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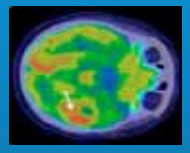
Imaging Transporters

Jan Passchier, COO Imanova Ltd

Imanova - A Unique Partnership

- Operational October 1st, 2011
- Independent business
- Special status to receive direct grant funding from RCUK

Vision



- To become the leading Centre for methodology development and translational applications of molecular imaging

- To be the international ‘partner of choice’ for Pharma and Biotech companies

- To provide world class training in imaging methodology and clinical applications

A Pharma Company Pedigree

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Positron Emission Tomography - PET

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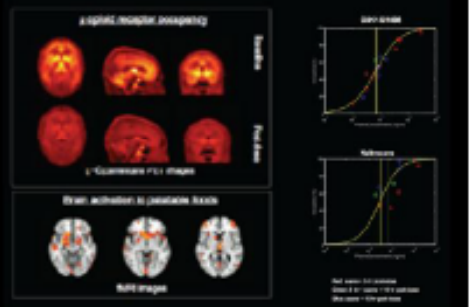
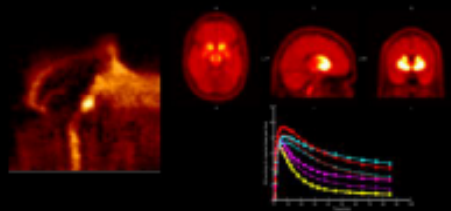
- True molecular imaging
  - Exquisite sensitivity – sub-fmol concentrations
  - Molecular specificity
  - Absolute quantification feasible

- Limited spatial (mm^3) and temporal (10's of minutes) resolution
- Complex technology – limited availability
  - High cost
  - Requires sophisticated research team

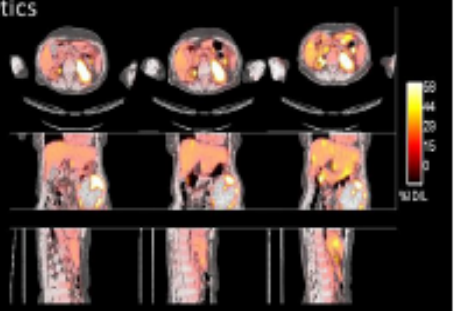
- Quantification of Target Density
  - Physiological distribution of target
  - Dynamic changes in target density
    - Effects of Disease
    - Effects of Treatment



PK/PD for Dose Selection & Product Differentiation



Biodistribution and Kinetics



Quantitative Metabolic Imaging

A PET Scan Overview

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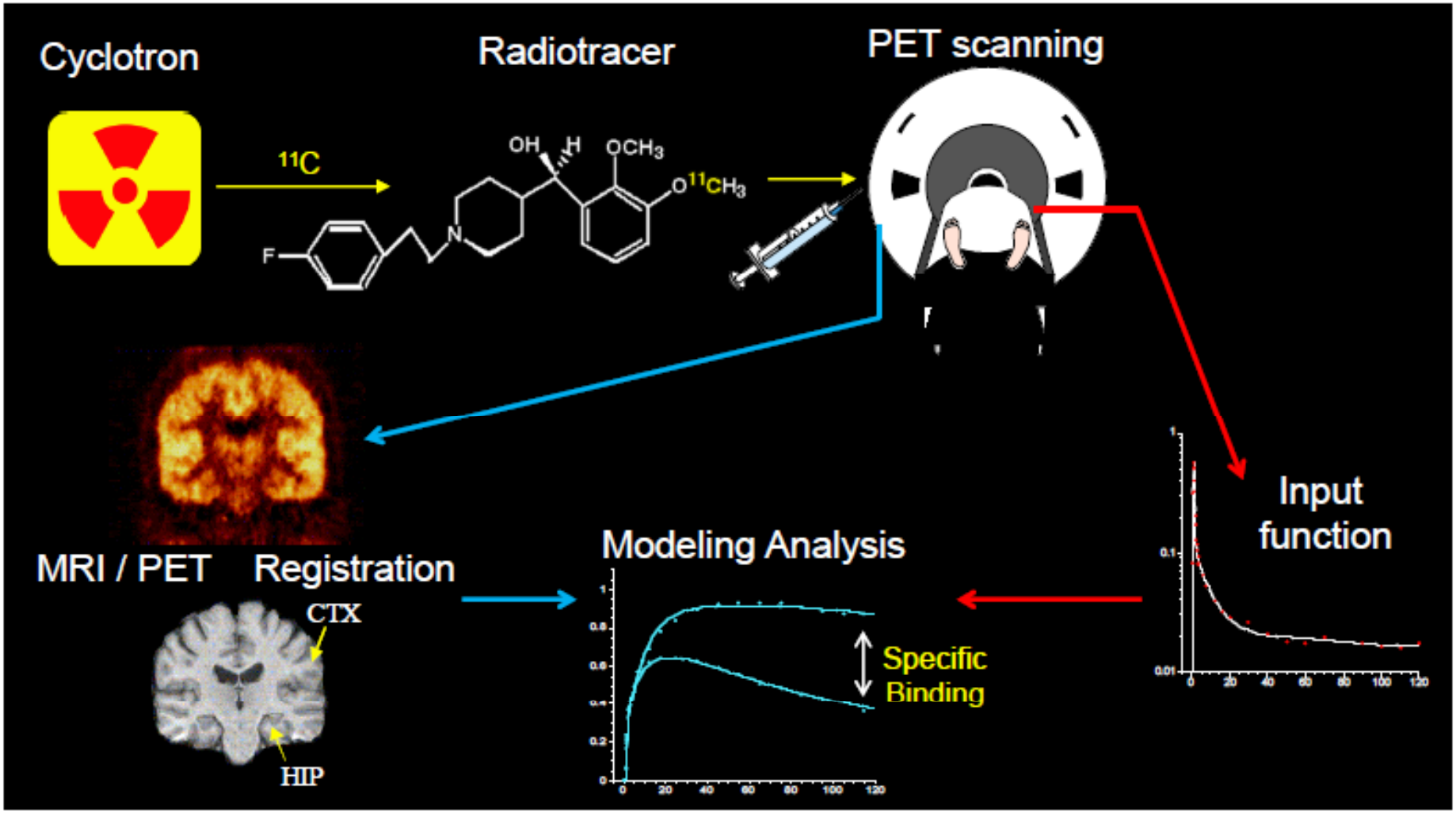
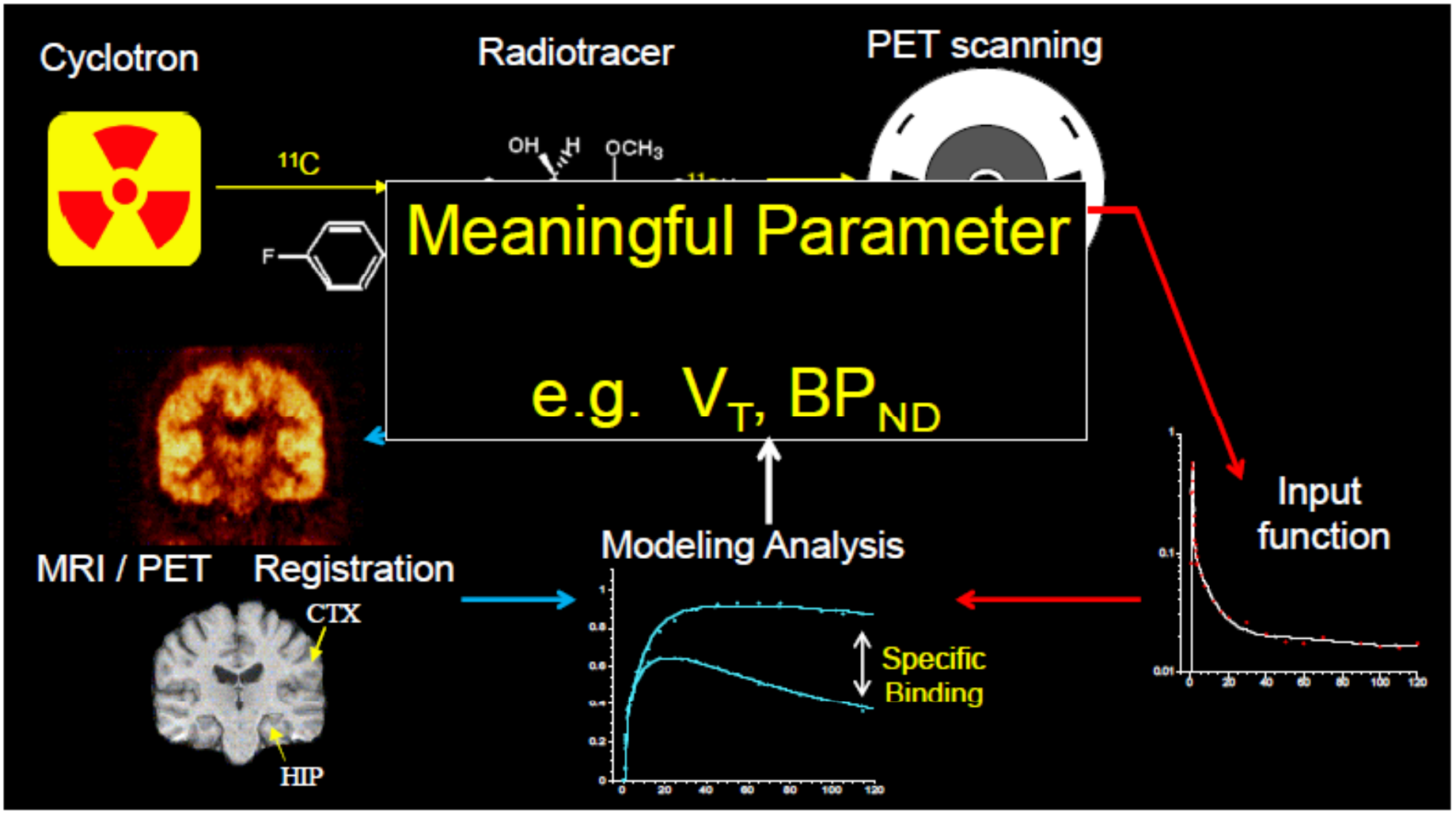
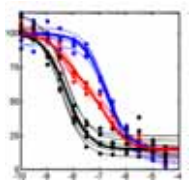
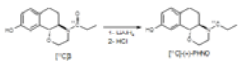


