INTRODUCTION TO ^{18}F LABELING CHEMISTRY

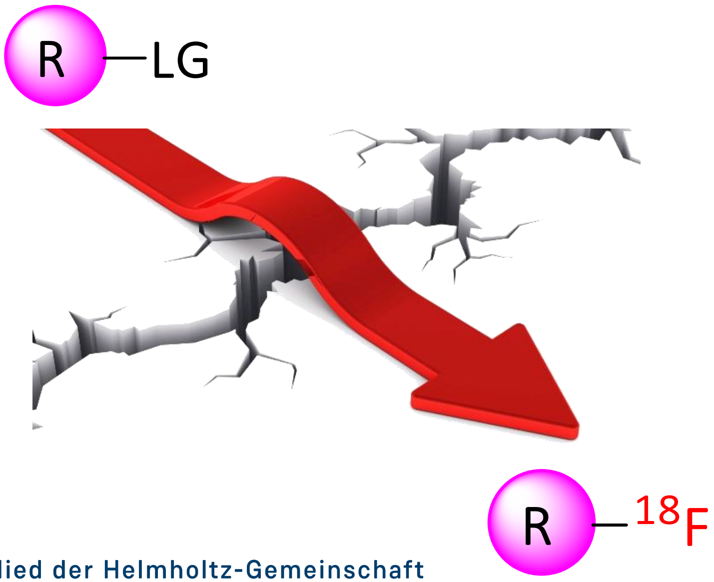
10.09.2019 | BERND NEUMAIER | JÜLICH | 2019

Mitglied der Helmholtz-Gemeinschaft

JÜLICH
Forschungszentrum

^{18}F-CHEMISTRY

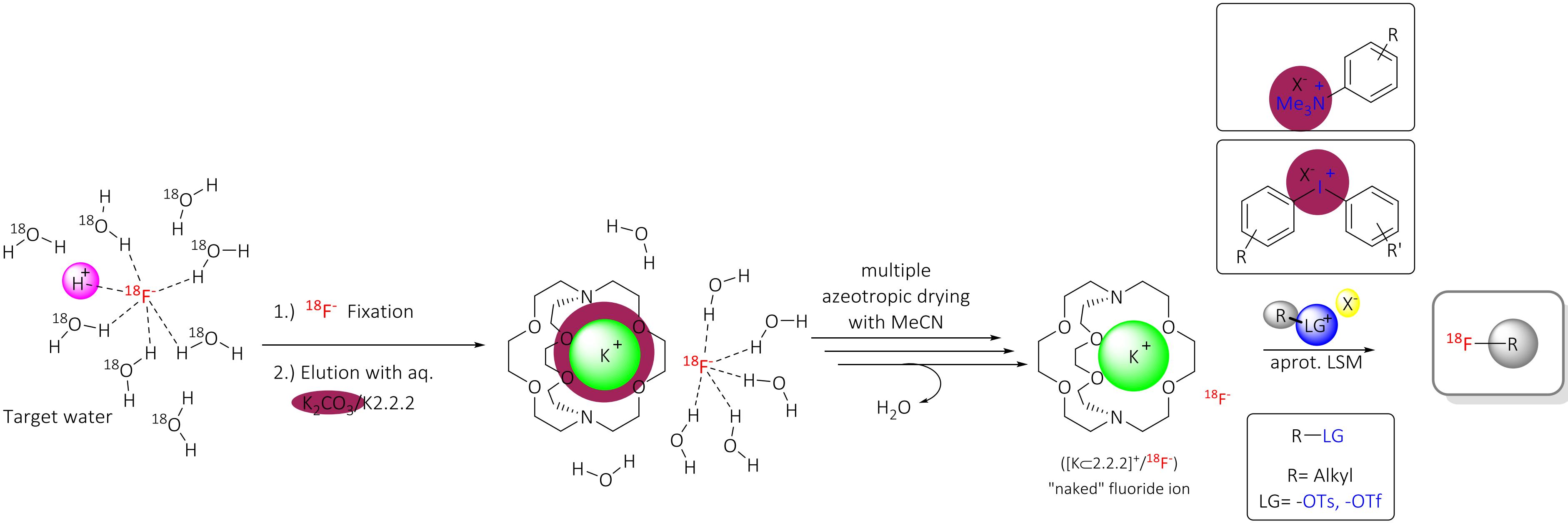
PET Isotope	Half-life [min]	$E_{\beta+}$max [MeV]	Range max/average [mm]	Nuclear reaction	Decay product
^{18}F	109,8	0,64	2,4/0,6	$^{18}O(p,n)^{18}F$	^{18}O



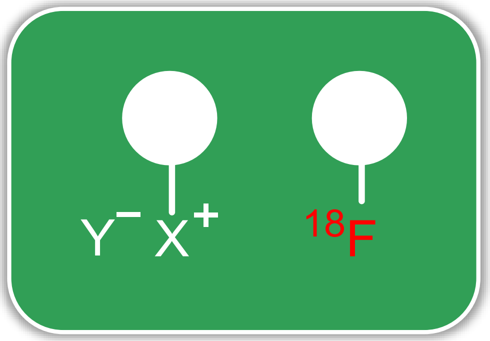
Difficulties associated with ^{18}F-chemistry:

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

CONVENTIONAL PRE-PROCESSING OF [^{18}F]FLUORIDE



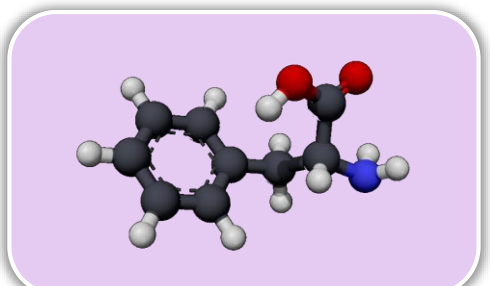
INNOVATIVE RADIO-FLUORINATION METHODS



"Minimalist" approach

Alcohol-enhanced Cu-mediated radiofluorination

Ni-mediated radiofluorination



Limitations of the “minimalist” approach

„Minimalist" Cu-mediated radiofluorination

"MINIMALIST" RADIOFLUORINATION PROTOCOL

Precursor —$X^+ Y^-$

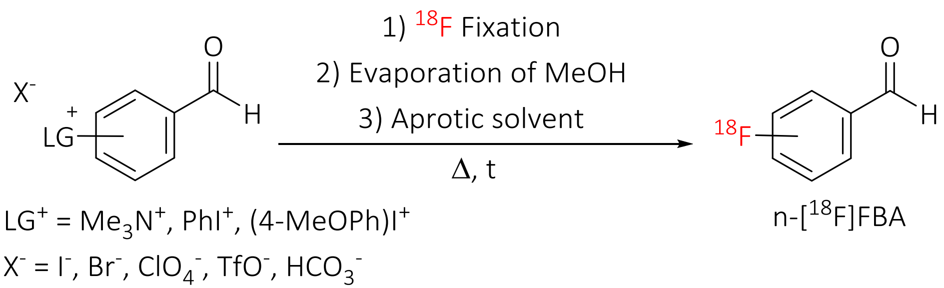
R. Richarz *et al.*, *Org. Biomol. Chem.* 2014

SIMPLE and FAST

- $^{18}F^-$-Fixation
- Resin flushed with MeOH
- $^{18}F^-$-Elution with onium precursor in MeOH
- Evaporation of MeOH (2-3 min)
- Addition of solvent

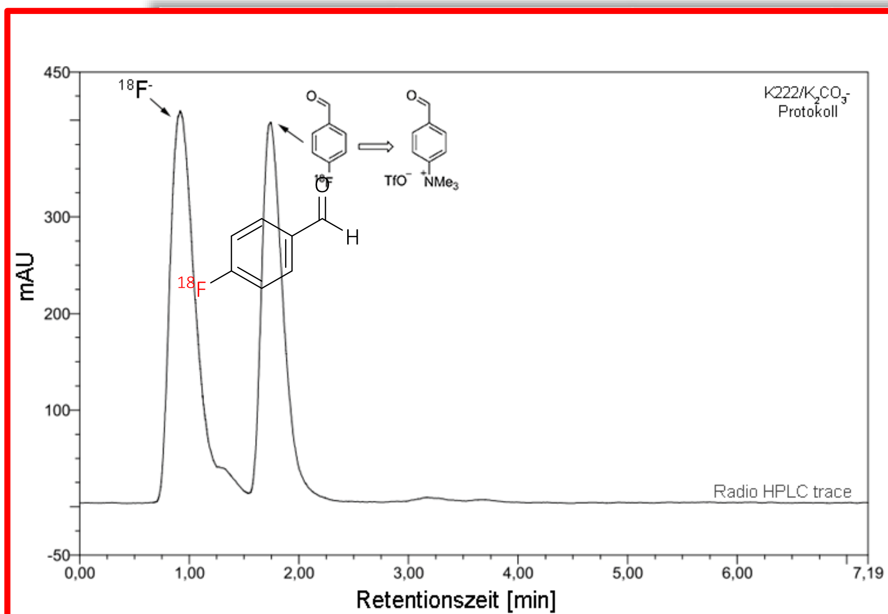
Product —^{18}F

"MINIMALIST" SYNTHESIS OF [^{18}F]FLUORO-BENZALDEHYDES

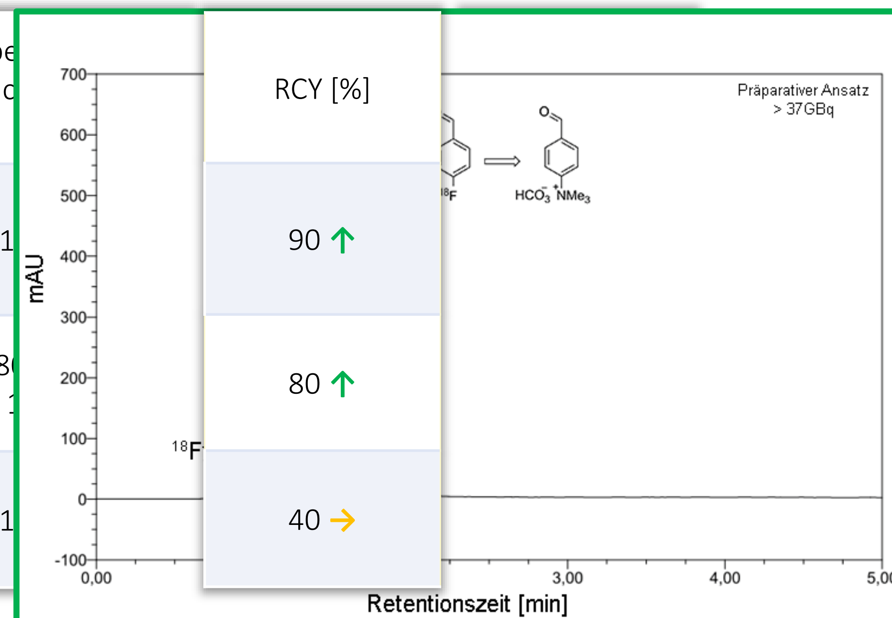


R. Richarz *et al.*, *Org. Biomol. Chem.* **2014**

Conventional method

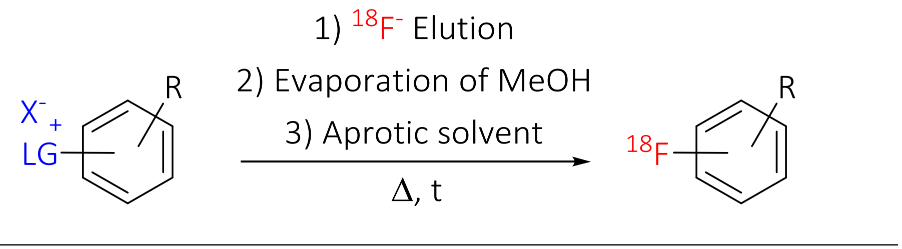


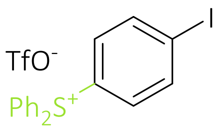
"Minimalist" approach



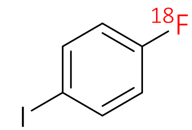
RCY [%]
90 ↑
80 ↑
40 →

„MINIMALIST" AROMATIC ^{18}F-FLUORINATION

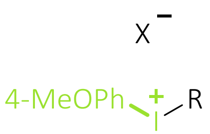




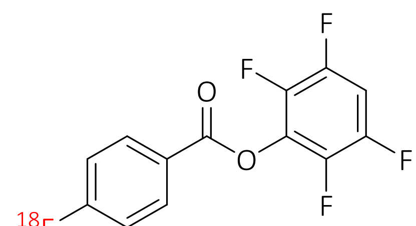
Sulfonium



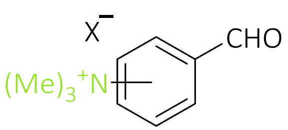
66%



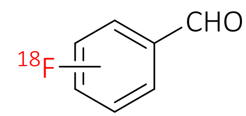
Iodonium



25%



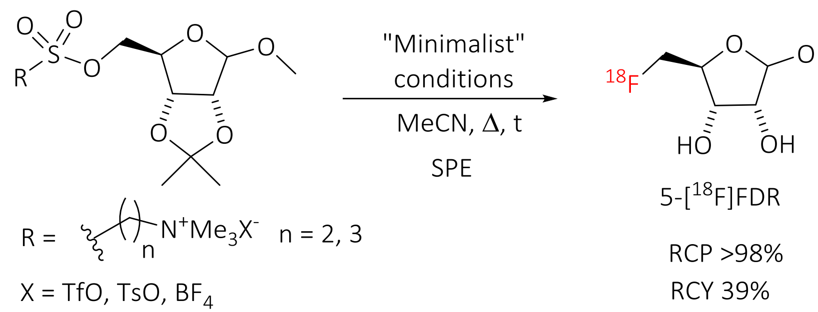
Ammonium



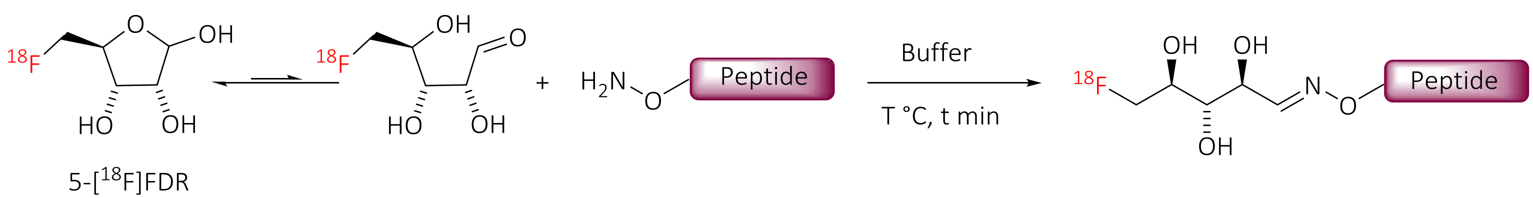
40-90%

S_N2-RADIOFLUORINATION UNDER "MINIMALIST" CONDITIONS

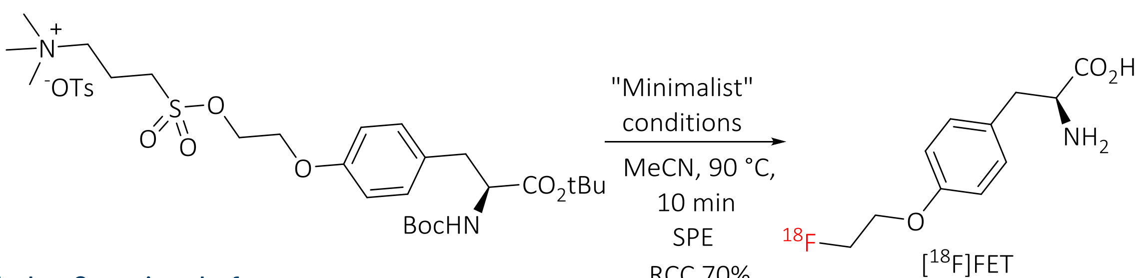
Aliphatic S_N2 radiosynthesis of [^{18}F]FDR



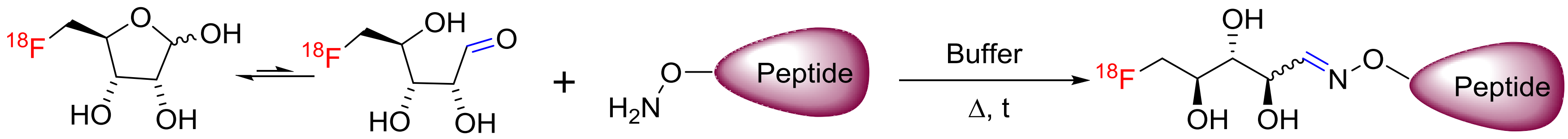
Peptide conjugation



Radiosynthesis of [^{18}F]FET



S_N2-RADIOFLUORINATION UNDER "MINIMALIST" CONDITIONS



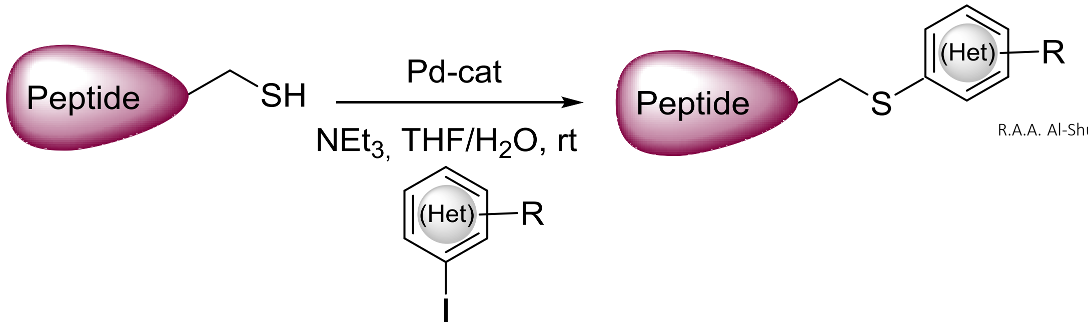
Abbreviation	Sequence
AOA-C-CPE-17-KKK	AOA-βA-NSSYSGNYPYSILFQKFKKK
AOA-M19	AOA-βA-NAPYRGHYPYHILFQKF
AOA-CC4P-5	AOA-βA-SPWSEPAYTLAP
AOA-Clone 27	AOA-βA-KTLLPTP

L. Feni, M. Omrane, M. Fischer, B. Zlatopolskiy, B. Neumaier, I. Neundorf, *Pharmaceuticals* **2017**, *10*, 99.

Claudin-4 binding peptides

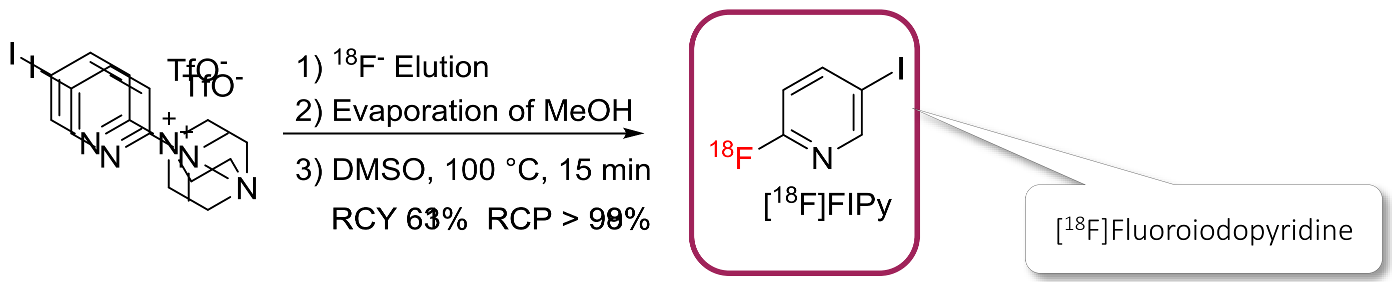
- Overexpression of claudin-4 in various tumors, such as pancreatic carcinomas
- Claudin-4 promising target for the visualization of pancreatic tumors

Pd-CATALYSED S-ARYLATION



R.A.A. Al-Shuaeeb, *et al.*, *Chem. Eur. J.* **2016**, *22*, 11365-11370

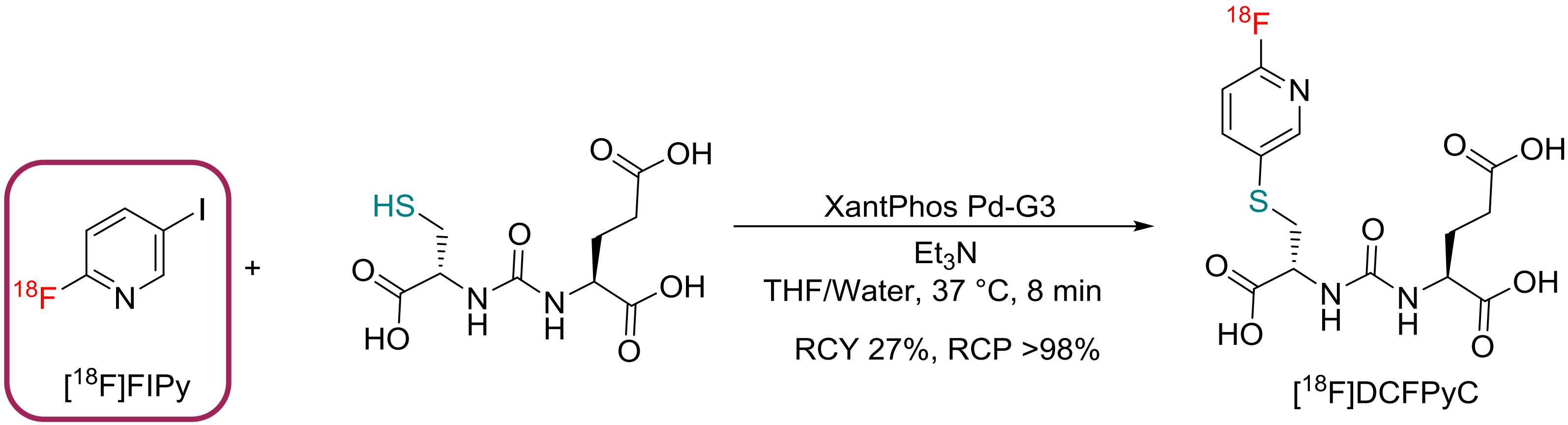
[18]F]Fluoroiodopyridine as a building block

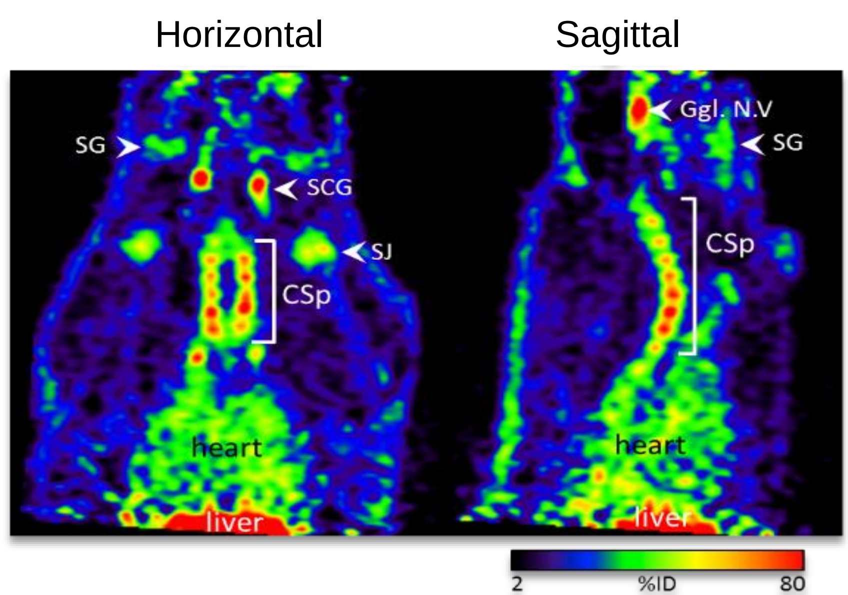


- In contrast to [18]F]Fluoroiodobenzene:

