Center for Radiopharmaceutical Sciences

Yale University PET Center

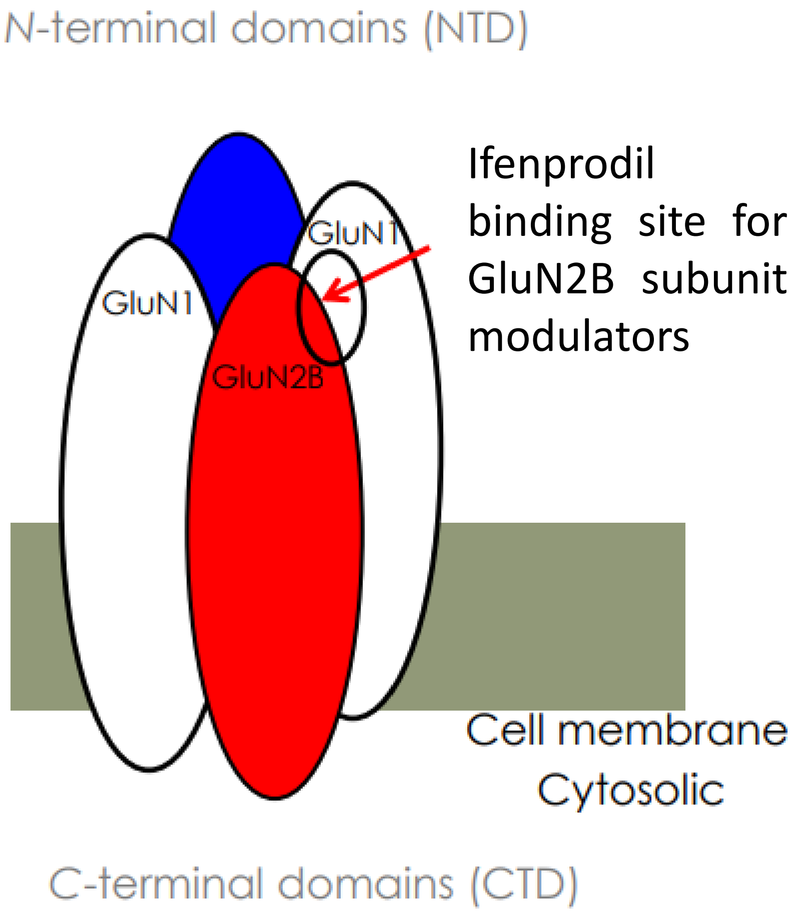
Radiosynthesis and evaluation in non-human primates of novel ^{18}F-labeled radioligands for imaging the GluN2B subunit of the NMDA receptor

Hazem Ahmed[1], Ming-Qiang Zheng[2], Kelly Smart[2], Daniel Holden[2], Yuping Xu[2,3], Li Zhang[2], Paul R. Emery[2], Jim R. Ropchan[2], Gilles D. Tamagnan[2], Richard E. Carson[2], Simon M. Ametamey[1], Yiyun Huang[2]

[1]Institute of Pharmaceutical Sciences, ETH Zurich, Zurich, Switzerlan
[2]PET Center, Yale University, New Haven, CT, USA
[3]Jiangsu Atomic Institute, Jiangsu, China.

