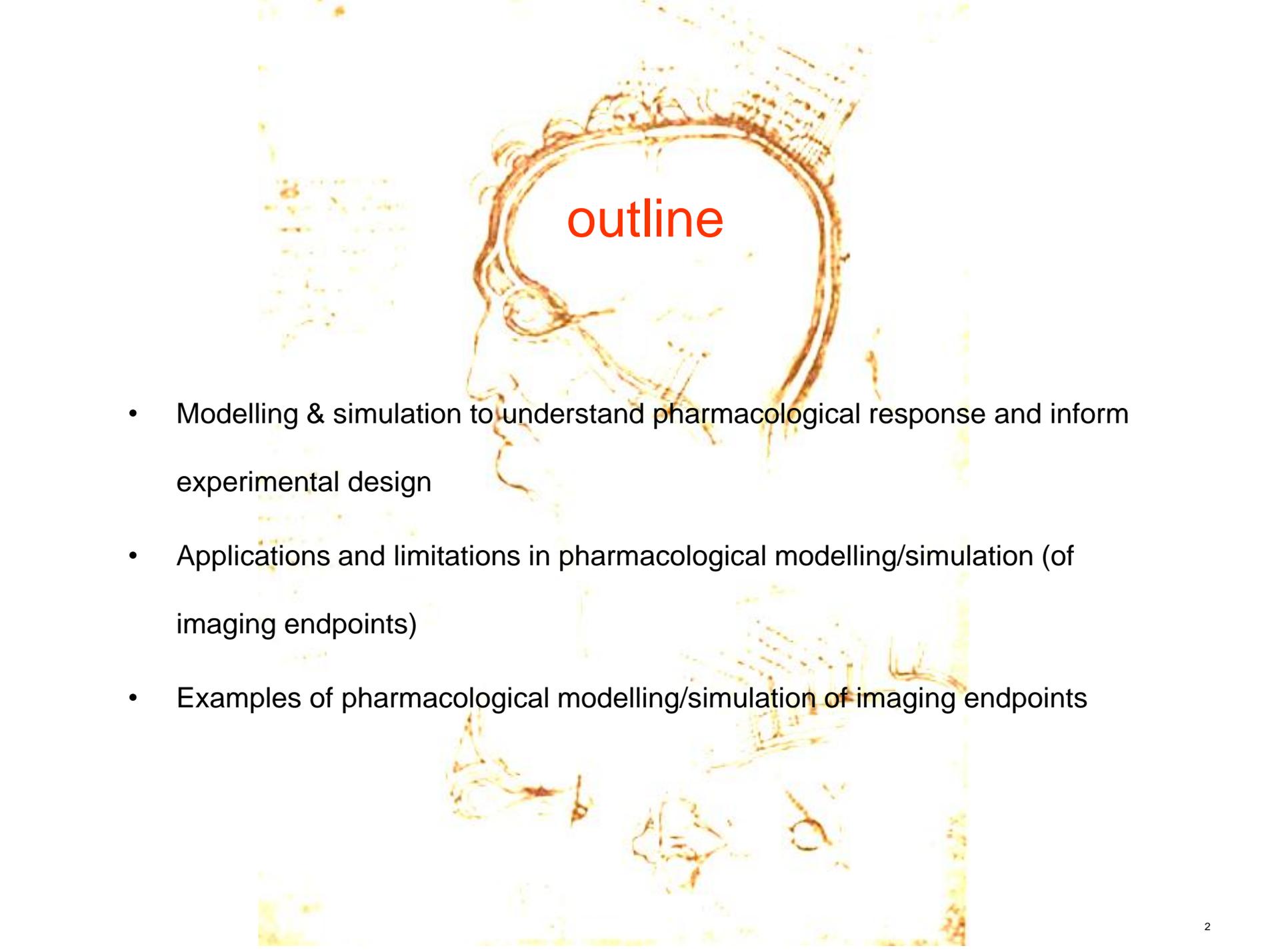


# Principles of pharmacological modelling relevant to applications of imaging endpoints

Chao Chen and Stefano Zamuner  
Clinical Pharmacology Modelling and Simulation  
GlaxoSmithKline  
London, UK

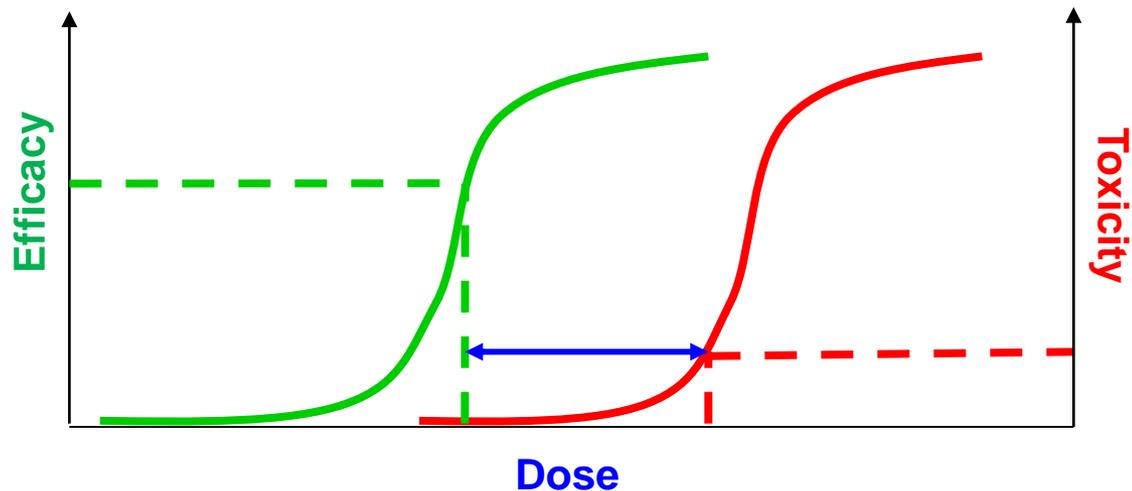


# outline

- Modelling & simulation to understand pharmacological response and inform experimental design
- Applications and limitations in pharmacological modelling/simulation (of imaging endpoints)
- Examples of pharmacological modelling/simulation of imaging endpoints

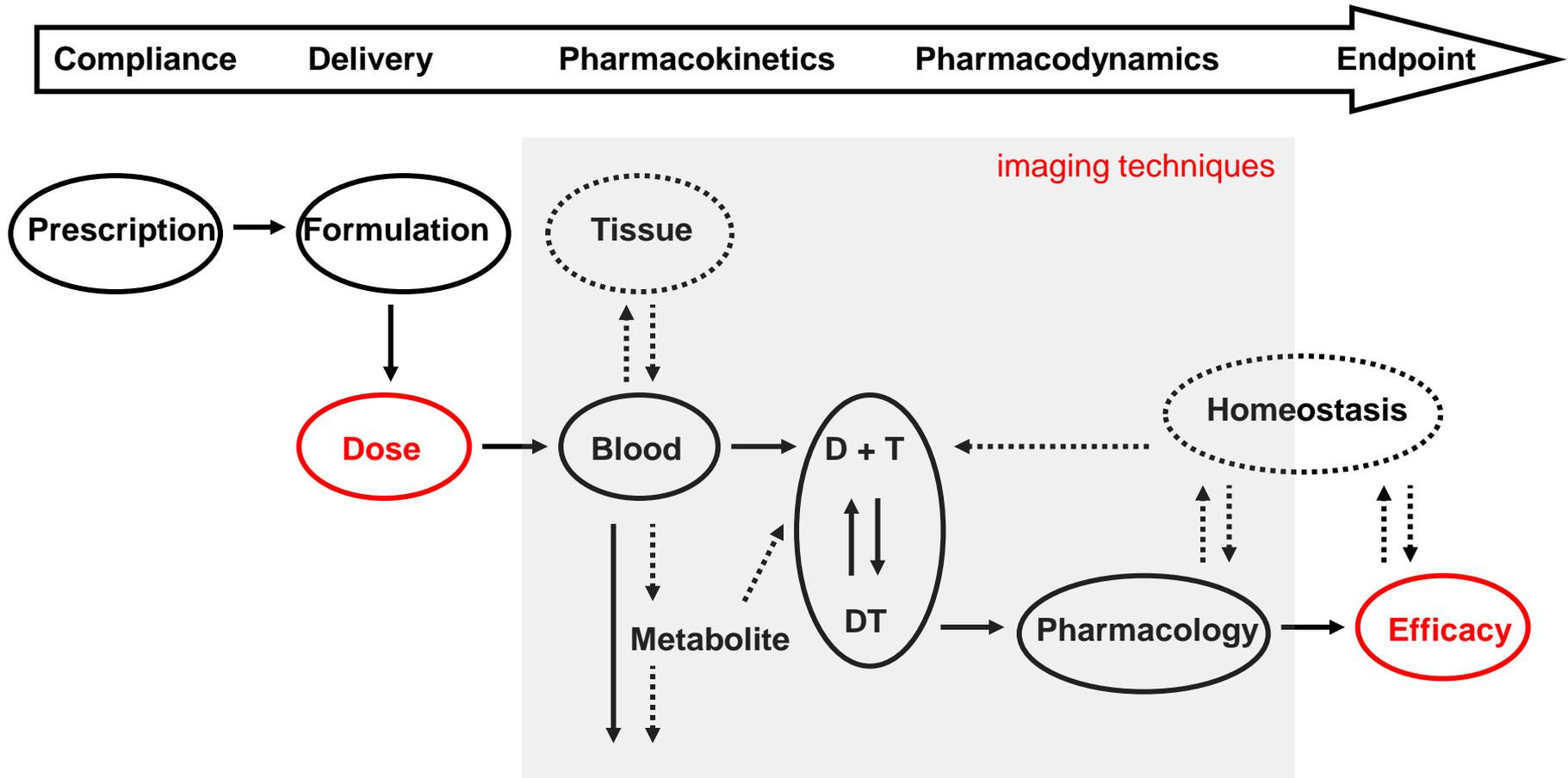
# a key question for drug trials and use

- What dose (regimen) is required to achieve a desired response level, and maintain such level for a required duration?