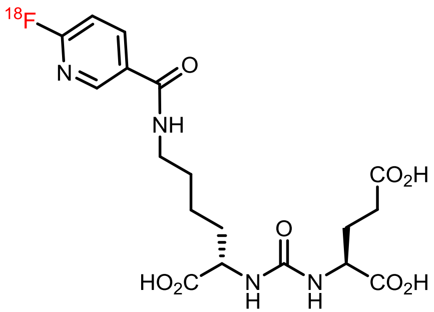
  -high yields, no by-products, easy purification via SPE

PSMA-SPECIFIC TRACER USING Pd-CATALYZED S-ARYLATION

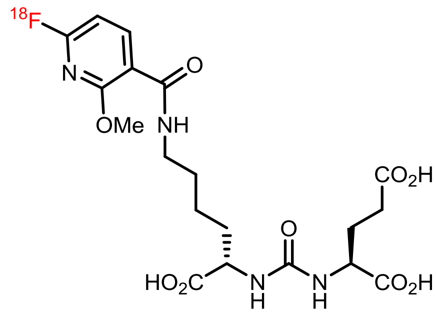




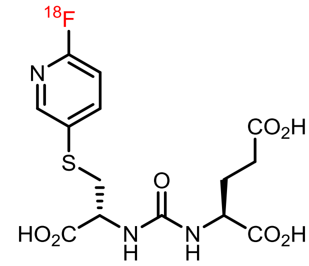
DESIGN OF NEW PSMA SELECTIVE PROBES



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

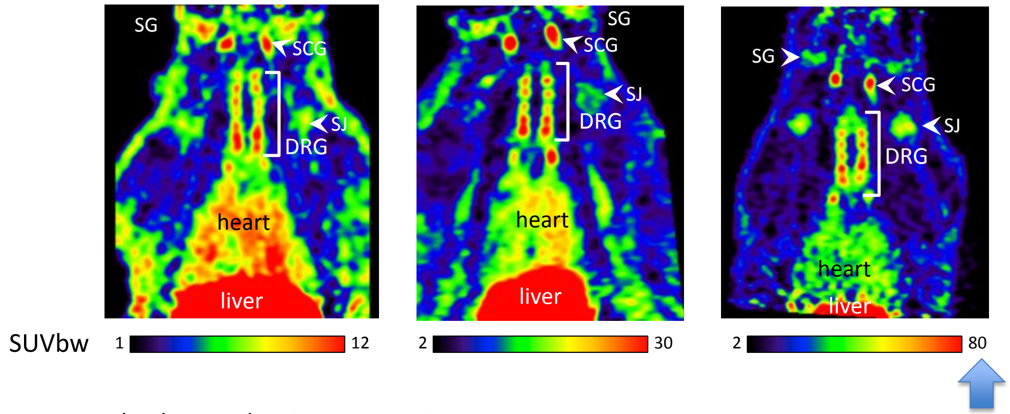


2-MeO-$[^{18}F]$PSMA-7



$[^{18}F]$PSMA-9

$[^{18}F]$PSMA-6 **$[^{18}F]$PSMA-7** **$[^{18}F]$PSMA-9**



Target-to-background ratio 60-120 min:

$[^{18}F]$PSMA-6	$[^{18}F]$PSMA-7	$[^{18}F]$PSMA-9
6.38 ± 1.87 n=3	8.15 ± 1.71 n=3	10.3 n=1

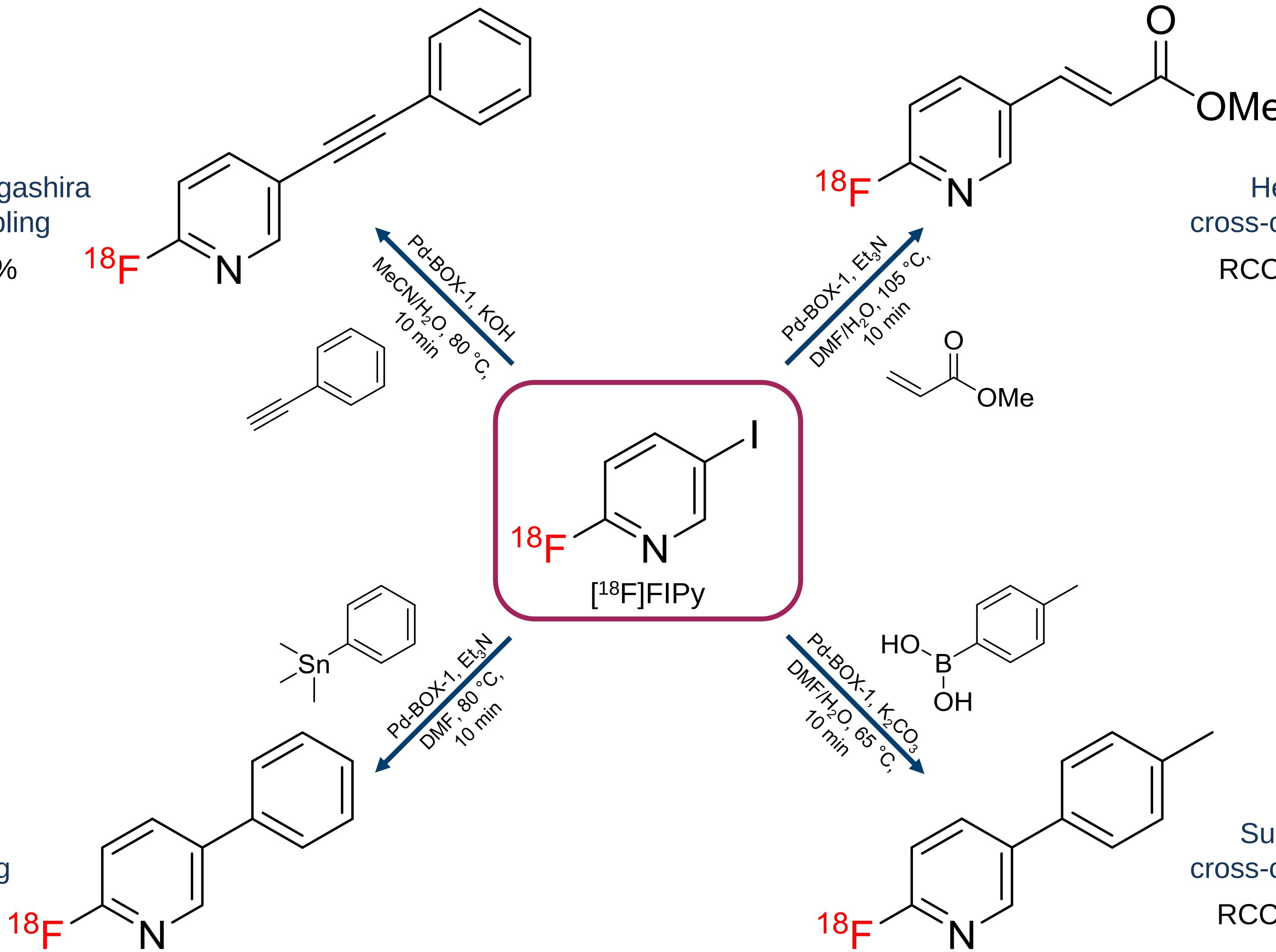
Pd-CATALYSED CROSS-COUPLING REACTIONS

Cu-free Sonogashira cross-coupling

RCC 89%

Heck cross-coupling

RCC 85%

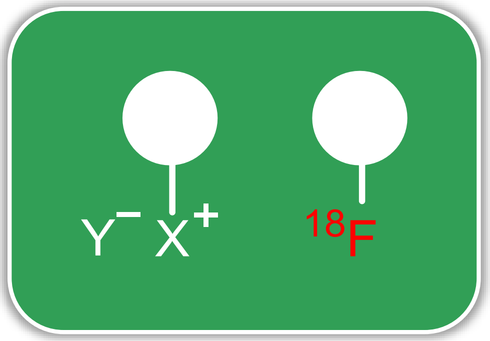


Stille cross-coupling

RCC 88%

Suzuki cross-coupling

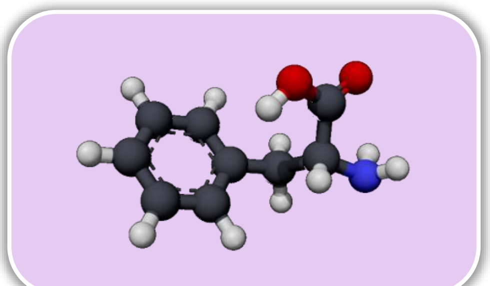
RCC 98%



"Minimalist" approach

Alcohol-enhanced Cu-mediated radiofluorination

Ni-mediated radiofluorination

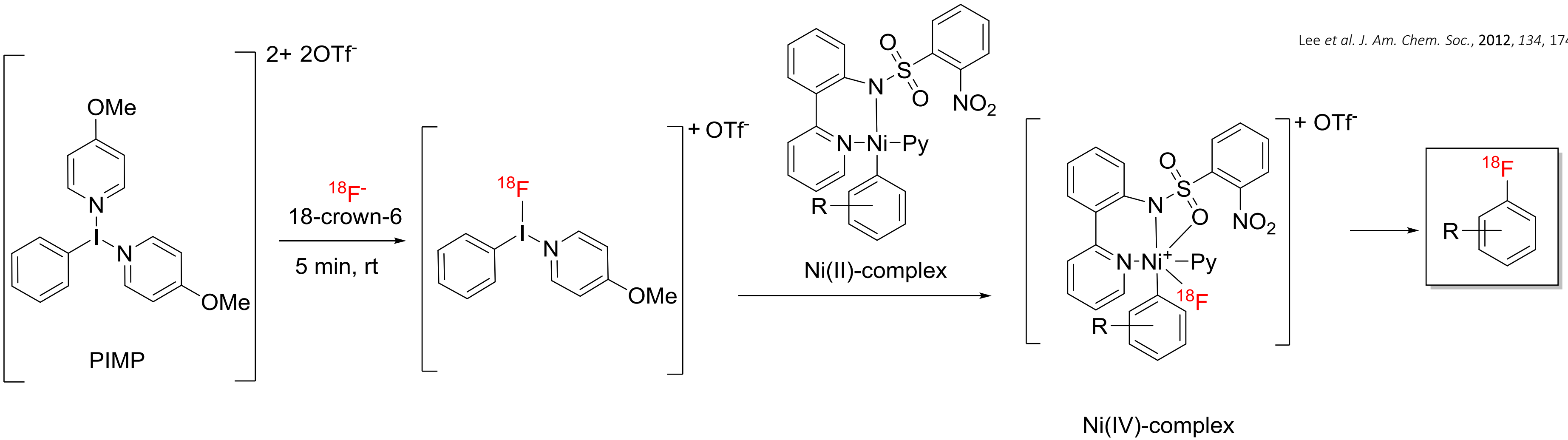


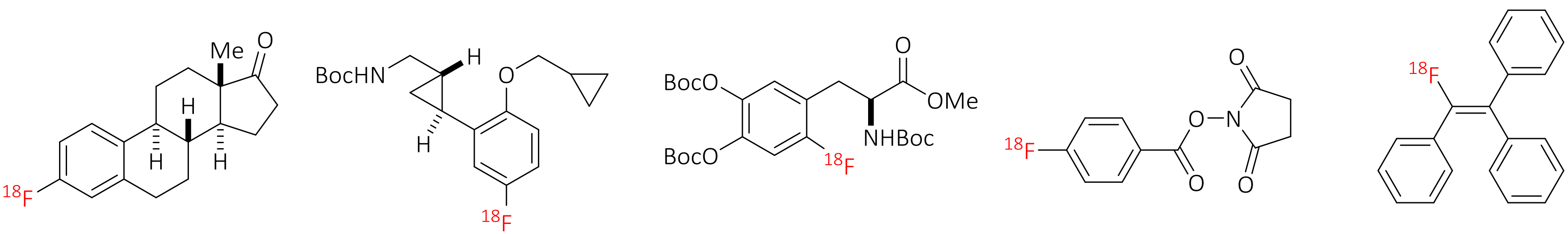
2-[^{18}F]Fluorophenylalanine: Synthesis by Nucleophilic ^{18}F-Fluorination

„Minimalist" Cu-mediated radiofluorination

Ni-MEDIATED OXIDATIVE ^{18}F-FLUORINATION

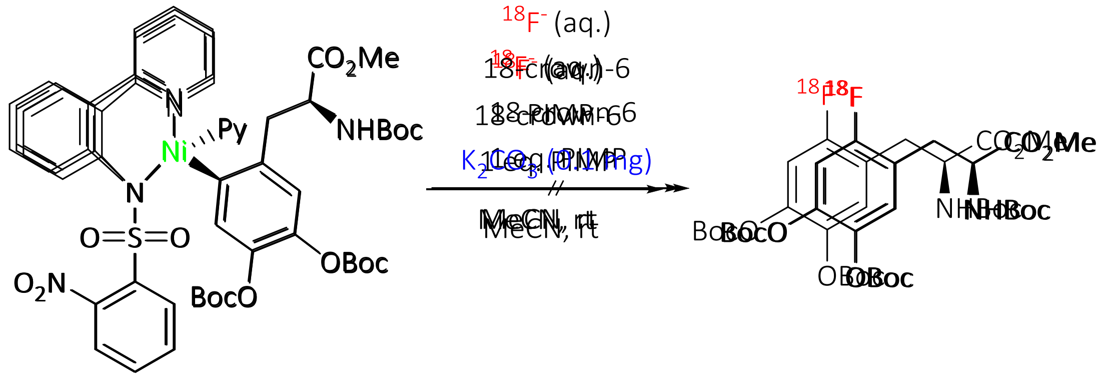
Lee *et al. J. Am. Chem. Soc.*, **2012**, *134*, 17456.



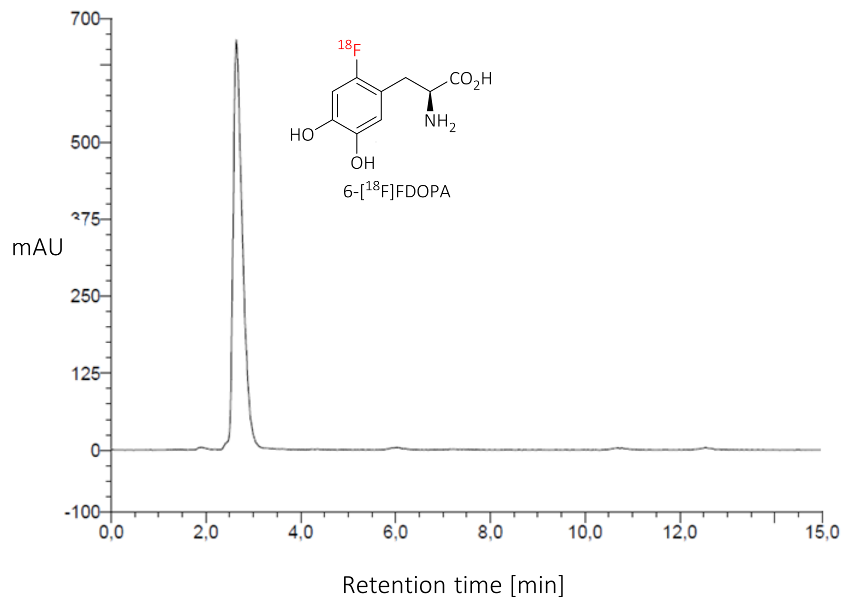


58% ± 6% RCY (n = 6) 43% ± 9% RCY (n = 6) 15% ± 7% RCY (n = 6) 21% ± 4% RCY (n = 6) 13% ± 3% RCY (n = 6)

RADIOSYNTHESIS OF 6-[^{18}F]FDOPA



B.D. Zlatopolskiy *et al.*, *ChemistryOpen* 2015.



obtained 6-[^{18}F]FDOPA!

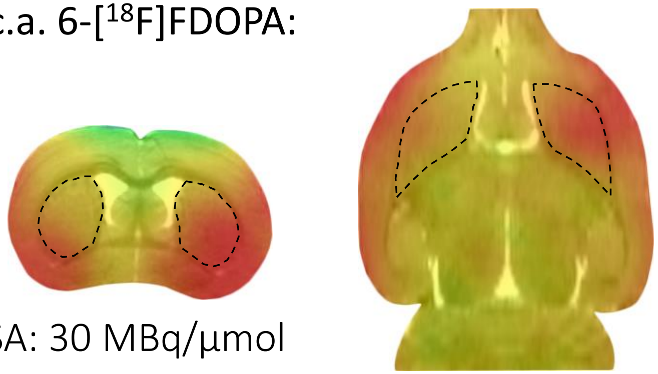
RCY = 7%
175 MBq
starting from 7GBq $^{18}F^-$;
very limited shelf life of the oxidant!

n.c.a. vs c.a. 6-[^{18}F]FDOPA

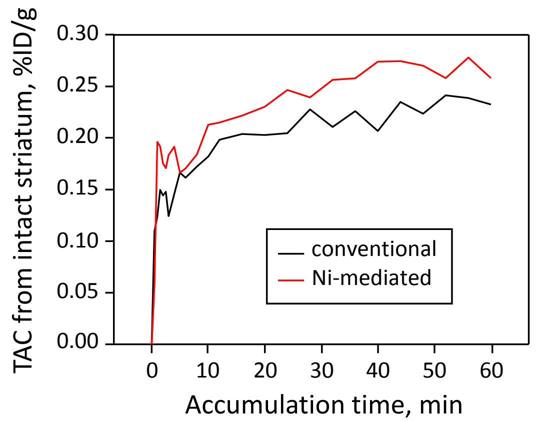
A rat model of Parkinsons disease

B.D. Zlatopolskiy *et al.*, *ChemistryOpen* 2015

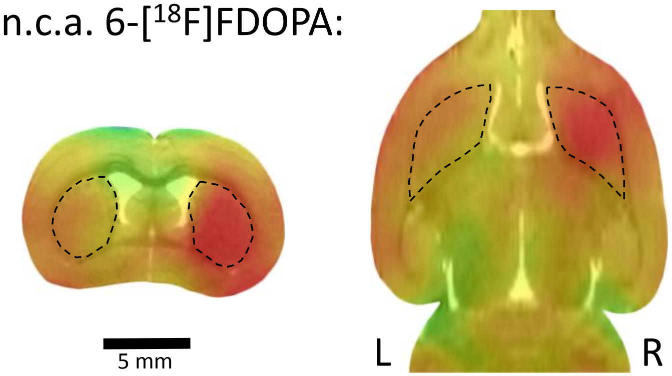
c.a. 6-[^{18}F]FDOPA:

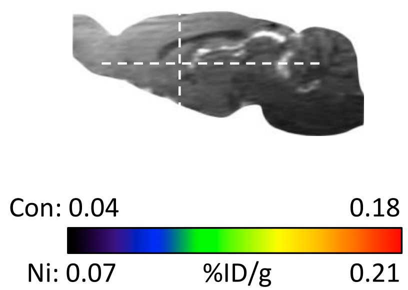


SA: 30 MBq/µmol

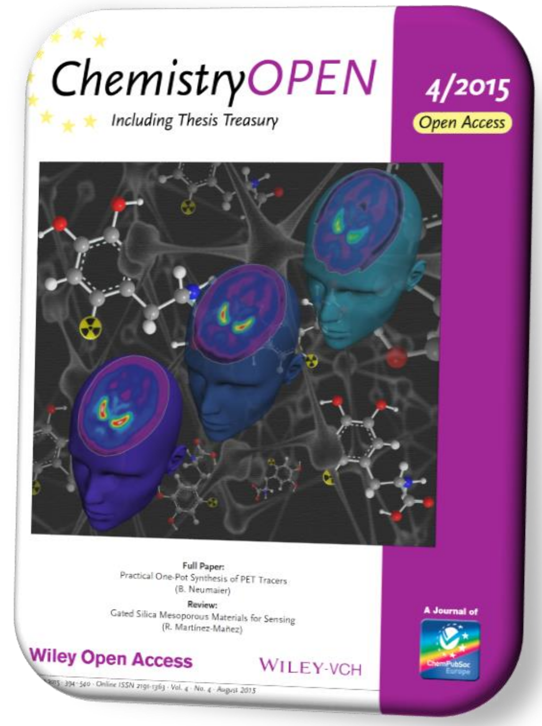


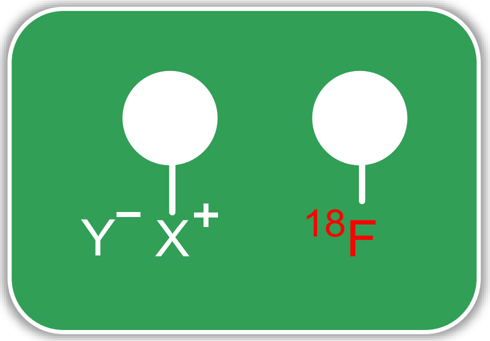
n.c.a. 6-[^{18}F]FDOPA:





