Future considerations and the impact of the 3Rs: The impact on Neuroscience Drug Discovery and Development

Jackie Hunter PhD, CBE

Outline

- Will increased target validation in man replace animal studies?
- Models of mechanism vs models of disease – refinement?
- Changes in business models to more open, precompetitive collaborations and other ways of working together – reduction

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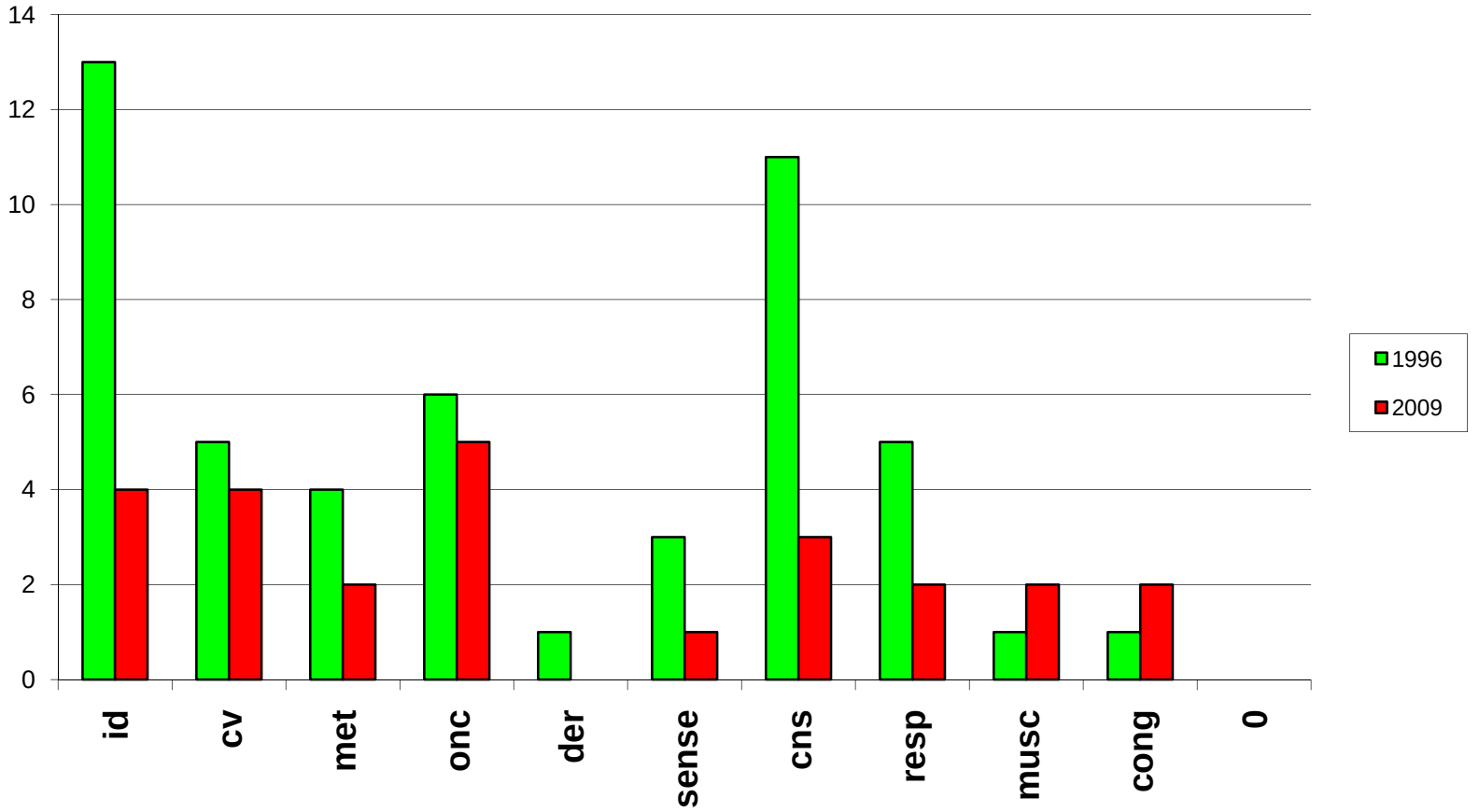
Fall in new drug approvals for CNS

