Van Gen tot Geneesmiddel: Nuclear Imaging techniques

Part 4. PET in the Clinic

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Outline

2 cases:

[^{89}Zr]trastuzumab (herceptin)

[^{11}C]PIB

HER2 and breast cancer

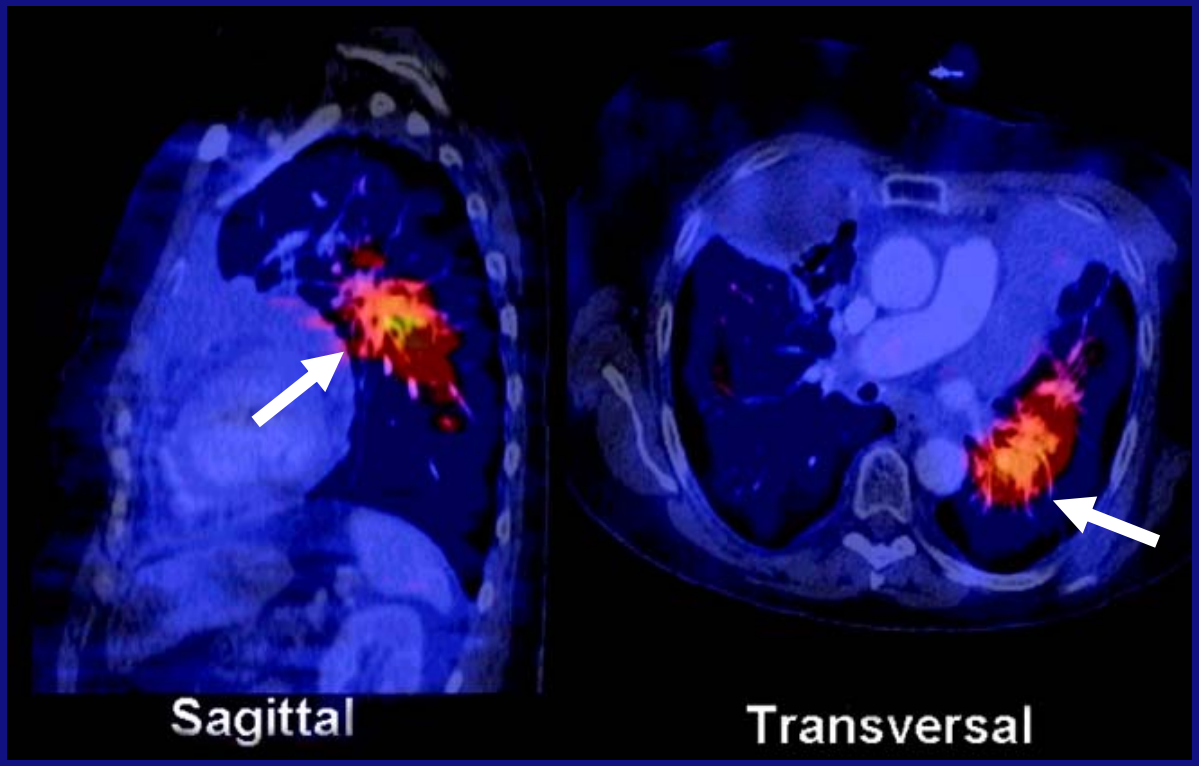
HER2 amplification/overexpression correlates with worse prognosis

Trastuzumab: anti-HER2 monoclonal IgG1 antibody for treatment of HER2 positive breast cancer

Rationale for imaging HER2 in breast cancer

Non-invasive measurement of HER2 receptor status

^{111}In-DTPA-trastuzumab SPECT/CT



Newly discovered tumor lesions in 13/15 patients

Optimization of HER2 imaging

Use PET to:

