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

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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
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)

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
Will increased target validation in man replace animal studies?

- Genetics of rare diseases and phenotypes
- GWAS
- Imaging
- Pharmacogenomics
- Stem cells
Modelling schizophrenia using human induced pluripotent stem cells

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

Brenand et al
Studies of rare diseases/syndromes

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

Erythermalgia
Ectopic excitability

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

ARTICLES

An SCN9A channelopathy causes congenital inability to experience pain

James J. Cox1, Frank Reinmann2, Adeline K. Nicholas1, Gemma Thornton1, Emma Roberts1, Kelly Springell1, Gulshan Karbani1, Hussain Jeffer3, Jovaria Mannani2, Yasmin Radi2, Li Alistair Gaskell2, Helen Hamamy2, Enza Maria Valente19, Shaun Gorman1, Richard Williams15, Duncan P. McHale17, John N. Wood13, Fiona M. Gribble2, & C. Geoffrey Woods1

Nature 444:894-8, 2006
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
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
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
Mechanical threshold → 0.6µM
0.5µM

EC90 rat model 3 → 0.05µM

Plasma concentrations of drug in man

Time (h)
0 2 4 6 8 10 12 14 16 18 20 22 24

100mg
200mg
400mg
800mg

pharma partnrs
open innovation in bioscience
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
PD assay for VLA4 antagonists

In MS, activated lymphocytes enter and damage the CNS

VLA4 antagonists prevents lymphocytes entering CNS,
PD effect of an oral VLA4 antagonist - firategrest
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*
Precompetitive research is science participated in collaboratively by those who “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 who...
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
NEWMEDS project

Phase 1
WP 4, 5, 6
Experimental Human Imaging to Guide Early Efficacy Decisions

Phase II
WP 3, 7, 8, 9, 10
Greater Clinical Success via Patient Stratification, superior Trial Design and special tools for Cognition

Phase 2b, Phase 3 Submission

Novel Drugs

DISCOVERY PHASE
WP 1, 2, 4
Superior Translational Models for Target Validation

WP 7, 8, 9
Biologically Validated Targets

Ei Pharma Partners
Open Innovation in Bioscience
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**
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.