The utility of biomarkers in CNS drug development

Professor Alan M. Palmer

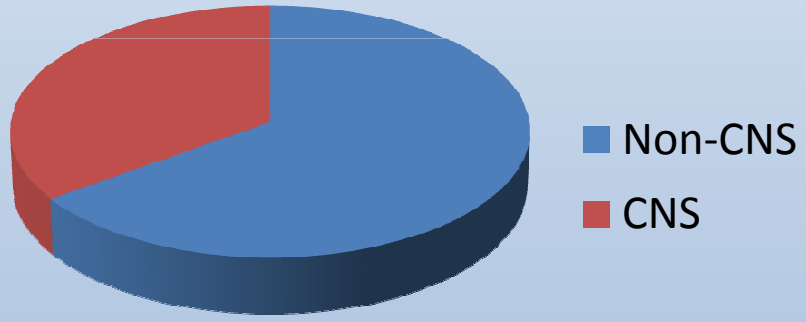
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alan.palmer@Cerebroscience.com

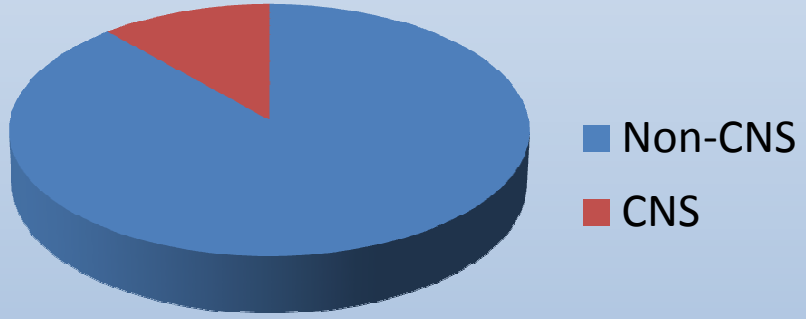
Nov 2009

Global burden of CNS disorders and CNS medicines research

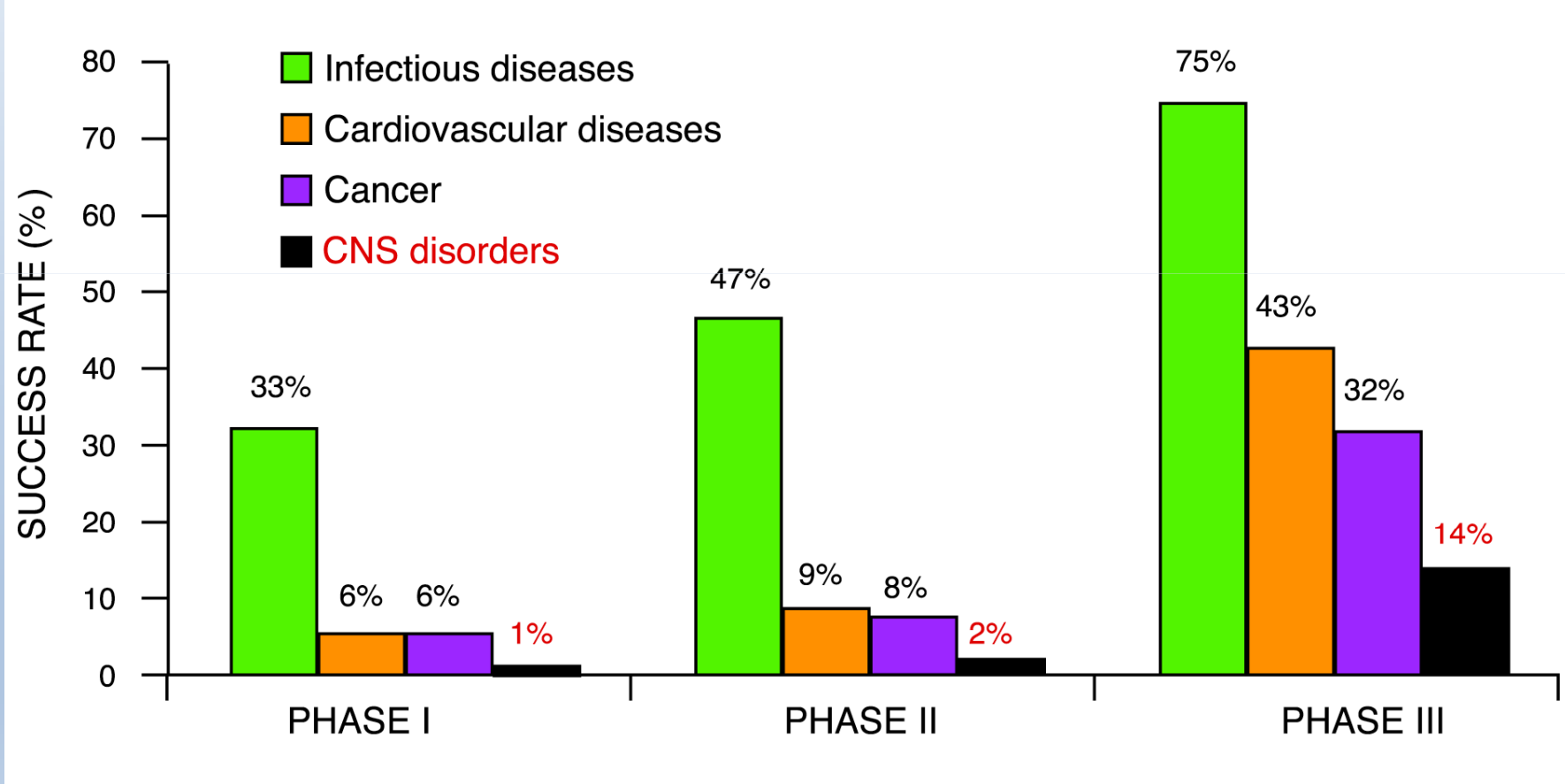
Global disease burden



Proportion of drugs and drug candidates



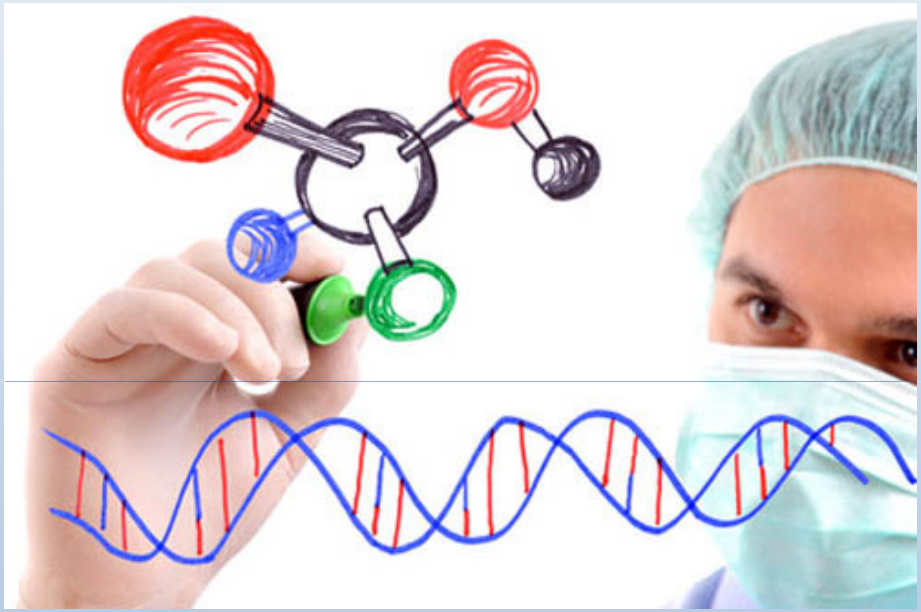
Cumulative success rates to market by therapeutic area



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Biomarkers in drug development