Improve spatial resolution

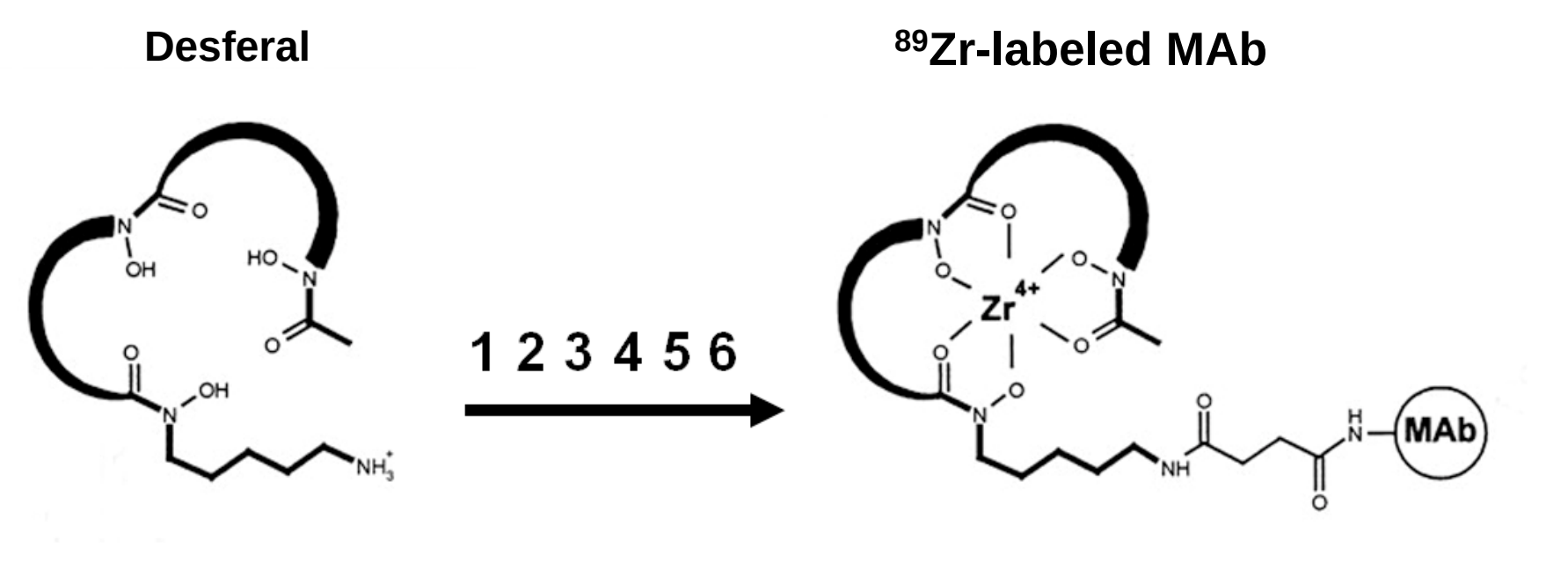
Increase signal-to-noise ratio

Development of PET tracer:

Zirconium-89 (^{89}Zr)

- Long-living isotope ($T_{½}$ = 78 hr)
- Suitable for clinical use

Trastuzumab radiolabeling



^{89}Zr-trastuzumab is obtained in 6 simple steps

Characteristics of ^{89}Zr-trastuzumab

Excellent radiochemical purity (>95%)

High specific activity (>50 MBq/mg)

Maintenance of antigen binding (>80%)

Long-term stability in 37°C human serum

Animal study design

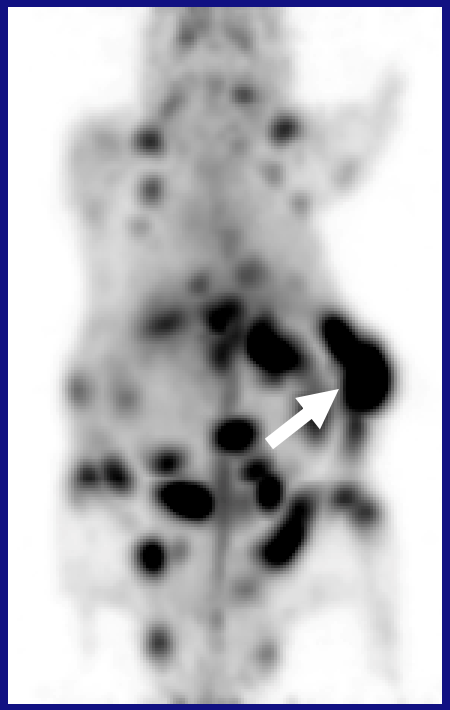
Athymic mice with HER2 positive or negative xenograft

5 MBq ^{89}Zr-trastuzumab iv

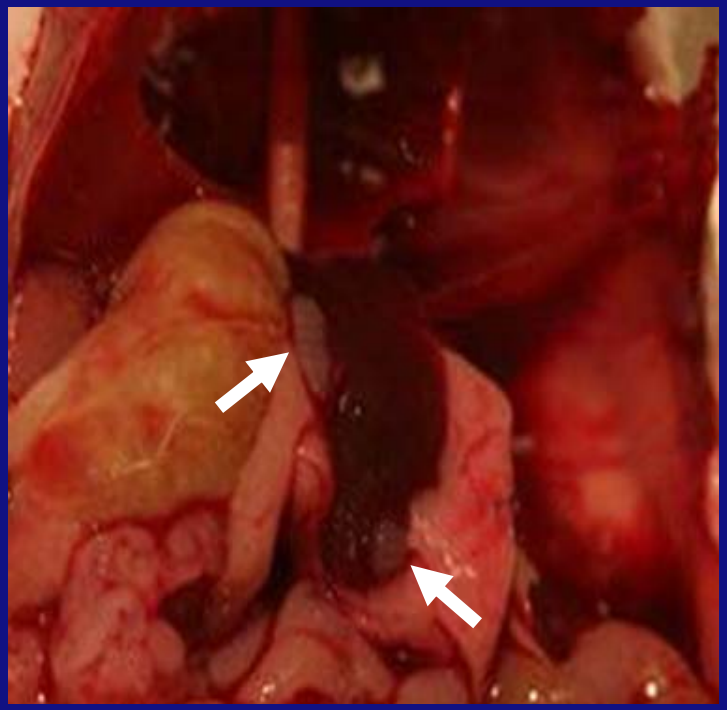
At 1, 3 & 6 days: microPET imaging & biodistribution