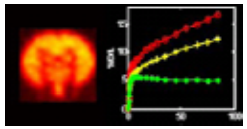
A PET Scan Overview

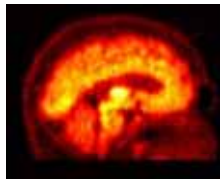


Tool compound development









Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7
Acquire in-silico / in-vitro Data	In-silico bio-mathematical Modelling	Labelling Feasibility	Radio-labelling proof of principle	Preclinical Evaluation	Translation	Clinical Evaluation
Extract existing data from databases	Perform Biomathematical Analysis to rank candidates	Structural analysis to determine radiolabelling routes	Laboratory radiolabelling of compound	Evaluation of Tissue penetration and Target Signal	GMP, dosimetry	Evaluation of Tissue penetration and Target Signal

Capabilities

Relationships with Pharma Access to compound libraries Quantitative determinations of specific binding and affinity	Unique in-silico prediction model to select candidate leads	Pioneering radio-chemistry: CF3 Enzymatic CO complexation Negishi	Versatile/custom radiosynthesis small/medium/large size molecules complex, multi-step synthesis Carbon-11 Fluorine-18	Quantitative dynamic microPET:CT imaging Generation of serial plasma input and metabolite curves from blood samples Respiratory-gated microCT imaging	Fast translation to GMP settings (R&D labs mirroring production labs) Pharma standard GMP & GCP	Advanced quantitative molecular imaging analysis pipeline incorporating motion correction, multi-modal registration, image segmentation and tracer kinetic modeling MIAKAT®

Pharma Pedigree | **Customer Focus** | **Quality and Delivery** | **Sensible IP and Contracting**

Transporters

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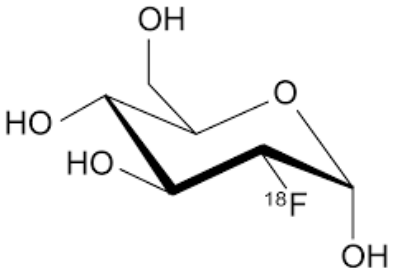
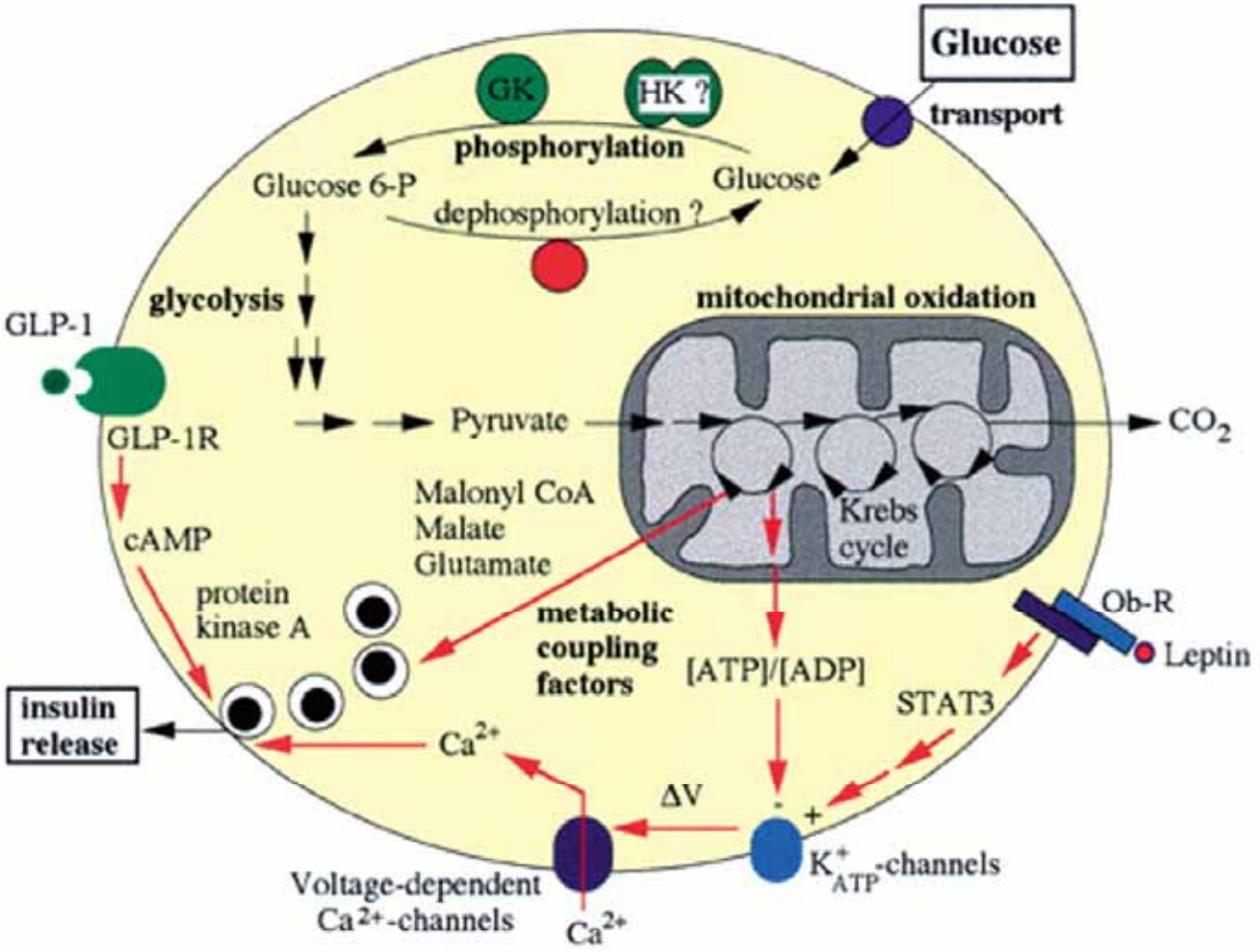
3 categories:

- Facilitating
  - E.g. [^{18}F]FGD, [^{18}F]FLT, [^{11}C]methionine, [^{18}F]BF_4
- Target
  - E.g. SERT, DAT, 18kDa TSPO
- Prohibiting
  - Efflux, e.g. P-glycoprotein

[^{18}F]FDG





From: http://diabetes.diabetesjournals.org/content/50/1/1/F1.expansion

“Typical” [^{18}F]FDG study (metastatic breast cancer):

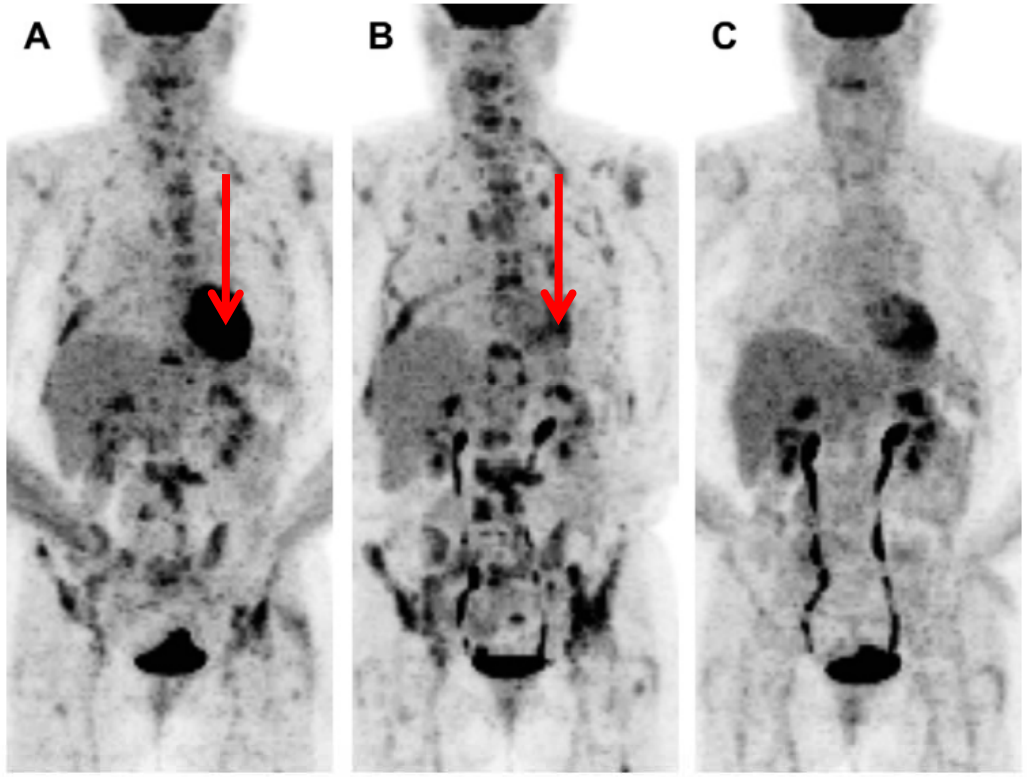


Fig. 1. Coronal maximum intensity projection fluorodeoxyglucose positron emission tomography (FDG-PET) images on the same patient showing different metabolic responses during consecutive treatment phases. (A) FDG-PET baseline shows multiple bone metastases. (B) An FDG-PET follow-up study carried out 3 months later during chemotherapy (mitoxantrone) shows metabolically progressive disease. (C) An FDG-PET follow-up study carried out 7 months later during another chemotherapy (capecitabine) shows a metabolic response.

