TRANSLATION FROM BENCH TO BEDSIDE: PET TRACERS FOR USE IN NEUROSCIENCE DRUG DEVELOPMENT

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Presentation Outline

- Strategies to improve clinical drug development: a role for PET
- Target engagement PET in neuroscience drug development
- PET: beyond target engagement

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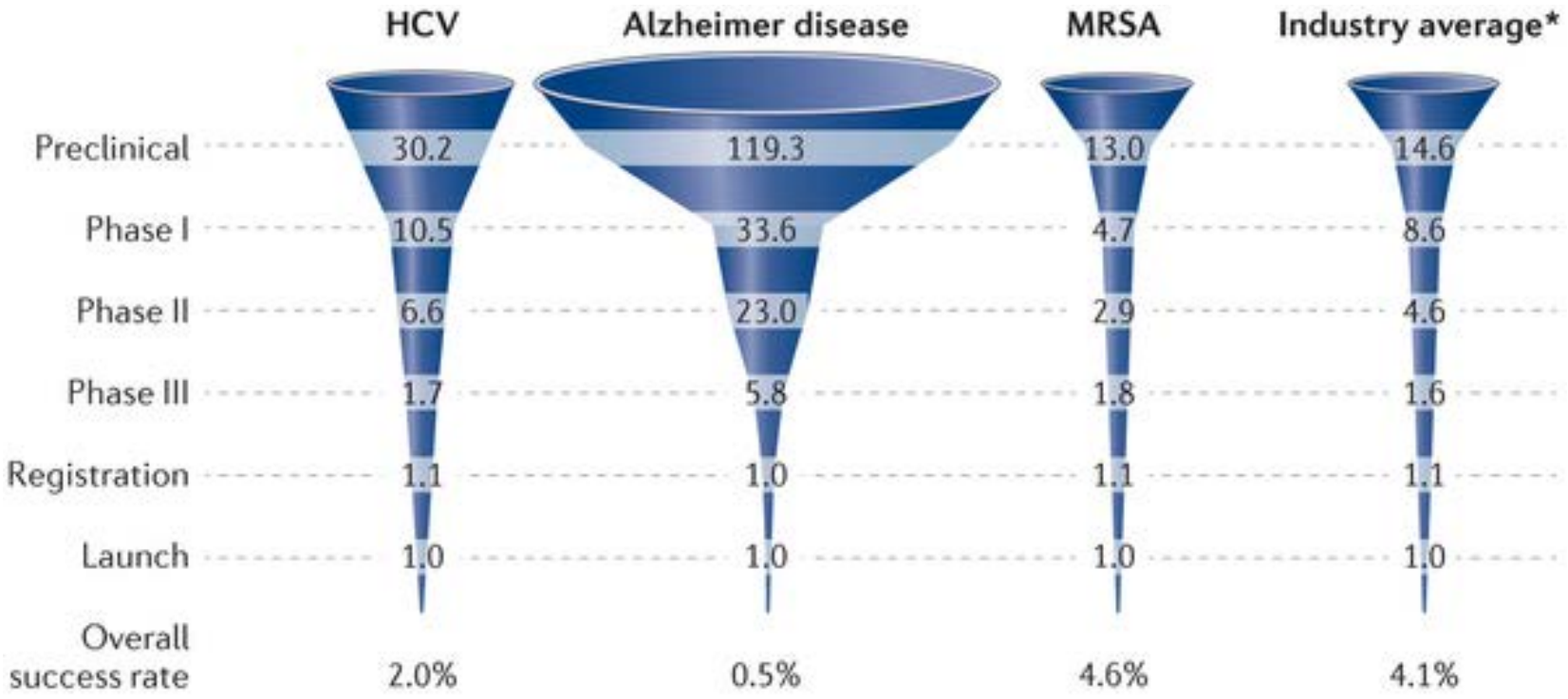
Drug Development Success Rates
The Need for Earlier Clinical Decisions



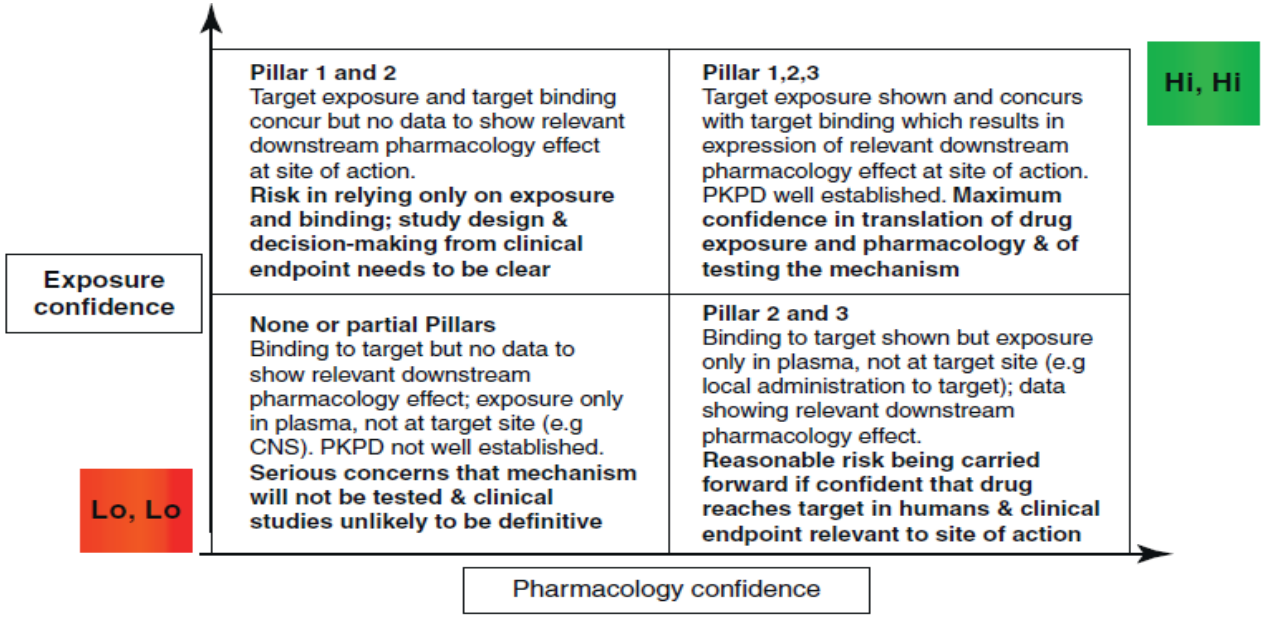
Calcoen D, et al. Nat Rev Drug Disc (2015) 14:161-162