^{89}Zr-trastuzumab tumor uptake

Day 1



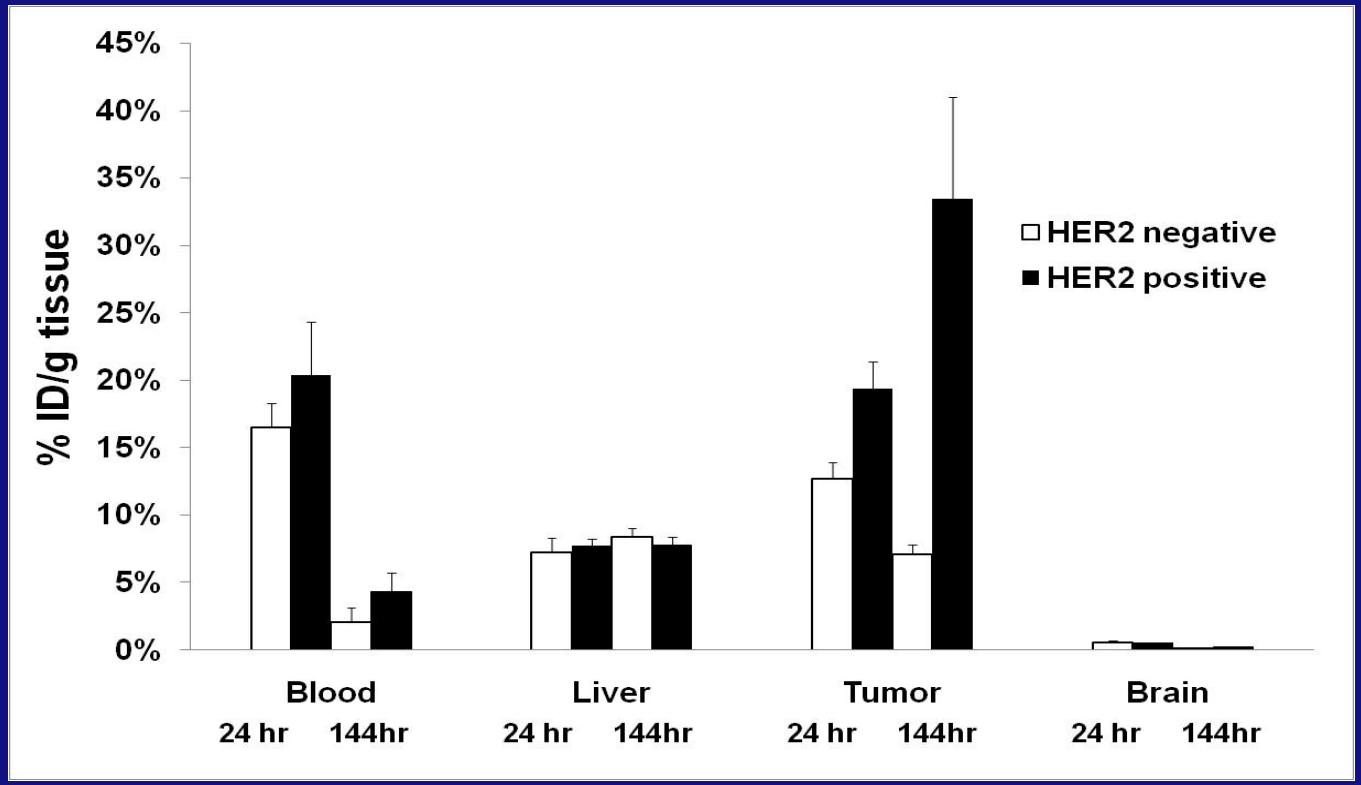
Day 6



Macroscopic metastases

IHC confirmed HER2 expression

^{89}Zr-trastuzumab specific tumor uptake in mice



Design clinical HER2 imaging study

Aim

- Visualize HER2 positive tumors
- Find minimal trastuzumab dose required for optimal imaging

