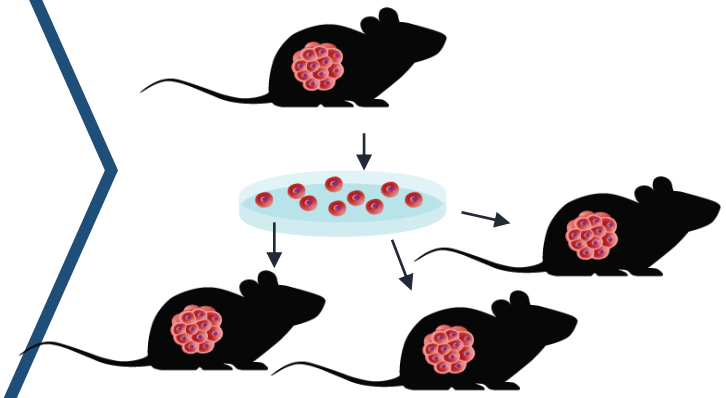
Comparison with existing standards



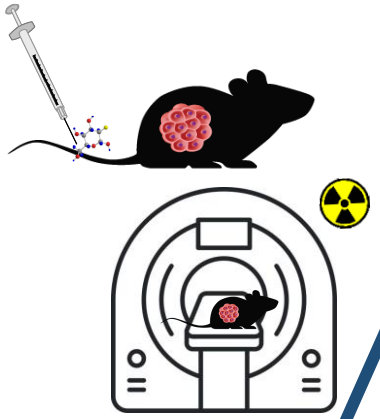
approximate time: 5–15 years

Preclinical Imaging

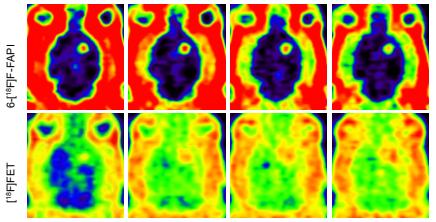
Pre-clinical model for testing



Pre-clinical evaluation



Comparison with existing standards



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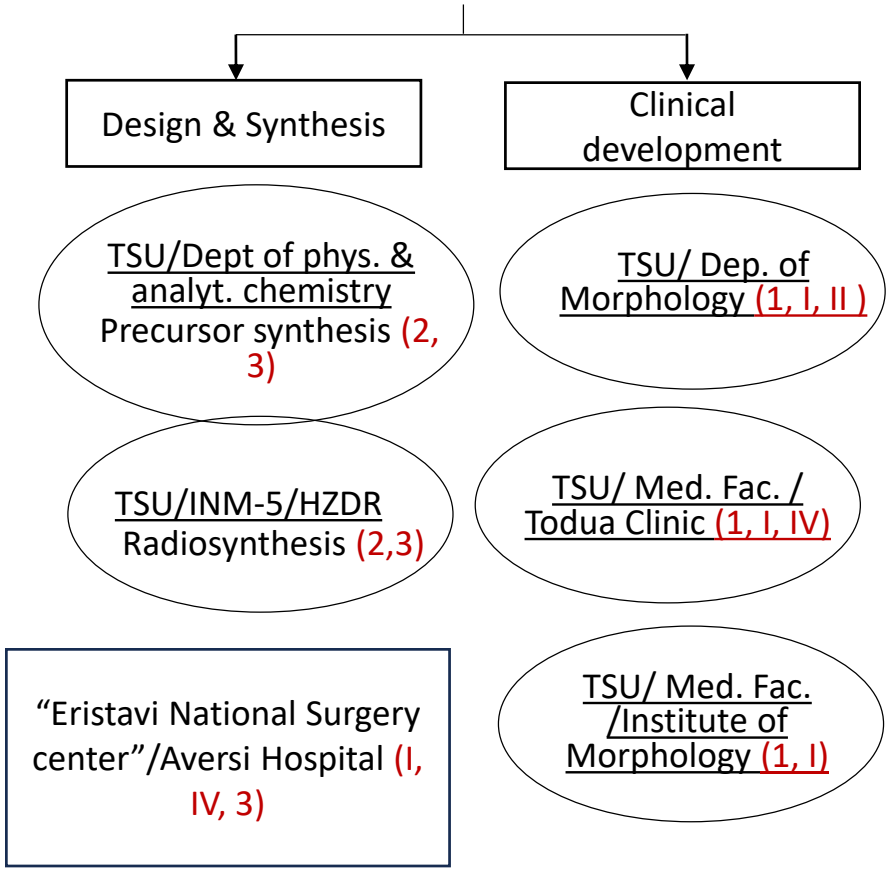
SMART|Biomedical Tracer_Lab

Design & production

1. **Identification of an appropriate target.**
2. **Selection of precursor ligands.**
3. **Development of labelling strategies.**
4. **Optimization of labelling**
5. **GMP conform synthesis**



Clinical Development

I. **Definition of clinical need**
II. **Establishment of an appropriate pre-clinical model for testing**
III. **Evaluation in an appropriate clinical setting**
IV. **Comparison with existing standards**
V. **Documentation of safety and efficacy.**