Principles to Improve Phase II Outcomes
Three Pillars of Survival

Pillar 1: Exposure at the target site of action

Pillar 2: Binding to the pharmacological target

Pillar 3: Expression of pharmacology



"The highest level of confidence and direct evidence at the site of action that required levels of target binding were being achieved is most probably obtained from PK/PD studies of in vivo occupancy measurements with positron emission tomography (PET) or radiolabeled ligands."

Morgan P, et al. Drug Disc Today (2012) 17:419-424

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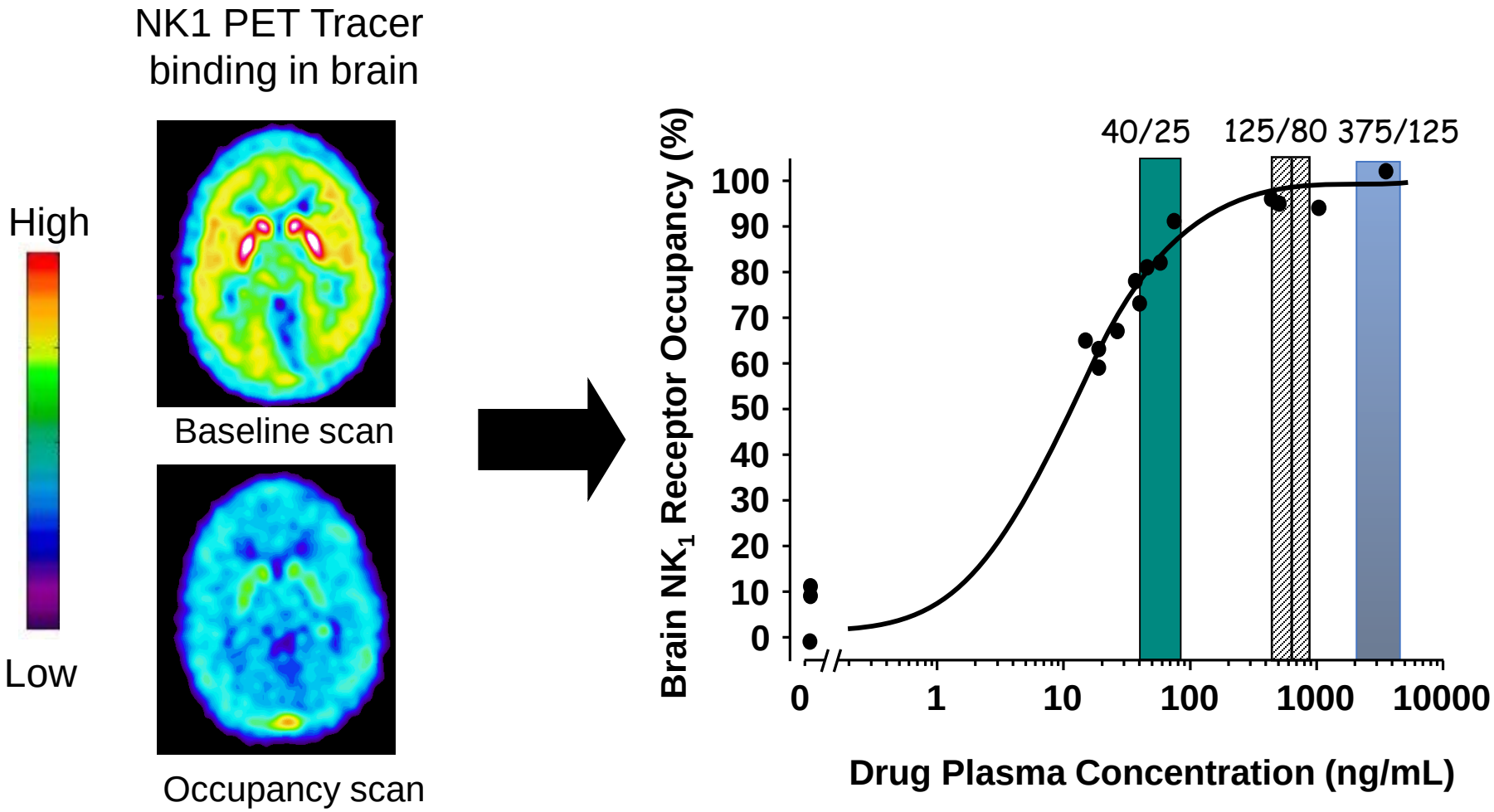
- PET: beyond target engagement

Neuroscience Biomarker Strategy

PET tracers for Target Engagement/Dose Selection



Bergstrom *et al,* (2004), Biological Psychiatry, 55:1007-1012

Substance P: NK_1 Receptor Antagonists

REDUCTION OF CISPLATIN-INDUCED EMESIS BY A SELECTIVE NEUROKININ-1–RECEPTOR ANTAGONIST

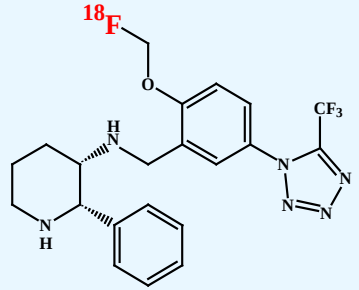
RUDOLPH M. NAVARI, M.D., RICK R. REINHARDT, M.D., PH.D., RICHARD J. GRALLA, M.D., MARK G. KRIS, M.D., PAUL J. HESKETH, M.D., ALI KHOJASTEH, M.D., HEDY KINDLER, M.D., THOMAS H. GROTE, M.D., KELLY PENDERGRASS, M.D., STEVEN M. GRUNBERG, M.D., ALEXANDRA D. CARIDES, PH.D., AND BARRY J. GERTZ, M.D., PH.D., FOR THE L-754,030 ANTIEMETIC TRIALS GROUP*