‘Static’ image, ~60min post [^{18}F]FDG adminstration

[^{11}C]DASB – SERT PET ligand

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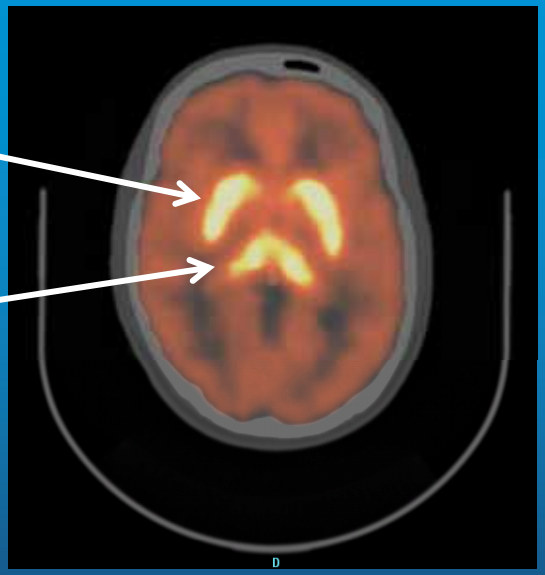
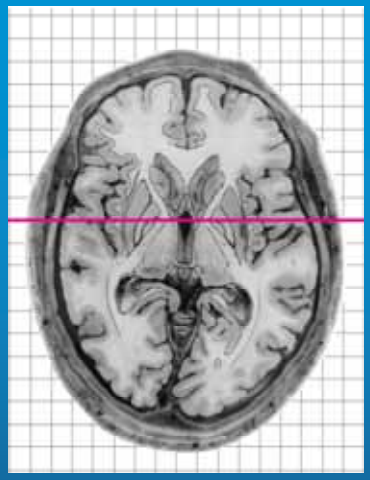
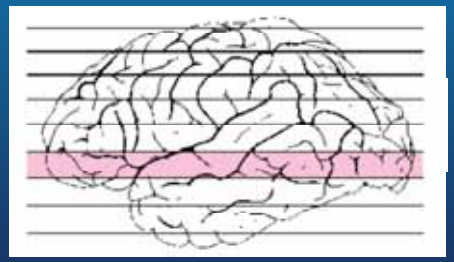
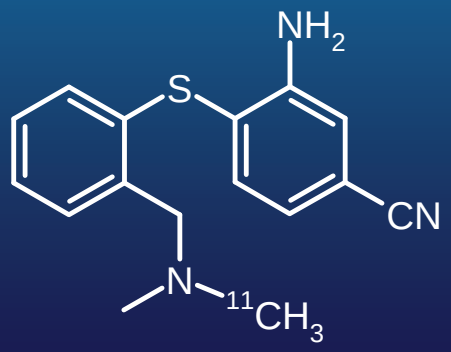
Striatum

Thalamus









Single Dose Study – Repeat Dose Occupancy

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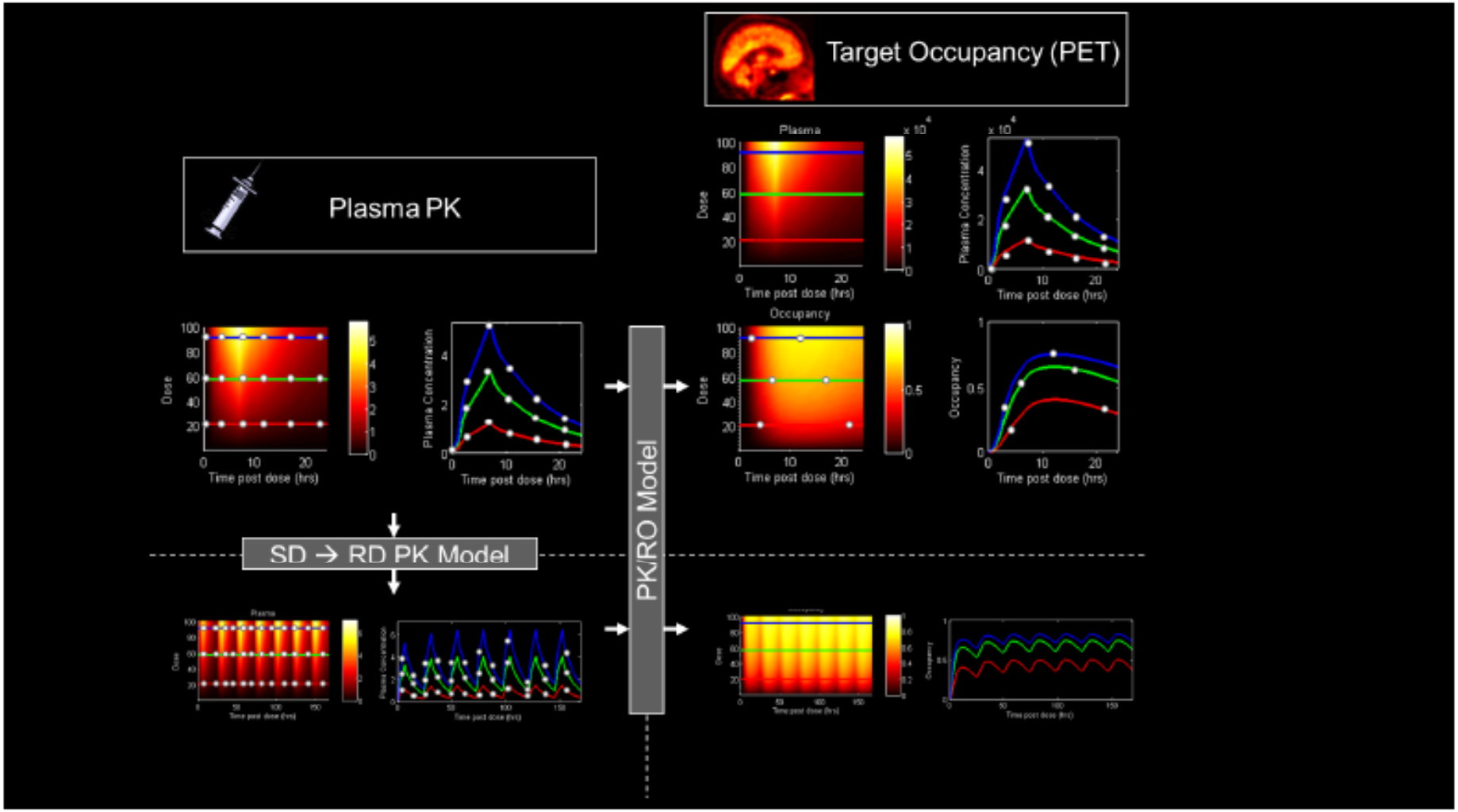
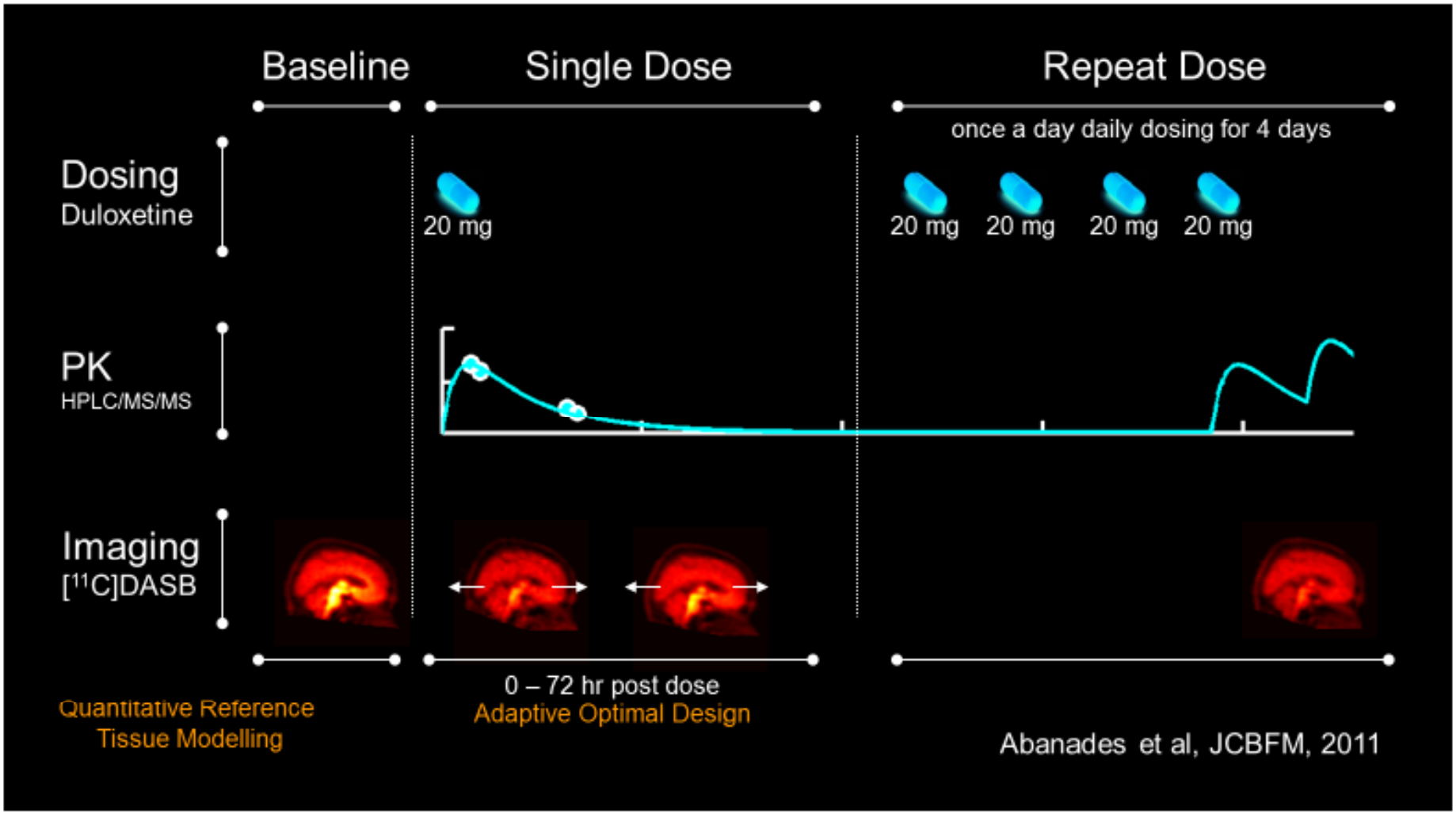


