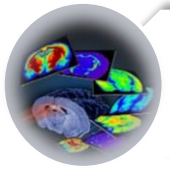
“APPLICATION OF RADIOACTIVE IMAGING AGENTS AS POWERFUL TOOLS IN CLINICAL PRACTICE”

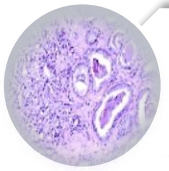
23.08.2018| B. NEUMAIER

O



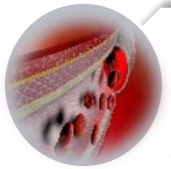
Introduction: Molecular imaging/PET

U



Prostate cancer

T

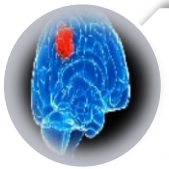


Reendothelialization

L

Neuropathic pain

I

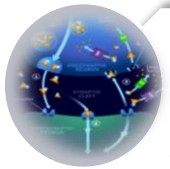


Glioma

N

Inflammation

E



Tryptophan metabolism

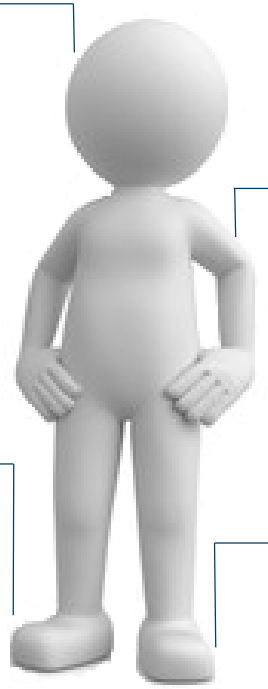
RADIOACTIVE IMAGING AGENTS- WHY?

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

Evaluation of molecular response



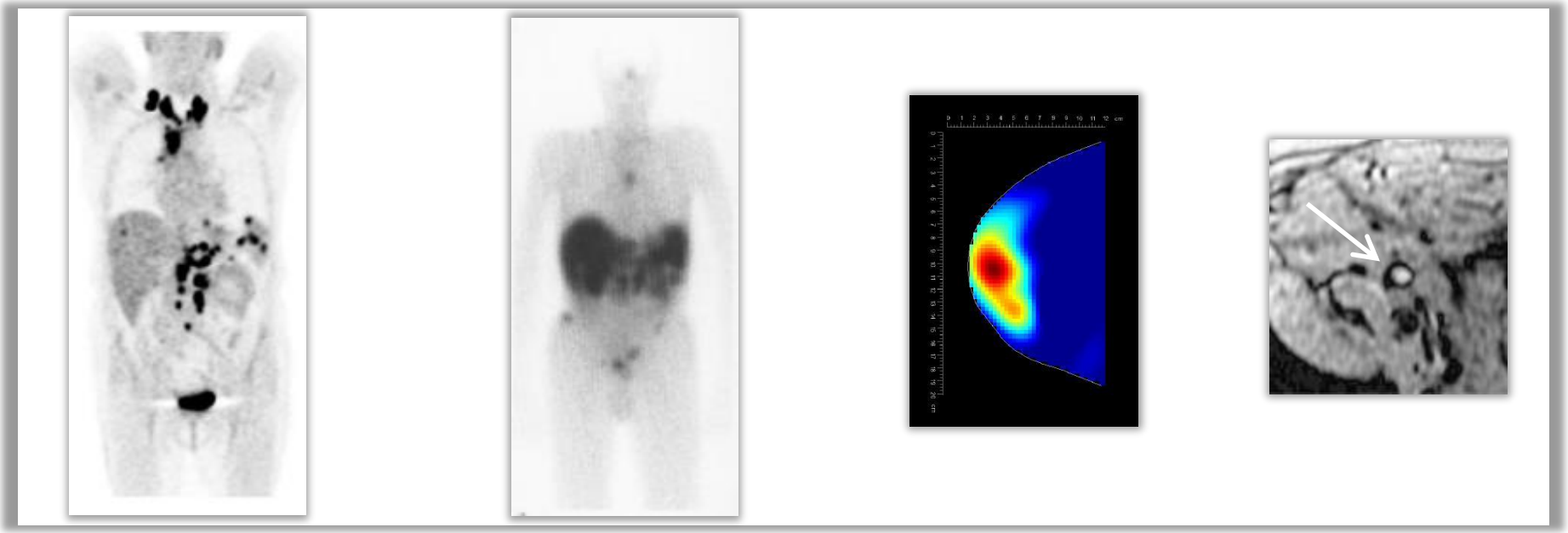
Disease detection as early as possible

Patient stratification – optimal and individual therapy for each patient

Monitoring of therapy efficacy

DIFFERENT METHODS OF MOLECULAR IMAGING

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



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

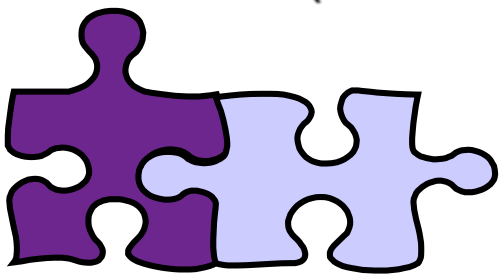
SPECT
Single Photon Emission Computed Tomography
(NET; ^{111}In-DTPA-Octreotid)

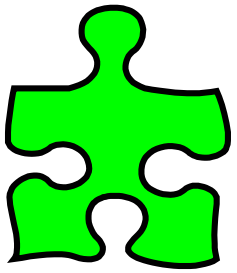
Softscan
NIR Fluorescence Imager
(Breast cancer; DeoxyHb)

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

PRINCIPLE OF MOLECULAR IMAGING

Targeting molecule
(Vehicle)



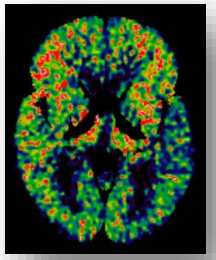


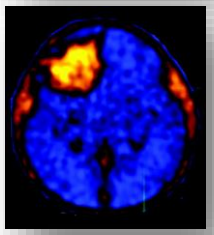
Reporter
(Radionuclide,
fluorescent dye or
magnetic label)

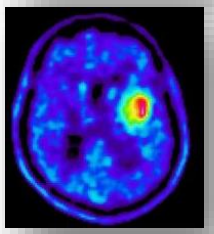
Biological targets

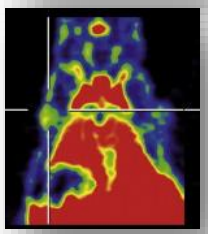
BIOLOGICAL TARGETS FOR DISEASE DETECTION

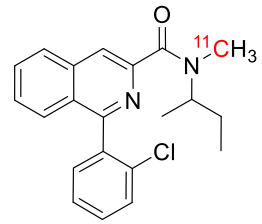
Visualization of molecular processes - measurement of molecular alterations UP- or DOWN regulation of

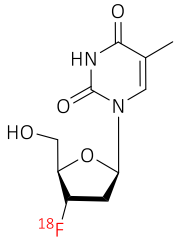


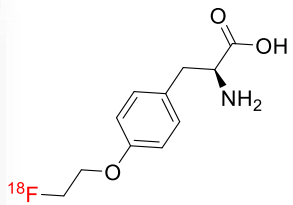


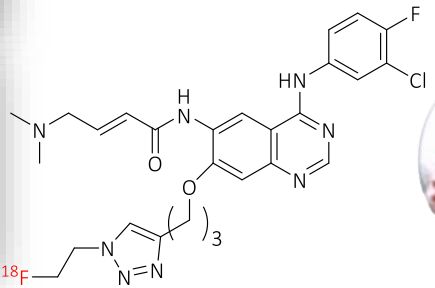


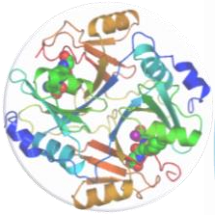


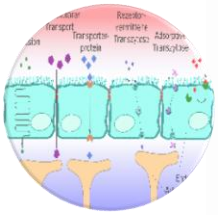


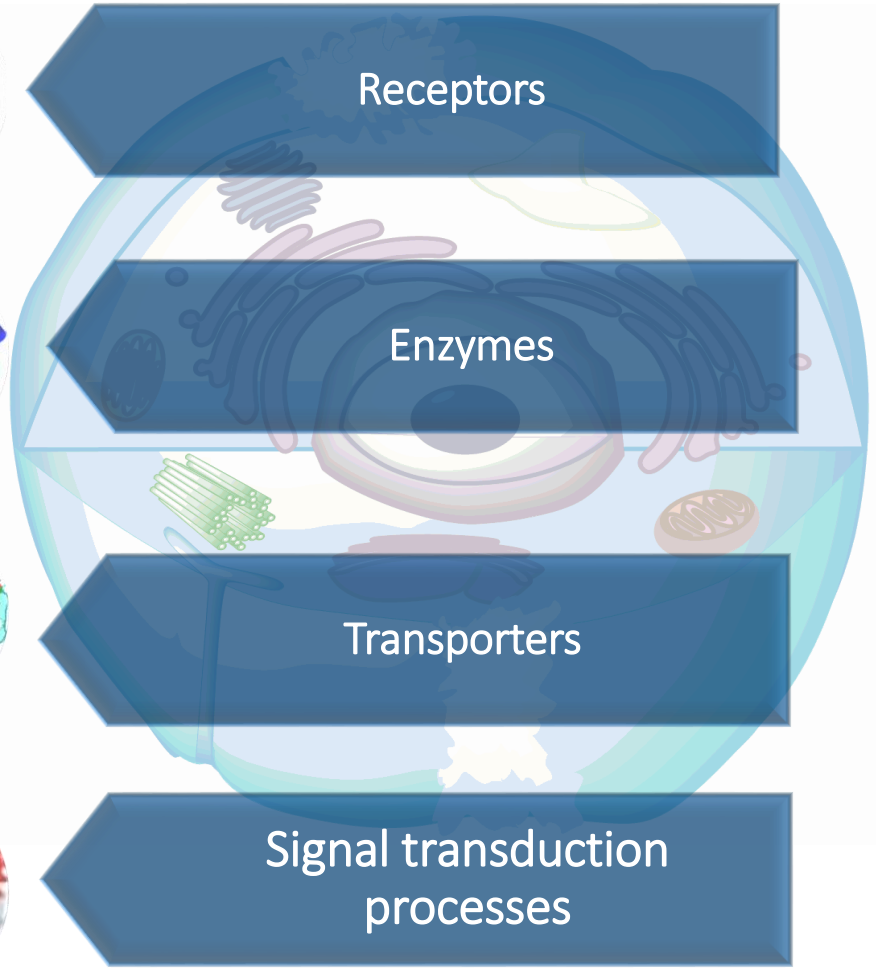






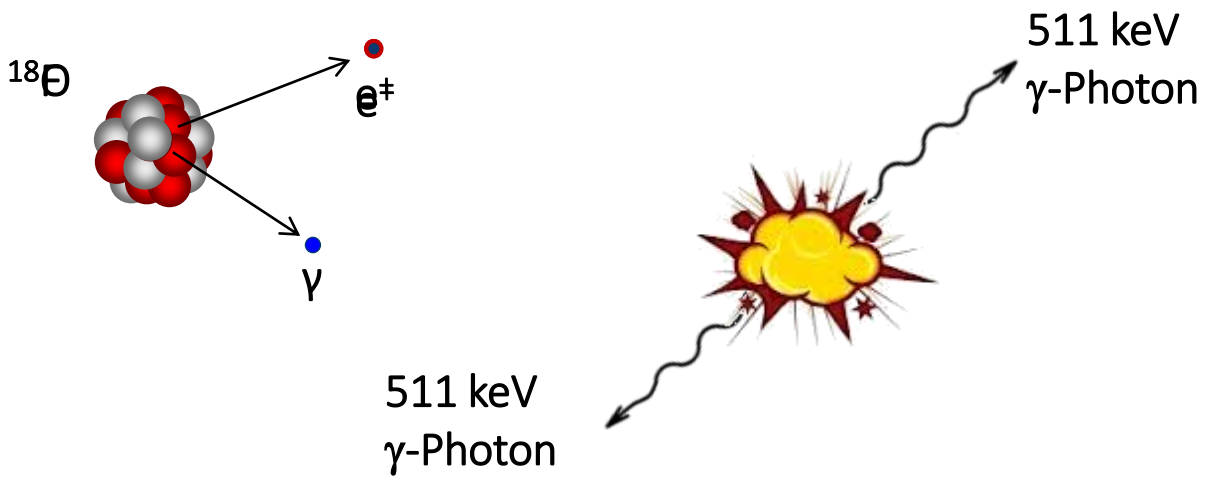






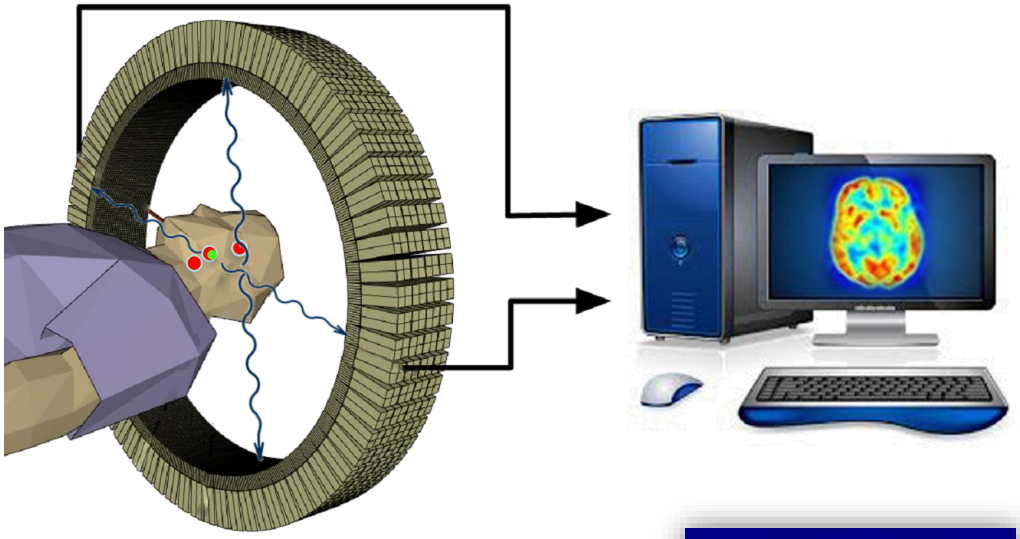
PET: PHYSICAL BACKGROUND

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



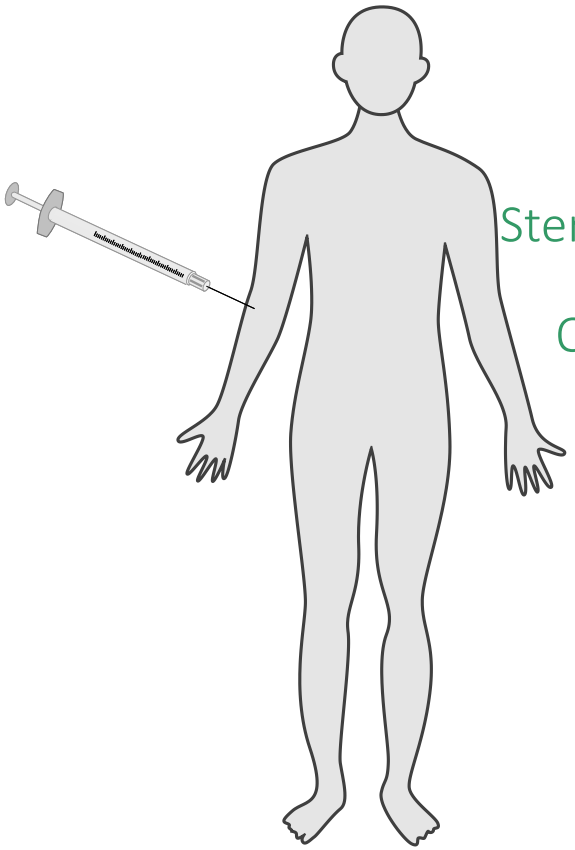
- Emission of an positron as a result of β^+ decay
- Positron is thermalized and undergoes recombination with electron
- Conversion of mass into energy by $E = m \cdot c^2$
- Emission of 2 γ-quants in opposite directions (180°)