The New England Journal of Medicine 190 · January 21, 1999

11 SEPTEMBER 1998 VOL 281 SCIENCE www.sciencemag.org

Distinct Mechanism for Antidepressant Activity by Blockade of Central Substance P Receptors

Mark S. Kramer,* Neal Cutler, John Feighner, Ram Shrivastava, John Carman, John J. Sramek, Scott A. Reines, Guanghan Liu, Duane Snavely, Edwina Wyatt-Knowles, Jeffrey J. Hale, Sander G. Mills, Malcolm MacCoss, Christopher I. Swain.

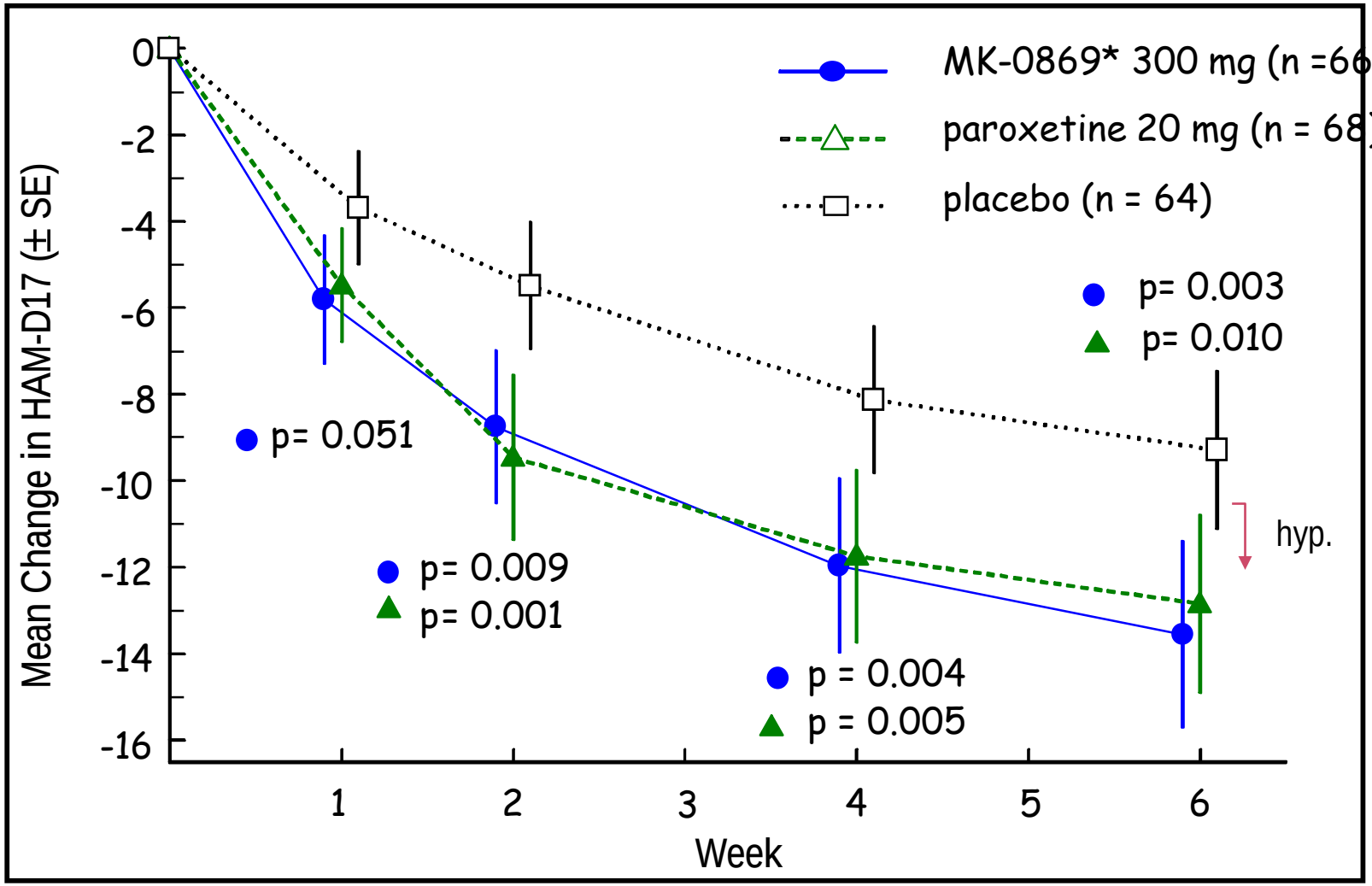