Prediction of RD Occupancy from SD Data



Prediction of RD Occupancy from SD Data

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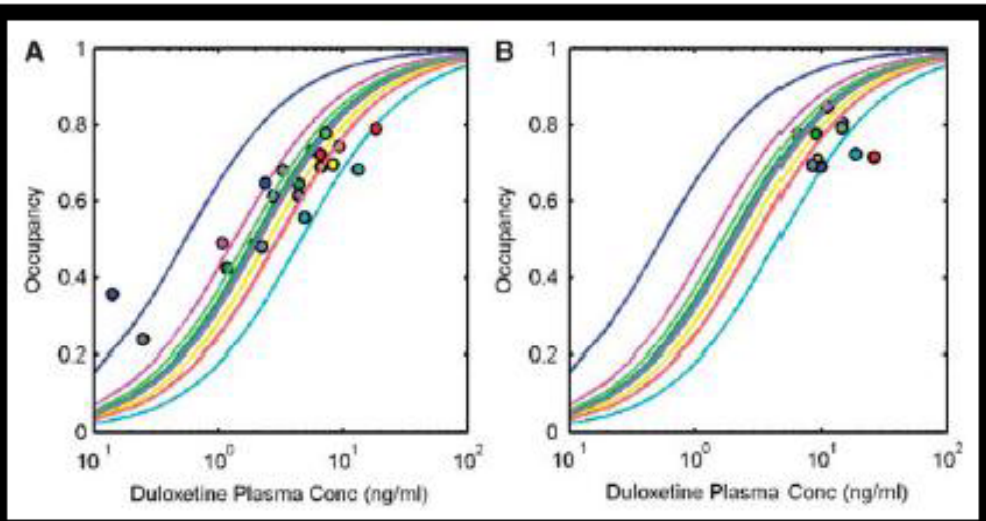
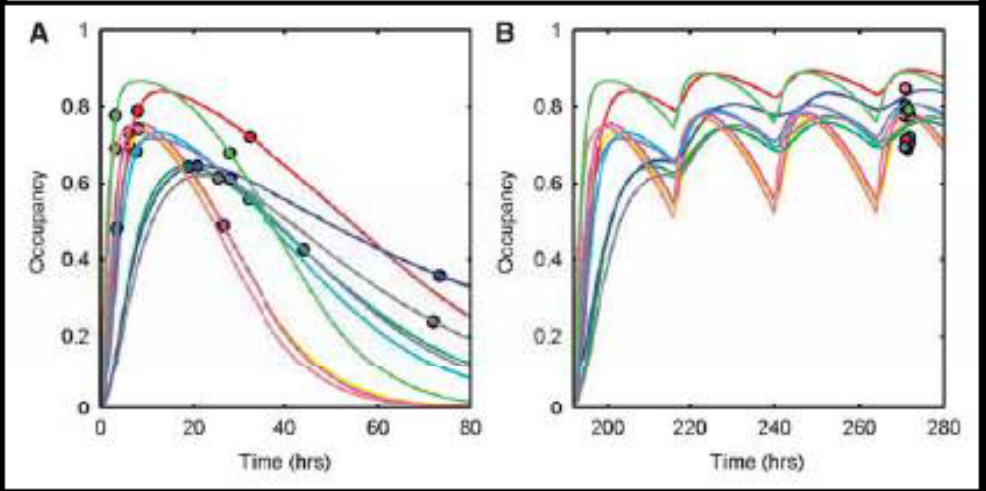


Direct Model



Indirect Model

Conclusion: Small, but significant improvement in prediction using the indirect model

GlyT1 – [^{11}C]GSK931145 species difference

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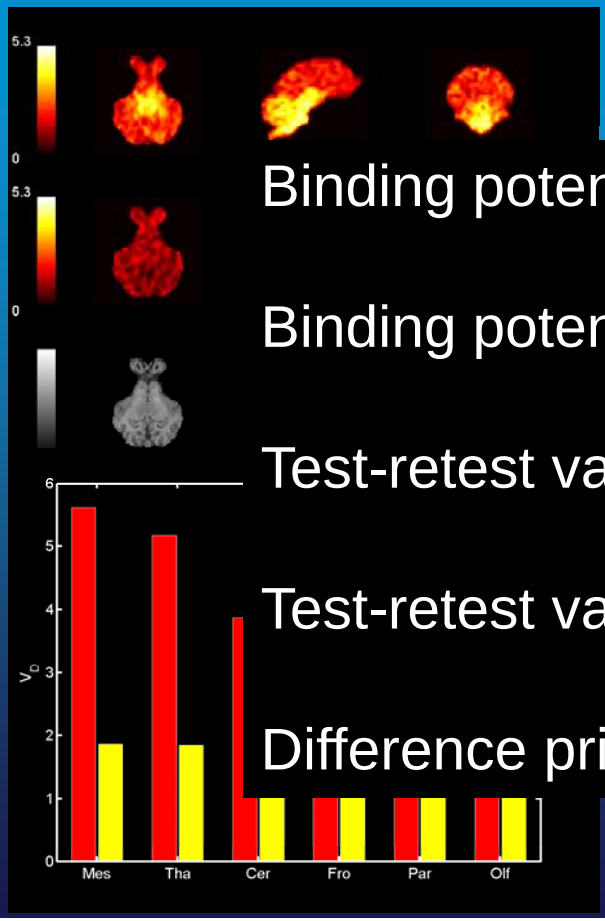
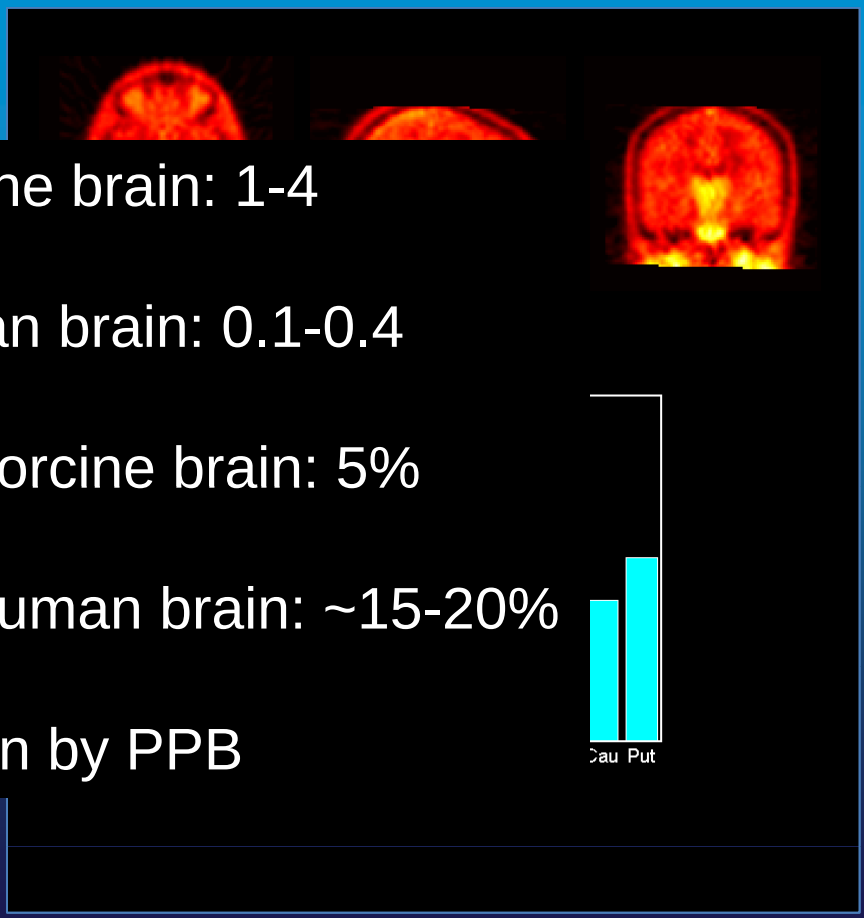
Porcine brain