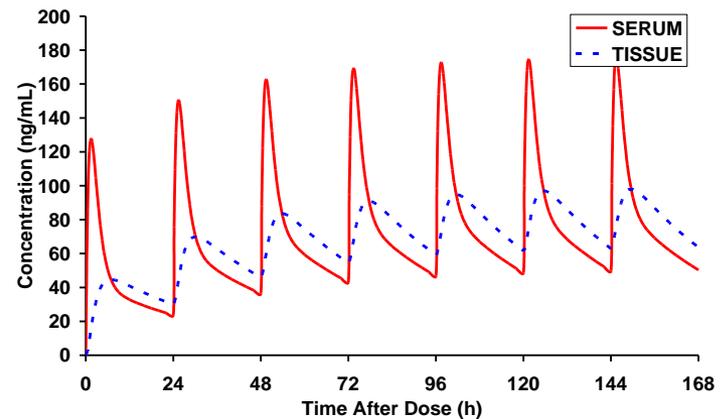
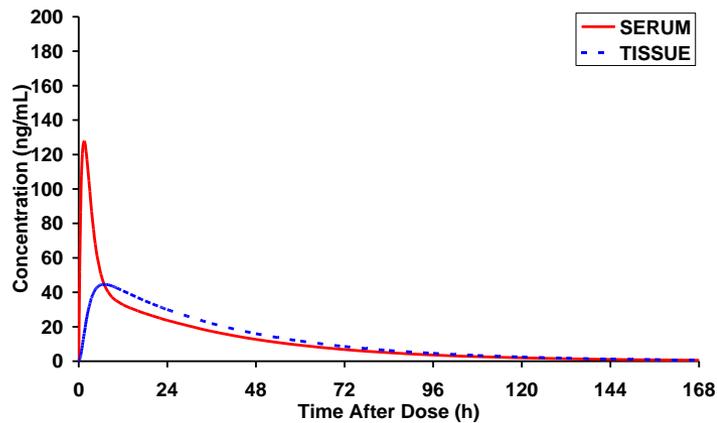
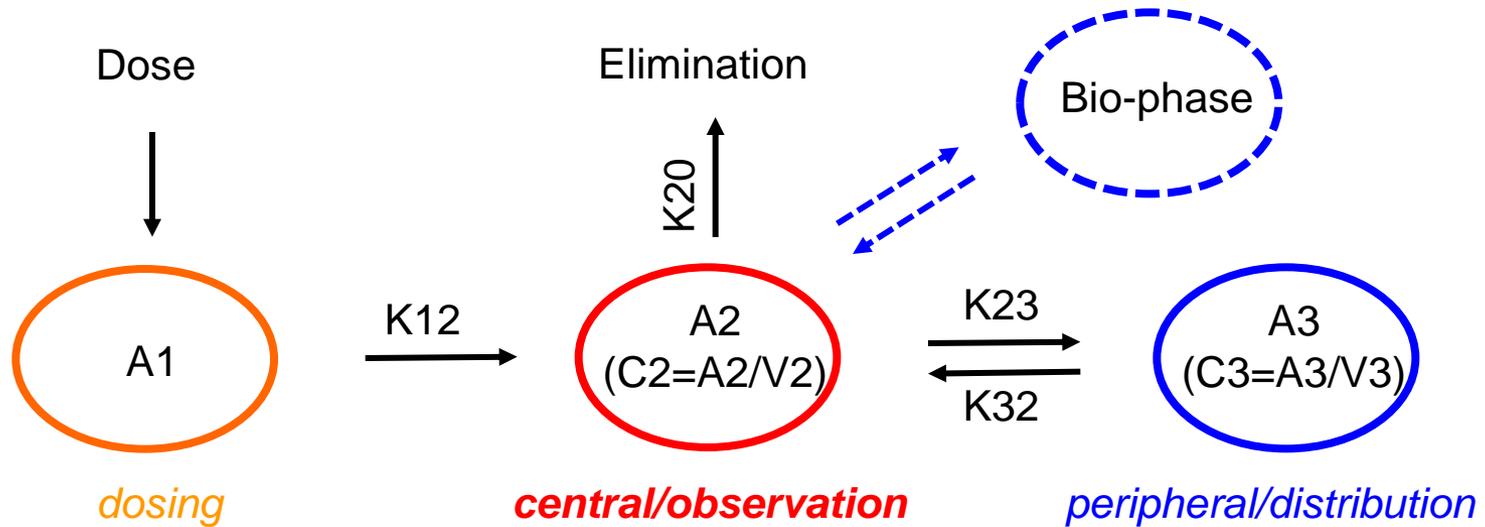
- “... new molecular entities approved by the FDA between 1980 and 1999. Of the 354 drugs that had evaluable information, **one in five had had a dosage change post approval**, with 20% of these resulting in an increase in dose and, importantly, 80% in a decrease.” – *Stanski, Rowland and Sheiner. JPP 2005.*
- Understanding the relationships among **exposure**, **response** and **time** (for a defined patient group under given conditions) is the basis for finding the optimal dose.

# dose to response: mechanism and variabilities



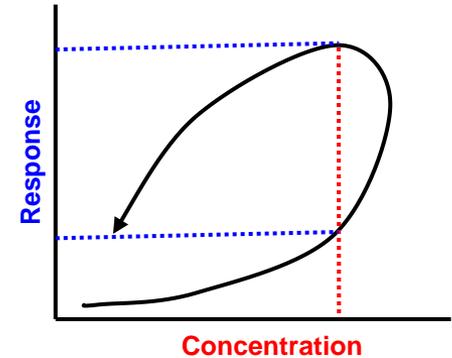
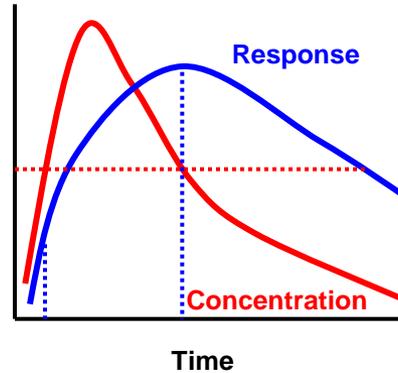
Modelling/simulation (interpret/forecast): quantify the links for selecting the optimal dose

# a simple linear PK model

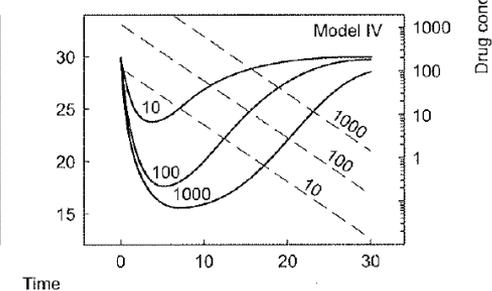
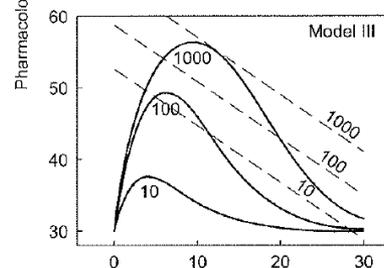
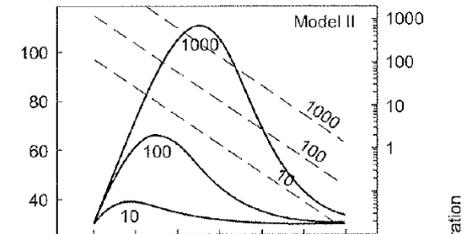
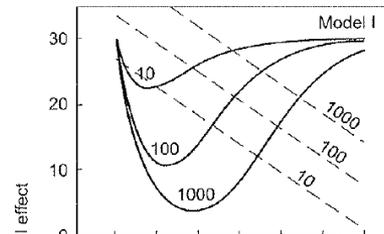
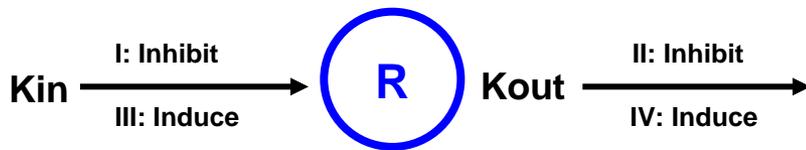