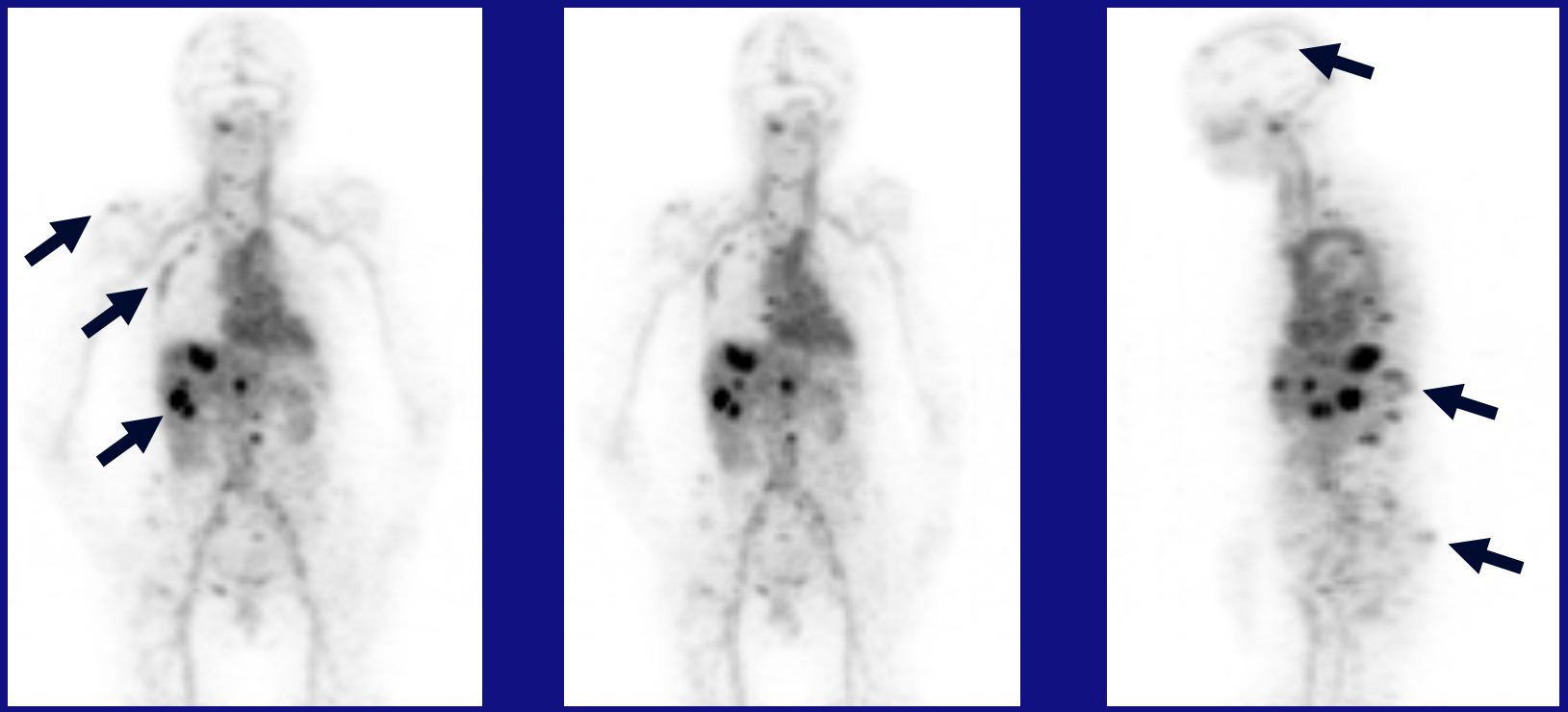
Eligible patients

- Metastatic HER2 positive breast cancer (n=8)

Imaging procedure

- 37 MBq ^{89}Zr-trastuzumab (≈ 20 mSv) and PET scans days 1-5
- Compare to available CT, MRI and bone scans

Tumor visualization



Day 4

Metastasis in the brain

Conclusion

[^{89}Zr]trastuzumab imaging is developed as a non invasive imaging technique to determine HER2 receptors in vivo

Next: larger trial in patients to validate diagnostic value

^{89}Zr labelling applicable to any MAb.

Further reading

Immuno-PET: A Navigator in Monoclonal Antibody Development and Applications

By Guus van Dongen *et al*
(Blackboard)

Alzheimer's disease

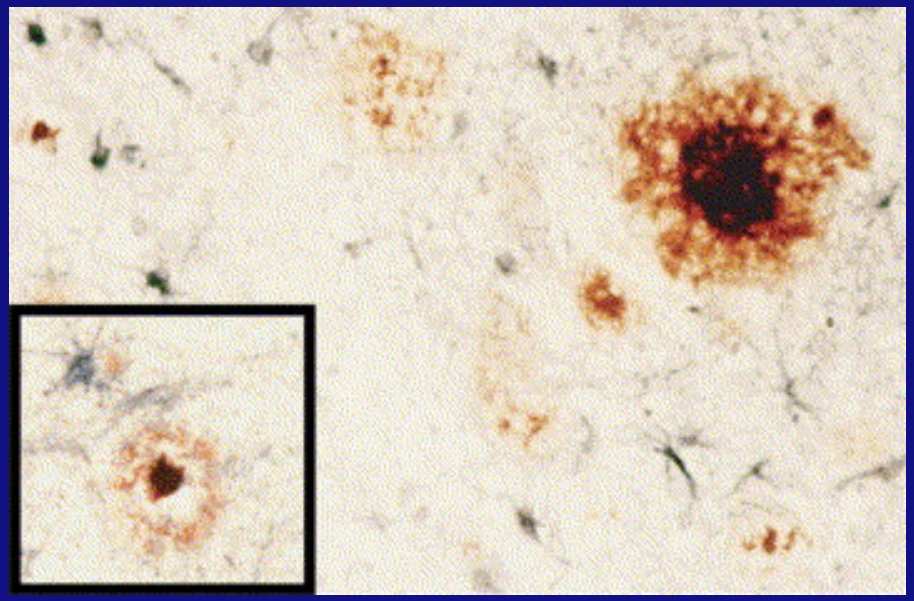
[^{11}C]PIB imaging,
from research tool to clinical practice