- A biological variable with a statistically significant relationship with parameters of
  - disease states
  - drug activity



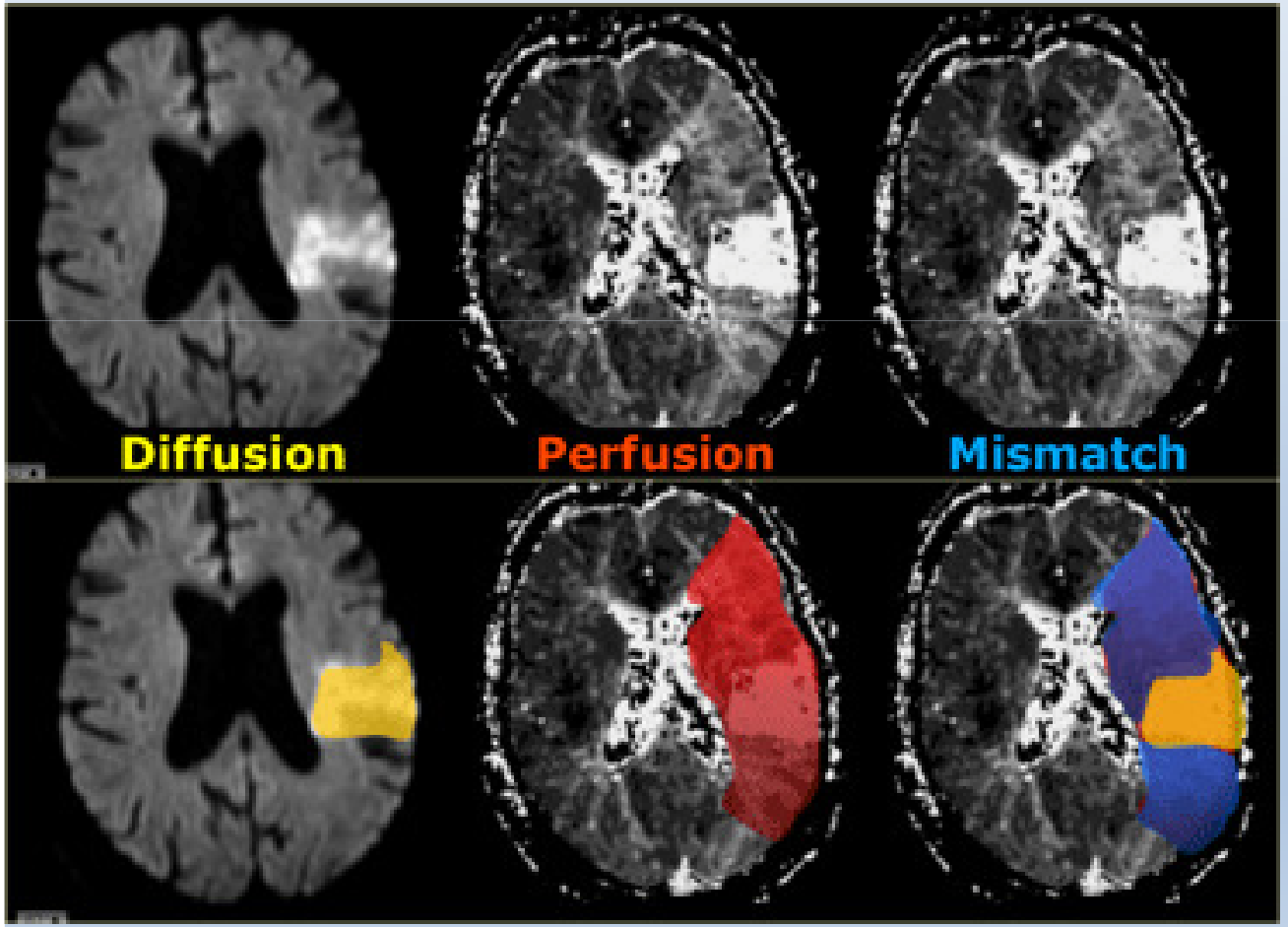
Biomarker candidate → Biomarker

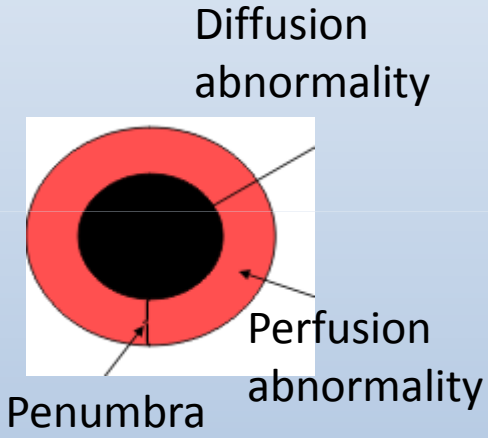
The utility of biomarkers in CNS drug development

- Patient selection and stratification
  - Improves the likelihood of patient to respond (or not) to the compound
- Target engagement
  - Indirect measure of CNS penetration
- Pharmacodynamics
  - Define the consequences of a compound's interaction with its target
- Disease and disease modification
  - Biomarkers that correlate with disease progression

Palmer A.M. (2013) The utility of biomarkers in CNS drug development. *Drug Discovery Today*, 19: 201-203

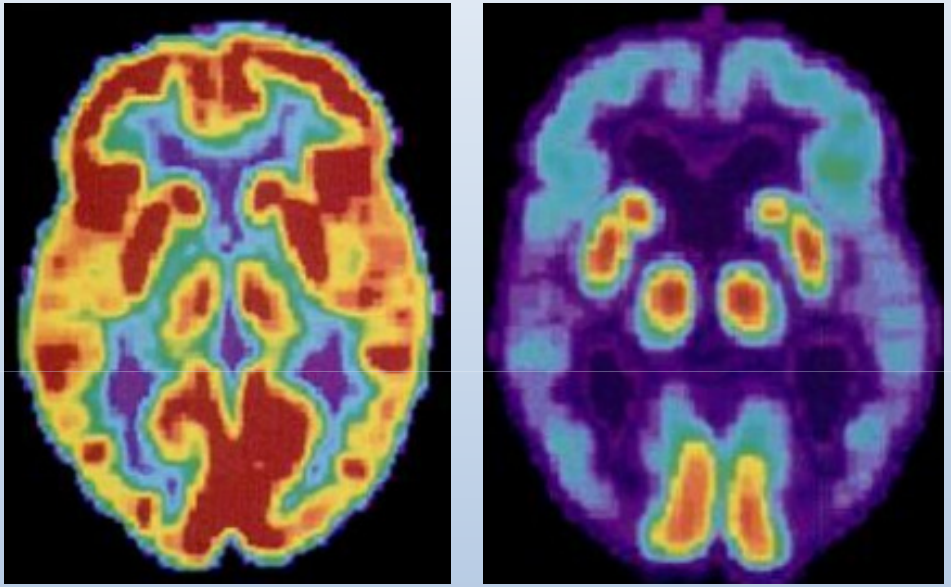
MRI diffusion-perfusion mismatch to select stroke patients with a penumbra