SA: 175 GBq/µmol

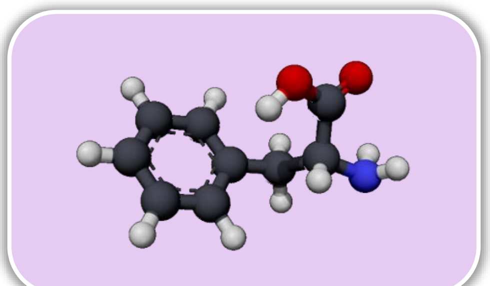




"Minimalist" approach

Alcohol-enhanced Cu-mediated radiofluorination

Ni-mediated radiofluorination

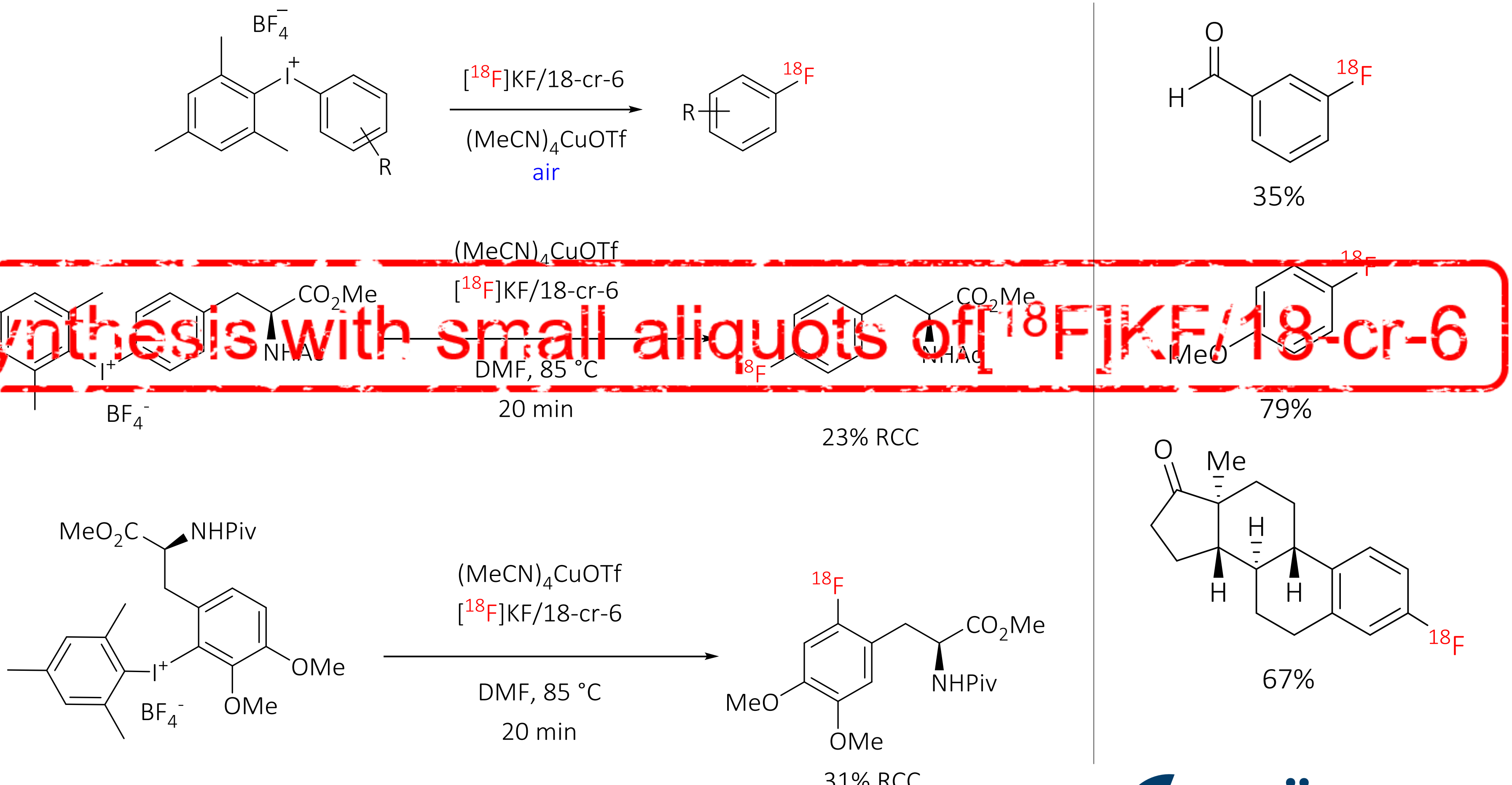


2-[^{18}F]Fluorophenylalanine: Synthesis by Nucleophilic ^{18}F-Fluorination

„Minimalist" Cu-mediated radiofluorination

Cu-MEDIATED ^{18}F-FLUORINATION OF (MESITYL)(ARYL)IODONIUM SALTS

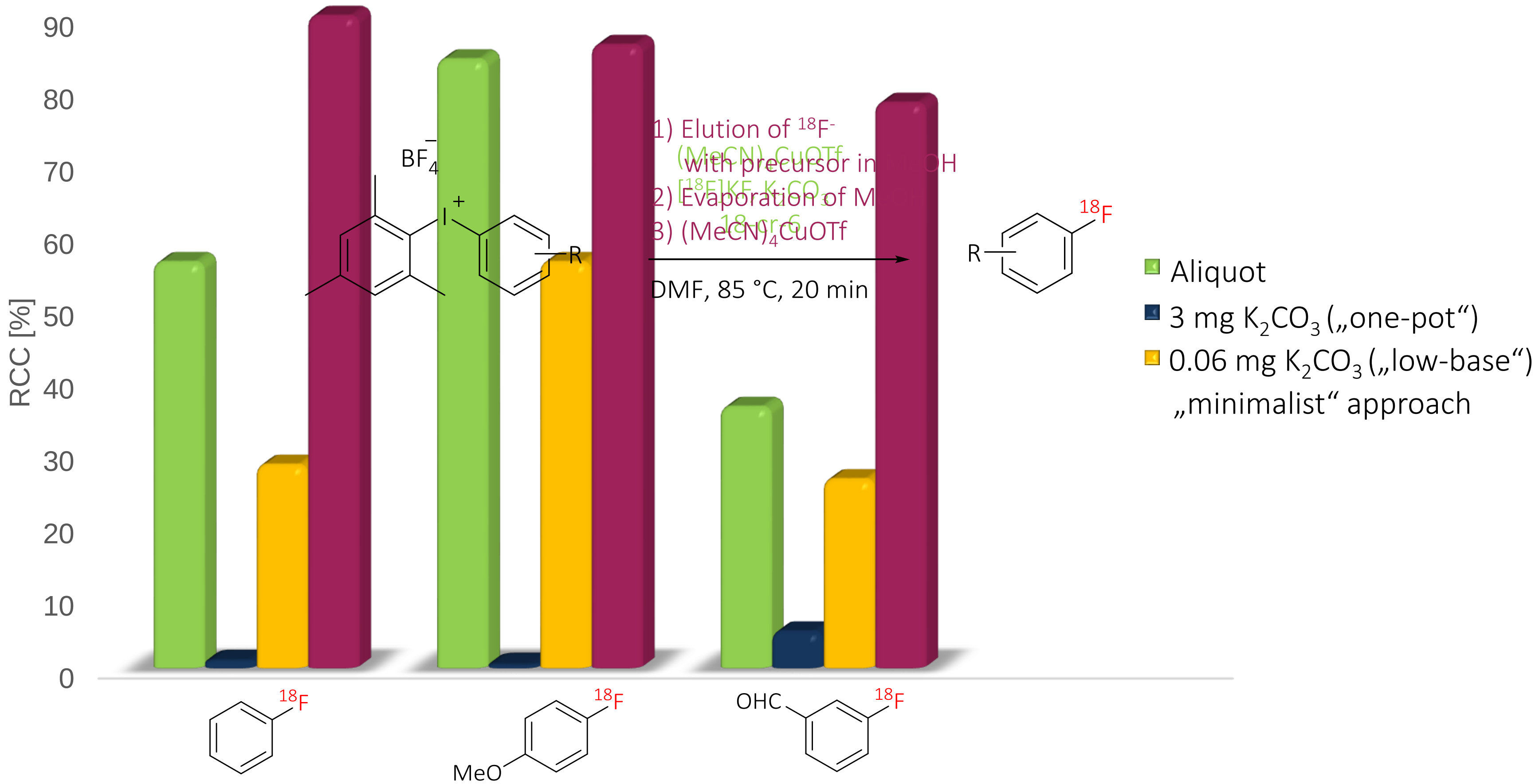
Ichiishi *et al. Org. Lett.*, **2014**, *16*, 3224-3227



1.1% (one-pot synthesis)

COMPARISON BETWEEN DIFFERENT PROTOCOLS

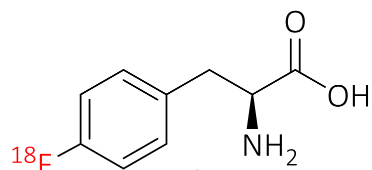
B. D. Zlatopolskiy *et al.*, *Chem. Eur. J.* **2015**, *21*, 5972-5979



"MINIMALIST" APPROACH TO Cu-MEDIATED RADIOFLUORINATION

Production of PET-Tracers

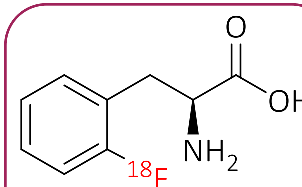
B. D. Zlatopolskiy *et al.*, *Chem. Eur. J.* 2015;
J. Zischler *et al.*, *Appl. Radiat. Isot.* 2016;
D. J. Modemann et al., *Synthesis* 2019



4-[18F]FPhe

RCY = 66%

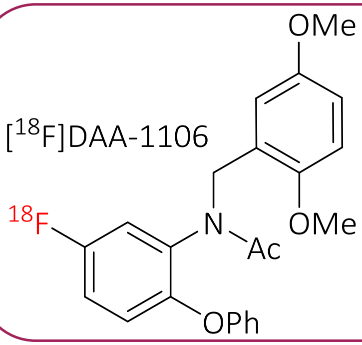
109 GBq/µmol (14 GBq)



2-[18F]FPhe

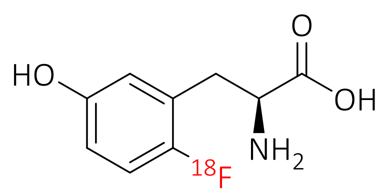
RCY = 42%

[18F]DAA-1106



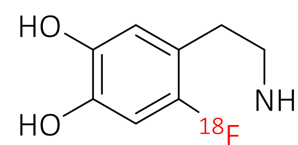
RCY = 60%

62 GBq/µmol (1.2 GBq)



6-[18F]FMT

RCY = 17%



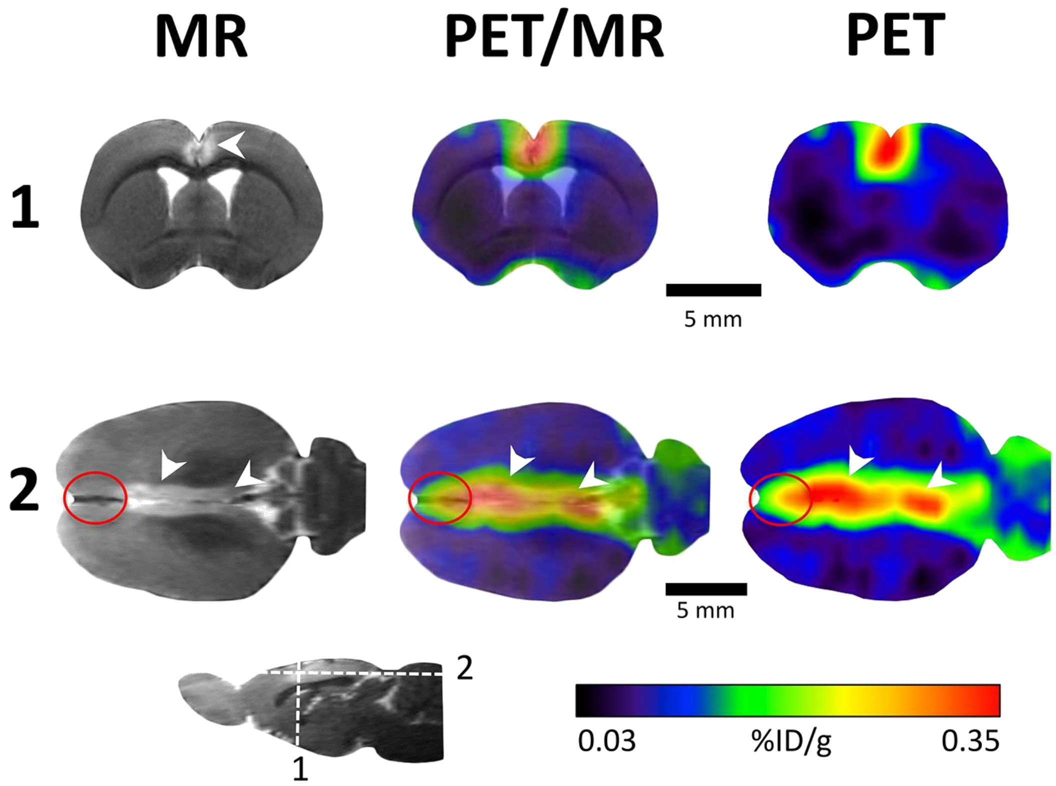
6-[18F]FDA

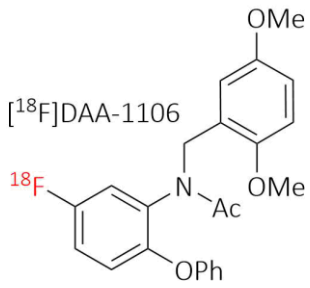
RCY = 46%

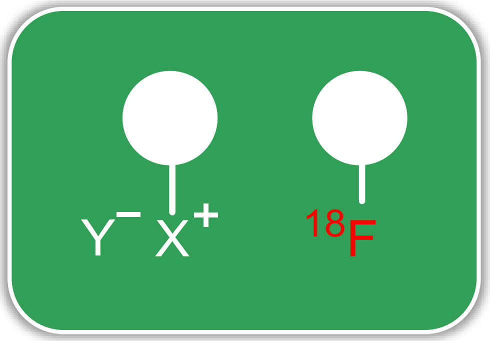
[^{18}F]DAA1106-PET

Stroke model in rats

B. D. Zlatopolskiy *et al.*, *Chem. Eur. J.* 2015







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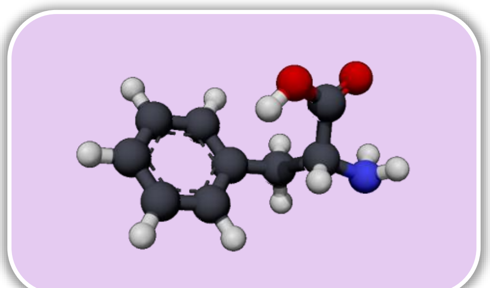

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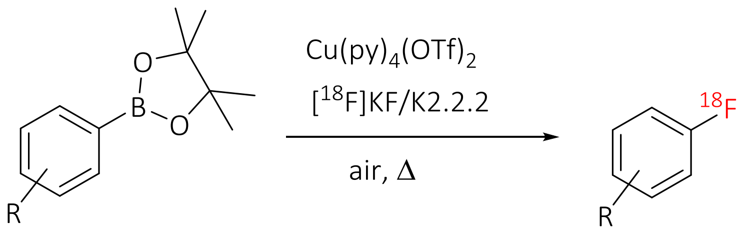
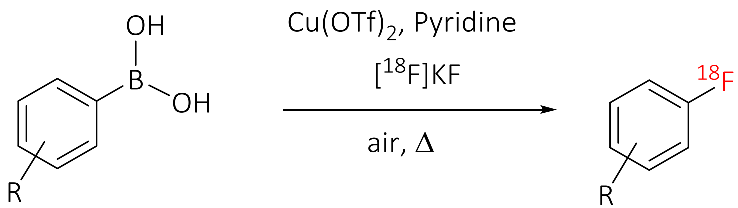
„Minimalist" Cu-mediated radiofluorination

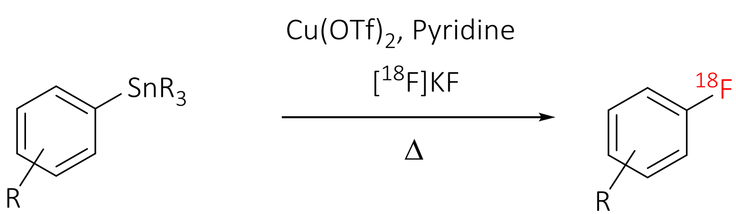
Cu-MEDIATED AROMATIC ^{18}F-FLUORINATION OF BORONATES AND STANNANES



TREDWELL *et al.* 2014
PRESHLOCK *et al.* 2016



MOSSINE *et al.* 2015

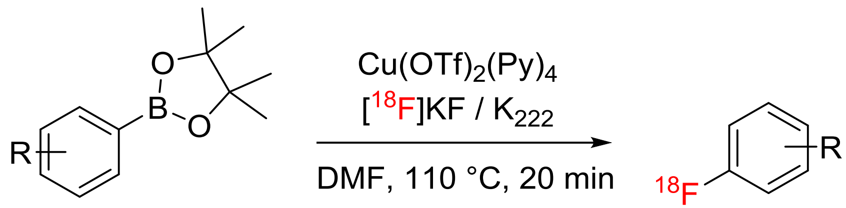


MAKARAVAGE *et al.* 2016

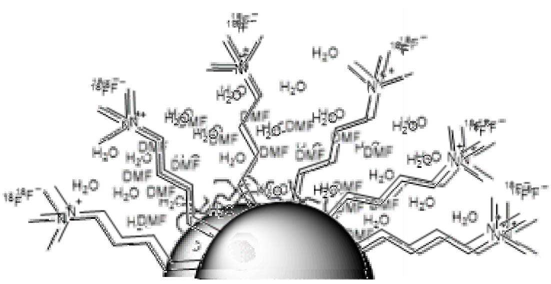
- Easily accessible and stable precursors
- Broad scope of application

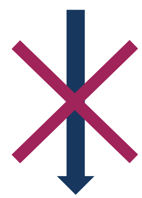
- Complicated procedure
- Long synthesis times
- Moderate yields
- Unsuitable for automation

Cu-MEDIATED AROMATIC ^{18}F-FLUORINATION OF BORONATES AND STANNANES

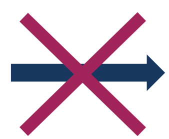


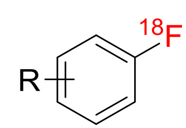
Tredwell et al., **2014**





- Rinsing the cartridge with DMF/water
- Elution with K_2CO_3 in DMF/pyridine





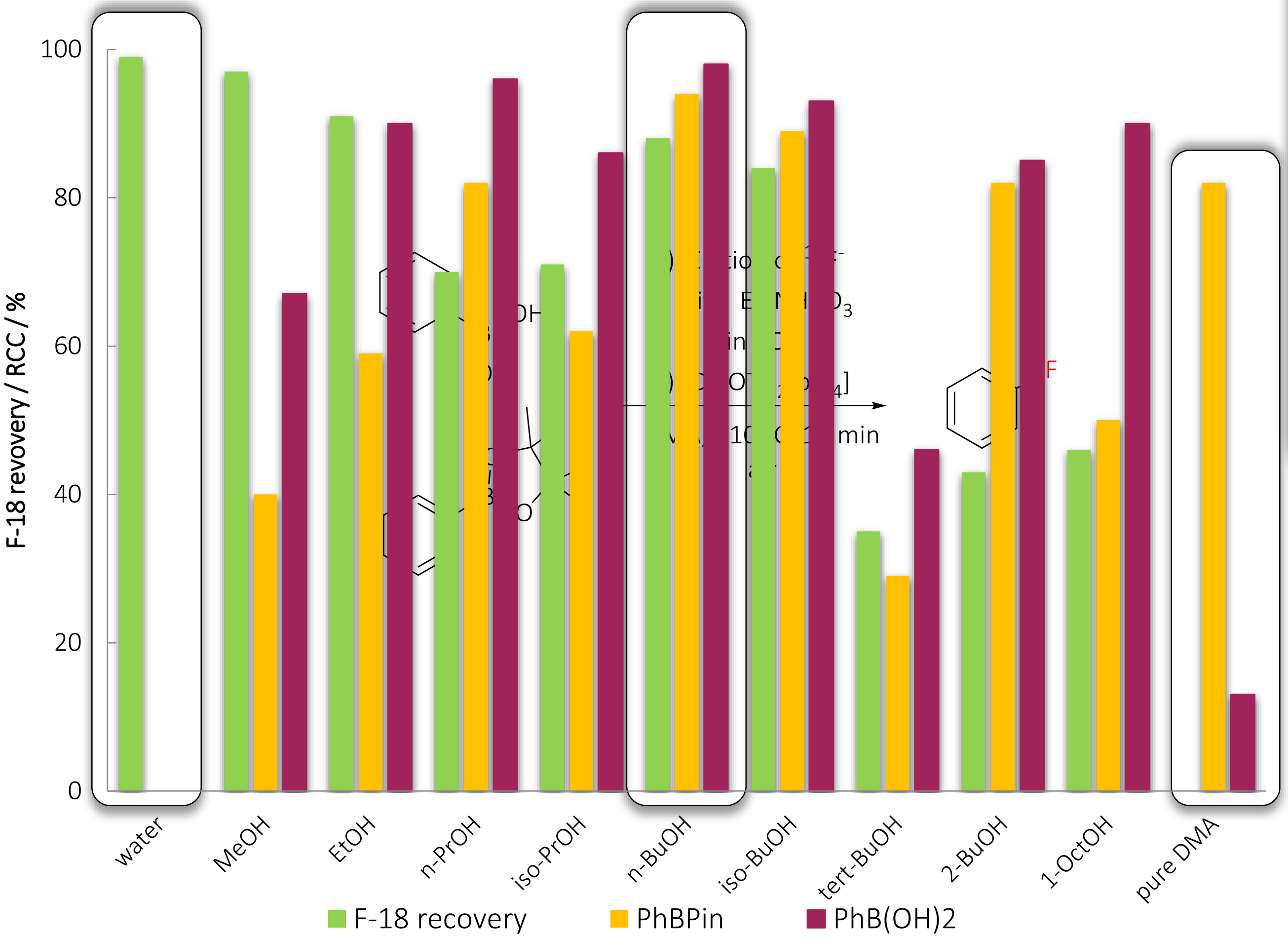
high yields

Mitglied der Helmholtz-Gemeinschaft

JÜLICH Forschungszentrum

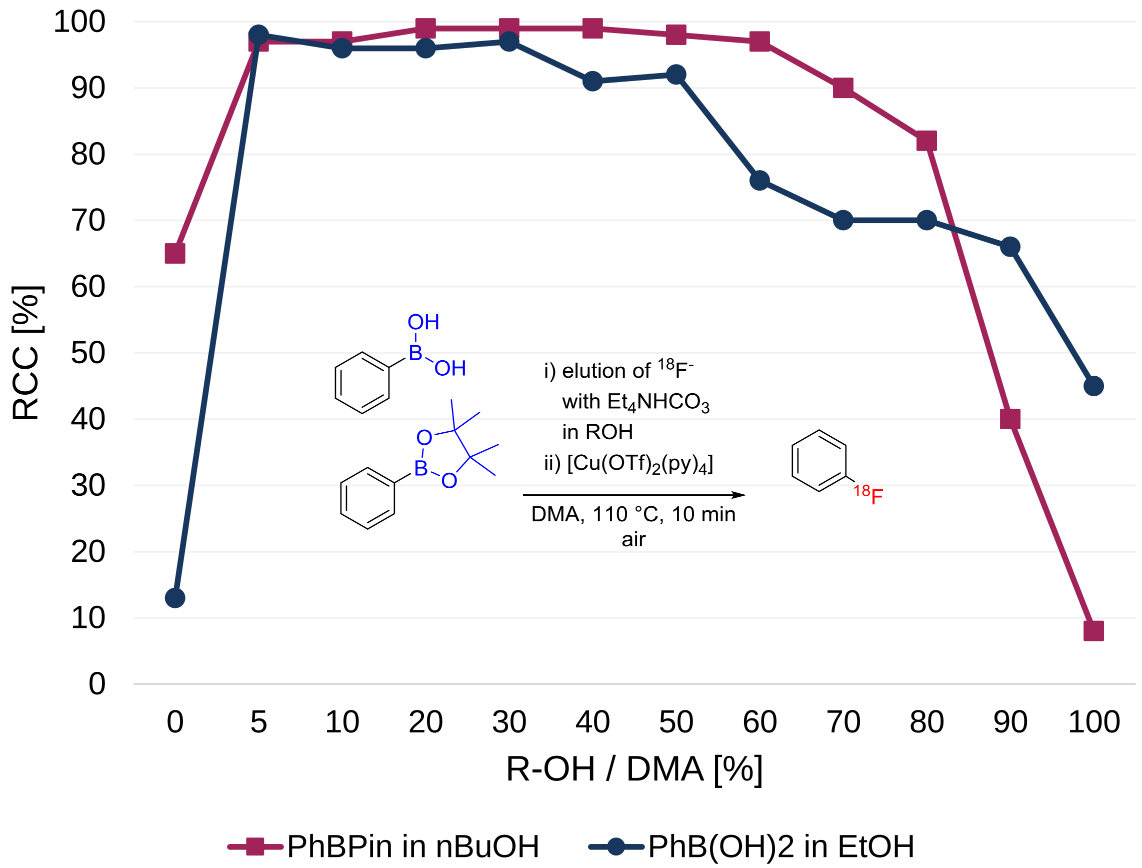
ALCOHOL-ENHANCED Cu-MEDIATED RADIOFLUORINATION

Alcohol is the solution!