Focus moving away from diseases with high need based on morbidity – towards rare diseases (congenital, and highly defined oncology niches)



www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu

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Drug discovery and development process

Animal research plays vital role in:

- Validation of target
- Screening of compounds to optimise PK and efficacy
- Safety and toxicology

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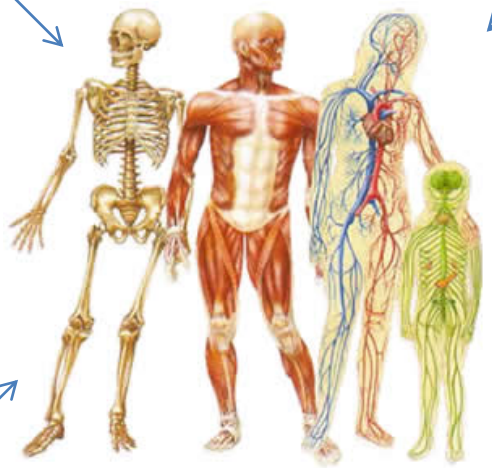
Will increased target validation in man replace animal studies?

Genetics of rare diseases and phenotypes

GWAS



Pharmacogenomics

Imaging

Stem cells

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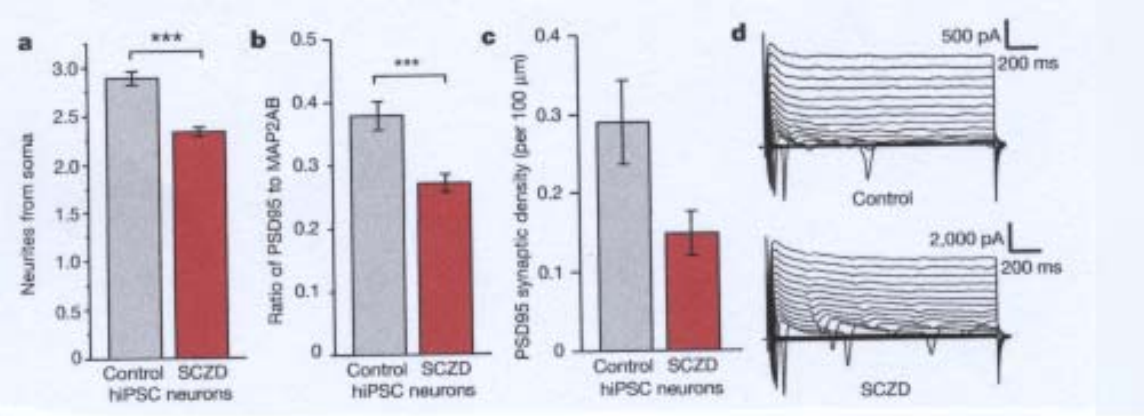
Modelling schizophrenia using human induced pluripotent stem cells



Brenand et al
Nature (2011)
473:221-5

Brenand et al used fibroblasts and reprogrammed them using lentiviruses

- Changes in neurite number and connectivity
- 596 genes differentially expressed – 25% previously linked to schizo
- Strengthened links with previously identified pathways
- New pathways identified eg NOTCH

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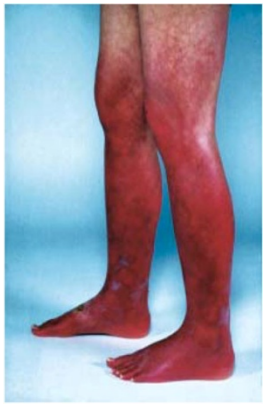
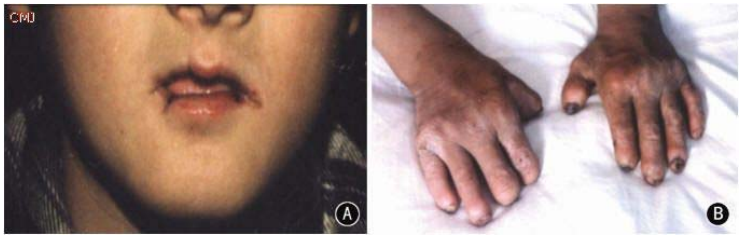
Studies of rare diseases/syndromes