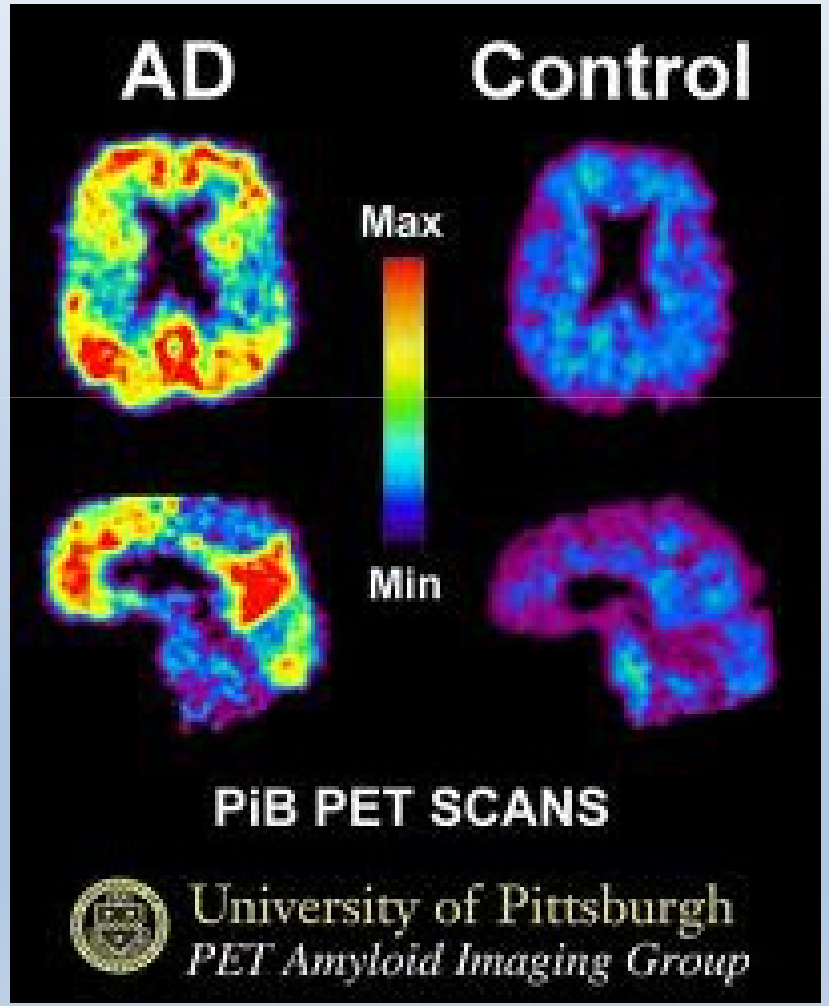


Neuroimaging

- Structure
  - MRI
- Molecular probes of structure
  - SPECT
  - PET
- Functional measures
  - [^{18}F]Fludeoxyglucose
  - EEG
  - MEG
  - fMRI
    - Blood oxygen level-dependent contrast



Visualising amyloid plaques in the intact brain



- [^{18}F] Florbetapir
  - FDA approval in 2012
  - Strictly limited to “ruling out AD”

Defining prodromal disease

Clinically isolated syndrome

- A transient impairment in motor or sensory function
- White matter abnormalities shown by MRI
- IFNβ drugs and glatiramer delay the conversion of CIS to RRMS

Palmer AM (2013)
Br J Clin Pharmacol 78: 33-43

Mild cognitive impairment

- Mild memory loss (MMSE: 26-30)
- Some indication of AD pathology
  - Increased CSF [$A\beta_{42}$]
  - PET amyloid imaging
  - Cortical/hippocampal atrophy (MRI)
  - Pyramidal cell loss (FDG-PET)
  - Increased CSF [Tau]

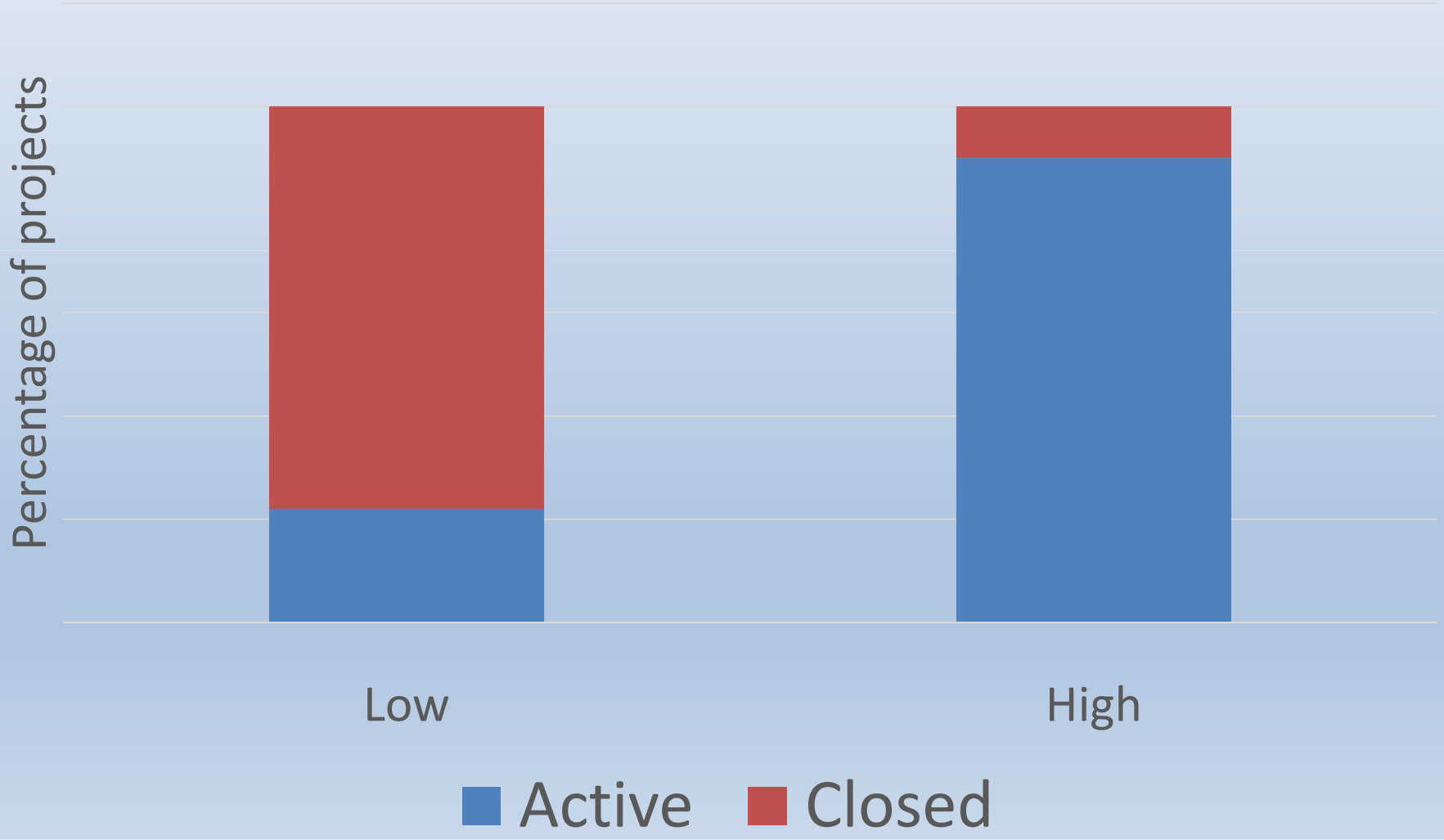
Sperling et al (2013)
Nat Rev Neurol. 9: 54–58

Clinical trials of premanifest AD (autosomal dominant AD)

Sponsor	Drug candidate	Selection	Outcome measures
Alzheimer's Prevention Initiative	Crenezumab	PS1-positive subjects within 10 years before apparent cognitive decline	PET- Aβ PET-FDG Structural MRI Cognitive tests
Dominantly Inherited Alzheimer Network	Solanezumab and gantenerumab	Confirmed family pedigree for autosomal dominant AD (mutations in APP, PS1 and PS2)	PET- Aβ PET-FDG Structural MRI Cognitive tests

Confidence in patient selection in Phase 2b studies

Cook D et al (2014)



