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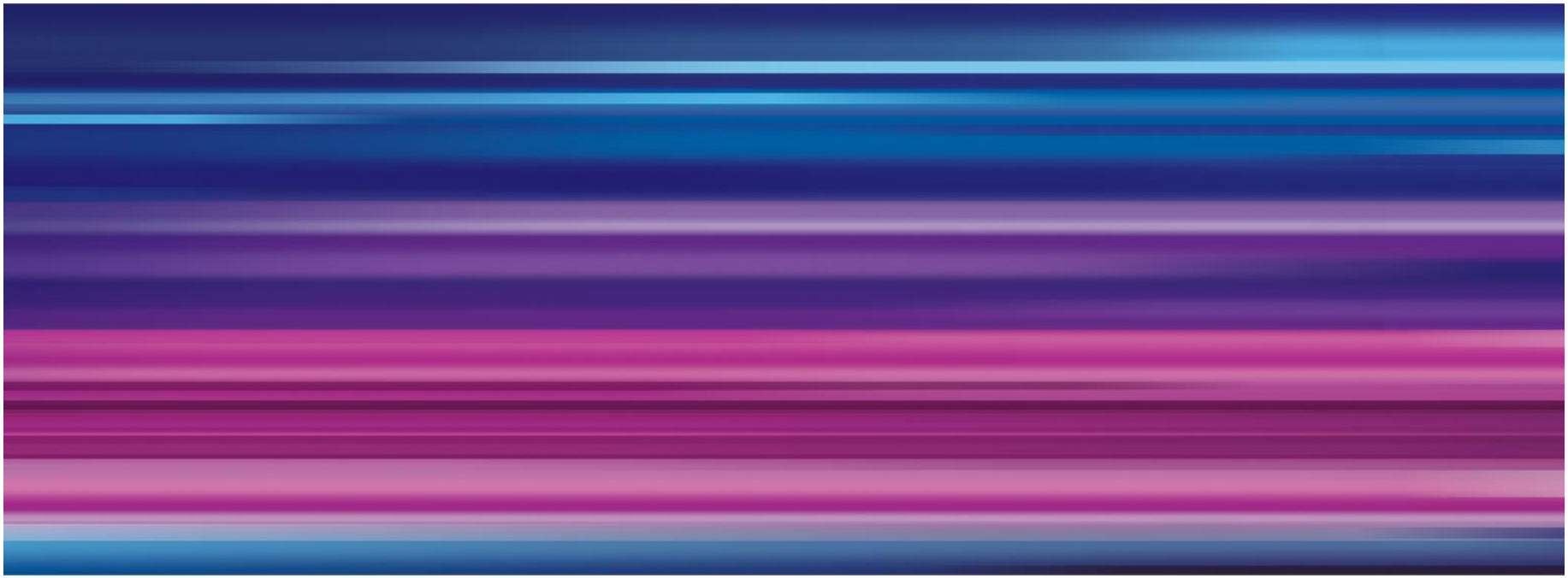
Imaging in Drug Development