# accounting for PK-PD disconnect

- drug distribution to bio-phase
- active metabolite
- slow off-target rate
- irreversible target binding
- indirect response
- signal transduction
- time-variant: tolerance or sensitisation



Indirect response (response turnover):



Sharma & Jusko, 1998

# utility of modelling/simulation: an illustration

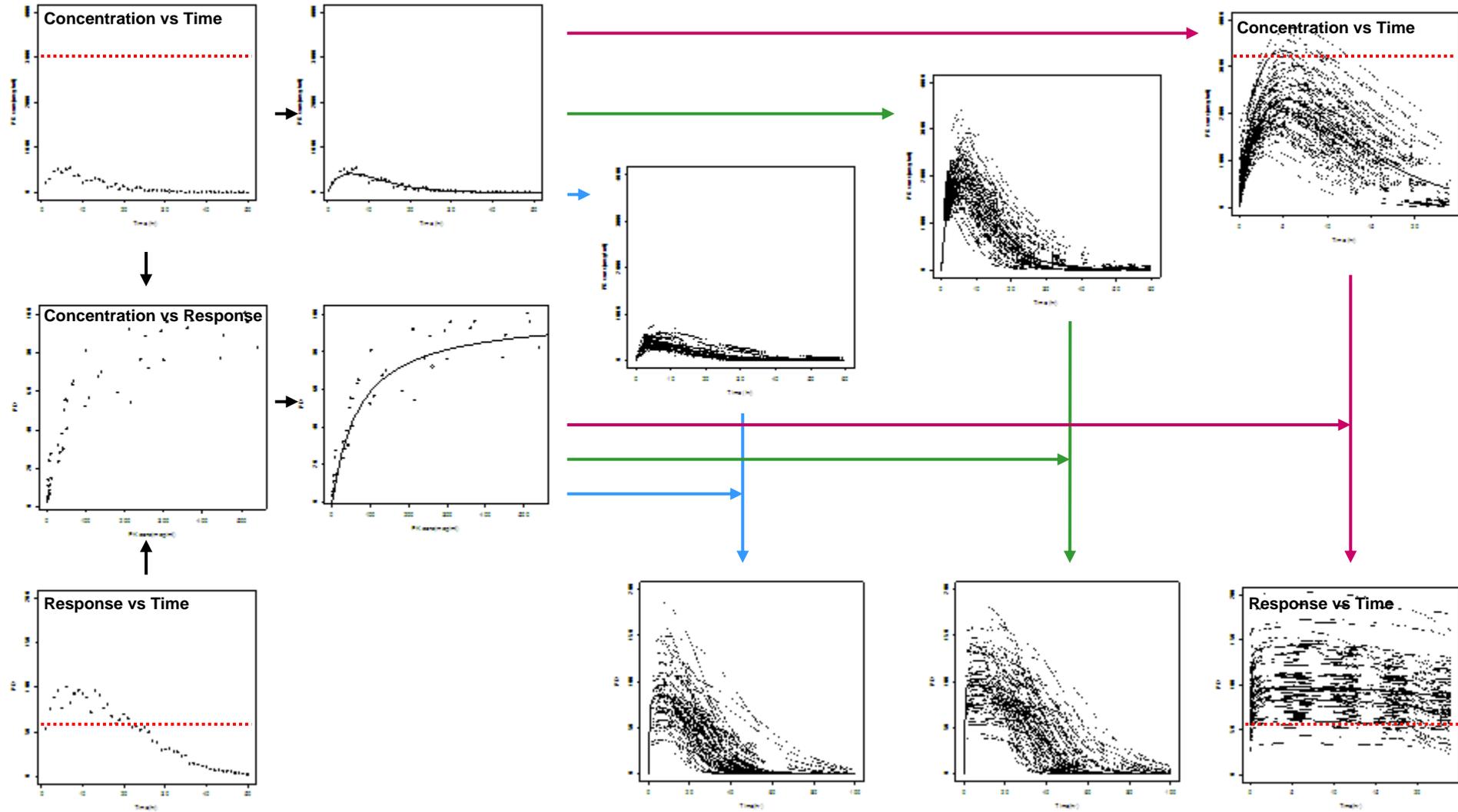
**Observation**

**Model**

**Simulation**

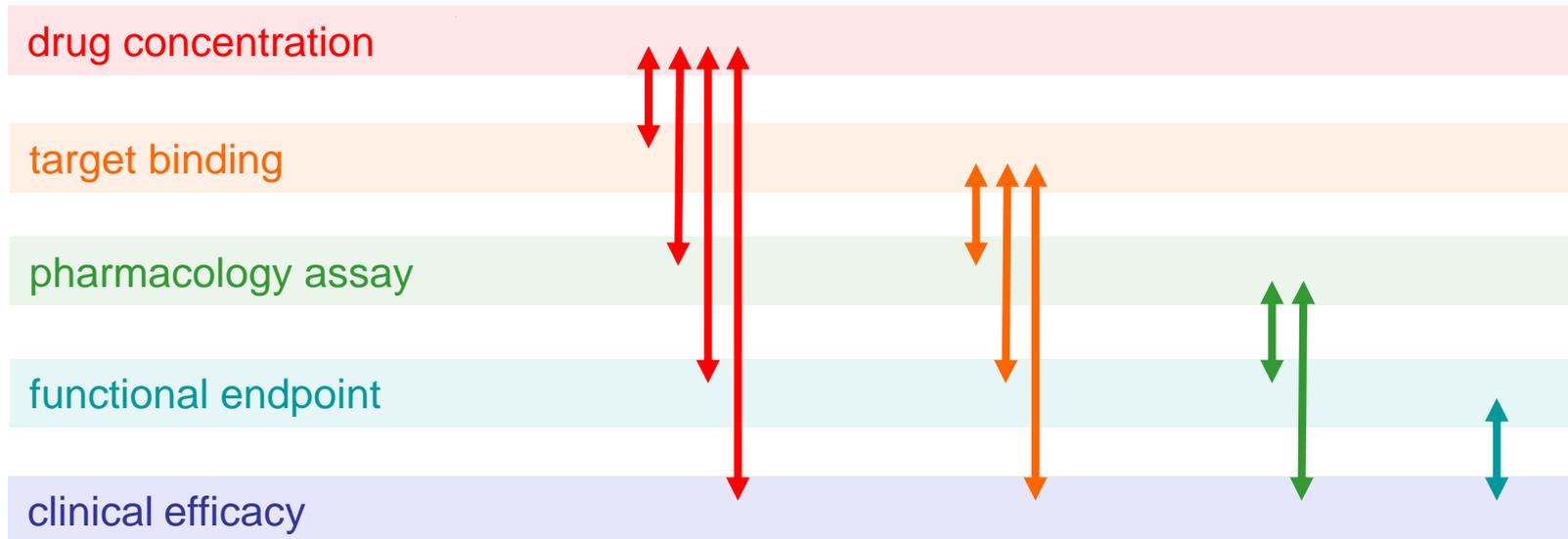
**Higher Dose**

**Chronic Dosing**



# applications of *in vivo* pharmacological modelling

- PK: drug concentration in circulation/biophase as a function of time
- PD: response as a function of drug concentration
- Correlation between response measures



# points to consider – preparation

- Select **meaningful endpoint**
  - mechanism-related? clinically relevant? regulatory acceptance?
  - response at a given point in time? rate of onset? change in disease progression?
- Ensure informative outcome by having **clear objective** and **quantifiable hypothesis**
  - adequate for designing trials with relevant effect size, sufficient power for detection, tolerable type I error, adequate estimation precision
- Use prior knowledge to build model with quantified uncertainty and variability, including **data from all sources**
  - **population**: healthy or patient? select a sub-population?
  - **placebo** module: baseline level? time course? circadian rhythm? intrinsic/extrinsic factors for baseline?
  - **drug** module: dose/concentration-response? tolerance/sensitization over time? intrinsic/extrinsic factors on PK and PD?
  - **adherence/dropout**: efficacy/tolerability-dependent?
- Clearly articulate all **assumptions** associated with all parts of the model

# points to consider - design

- Use the model to **simulate** alternative design/observation scenarios
  - patient types? inclusion criteria? sample size? dose levels and regimen? data collection frequency and timing?
  - adaptation criteria?
- **Analyse** simulated trial data
  - **integrate all data** cross times, treatments and populations to maximise precision
  - implement (reduced) structure and variance models, missing data imputation
  - adequate design and sufficient data to identify model structure and variance matrix for future use (e.g. within-subject inter-occasion variability for repeat-treatment design)
- **Summarise** outcome metrics for each scenario and measure against success criteria
  - power, type I error, estimation precision, feasibility, cost
- **Compare** performance of alternative design/observation scenarios to select informative and efficient design
- Write **detailed analysis plan** including assumptions, foreseeable adaptation and imputation methods