Genetic basis of neuropathic pain – identified gain and loss of function mutations of SC9a



Erythermalgia

Ectopic excitability



Neuron 52, 767–774, December 7, 2006 ©2006 Elsevier Inc. DOI 10.1016/j.neuron.2006.10.006

SCN9A Mutations in Paroxysmal Extreme Pain Disorder: Allelic Variants Underlie Distinct Channel Defects and Phenotypes

Clinical Study

ARTICLES

An *SCN9A* channelopathy causes congenital inability to experience pain

James J. Cox[1]*, Frank Reimann[2]*, Adeline K. Nicholas[1], Gemma Thornton[1], Emma Roberts[3], Kelly Springell[3], Gulshan Karbani[4], Hussain Jafri[5], Jovaria Mannan[6], Yasmin Raashid[7], Lihadh Al-Gazali[8], Henan Hamamy[9], Enza Maria Valente[10], Shaun Gorman[11], Richard Williams[12], Duncan P. McHale[12], John N. Wood[13], Fiona M. Gribble[2] & C. Geoffrey Woods[1]

Nature 444:894-8. 2006

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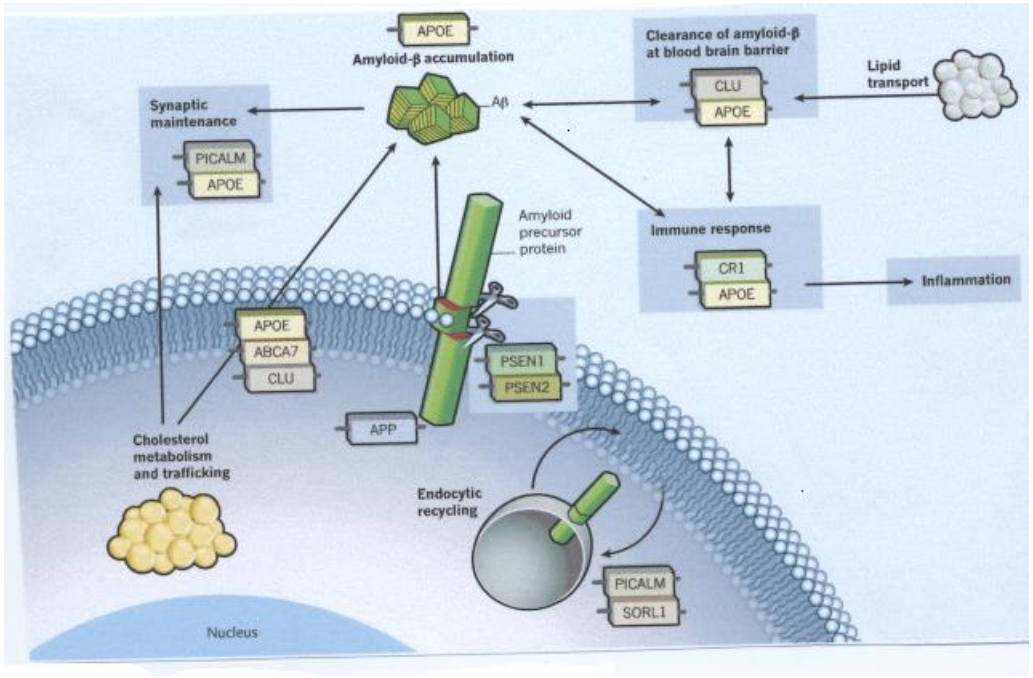
Genetics of complex neurological diseases is expanding