[^{18}F]SPA-RQ

hNK_1 IC_{50} 0.067 nM

Substance P: NK_1 Receptor Antagonists

Phase IIa Study for Depression

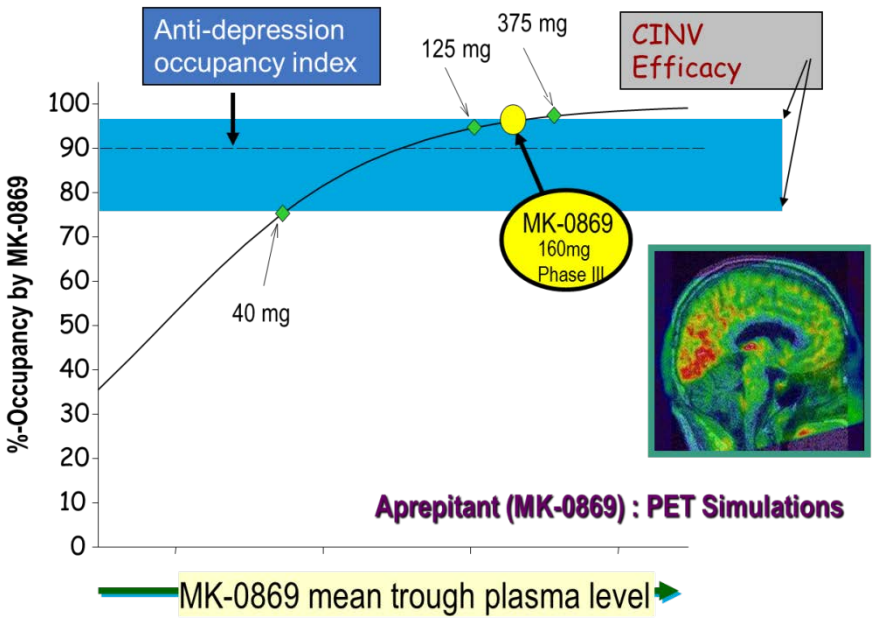


*Aprepitant

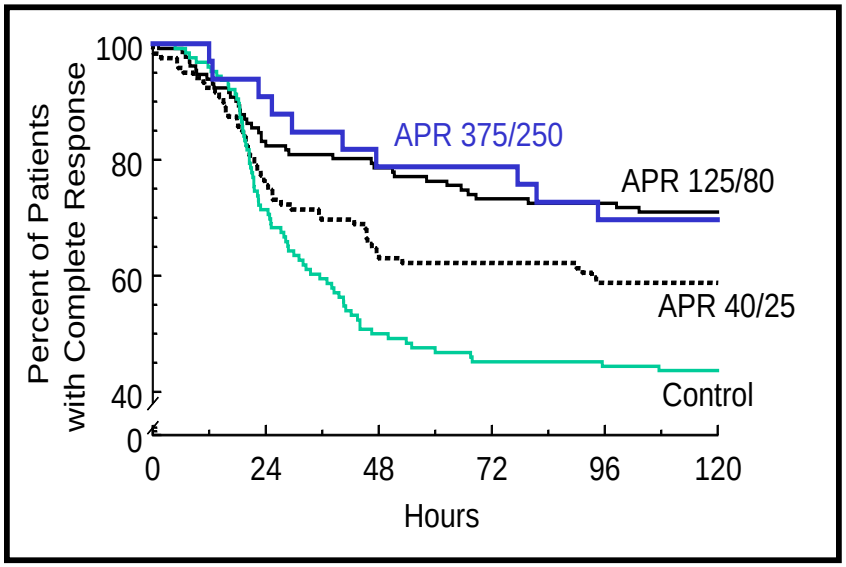
Kramer *et al*, (1998), Science, 281:1640-1645

Aprepitant - Clinical PET Occupancy Study

Target Engagement Guiding Dose Selection

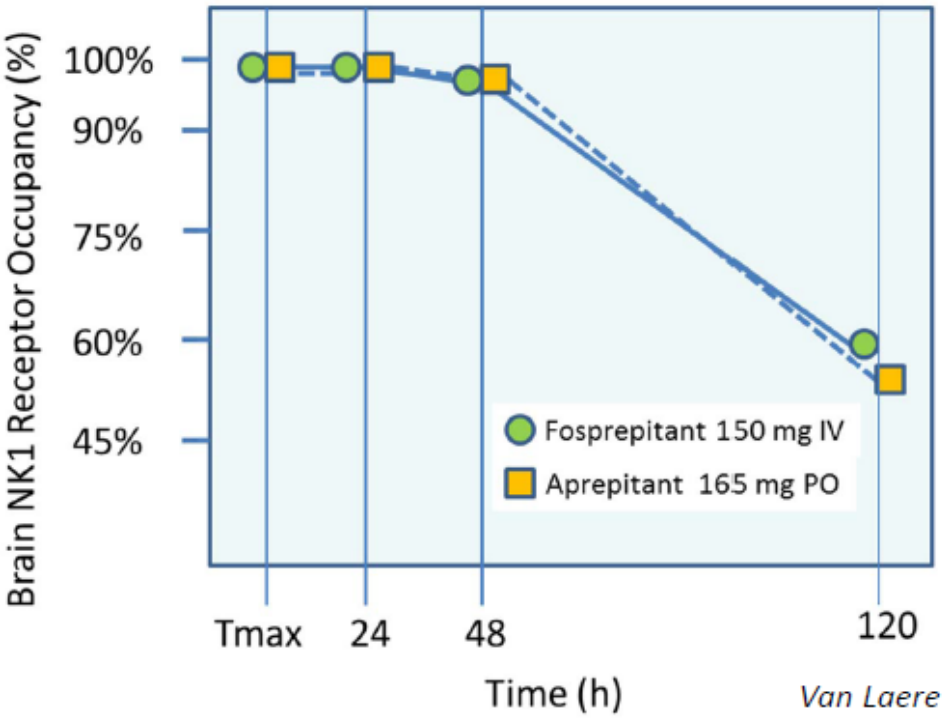


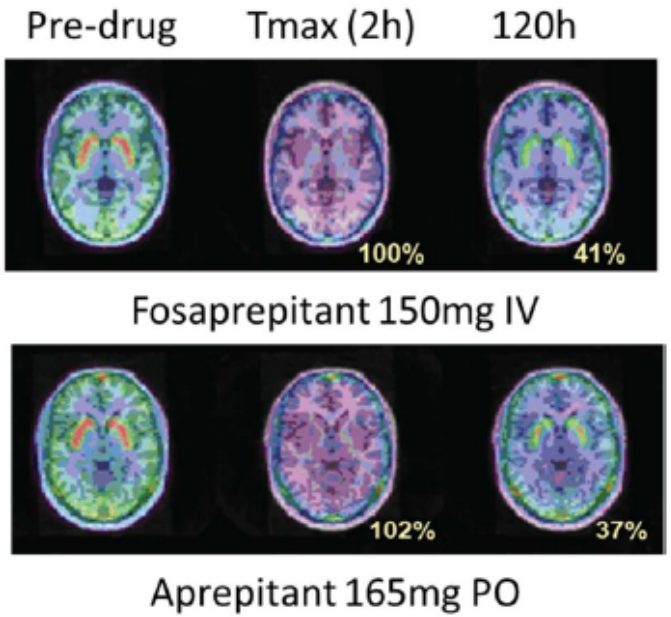
Cisplatin chemotherapy followed by Aprepitant