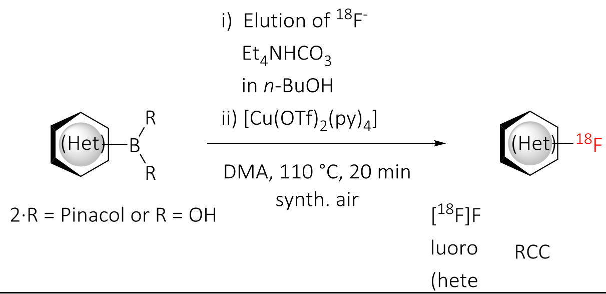


J. Zischler *et al.*, *Chem. Eur. J.* **2017**, *23*, 3257-3256

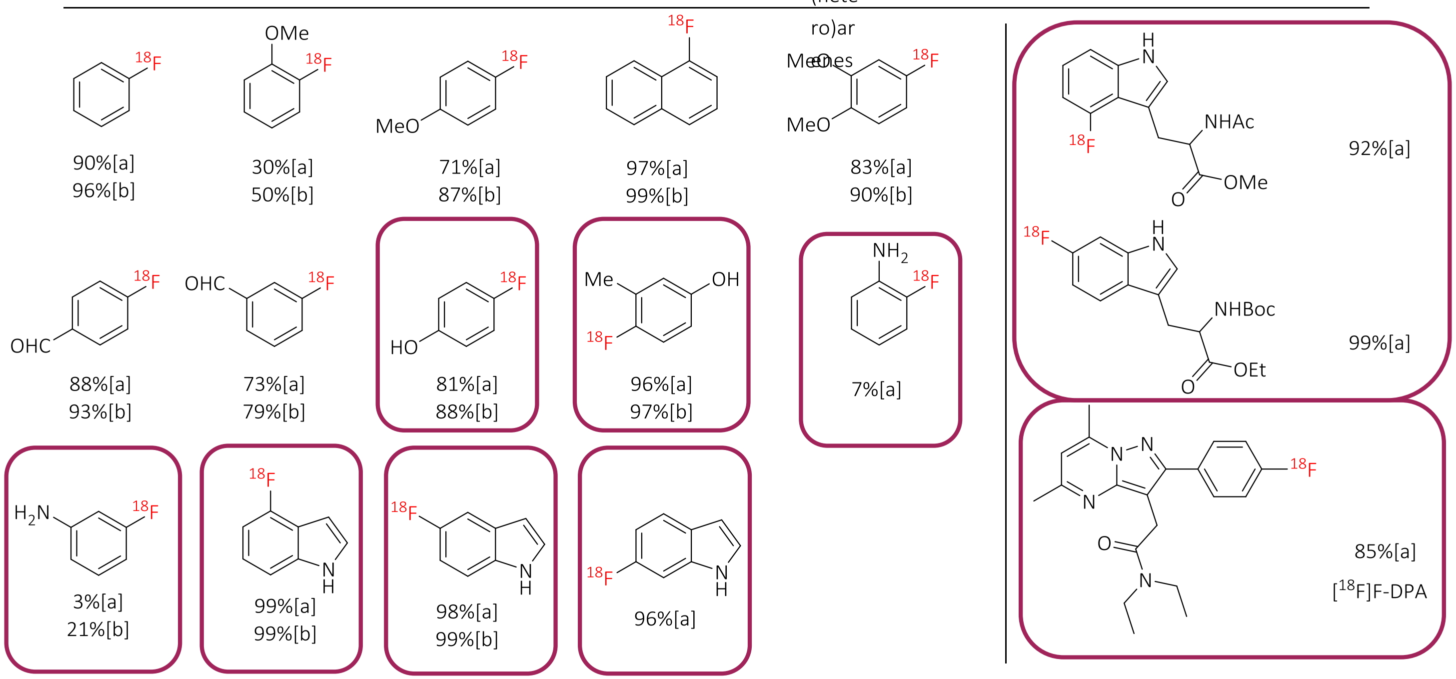
ALCOHOL-ENHANCED CU-MEDIATED RADIOFLUORINATION



ALCOHOL-ENHANCED Cu-MEDIATED RADIOFLUORINATION



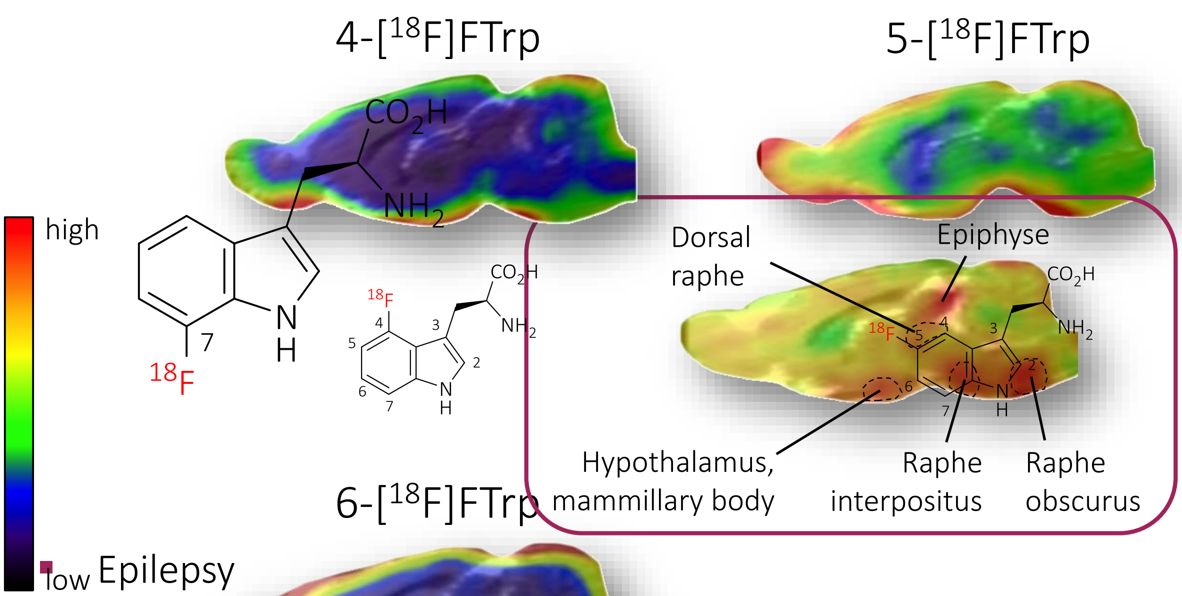
J. Zischler *et al.*, *Chem. Eur. J.* **2017**, *23*, 3257-3256



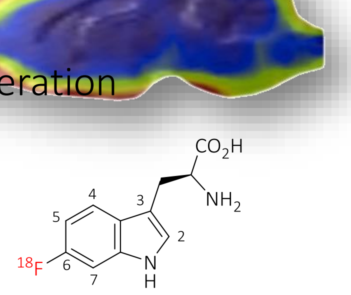
[a] (Hetero)arylboronic acid pinacolester
[b] (Hetero)arylboronic acid

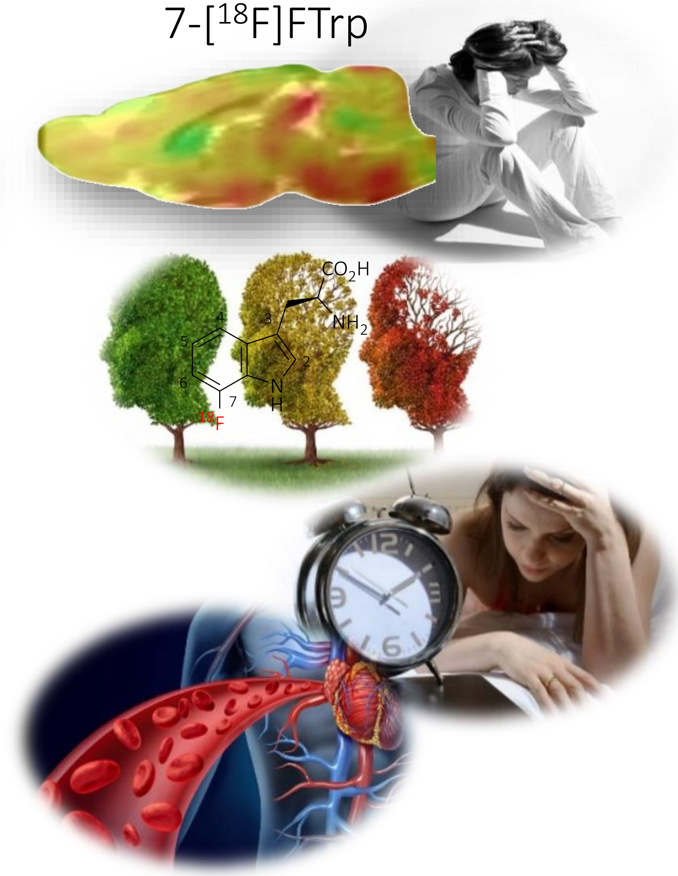
PRECLINICAL EVALUATION OF [18F]FLUOROTRYPTOPHAN

B. D. Zlatopolskiy *et al.*, *J. Med. Chem.* 2017, *61*, 189-206

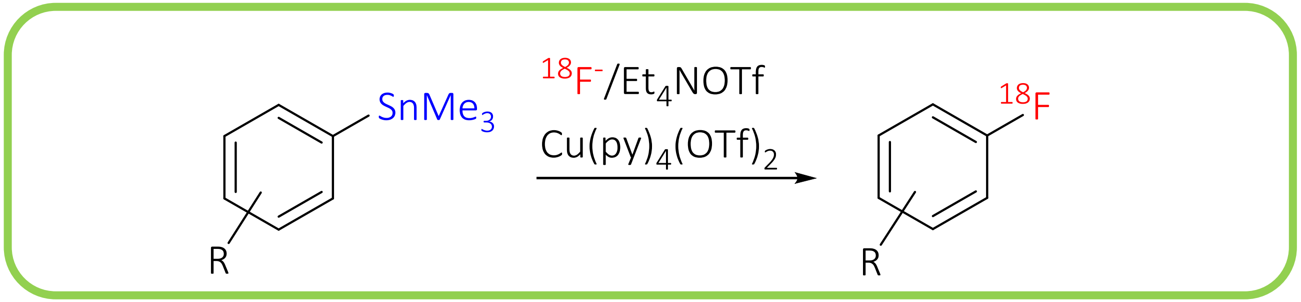


- Epilepsy
- Depressions
- Neurodegeneration
- Insomnia
- Cancer
- Spillover from bone



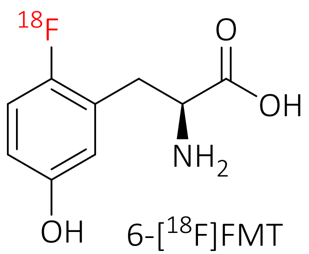


Cu-MEDIATED RADIOFLUORINATION OF STANNANES



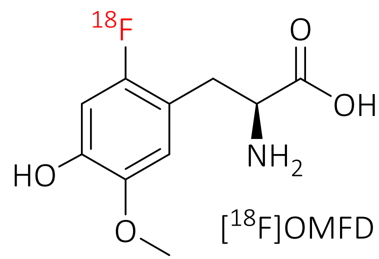
J. Zischler *et al.*, *Chem. Eur. J.* **2017**;
F. Zarrad *et al.*, *Molecules* **2016**

High yields ▪ Commercially available precursors ▪ Easy to automate



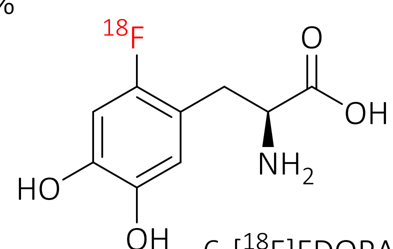
6-[^{18}F]FMT

RCY 42%



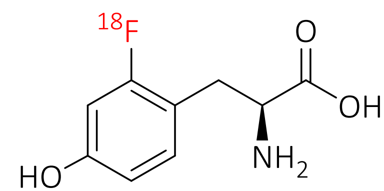
[^{18}F]OMFD

RCY 32%



6-[^{18}F]FDOPA

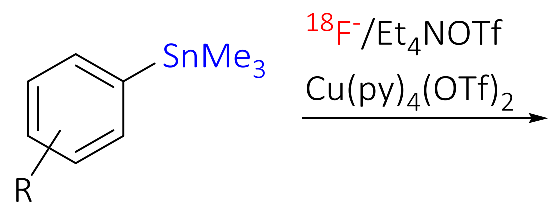
RCY 54%



6-[^{18}F]F-Tyr

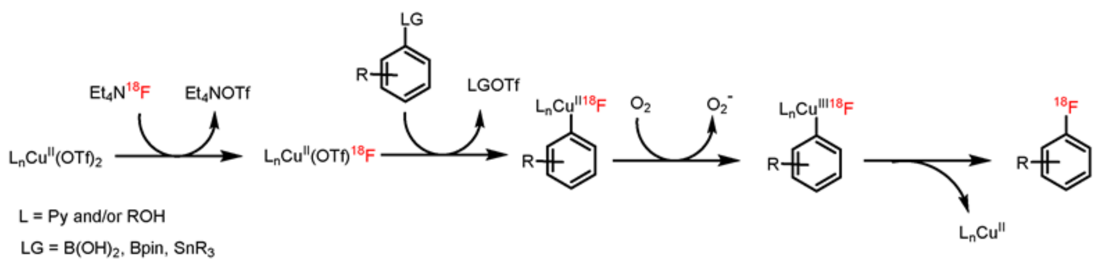
RCY 48%

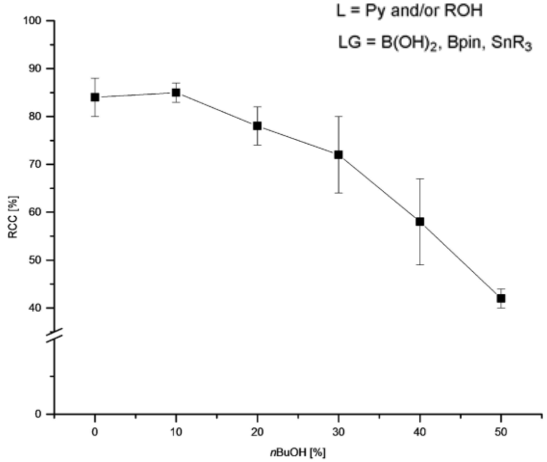
Cu-MEDIATED RADIOFLUORINATION OF STANNANES

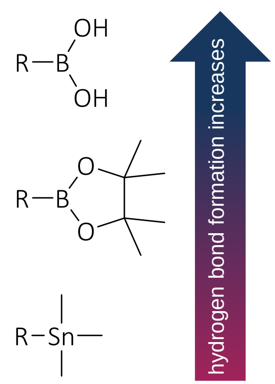


J. Zischler *et al.*, *Chem. Eur. J.* 2017; F. Zarrad *et al.*, *Molecules* 2016

High yields ▪ Commercially available precursors ▪ Easy to automate

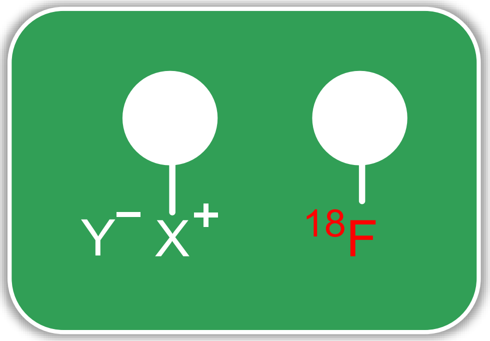






Entry	LG	RCY [%]
1	$PhB(OH)_2$	96* / 13**
2	PhBpin	90* / 82**
3	$Ph(CH_3)_3Sn$	66* / 85 **

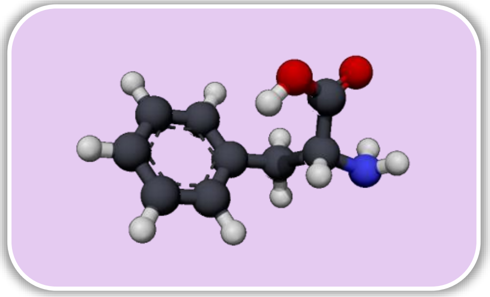
* n-BuOH content = 33%, ** n-BuOH content = 0%



"Minimalist" approach

Alcohol-enhanced Cu-mediated radiofluorination

Ni-mediated radiofluorination



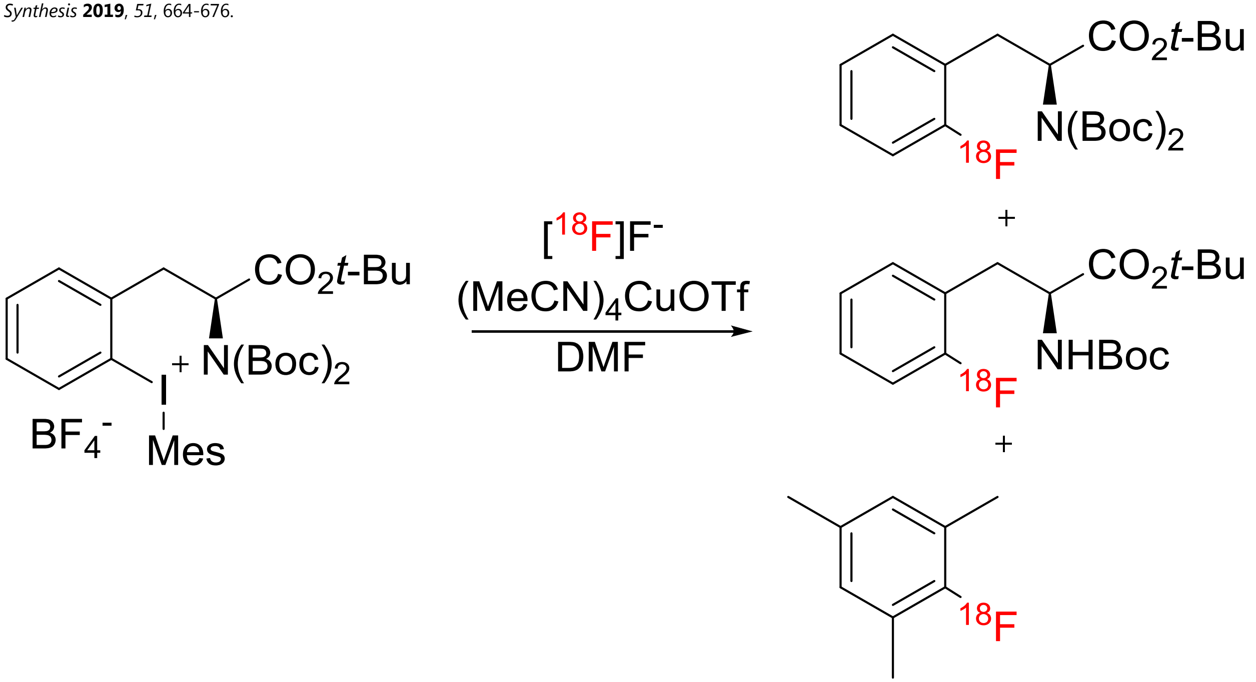
2-[^{18}F]Fluorophenylalanine: Synthesis by Nucleophilic ^{18}F-Fluorination

„Minimalist" Cu-mediated radiofluorination

LIMITATIONS OF THE MINIMALIST APPROACH

Radiosynthesis of 2-[^{18}F]fluorophenylalanine

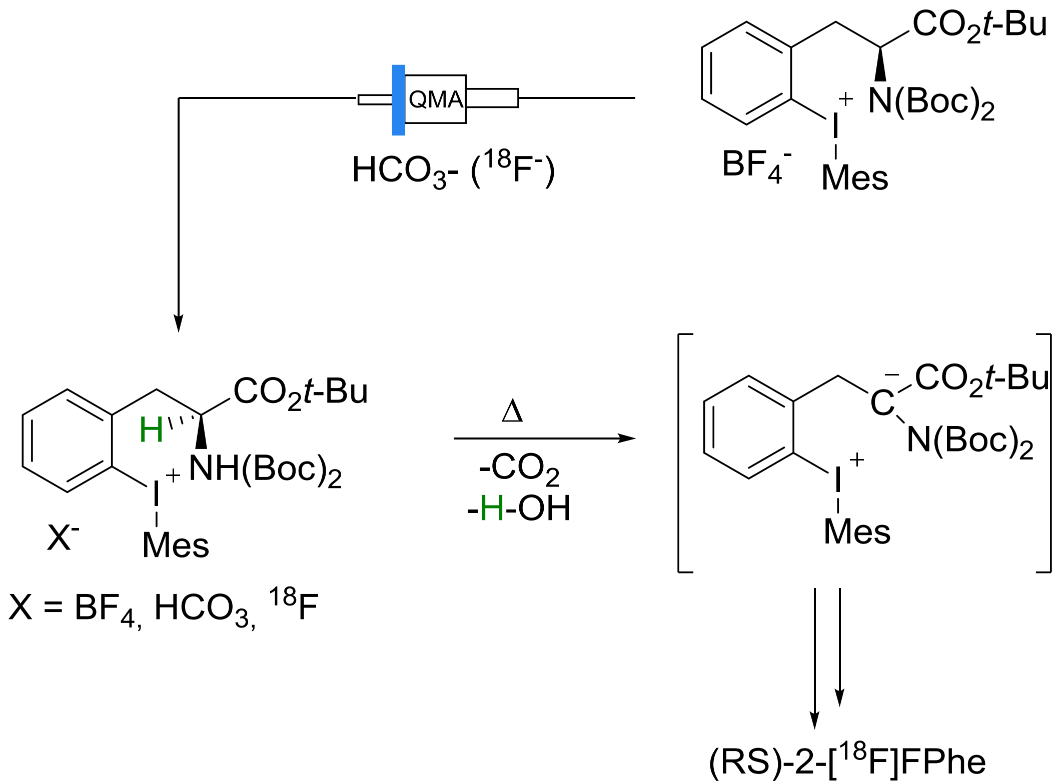
D. J. Modemann et al., *Synthesis* **2019**, *51*, 664-676.



However only 63% enantiomeric purity

RACEMIZAION OF IODONIUM SALT PRECURSOR

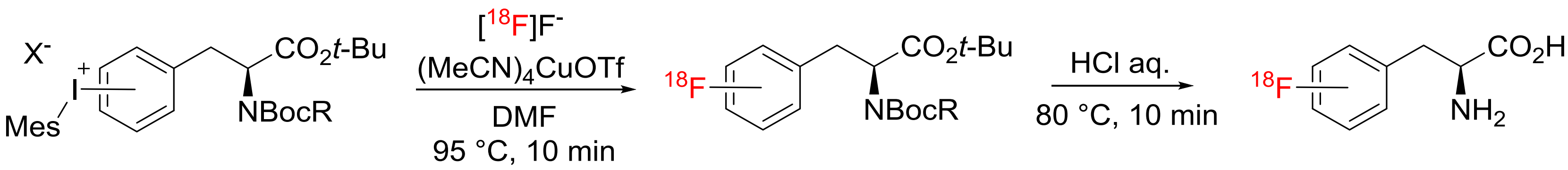
D. J. Modemann et al., *Synthesis* **2019**, *51*, 664-676.