# points to consider - analysis

- **Explore** data pattern, stratified by covariates where applicable
  - verify assumptions, check missing values and look for unexpected
- **Analyse** observations
  - start from simple structure/variance model, check for delay and add theoretically or statistically justifiable internal/external covariates
- **Model evaluation**, stratified by covariates where applicable
  - consistency between observations and predictions
  - random distribution of (weighted) residual versus independent variables and model predictions
  - visual and numerical predictive check for structure and variance models by simulation
  - parameter estimation precision and correlation
- **Simulation** (real purpose)
  - monte carlo simulation to **quantify uncertainty**
  - make inference from current findings, by **interpolation/extrapolation**, and generate hypothesis for future

# pharmacological modelling & imaging

- **Broad applications** to provide morphological or functional insight:
  - understand baseline physiology and disease pathology
  - assess drug distribution to difficult-to-sample bio-phase
  - visualise drug-target engagement
  - quantify pharmacology at otherwise un-accessible sites
  - measure clinical response
- **Mechanistic models** are preferred over empirical ones
  - better reflection of physiology and drug mechanism
  - allow integration of pharmacodynamics and clinical endpoints
  - inform reliable **extrapolation** cross species
  - enable **bridging/comparison** between drugs of different mechanisms
- Imaging techniques are powerful tools for **dose selection**
  - “PET studies have shown a relationship between striatal D<sub>2</sub> receptor occupancy and clinical effect for most typical antipsychotic medications, with clinical efficacy occurring when at least 60% of striatal D<sub>2</sub> receptors are occupied, whereas extrapyramidal side effects occur at D<sub>2</sub> receptor occupancy above 80% [Lim et al, 2007]”
- **Multiple disease areas**: oncology, neurology, infection and inflammation

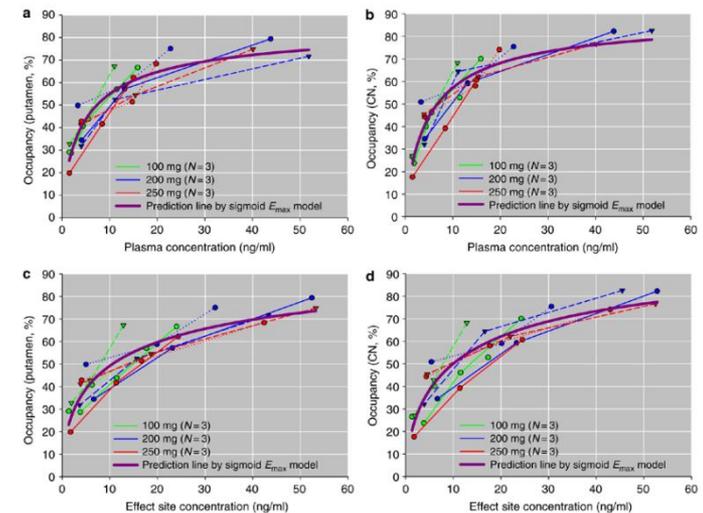
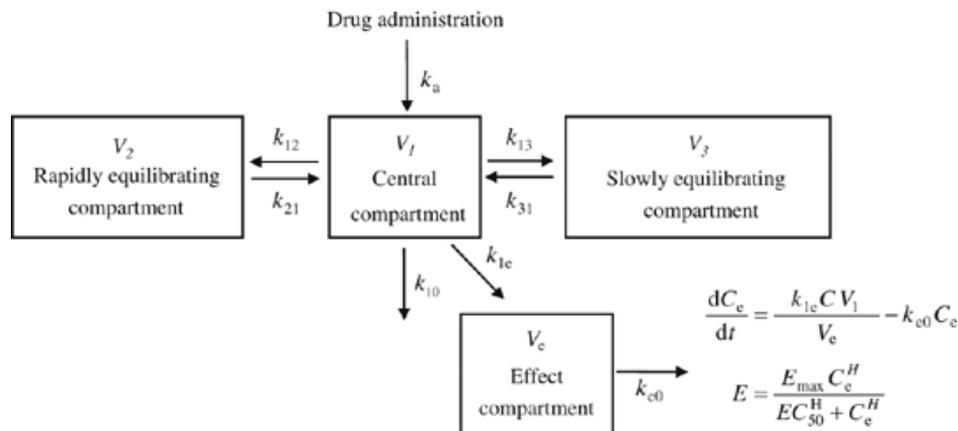
# limitations of modelling imaging endpoints

- Cost and logistics for using imaging endpoints
  - long lead time/high expenses to set up drug/target-specific assays
  - in-trial assessments can be time consuming
  - requires precious expertise/labs to conduct experiments
- Imprecision due to small number of subjects and sparse measurements
  - informative and flexible experimental **design** (adaptive-optimal design in PET occupancy study, *Zamuner et al 2010*)
  - **mixed-effect modelling** to maximise information content (*Lim et al 2007; Abanades et al 2010, Kim et al 2010*)
  - **longitudinal** model to integrate data (PET imaging of amyloid deposition in Alzheimer's disease; FDG-PET as indicator of tumor metabolism)
  - **meta-analysis** to combine data from multiple sources (*Abi-Dargham et al 1998*)
- Unclear clinical relevance and risk of false positive due to multiple endpoints
  - investigate relationships between clinical and pharmacological endpoints (fMRI vs PK/RO and clinical efficacy)
  - hypothesis-drive choice of **relevant endpoints** a priori; correction for multiple comparisons

# PET Occupancy Studies

# Modeling of Brain D2 Receptor Occupancy-Plasma Concentration Relationships with a Novel Antipsychotic, YKP1358, Using Serial PET Scans in Healthy Volunteers

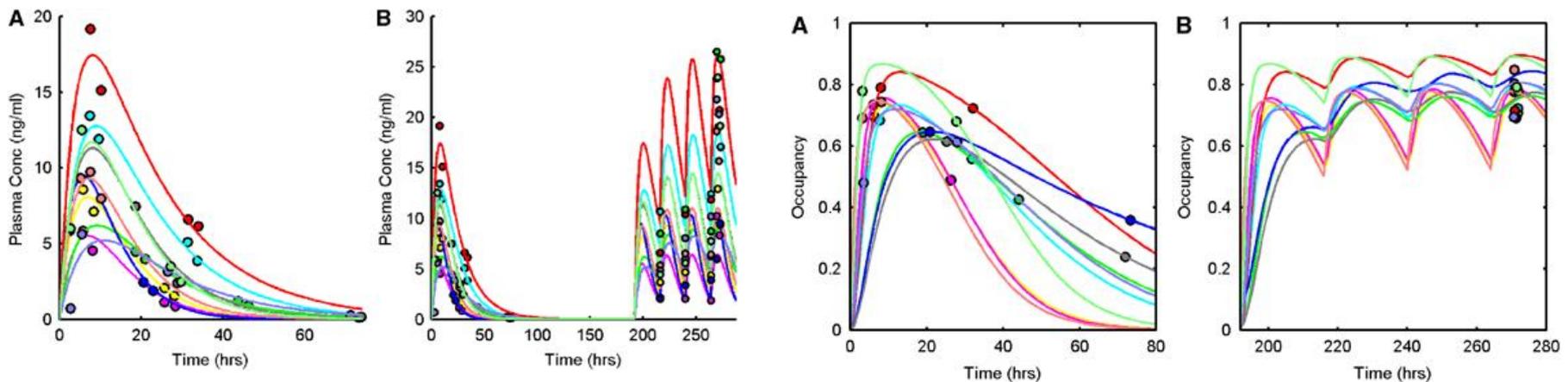
K S Lim, J S Kwon, I-J Jang, J M Jeong, J S Lee, H W Kim, W J Kang, J-R Kim, J-Y Cho, E Kim, S Y Yoo, S-G Shin and K-S Yu - **CPT 2007**



“To our knowledge, this is the first study in which the relationship between plasma concentration and the biomarker of D2 receptor occupancy was modeled using nonlinear mixed effects modeling. It is anticipated that these results will be useful in estimating for subsequent studies the initial doses of YKP1358 required to achieve a therapeutically effective range of D2 receptor occupancy.”