Chawla *et al,* (2003), Cancer, 97:2290-300

PET Target Engagement
Increasing Patient Options



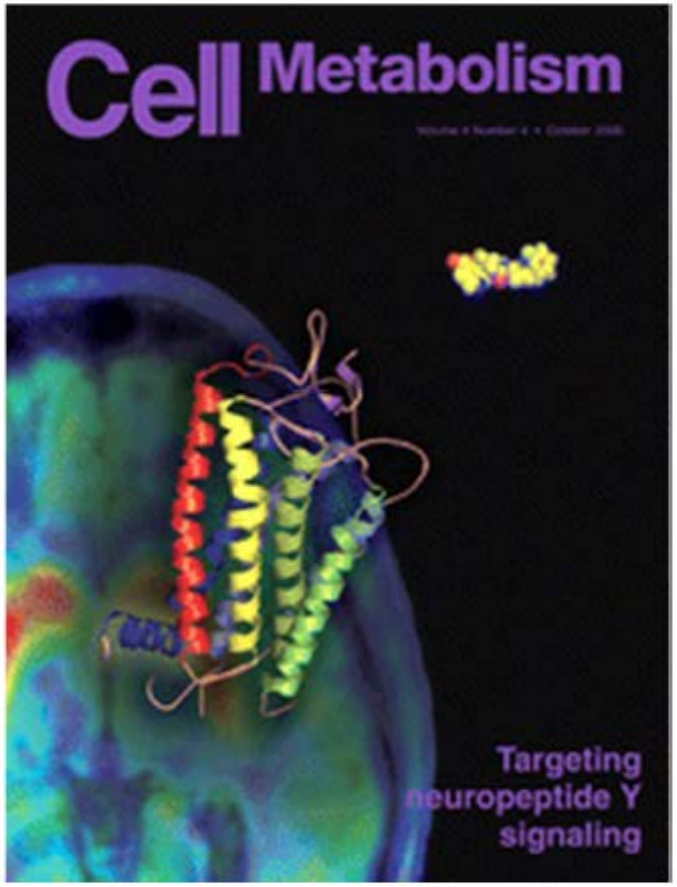


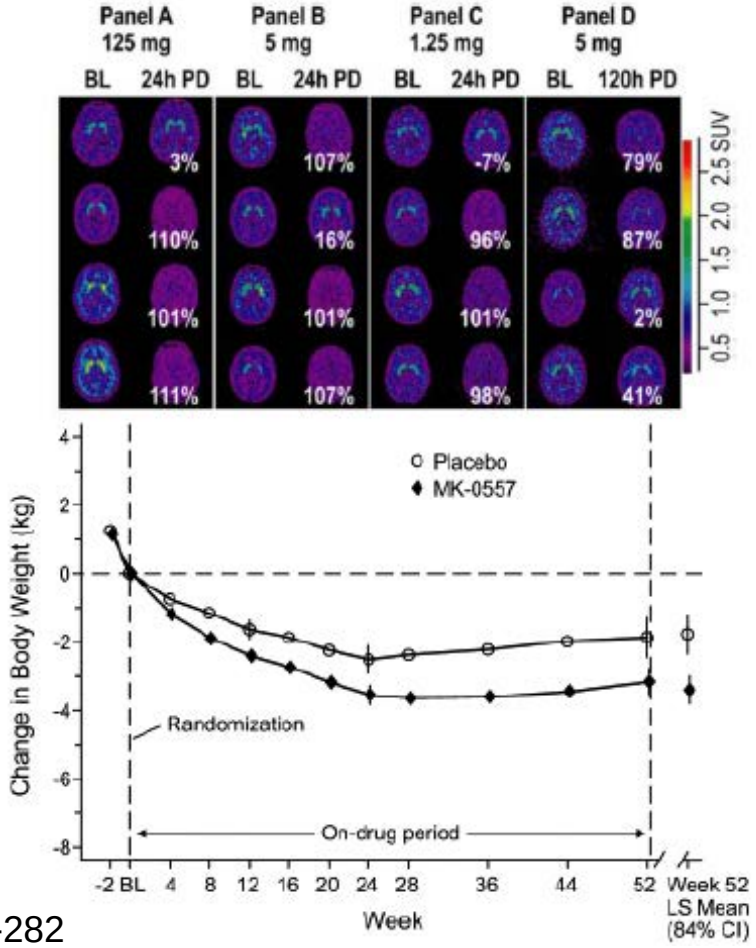
Van Laere et al (2012) Clin Pharm Exp Ther 92: 243-250

- PET shows bioequivalence, supporting registration of alternate dosage form without need for clinical efficacy trials

PET Target Engagement

Definitive proof of concept: NPY5-R antagonism for obesity



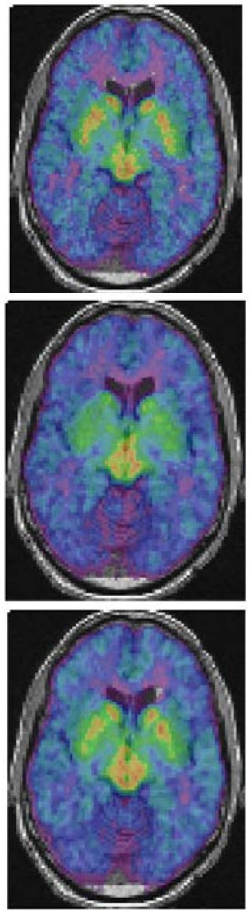


Erondu, et al. *Cell Metabolism* (2005) 4: 275-282

- NPY5 implicated in weight loss but effect is clinically insufficient
- PET data ensures mechanism was adequately tested