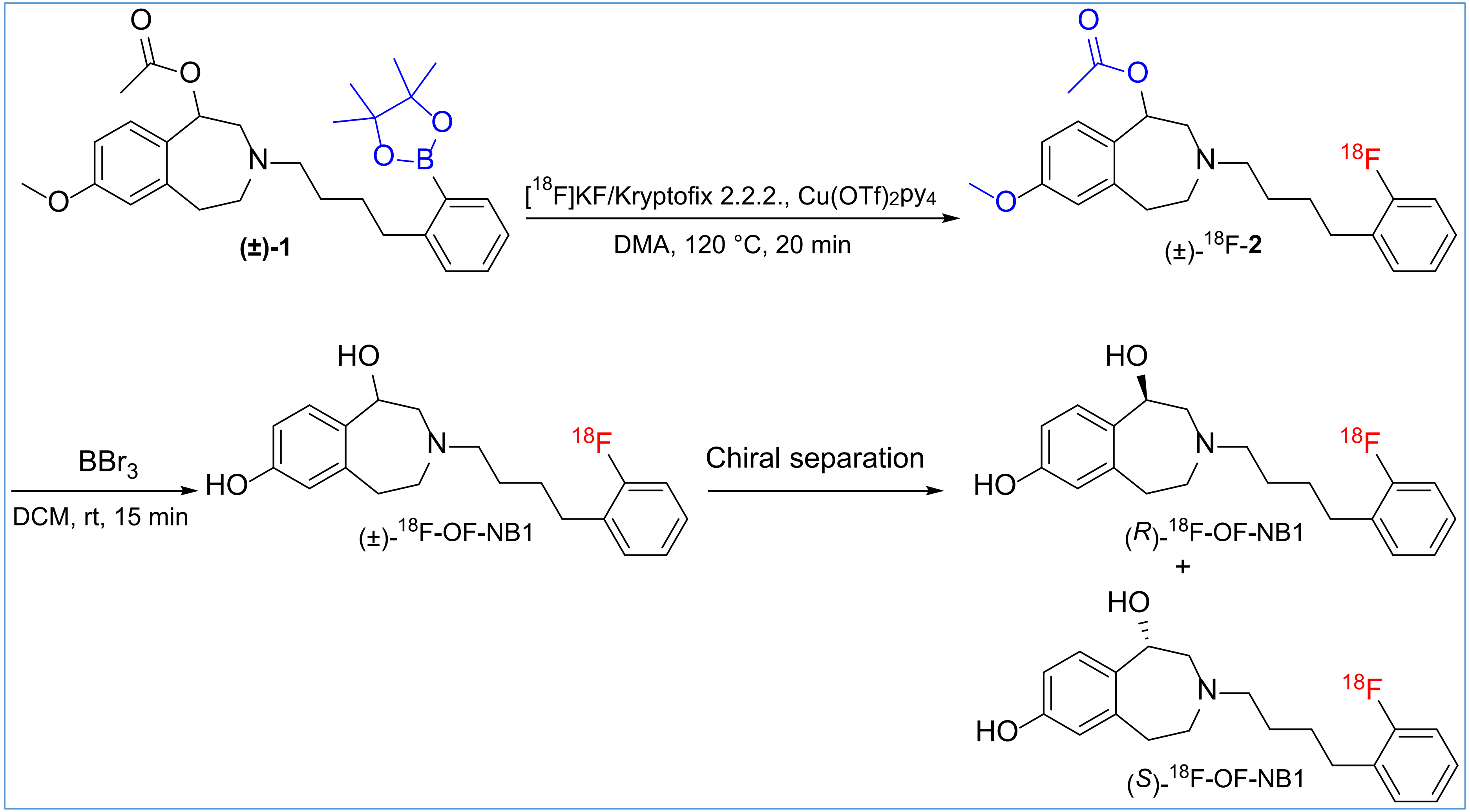
The NMDA Receptor

- ✓ Ionotropic glutamate receptor
- ✓ Heterotetramer, consisting of three different subfamilies (GluN1a-h, GluN2A-D, GluN3A/B).
- ✓ GluN2 subunits exhibit heterogeneous expression and dictates the receptor function.
- ✓ Physiological: involved in learning processes, memory function and synaptic plasticity.
- ✓ Pathological: neurological diseases comprising Alzheimer's disease, Parkinson’s disease, amyotrophic lateral sclerosis, schizophrenia and depression amongst others.