Work without radioisotopes

Work with radioisotopes

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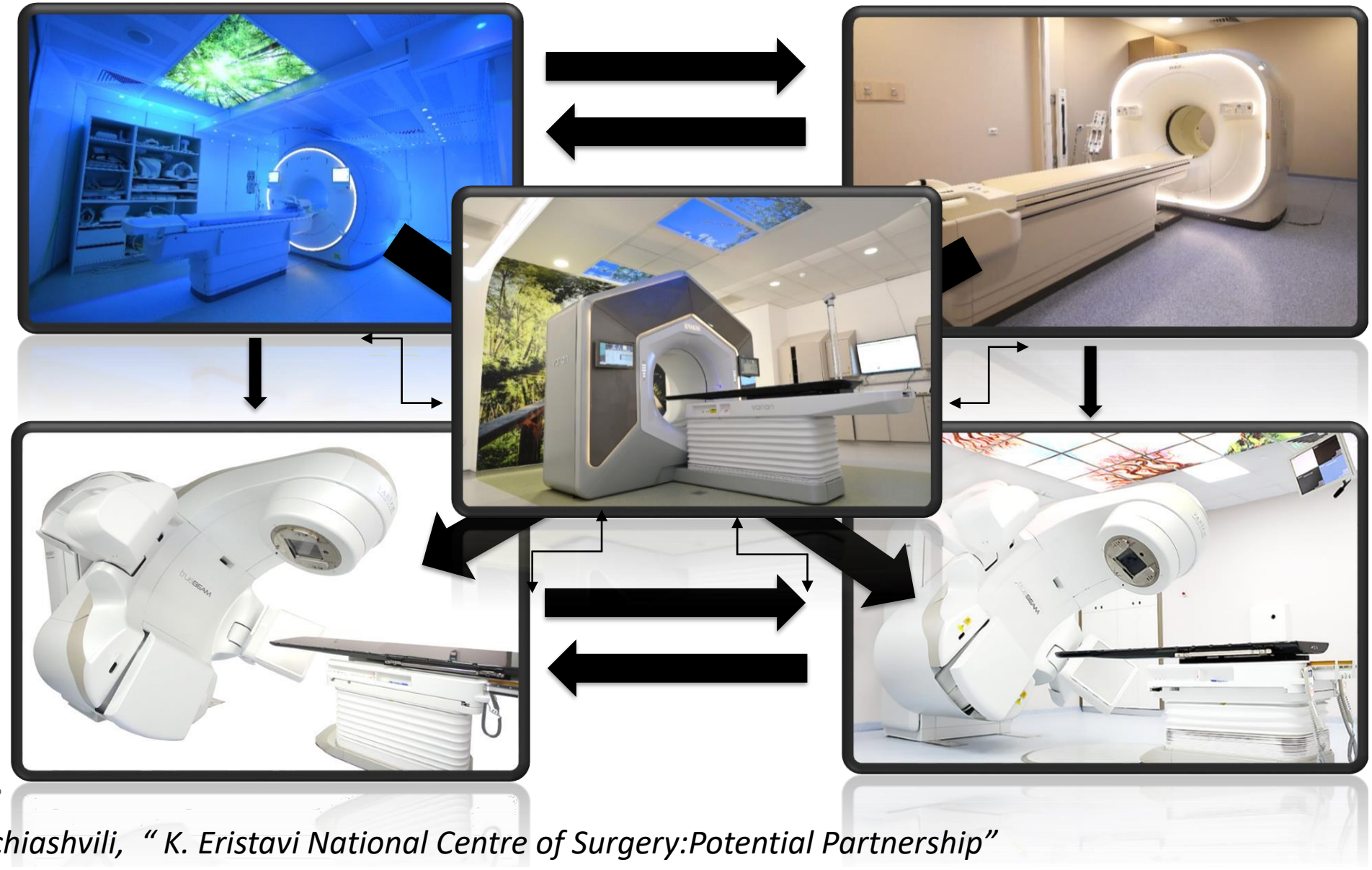
Vereos Digital PET/CT

- 5min-5cm-5mCi
- Patient's condition;
- Technology possibility;
- Patient's comfort;
- New pattern of work;

- Gain insight through the advanced power of AI-enhanced image segmentation and AI-driven treatment planning
- Apply automated dose accumulation and forecasting to monitor treatment progress
- Harness relevant knowledge to monitor and forecast dose accumulation

Tamar Khechiashvili, " K. Eristavi National Centre of Surgery:Potential Partnership"

Smart Fusion



Mitglied der Helmholtz-Gemeinschaft

Tamar Khechiashvili, " K. Eristavi National Centre of Surgery:Potential Partnership"