Suppression of racemization:

- Less electron-withdrawing (or better electron-donating) N-protecting groups
- Anion exchange resin in non-basic form (no formation of CO_3^{2-} and/or HCO_3^- salts)
- ‘Low base’ protocol - no contact of the precursor with the anion exchange resin

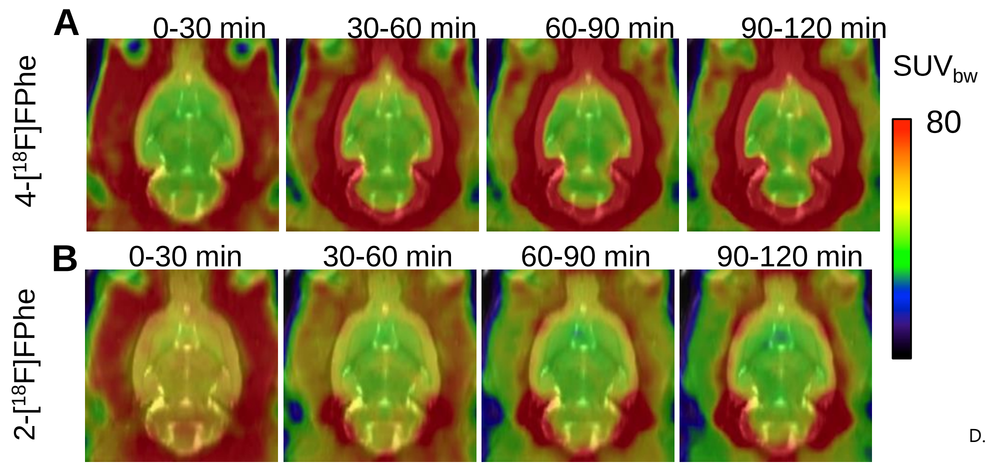
LIMITATIONS OF THE MINIMALIST APPROACH



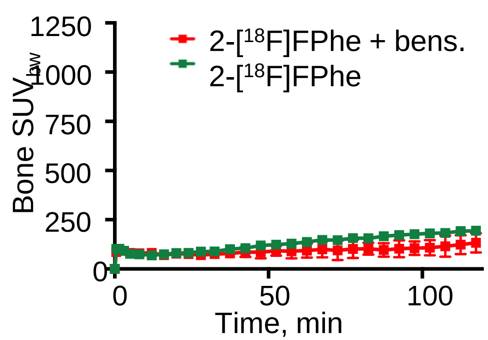
Entry	Precursor	Radiolabeling method	Product	RCY [%]	ee [%][L/D]
1	R = Boc, X = BF_4	minimalist	2-[^{18}F]FPhe	32 ± 14	63 ± 7
2	R = Boc, X = BF_4	minimalist	4-[^{18}F]FPhe	35 ± 6	>99 (>99:1)
3	12 R = MOM, X = BF_4	minimalist	2-[^{18}F]FPhe	25, 14	77, 80
4	X =·BF_4	minimalist	2-[^{18}F]FPhe	27,28	>99 (>99:1)
5	X =·BF_4	minimalist	2-[^{18}F]FPhe	42	92
6	X = BF_4	minimalist	2-[^{18}F]FPhe	35	98
7	X = BF_4	low-base	2-[^{18}F]FPhe	48 ± 8 (n = 3)	>99 (>99:1)

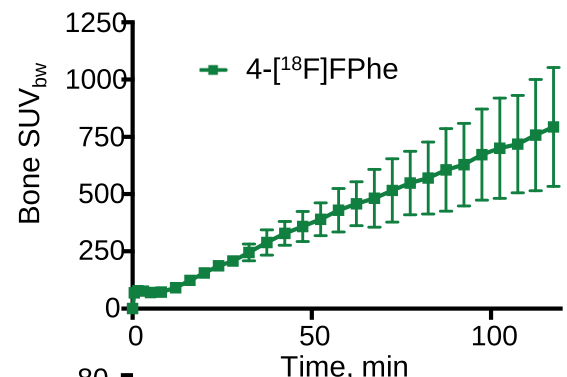
D. J. Modemann et al., *Synthesis* **2019**, *51*, 664-676.

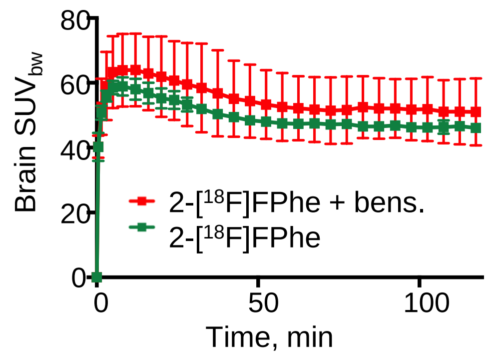
PRECLINICAL EVALUATION OF 2- and 4-[^{18}F]FPhe

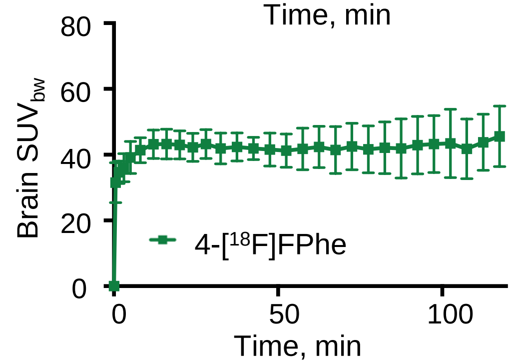


D. J. Modemann et al., *Synthesis* **2019**, *51*, 664-676.









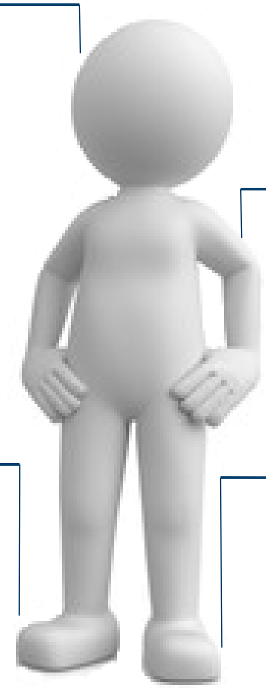
Translation into clinic

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

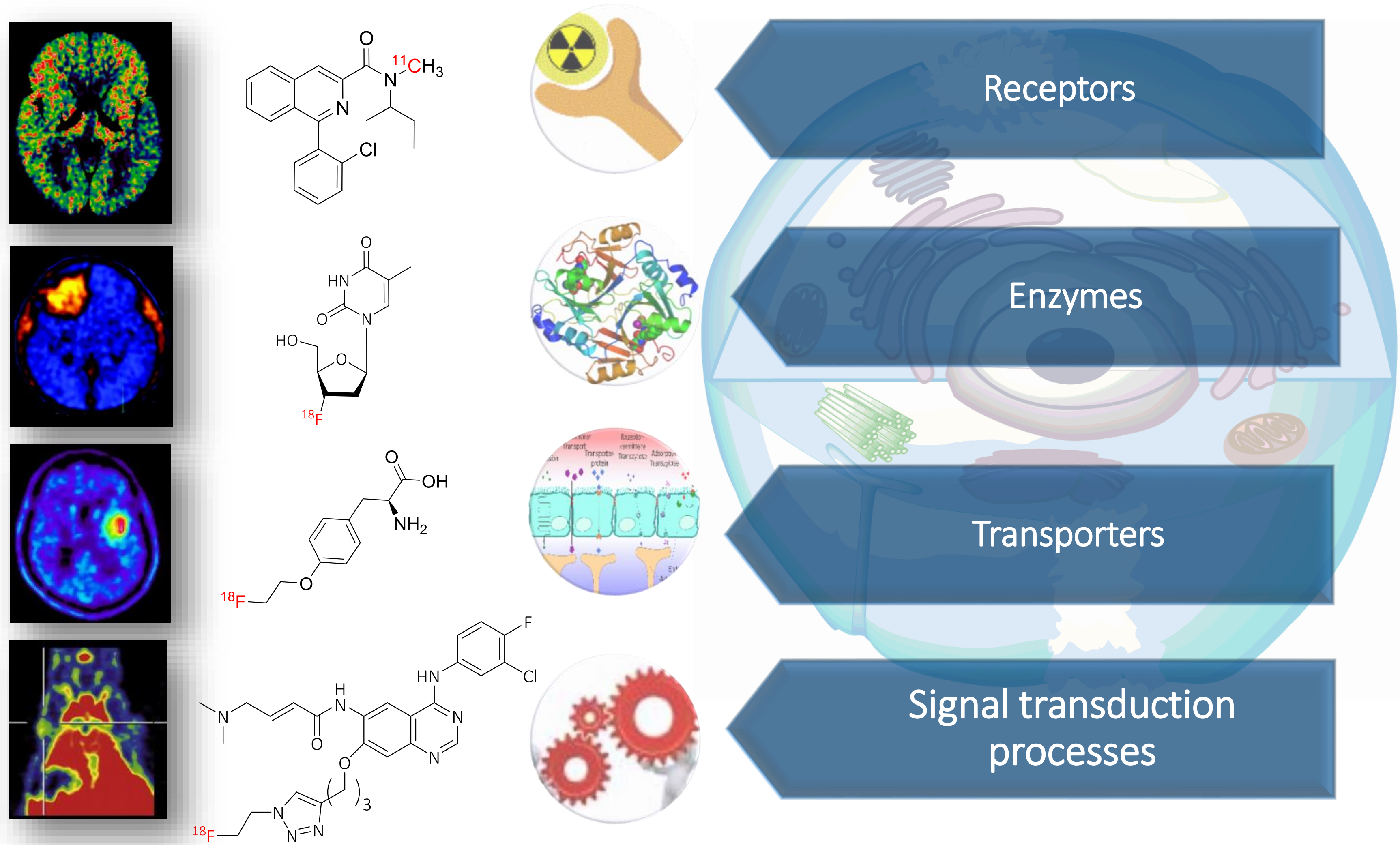
Monitoring of therapy efficacy

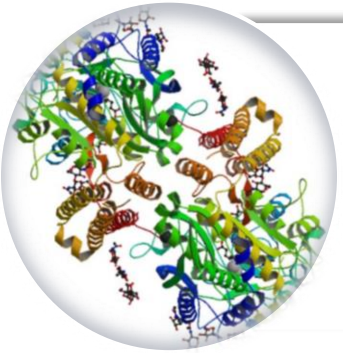
PRINCIPLE OF MOLECULAR IMAGING

BIOLOGICAL TARGETS FOR DISEASE DETECTION

Visualization of molecular processes - measurement of molecular alterations

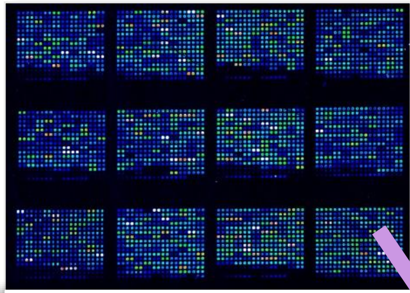
UP- or DOWN regulation of



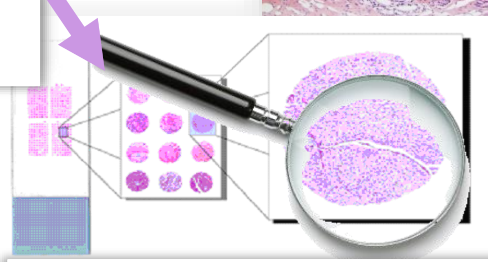


Prostate specific membrane antigen

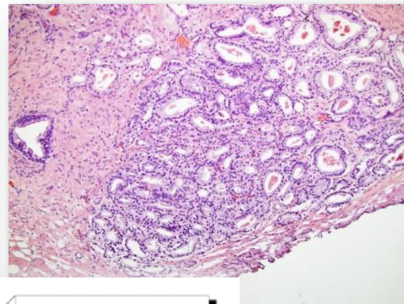
PSMA SELECTIVE PROBES

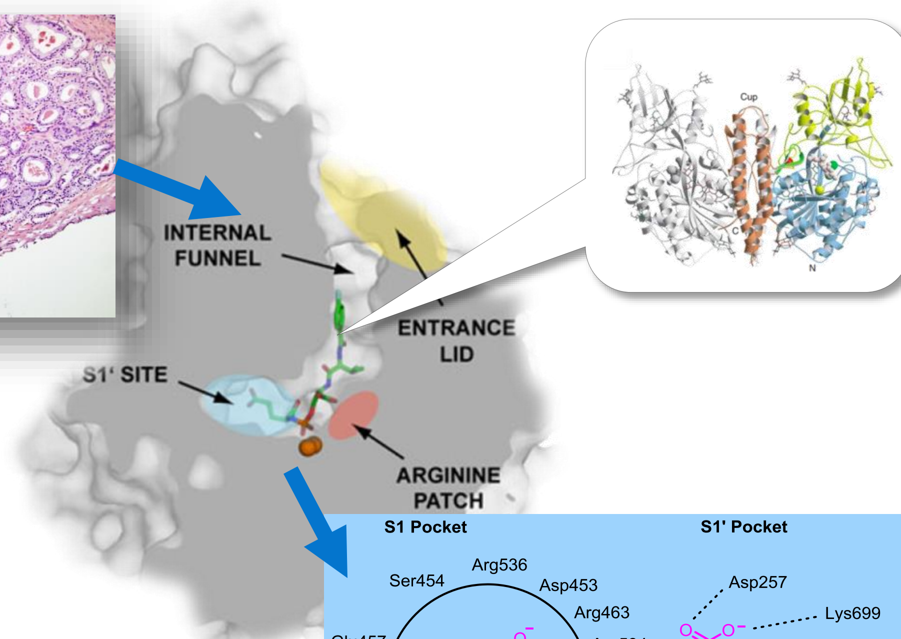


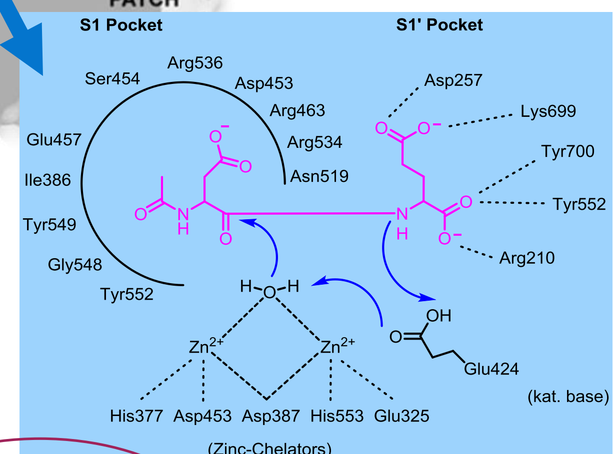
Molecular biological screening



Selection of key processes and target identification

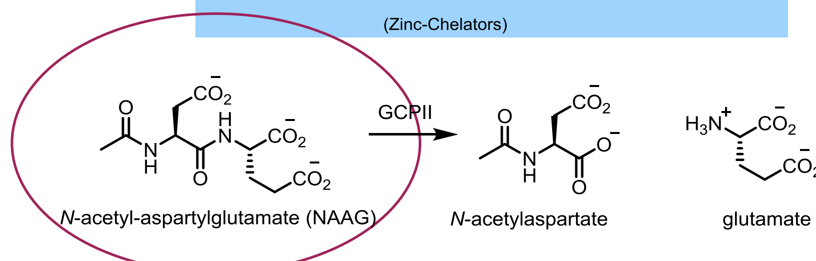




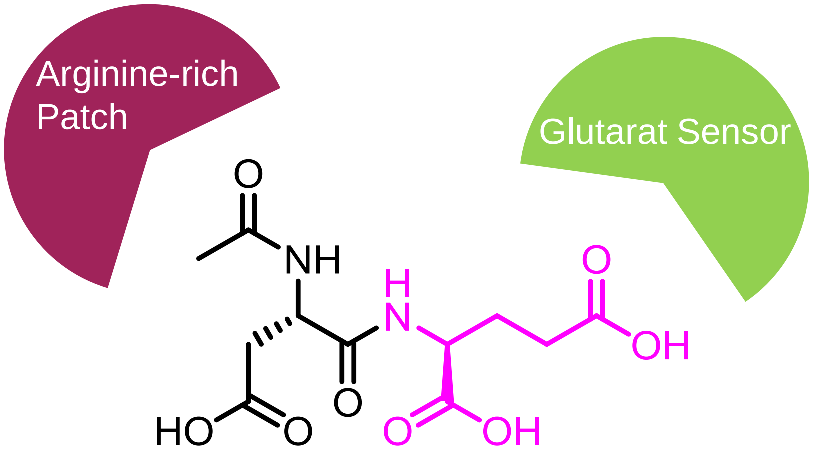


Prostate-Specific-Membrane-Antigen:

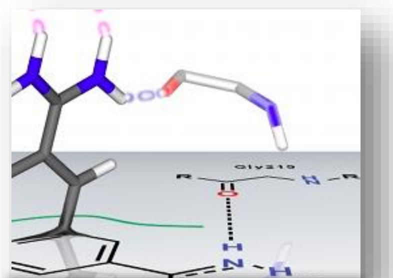
- Membrane-bound zinc metallopeptidase
- in vivo: Hydrolysis of *N*-acetylaspartylglutamate (NAAG) into glutamate and N-acetylaspartate
- High expression in the ephithel cells of most PCa tumors



TRACER DESIGN - PSMA-PET LIGAND

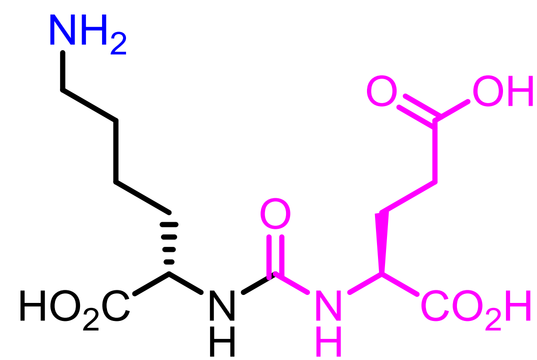


N-Acetylaspartylglutamic acid (NAAG)



Tracer design and development

Kozikowski *et al.* (2001)

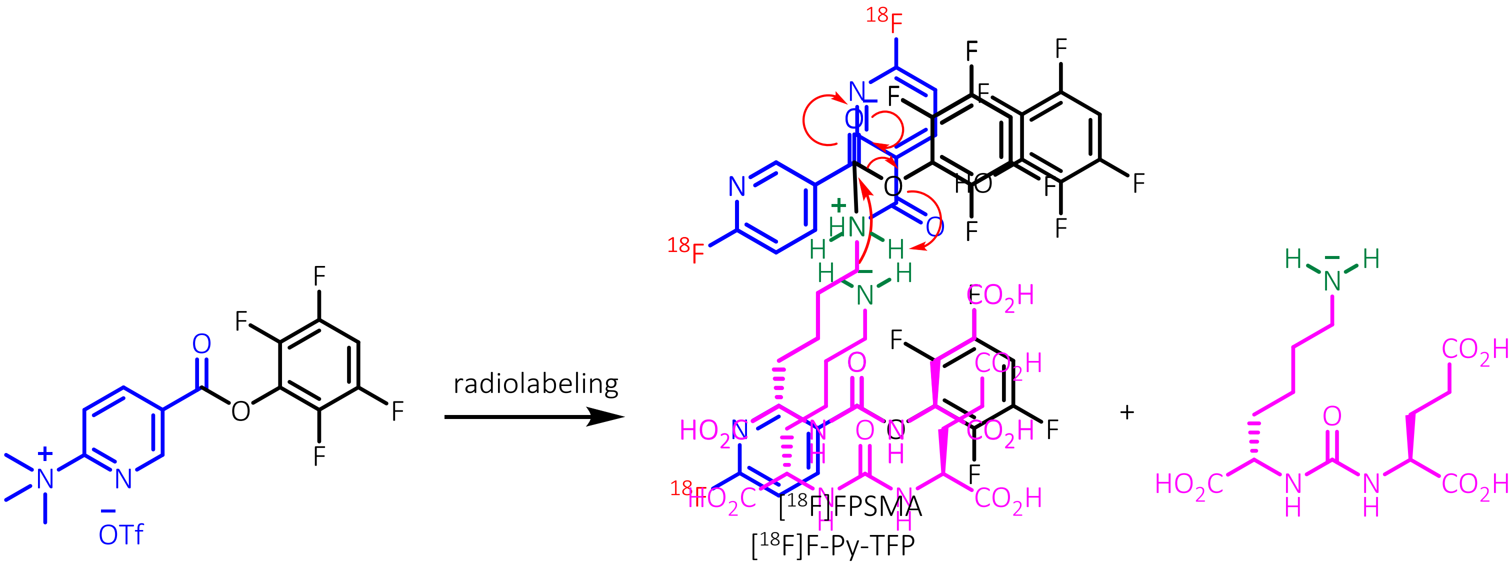


(*S*)-Lys-Urea-(*S*)-Glu

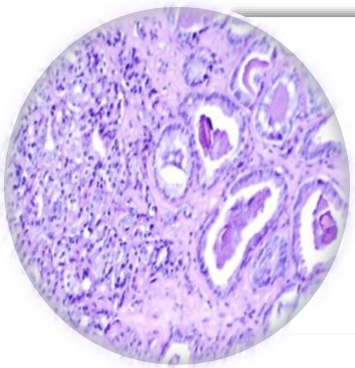
- Endogenous ligand of PSMA
- *in-vivo*: Cleavage to *N*-acetylaspartate and glutamate => short plasma half life
- Not suitable as PET probe