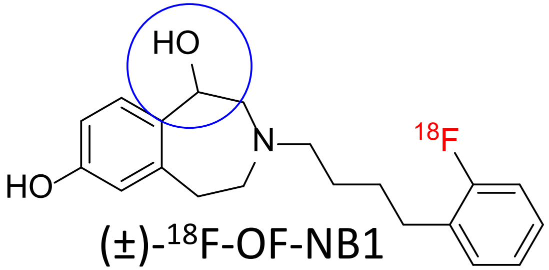


ETH zürich

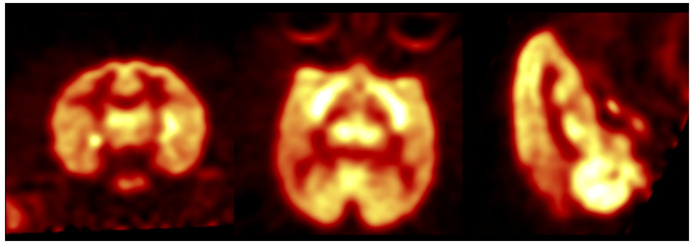
Radiosynthesis



PET Imaging in Rhesus Monkeys

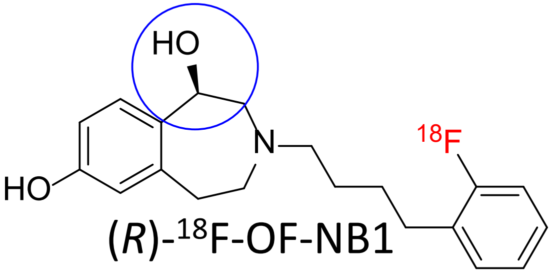


(±)-^{18}F-OF-NB1

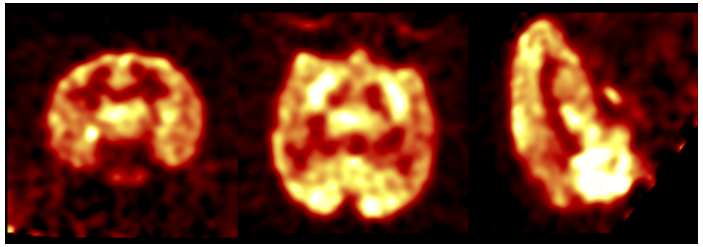


Baseline

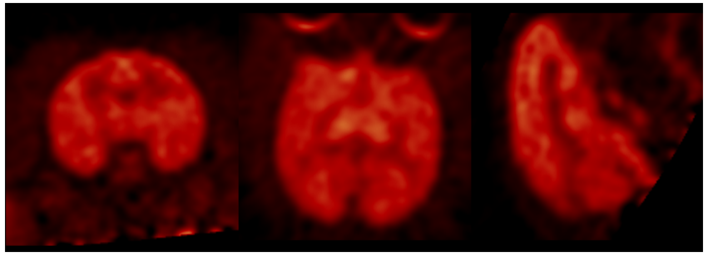
0 6



(*R*)-^{18}F-OF-NB1

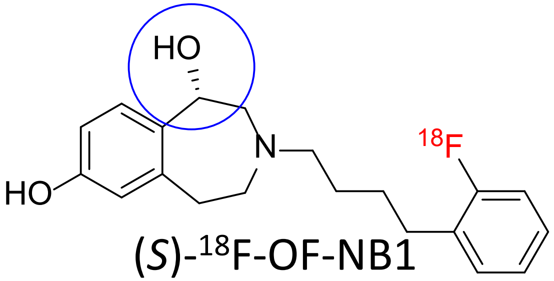


Baseline

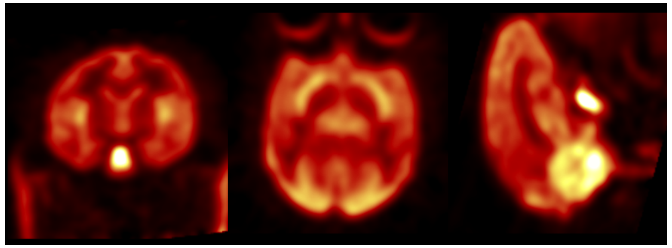


Blockade (CO-101244, 0.25 mg/kg)

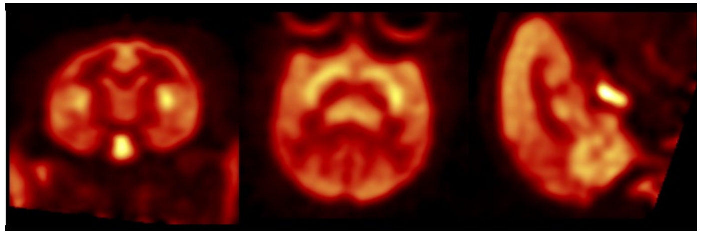
0 7



(*S*)-^{18}F-OF-NB1



Baseline



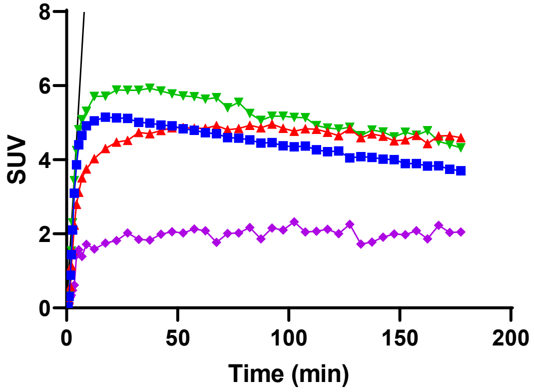
Blockade (CO-101244, 0.25 mg/kg)