Numerous genes for brain disorders now identified

New pathways mapped

Also complexity increased

Refinement of phenotypes will increase power of genetic analyses

M. Eisenstein: Nature June 2011

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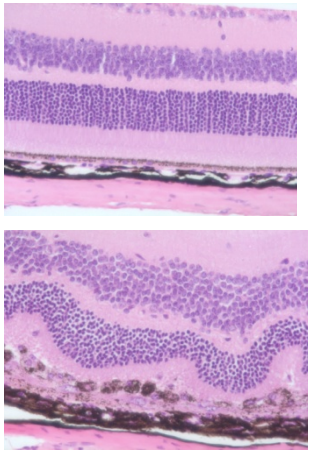
Will increased target validation in man replace animal studies?

- No but……
- Can refine the questions asked of the models
  - More focus on mechanism
  - Refine the approaches in modelling disease
  - Potential to create models of more relevance to overall patient population
  - Importance for looking for unwanted target-related effects



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Animal models of mechanism vs disease

- Very few animal models of disease that faithfully
  - Model pathology
  - Model symptoms
  - Accurately predict treatment efficacy
- Most animal models of neurological and psychiatric disease
  - Do not model all aspects of the disease
  - Limited in predicting efficacy
  - May provide conflicting data in terms of exposures of drugs required
  - May have resulted in false negatives

Many models of disease have limitations from a drug development perspective

- β–amyloid transgenic models
- α-synuclein models
- EAE
- Neuropathic pain

Many variants of these models exist with no consensus on their relative merits

So frequently compounds tested in multiple variants of these models

Models can help translation

- To rule out target in man, need to know
  - Compound acts on the mechanism in man
  - Compound reaches the target in man
  - Compound reaches the required levels for efficacy on the target in man
- But tension
  - Need validated animal models of mechanism

Real life example – which plasma exposure to target?