Human brain



Binding potential in porcine brain: 1-4

Binding potential in human brain: 0.1-0.4

Test-retest variability in porcine brain: 5%

Test-retest variability in human brain: ~15-20%

Difference primarily driven by PPB

Human occupancy of GSK1018921

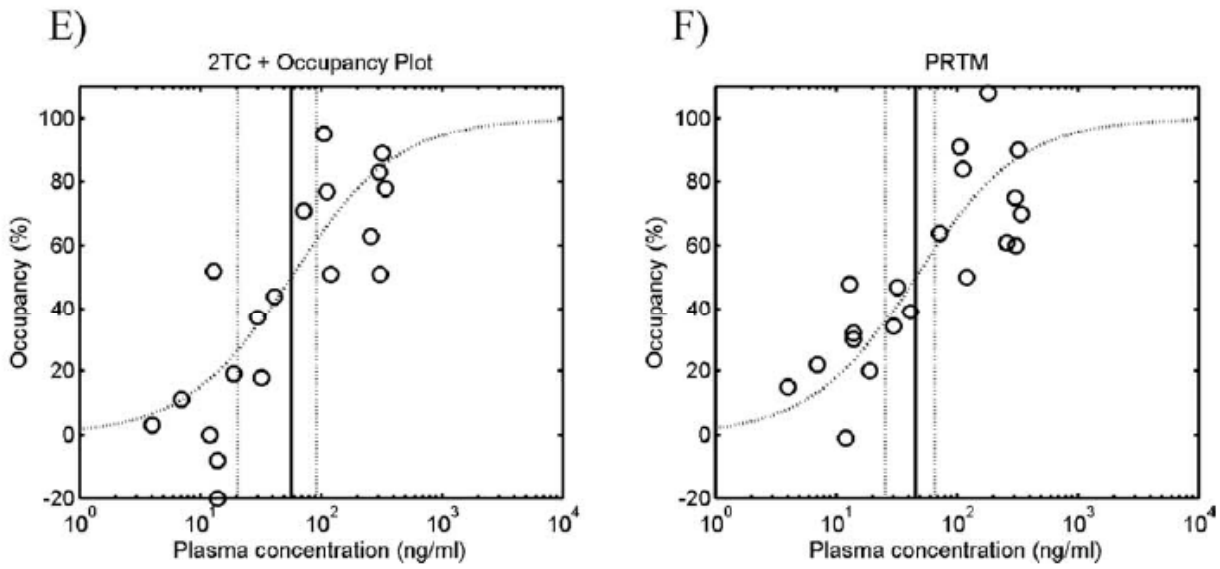


Fig. 4. GSK1018921 occupancy in humans. Example occupancy plots (A,B,C,D) derived from four post dose scans using thalamus (◇), cerebellum (o), brain stem (x), cortex (+) and middle temporal gyrus (*). (A,B) Strong linear relationship with non-negative x-intercept and occupancy values, (C) increased noise, and (D) V_T post dose is higher than baseline. E_{max} model fit relating GSK1018921 plasma concentration to central GlyT-1 occupancy for occupancy results (E) derived from 2TC analysis and occupancy plot, and (F) occupancy results derived from PRTM.

From: Gunn et al., SYNAPSE 65:1319–1332 (2011)

For a recent review on PET tool compounds for GlyT1 imaging, see:
Imaging Type 1 Glycine Transporters in the CNS Using Positron Emission Tomography
PET and SPECT of Neurobiological Systems (2014): 321-330

18kDa TSPO

Previously known as Peripheral Benzodiazepine Receptor

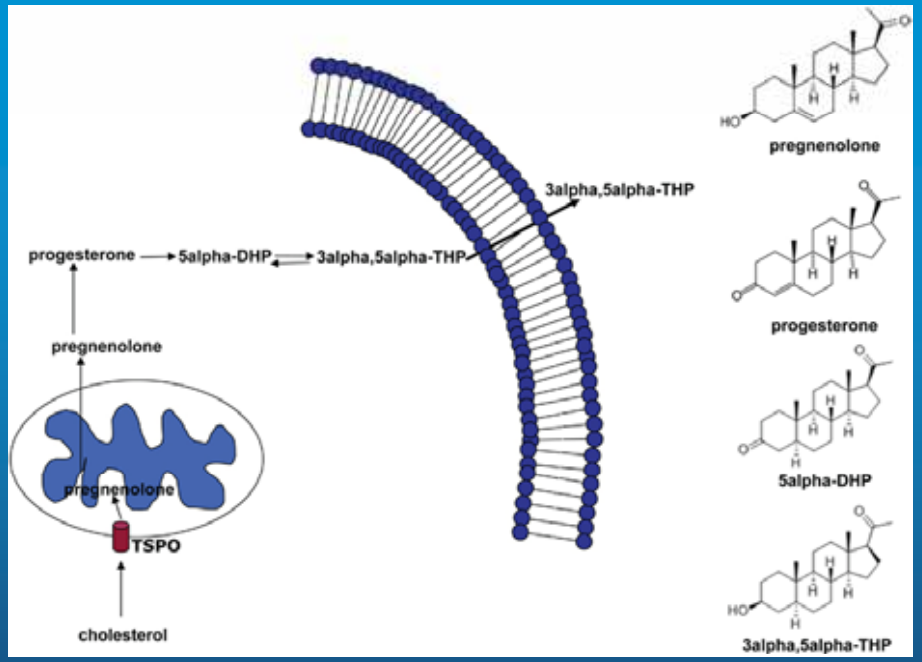
Expressed in mitochondrial membrane

Primary function is transport of cholesterol into mitochondria

Highly expressed in astrocytes and activated microglia

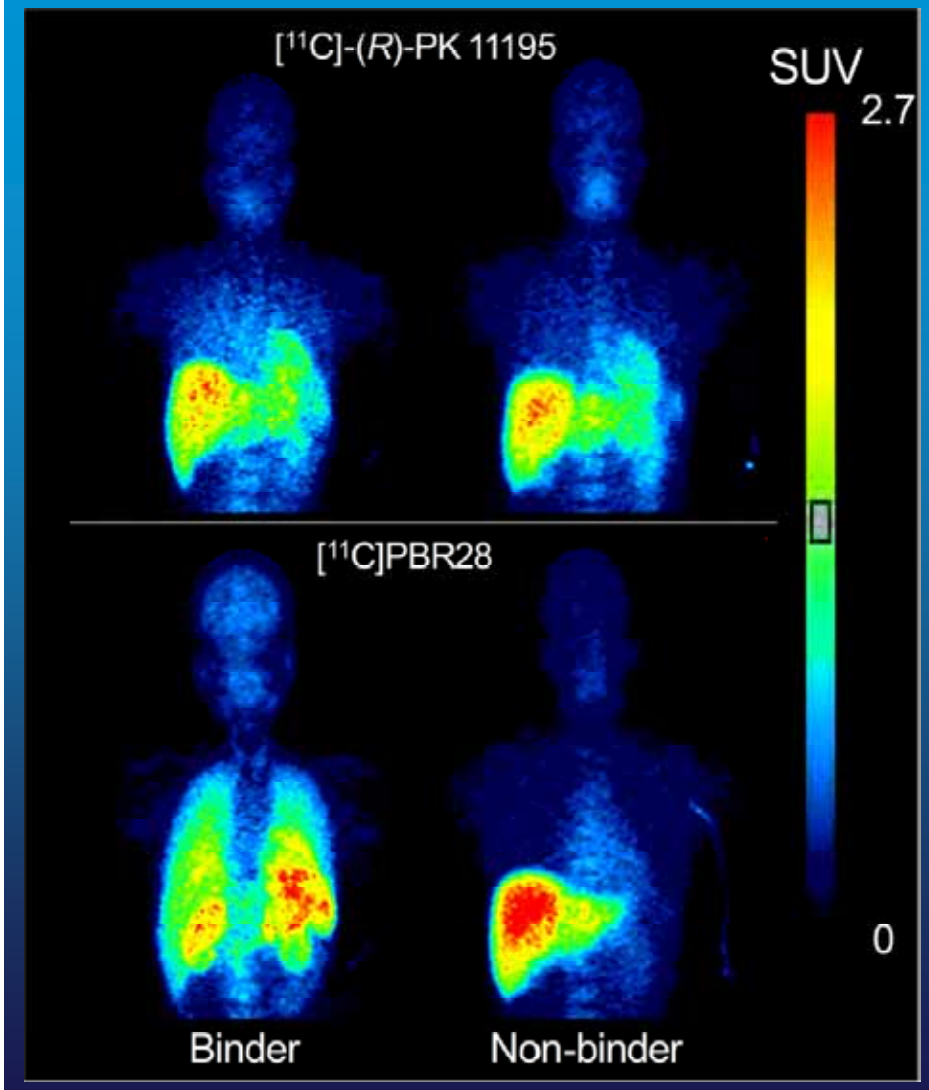
Of therapeutic interest for e.g. neuroprotection in TBI, anxiety and inflammation

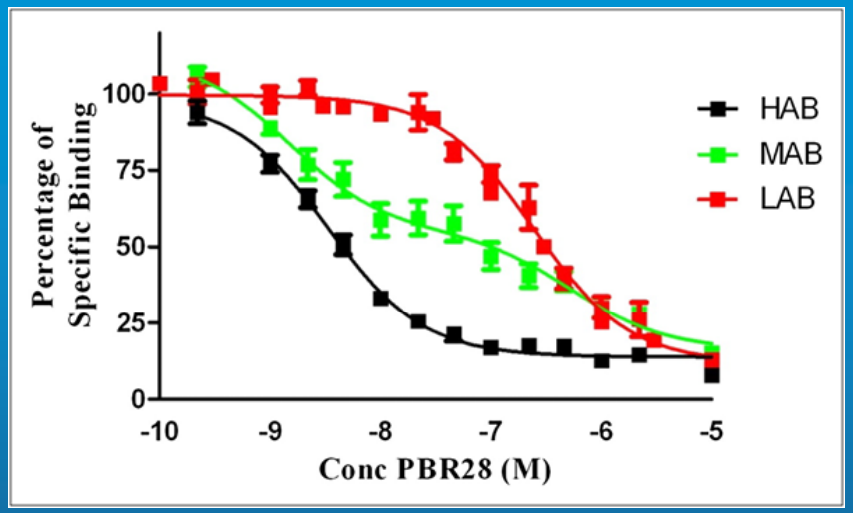
Of interest as a marker of inflammation



See also: PET Imaging of Translocator Protein Expression in Neurological Disorders PET and SPECT of Neurobiological Systems (2014): 321-330