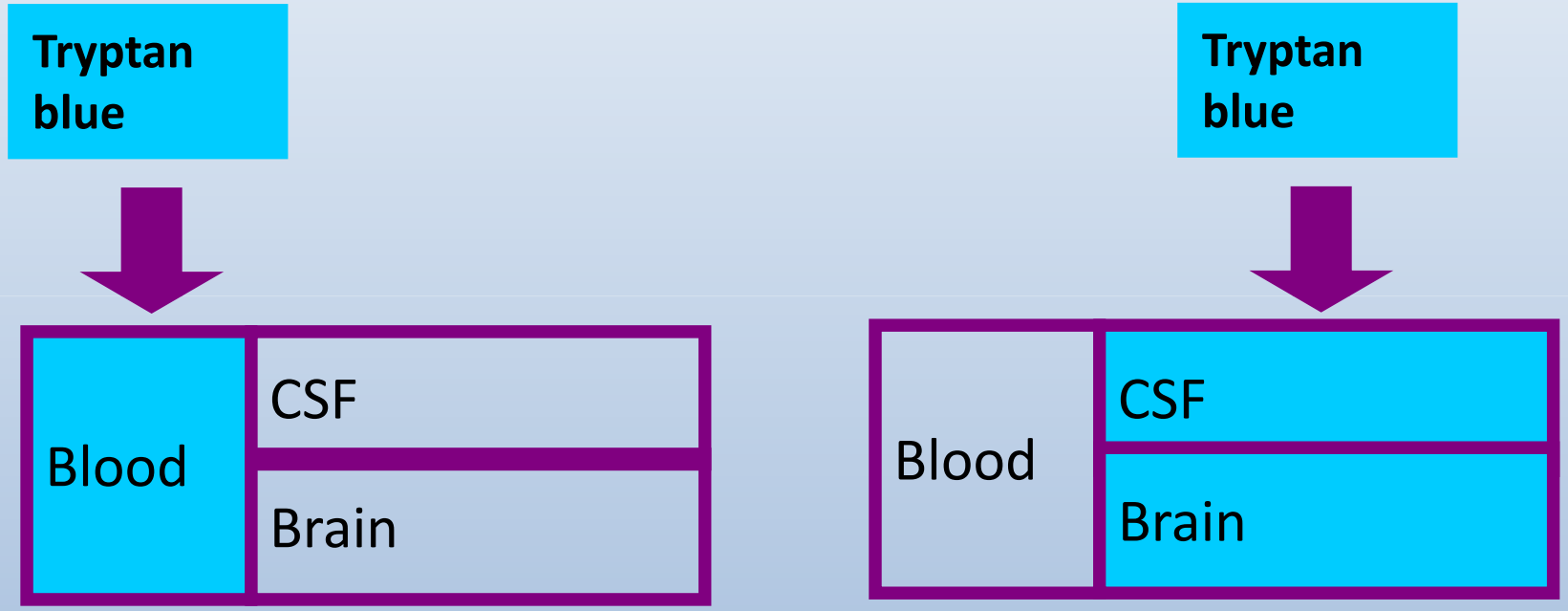
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The blood-brain barrier

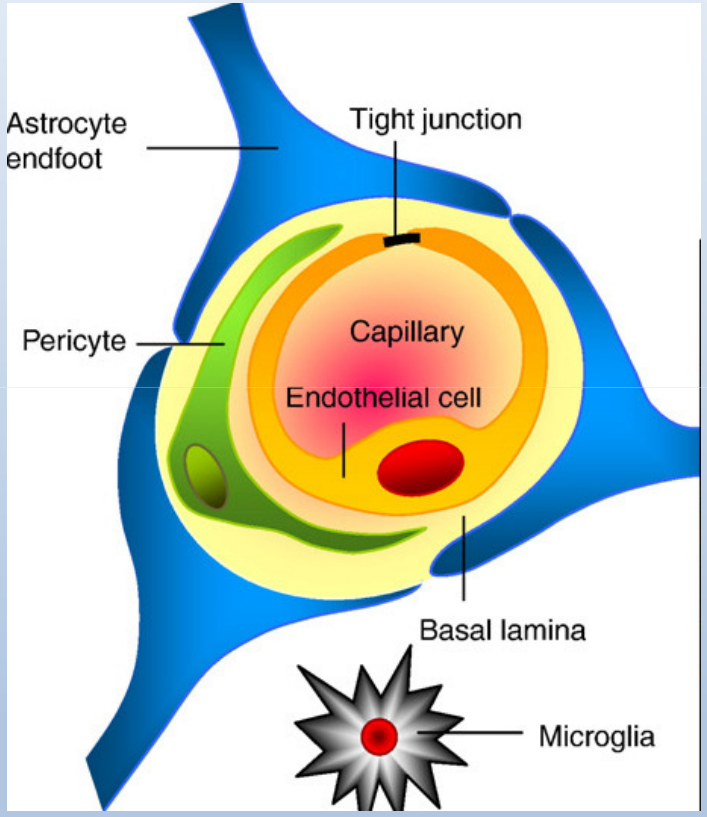
Paul Ehrlich (1884-1915)



Palmer AM (2010) The blood-brain barrier. *Neurobiol. Disease,* 37: 1-2

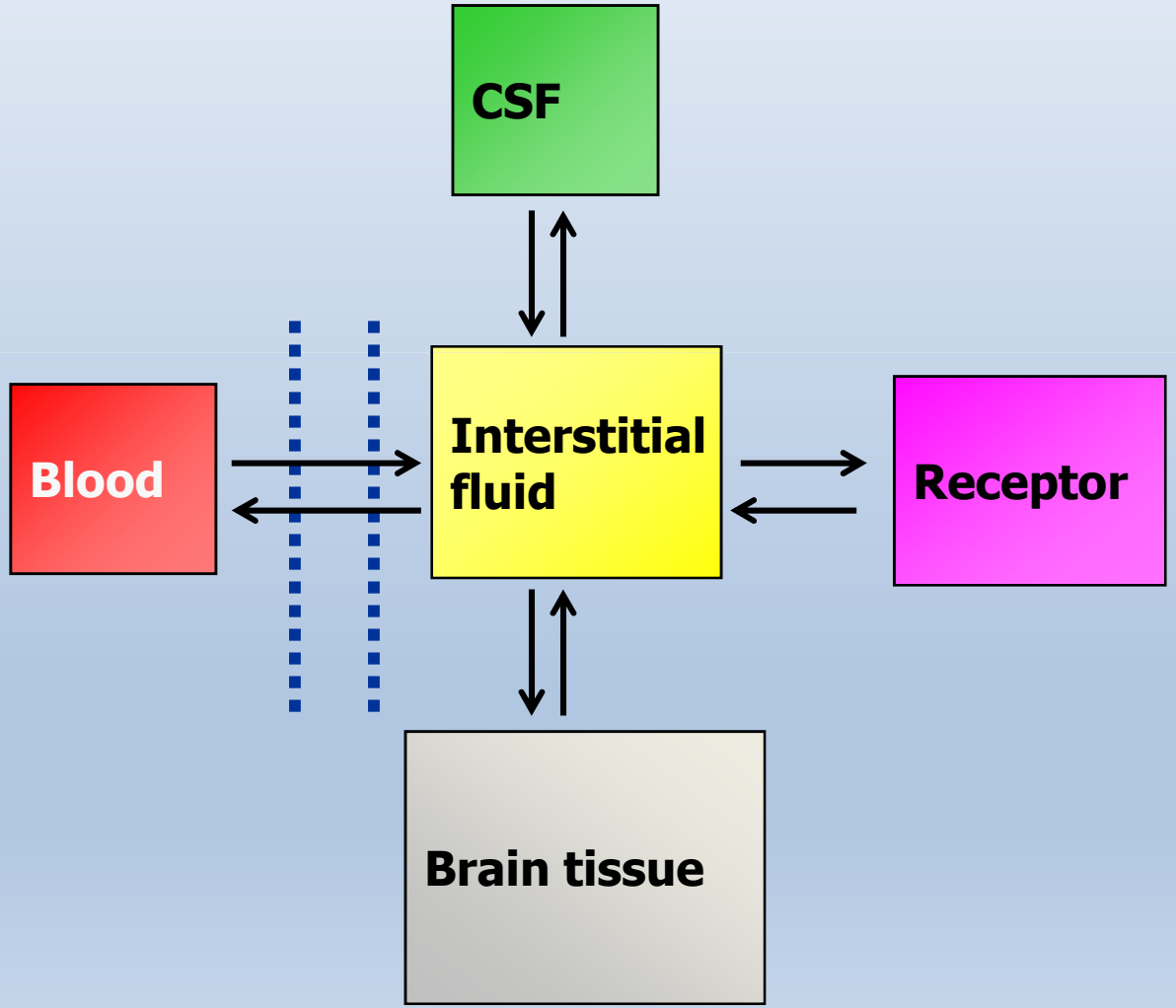
The blood-brain barrier (BBB)