AD at the cellular level

Senile plaques

Cause of degeneration

Post-mortem



Biological targets to image

Amyloid-β (Aβ)

Neurofibrillary tangles (NFTs)

Several leads explored

^{125}I Aβ – peptides

Early 90's,

in vivo: rapid metabolism, low brain uptake

(Maggio et al, PNAS, 1992;89:5462)

^{99m}Tc labelled antibodies (mouse and Fab)

Human trial: no specific signal

Friedland et al, Ann NY Acad Sci, 1997;826:242
Bickel et al, Bioconjug Chem, 1994;5:119

Staining compounds as leads

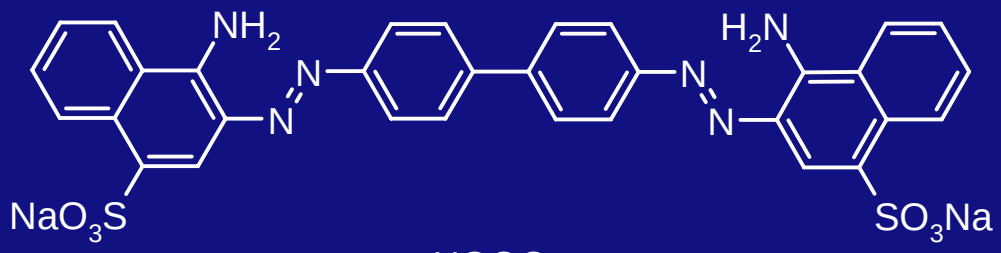
A few of compounds

In vitro assays, hydrophilic compounds

Lead optimization via

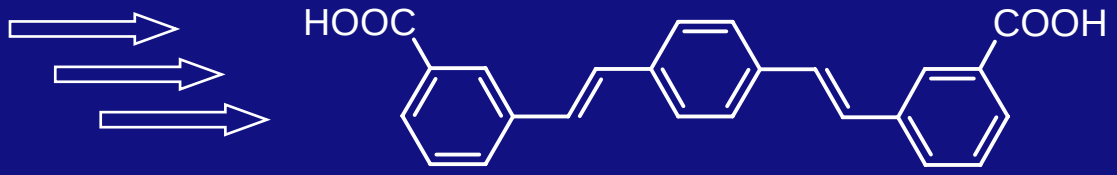
- Affinity
- Lipophilicity

First lead: Congo Red



congo red
Kd 1100 nM
$LogD_{7.4}$ -0.18

chrysamine-G
Kd 350 nM
$LogD_{7.4}$ 0.57

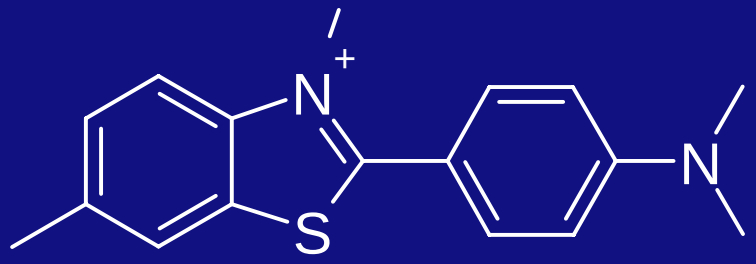


X-34
Ki 452 nM