The Drug Response Pathway

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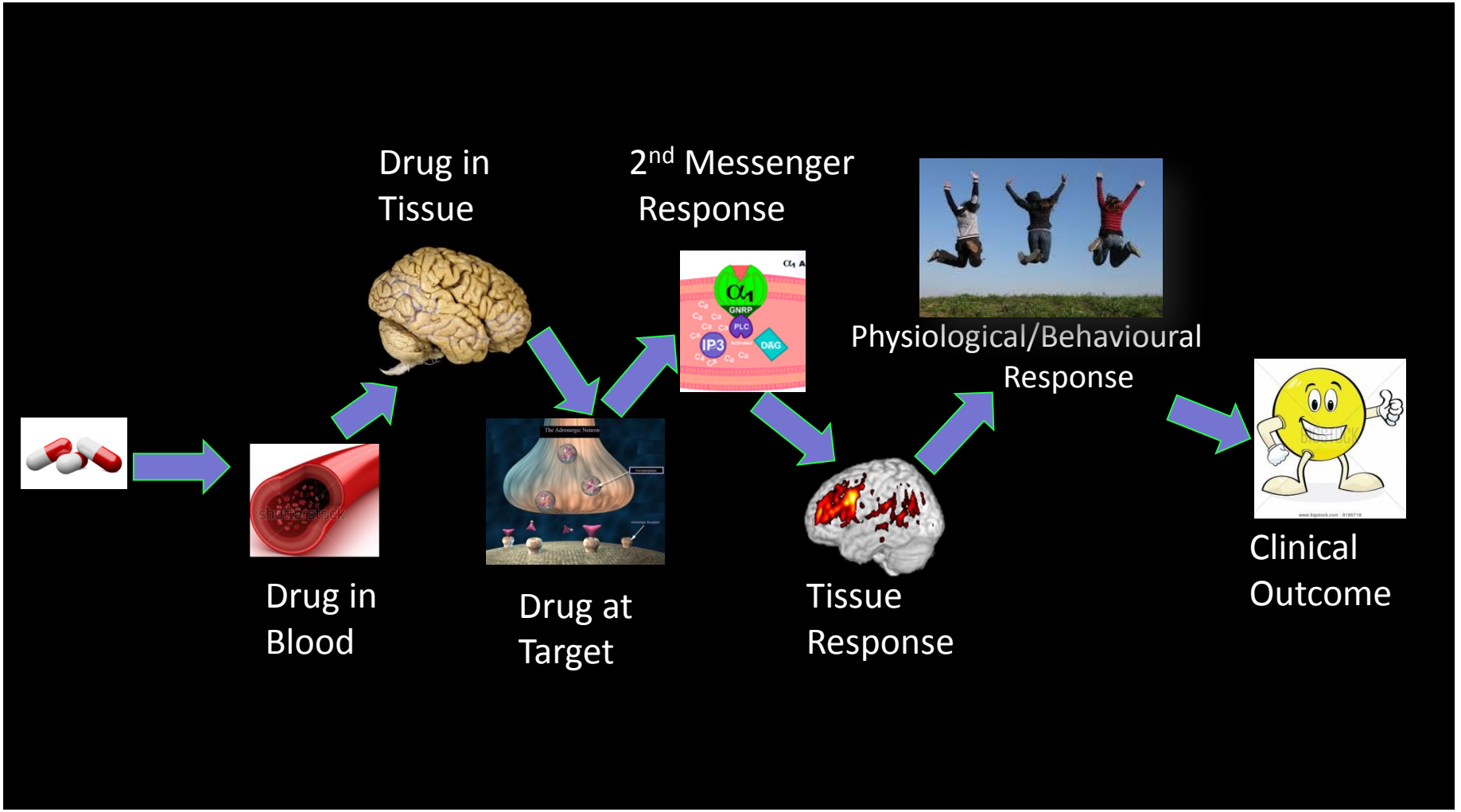