- Separates the blood and brain compartments
- It severely constrains potential CNS therapeutics
- Generally, blood biomarkers do not reflect drug activity in the brain



Palmer AM and Alavijeh MS (2013) Overview of Experimental Models of the Blood-Brain Barrier in CNS Drug Discovery. Current Protocols in Pharmacology 62:7.15.1–7.15.30

Interstitial fluid is the key compartment for CNS drugs



The three pillars of success

Morgan P et al (2012)

3 pillars

- Tissue exposure
- Target engagement
- Pharmacodynamic action

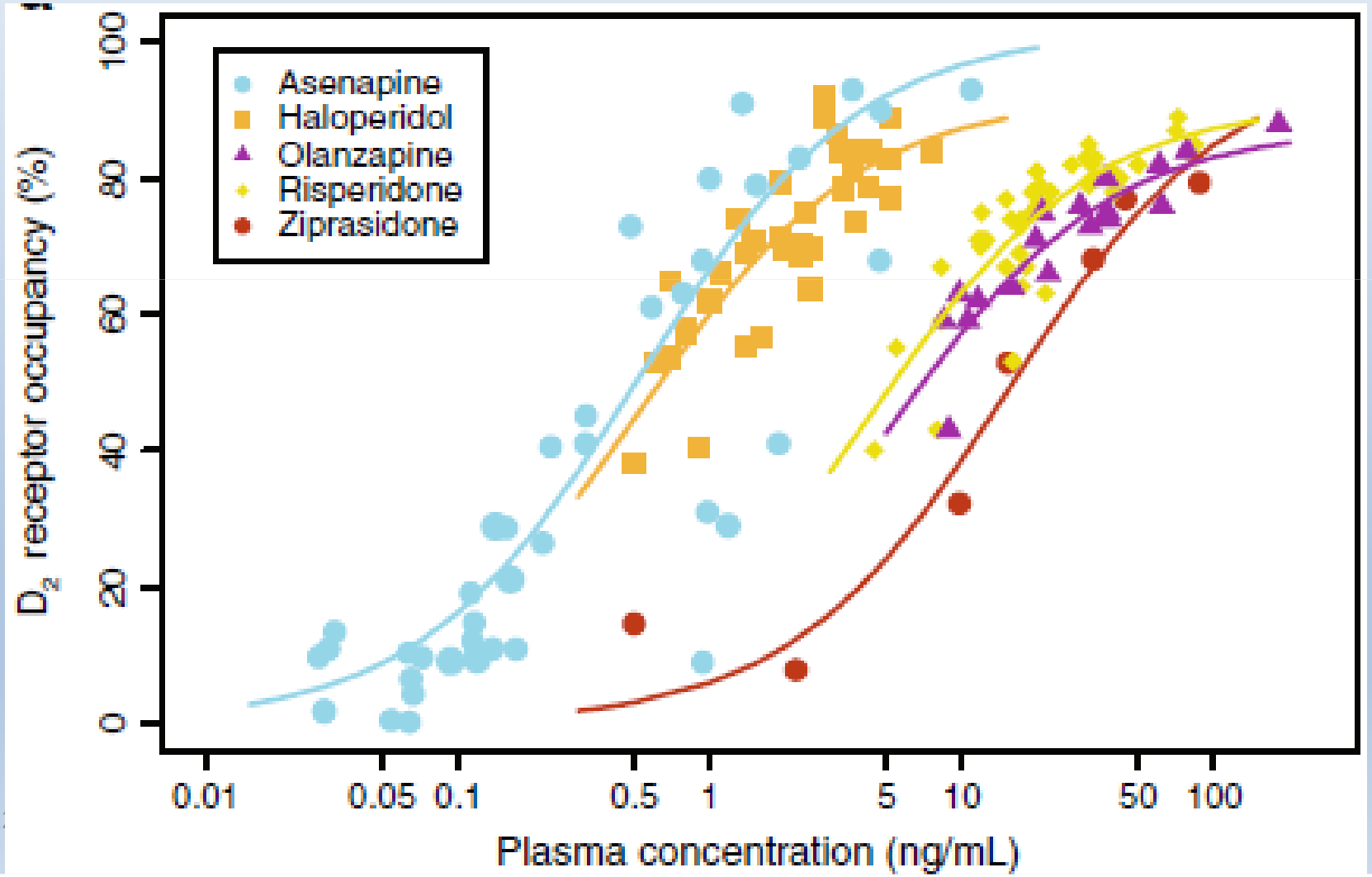
Brain ISF concentration is key

	Blood	Brain
Animal	✓	✓
Human	✓	?



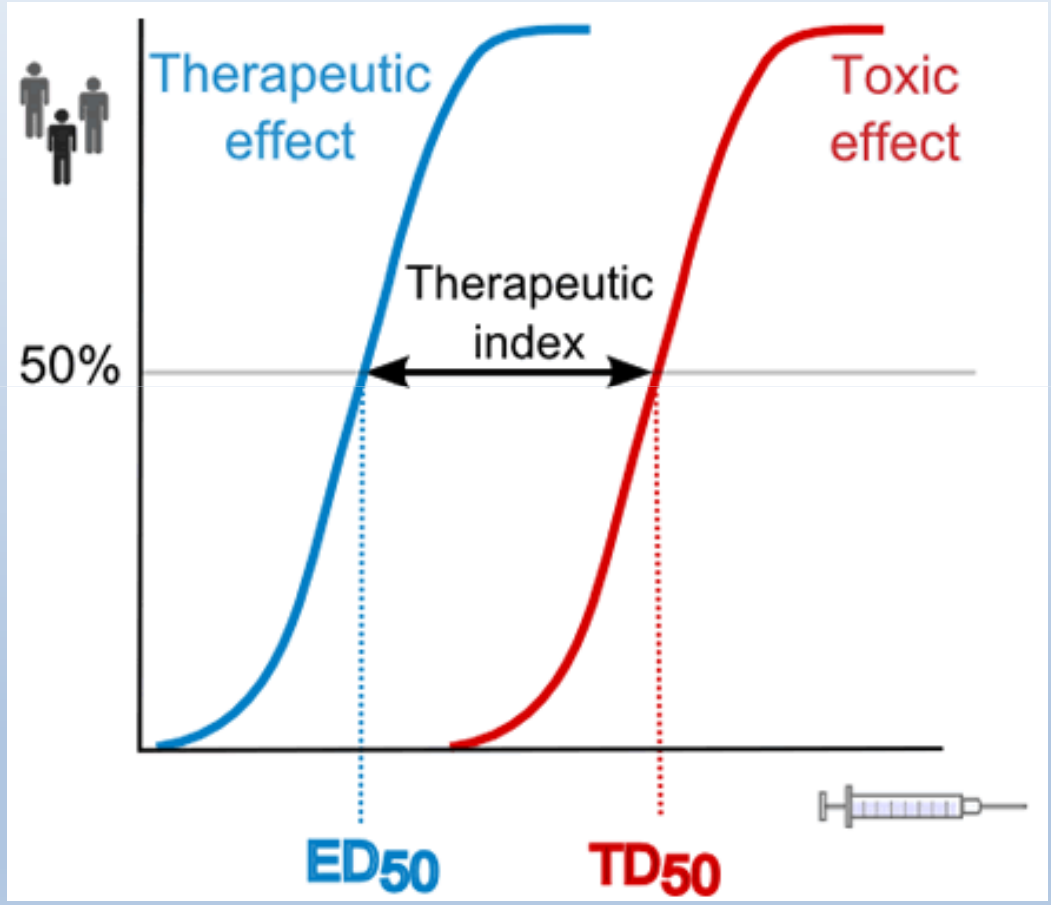
Target engagement

de Greef R. et al (2011)