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 RADIO-PHARMACEUTICALS

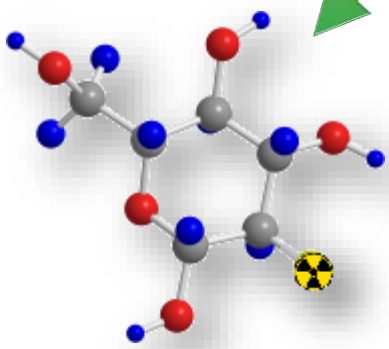


Radionuclide production — 60 min

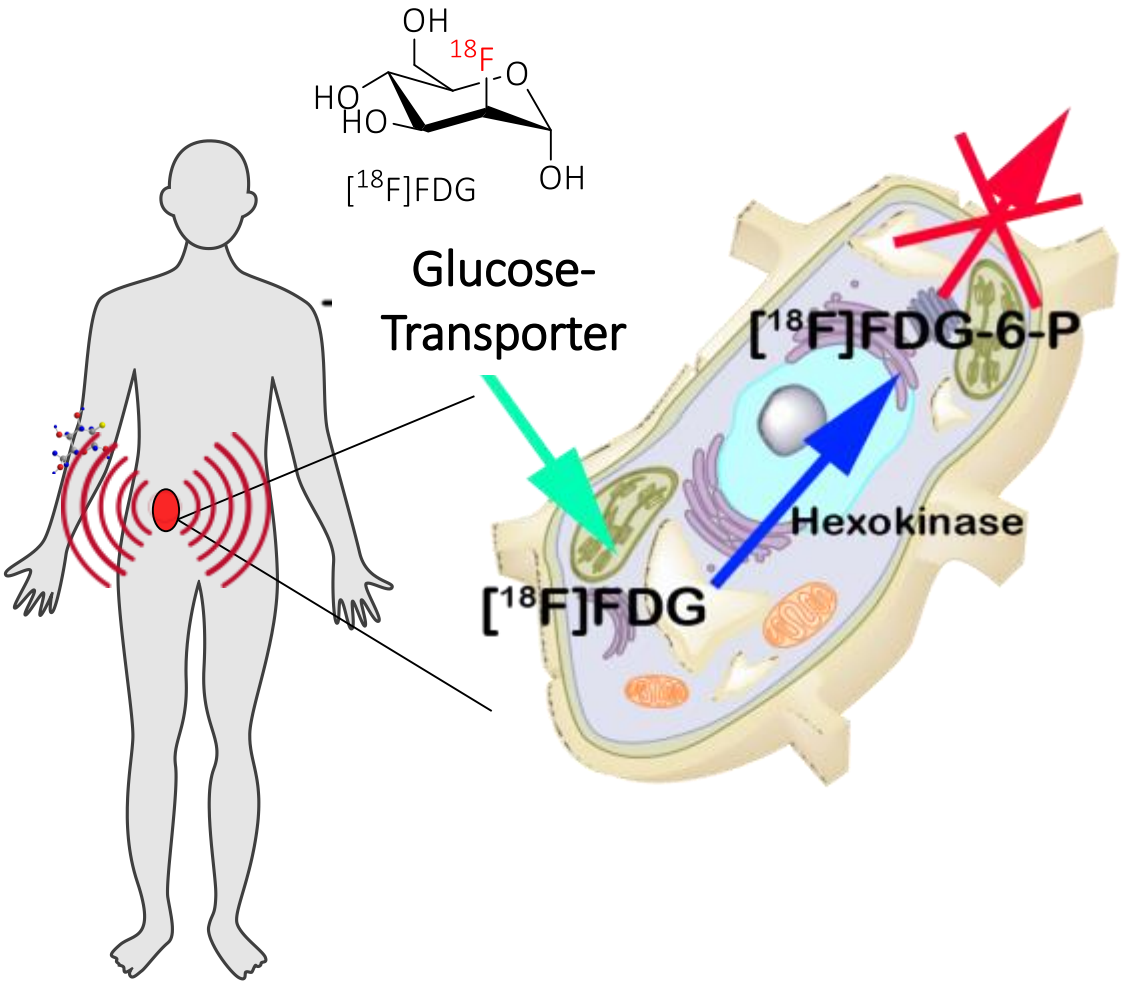
Radiosynthesis — 90 min

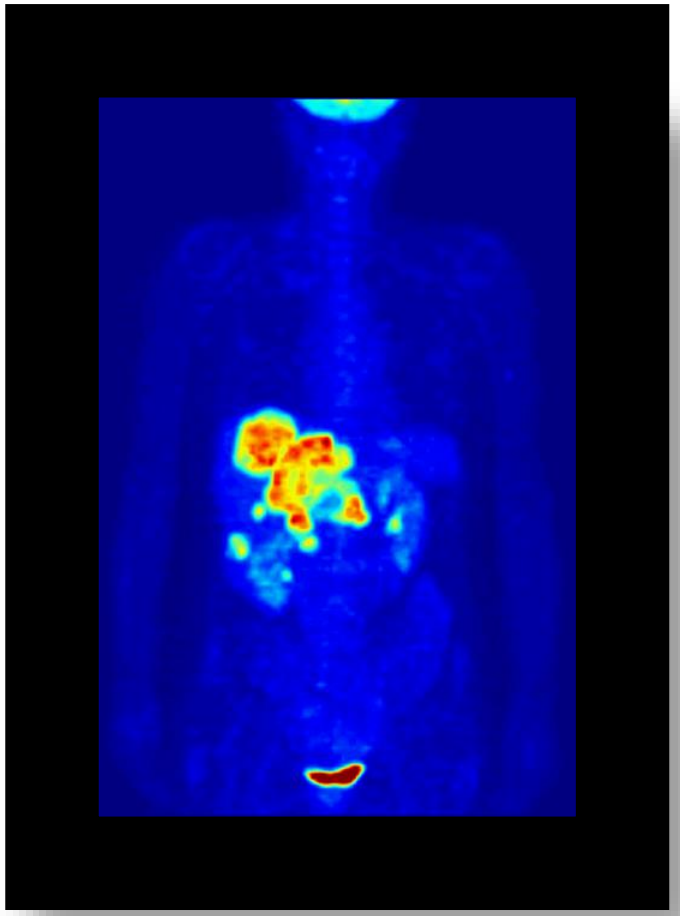
Sterilization / Dispensing — 115 min

Quality control — 125 min



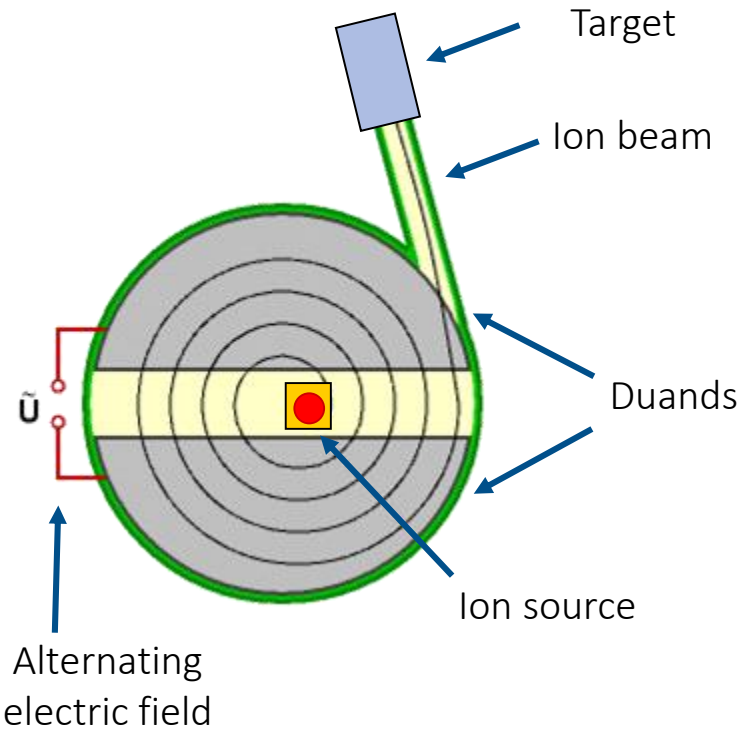
PET DIAGNOSTICS WITH [^{18}F]FDG

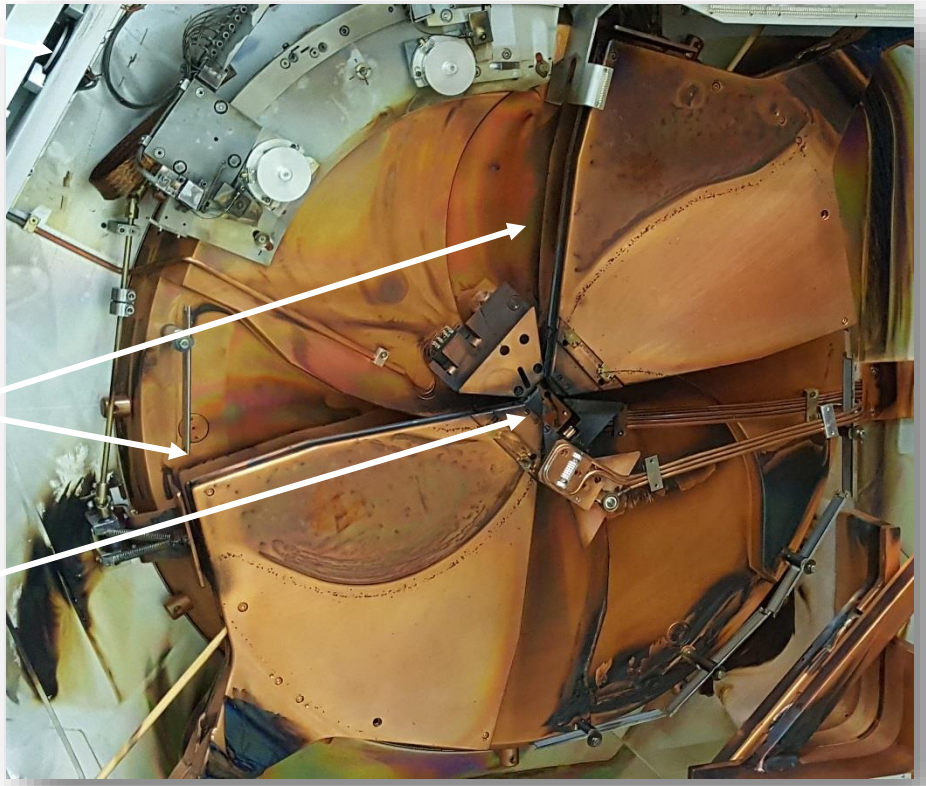




RADIONUCLIDE PRODUCTION AT A CYCLOTRON

RADIONUCLIDE PRODUCTION AT A CYCLOTRON





NUCLEAR REACTION FOR THE PRODUCTION OF ^{18}F

neutron

^{18}Oxygen

proton

≠

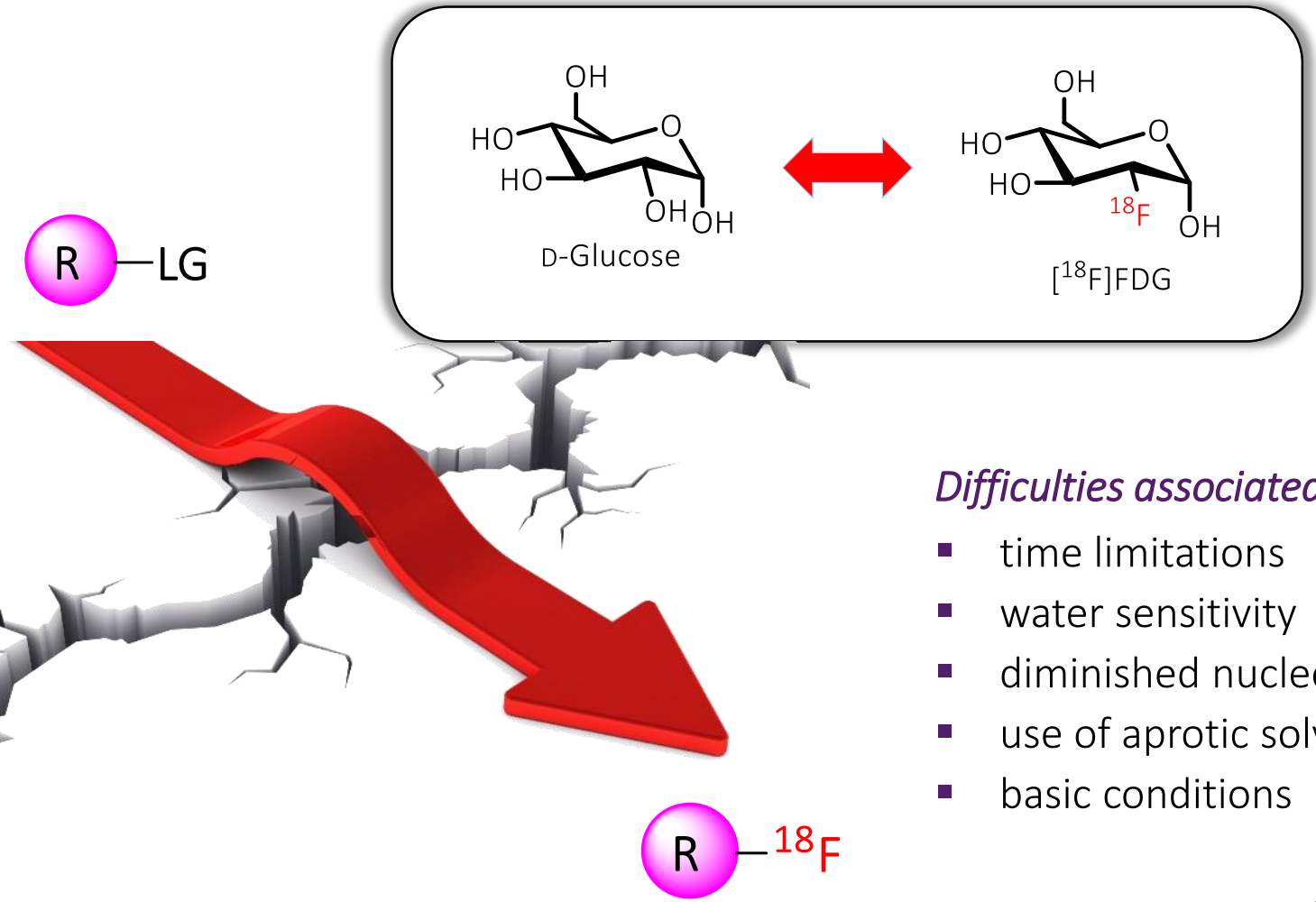
^{18}Fluoride

Compound nucleus $[^{19}F]^*$

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

^{18}F half life: 110 min

^{18}F-CHEMISTRY

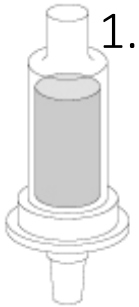


Difficulties associated with ^{18}F-chemistry:

- time limitations
- water sensitivity
- diminished nucleophilicity of ^{18}F
- use of aprotic solvents
- basic conditions

PREPARATION OF [^{18}F]FDG

-the working horse in clinical PET-

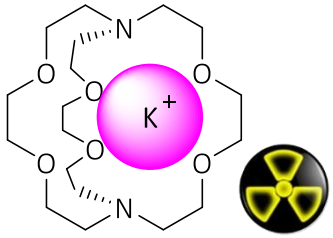


1. Recovery of ^{18}O-water and fixation of $^{18}F^-$ aq.

- Trapping of $^{18}F^-$ on anion exchange cartridge
- Elution of $^{18}F^-$ with K_2CO_3-solution as [^{18}F]KF

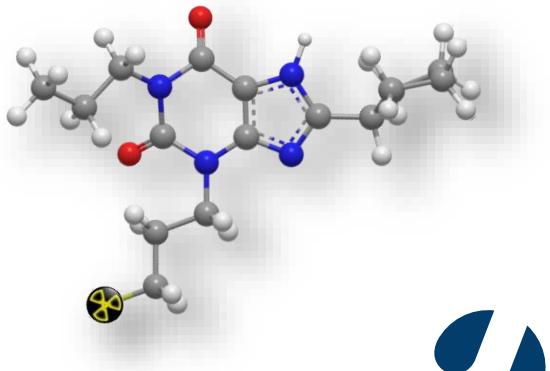
2. ^{18}F-Activation, incorporation & deprotection

- Addition of K 2.2.2 cryptand for $^{18}F^-$ activation
- Removing of water by several azeotropic drying steps
- Reaction at 85 °C with precursor in aprotic solvent
- Deprotection



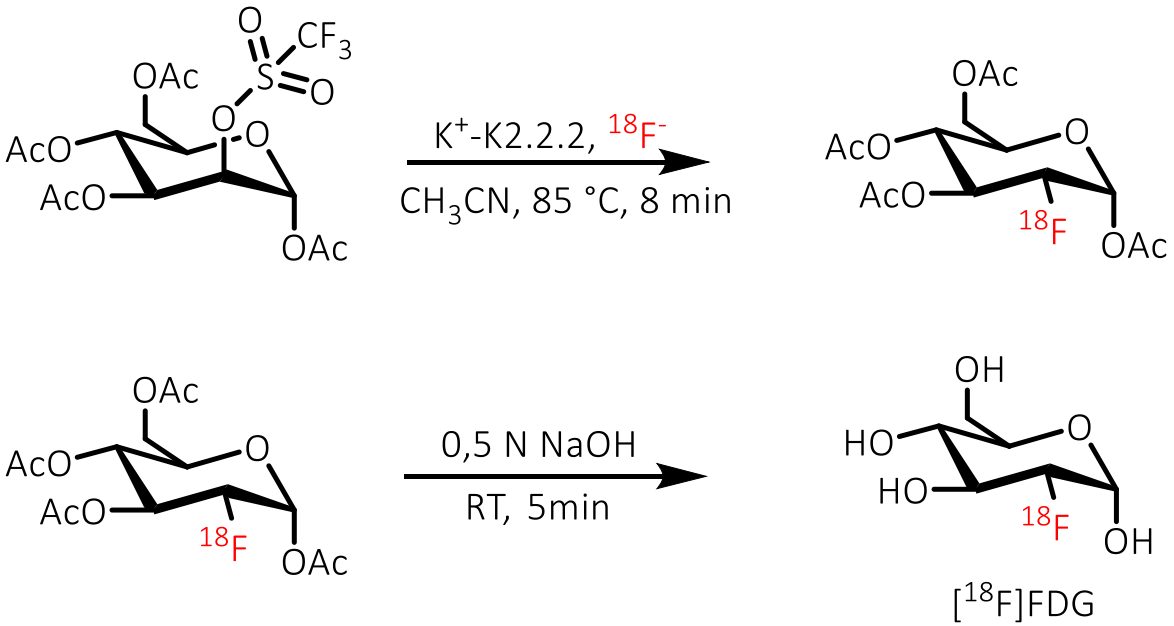
3. Purification

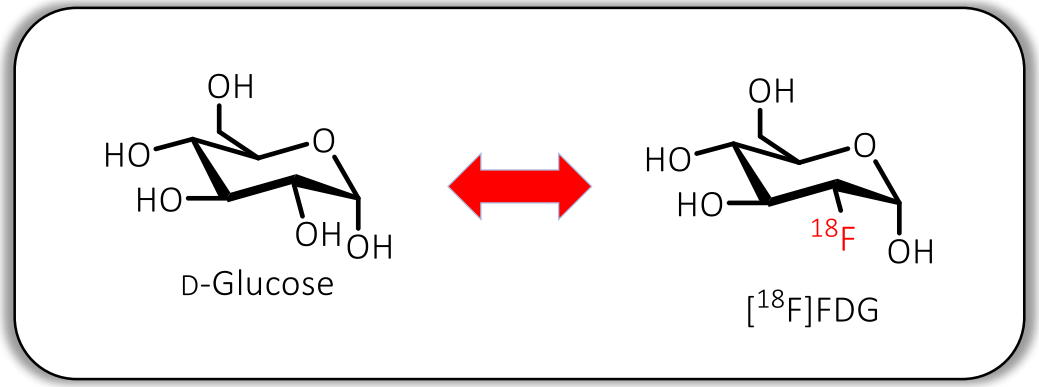
- Solid phase extraction purification
- Formulation
- Sterilization
- Quality control



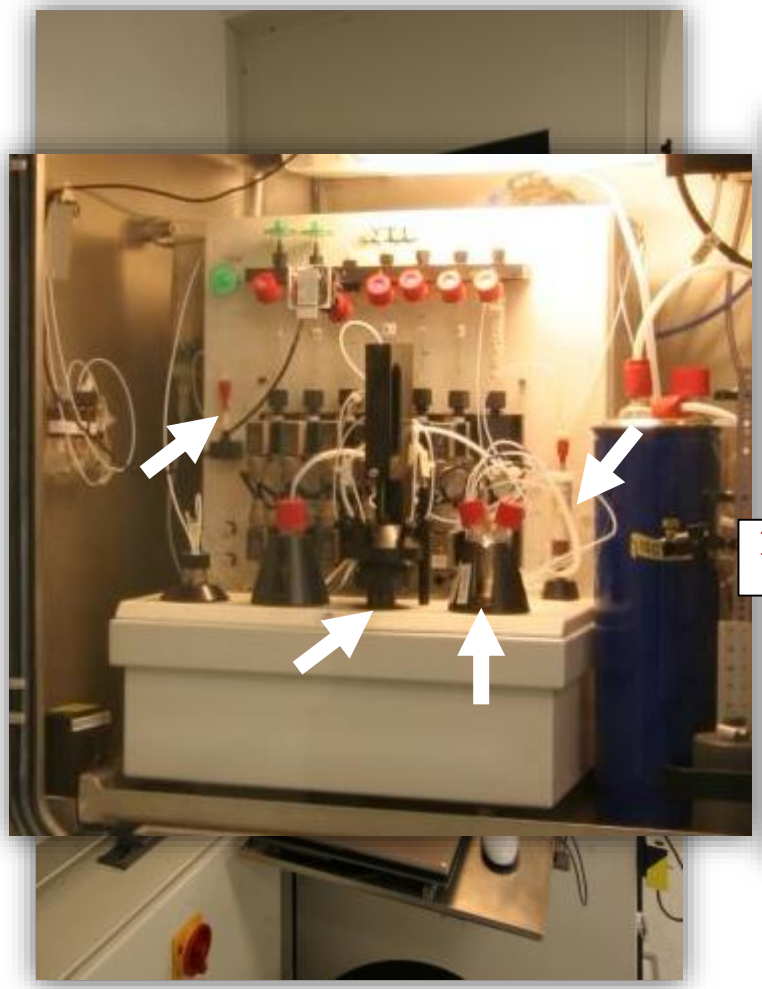
PREPARATION OF [^{18}F]FDG

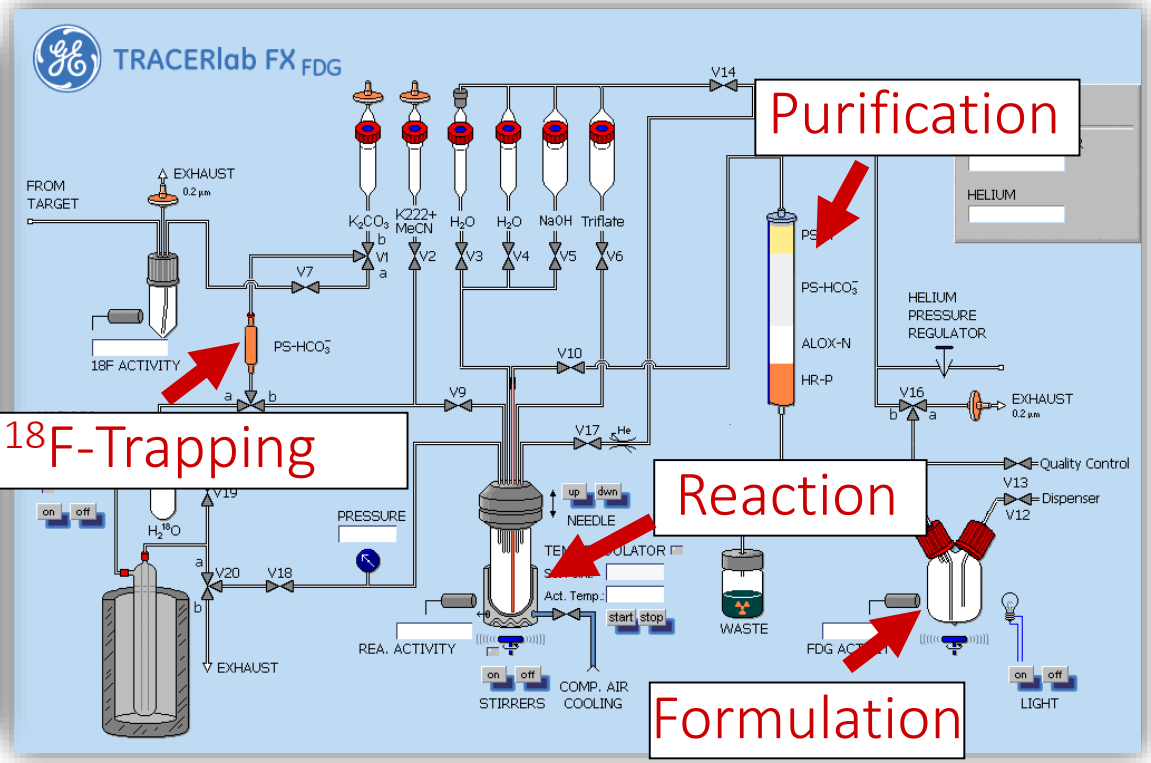
-the working horse in clinical PET-





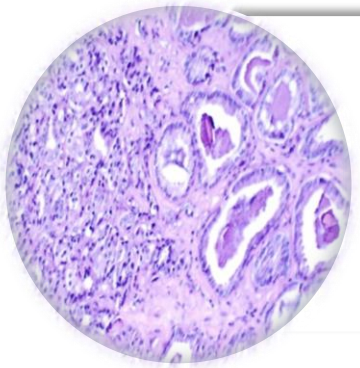
RADIOSYNTHESIS IN HOT CELLS





Remotely controlled synthesis module

IMAGING OF PCa RECURRENCE BY [^{18}F]PSMA-PET

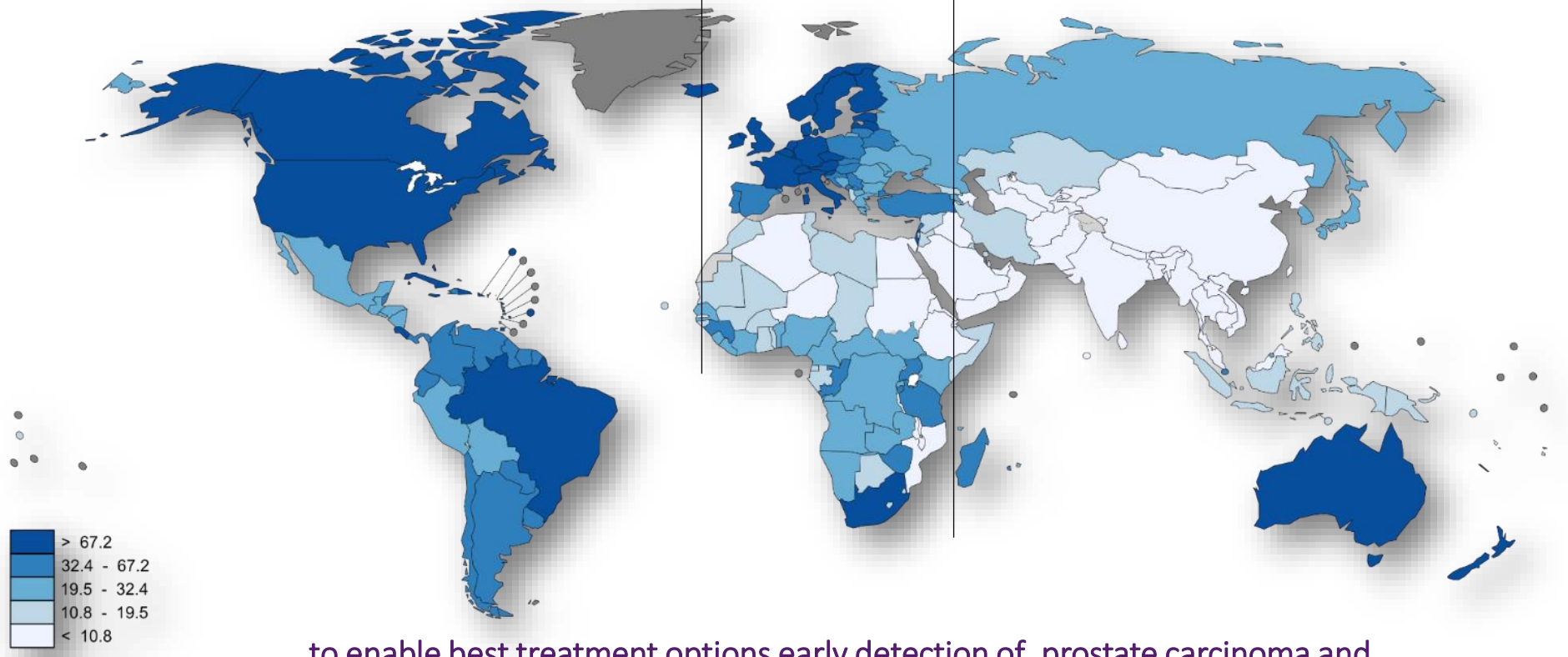


Prostate cancer

PROSTATE CARCINOMA (PCa)