# Prediction of repeat-dose occupancy from single-dose data: characterisation of the relationship between plasma pharmacokinetics and brain target occupancy

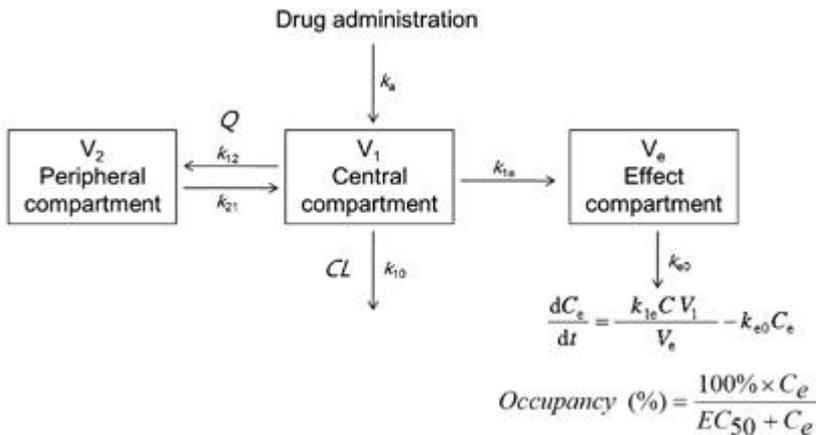
Sergio Abanades, Jasper van der Aart, Julien AR Barletta, Carmine Marzano, Graham E Searle, Cristian A Salinas, Javaad J Ahmad, Richard R Reiley, Sabina Pampols-Maso, Stefano Zamuner, Vincent J Cunningham, Eugenii A Rabiner, Marc A Laruelle and Roger N Gunn - **JCBFM 2011**



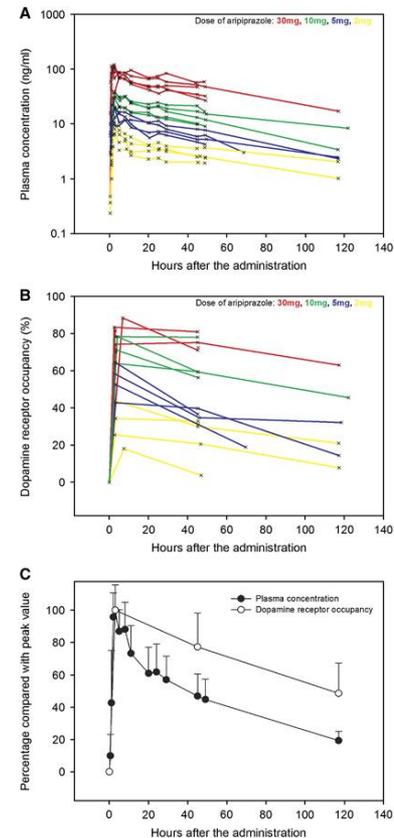
“Both direct and indirect PK/TO models were fitted to the SD data to characterise the model parameters and then applied to a predicted RD duloxetine plasma time course to predict the 5-HTT occupancy after RD”

# Predicting brain occupancy from plasma levels using PET: superiority of combining pharmacokinetics with pharmacodynamics while modeling the relationship

Euitae Kim, Oliver D Howes, Bo-Hyung Kim, Jae Min Jeong, Jae Sung Lee, In-Jin Jang, Sang-Goo Shin, Federico E Turkheimer, Shitij Kapur and Jun Soo Kwon - **JCBFM 2011**

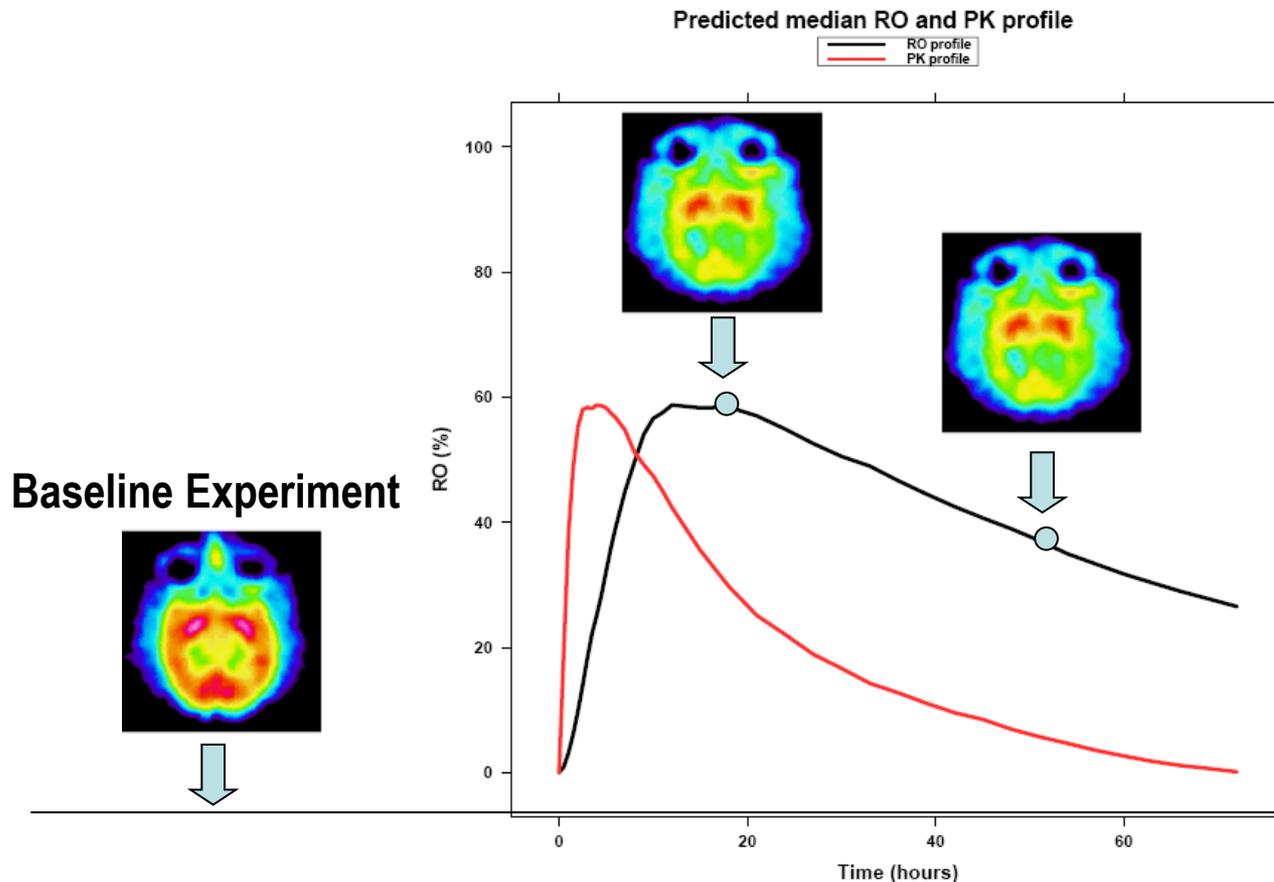


“Dopamine receptor occupancy after the administration of aripiprazole using [<sup>11</sup>C]raclopride PET and obtained serial measurements of the plasma aripiprazole concentration in 18 volunteers. We then developed a PK–PD model for the relationship, and compared it with conventional approach (PD modeling alone)”



# Why Study PK/RO over time?

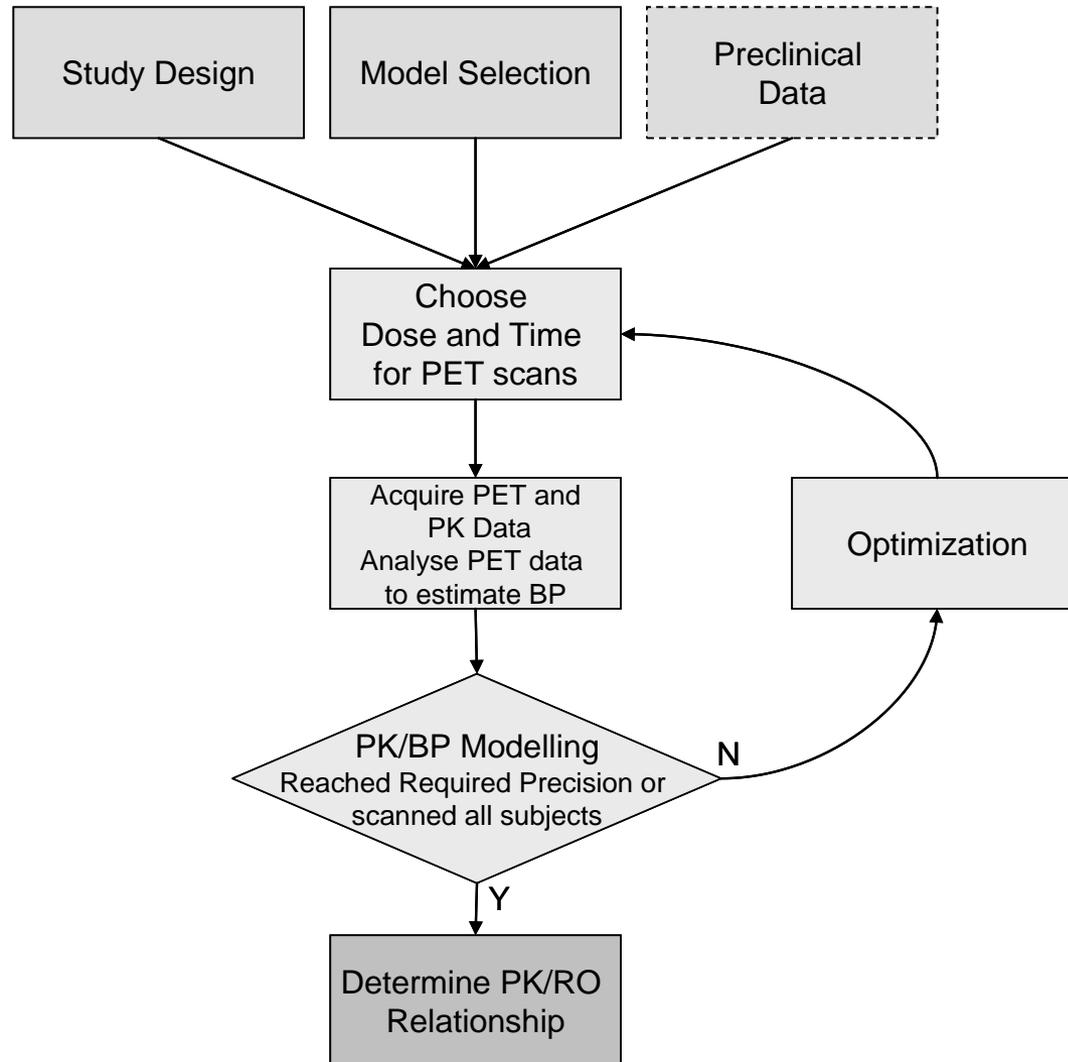
- Positron emission tomography (PET) is one of the most effective imaging in vivo techniques to estimate RO
- The assessment of the RO-time profile is critical to predict the time course of pharmacological response