Strategies of cancer PET-imaging

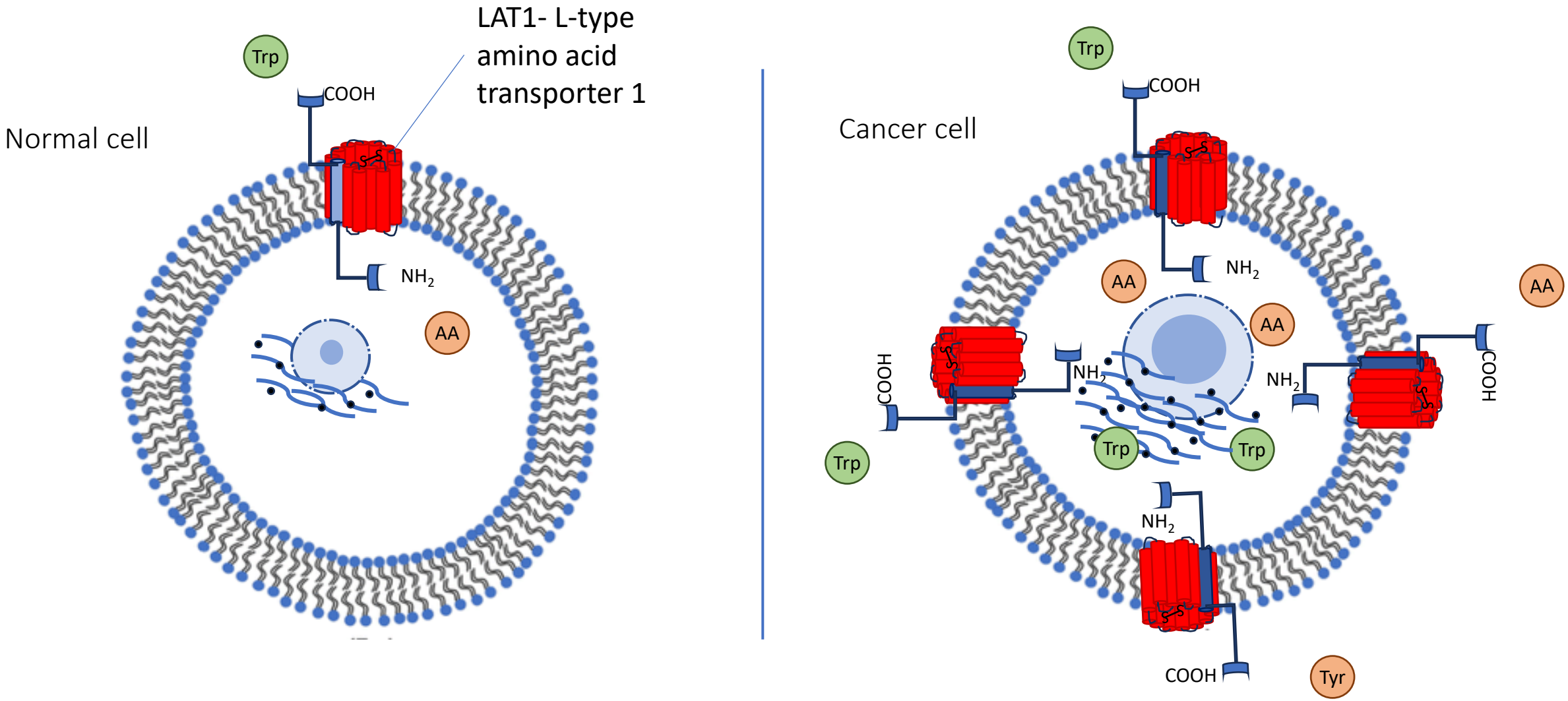
Find a PET tracer which is specific for one type of cancer:

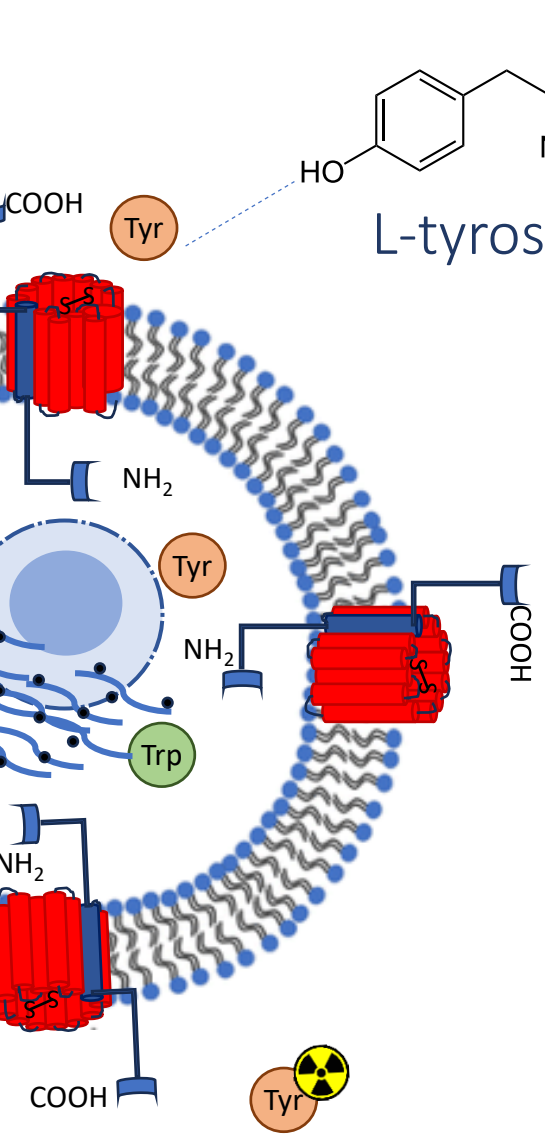
- Ligands of prostate-specific membrane antigene (PSMA)
- Tracers that distinguish between mutated and wild type isocitrate dehydrogenase (wtIDH vs mIDH) in brain tumors

Find a PET tracer, which visualizes several kinds of cancer:

- High lipid metab.→ [^{11}C]Choline
- High glucose metab. → [^{18}F]FDG
- High amino acid metabolism → [^{18}F]FET, 7-[^{18}F]FTrp
- Cancer-associated fibroblasts →[^{18}F]AlF-FAPI

Transport system for tyrosine and tryptophan





L-tyrosine

[18F]FET

Tyr.-
hydroxylase

Adrenergic
pathway

DOPA

Dopamine

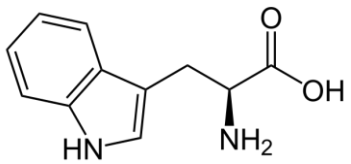
Norepinephrine

Epinephrine

Adrenal glands,
Nerve tissue,
Glioma ↑

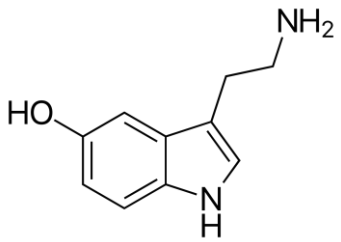
Tyr

5-[18F]FMT



L-tryptophan

Serotonin pathway

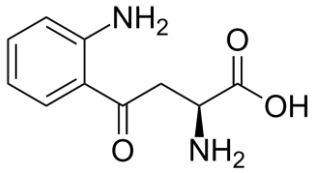


Serotonin

Raphe neurons

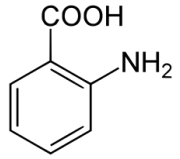
Nervous system: serotoninergic activity

Kynurenine Pathway (IDO-1)