$LogD_{7.4}$ 0.48

MeO-X-04
Ki : 27 nM
$LogD_{7.4}$: 2.6

Second lead: Thioflavin-S

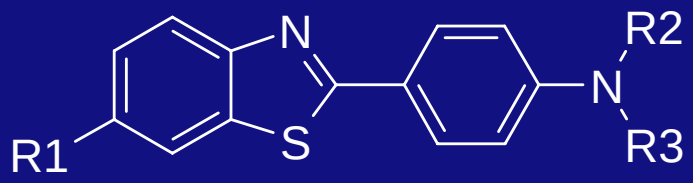
Major compound: Thioflavin-T



Ki : 890 nM

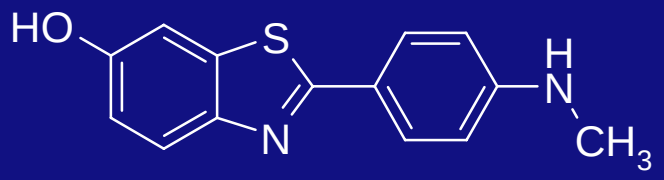
$LogD_{7.4}$: 0.57

Development of [^{11}C]PIB



R1: OH, MeO, fluoroalkyl ether
R2/R3: Me, fluoroalkyl

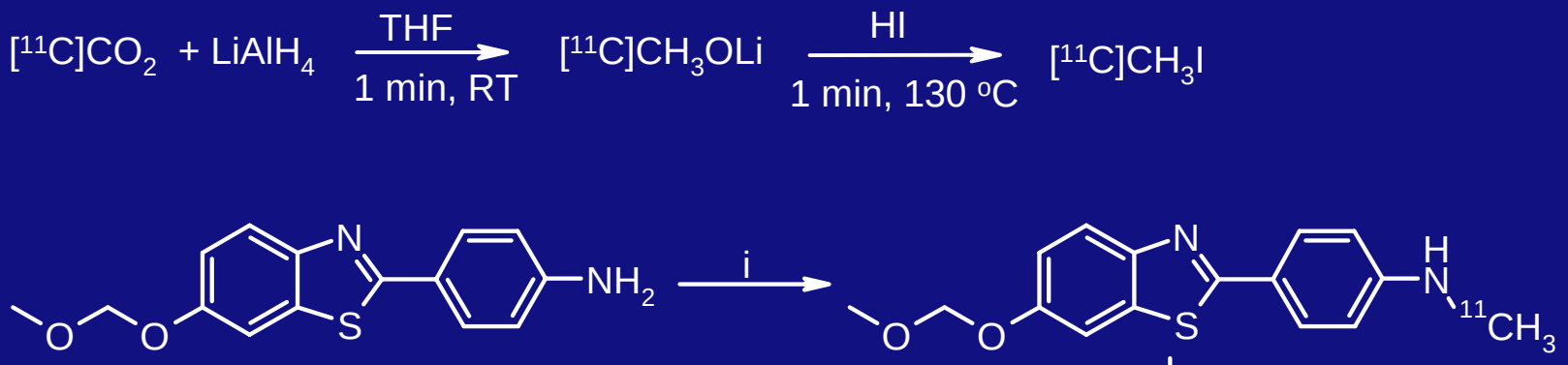
Development of [^{11}C]PIB



N-methyl-2-(4'methylaminophenyl)-6-hydroxybenzothiazole
6-OH-BTA-1, PIB

Ki 4 nM
$LogD_{7.4}$ 1.2

[^{11}C]PIB labeling

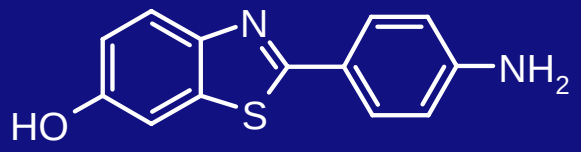


i) [^{11}C]CH_3I, 130 ºC, 5 min
ii) MeOH/HCl, 80ºC, 3min ; 60%

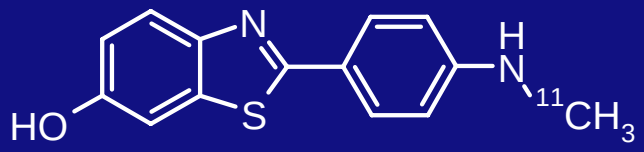
Yield: 400-1600 MBq EOS (10% cfd)
SA: 20-50 GBq/µmol
N > 40, fail rate>15%

[^{11}C]PIB labeling

$[^{11}C]CH_3I + CF_3OSO_2Ag \xrightarrow[200\ ^oC,\ on\text{-}line]{GraphPac} CF_3OSO_2[^{11}C]CH_3$