second most frequently diagnosed cancer worldwide

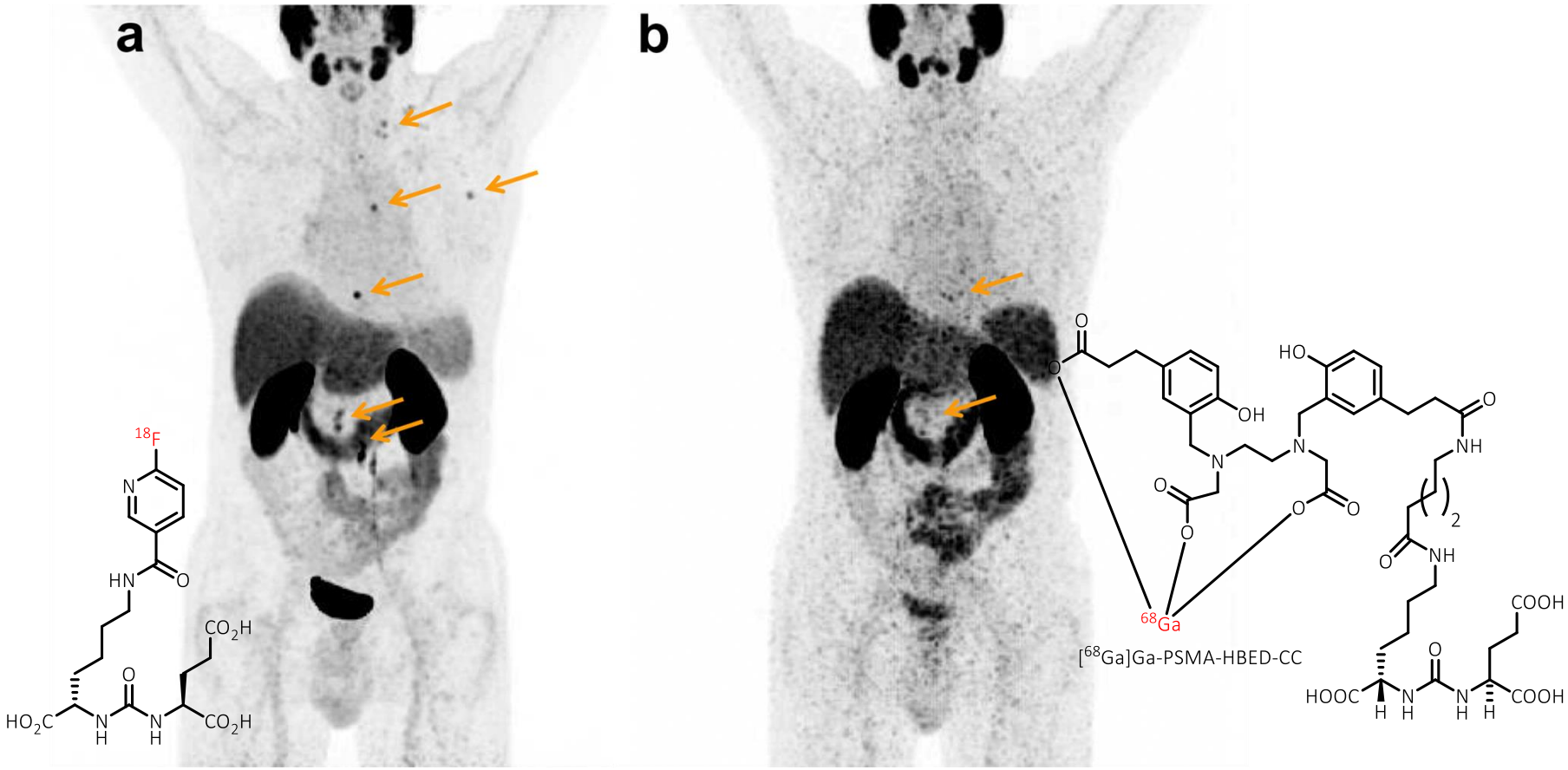
sixth leading cause of cancer death in males



Estimated age-standardised rates (World) per 100,000

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

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



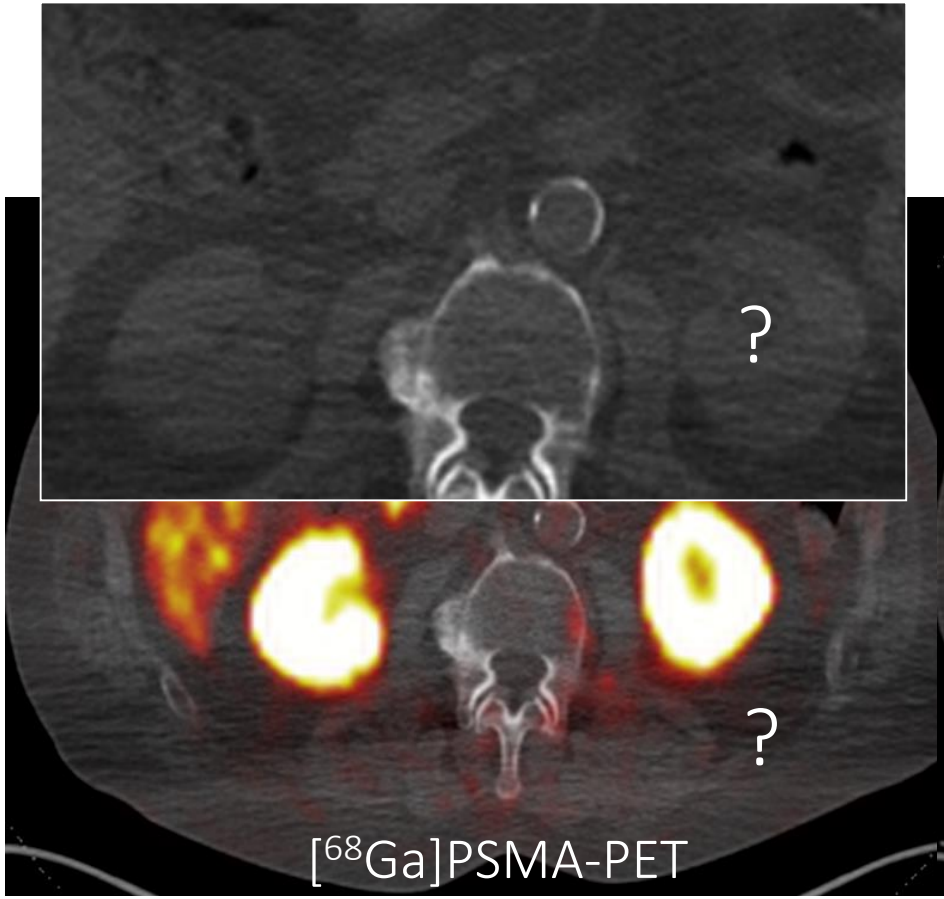
[^{18}F]PSMA

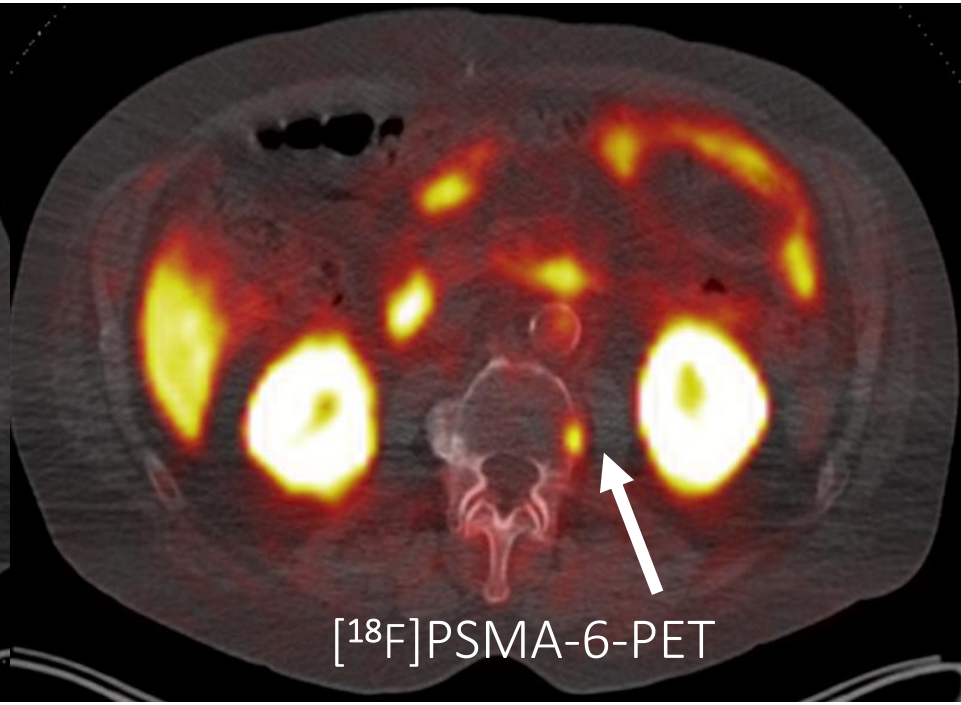
[^{68}Ga]Ga-PSMA-HBED-CC

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

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

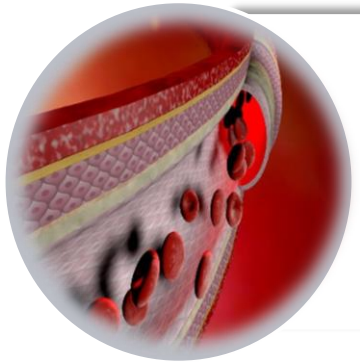
Detection of even very small lesions





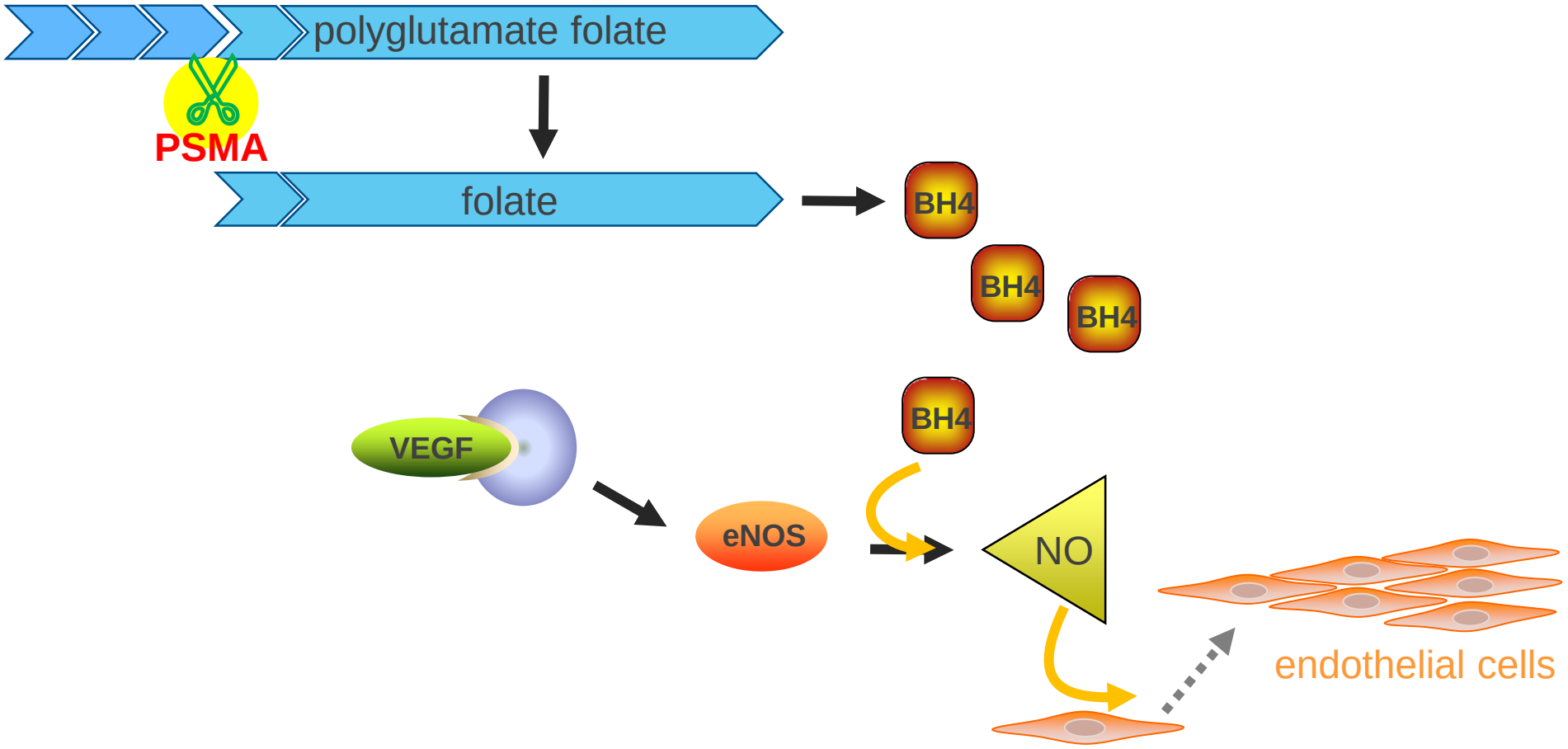
Courtesy of C. Kobe, M. Dietlein, Nuklearmedizin UKK

