Essential Translational Pharmacology

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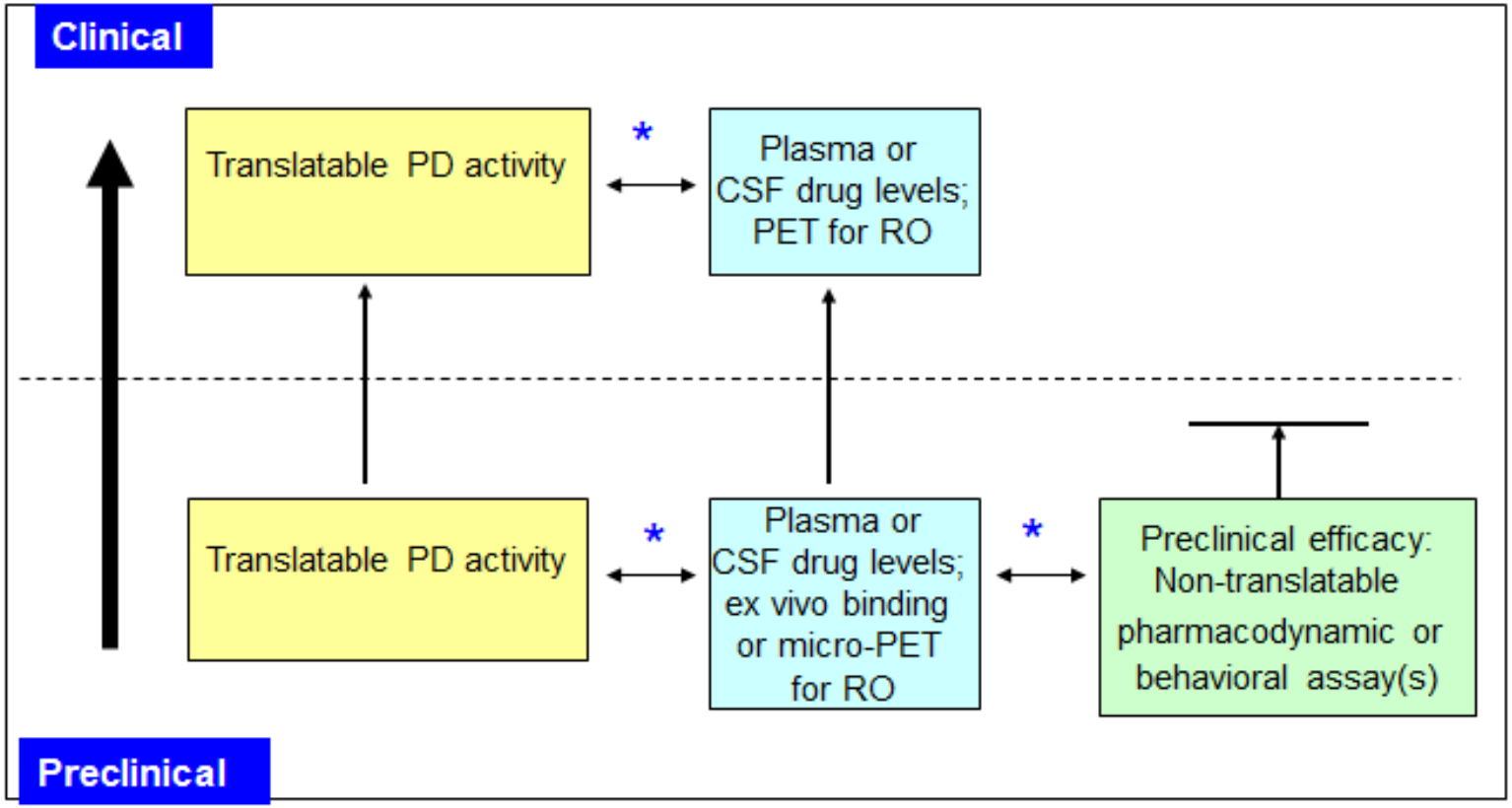
Potential Conflicts of Interests

- I am an employee of AbbVie Inc.
- I am on the scientific board of Embera Neurotherapeutics.
- I am a stockholder in Pfizer Inc.

Why Do Translational Pharmacology?