EC50 rat model 1 → 3.8μM

Thermal threshold → 1.9μM

EC50 rat model 2 → 1.0μM

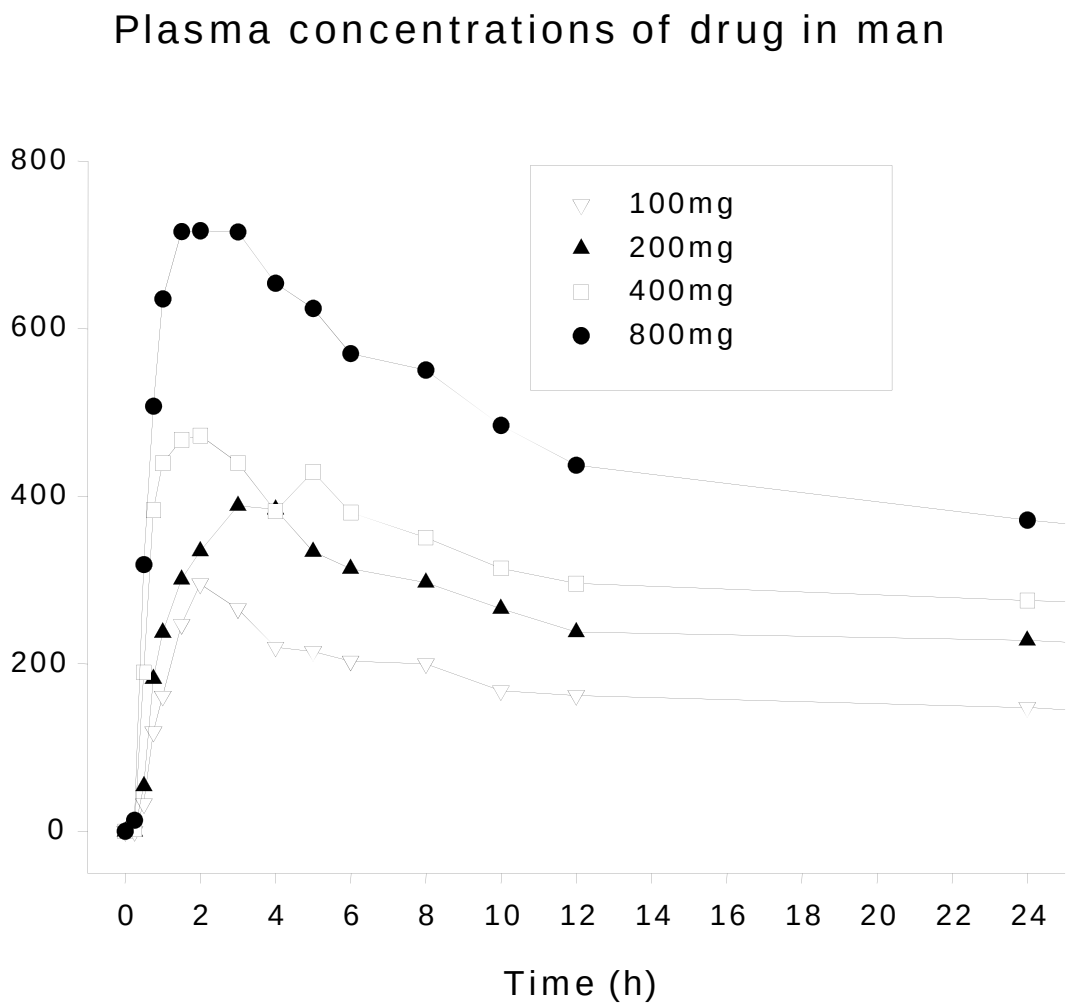
In vitro potencies → 1.0μM

Mechanical threshold → 0.6μM

0.5μM

EC90 rat model 3 → 0.05μM

EC50 rat model 3



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Is there a need to move towards more mechanistic models

- With increasing disease knowledge comes better identification of key mechanisms
- Need to focus on developing mechanistic in vivo assays that can be translated to man
  - Demonstrate compound affects mechanism
  - Understand the exposures required for efficacy on the mechanism
  - Should need fewer models/experiments
  - Allow comparison of pharmacodynamics with pharmacokinetics
- Requires different mindset