PET Target Engagement

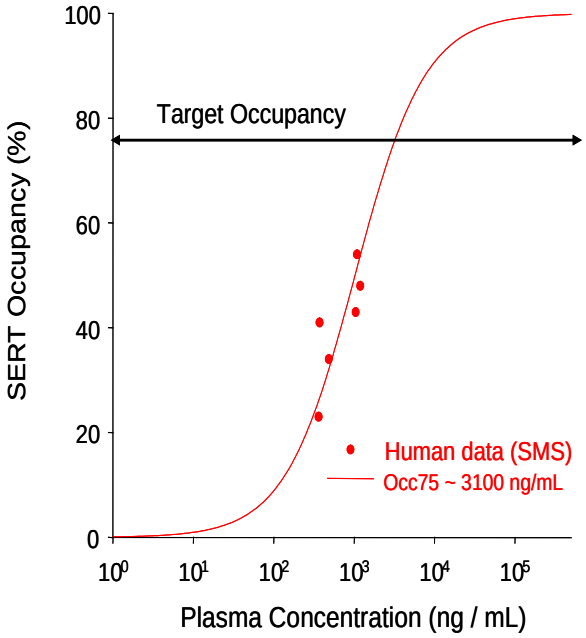
Early No Go Decision: Depression

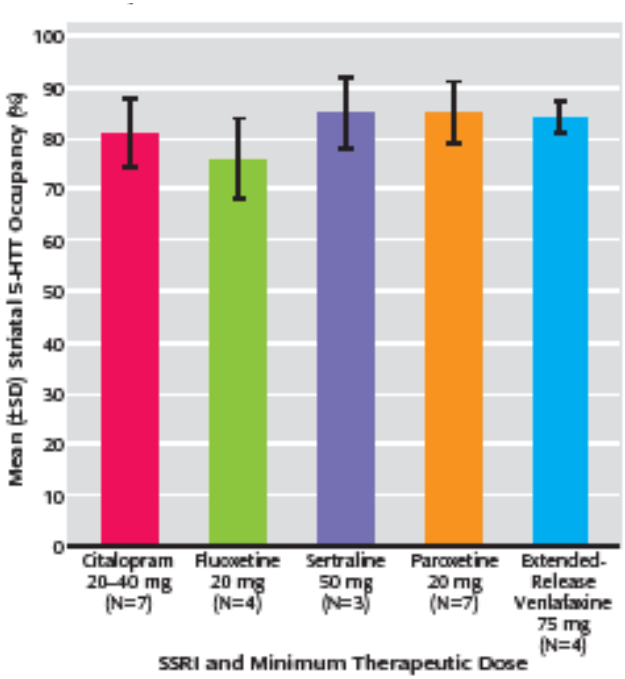


Baseline

2hr post-dose ~ 55% SERT occupancy at Cmax

7hr post-dose ~ 35% SERT occupancy

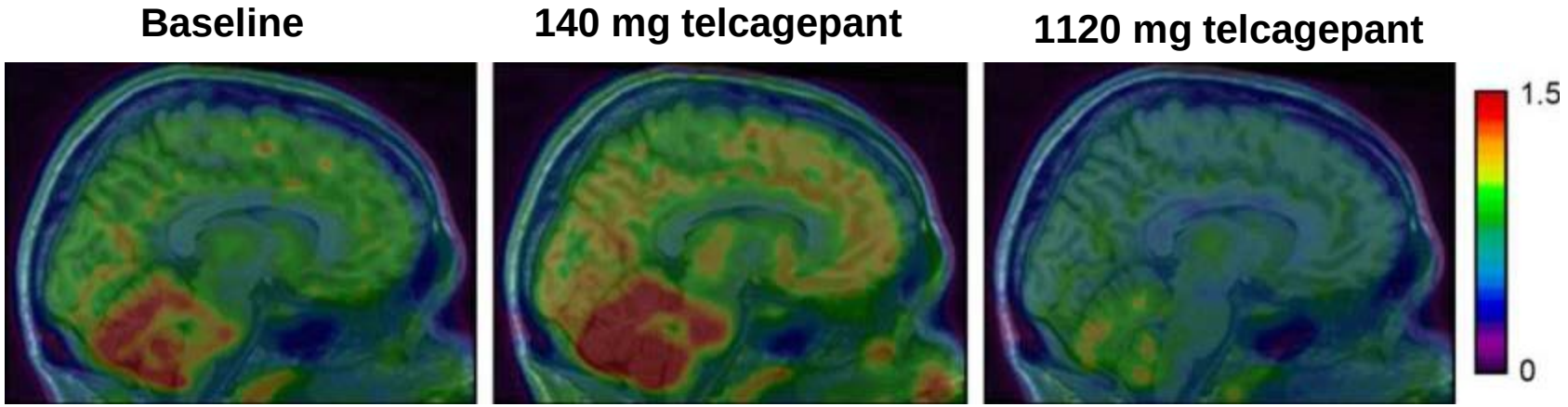




Meyer et al. Am. J. Psychiatry (2004) 161: 826.

- All SSRIs require 80% SERT occupancy
- Novel Rx candidate only reaches 55% occupancy @ Cmax
- M&S predicts high multiple daily doses needed to achieve target occupancy
- Early No Go decision

PET Target Engagement
Proof of Mechanism: CGRP-R and Migraine



Hostetler et al. JPET (2013) 347:478-486.