REENDOTHELIALISATION BY [^{18}F]PSMA

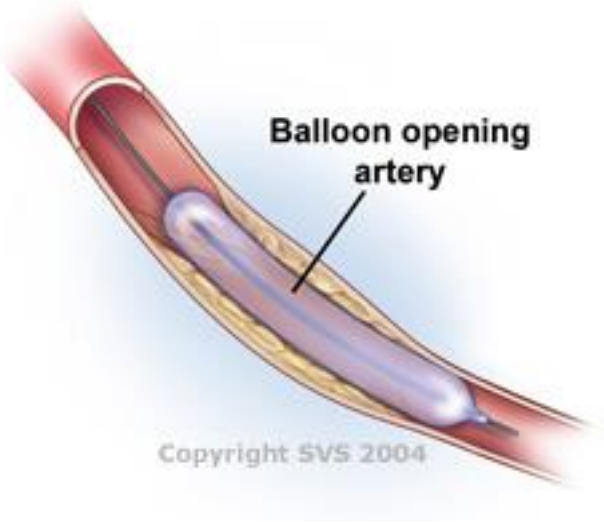


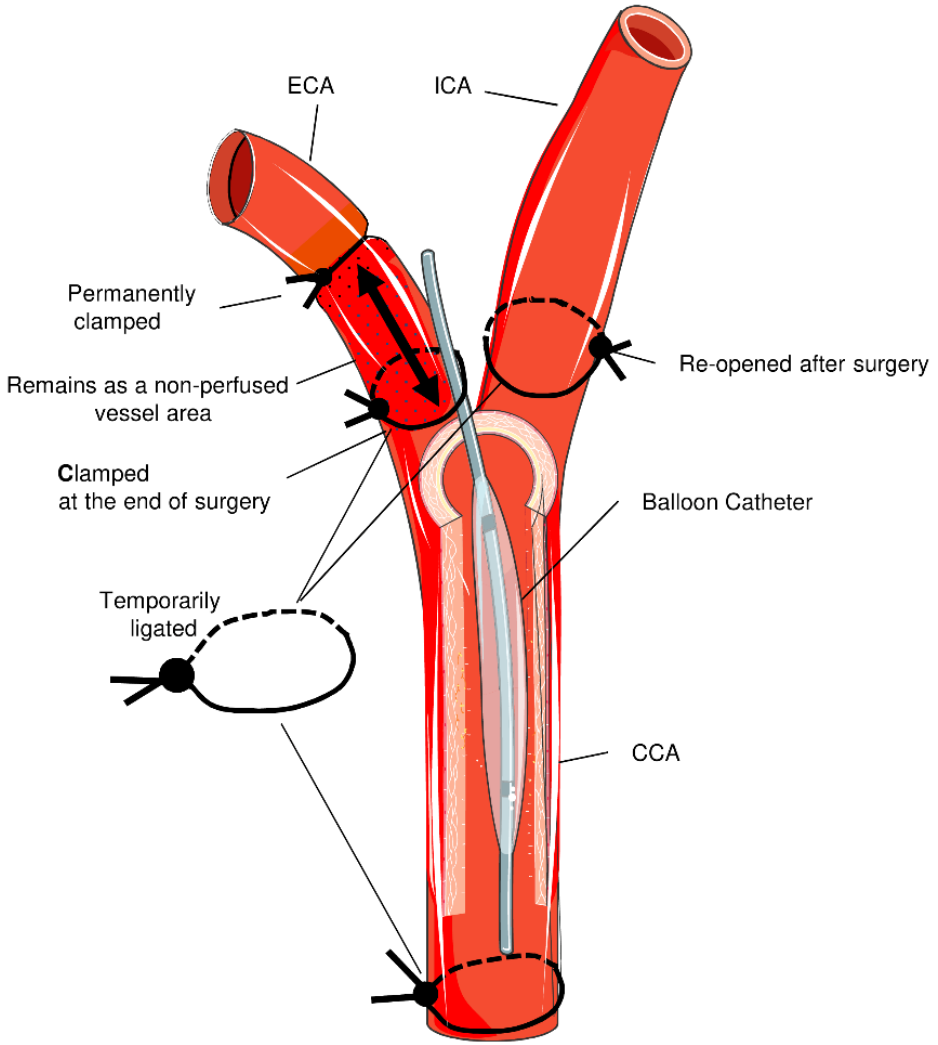
Reendothelialisation

THE ROLE OF PSMA IN REENDOTHELIALISATION



BALLOON DILATATION MODEL





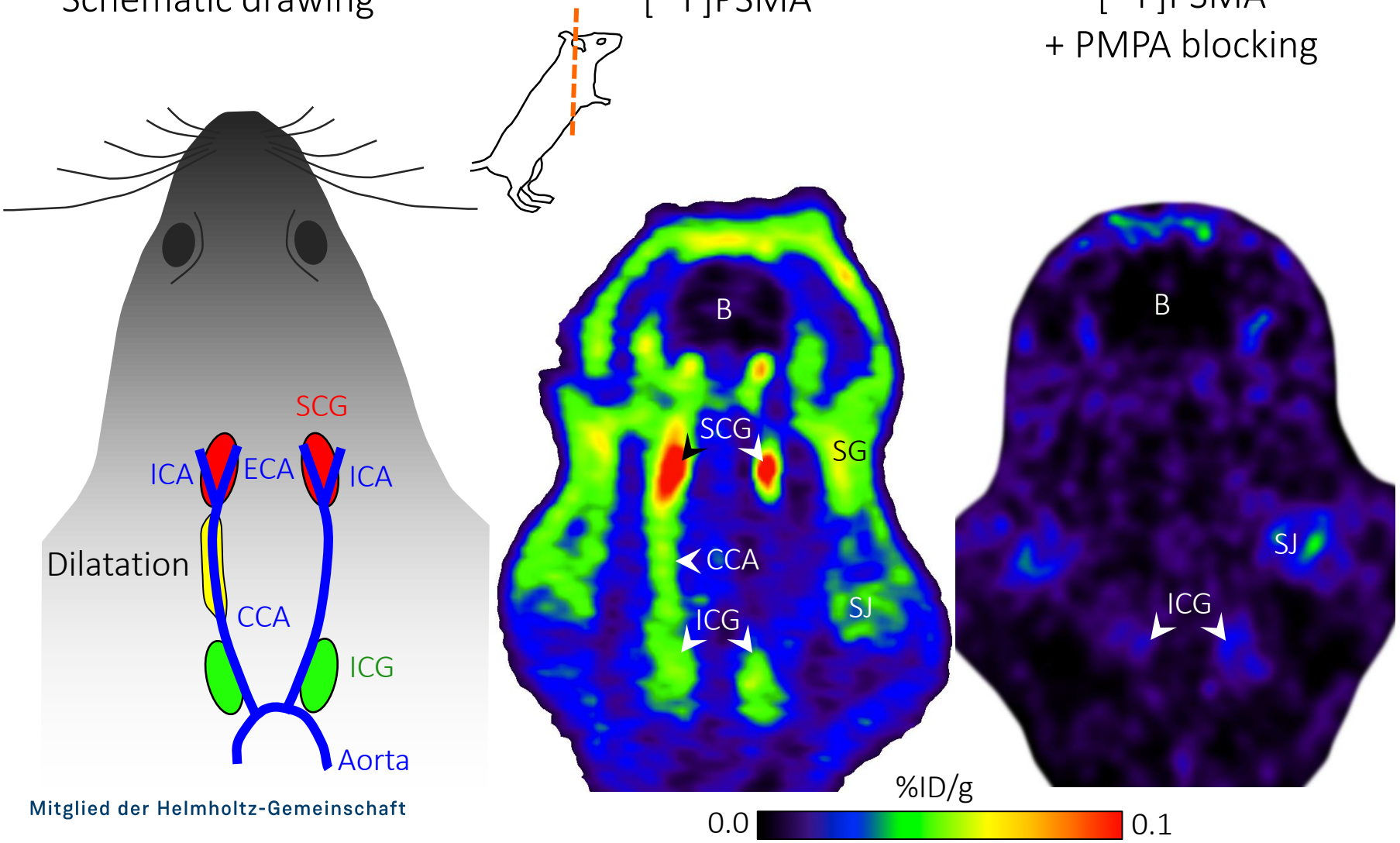
Balloon dilatation model

IMAGING OF REENDOTHELIALISATION BY PSMA PET

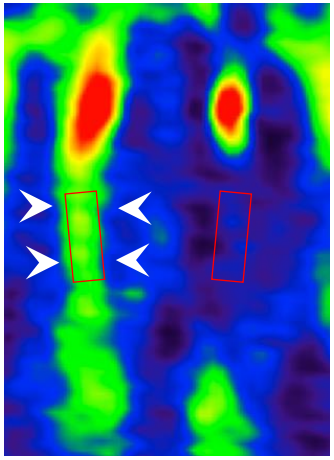
Schematic drawing

[18F]PSMA

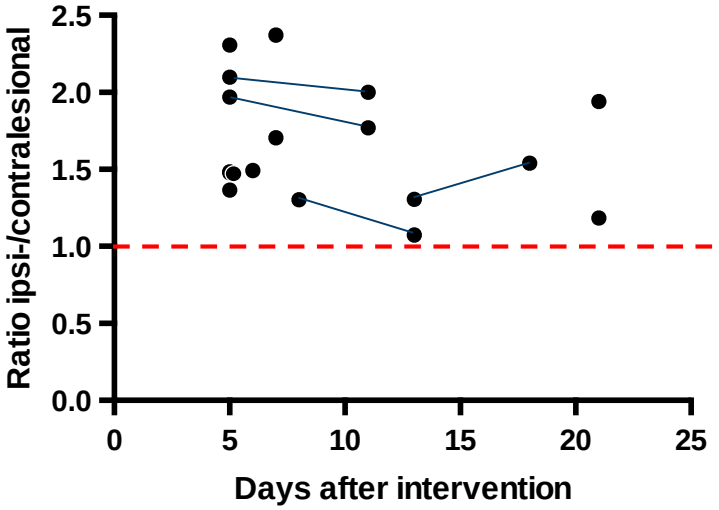
[18F]PSMA
+ PMPA blocking



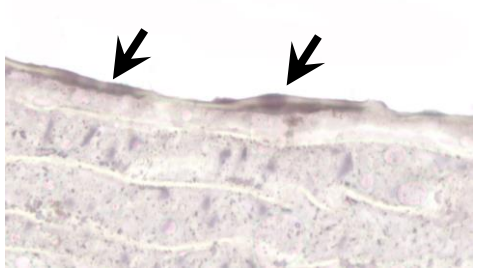
ANALYSIS OF PSMA EXPRESSION



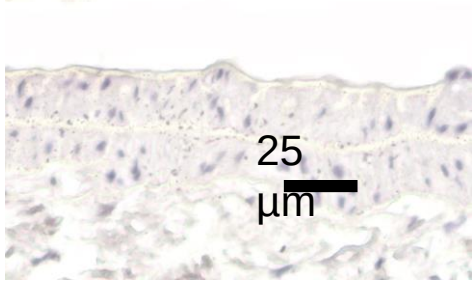
VOIs (red squares) used for analysis



VOI ratios (ipsi-/contralateral) over time after dilatation



immunostaining of the dilated CCA



immunostaining of the contralateral CCA

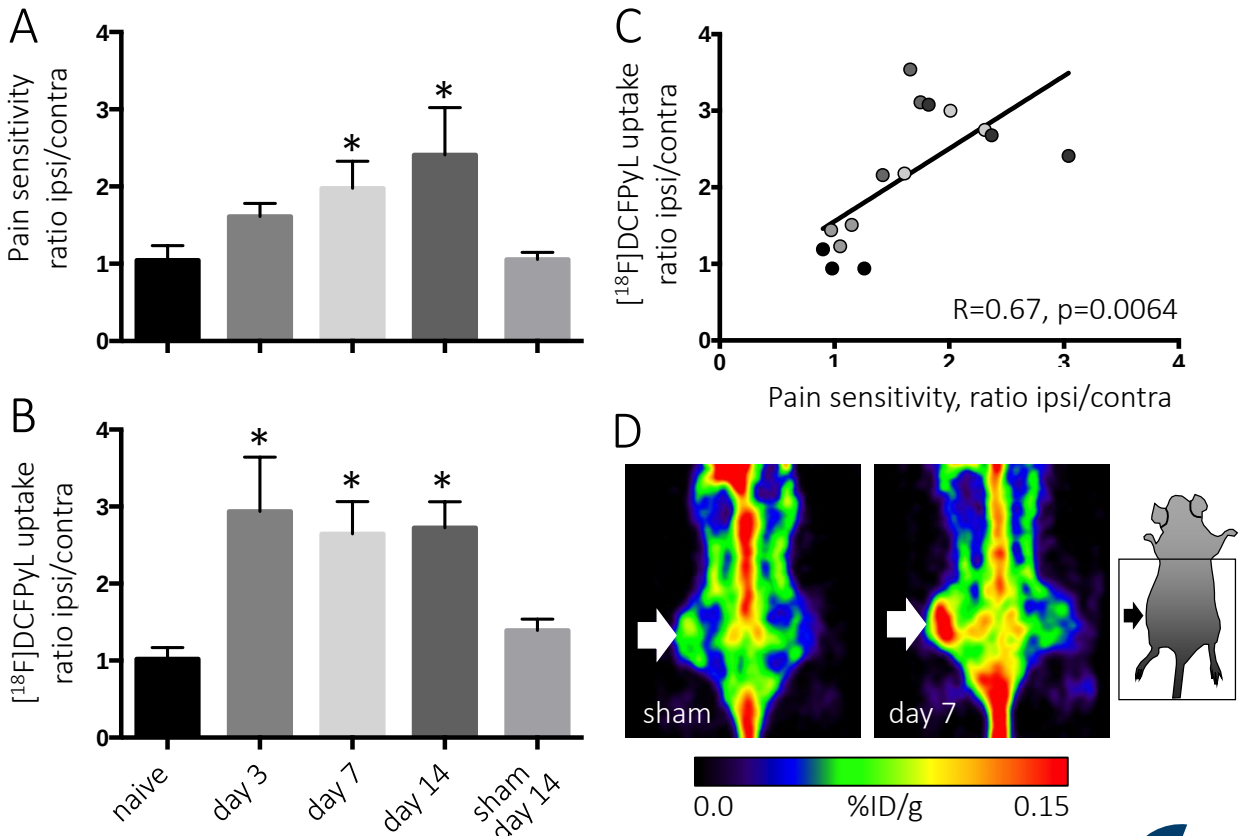
NEUROPATHIC PAIN BY [^{18}F]PSMA PET

Neuropathic pain

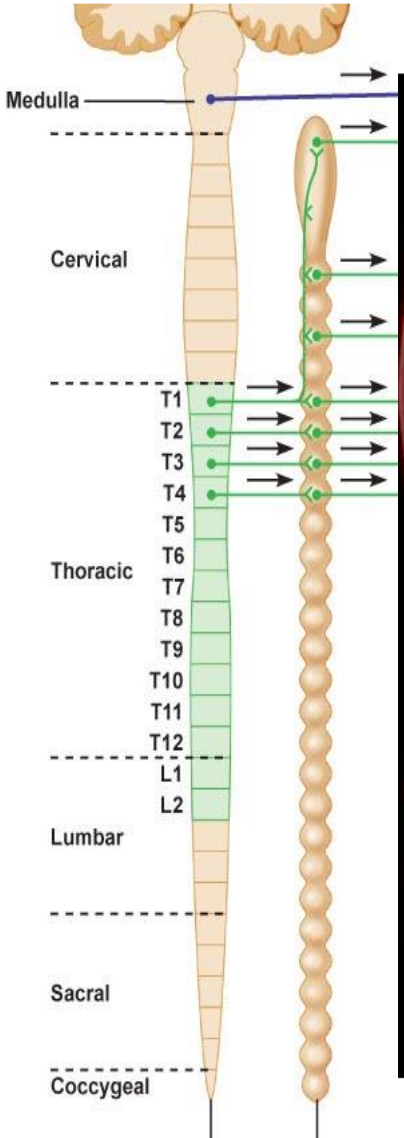
- Methods to visualize the location and/or the intensity of pain are missing
- Pain diagnosis refers to self-reports of patients
- PSMA increases the local concentration of the neurostimulatory transmitter glutamate involved in neuropathic pain
- Glutamate, is an excitatory transmitter inducing strong nociceptor activation