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

RADIOSYNTHESIS OF [^{18}F]PSMA



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



Prostate cancer

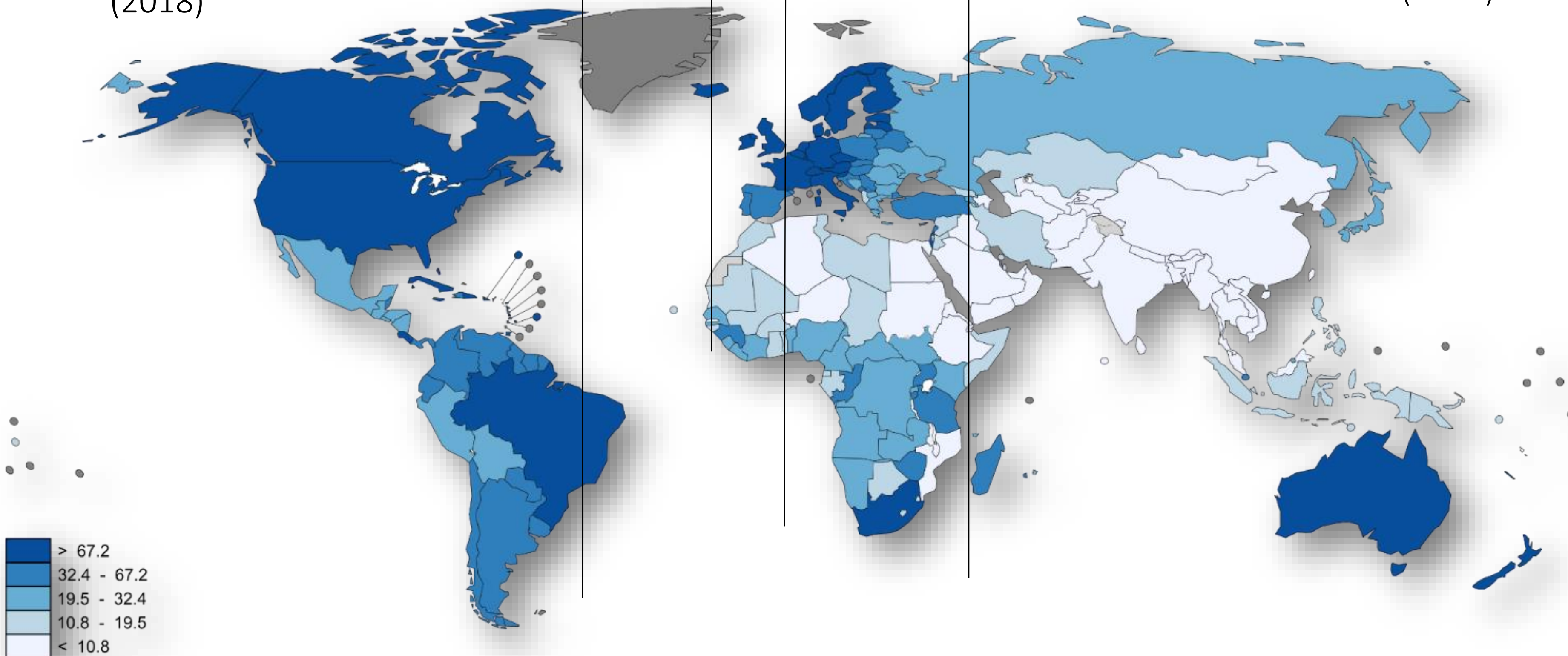
PROSTATE CARCINOMA (PCa)

2nd most common type of cancer in man (2018)

1.3 million man with PCa (2018)

Very high incidence (>70%) in developed countries

5th leading cause of cancer-related death in man (2018)

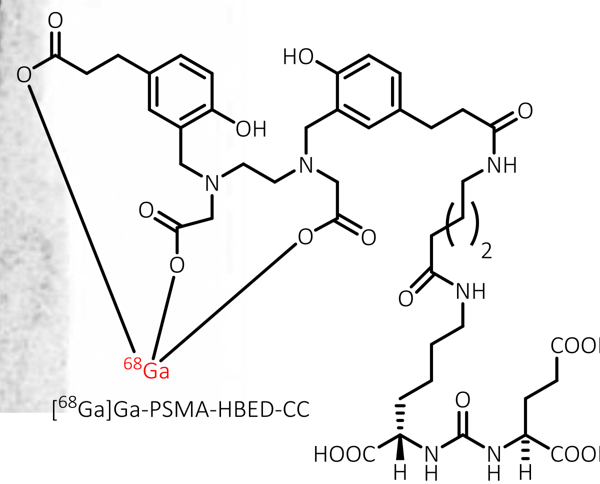


Estimated age-standardised rates (World) per 100,000

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

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

[^{18}F]PSMA-6

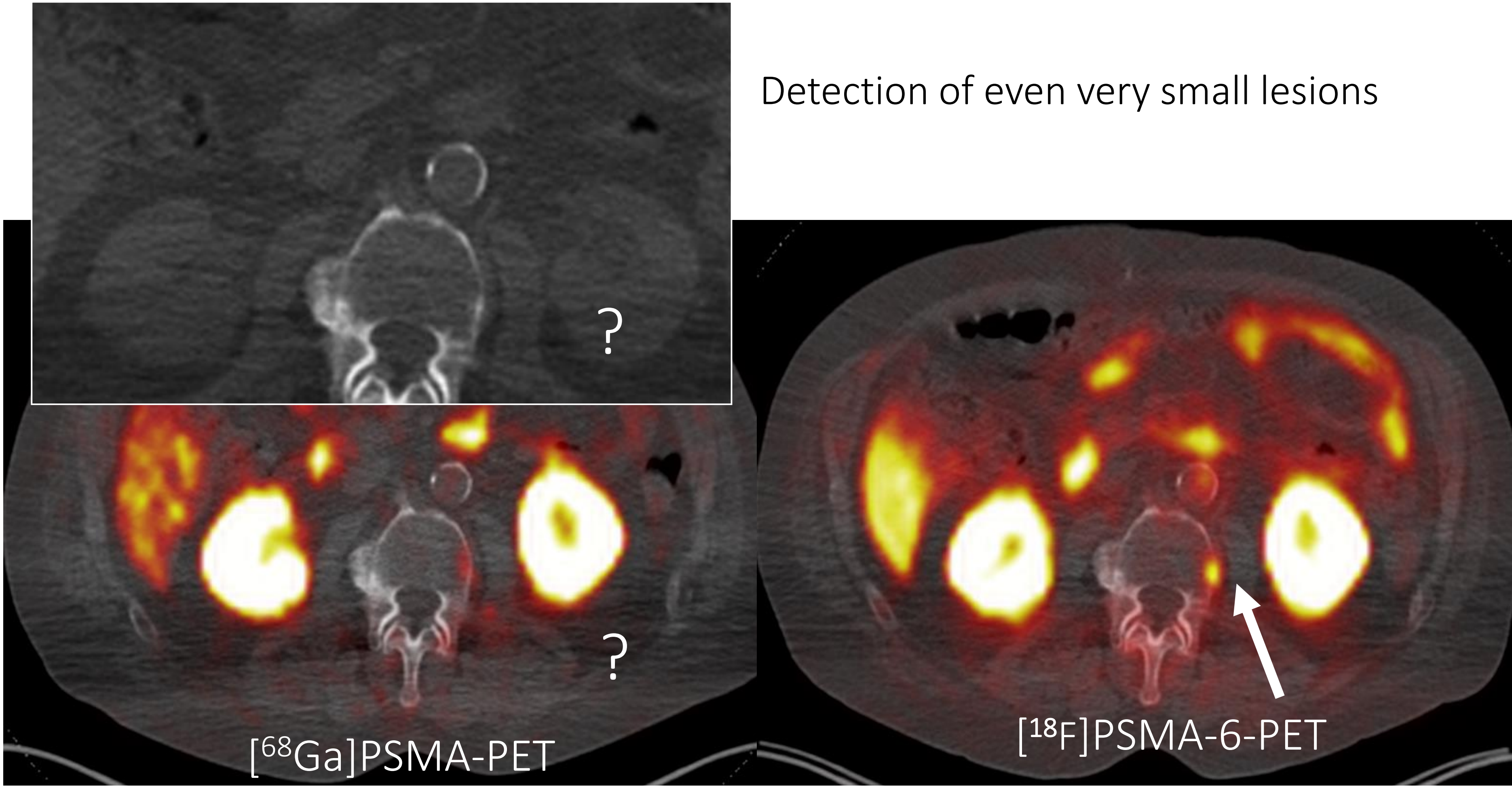


[^{68}Ga]Ga-PSMA-HBED-CC

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

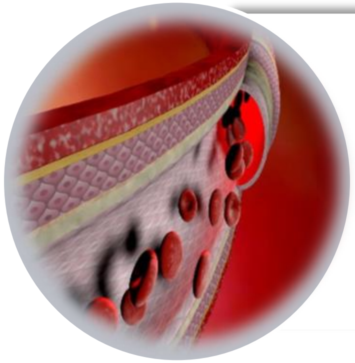
IMAGING OF PCa BONE METASTASIS BY [^{18}F]PSMA-6-PET

Detection of even very small lesions



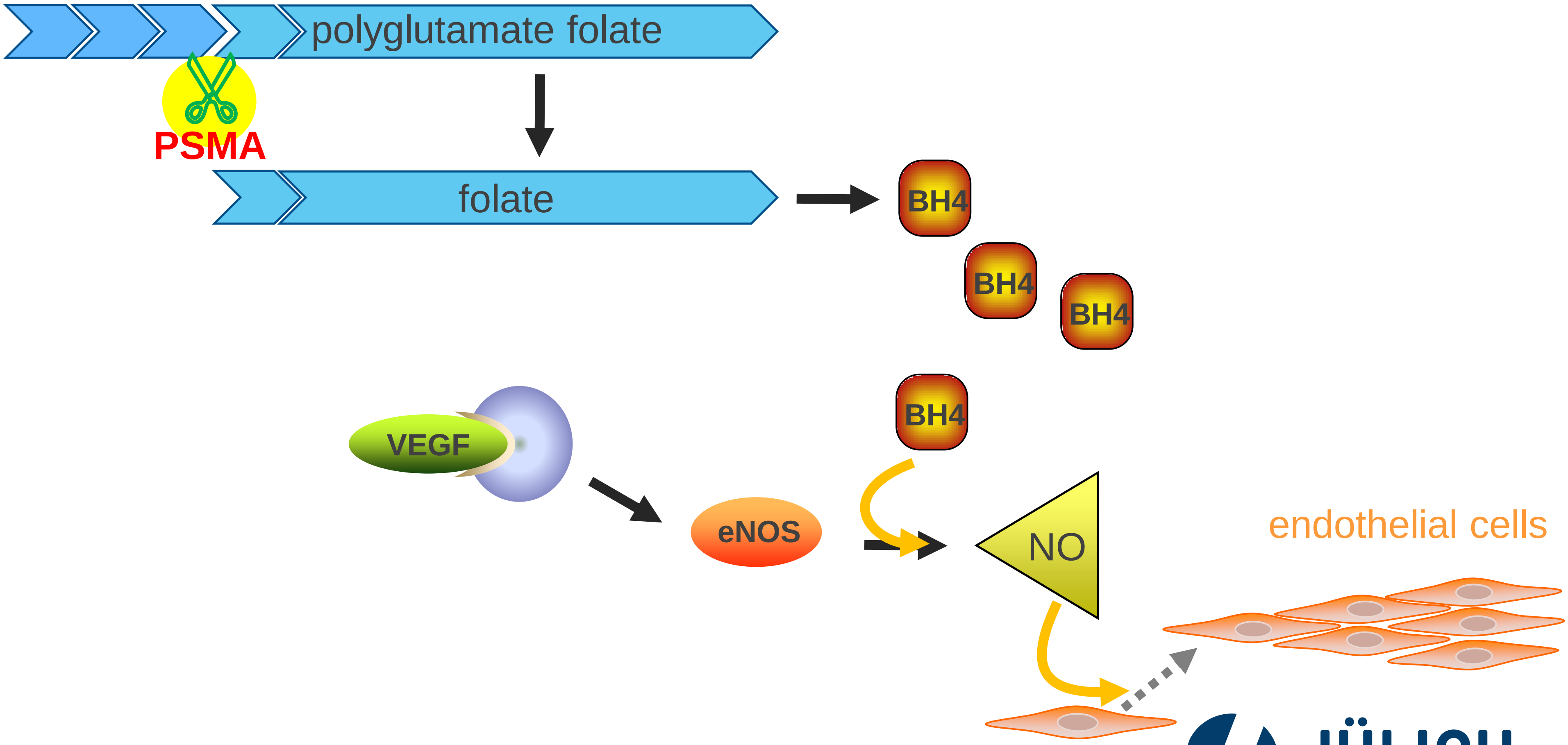
Courtesy of C. Kobe, M. Dietlein, Nuklearmedizin UKK

REENDOTHELIALIZATION BY [^{18}F]PSMA

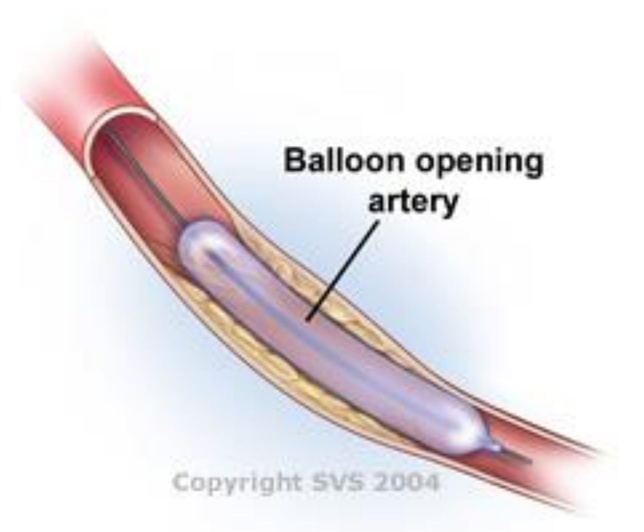


Reendothelialization

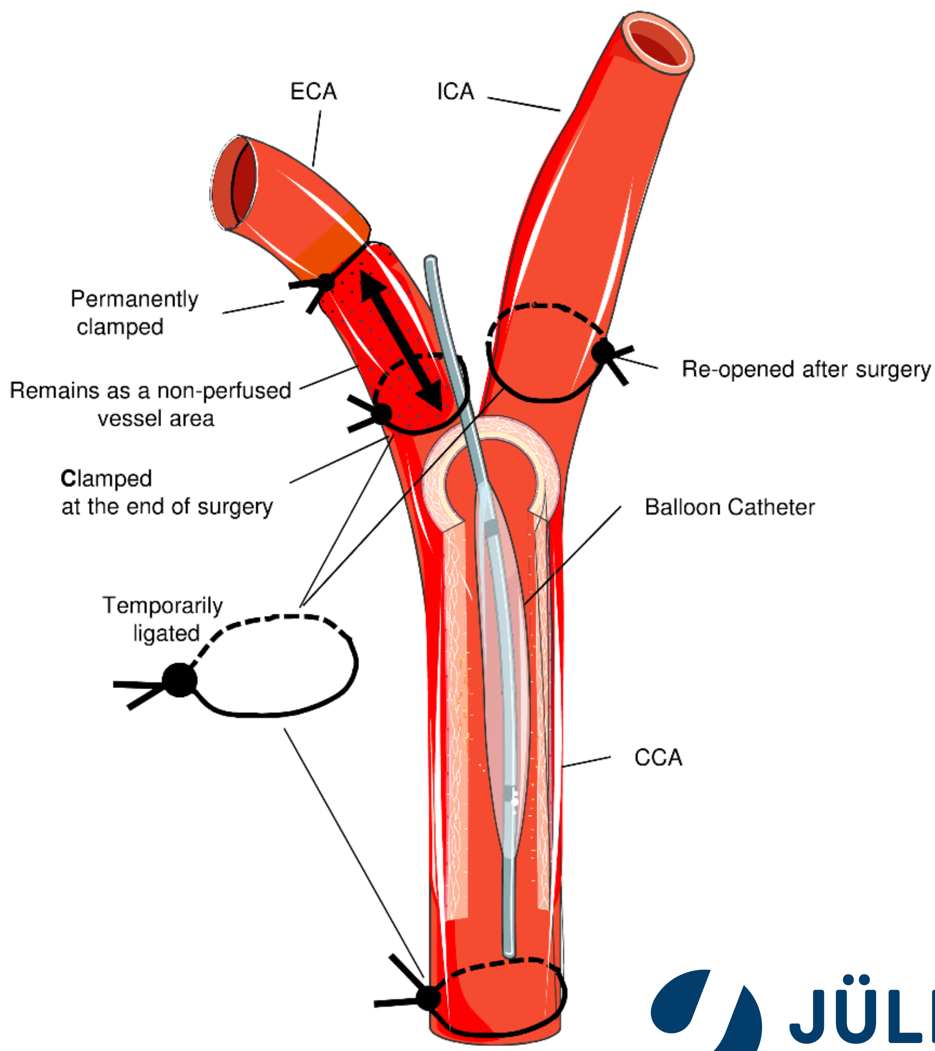
THE ROLE OF PSMA IN REENDOTHELIALISATION