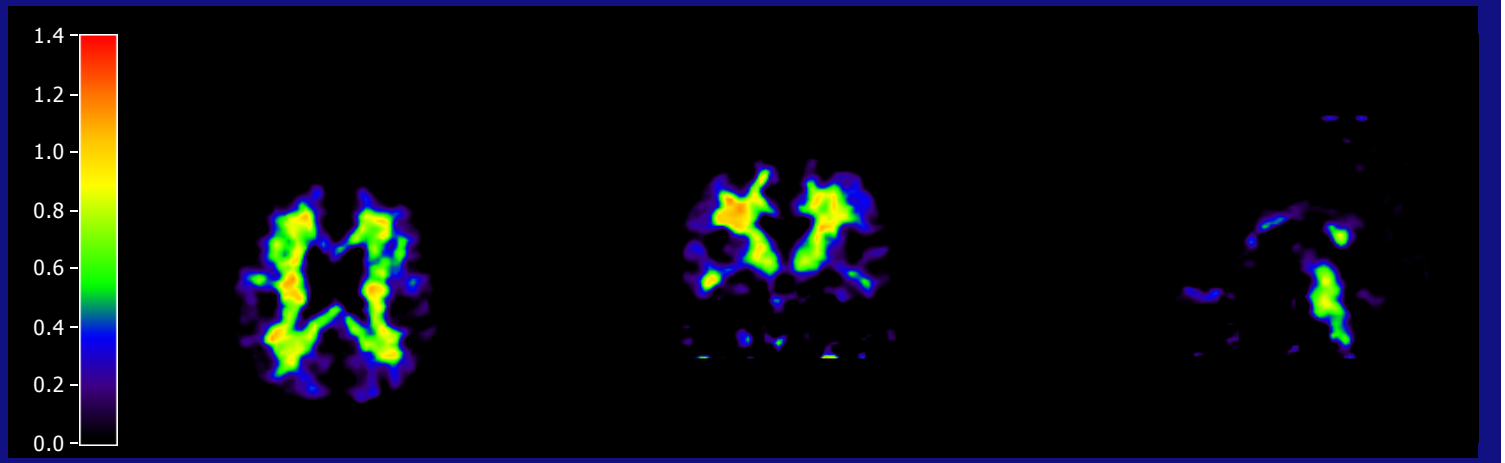
MEK, 80 °C, 1 min



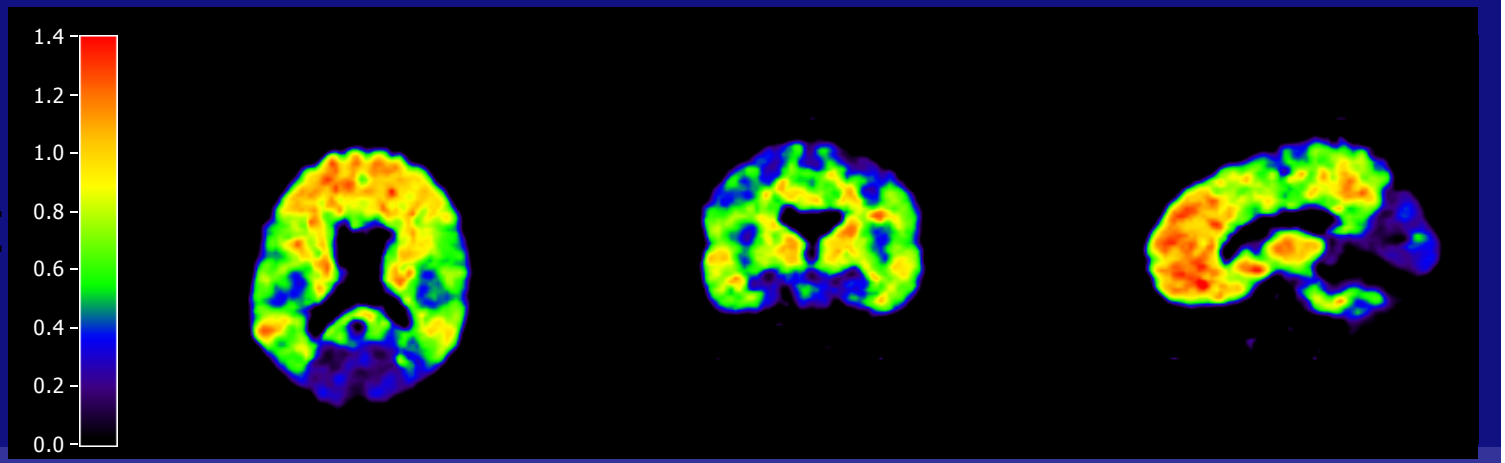
[^{11}C]PIB

Control vs AD patient

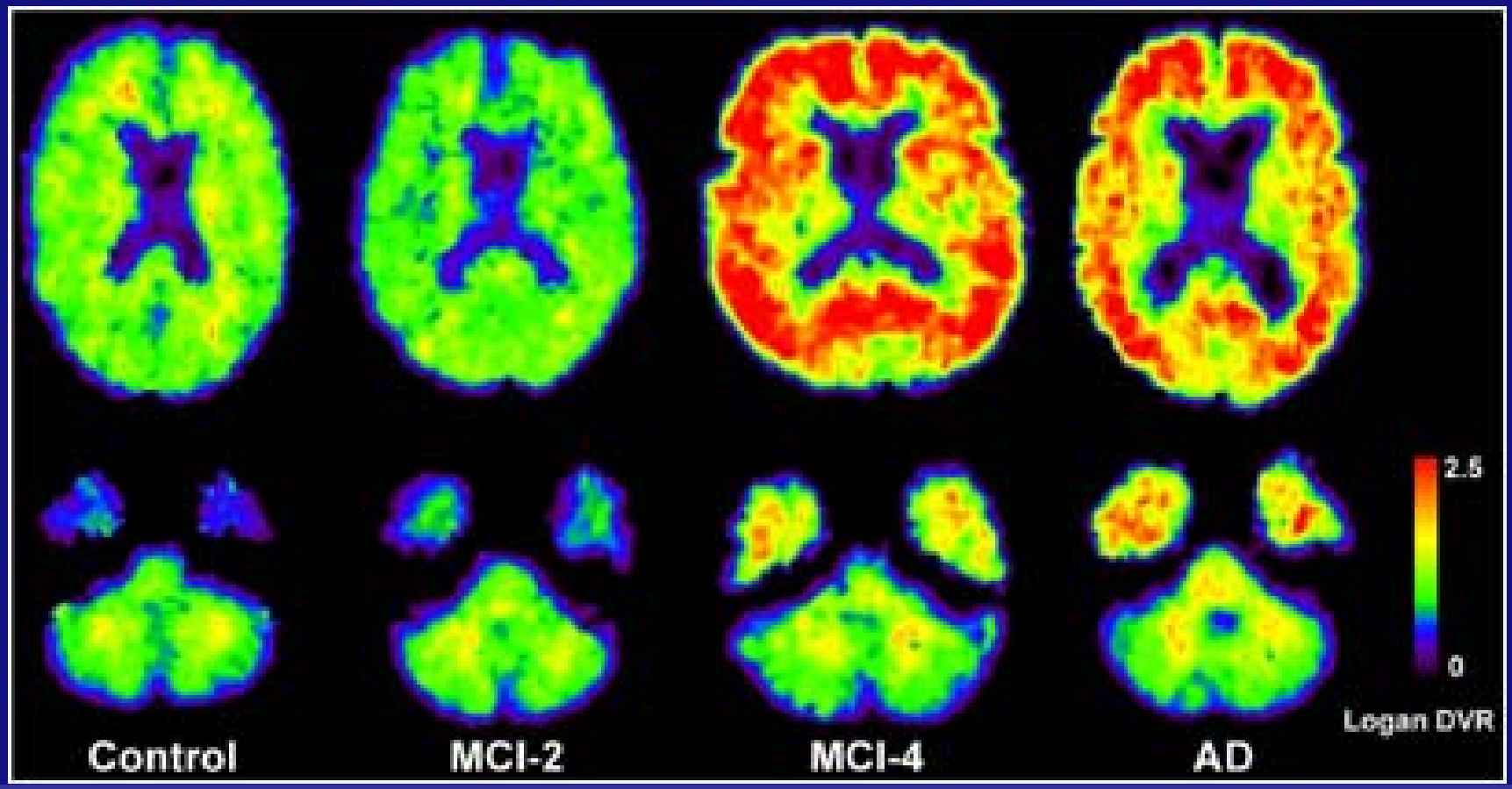
control



patient



Disease progress



Conclusion

Amyloid plaques imaging with [^{11}C]PIB works good

New tool in standard diagnosis

Used in clinical research as well

Further reading

Amyloid imaging in Alzheimer's disease:
a promising new direction in Nuclear Medicine

By Bart van Berckel
(on blackboard)

The Gene-to-Medicine paradigm