[^{11}C]PBR28 – Binders vs Non-Binders



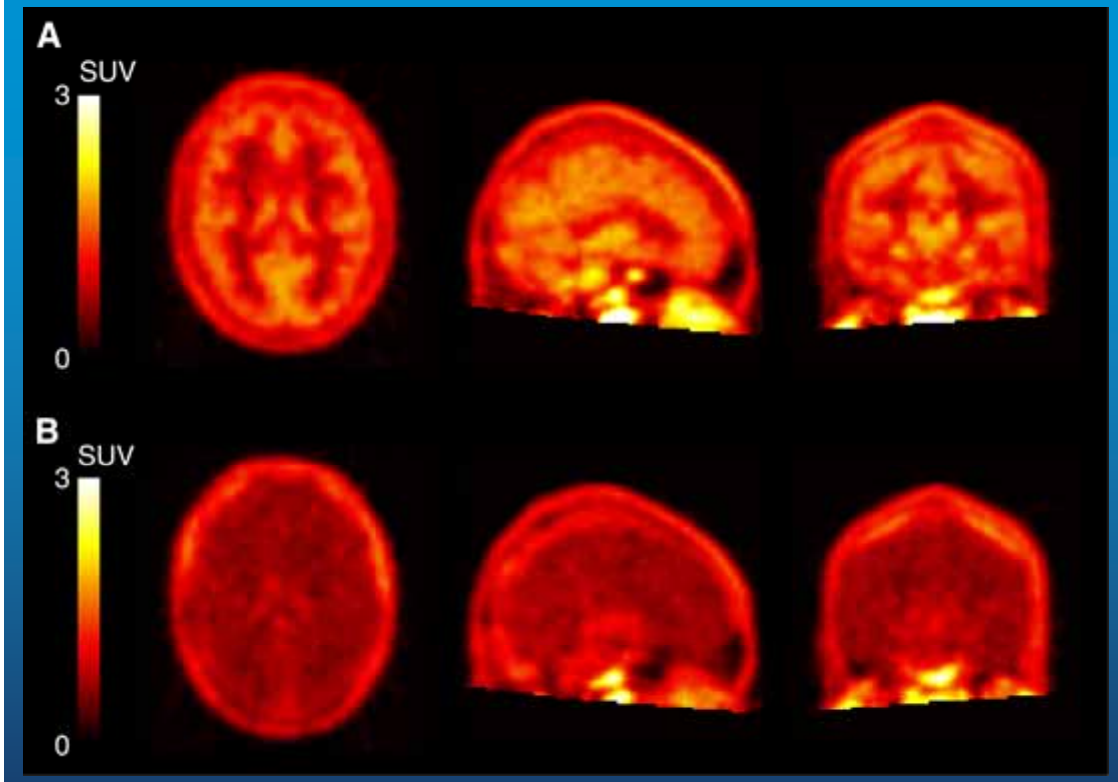


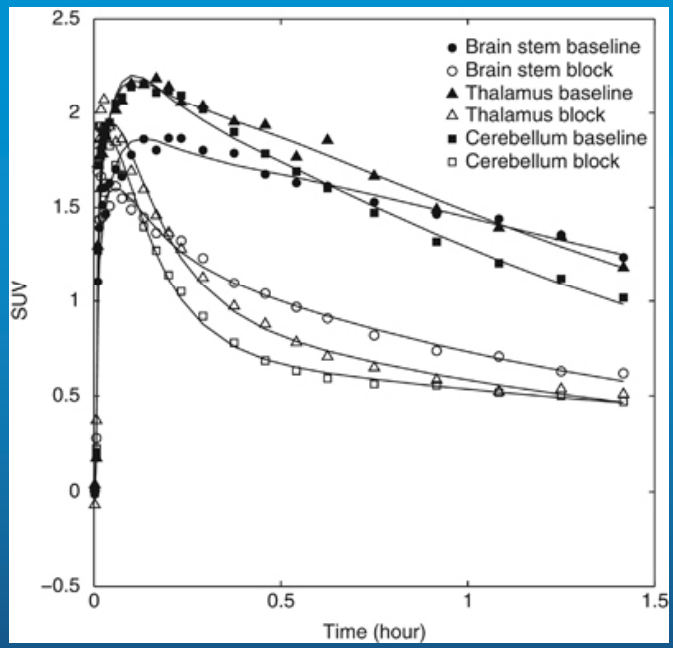
Demonstrated to be result of common polymorphism (rs6971) in the TSPO gene which leads to an amino-acid substitution (Ala147Thr)

Owen et al., Journal of Cerebral Blood Flow & Metabolism (2012) 32, 1–5

Kreisl et al., Neuroimage. 2010 February 15; 49(4): 2924–2932.