# Experimental Design Issues in a PET study

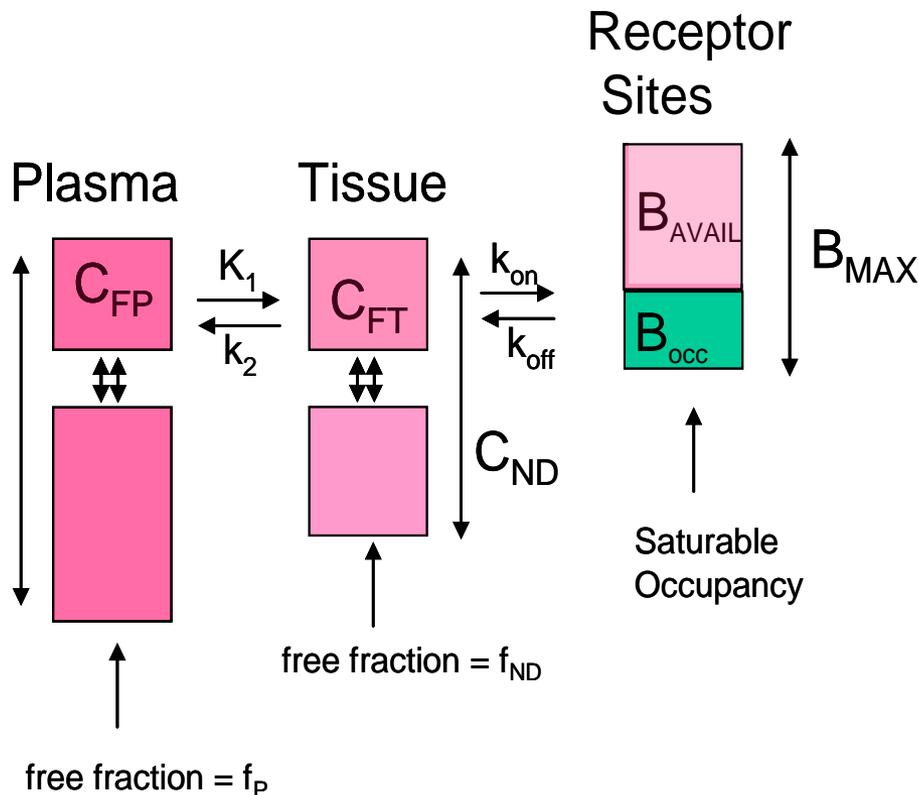
- Cost and ethical reasons limit the total number of subjects (usually  $n < 20$ ) and the number of PET scans per individual ( $\leq 3$  scans)
- **Uncertainty** in the structure of the mechanistic model relating RO and PK (Equilibration delay, Mechanistic delay, Tolerance)
- **Inter- and intra-subject variability** in PK and in drug-to-receptor binding resulting in an overall inflation in variability
- Need to estimate **typical exposure/RO link in a target patient population** (fraction of subjects achieving an 'effective' RO in a chronic treatment)
  - PET studies are typically conducted using a sequential adaptive design. The decision on sample size, dose and scan times for subsequent cohorts is derived from the analysis of previous data.
  - The selection of informative doses and scan times remain critical issues for a precise and accurate characterization of the PK-RO relationship.
  - The evaluation of PK-RO relationship is more crucial when there is no direct link between plasma and occupancy kinetics

# Adaptive-Optimal Algorithm



# Receptor-Time Course Model using Binding Potential Data

- In PET studies where only a few PET scans per subjects can be acquired a “full PK-occupancy time-course” model can not be applied and a simplified version needs to be considered
- In our simulation study, a kon-koff model using the binding potential data was considered.



$$RO = \frac{BP_0 - BP}{BP_0}$$

$$\frac{dBP}{dt} = k_{off} \cdot BP_0 - (C_P \cdot k_{on} + k_{off})BP$$

where  $BP_0$  is the baseline binding potential and  $BP$  that after dosing.  $C_P$  is the plasma concentration,  $k_{on}$  and  $k_{off}$  are the association and dissociation rates constants.

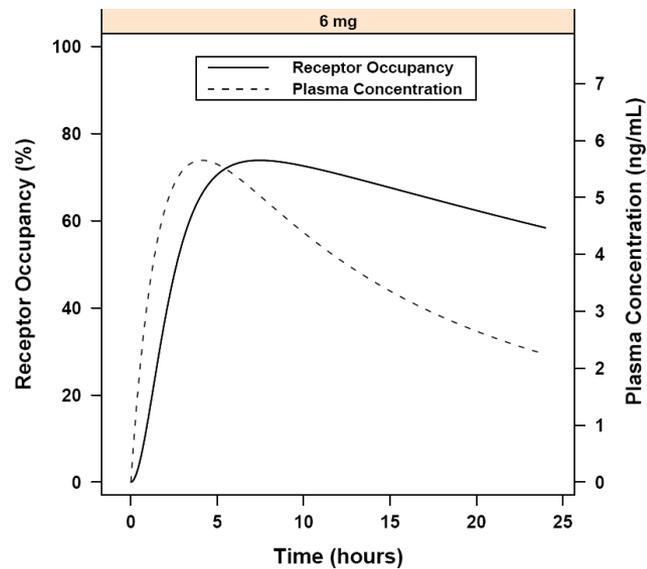
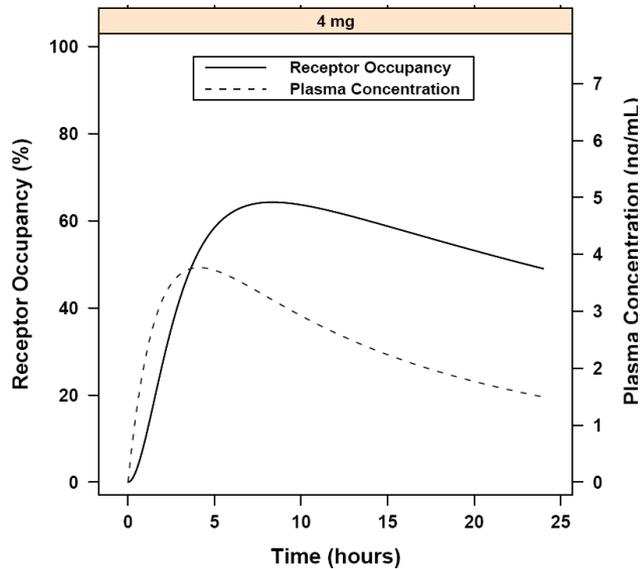
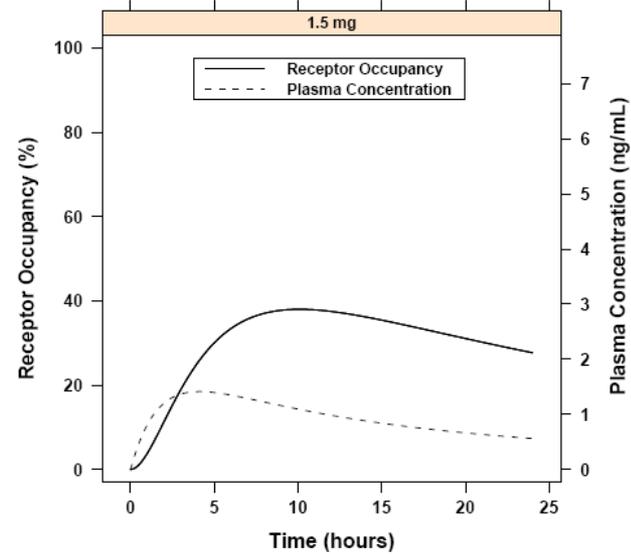
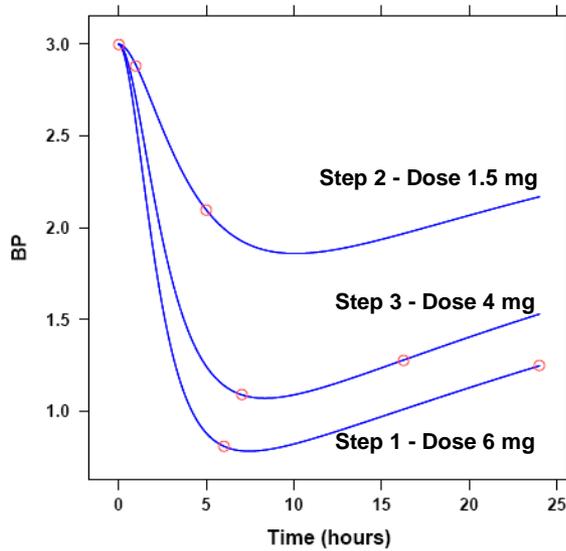
# Study Design