Kynurenine

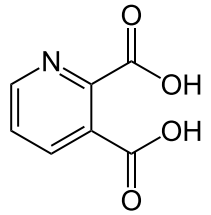
KYNU-branch



Anthranilic acid

Microglia
Cancer cells

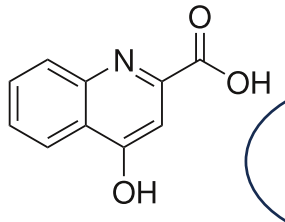
KMO-branch



Quinolinic acid

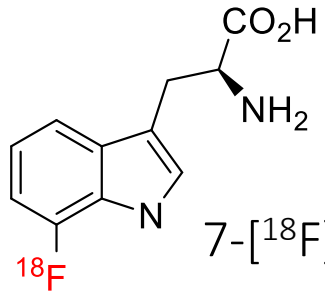
Microglia
Macrophages
Cancer cells

KAT-branch



Kynurenic acid

Astroglia
Cancer cells



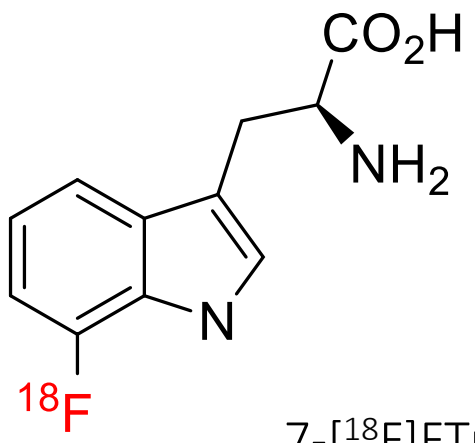
7-[^{18}F]FTrp

Nervous system: neuroinflammation

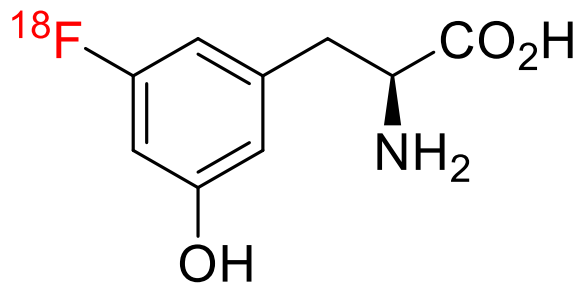
Cancer: Tryptophan depletion immune escape protein synthesis

Aim of the Study

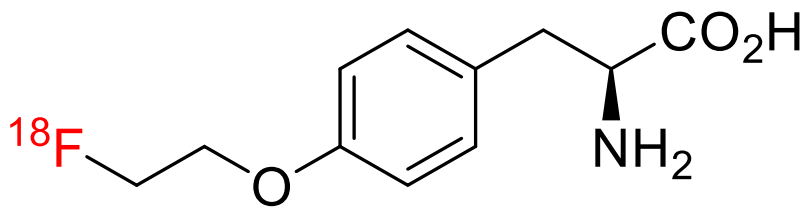
- To assess the efficiency of 7-[^{18}F]FTrp and 5-[^{18}F]FMT for Tumor diagnosis.
- Compare them with [^{18}F]FET in U87 glioma model.



