BACKGROUND

• Problem:
  • Neuropsychiatric drug discovery has almost completely stalled
  • Breakthroughs occur almost entirely serendipitously
  • Understanding is usually post hoc rather than from hypothesis
• There are a number of explanations and factors but:
  • Diagnosis of neuropsychiatry conditions is still based on **qualitative** assessment of symptoms, defined by convention, rather than **quantitative** analysis of aberrant biology

  Truism: Drugs work on biological substrates not symptoms
NEED

- Both psychotic and affective disorders still present significant issues
  - speed and level of treatment response, relapse, resistance, compliance, side-effect profile etc.

- Treatments for other aspects of neuropsychiatry, e.g. cognitive dysfunction, have only minimal effect

- There are no licensed treatments for neuropsychiatric disorders associated with dementia

- Many of the patient groups are growing in size with the increasing aged population. Neurodegenerative retardation would exacerbate
CHALLENGES

• Industry, and academe, needs new targets and rationales to initiate truly novel neurosymptomatic research & drug discovery

• Development of biologically based diagnostic criteria would enhance:
  • Identifying criteria to chose the right treatment for the right patient
  • Better and more consistent stratification for clinical trials
  • Identify new routes for registration
  • Reverse and forward translation
OPPORTUNITY

- A wide range of technologies & opportunities for determining brain function and status are emerging including:
  - EEG, evoked responses, MEG, Imaging – MRI & PET, Neuropsychology testing, Improved Blood biomarker platforms etc.
  - Ability to collect, collate, analyse and interpret multi-site, multi-factor data sets
  - Many clinical indices now have direct pre-clinical homologues
  - Neuropsychiatric genetics
  - Well defined clinical cohorts
  - Understanding of neural circuits and the connectome
CONCEPT

• A battery of techniques would be implemented to assess subjects in an unbiased manner both clinically and by homology pre-clinically.

• One or more traditional symptom domains (e.g. psychosis) would be used to identify two patient groups for comparison (e.g. dementia and schizophrenia).

• Post-hoc analysis would identify:
  • a minimal diagnostic set and rational criteria for stratification
  • differences in underlying biological substrates
  • allow reverse translation to validate pre-clinical protocols
ARCHITECTURE

• The successful consortia would selected 1, 2 or 3 symptom constellations, or domains that should be widely present in most disorders, neuropsychiatric and degenerative
  • Thus if biological substrates were confirmed these would translate in many areas.

• Examples that could be recruitment and offer reverse translation:
  • Cognition (Working memory, Episodic, Reasoning and Problem solving, Attention), Reward, Stress, Affect, Agitation, Perception and sensory processing.

• Appropriate study cohorts of patients could stem from disease populations, for which selected symptom domains are described, such as:
  • Neurodegenerative diseases, Alzheimer’s disease, Parkinson’s disease or FTLD
  • Affective disorders such as Major Depressive Disorder/Treatment Resistant Depression or Schizophrenia.
APPLICANT CONSORTIUM

Expected Experience & Capabilities

• A range of clinical Imaging and Biomarker platforms
• Statistics and study design
• Clinical study support
• IT – Data communication and data basing
• Pre-clinical imaging and biomarkers
• Pre-clinical technologies
• Regulatory expertise
• Project management

Valuable Assets

• Relevant existing datasets and existing clinical studies
• Relevant Clinical cohorts and registries
• Relevant bio-banks and bio-samples
• Involvement of patient organizations and its ethical considerations
PROJECT & EFPIA CONSORTIUM

• Project planned for 3 years, but extension of 2 years envisaged if progress in first phase warrants

• Proposal still at draft stage and subject to change during final stages of consultation

• Consortium
  • Eli Lilly & Boehringer-Ingelheim (Hugh Marston & Bernd Sommer co-leads), Lundbeck, Roche, Pfizer and Novartis
  • Discussion with equipment suppliers on going
WORKFLOW

- WP1  Consortium management and governance
- WP2  Scientific consensus (Clinical/Pre-clinical) on study designs, instruments and methodology
- WP3  Data management and statistics - to allow integrated analysis of data set
- WP4  Clinical study implementation and operations
- WP5  Clinical harmonization of experimental approaches
  - Imaging  Electrophysiology  Biosample analysis  Neuropsychological
- WP6  Pre-clinical harmonization of experimental approaches
  - Imaging  Electrophysiology  Biosample analysis  Neuropsychological
- WP7  Engagement with regulatory groups, agencies and other stakeholders
- WP8  Dissemination and communication