18kDa TSPO – Blocking with XDB173



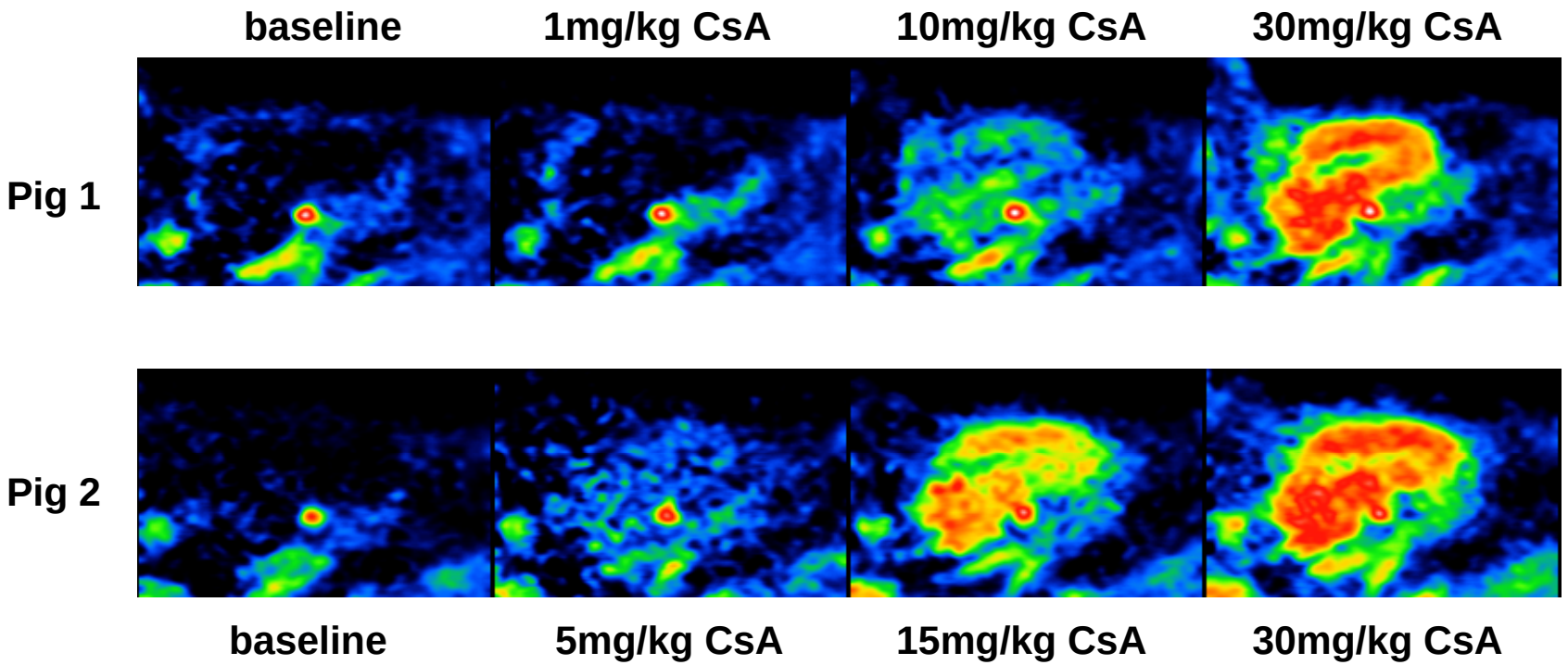


Owen et al., J Cereb Blood Flow Metab. 2014 Jun;34(6):989-94

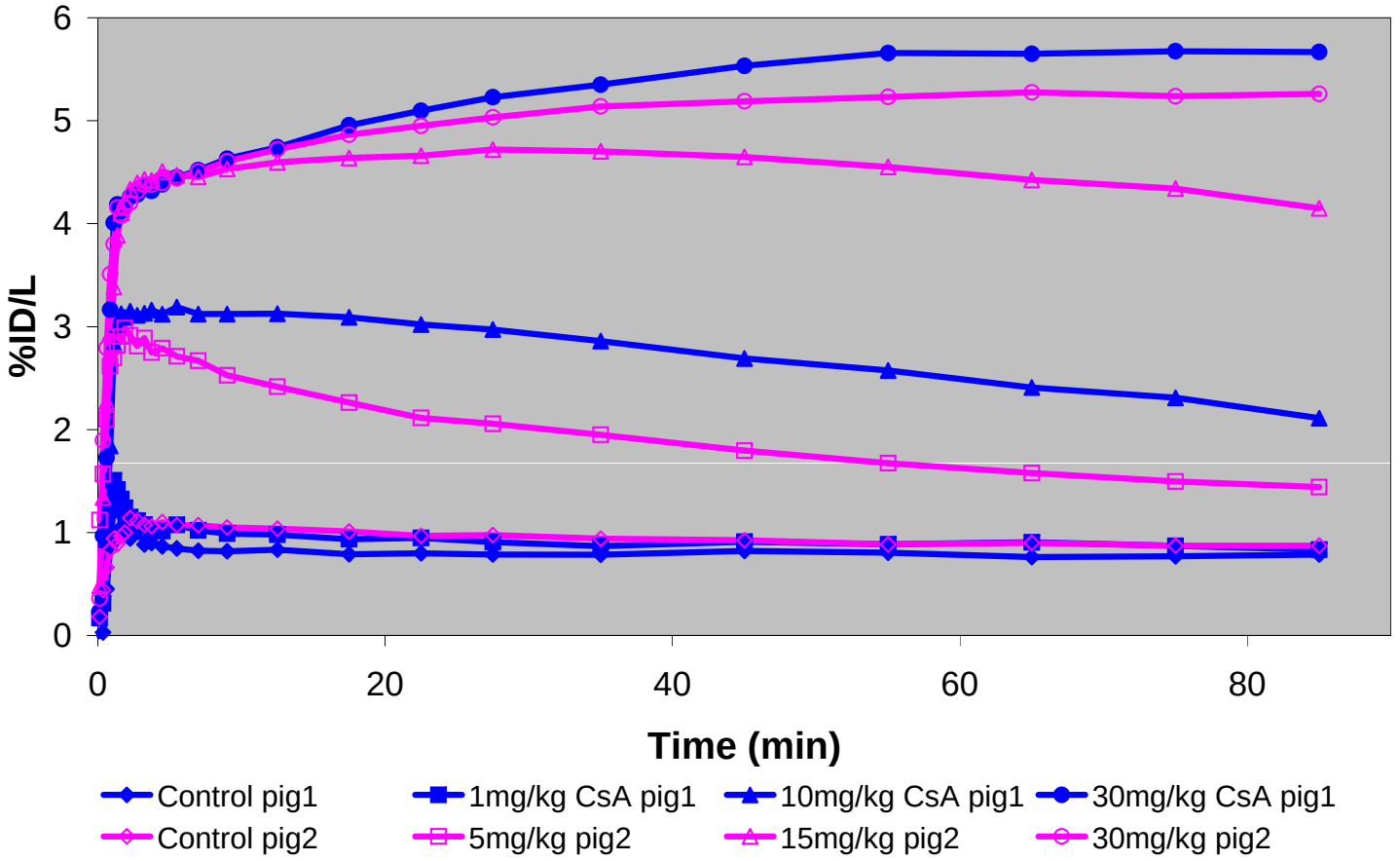
Loperamide

- Marketed as Imodium™ as an anti-diarrhoea agent
- Opioid receptor agonist without central side effects
- Shown to be P-gp substrate
- P-gp inhibition *in vivo* leads to central side effects (*e.g.* breathing depression)
- ~13.5 fold difference in CNS penetration between wild type and *mdr1a/b* knockout mice
  - *A Schinkel *et al.* (1996) *J Clin Invest* **97**(11):2517-2524
- Potentially more sensitive than exisiting PET probes

Loperamide - dose dependent inhibition of P-gp



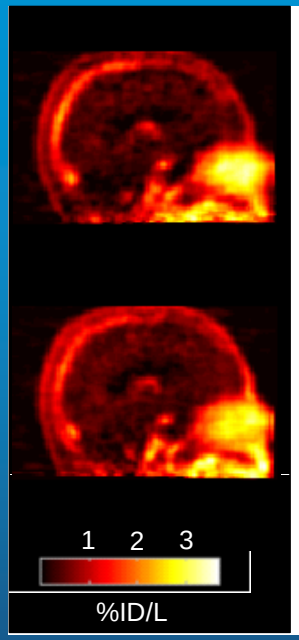
[^{11}C]Loperamide - comparison whole brain

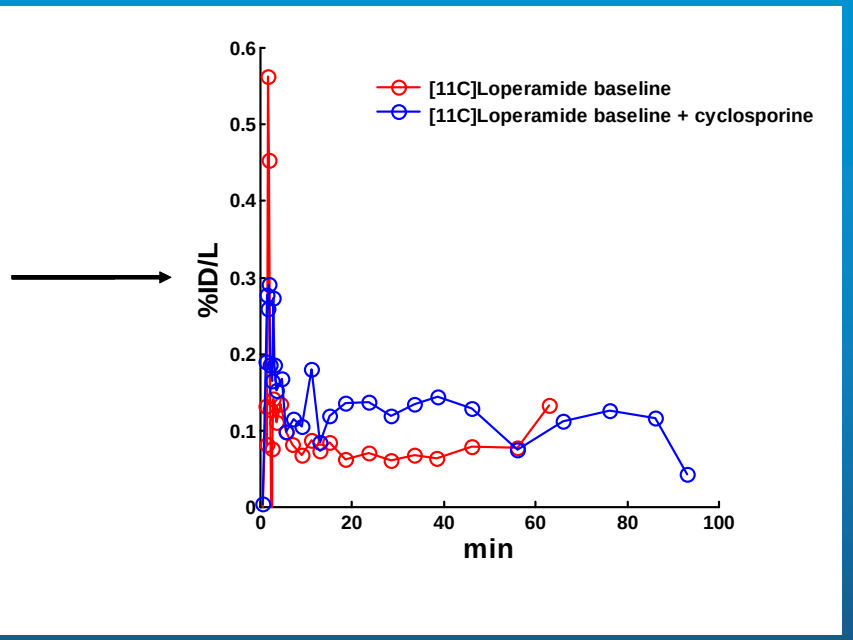


The human surprise!

Baseline

10mg/kg CsA





Volunteer	Baseline K_1(mL.cm^{-3}.min^{-1})	Quinidine (600mg) K_1 (mL.cm^{-3}.min^{-1})	Cyclosporin (10mg/kg) K_1 (mL.cm^{-3}.min^{-1})	Significance P (paired t-test)
1	0.0026	0.0020	--	--
2	0.0027	0.0034	--	--
3	0.0010	0.0031	--	--
Mean ± SD	0.0021±0.001	0.0028±0.0007	--	0.24
4	0.0021	--	0.0057	--
5	0.0020	--	0.0043	--
6	0.0023	--	0.0033	--
Mean ± SD	0.0021±0.0002	--	0.0044±0.0012	0.047

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UNIVERSITY OF CALIFORNIA

EXPLORER

Proposal

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To establish the

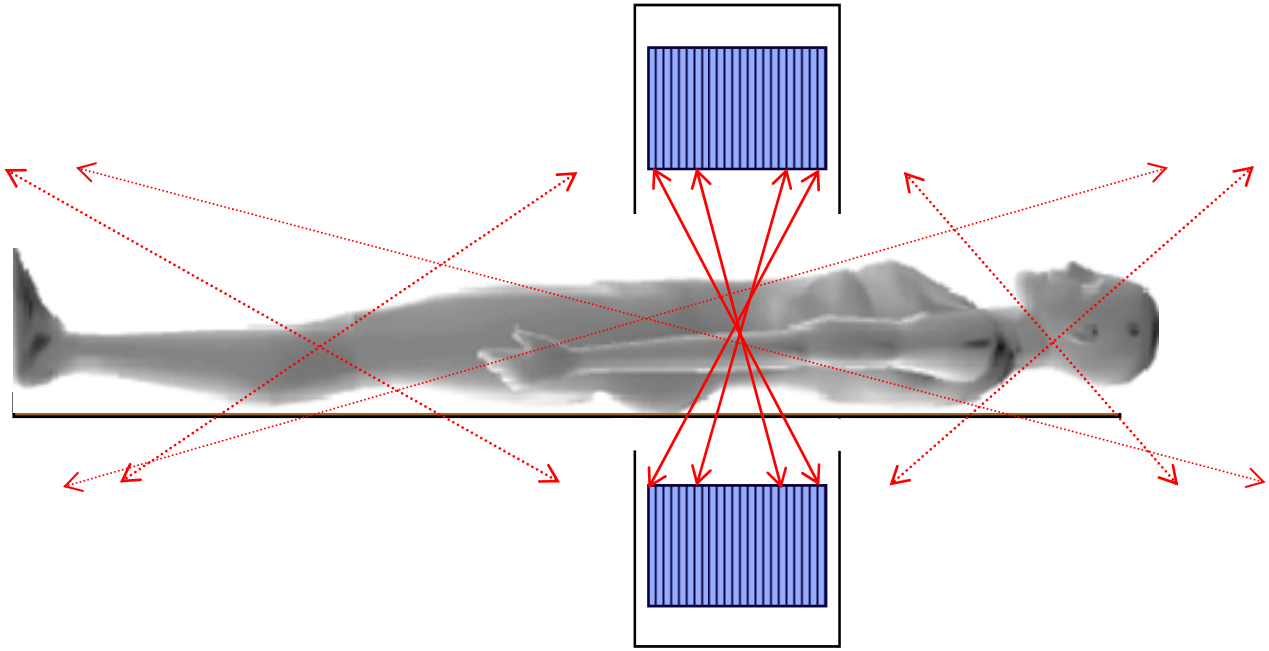
World's first Ultra Sensitive Total Body PET scanner