7-[^{18}F]FTrp



5-[^{18}F]FMT



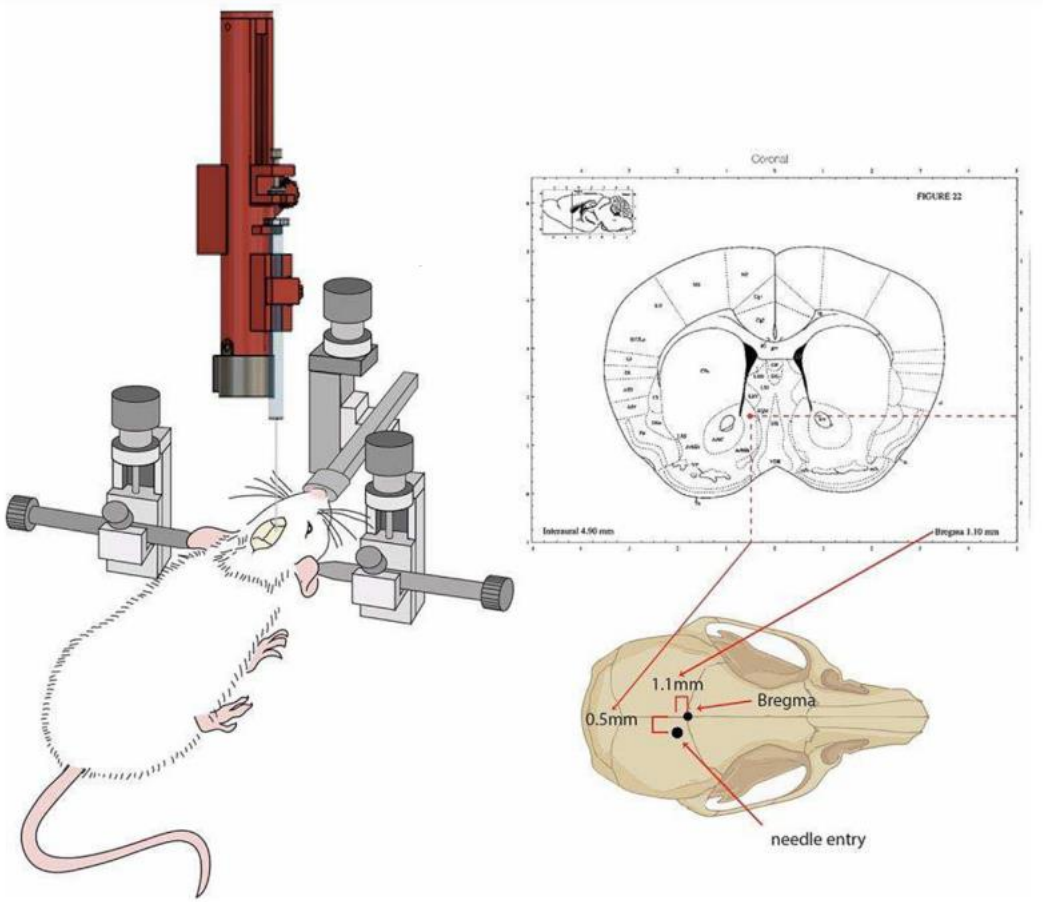
[^{18}F]FET

Materials and methods

For rat glioma model

In orthotope U87 GB experiment was used:

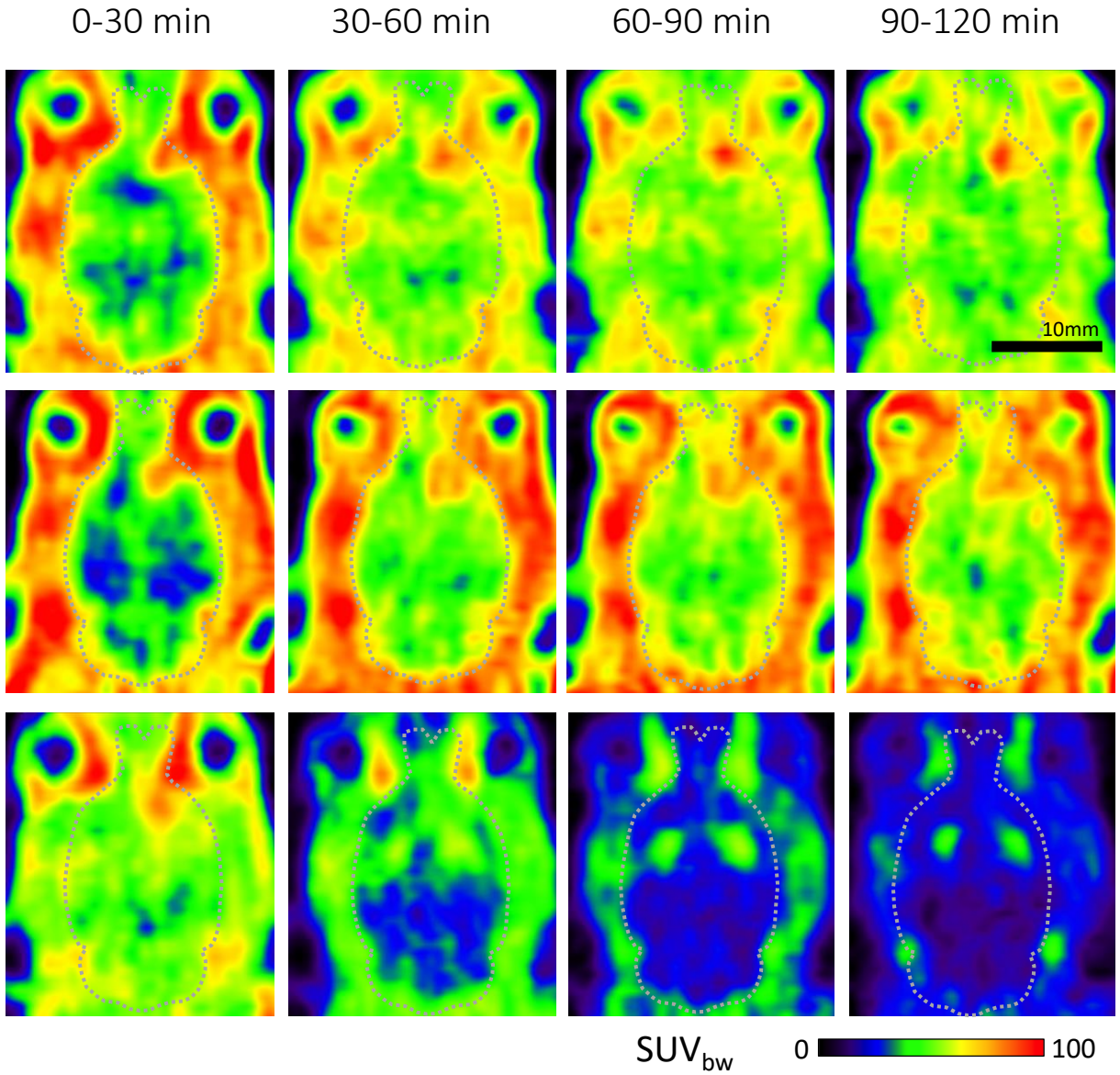
- Male Rowett Nude rats (n=4) ; Stereotaxic Surgery for U87 cell implantation.
- MRI
- PET scanning:
  - 7-[^{18}F]FTrp
  - [^{18}F]FET
  - 5-[^{18}F]FMT