- Assure that drug candidate is capable of testing the drug efficacy hypothesis
- Increase likelihood of successful proof-of-concept (Morgan, 2012)

Translational Pharmnacology Model

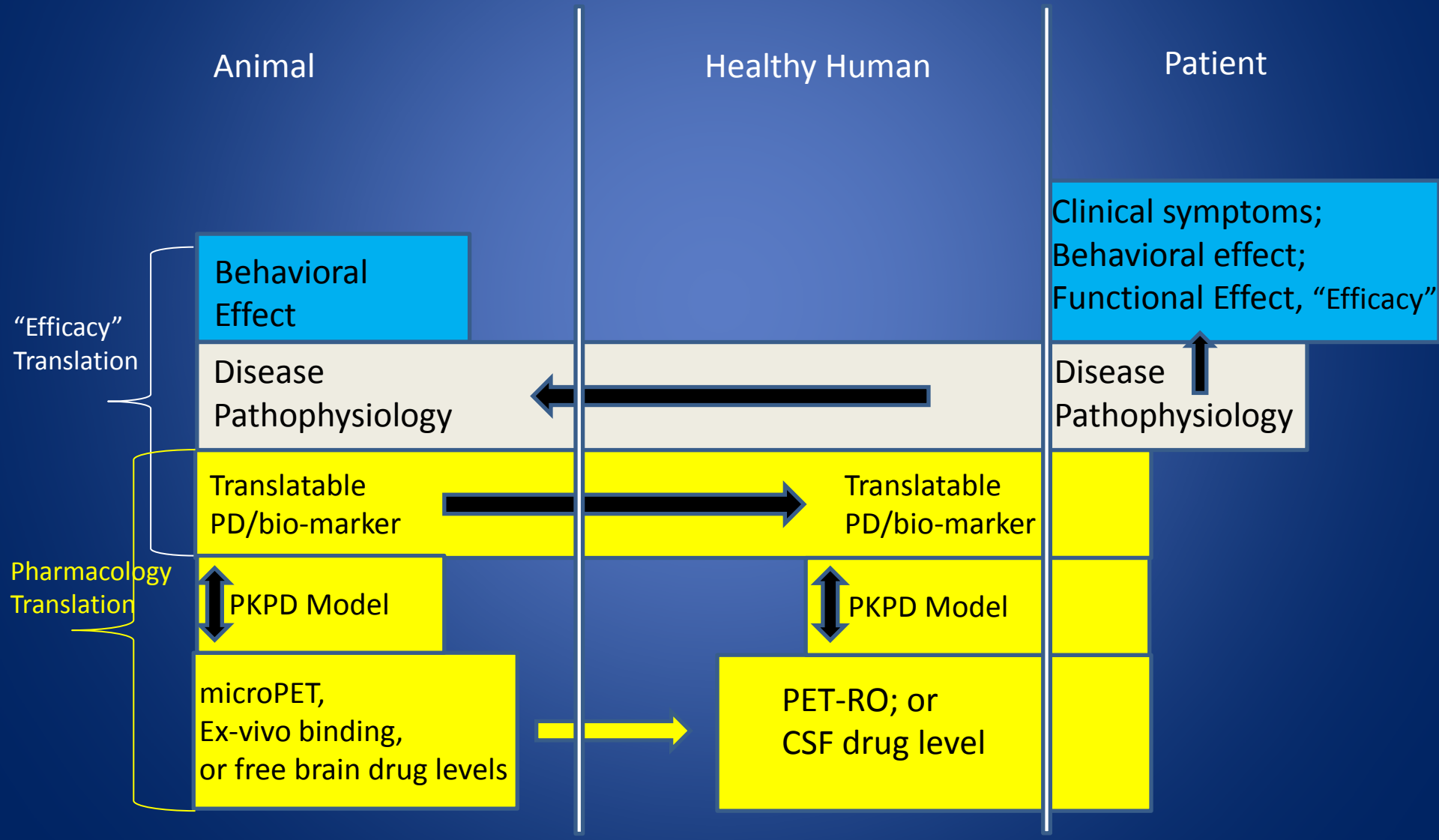


* Establish exposure-related response.

Examples

Mechanism	Preclinical Quantitation associated with "efficacy"	Clinical Decision Criteria	Comments
D1 agonist			
Occupancy/ Exposure	Brain ECF drug level > 200 ng/ml	CSF drug level > 200ng/ml; (LL 90% CI)	Not closely linked to target.
PD Marker	Increased FDG-PET signal in PFC in NHP and 2DG in rat at > 200 ng/ml	Increased FDG-PET signal in human PFC at > 350 ng/ml.	Provides regional localization; not closely linked to target
GLYT1 RUI			
Occupancy/ Exposure	>60% target occupancy	>60% target occupancy via human PET	Closely linked to target.
PD Marker	CSF glycine levels increase at >60% occupancy	CSF glycine levels increase at >60% target occupancy	Where is CSF glycine coming from (spinal cord?)

Translational Pharmacology Bridge Supports "Efficacy" Translation



Caveats and Complexities

- Preclinical data on required target exposure/occupancy may be inconsistent
  - Less certainty in quantitative translation
- “Inverted U” dose response curves may be invoked
  - Careful review of data and discussion
- Off-target pharmacology may impact biomarker/PD marker responses
- Manner of use of drug in humans may complicate translation
  - Chronic use of agonists; adjunctive use and interaction on PD effects
- Occupancy/exposure required in an animal model may differ from that required in human disease
  - Quantitative translation sets a minimum;
  - Look for consistency in the exposure/occupancy and biomarker/PD data
  - Work with precedented mechanisms (human data are most useful)