The Drug Response Pathway

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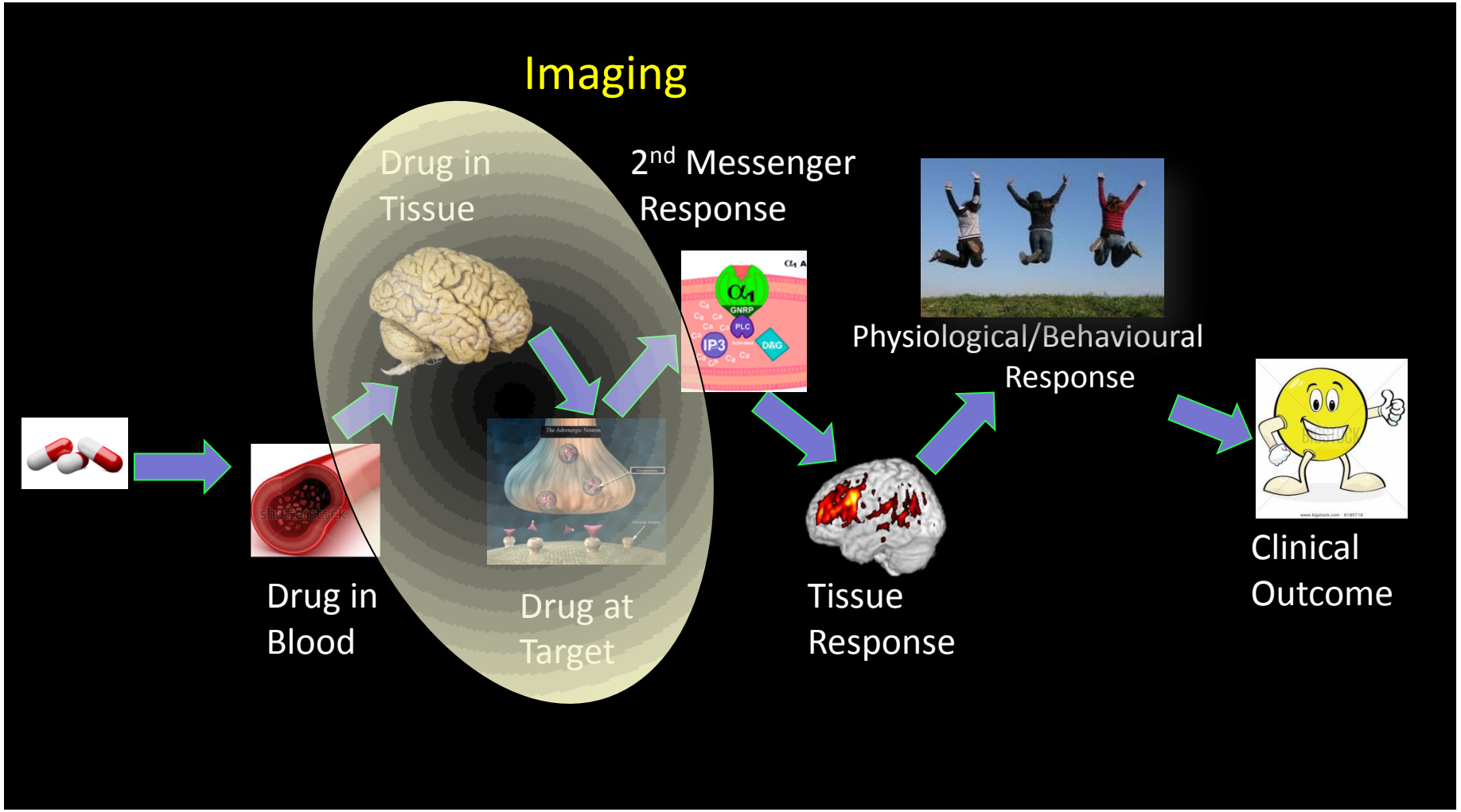