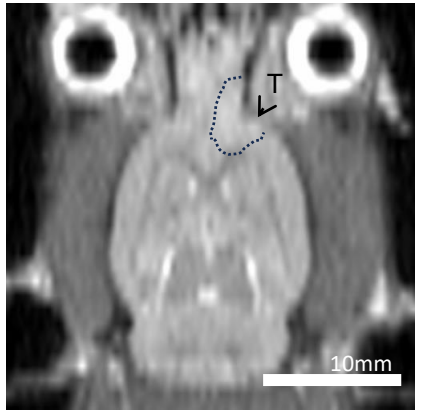
Results

rat glioma model

A



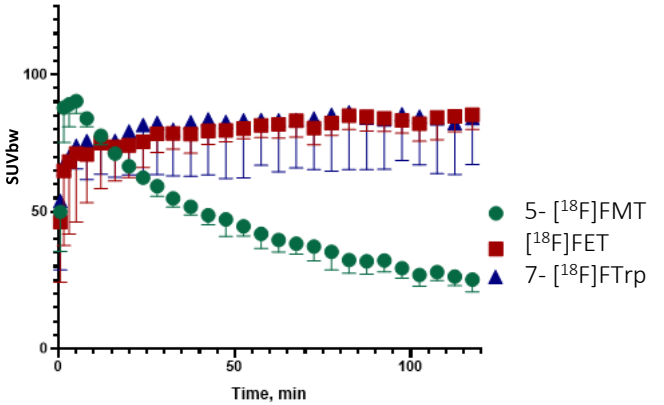
B



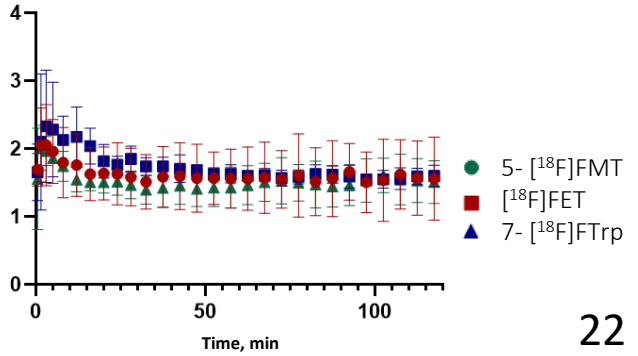
MRI, T2w image
NURNU – 056
7 days after implantation

C

Comparison of 5- [18F] FMT, [18F] FET and 7- [18F] FTrp SUVbw in U87 orth.

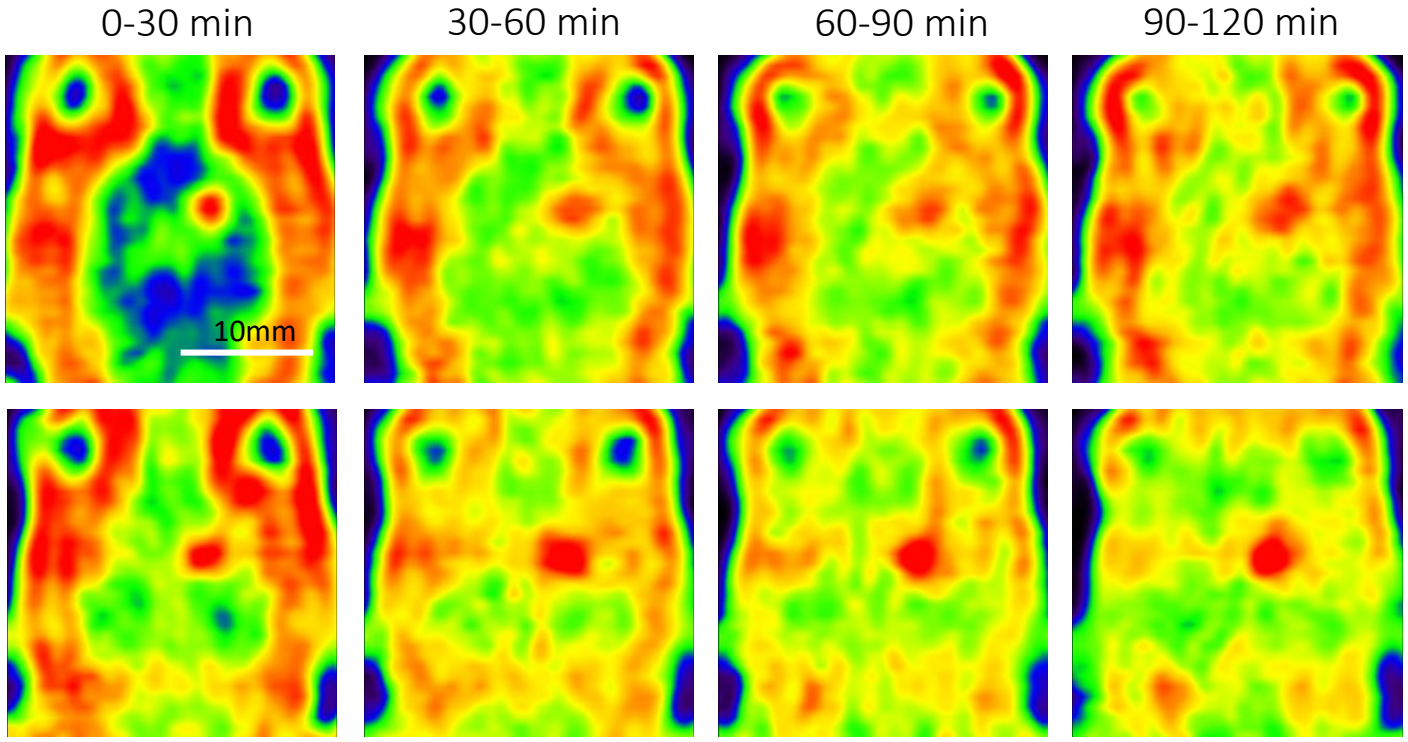


Tumor to background ratio (TBR)