- Is it possible to detect neuropathic pain by PSMA PET?

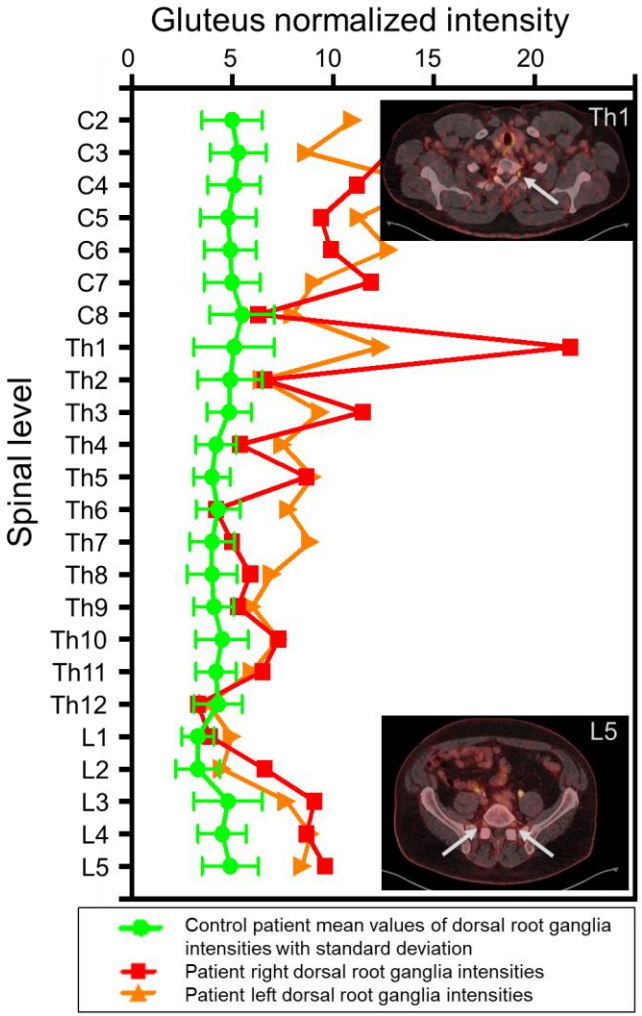
VISUALIZATION OF NEUROPATHIC PAIN BY [18F]PSMA PET

Neuropathic pain induced by sciatic nerve lesion (SNI)



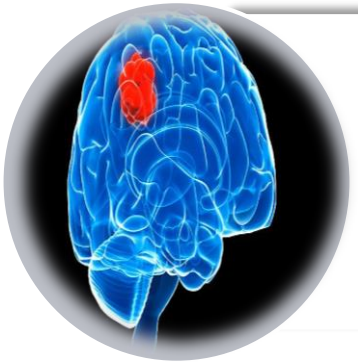
[^{18}F]PSMA PET OF A PATIENT WITH CHRONIC PAIN





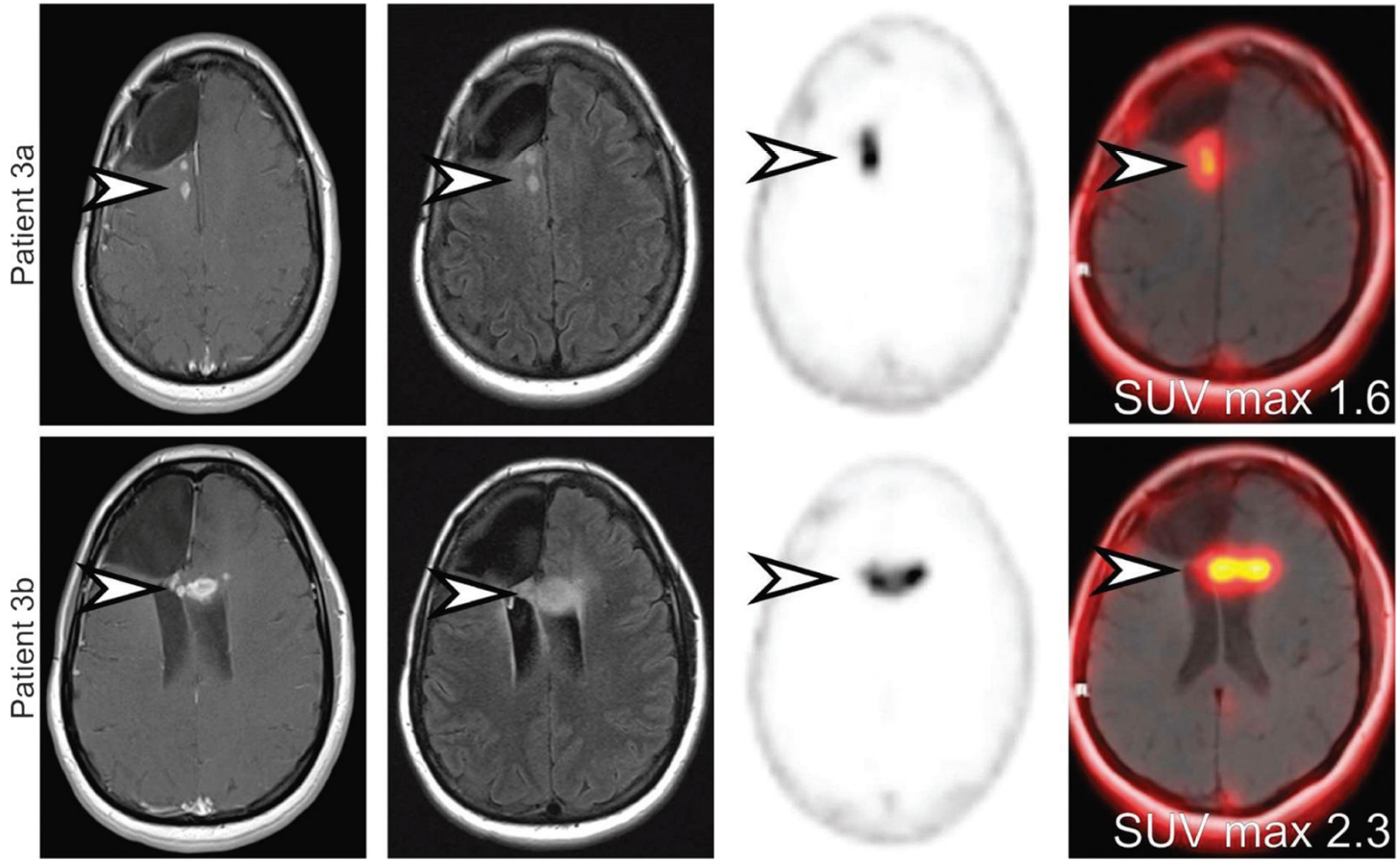
Courtesy of C. Kobe, M. Dietlein, S. Stockter Nuklearmedizin UKK

GLIOMA BY [^{18}F]PSMA PET



Glioma

[^{18}F]PSMA PET OF PATIENTS WITH HIGH-GRADE GLIOMAS



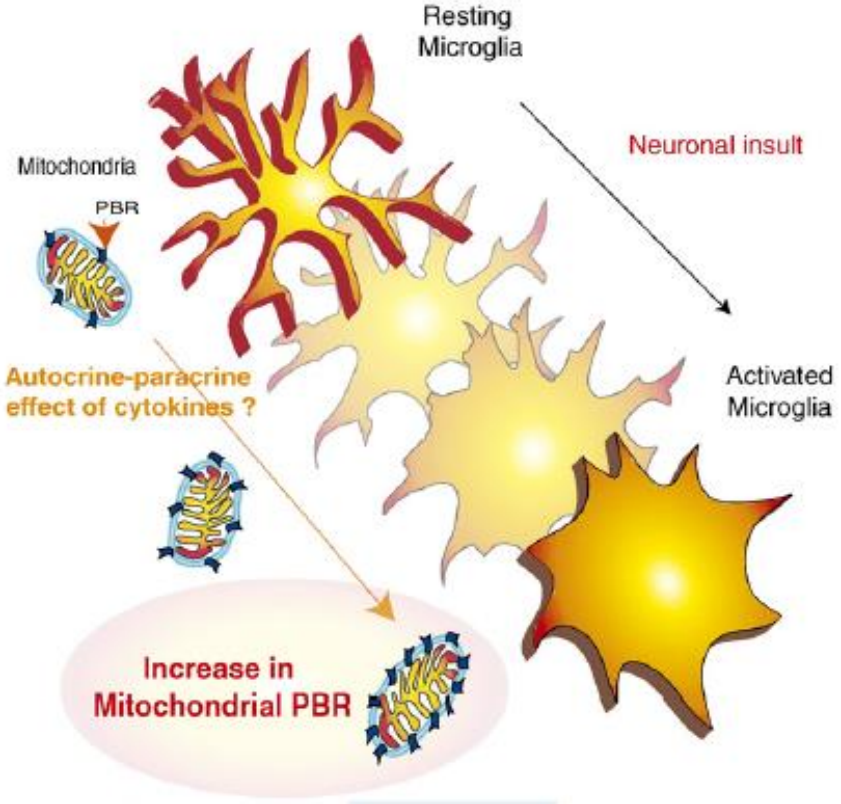
Inflammation

POST-CARDIAC ARREST SYNDROME "POST-RESUSCITATION SYNDROME"

- Strong inflammatory reaction in whole body
  - Triggered by cytokines (interleukins, tumor-necrosis-factor)
  - Sepsis like symptoms
- Activation of blood coagulation
  - Reperfusion damage
- Reperfusion injury („reperfusion paradoxon“)
  - Formation of oxygen radicals
- In particular vulnerable: the brain
  „time is brain“

Bild: Canstock

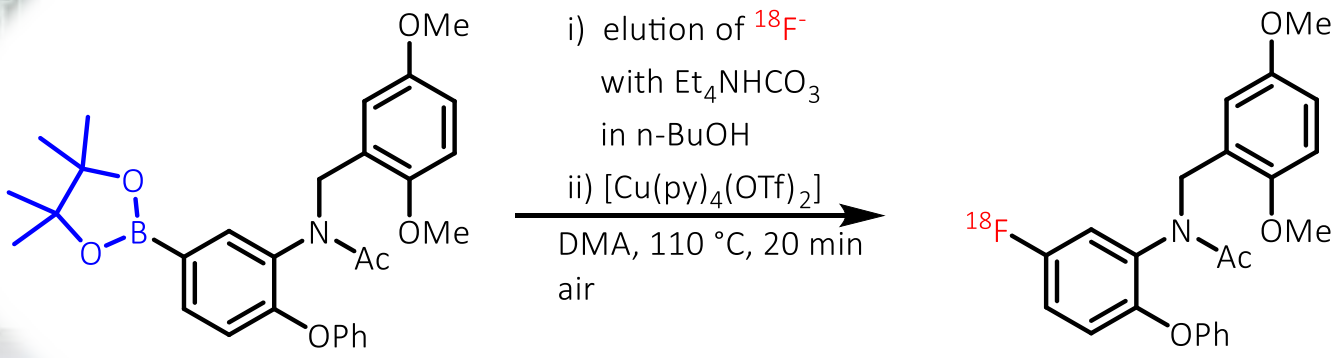
CARDIAC ARREST INDUCES MICROGLIA-ACTIVATION IN THE BRAIN



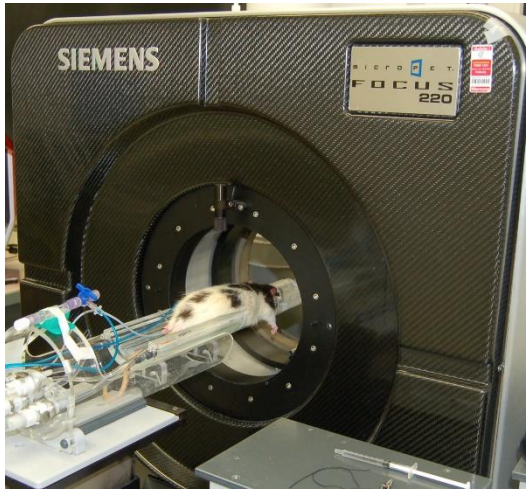
Question:

Characteristic and persistence of inflammation in the brain?

