ECNP
European Human Experimental Medicine Network
Meeting Report
London, 24-25 July 2013

Network Leaders: David Nutt - Imperial College, London and Gerard Dawson - P1vital LTD
Meeting Secretary – Angela Rylands – P1vital LTD.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMI</td>
<td>Innovative Medicines Initiative</td>
</tr>
<tr>
<td>Horizon 2020</td>
<td>Research and Innovation Horizon 2020 European Commission</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>pMHI</td>
<td>Pharmaco Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>IPEG</td>
<td>International Pharmaco-EEG society</td>
</tr>
<tr>
<td>ECNP</td>
<td>European Committee of Neuropsychopharmacology</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography (PET)</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalography</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>EM</td>
<td>Experimental Medicine</td>
</tr>
<tr>
<td>EEMN</td>
<td>ECNP Experiment Medicine Network</td>
</tr>
<tr>
<td>IPPEC</td>
<td>International Pre-Competitive Pharmaco EEG Consortium</td>
</tr>
<tr>
<td>D2</td>
<td>Dopamine 2 Receptor</td>
</tr>
<tr>
<td>BOLD</td>
<td>Blood Oxygenated Level Dependent</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s Disease</td>
</tr>
<tr>
<td>CANTAB</td>
<td>Cambridge Cognition</td>
</tr>
<tr>
<td>NAB</td>
<td>Negative Affective Bias</td>
</tr>
</tbody>
</table>
Executive Summary

The European College of Neuropsychopharmacology (ECNP) recently supported an initiative to build a European wide consortium of academic centres to develop, validate and maintain state of the art human experimental medicine models to support the discovery and development of new drug treatments in psychiatry. Given that expertise in experimental medicine resides largely in clinical academic centres that have access to volunteers, patients and the technology to develop such models, the aim of the ECNP led consortium is to initiate a coordinated effort across academia and industry to develop, validate and maintain new human experimental medicine models in psychiatry and build sub networks of European Centres with complimentary expertise. To determine the level of interest in the network in academia and industry a two day meeting was held in London (24-25th July 2013). The meeting supported the establishment of an ECNP led network in experimental medicine with the main areas of interest as Alzheimer’s Disease, mood disorders, schizophrenia and cognition and with a focus on human experimental medicine models with back translation from patient studies. The standardisation of common tools, outcome measures and tasks across disorders is seen as a crucial element in the development of biomarkers that can be reliably deployed across centres and used with confidence in early phase drug development studies. A common goal across the network should be methods for stratifying patients, for enriching studies and better matching them to treatments potentially through the development of companion diagnostics. The network should seek to develop the ability to conduct multi-centred studies utilising fMRI/phMRI, PET, EEG, MEG. To support its aims and objectives it is important that the network begins to influence the agenda for Horizon 2020 not only focussing on funds to support studies but also support for a training network of medics to provide them with specialist training in experimental medicine studies. The group agreed to re-convene at the ECNP meeting in Barcelona on Monday 7th of October at 8.00 AM.

Meeting Report

1. Introduction

In the past 15 years there has been little improvement in the overall success rate of novel CNS compounds in clinical development. The principal cause of failure is lack of efficacy accounting for approximately 30% of all failures. While there are a number of factors contributing to these failures high among them is the poor translation from pre-clinical models to clinical response. It is increasingly recognised that the introduction of experimental and translational medicine models at the interface between Phase 1 and Phase 2 clinical trials is a potential route to improving the success rate of potential new treatments for psychiatric disorders. Experimental medicine (EM) aims to provide a faster route through clinical trials by providing an array of assays that can detect the therapeutic potential of new compounds and provide more precise information on which patient groups are more likely to respond to potential treatments. To achieve this EM studies can use healthy volunteers, healthy volunteers with particular behavioural phenotypes or personality traits or small patient groups. Such studies also aim to employ an experimental design with objective endpoints that can be readily deployed in multiple centres with reproducible results. This
reproducibility is critical to build confidence in the endpoints as reliable predictors of efficacy in patients with the eventual aim of building a consensus on which biomarkers can be ‘qualified’ that is used routinely to confirm the efficacy of a new treatment.