Quantifying drug-target engagement to refine the dose range

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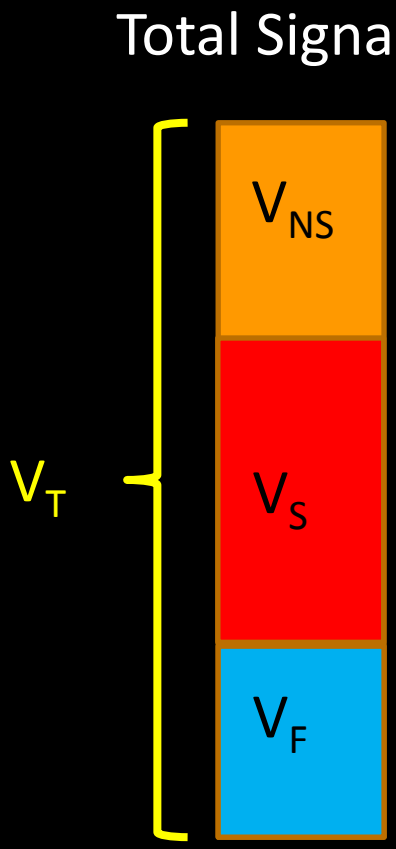
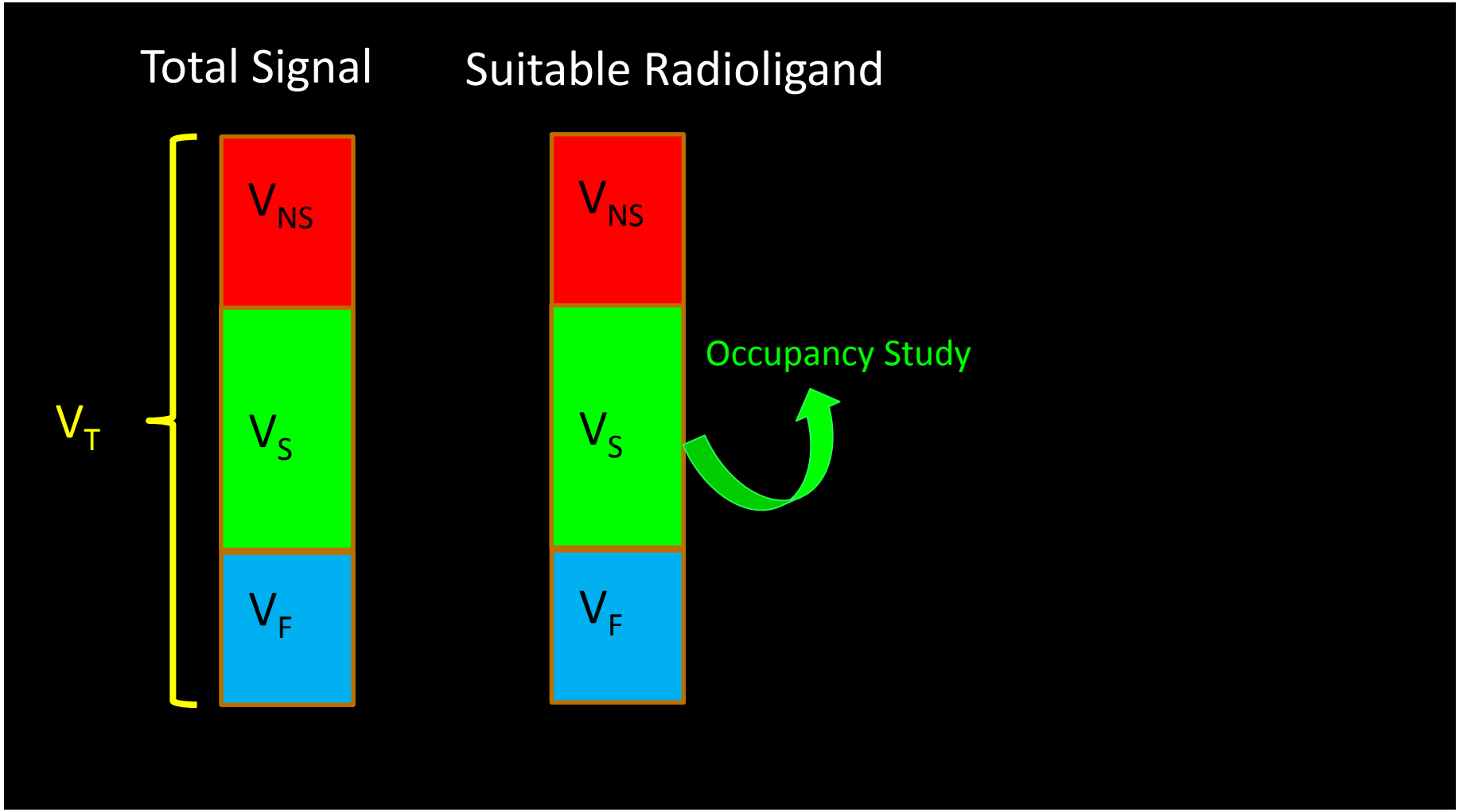
Imaging The Drug - Biodistribution	Imaging The Target - Occupancy
➢ Measures brain uptake of the radiolabelled drug candidate	➢ Measures the change in target availability post drug administration
➢ Provides a measure of "free" drug concentration (V_F)	➢ Provides direct measure of target occupancy by the drug (ΔV_S)
➢ Requires radiolabelling of the drug candidate with a positron emitting nucleide - often feasible	➢ Requires a usable radioligand – often unavailable