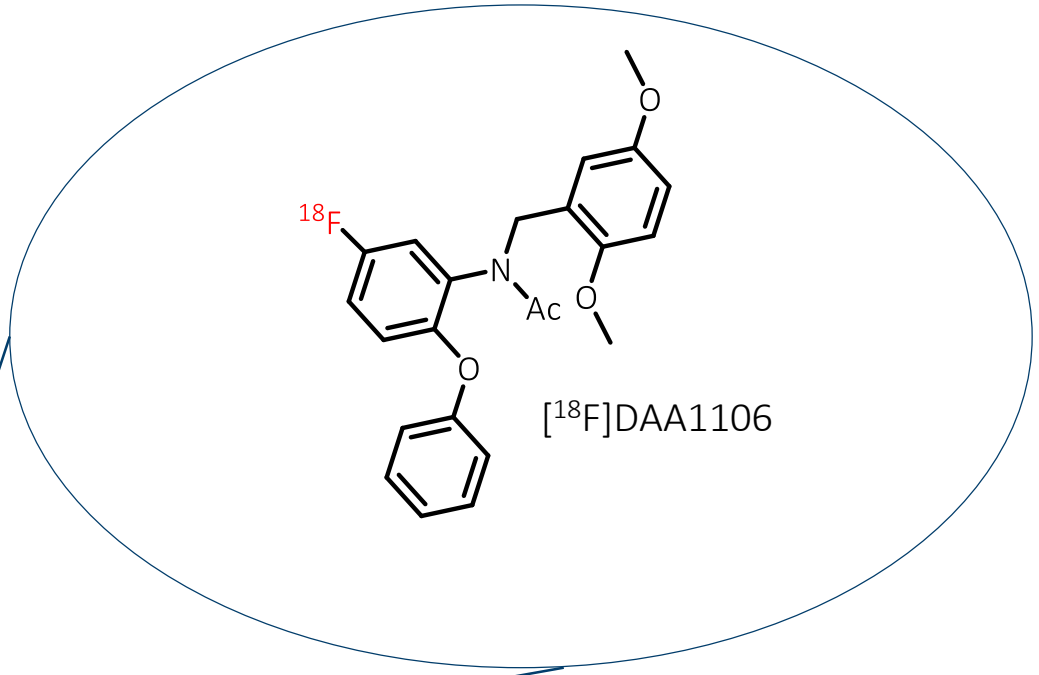
RADIOSYNTHESIS OF INFLAMMATION MARKER

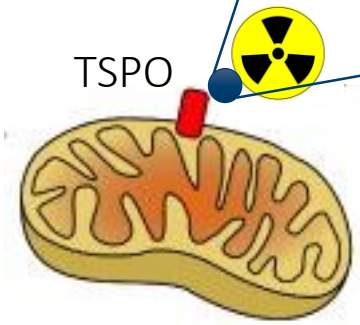


BRAIN IMAGING OF RESUSCITATED RATS WITH [^{18}F]DAA1106



5 resuscitated rats
3 controls

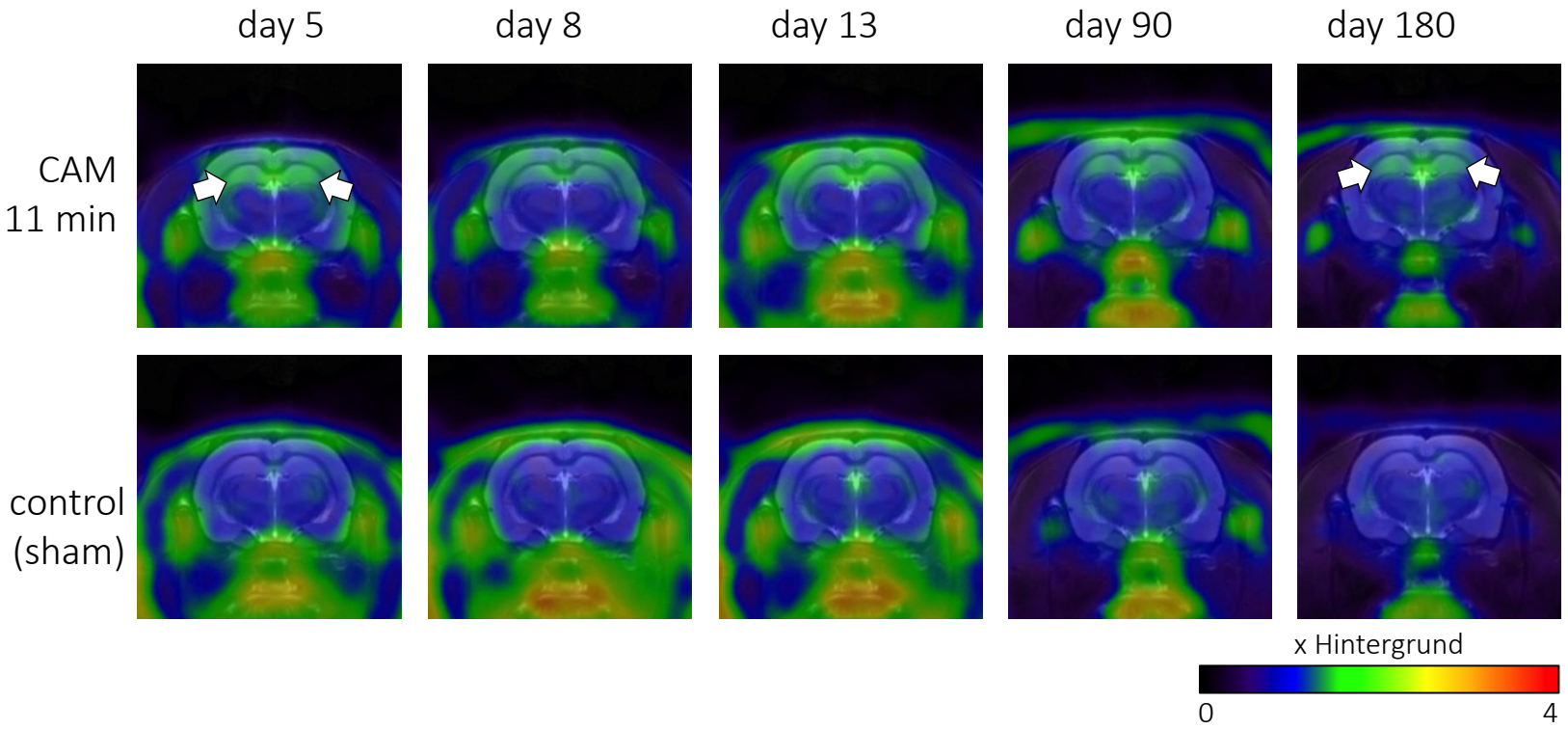




74 MBq i.v., Measurement 30 min
Time of measurement:
day 5, 8, 14, 90, 180 after cardiac arrest

JÜLICH
Forschungszentrum

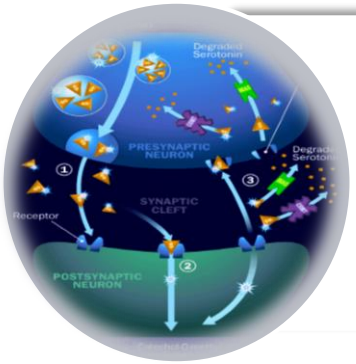
BINDING OF [^{18}F]DAA1106 IN HIPPOCAMPUS AFTER CARDIAC ARREST



POST-RESUSCITATION SYNDROME:

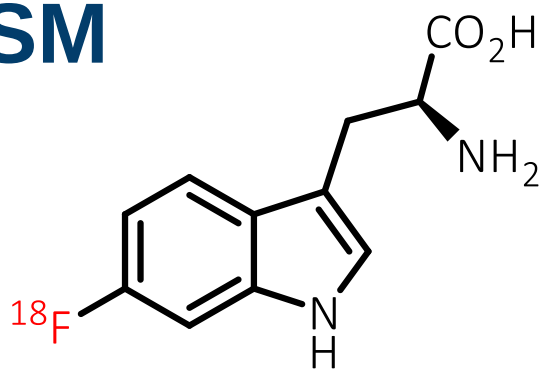
Conclusion

- 6 Month after cardiac arrest persistent activation of microglia
- Inflammation associated with tissue necrosis
- Correlation of PET with immunhistochemistry
- Perspective: Inflammation associated with cognitive symptoms?



Tryptophan metabolism

RADIOLABELED TRYPTOPHAN DERIVATIVES FOR IMAGING OF TRYPTOPHAN METABOLISM



Tryptophan characteristics:

-Essential proteinogenic amino acid

-Contains indole ring in the side chain

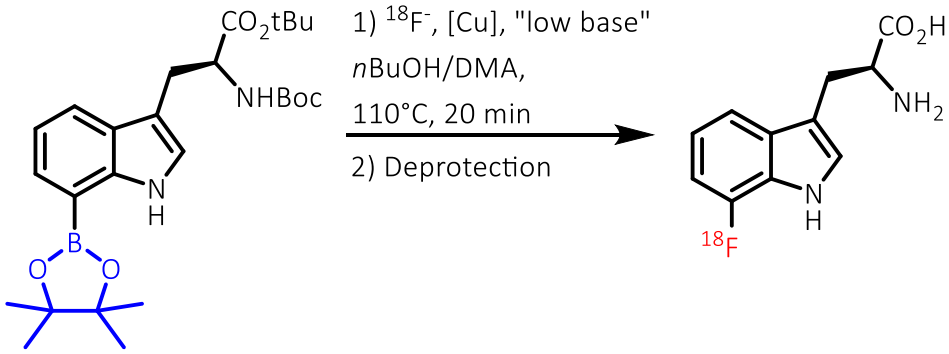
-Cannot be synthesized by mammals and must be obtained from external sources

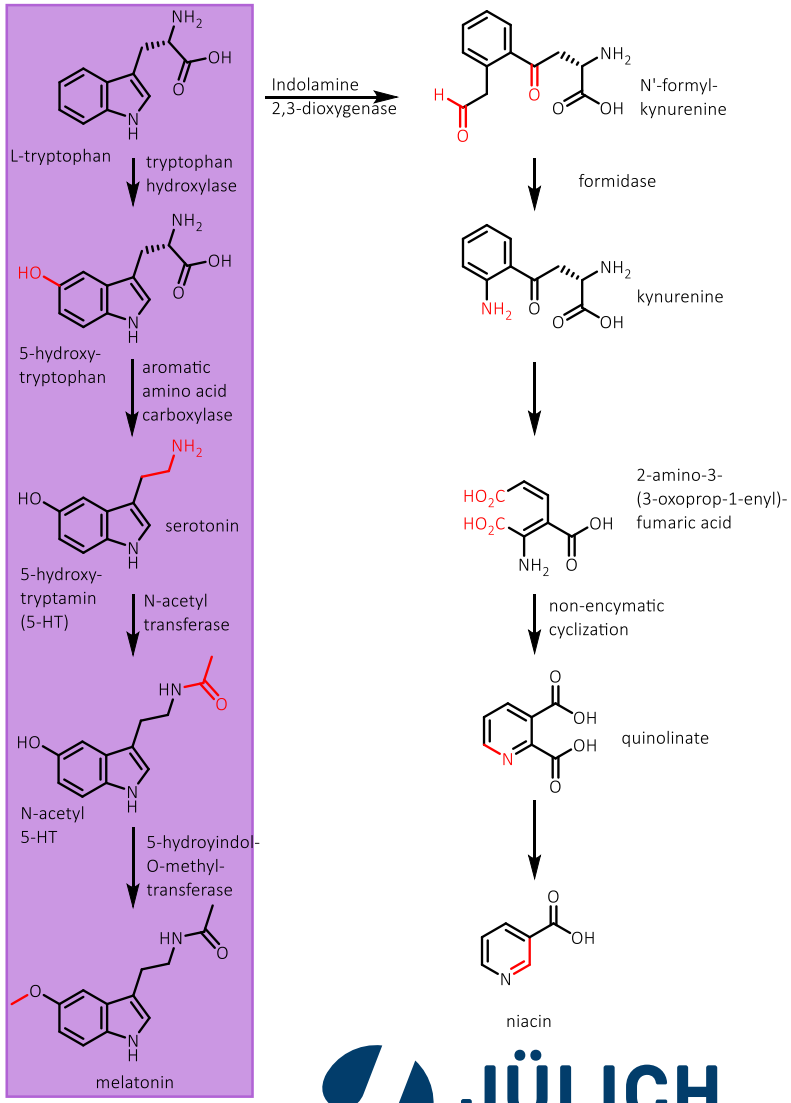
-Least abundant amino acid in animal proteins