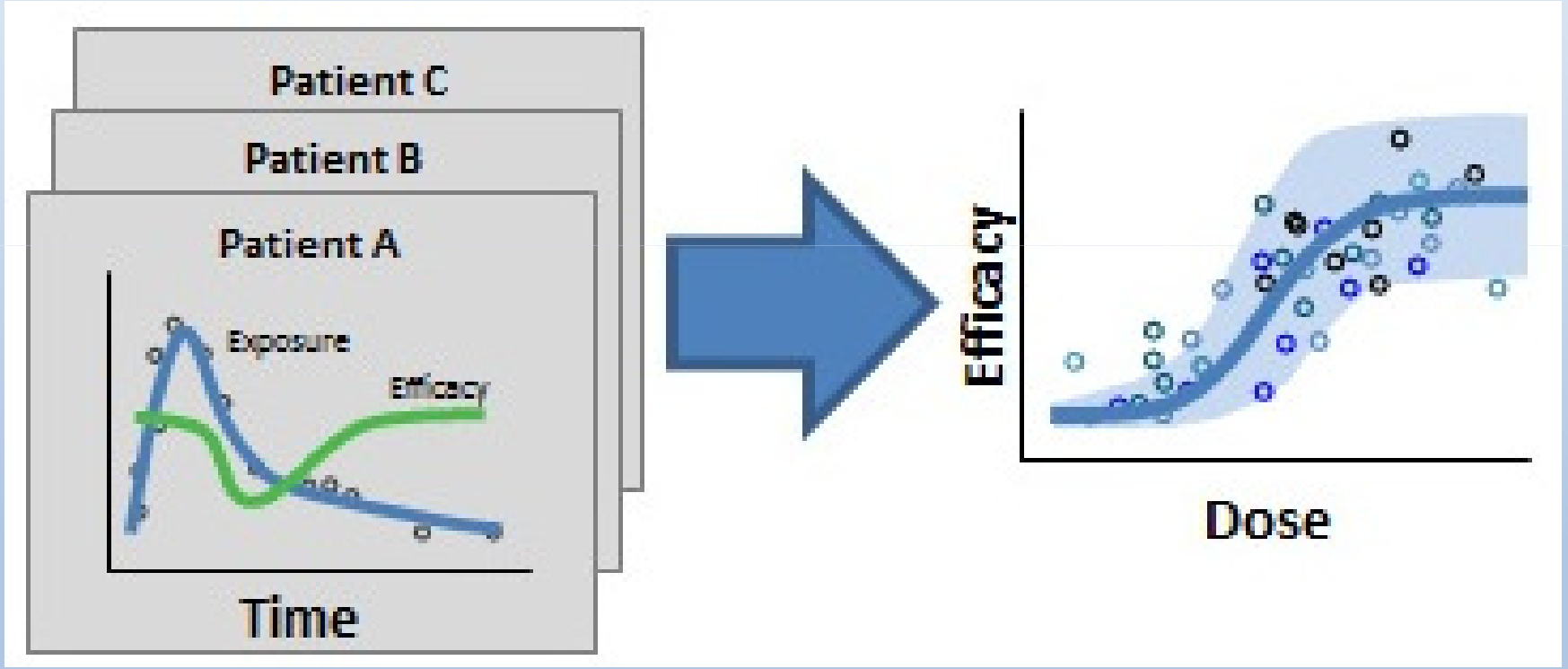


Pharmacodynamic biomarkers

- Biochemical
- Physiological
- Behavioural
- Imaging



A PK-PD relationship is essential for successful CNS medicines research



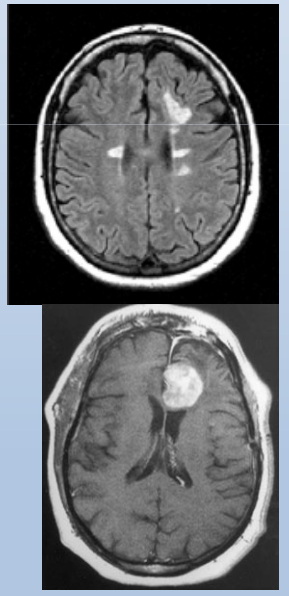
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Palmer A.M. (2013) The utility of biomarkers in CNS drug development. *Drug Discovery Today*, 19: 201-203

MRI has revolutionised the diagnosis and management of MS

- Diagnosis
  - Greater accuracy and precision
  - The MacDonald criteria: more weight to MRI data
- Can measure:
  - White matter damage
  - Grey matter damage
  - BBB breakdown
  - New lesion formation
- Used as:
  - Primary endpoint in POC clinical trials
  - Surrogate endpoint in Phase III trials

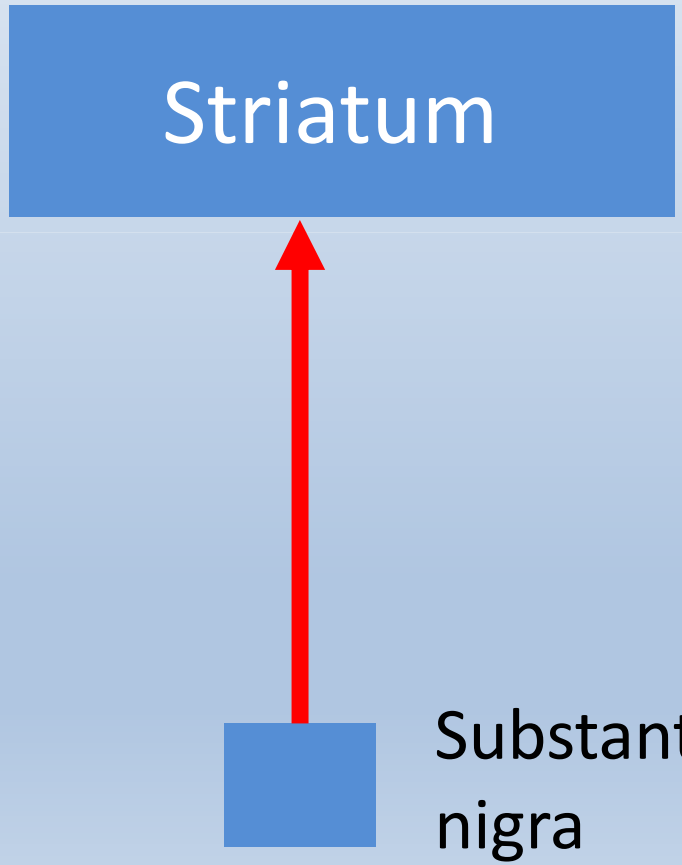


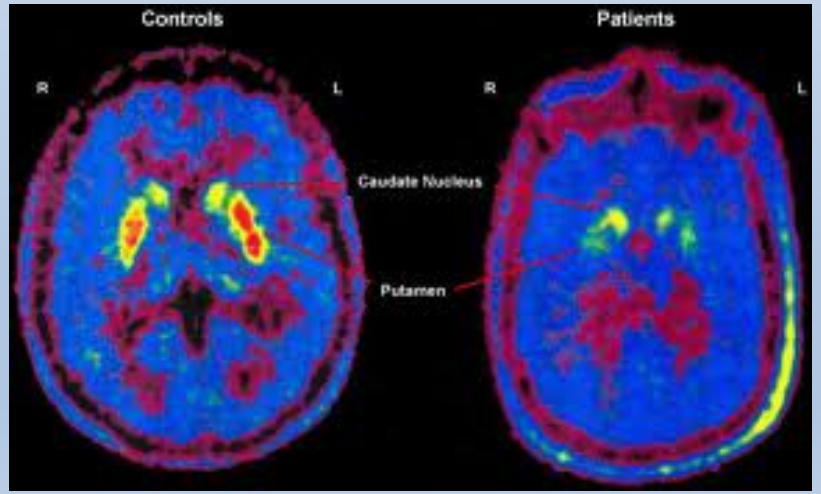
Palmer A.M. (2012) Pharmacotherapeuetic options for the treatment of multiple sclerosis. *Clin. Med. Insights:Therapeutics*, 4: 1 -24