Although this strategy commands a wide consensus, the tactics to enable its implementation need to be developed. Thus ECNP has initiated a human experimental medicine network and convened an initial meeting to:

1. Bring together representatives from academia, industry and public offices to set the agenda for the development of a European wide Experimental Medicine Network.
2. Identify capabilities and capacities of the academic members of the Network and suggest appropriate alliances (e.g. based on technologies or geography) as specialist nodes in the network.
3. Determine near and medium term funding priority areas for the Network members.

To develop these objectives the meeting was divided into six sessions

a) Why do we need experimental medicine?

b) What makes a good experimental medicine model?

c) New methods and tools for experimental medicine

d) Capabilities of the academic members of the network

e) An industry perspective on role of experimental medicine in drug discovery

f) Brain storming and meeting conclusions

DN stated that the proposed ECNP experimental medicine network (EEMN) is aligned with the aims of the ECNP. With over 1000 members and fellows it bridges between basic research, clinical science and medical practice. It has a strong commitment to championing the development of pharmacological treatments to improve the quality of life of people suffering from mental disorders. The recent ECNP 2011 summit report (Nutt and Goodwin, 2011) underlined the need to remedy the loss of pharmaceutical company investment from Europe by supporting new approaches to shortening the development pathway for new treatments. Experimental medicine is closely aligned with this objective. It can support the development of the Network by lobbying the European Commission to provide calls and eventual funding to support the work of the Network.
GRD provided a mission statement objectives and deliverables for the EEMN:

**Mission Statement**

To build a European wide consortium of academic centres to develop, validate and maintain state of the art human experimental medicine models to support the discovery and development of new drug treatments in psychiatry.

**Objectives for 2013**

Hold a meeting with representative from industry, academia and public offices to set the agenda for the development of a European wide Experimental Medicine Network.

**Deliverables**

Meeting report and a Network steering committee.

A set of joint objectives for Network members and industry representative that differentiate the Network from existing consortia.

Identify capabilities and capacities of the Network and suggest appropriate alliances (e.g. based on technologies or geography).

Identify funding opportunities for 2014 and beyond.

GRD provided an account of P1vital’s experimental medicine network in the UK. The network focuses on EM models in depression, schizophrenia, cognition and anxiety. Despite the widespread reporting of industry’s exit from psychiatry, the demand for studies with propriety compounds is high and growing. Key factors for success are (i) models that have been validated with positive and negative control drugs; (ii) the ability to conduct multi-centred studies without centre effects; (iii) the ability to combine fMRI data from multiple scans without centre effects. The ability to conduct multiple centres studies is critical for credibility as it demonstrates that the results obtained are robust and reproducible.

### 2.2. Examples of EM Models

| c) ECNP Experimental medicine network: Biomarkers for depression and its treatment | Catherine Harmer — Oxford (UK) |

Catherine Harmer presented an EM model employing well validated biomarkers for the efficacy of antidepressant drugs in patients with depression. The model is predicated on the observation that negative affective bias (NAB) is a key maintaining factor in depression and recent evidence suggests
antidepressant drugs affect these processes very early in treatment before changes in the patient’s mood are apparent. This early change in NAB induced by antidepressants can be detected by a number of optimised cognitive tests as early as 7 days after treatment is initiated. It is thought that antidepressants exert this effect by reducing the response of the amygdala to fearful stimuli, a proposal supported by fMRI studies. Critically, with regard to developing robust EM models; a) the behavioural and fMRI results have been validated with both positive and negative control drugs and b) the drug effects seen in patients are also apparent in healthy volunteers.

Val Curran described an EM model that is being used to investigate the effects of drug taking on cognitive processes. She described the effects of frequent Ketamine use on various cognitive tasks including long-term memory, planning and problem solving and showed that frequent ketamine use significantly impairs performance on these tasks when compared to the performance of infrequent ketamine users, ex-ketamine users, poly drug users and non-drug users. Thus chronic ketamine users may provide a naturalistic cognitive deficit model in which to assess the effects of cognition enhancers. VC also described the potential protective effects of cannabidiol amongst cannabis users. Skunk-type strains of cannabis contain a higher ratio of THC to cannabidiol than do hashish or herbal types. The cognitive performance of skunk-users compared to those that use cannabis with a higher ration of cannabidiol to THC, is significantly impaired while intoxicated.