0 6

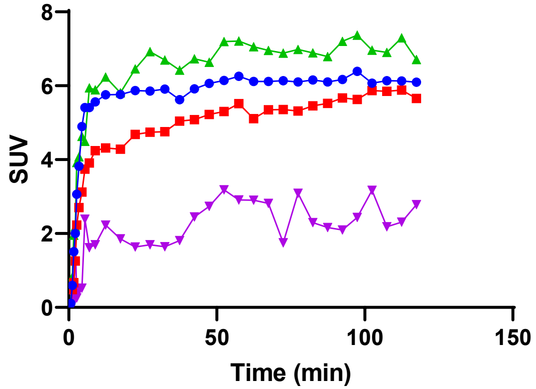
ETH zürich

Time Activity Curves: Baseline vs Blockade with Co-101244

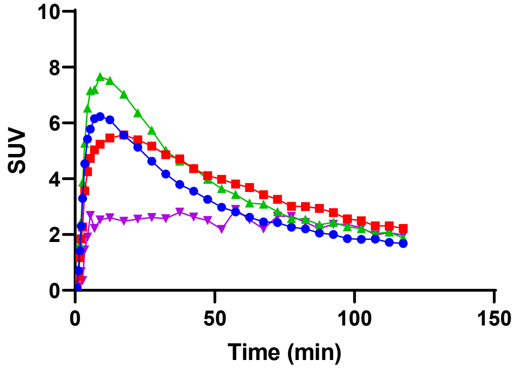
Baseline_(±)-^{18}F-OF-NB1



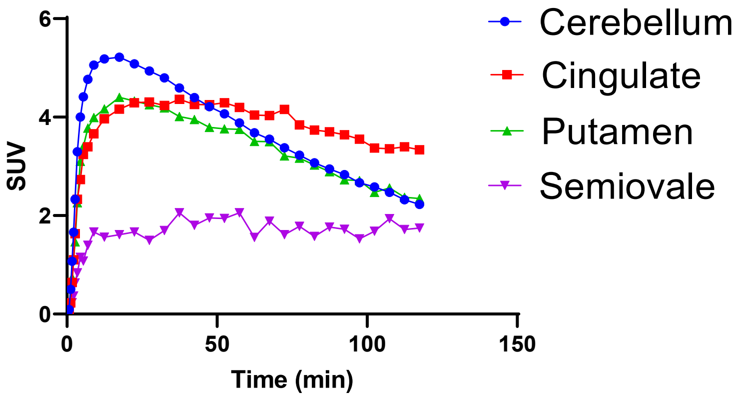
Baseline_(*R*)-^{18}F-OF-NB1



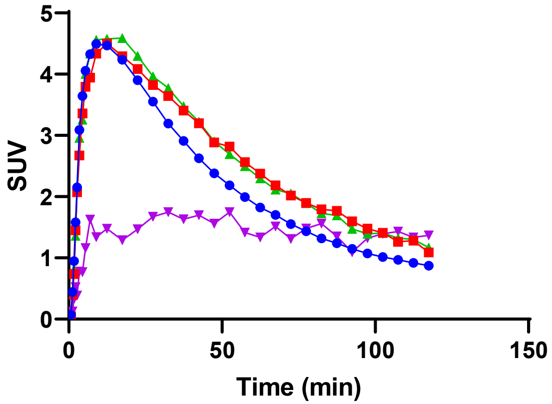
Blockade_(*R*)-^{18}F-OF-NB1



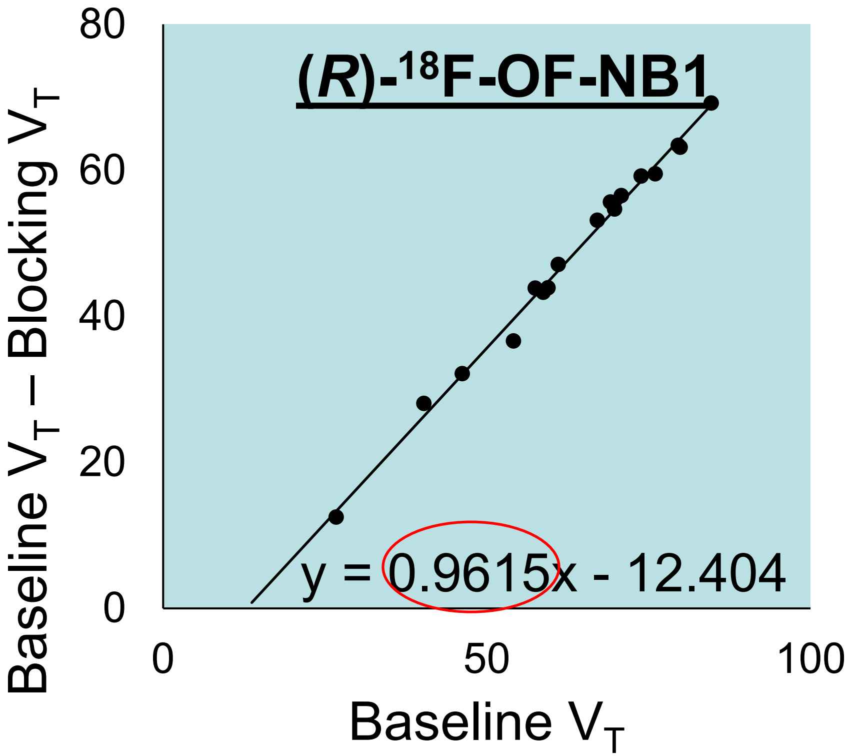
Baseline_(*S*)-^{18}F-OF-NB1

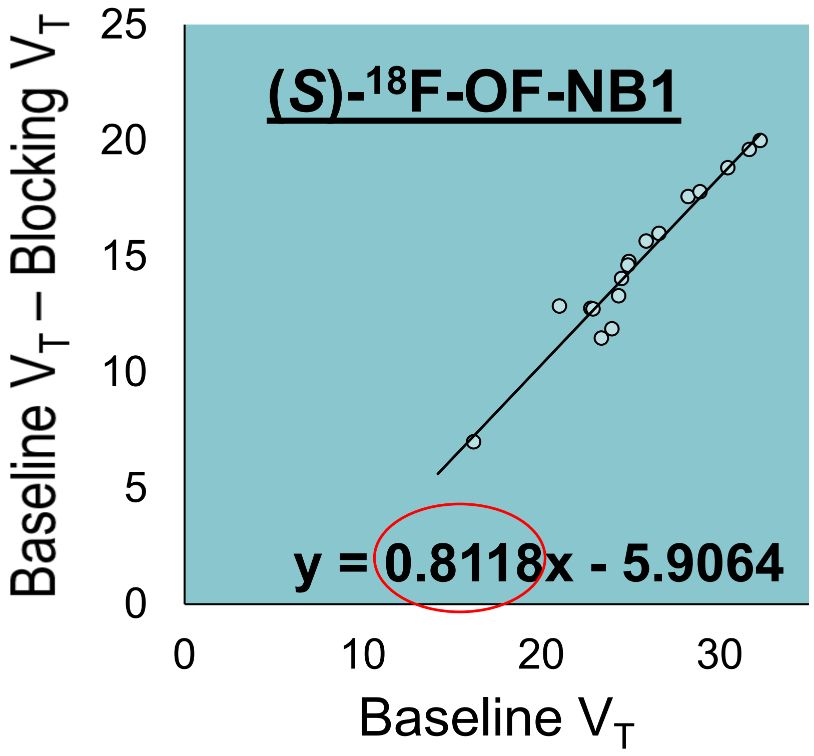


Blockade_(*S*)-^{18}F-OF-NB1



Baseline vs Blockade with Co-101244: Receptor Occupancy





(R)-^{18}F-OF-NB1 vs (S)-^{18}F-OF-NB1: V_T and BP_{ND}

Region	V_T (±)-^{18}F-OF-NB1	V_T (R)-^{18}F-OF-NB1	V_T (S)-^{18}F-OF-NB1
Cerebellum	54.9	69.1 (4.35)	24.9 (2.42)
Cingulate	74.8	79.9 (5.19)	31.7 (3.35)
Frontal cortex	60.1	67.1 (4.20)	28.2 (2.88)
Hippocampus	64.5	69.7 (4.40)	26.6 (2.65)
Semiovale	35.7	26.7 (1.07)	16.2 (1.22)
Thalamus	44.7	46.2 (2.58)	22.9 (2.14)

ETH zürich

Conclusion and Future Perspectives

- ✓ Tissue kinetics is slow for (*R*)-^{18}F-OF-NB1 and fast for (*S*)-^{18}F-OF-NB1, with (±)-^{18}F-OF-NB1 in between.

- ✓ Blocking with the GluN2B subunit ligand Co-101244 induced high receptor occupancy, indicating binding specificity of (*R*)-^{18}F-OF-NB1 and (*S*)-^{18}F-OF-NB1.

- ✓ (*S*)-^{18}F-OF-NB1 appears to be a specific PET radioligand for the GluN2B subunit of NMDA receptor with appropriate tissue kinetics in rhesus monkey and warrants further investigation.

- ✓ Further experiments including blocking studies are currently ongoing to assess the binding specificity and selectivity of (±)-18F-OF-NB1.

ETH zürich

Acknowledgment

FNSNF
FONDS NATIONAL SUISSE
SCHWEIZERISCHER NATIONALFONDS
FONDO NAZIONALE SVIZZERO
SWISS NATIONAL SCIENCE FOUNDATION

ETH zürich

CRS