Receptor occupancy studies

Measurement of disease activity

- Loss of dopaminergic neurons from the striatum of the intact brain of a PD patient





The progression of Alzheimer's disease

Mild

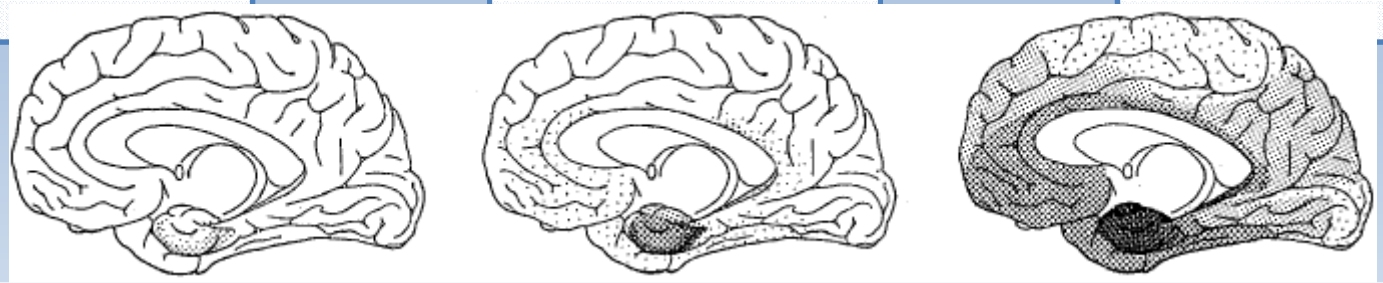
- Entorhinal cortex (ECX)
- Episodic memory
- MMSE: 20-25

Moderate

- ECX + cortex + LC, RN, nbM
- Executive function + working memory
- MMSE: 10-19

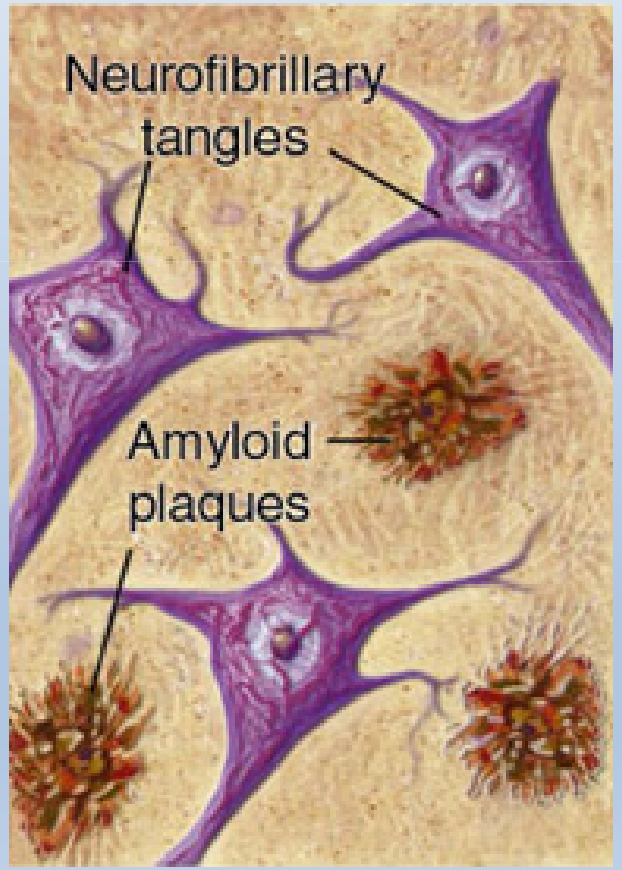
Severe

- Cortical association areas + amygdala + thalamus,+ striatum
- Extensive deficits not restricted to cognition
- 0-9



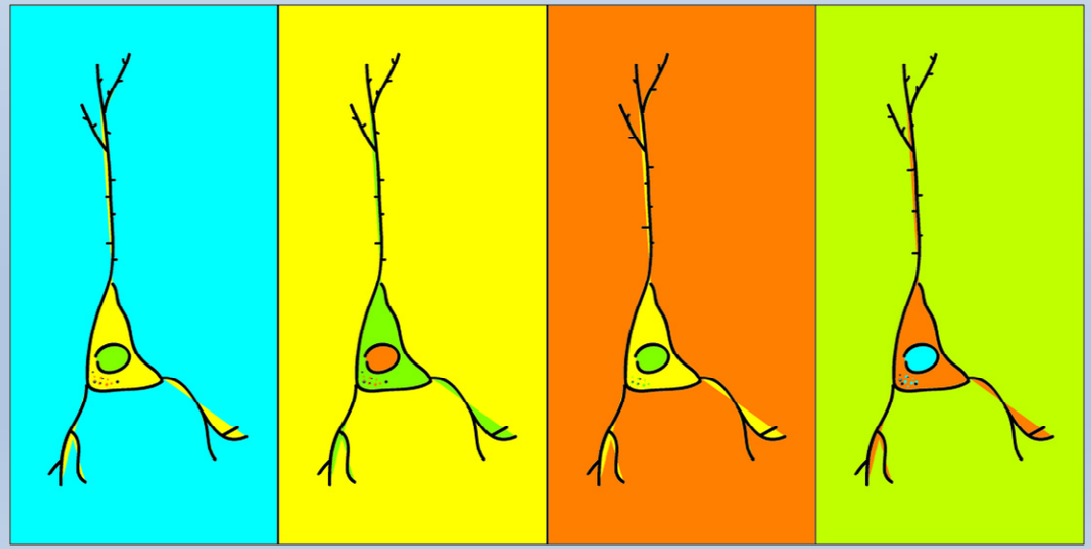
The three cardinal pathologies of Alzheimer's disease