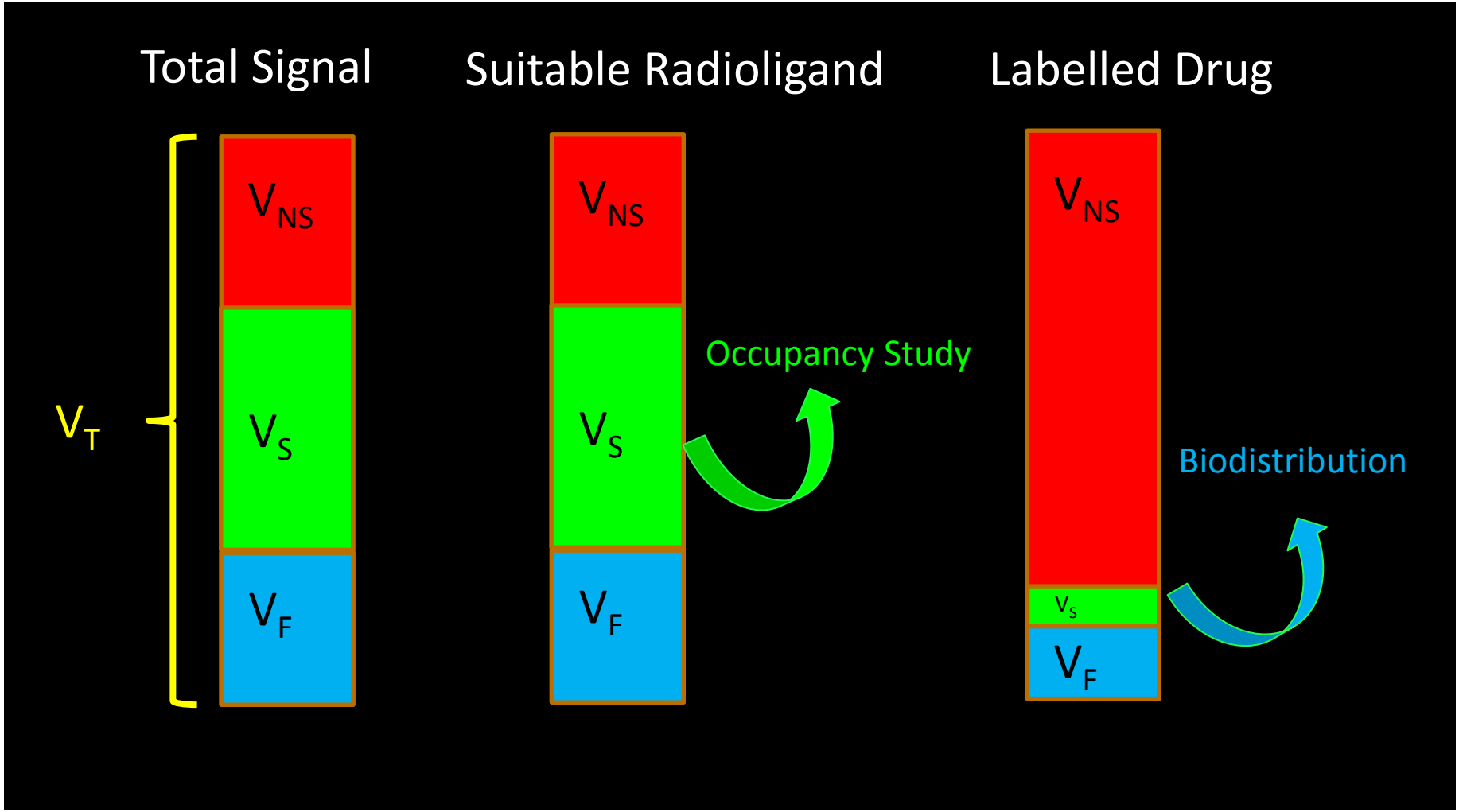
Quantification of Radiotracer Binding



Quantification of Radiotracer Binding



Quantification of Radiotracer Binding



Brain Penetration

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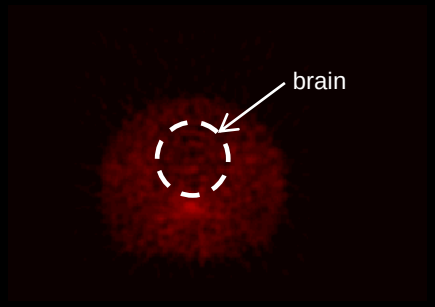
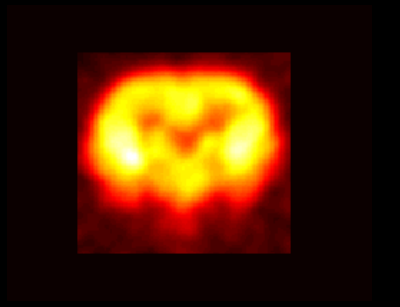
A

- Brain penetration – candidate selection
- [Free Drug] brain – single dose-occupancy prediction