BALLOON DILATATION MODEL

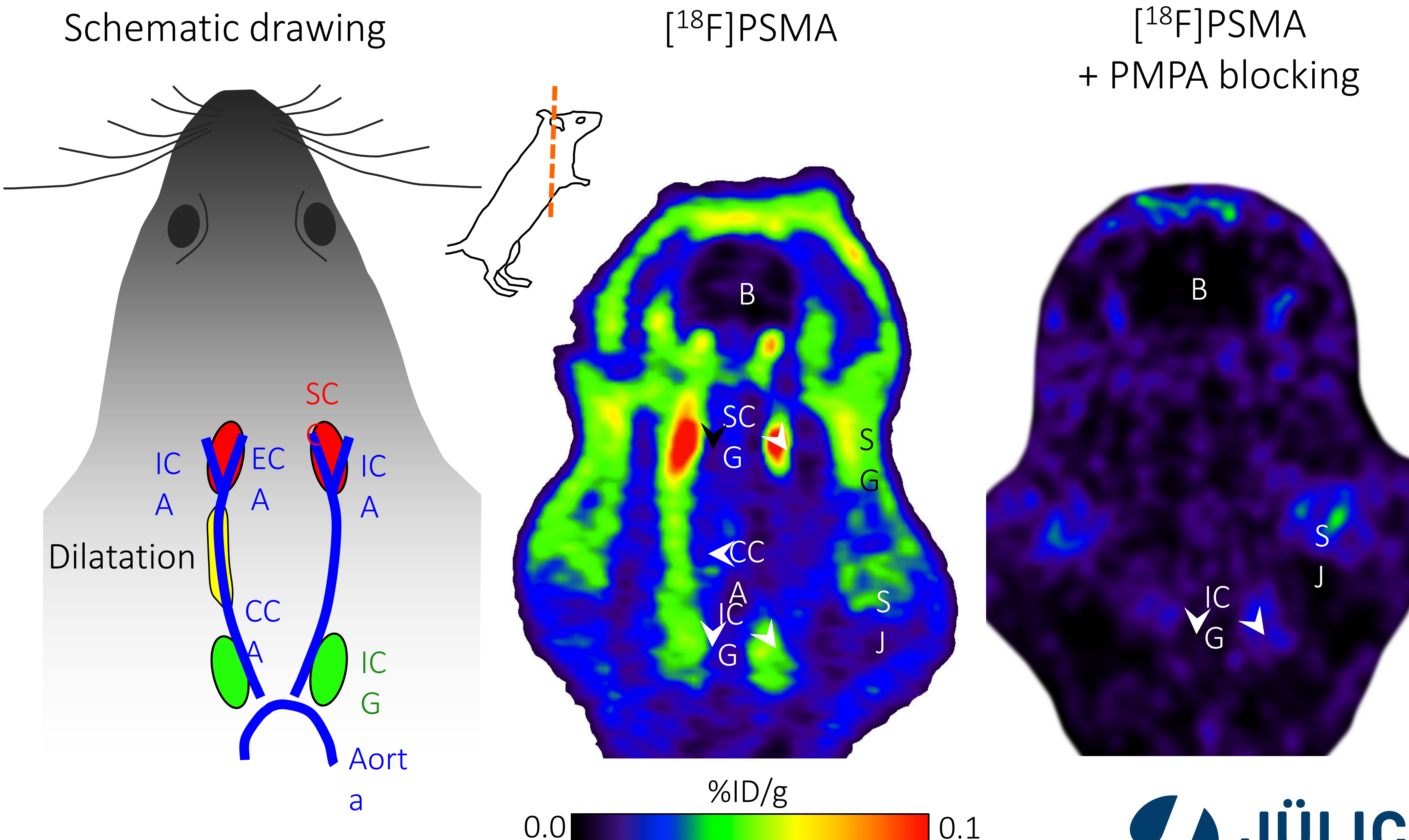


Balloon dilatation model



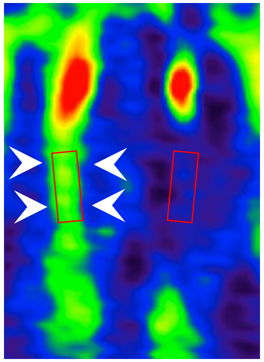
JÜLICH Forschungszentrum

IMAGING OF REENDOTHELIALIZATION BY PSMA PET

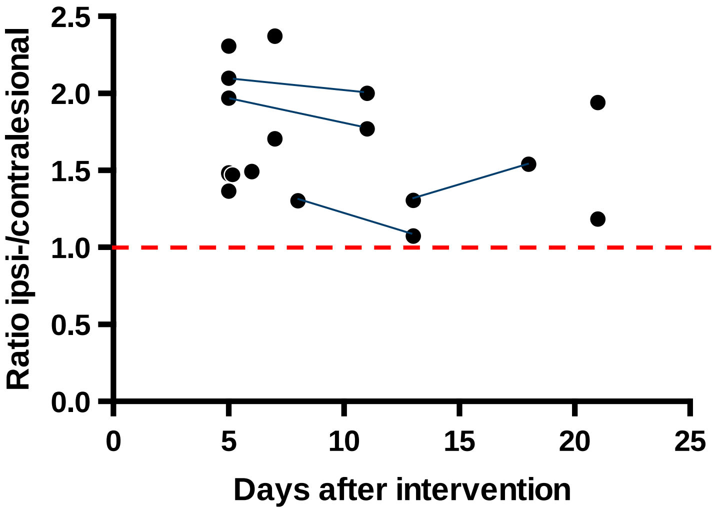


JÜLICH
Forschungszentrum

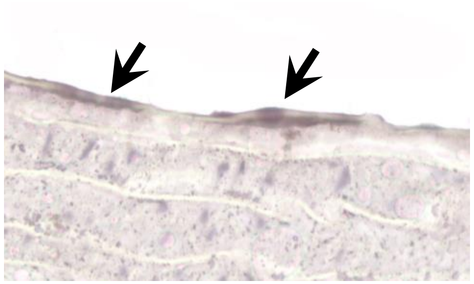
ANALYSIS OF PSMA EXPRESSION



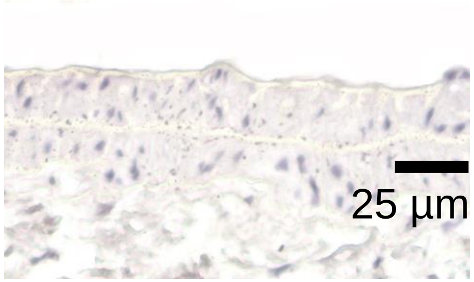
VOIs (red squares) used for analysis



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



immunostaining of the dilated CCA



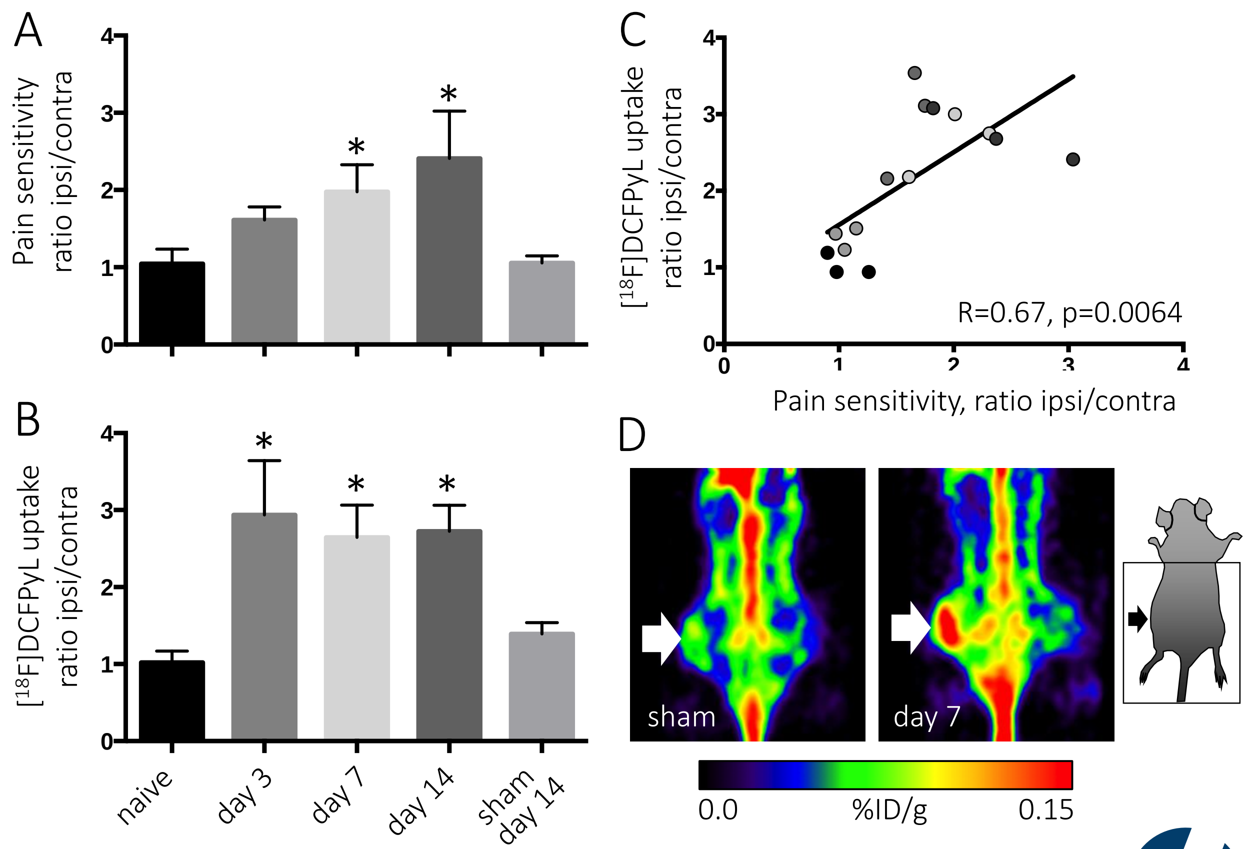
immunostaining of the contralateral CCA

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

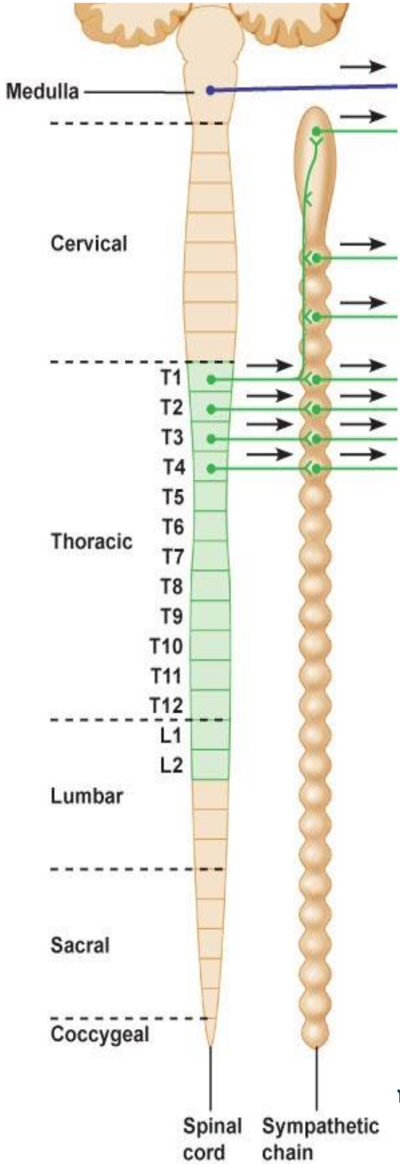
Neuropathic pain

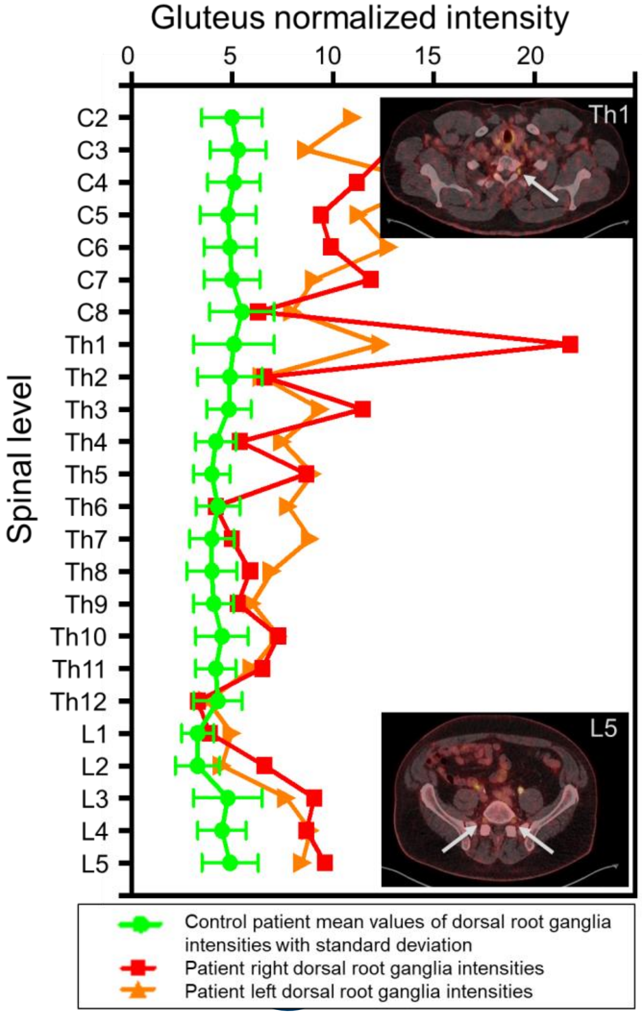
VISUALIZATION OF NEUROPATHIC PAIN BY [^{18}F]PSMA PET

Neuropathic pain induced by sciatic nerve lesion (SNI).



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



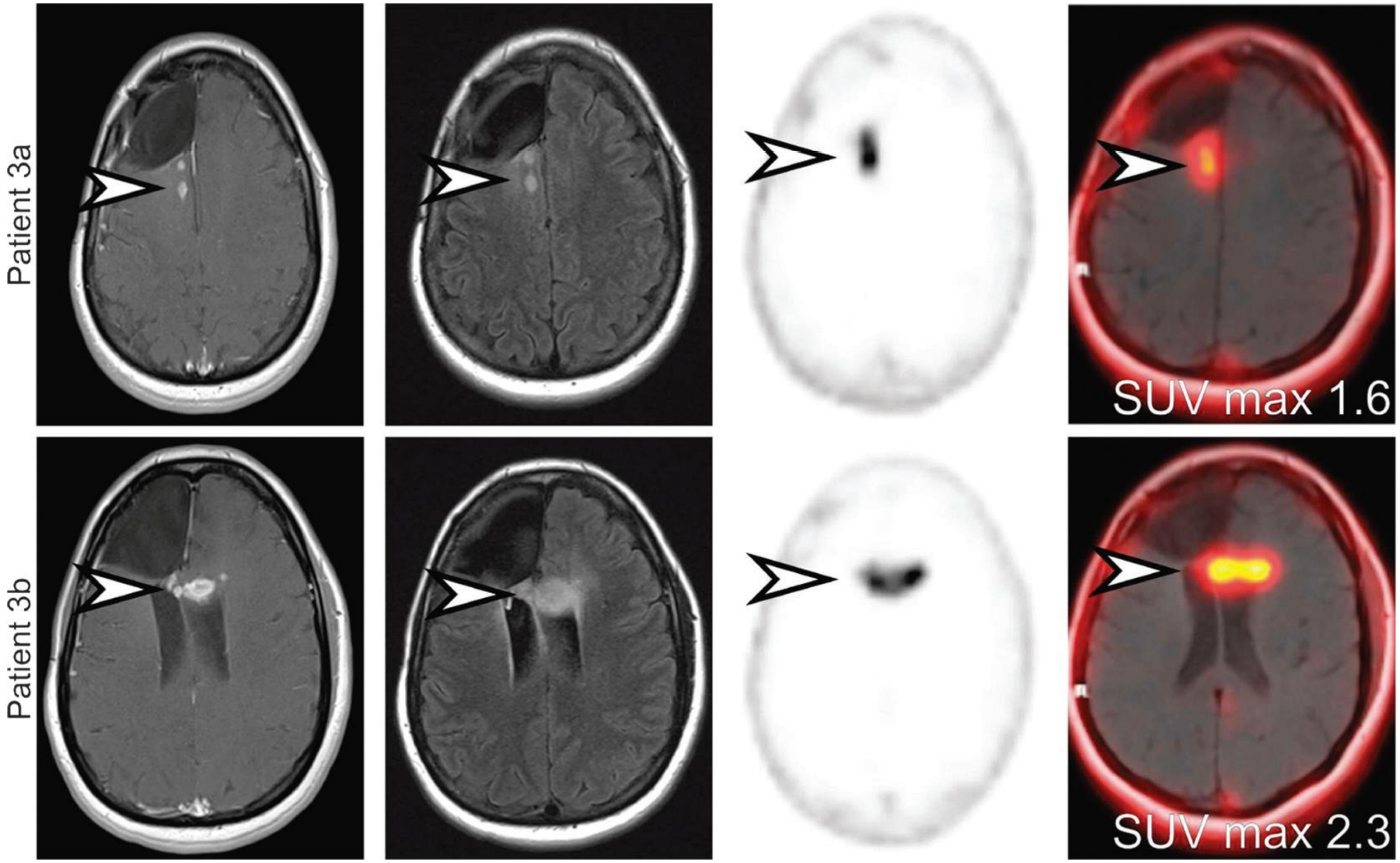


Courtesy of C. Kobe, M. Dietlein, S. Stockter Nuklearmedizin UKK

GLIOMA BY [^{18}F]PSMA PET

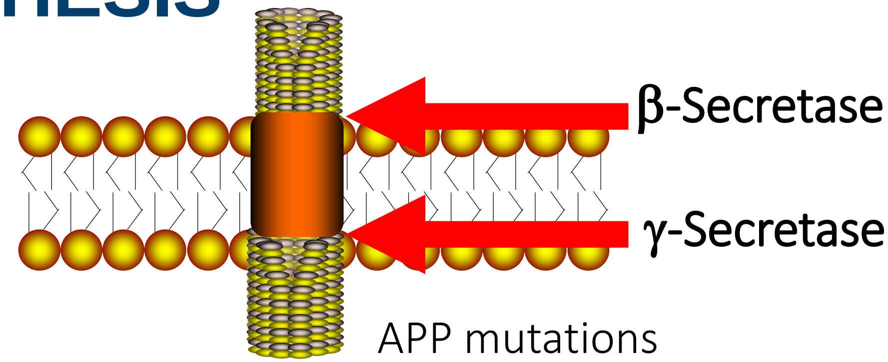
Glioma

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

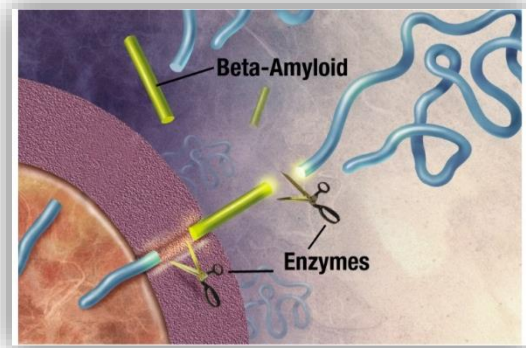


Neurodegenerative diseases

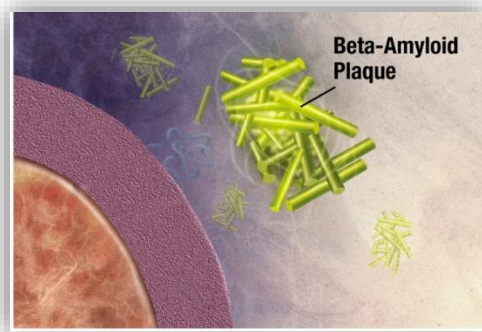
ALZHEIMER'S DISEASE: AMYLOID CASCADE HYPOTHESIS

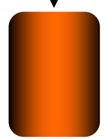


APP mutations
Presenilin 1 mutations
Presenilin 2 mutations



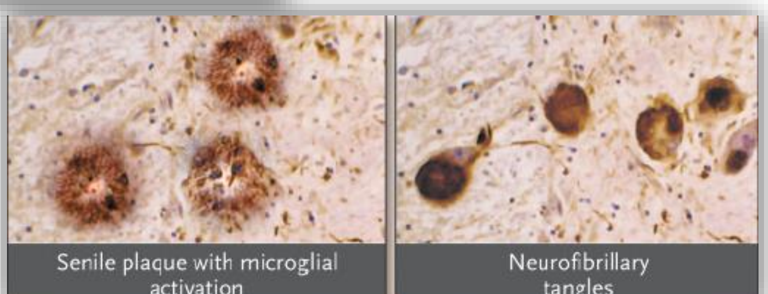
Increase of Aβ production





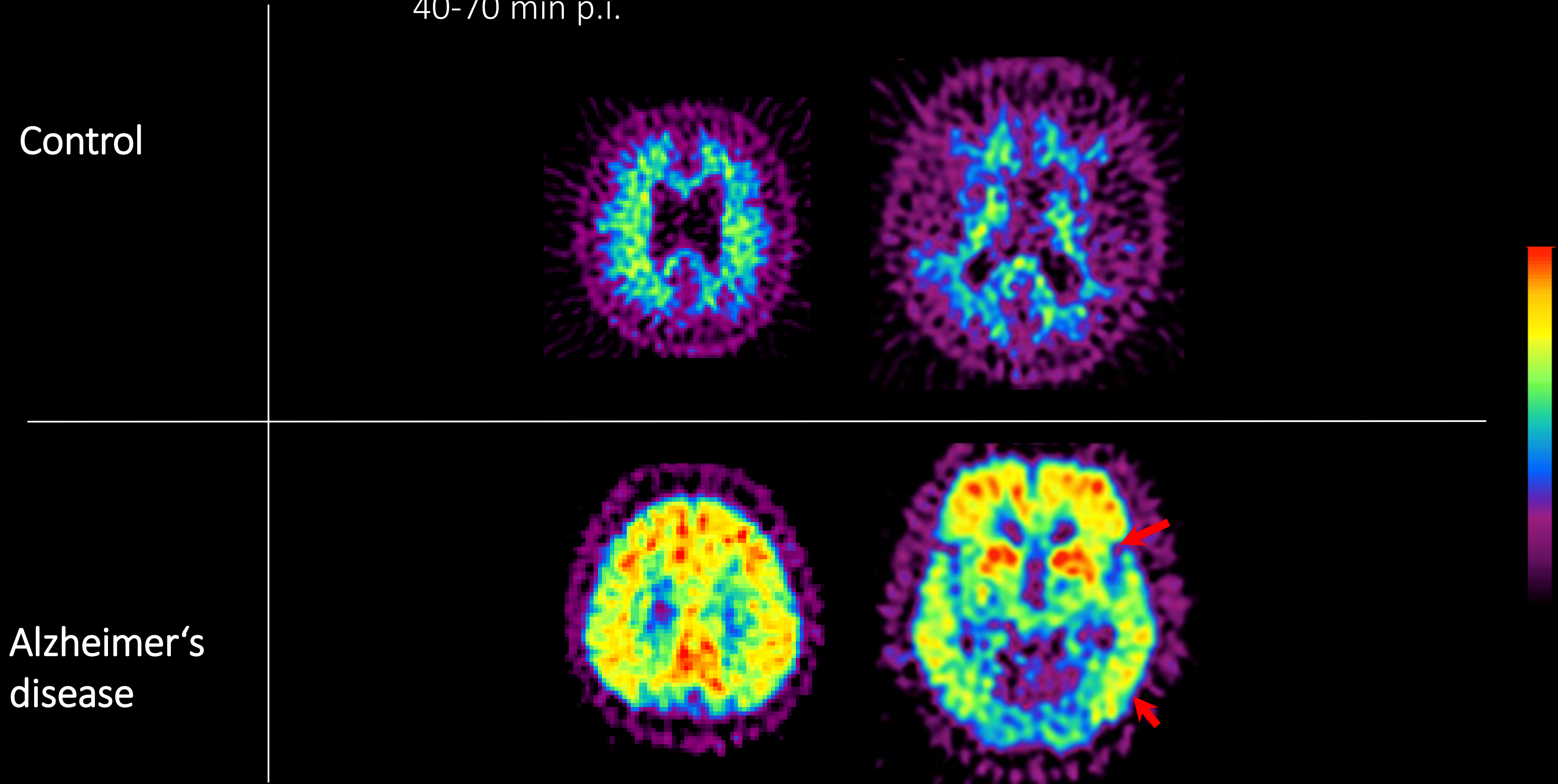
Lipoprotein ε4
LRP
Cholesterol
α2 Macroglobuline

Aggregation triggered and clearance of amyloid decelerated



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

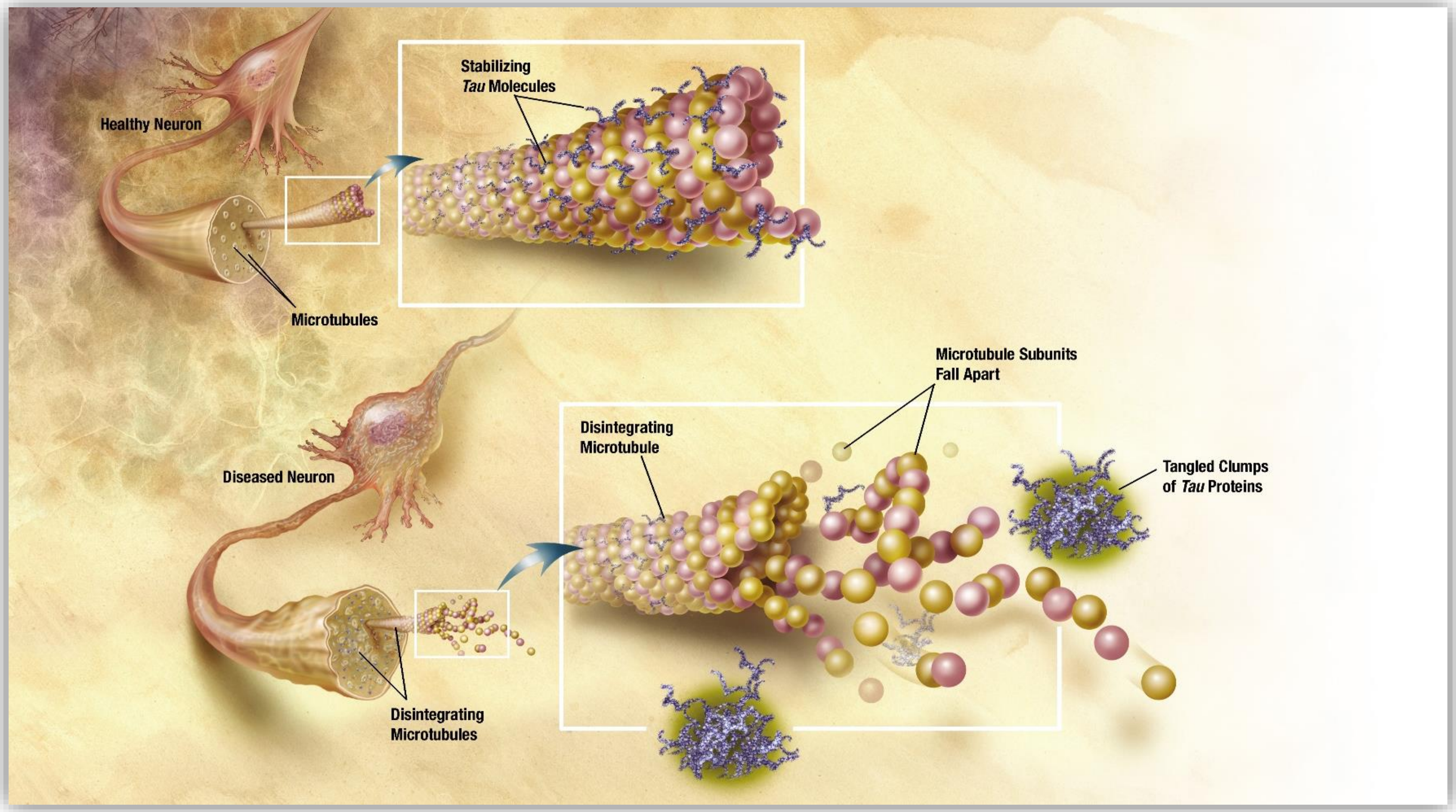
Amyloid Plaque Imaging C-11 PIB
40-70 min p.i.



