Linking clinical neuropsychiatry and quantitative neurobiology

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Background

- Neuropsychiatric drug discovery has almost completely stalled in the past years.
- Both psychotic and affective disorders still present significant issues.
  - Speed and level of treatment response, relapse, resistance, compliance, side-effect profile etc. remain major unmet needs.
- Treatments for other aspects of neuropsychiatry, e.g. cognitive dysfunction, have only minimal effect.
- There are no licensed / approved treatments for neuropsychiatric disorders associated with dementia.
- Many of the patient groups are growing in size with the aged population increasing.
- Effective neurodegenerative retardation could exacerbate these scenarios.
Need for public-private collaboration

- Breakthroughs in psychiatric drug discovery have occurred almost entirely serendipitously.
- Understanding is usually post hoc rather than from hypothesis.
- There are a number of explanations and contributory 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.

- Consequently, there is a pressing need to establish a more quantitative framework to support treatment, research and drug discovery.
Pre-competitive nature

The scale of the problem is too large to be addressed by individual researchers or companies. To address these challenges, a pre-competitive research effort is needed, including:

- Pharmaceutical industry scientists with expertise in drug discovery
- Academic investigators with neuropsychiatric research experience
- Hospitals, clinical research centers, and practicing physicians with access to patients
- Patient, and Patient organizations, engagement in collection of clinical data, genetic information, and biosamples
- Biotechnology and diagnostics company expertise in assay development, delivery, and analysis
- Regulatory authorities
- Health care payers and economists
Objectives of the full project

- Establish a quantitative biological battery to assess subjects in an unbiased manner both clinically and by homology pre-clinically.
- Target one or more traditional symptom domains (e.g. psychosis) identifiable in two, or more, patient groups for comparison (e.g. dementia and schizophrenia).
- By post-hoc analysis identify amongst other objectives:
  - A minimal diagnostic set and rational criteria for stratification
  - Causal relationships with underlying biological substrates
  - Parameters for reverse translation to pre-clinical studies
- Facilitate the initiation pre-clinical studies utilising these new learnings

Project structured as 3 + 2 years. Option to grow in Phase 2 if strong, focused «Pilot» data can be achieved in Phase 1
Expected impact on the R&D process

- A successful project is expected to advance neuropsychiatric research, clinical practice and drug development by:
  - Establish that quantitative biological parameters can be used to effectively stratify psychological patient groups in at least one symptom domain
  - Provide a starting point the standardisation of procedures
  - As a consequence validate parameters, identify systems, suggest manipulations that can be back translated to pre-clinical studies
  - In turn this will provide a template for forward translation of novel therapeutics with pre-validated biomarkers and stratification tools for a specific target patient population
Suggested architecture of the project - 1

- The successful consortia would select symptom constellations that are widely present in neuropsychiatric and degenerative disorders
  - Examples of that could be addressed 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:
    - Neurological diseases, Alzheimer’s disease, Parkinson’s disease or FTLD
    - Affective disorders such as Major Depressive Disorder/Treatment Resistant Depression or Schizophrenia
Suggested architecture of the project - 2

<table>
<thead>
<tr>
<th>Examples</th>
<th>Idiopathic</th>
<th>Degenerative</th>
</tr>
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<tbody>
<tr>
<td>Psychosis</td>
<td>A=Schizophrenia</td>
<td>A’=Alzheimer’s</td>
</tr>
<tr>
<td>Executive Function</td>
<td>B=Schizophrenia</td>
<td>B’=Parkinson’s</td>
</tr>
<tr>
<td>Affect</td>
<td>B=TRD</td>
<td>B’=Alzheimer’s</td>
</tr>
</tbody>
</table>

**Required Patient Cohorts**

Symptom Cluster 1: A

Symptom Cluster 2: B

Symptom Cluster n: N

Idiopathic

Neurosymptomatic

Idiopathic

Neurosymptomatic

Examples:

- Idiopathic Degenerative
  - Psychosis: A=Schizophrenia, A’=Alzheimer’s
  - Executive Function: B=Schizophrenia, B’=Parkinson’s
  - Affect: B=TRD, B’=Alzheimer’s
Suggested architecture of the project - 3

- **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, Neuropsychology
- **WP6**  Pre-clinical harmonization of experimental approaches
  - Imaging, Electrophysiology, Biosample analysis, Neuropsychology
- **WP7**  Engagement with regulatory groups, agencies and other stakeholders
- **WP8**  Dissemination and communication
Expected contributions of the applicants

**Expected Expertise & 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
Possible CORE TECHNOLOGIES To be assessed in all subjects

Imaging
EEG
Neuropsychological
Blood Biomarkers
Genetics
Standard Assessment Tools

Possible SPECIFIC TOOLS

Mania Scale  Symptom Cluster 1

Emotional Processing  Symptom Cluster 2
Expected (in kind) contributions of EFPIA members
Participating pharmaceutical companies in the project:
Eli Lilly & Boehringer-Ingelheim (Hugh Marston & Bernd Sommer co-leads), Lundbeck, Roche, Pfizer, Novartis and Takeda

EFPIA companies will contribute expertise in
- Data analysis
- Prospective clinical trial design
- Homologous pre-clinical technologies for reverse translation
- Biomarker discovery and validation
- Assay development and scaling

Other IMI projects may well be able to provide tools and support, e.g. eTricks – data knowledge management for translational research
What’s in it for you?

Participation in this project will enable:

- Academic researchers to access resources to advance quantitative neuropsychiatry research and drug development
- SMEs to contribute technical expertise to support quantitative neuropsychiatry research, project management, and diagnostics development
- Regulators to influence development of new approaches for disease quantification and treatment
- Economic experts and payers to influence development of approaches to improve effective treatment of neuropsychiatry conditions
Key deliverables of the full project

- A battery of techniques, standardised protocols and a clinical network capable of exploring the quantitative biology of a defined population of neuropsychiatric patients with different disease aetiologies
- A statistically validated subset of biological parameters that can identify and stratify the patient population
- An equivalent pre-clinical capability designed to back translate the clinical findings into a rational drug discovery context
- Novel insights into the neuro- and psycho-pathology of the chosen patient cohorts
- Clear routes for future translation and regulatory approval
- Through the above provide new means to address the growing public health challenges of neuropsychiatry
Questions?

Contact the IMI Programme Office
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