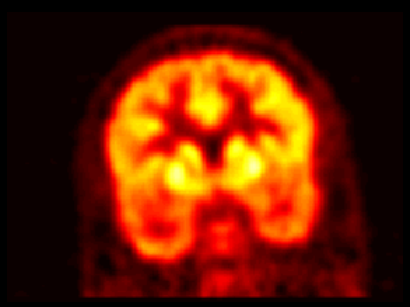
Rat



Pig



Human



Species variability in CNS penetration

Better predictive value of higher species for human BBB penetration

Characterisation of BBB Transport

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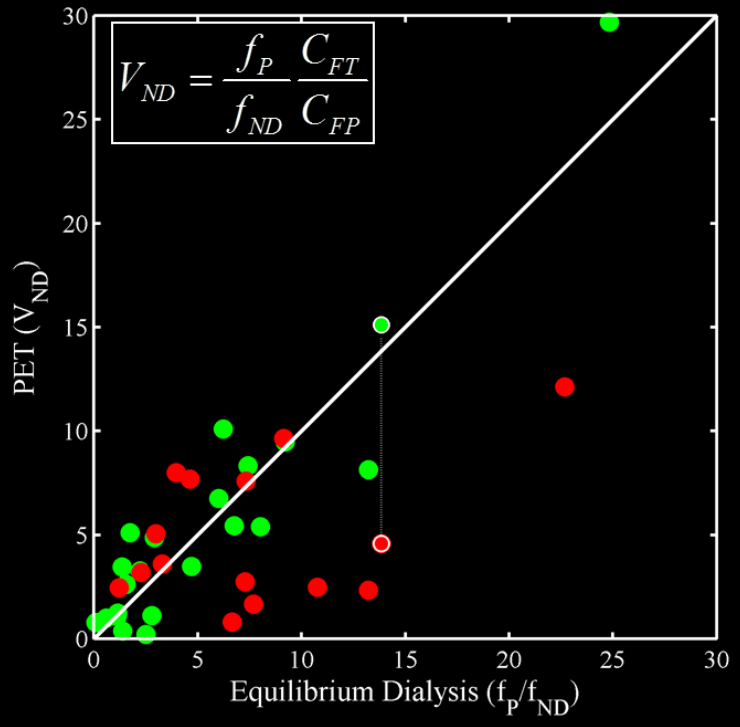
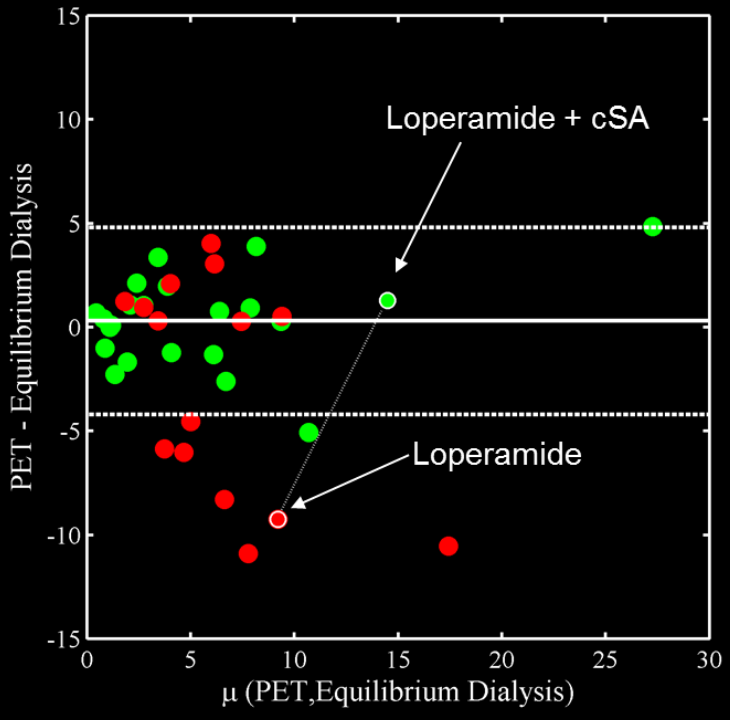
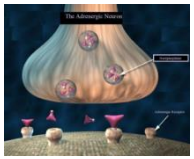
A

- Brain penetration – candidate selection