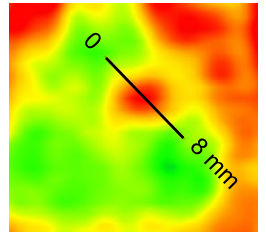


Results

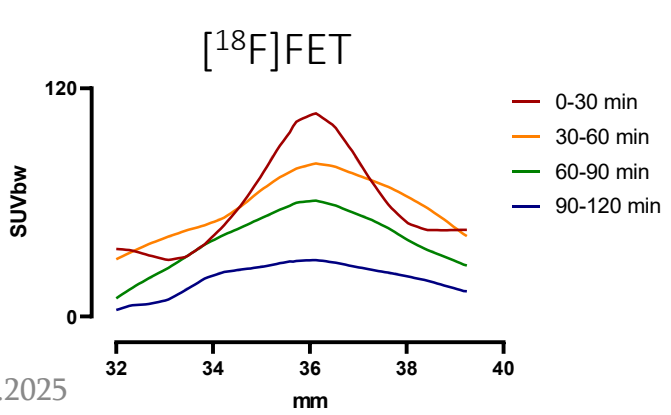
rat glioma model

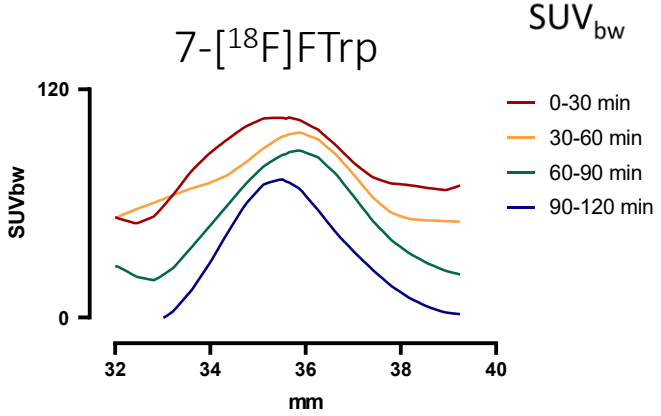


MRI, T2w image
NURNU – 056
7 days after implantation



Profile plot through tumor





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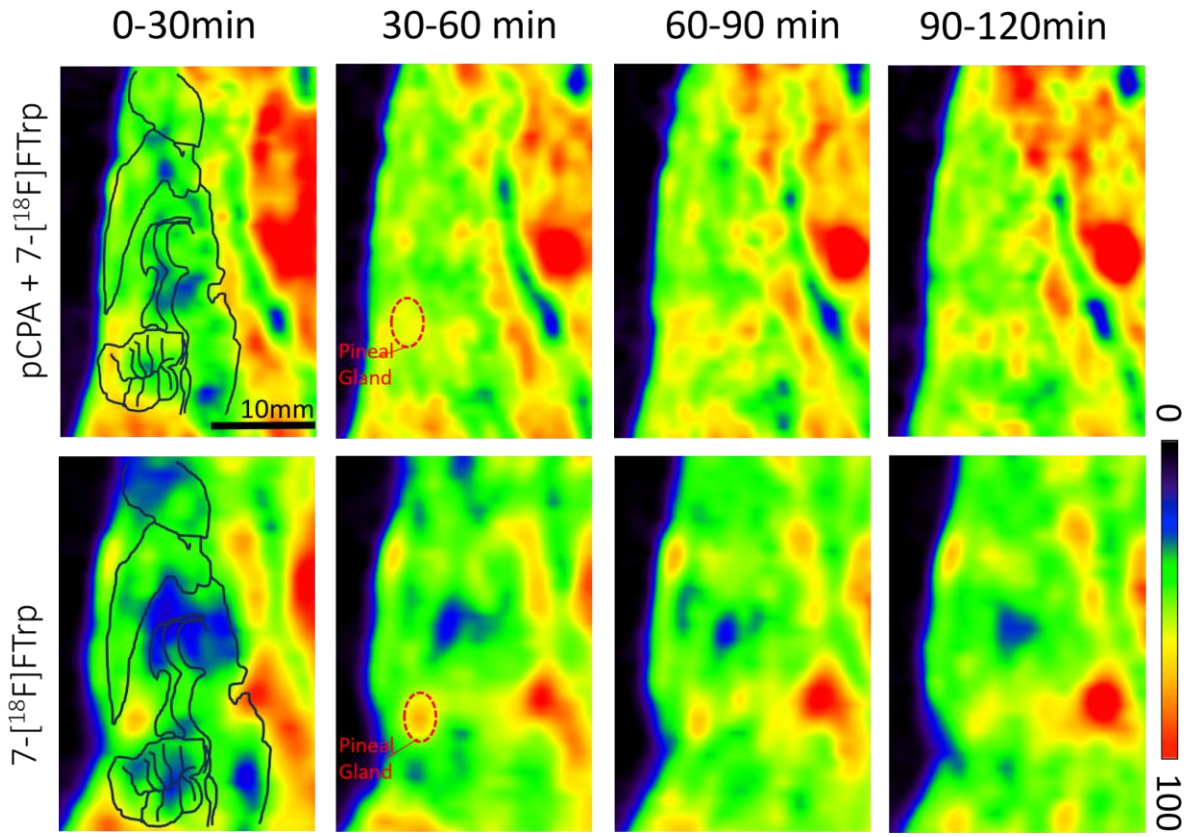
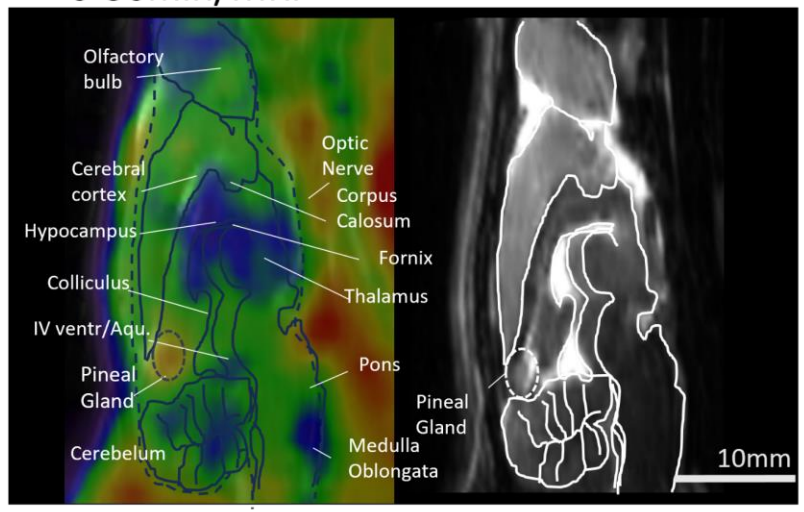
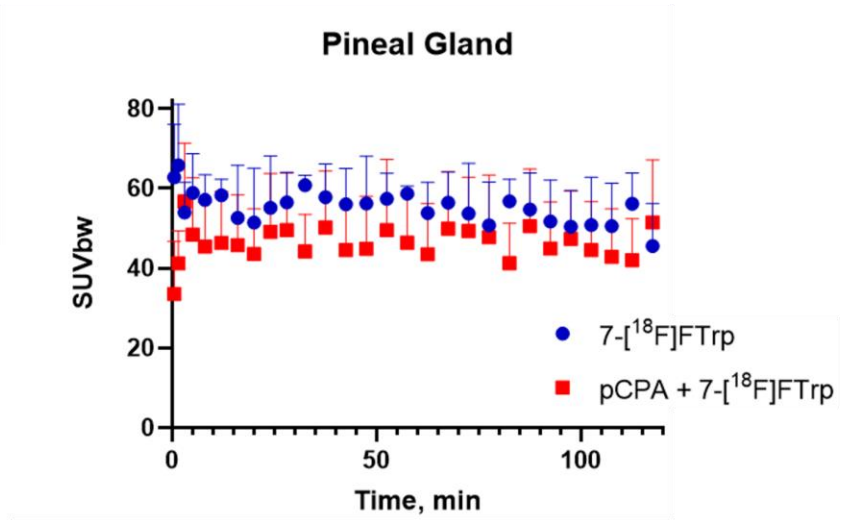
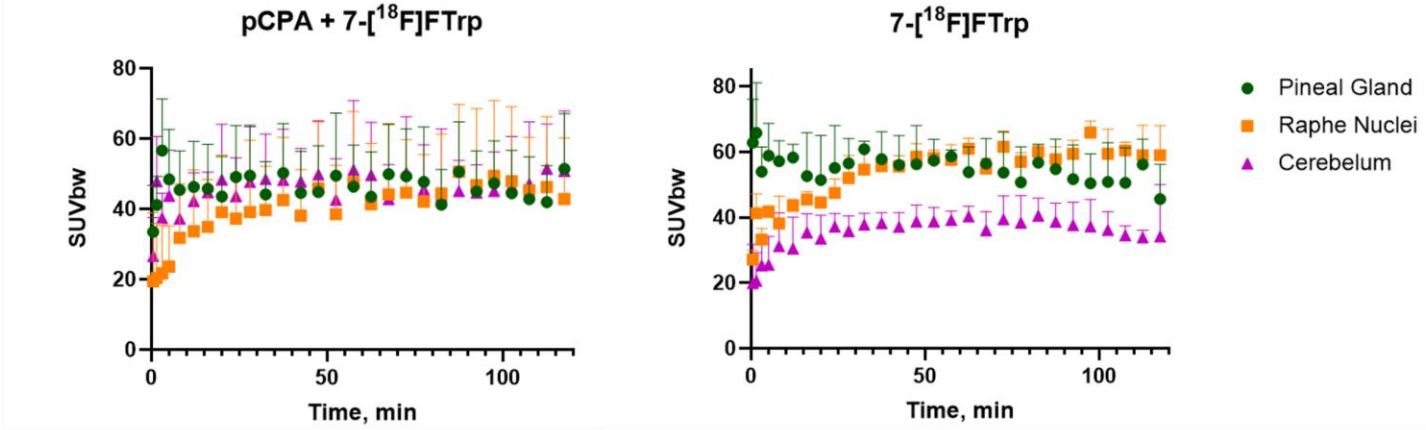

0-30min
30-60 min
60-90 min
90-120min
pCPA + 7-[18F]FTrp
7-[18F]FTrp
Pineal Gland
10mm
0
100

B


PET, 7-[18F]FTrp
0-30min/MRI
MRI/T2w
Olfactory bulb
Cerebral cortex
Hypocampus
Colliculus
IV ventr/Aqu.
Pineal Gland
Cerebelum
Optic Nerve
Corpus Calosum
Fornix
Thalamus
Pons
Medulla Oblongata
Pineal Gland
10mm

C


Pineal Gland
SUVbw
Time, min
7-[18F]FTrp
pCPA + 7-[18F]FTrp


pCPA + 7-[18F]FTrp
7-[18F]FTrp
SUVbw
Time, min
Pineal Gland
Raphe Nuclei
Cerebelum

Conclusions

- 5-[^{18}F]FMT shows higher initial tumor uptake, but the lack of substantial tumor retention may limit its utility for glioma imaging.
- 7- [^{18}F]FTrp is a promising PET probe for glioma imaging, comparable with the established tracer [^{18}F]FET.
- While [^{18}F]FET is particularly suitable at early timepoints after injection (first 30 min), 7-[^{18}F]FTrp provides good image quality for at least 2h after injection.
- According to preliminary results 7- [^{18}F]FTrp may reveal sensitivity towards serotoninergic activity in brain.