Target discovery

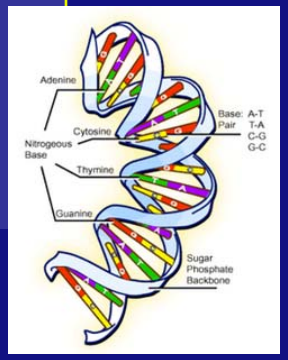
Chem diversity

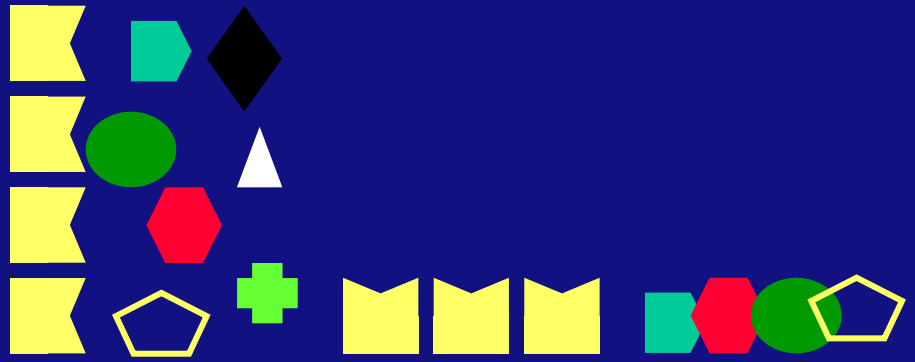
Hit

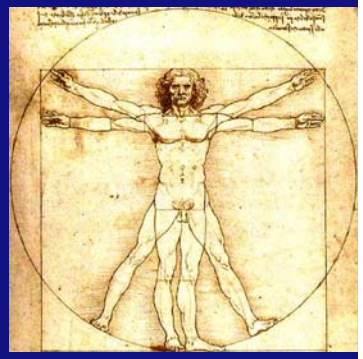
optimise

safety

efficacy







genomics

Lead chem

HTS

SAR

Pre clinical

human

bio informatics

chemo informatics

imaging

Final remarks

Imaging of biological targets is feasible

Molecular Imaging is a valueble tool

Especially in translational research. It is the bridge between bench and bedsie, between lab and clinic

Next years more indepth classes.