- [Free Drug] brain – single dose-occupancy prediction







Label the target: Drug occupancy

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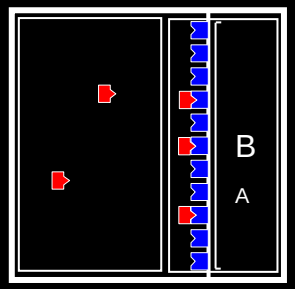
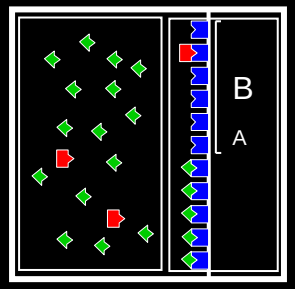
B

- Time-occupancy relationship - single dose-occupancy measurement
- repeat dose-occupancy prediction

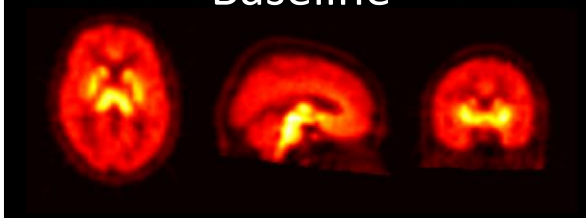
Abanades, JCBFM 2011; Salinas, JCBFM 2013