Doses and Sampling Times Selection for Fixed and Educated Designs

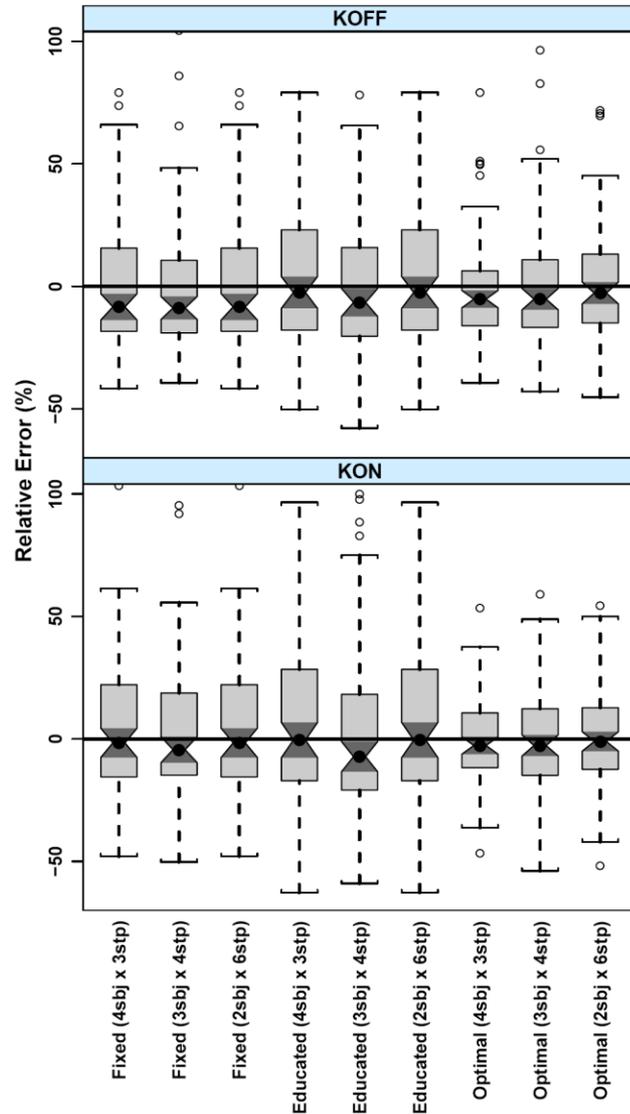
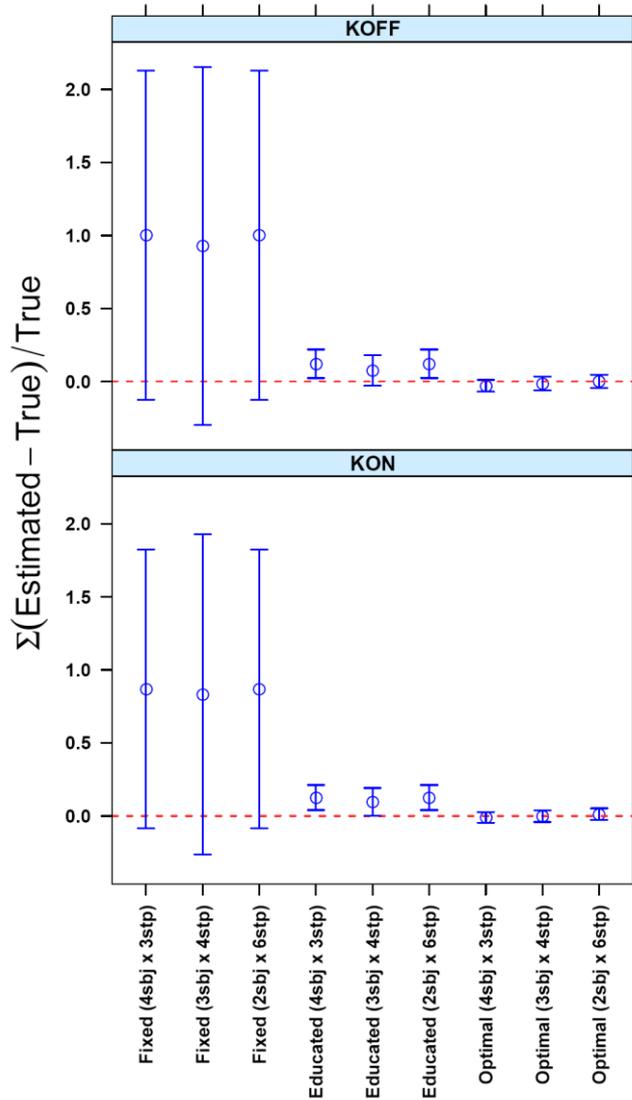
Case	Setup	Design	Method	Doses (mg)	Sampling times (hours)	
<b>1</b>	1	4 subj/3 group	Fixed	6, 1.5, 4	{0, 6, 24}; {0, 6, 24}; {0, 6, 24}	
	1	4 subj/3 group	Educated	6, 1.5, 4	{0, 6, 24}; {0, 3, 12}; {0, 8, 36}	
	Informative	2	3 subj/4 group	Fixed	6, 1.5, 4, 3	{0, 6, 24}; {0, 6, 24}; {0, 6, 24}; {0, 6, 24}
	Initial Dose	2	3 subj/4 group	Educated	6, 1.5, 4, 3	{0, 6, 24}; {0, 3, 12}; {0, 8, 36}; {0, 12, 48}
		3	2 subj/6 group	Fixed	6, 6, 1.5, 1.5, 4, 4	{0, 6, 24}; {0, 6, 24}; {0, 6, 24}; {0, 6, 24}; {0, 6, 24}; {0, 6, 24}
	3	2 subj/6 group	Educated	6, 6, 1.5, 1.5, 4, 4	{0, 6, 24}; {0, 6, 24}; {0, 3, 12}; {0, 3, 12}; {0, 8, 36}; {0, 8, 36}	
<b>2</b>	4	4 subj/3 group	Educated	0.5, 1.5, 6	{0, 6, 24}; {0, 3, 12}; {0, 8, 36}	
Non-Informative	5	3 subj/4 group	Educated	0.5, 1.5, 4, 6	{0, 6, 24}; {0, 3, 12}; {0, 8, 36}; {0, 12, 48}	
Initial dose	6	2 subj/6 group	Educated	0.5, 6, 1.5, 3, 4, 8	{0, 6, 24}; {0, 6, 24}; {0, 3, 12}; {0, 3, 12}; {0, 8, 36}; {0, 8, 36}	

Performance evaluated as bias (SME), accuracy (RMSE) and precision (CV)

# Adaptive-Optimal Selection - Example



# Performance of Design



**Doses: 1.5, 4 and 6 mg**

**Fixed:**

Sample Time: 6, 24 hrs

**Educated:**

Sample Time:

Step 1: 6, 24 hrs

Step 2: 3, 12 hrs

Step 3: 8, 36 hrs

Step 4: 12, 48 hrs

# Bioactivity Studies – PET FDG/MRI/fMRI

# <sup>18</sup>FDG-Positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec®)

S. Stroobants, J. Goeminne, M. Seegers, S. Dimitrijevic, P. Dupont, J. Nuyts, M. Martens, B. van den Borne, P. Cole, R. Sciot, H. Dumez, S. Silberman, L. Mortelmans, A. van Oosterom = **European J of Cancer 2003**