at Imanova

and demonstrate the

Unique Applications it enables in Experimental Medicine

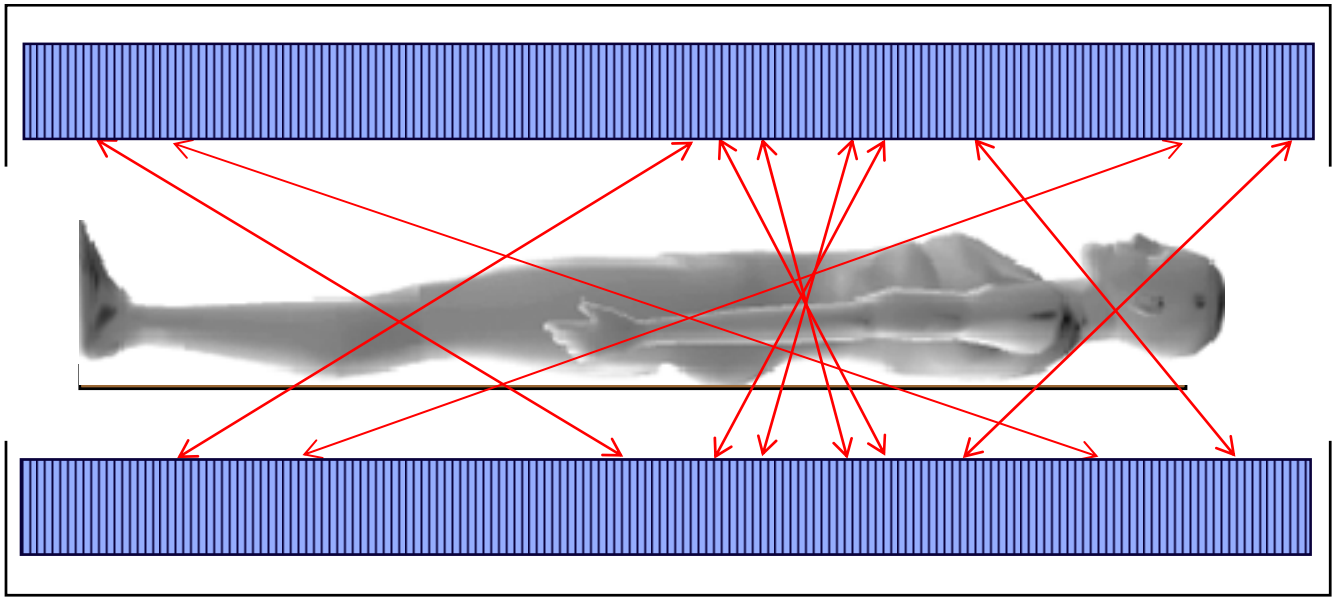
Current PET Scanners



< 3% EFFICIENT

97% OF INJECTED DOSE IS WASTED!

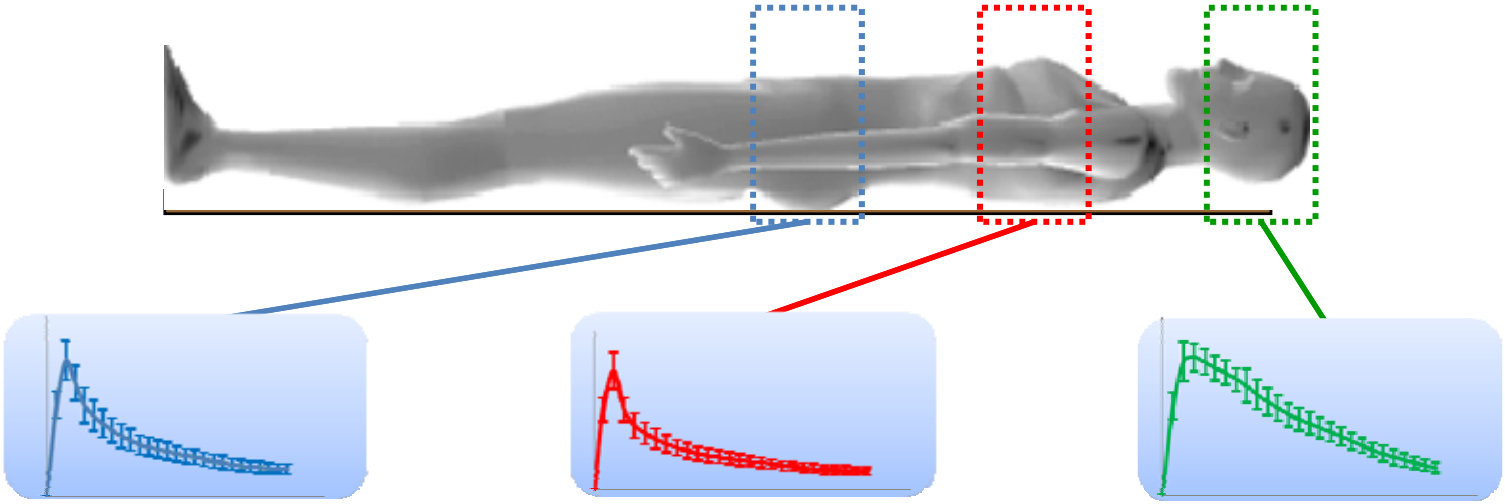
Total Body PET scanner



THE WHOLE DOSE IS USED
ALL BODY ORGANS ARE IMAGED

Total Body PET scanner

High Sensitivity Whole Body Field of View



Regional Tissue Kinetics with High Statistical Quality

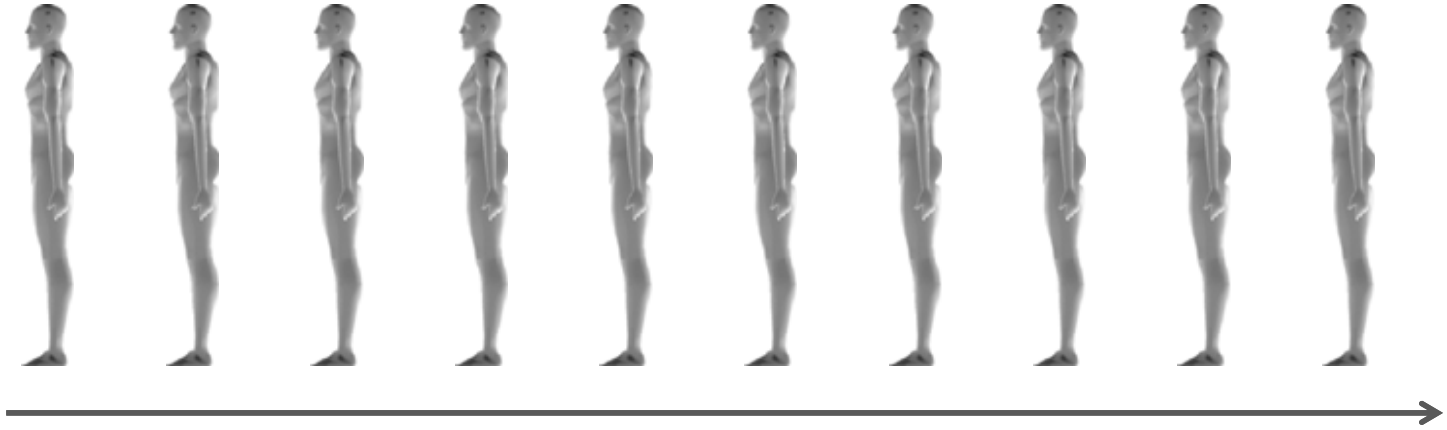
***ACCURATE* AND *SENSITIVE* QUANTIFICATION OF THE MOLECULAR TARGET IN MULTI-FOCAL DISEASE**

Total Body PET scanner

Current PET Scanners

Cross sectional or limited time point imaging in single organ of an individual

Total Body PET scanner



Multiple time point imaging in all organs of an individual

EQUIVALENT DOSE ENABLES 10 LONGITUDINAL PET SCANS COVERING ALL ORGANS COMPARED TO CURRENT 2 SCANS IN ONE ORGAN

The EXPLORER Consortium

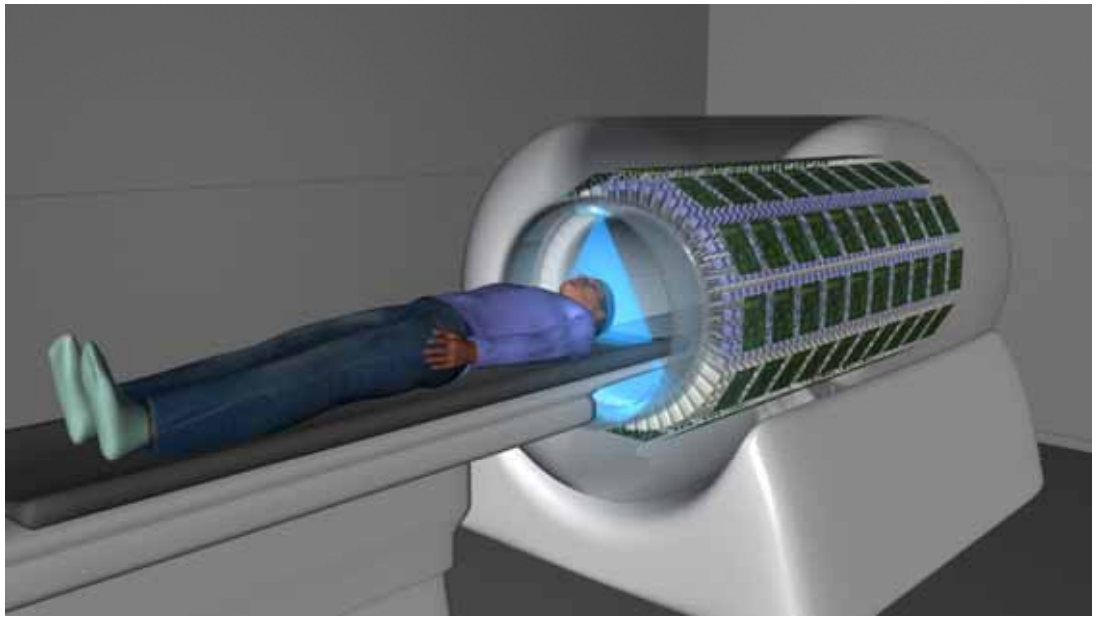
Design and Simulation of a Total Body PET Scanner

USA Academic Consortium (led by Simon Cherry)

UC DAVIS UNIVERSITY OF CALIFORNIA

BERKELEY LAB

Penn



- ✓ Team has built over 15 functional PET scanners
- ✓ Expertise in detectors, electronics, data corrections, image reconstruction
- ✓ 2 years of preparatory work
- ✓ Funded by NIH National Cancer Institute and UC Davis
- ✓ Strong relationships with Siemens, GE, and Philips

10 Conventional PET Scanners side by side

Summary

Many examples of ‘transporter imaging’ available for PET

Unmet needs?

- NET
- EAAT2
- ?

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Questions?