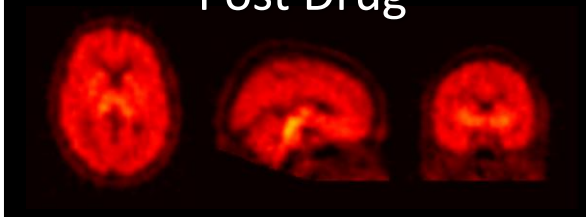
Radioligand
Drug
Target

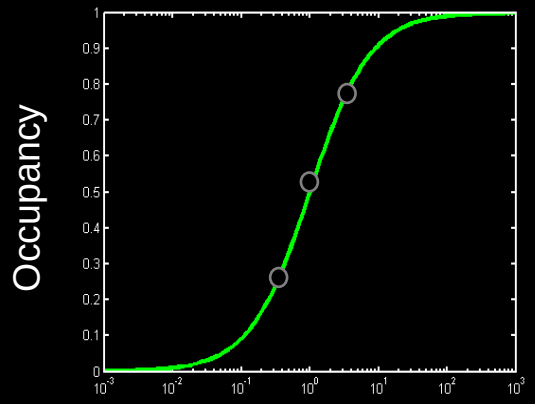


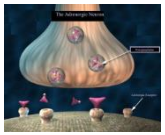
Baseline



Post Drug







Quantification of Target Engagement

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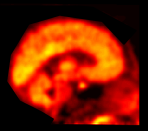
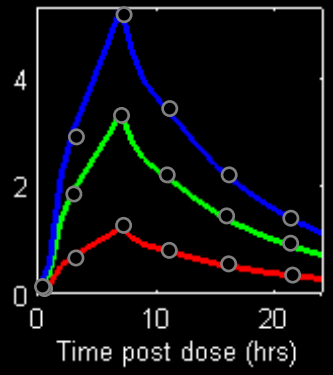
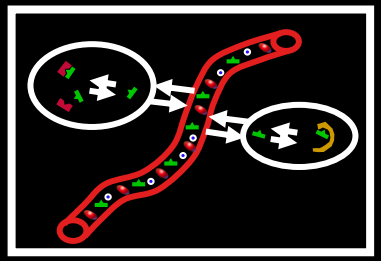
- Time-occupancy relationship - single dose-occupancy measurement
- repeat dose-occupancy prediction



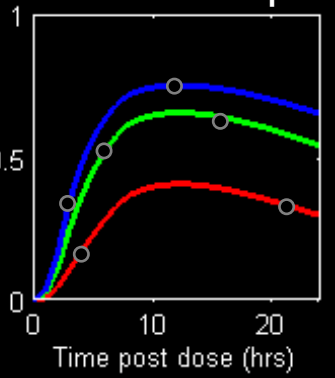
Plasma PK



PK/RO Model



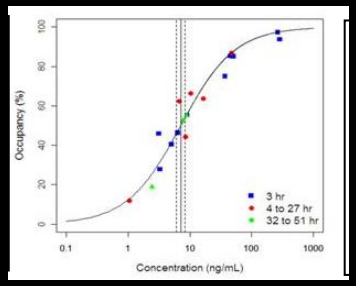
PET Occupancy



Model I: "Direct"

C_p - EC_{50} Model

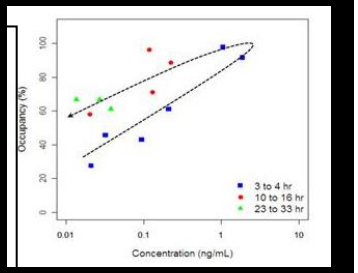
$$TOC(t) = \frac{C_P(t)}{C_P(t) + EC_{50}}$$

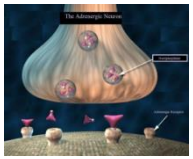


Model II: "Indirect"

k_{on} - k_{off} Limited Model

$$\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO$$





Quantification of Target Engagement – Study Design

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B

- Time-occupancy relationship - single dose-occupancy measurement
- repeat dose-occupancy prediction

Abanades, JCBFM 2011; Salinas, JCBFM 2013

- Repeat dose occupancy
  - Closer to the clinical situation
  - Cannot be performed early in the development cycle
  - May obtain biased results due to changes in baseline target number
- Single dose occupancy
  - Maximum impact - can be performed parallel with FTIH safety study
  - Time-dose-occupancy estimation - definition of pharmacokinetic model
  - Combined with repeat-dose plasma pharmacokinetics allows prediction of repeat dose occupancy
- Healthy volunteers vs patients
  - Same “free” drug concentration, Same target structure = No Difference