Neuropsy2QB

TOWARDS A QUANTITATIVE BIOLOGICAL APPROACH FOR NEUROPSYCHIATRY

Draft Proposal

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 asses 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