Plaques and tangles

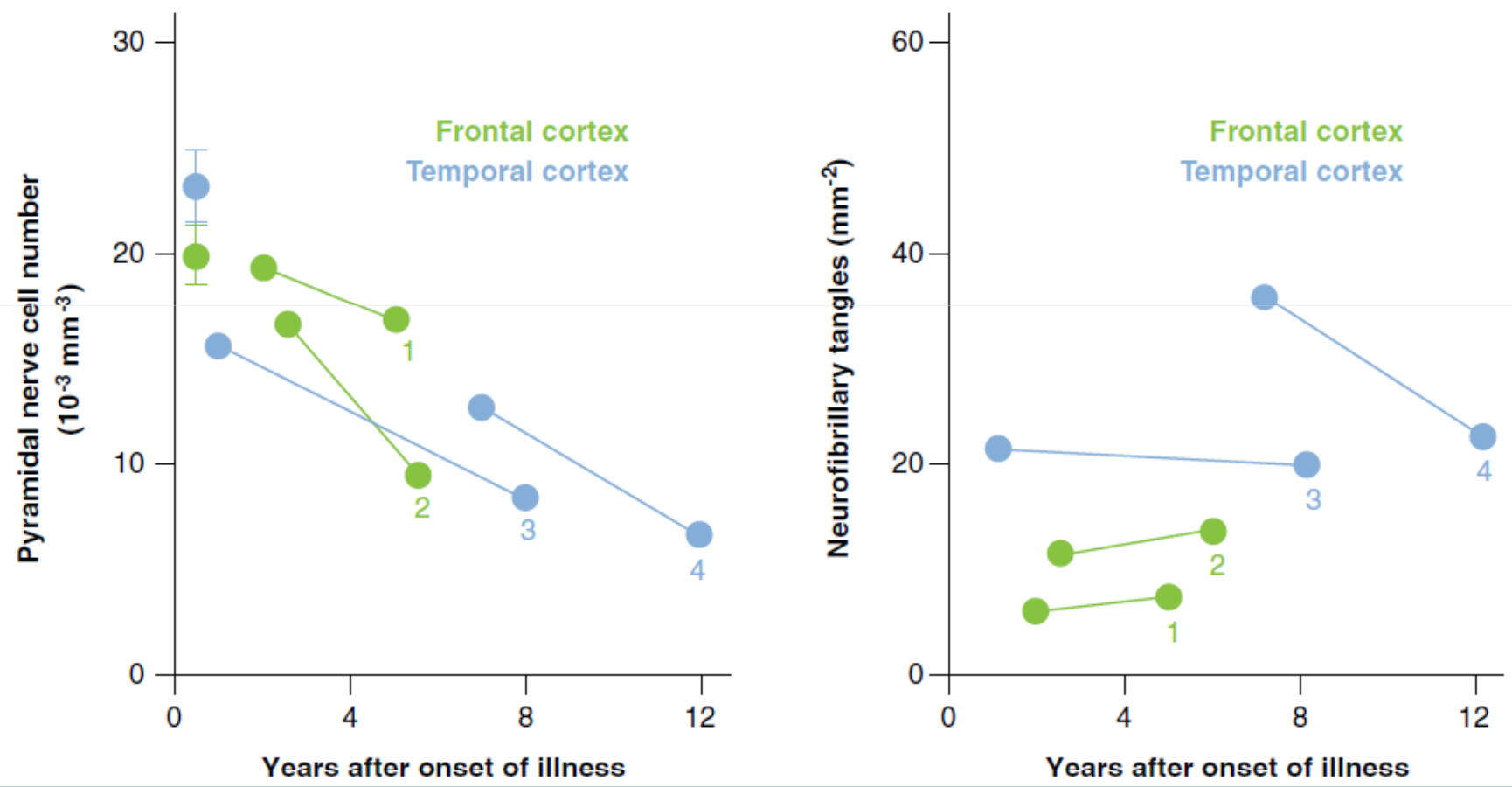


Pyramidal cell loss

- 70% of all neurons
  - Corticocortical pathways
  - Corticofugal pathways



The loss of pyramidal cells is progressive (Mann D et al 1988)



Correlations between neuropathology and clinical measures

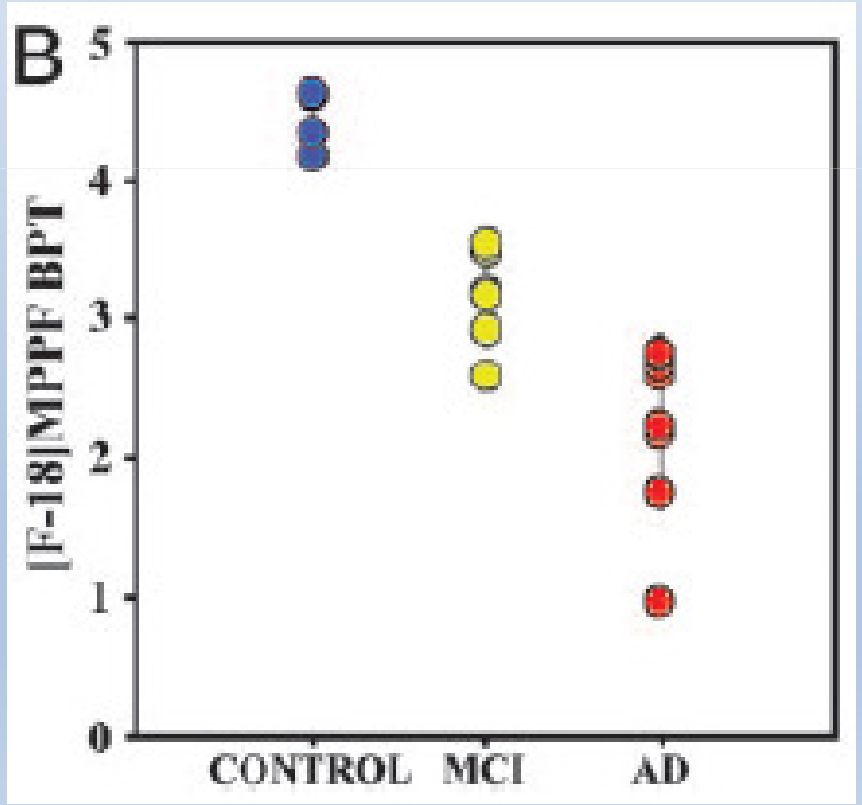
Clinical measure	Plaques	Tangles	Pyramidal cells In layer III	Pyramidal cells in layer V
Clinical rating*	x	x	✓	✓
WAIS verbal	✓	✓	✓	✓
WAIS performance	x	x	✓	✓
Token test	x	✓	✓	✓
Visual reaction time	x	x	✓	✓

*A rating of magnitude of dementia (0-9)
- Language (0-3)
- Perceptuo-spatial functions (0-3)
- Memory (0-3)

Neary, D. et al. (1986) Alzheimer's disease: a correlative study.
J. Neurol. Neurosurg.Psychiatry 49, 229–237

PET markers of pyramidal cells and tangles

- [^{18}F]MPPF hippocampal binding



- Tau ligands
  - [^{18}F]-T808
  - [^{18}F]-THK523
  - [^{11}C]PBB3

Kepe et al (2006) Serotonin 1A receptors in the living brain of Alzheimer's disease patients Proc. Natl. Acad. Sci. 103: 702-707

The utility of biomarkers in CNS drug development

- Patient selection and stratification
  - Improves homogeneity of patient population
- Target engagement
  - Indirect measure of brain penetration
- Pharmacodynamics
  - PK-PD relationship
- Disease and disease modification
  - Surrogate markers of disease progression

The utility of biomarker in AD clinical trials

Method	Biomarker	Utility
MRI (manual)	Hippocampal volume (and rate of atrophy)	Diagnosis, patient stratification, disease modification
MRI (automated)	Whole brain volume	Diagnosis, patient stratification, disease modification
fMRI	Blood oxygen-dependent level signal	Diagnosis, patient stratification
FDG-PET	Glucose uptake	Diagnosis, patient stratification, disease modification
Amyloid PET	Amyloid	Diagnosis, patient stratification, disease modification, target engagement
Aβ in CSF	Amyloid	Diagnosis, patient stratification, disease modification, target engagement
Tau in CSF	Tau	Diagnosis, patient stratification, disease modification, target engagement

Summary and future prospects

- Biomarkers have the potential to:
  - Reduce clinical trial time
  - Increase the power of clinical trials
  - Improve diagnosis, including for prodromal (and premanifest) disease
  - Establish the optimal dosing regimen
- Genomics, proteomics, metabonomics are providing many biomarker candidates
- The clinical need for effective biomarkers is huge
  - Particularly for biomarkers of disease progression