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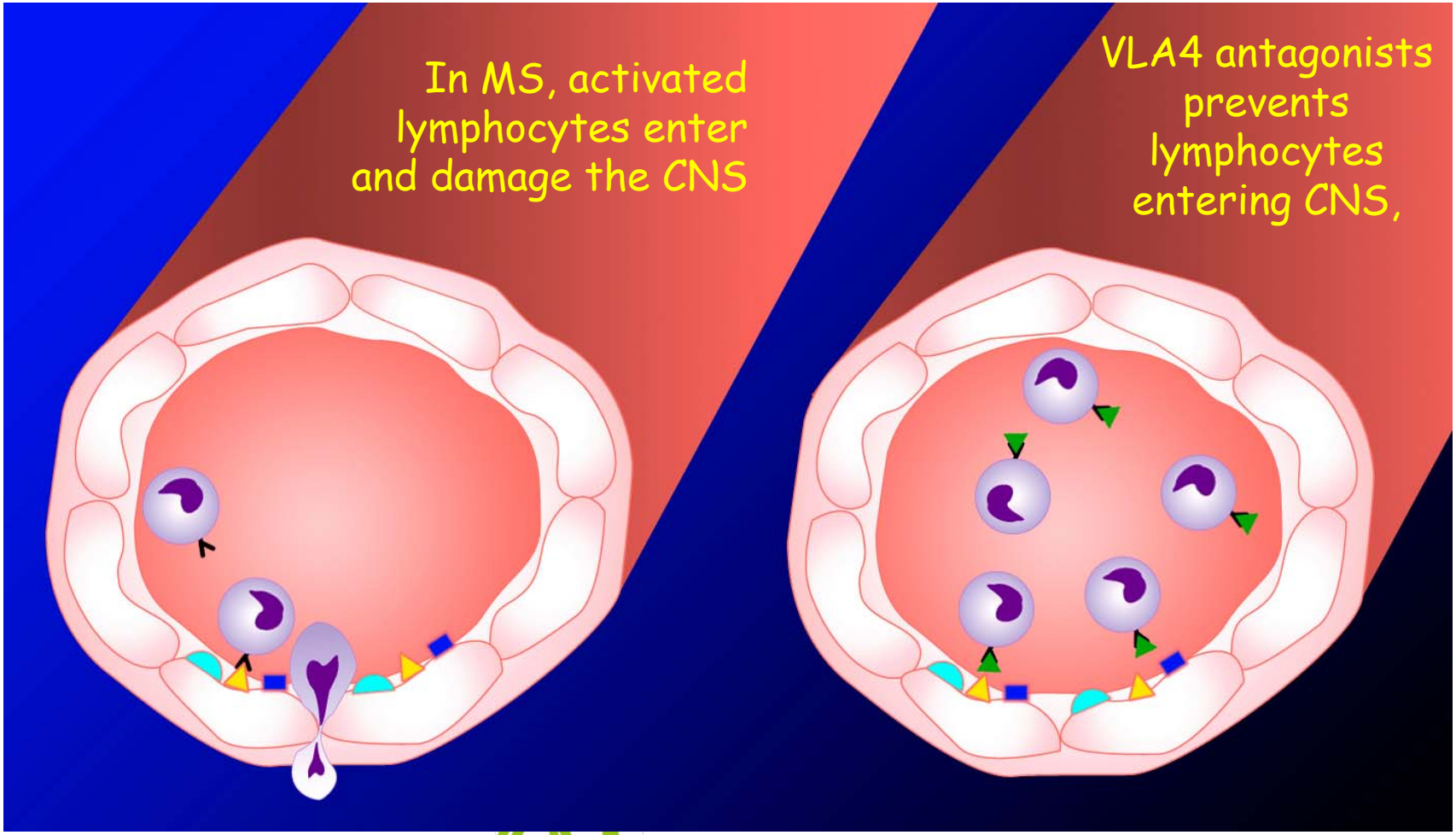
PD assay for VLA4 antagonists



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PD effect of an oral VLA4 antagonist - firategrast

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Technological developments have made this approach more practical

Eg

- EEG
- PET and other imaging technologies
- Cytokine and other systemic markers for inflammation
- Patient stratification to enable enrichment for the particular mechanism in question

Might allow molecules to move more rapidly through drug discovery and development process

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nature publishing group

MACROSCOPY

Precompetitive Research: A New Prescription for Drug Development?

J Woodcock[1]

"Precompetitive research" is being recommended by some as a treatment for the current malaise in drug development. What is this prescription, and why do the patients seem so reluctant to try it? Precompetitive research is science participated in collaboratively by those

There is some confusion between "translational research" and precompetitive research. Translational research usually refers to the scientific activities involved in moving candidate medical products from the laboratory into and through clinical evaluation. Translational

tinct possibility that the slow progress of preclinical and clinical development science is holding back the movement of innovative discoveries into the market. For many decades, biomedical science has been divided into two realms. One sector, government- or nonprofit-

Reduction through more collaboration and data sharing

- Number of initiatives globally
  - Diseases of the developing world
  - Safety and toxicology
  - Efficacy