Axial slices
caudal aspects

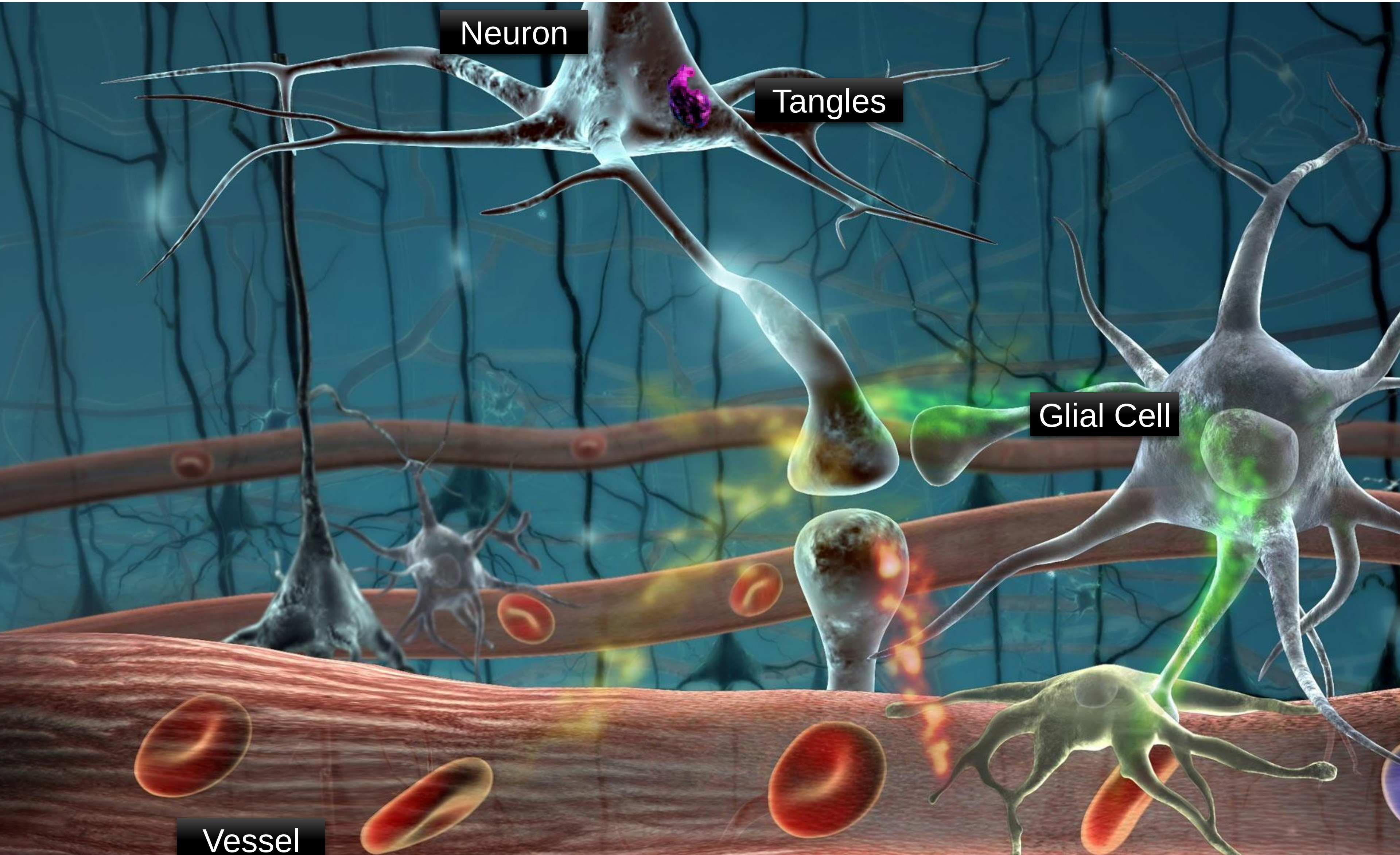
Drzezga *et al*. Ann. of Nuclear Med. 2009

ALZHEIMER'S DISEASE: TAU-HYPOTHESIS



- Changes in tau protein lead to the disintegration of microtubules in brain cells
- This may result in malfunctions and eventually the death of the neurons
- Over time damage may lead to pathogenesis of AD

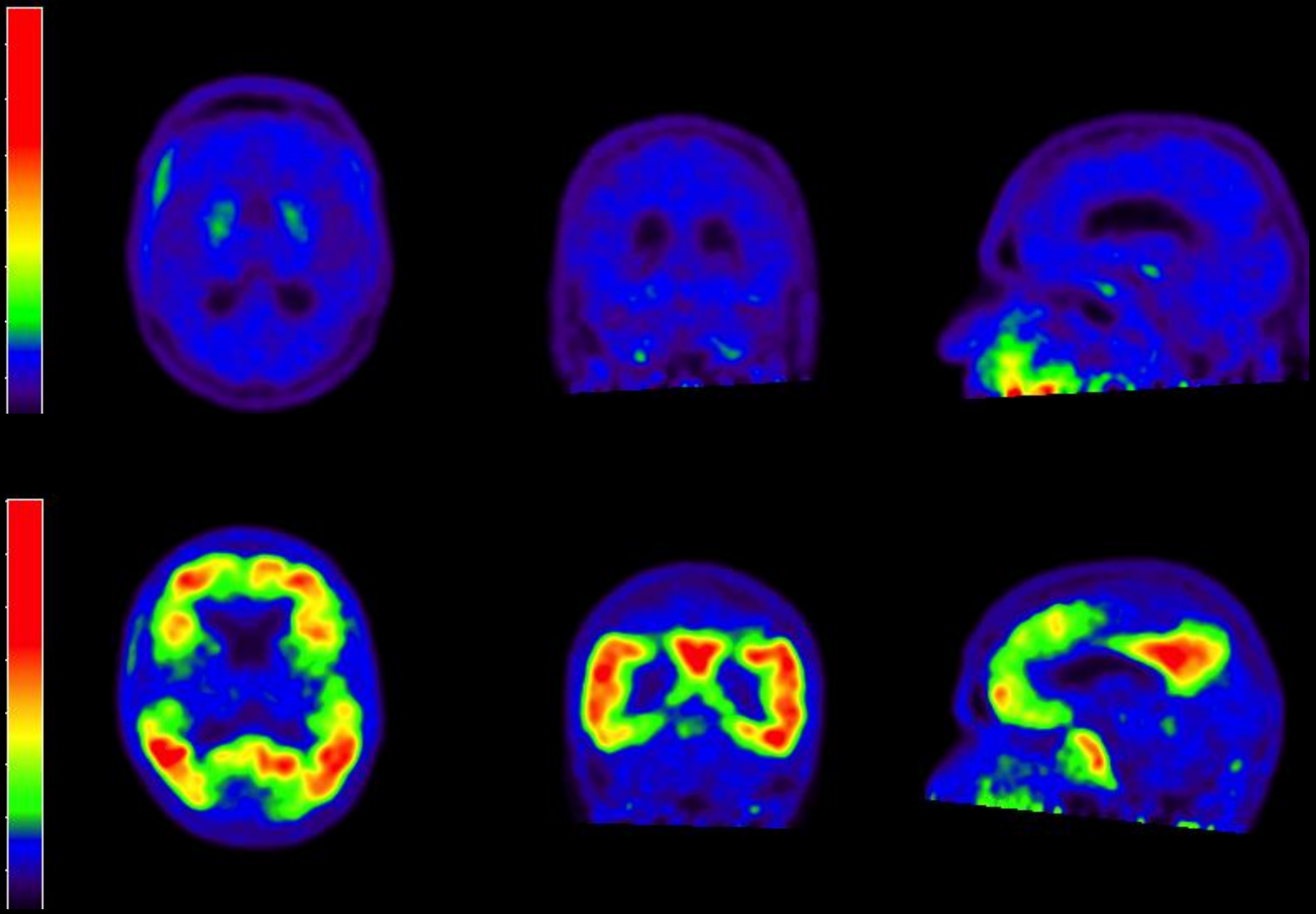
REQUIREMENTS OF TAU-TRACER



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

Healthy control person

Alzheimer‘s disease



Mitglied der Helmholtz-Gemeinschaft

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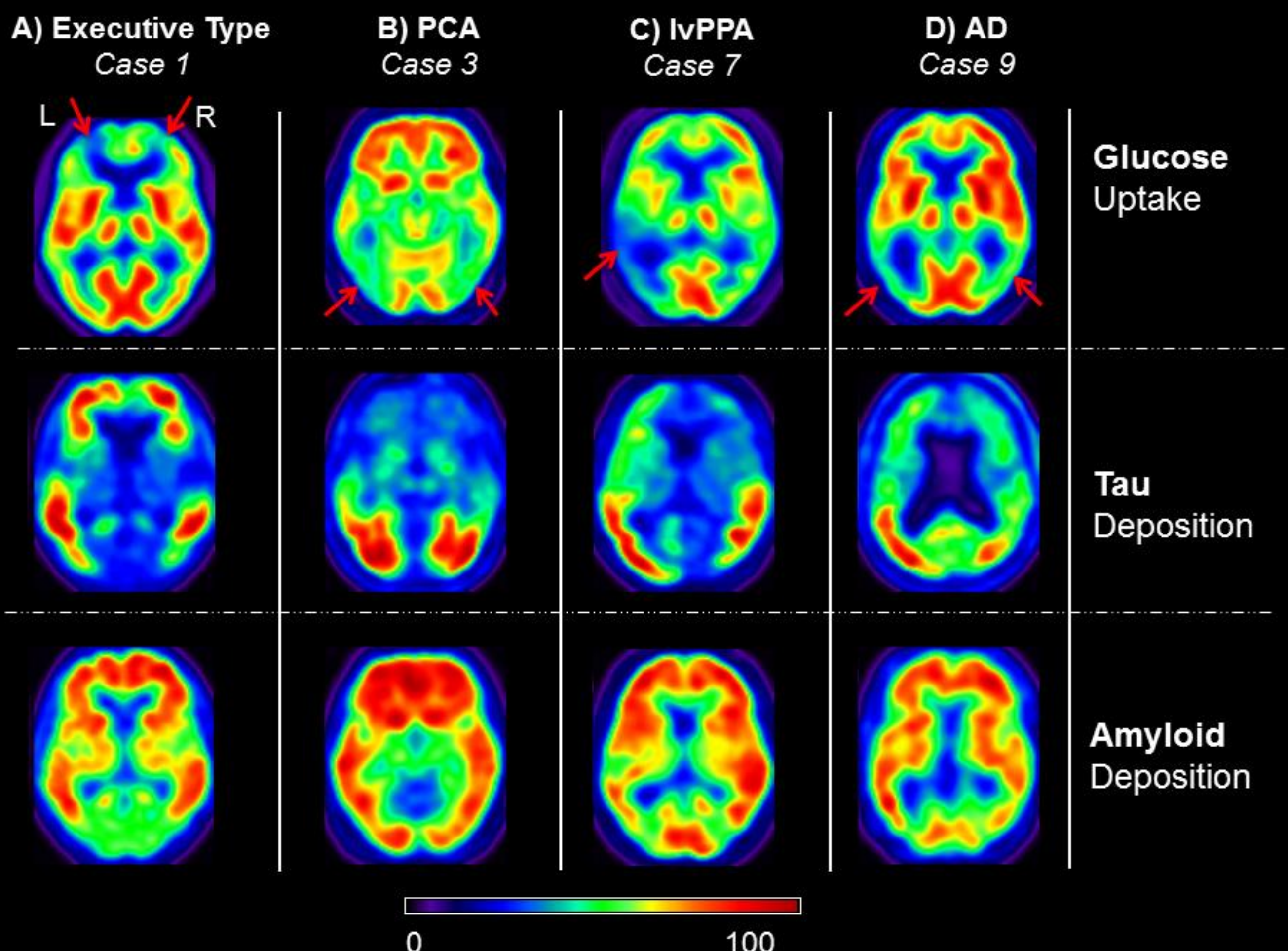
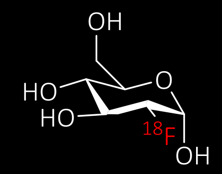
AMYLOID PLAQUE AND TAU IMAGING OF NEURODEGENERATIVE DISEASES USING [^{11}C]PIB AND [^{18}F]T807 PET

Posterior cortical atrophy

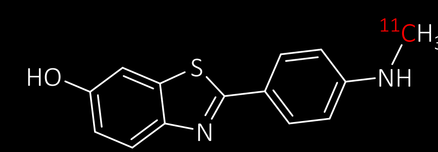
Logopenic variant primary progressive aphasia





[^{18}F]FDG

[^{18}F]T807



[^{11}C]PiB

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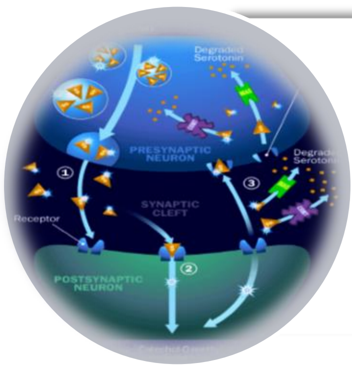
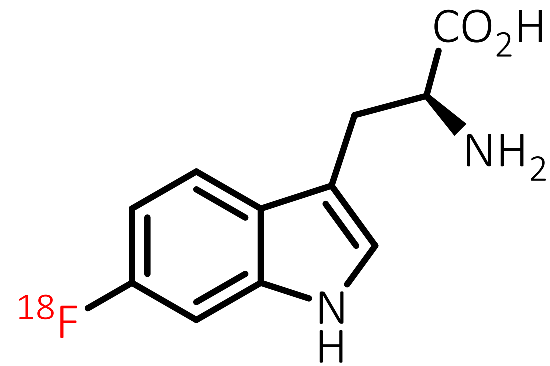
Dronse *et al*. J. Alzheimers Dis. 2017



Tryptophan metabolism

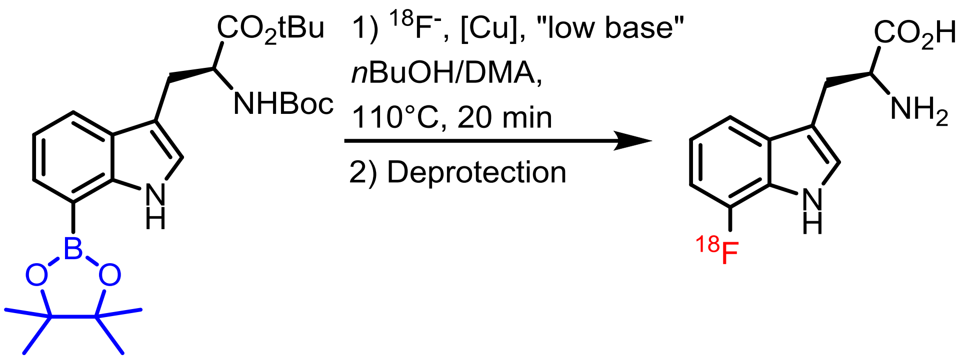
RADIOLABELED TRYPTOPHAN DERIVATIVES FOR IMAGING OF TRYPTOPHAN METABOLISM

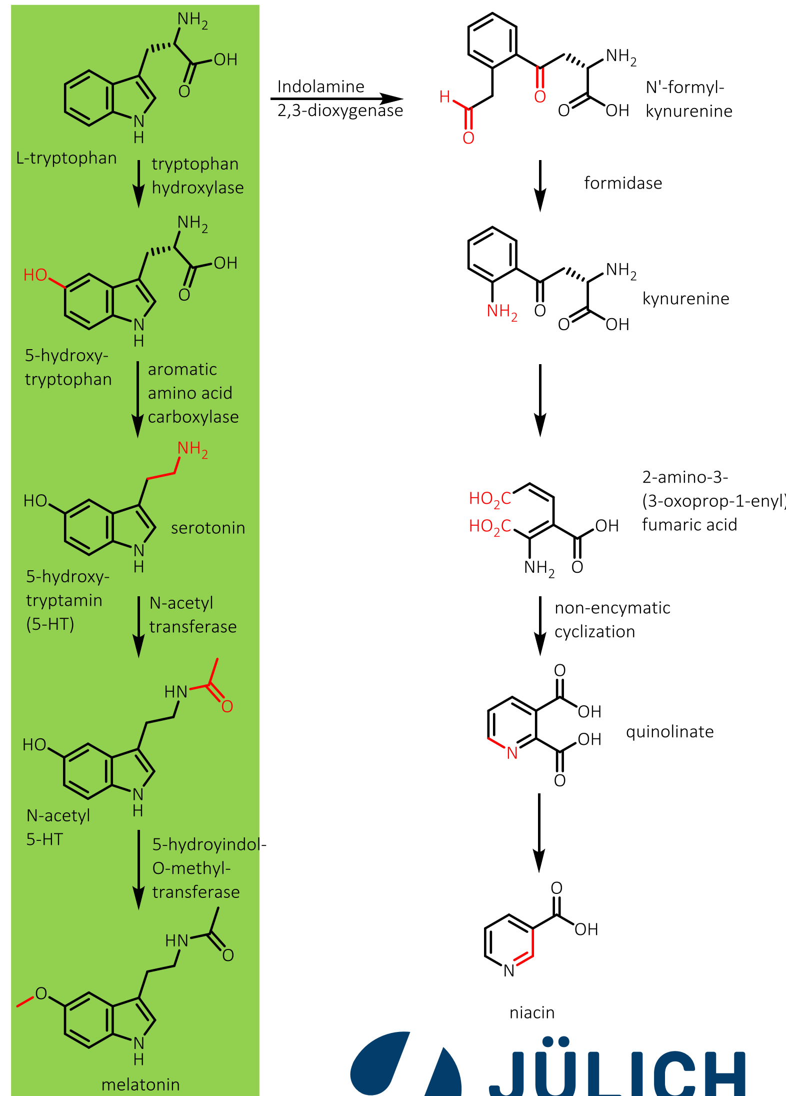


Tryptophan characteristics:

- 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

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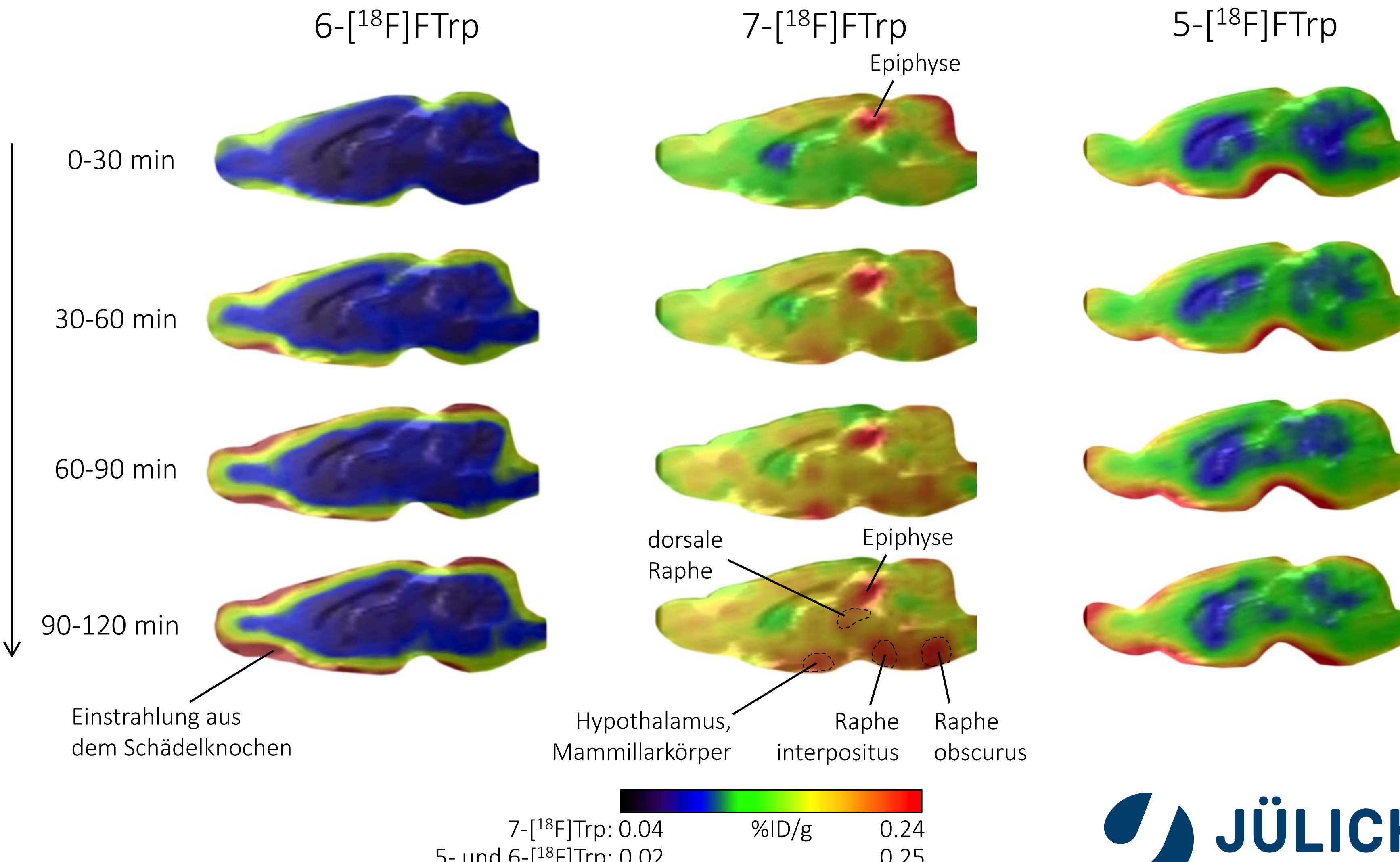
^{18}F-SUBSTITUTION POSITION DETERMINES CEREBRAL UPTAKE OF [^{18}F]TRYPTOPHAN



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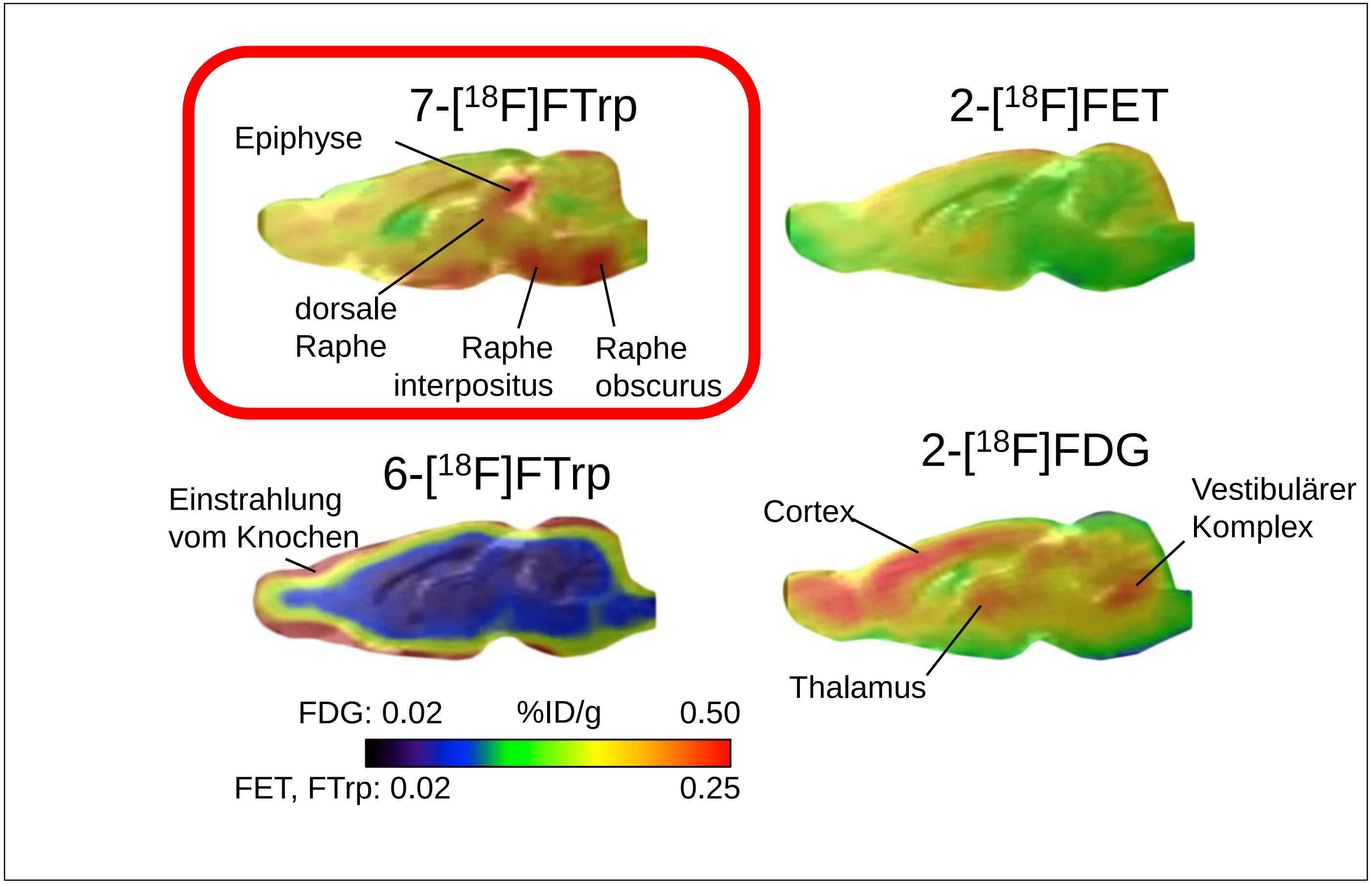
^{18}F-SUBSTITUTION POSITION DETERMINES CEREBRAL UPTAKE OF [^{18}F]TRYPTOPHAN



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

THANK YOU!

JÜLICH Forschungszentrum

Thank You