-Precursor for various metabolic pathways

-Products of tryptophan metabolism: serotonine, melatonin, niacin and kynurenins

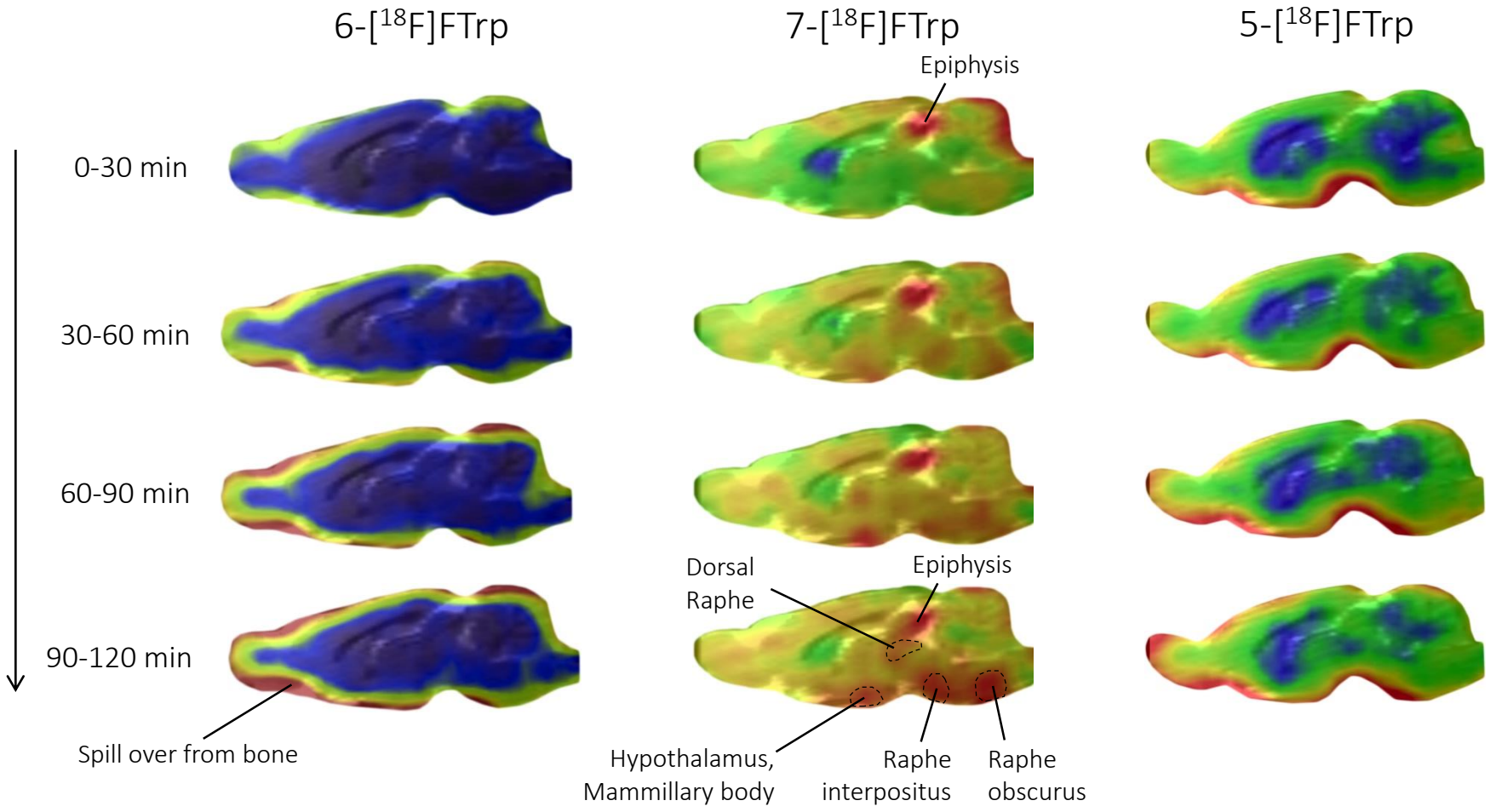
[^{18}F]FLUORTRYPTOPHAN AS PET TRACER



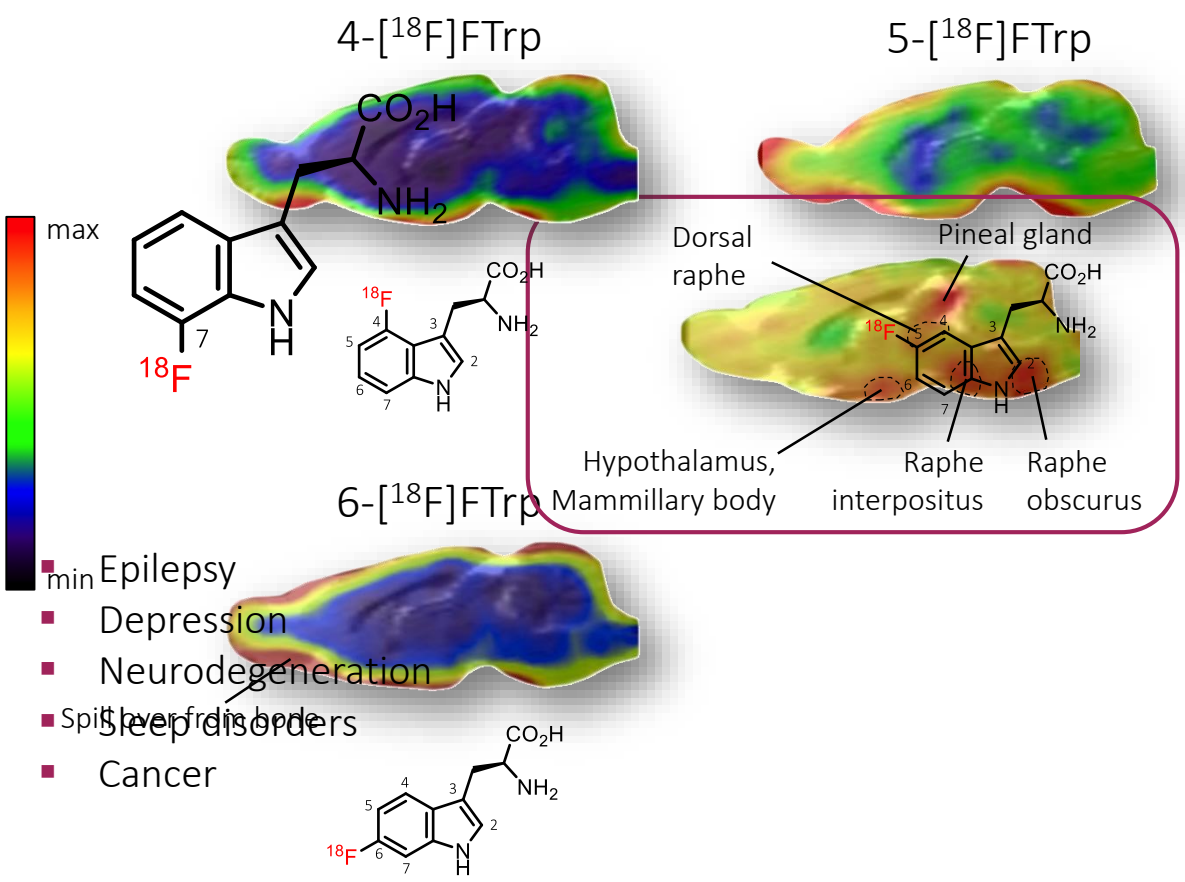


- Tumor detection / Staging
- Epilepsy
- Neurodegenerative diseases

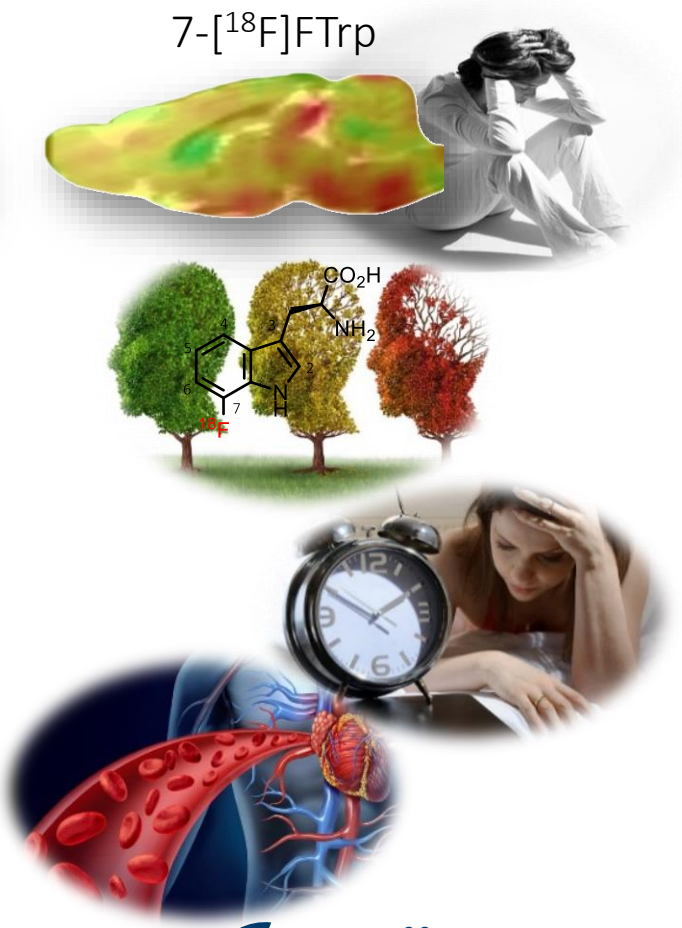
CEREBRAL UPTAKE OF [^{18}F]FLUORO-TRYPTOPHANS



PRECLINICAL EVALUATION

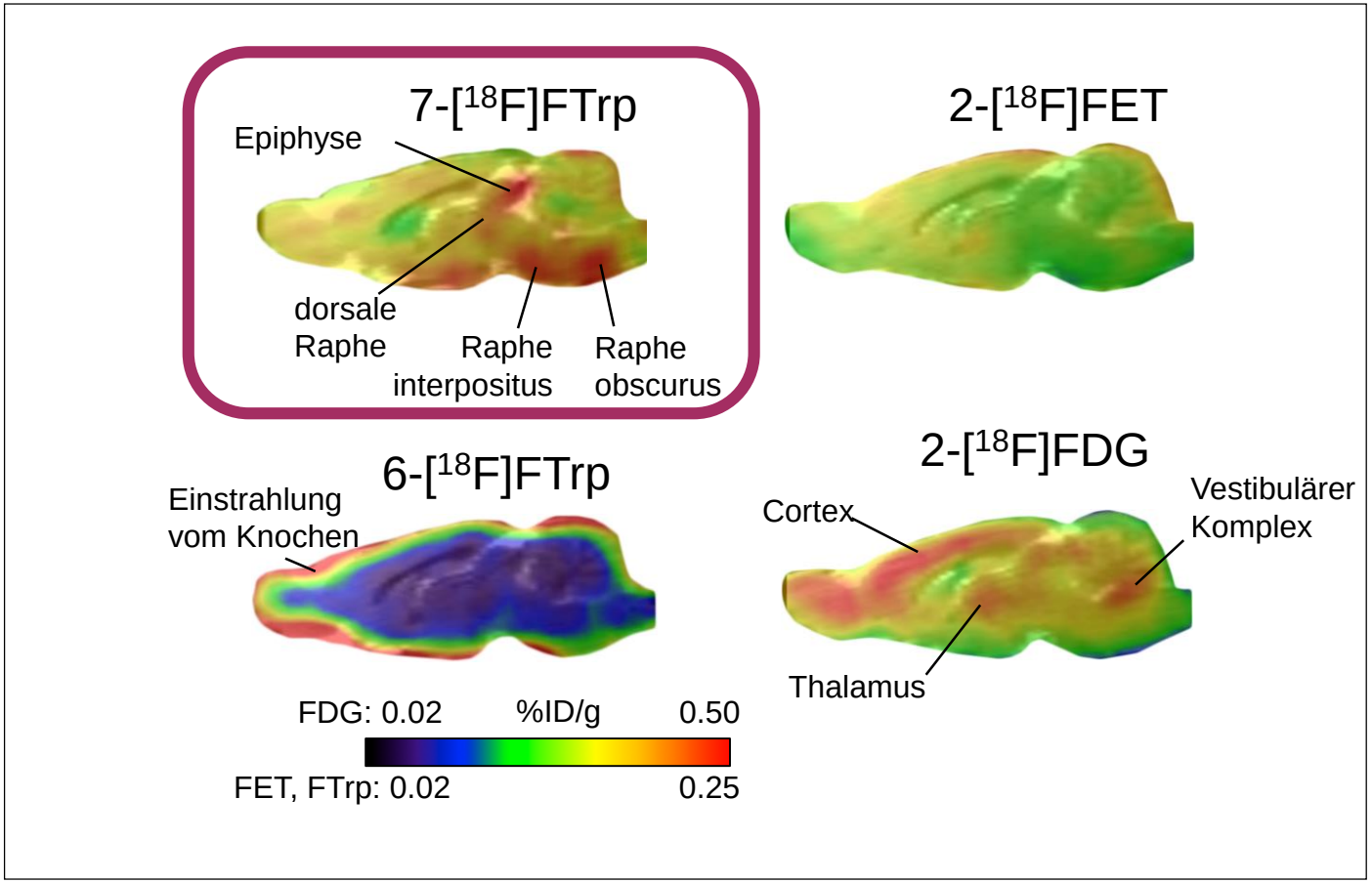


- Epilepsy
- Depression
- Neurodegeneration
- Sleep disorders
- Cancer



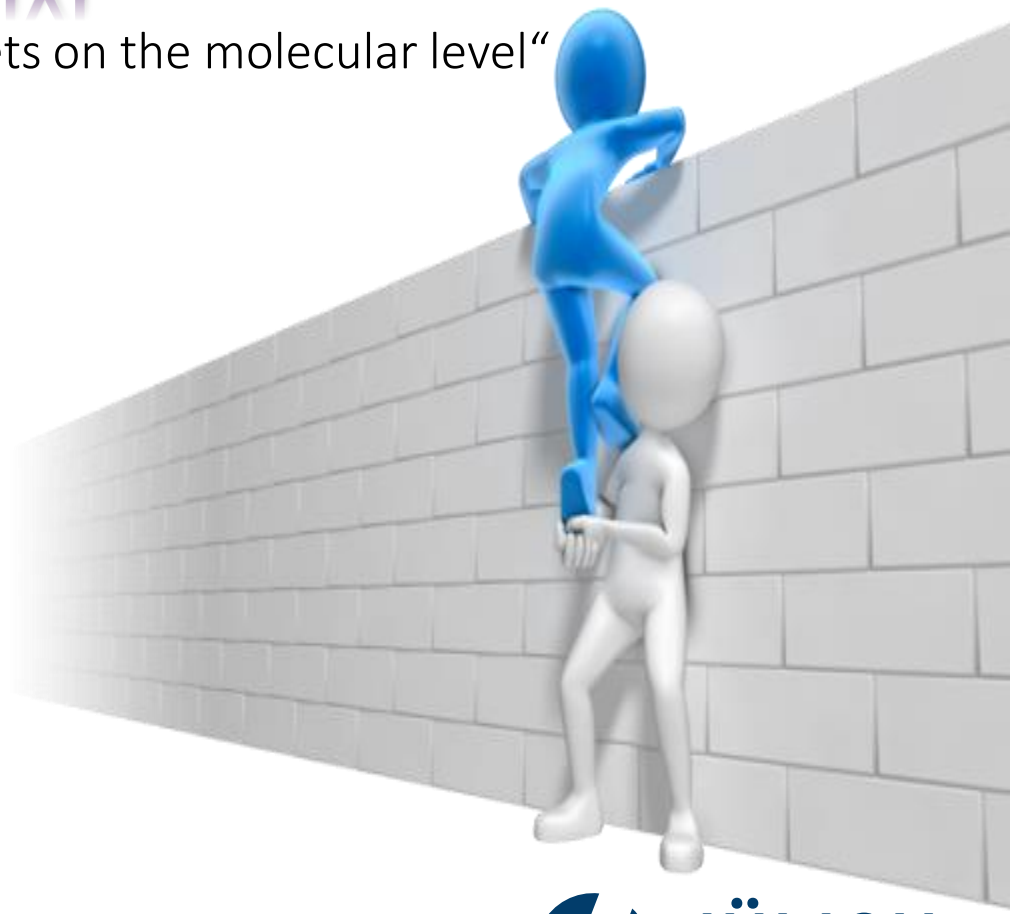
Spill over from body

CEREBRAL UPTAKE OF [^{18}F]FLUORO-TRYPTOPHANS



AIM

„Imaging of biological targets on the molecular level“



Challenges

- Identification of key processes and corresponding molecular targets
- Tracer design
- Development of radiolabeling strategies
- Amenability to automation

დიდი მადლობა