[^{11}C]MK-4232 and telcagepant

- Unknown if anti-migraine efficacy of telcagepant was driven by peripheral or central target engagement
- PET studies: negligible occupancy of central CGRP receptors at efficacious dose of CGRP-R antagonist telcagepant
- Mechanism of action is peripheral – focuses drug discovery program

Neuroscience Biomarker Strategy

Optimal design of PET occupancy studies

Pick initial dose and time based on NHP PK/RO and Phase I PK

Acquire PET & PK data in 2 subjects (4 occupancy studies)

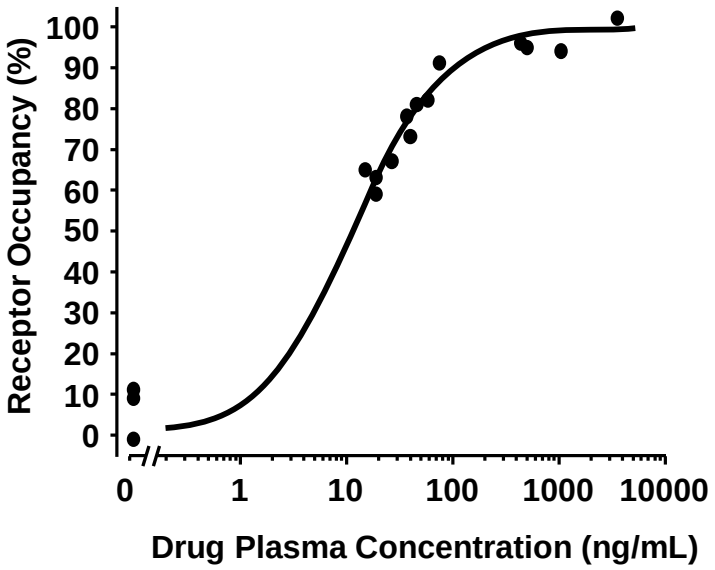
Construct initial PK/RO model

Use optimal design to select next dose(s)

Acquire PET & PK data in 2 subjects

Refine PK/RO model

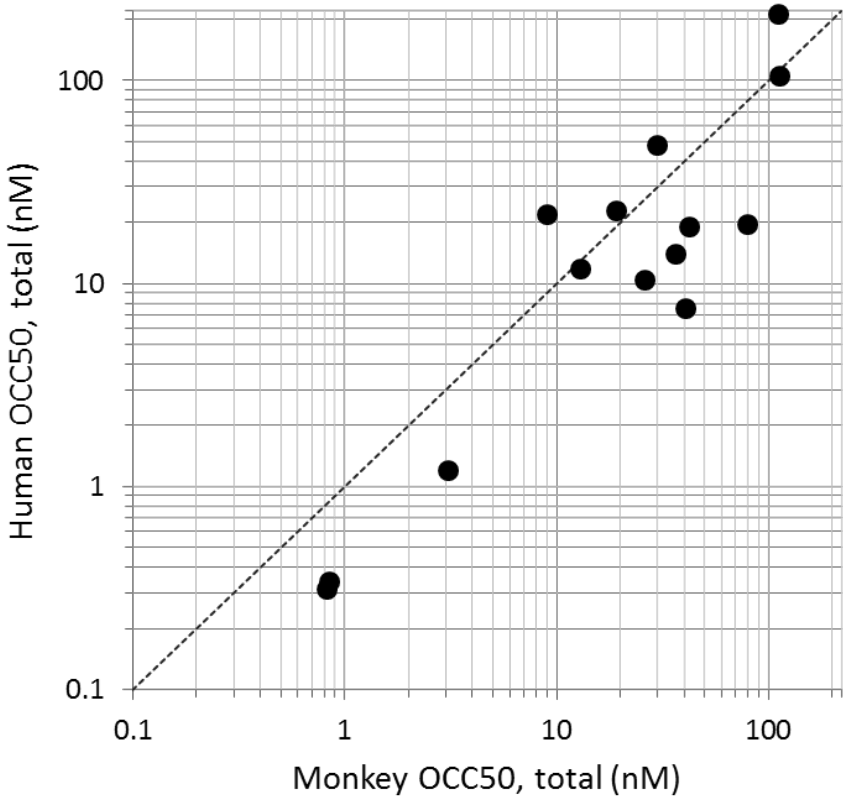
Simulate benefit of additional PET data to improve robustness of model



Zaumner S, et al. Clin Pharm Ther (2010) 87:563-571

PET Target Engagement

Monkey as a Predictive Model for Human



PET Target Engagement
Impact on decision-making

- Human dose prediction
- Go/No Go to Phase Ib/2
- Dose selection for POC study
- Maximize safety margins
- Confident testing of mechanism
- Demonstration of phamacodynamic bioequivalence
- Understanding mechanism of action

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Beyond Target Engagement

Patient Identification & Disease Progression Measure

Pillar 3: Expression of pharmacology

MCI

AD, DLB, vascular dementia, non-AD tauopathies, etc.

Select the right patients

Drug

Placebo

Quantify Disease Progression

Biomarker strategies to enable smaller, shorter POC trials are desperately needed