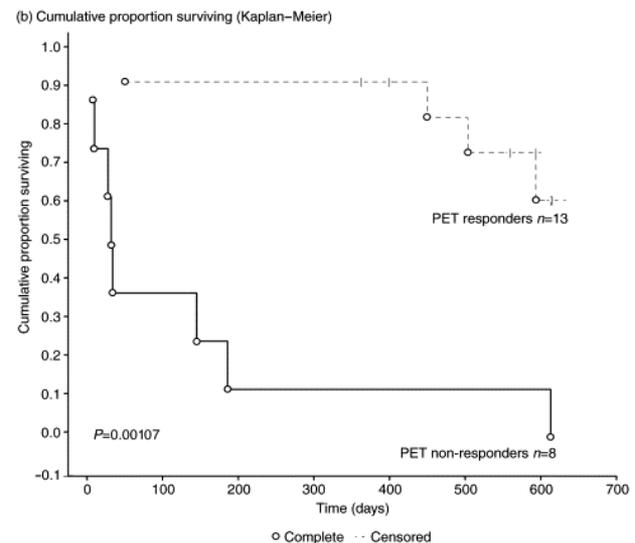
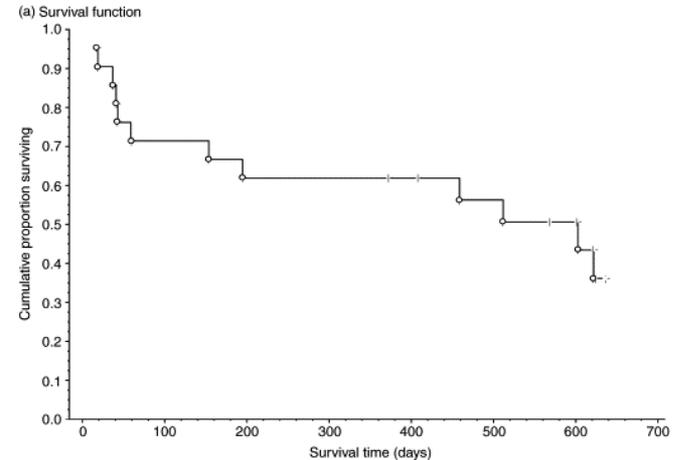
“FDG-PET is to separate – as early as possible – responders from non-responders in patient undergoing therapeutic intervention”

Table 1

PET response defined according to the EORTC PET recommendations [15]

CR	FDG uptake in all lesions comparable to background activity
PR	> 25% decrease of SUV in all target lesions
SD	Changes in SUV of less than 25%
PD	> 25% increase of SUV in at least one target lesion or the appearance of new lesions (regardless of the SUV changes in the target lesions)

EORTC, European Organization for Research and Treatment of Cancer; PET, positron emission tomography; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SUV, standardised uptake value.



# Dynamic Contrast-Enhanced Magnetic Resonance Imaging As a Biomarker for the Pharmacological Response of PTK787/ZK 222584, an Inhibitor of the Vascular Endothelial Growth Factor Receptor Tyrosine Kinases, in Patients With Advanced Colorectal Cancer and Liver Metastases: Results From Two Phase I Studies

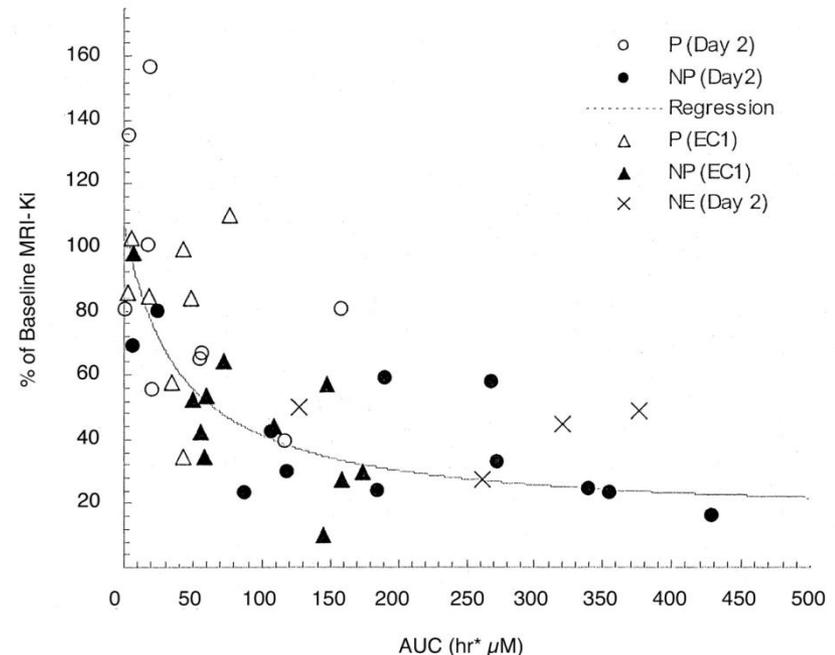
B Morgan, AL Thomas, J Drevs, J Hennig, M Buchert, A Jivan, MA Horsfield, K Mross, HA Ball, L Lee, W Mietlowski, S Fuxius, C Unger, K O'Byrne, A Henry, GR Cherryman, D Laurent, M Dugan, D Marmé and WP Steward – ASCO 2003

To describe the relationship between % of baseline Ki and exposure (AUC) in mathematical terms, pharmacodynamic modeling was performed by fitting the data to an inhibitory maximum effect ( $E_{max}$ ) model:

$$Effect = E_0 - (E_0 - E_{max}) \times \left( \frac{AUC}{AUC + EAUC^{50}} \right)$$

where:

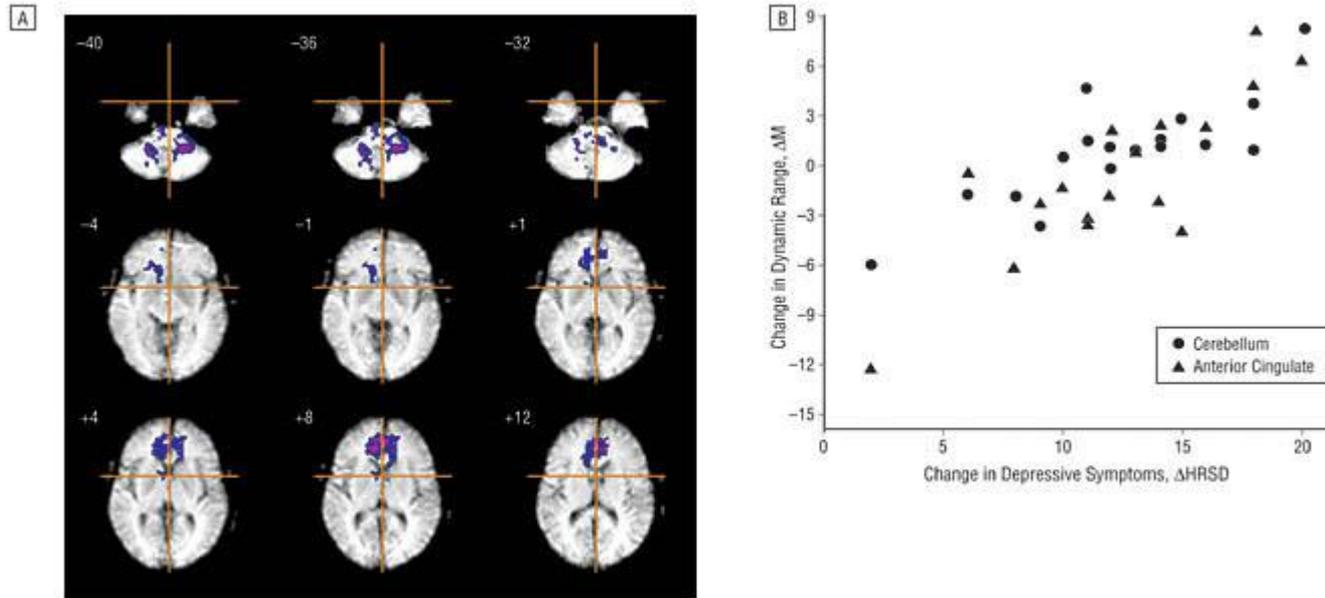
- Effect = % of baseline Ki
- $E_0$  = Approximated baseline (~100%), expressed as % of baseline Ki
- $EAUC^{50}$  = AUC in which 50% of  $E_{max}$  is achieved
- $E_{max}$  = Maximum effect, expressed as % of baseline Ki



# Attenuation of the Neural Response to Sad Faces in Major Depression by Antidepressant Treatment A Prospective, Event-Related Functional Magnetic Resonance Imaging Study

CY Fu, SCR Williams, AJ Cleare, MJ Brammer, ND Walsh, J Kim, CM Andrew; EM Pich, PM Williams, LJ Reed, MT Mitterschiffthaler, Jsuckling, ET Bullmore, *Arch Gen Psychiatry*. 2004

## Brain correlates of symptomatic response



“Scatterplot of data from depressed subjects only illustrates that reduction in depressive symptoms over time (Hamilton Rating Scale for Depression [HRSD] score at baseline minus HRSD score at 8 weeks;  $\Delta$ HRSD) is associated with reduction in dynamic range of sad facial affect processing (baseline minus 8 weeks;  $\Delta$ M) in the cingulate and cerebellar regions of interest.”