- Innovative Medicines Initiative has proved principle

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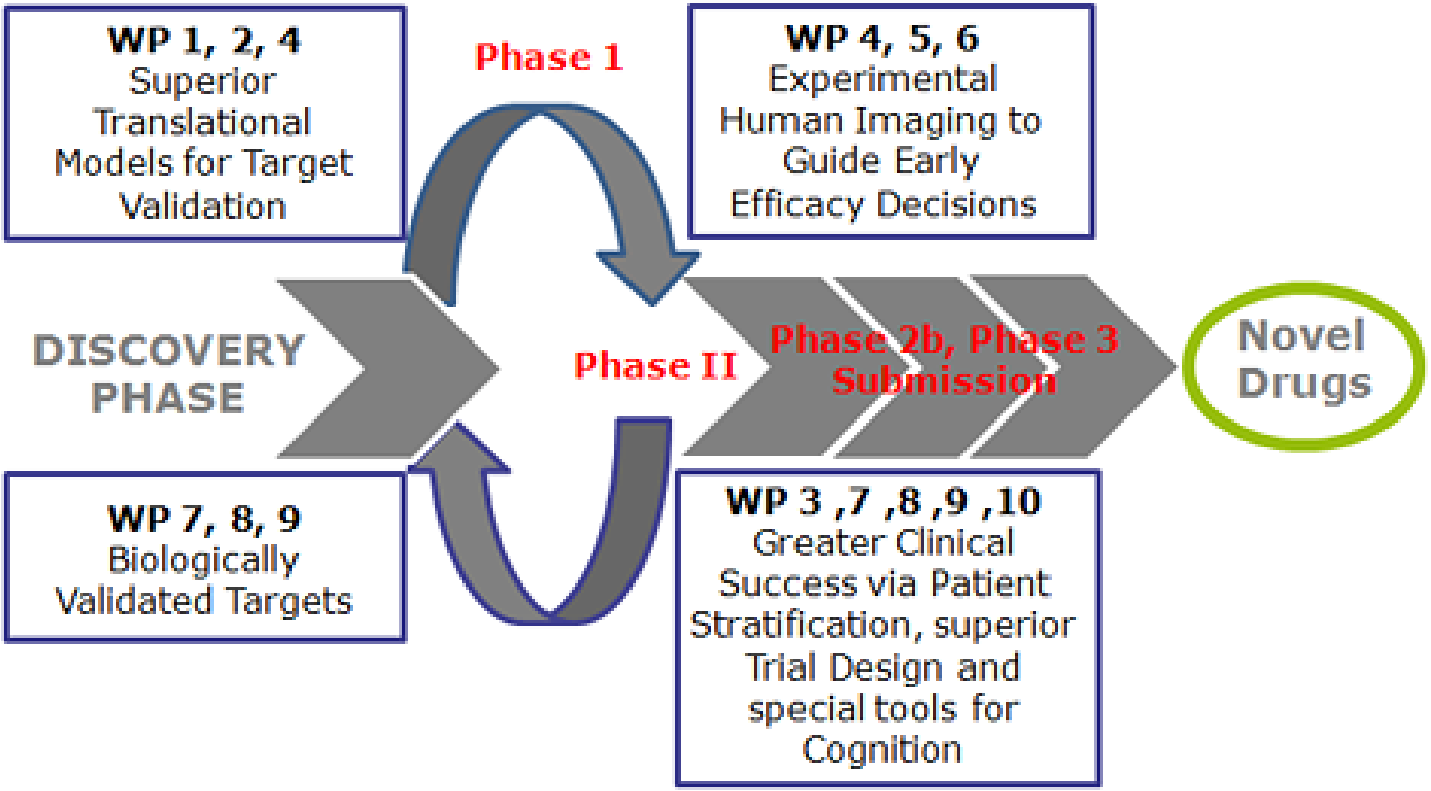
NEWMEDS project



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Overcome hurdles to better toxicology prediction by:-

- Sharing of high quality proprietary toxicity data.
  - Shared data will mostly be GLP or GLP-like and will be the basic set for all future prediction efforts.
  - These data will come from the archives of EFPIA companies and
  - Previously accessible for modelling or rule base development only for the owning company.
  - A database with harmonized ontologies will be created to store these data.

- Development of several models representing the different components in the mechanism leading to a toxic effect (including DMPK), which will then be integrated in an overall decision-making tool allowing prediction of *in vivo* toxicity

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Conclusions

- Advances in technology have and will provide opportunities for refinement and replacement
- New, more cooperative ways of working should ultimately reduce the numbers required and, hopefully, increase predictivity

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