Beyond Target Engagement

Amyloid PET: Patient Identification & Disease Progression Measure

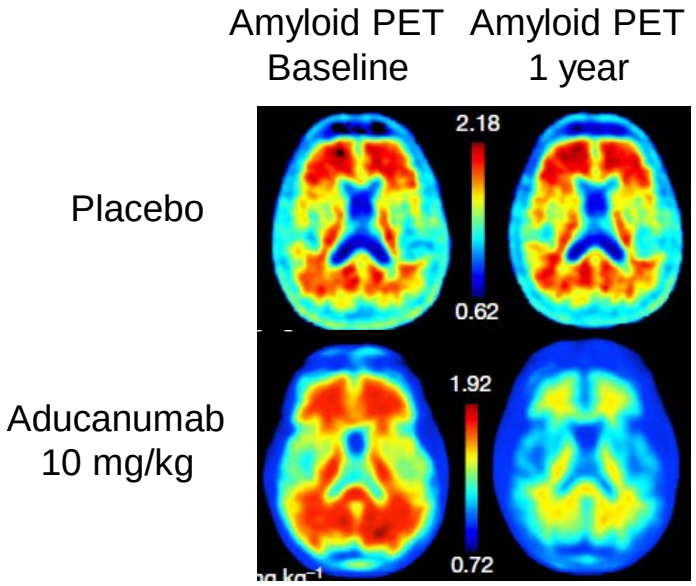
Amyloid PET Biomarker Strategy

Enroll amyloid plaque+ patients

Longitudinal ·····▸ *Studies*

Evaluate changes in plaque burden

Aducanumab: Amyloid-β fibril mAb



Sevigny J, et al. Nature (2016) 537:50-56

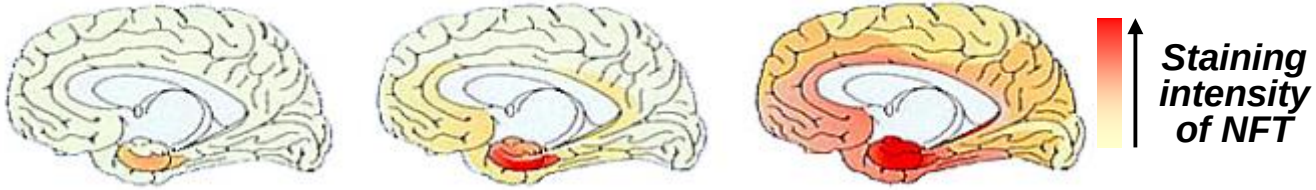
Beyond Target Engagement

Tau PET: Patient Identification & Disease Progression Measure

Tau Pathology & Disease Progression

Clinically silent → **Incipient AD** → **Fully developed AD**

transentorhinal stages I-II | **limbic stages III-IV** | **neocortical stages V-VI**

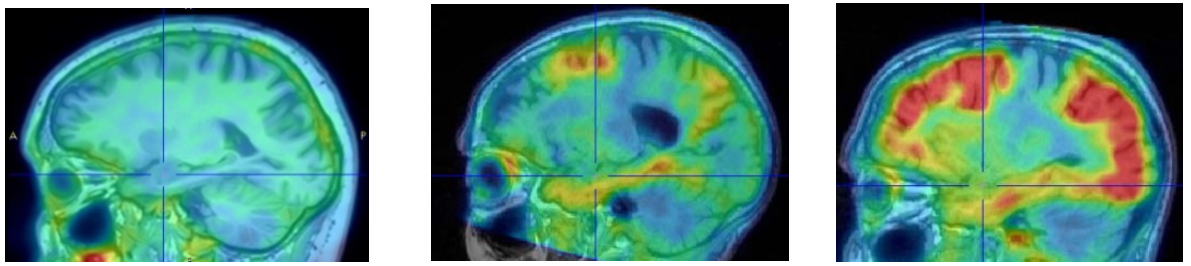


Tau PET Biomarker Strategy

Enroll tau+ patients → *Longitudinal Studies* → **Evaluate changes in tau burden**

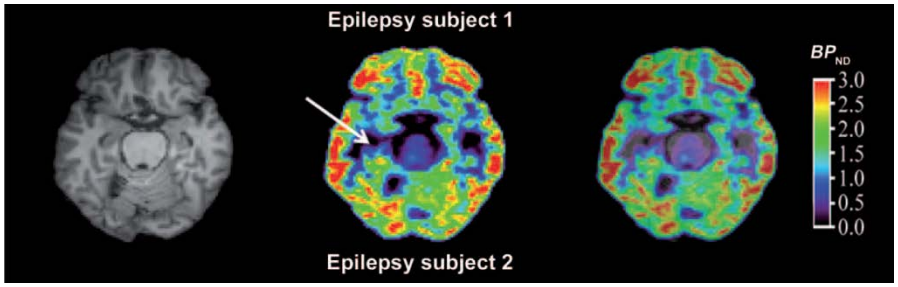
Tau PET tracer [^{18}F]MK-6240

HE, MMSE 29 | **AD, MMSE 26** | **AD, MMSE 18**



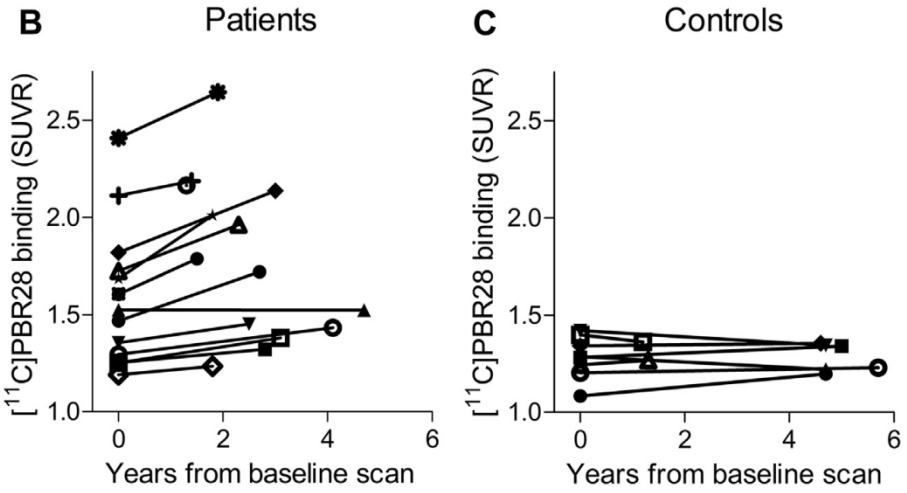
Beyond Target Engagement
Biomarker Needs for Neurodegenerative Diseases

Imaging Synaptic Density (SV2A) with [^{11}C]UCB-J



Finnema SJ et al. Sci Transl Med (2016) 8:348

Imaging Neuroinflammation (TSPO) in AD with [^{11}C]PBR-28



Kreisl WC et al. (2016) Neurobiol Aging 44:53-61

Summary

- The challenges of drug development require earlier and better clinical decision-making
- Application of PET tracers has improved the speed, quality, and confidence of early clinical decision-making for neuroscience drug development

THANK YOU!

MERCK

What Makes a Good CNS PET Tracer?

- NOT the radiolabeled version of a drug (in general)
- Relative to therapeutic candidates, PET tracers typically require:
  - Higher affinity
  - Lower lipophilicity
  - Better diffusion across blood-brain barrier
- Robust, reliable radiochemistry is a must
- Adequate selectivity for imaging
- Rigorous method for quantification of PET data is critical