3.3 EM Methodologies

Mital Mehta outlined the benefits of using human pharmacoMRI (phMRI) in both pre-clinical and clinical models to investigate pharmacological effects on task-free brain function. MM described the brain response to the effects of the NMDA receptor antagonist, ketamine (IV) which is being increasingly used as a mechanistic marker of glutamatergic dysfunction. PhMRI data were collected from 10 healthy male participants, at rest, on two separate occasions. The anatomical distribution of ketamine’s effects for all models was consistent with results of previous imaging studies in humans whereby BOLD signal increases in regions including midline cingulate and supracingulate cortex, thalamus, insula, anterior temporal lobe and ventrolateral prefrontal structures, and BOLD signal decreases in the subgenual cingulate cortex. Machine learning algorithm techniques can also potentially provide further rigour to the phMRI technique, improving both reproducibly and reliability of phMRI measurements. Thus phMRI can provide new insights into the mechanism of action of existing compounds and new treatments by indicating the areas of the brain modulating haemodynamic response.
Gitte Moos Knudsen summarised that positron emission tomography (PET) imaging can be used for drug assessment by providing a surrogate marker or biomarkers to characterise patient samples. It also allows assessment of the brain penetration of new drugs through receptor occupancy studies thereby helping to identify doses for experimental medicine and patient studies. GMK also described recent advances in simultaneous PET and fMRI (Sander et al. 2013) studies. Such studies provide the possibility of identifying the mechanisms of neurovascular coupling as well as the delineation of functional brain circuits by relating receptor binding to local and distant functional responses.

Philippe Danjou described recent advances in electroencephalography (EEG), a physiological brain biomarker that is largely used to measure qualitative and temporal changes in cortical electrical activity. The longstanding EEG technique is currently being revisited and improved, and it’s methodology validated. The advantage of EEG over other methodologies such as fMRI is that the equipment is relatively cheap and portable and thus can be deployed in many research settings. It is also usable in different species. EEG also has a higher temporal resolution, milliseconds microseconds vs. minutes/seconds for fMRI allowing event-related recordings. Although EEG is widely used in cognitive science, neuroscience and psychophysiological research many of these methods were not standardised sufficiently for meta-analyses and efficient GO/No-Go decisions in drug development. This issue is being addressed by the International Pre-Competitive Pharmaco-EEG Consortium (IPPEC) society who are establishing industry-wide standardisation of pharmaco-EEG recording techniques in humans and animals. The consortium is supported by Pharma companies including Abbott, AstraZeneca, J&J, Lundbeck, Pfizer, Servier and UCB. See also Wilson et al. 2013 for a more complete account of these activities.

1. Capabilities of the Academic Network

a) Studying antipsychotic treatment failure in animal models

Davide Amato – Erlangen, Germany
The response to antipsychotic treatment in patients is somewhat variable. For a given treatment, patients can reach remission or partial remission and about a third of them will never respond. Despite the initial treatment success as many as 80% of the individuals with schizophrenia who were responders to the treatment experience antipsychotic failure, according to CATIE figures - a large clinical trial aimed at monitoring the efficacy of first and second generation antipsychotic drugs. Davide Amato (DA) described a preclinical model of antipsychotic treatment failure using clinically relevant dosing via osmotic pumps in rats. The model combines behavioural and neurochemical techniques such as spontaneous and stimulated locomotion, pre-pulse inhibition test, microdialysis, western blotting, autoradiography (data not shown) and PET. Results suggested that D2 receptor occupancy predicts treatment response, but not treatment failure. In fact, treatment failure occurs despite the 70% of D2 receptors are still occupied by the antipsychotic. Antipsychotic treatment failure seems to be associated with increased levels of dopamine transporters and to consequent decreased levels of basal dopamine. This effect might lead to a behavioural supersensitivity, which is independent of increased D2 receptor availability and results in eventual treatment failure in patients.

b) Capabilities of the Hospital Gregorio Marañón (Universidad Complutense) and the CIBERSAM

Carmen Moreno - Madrid, Spain.

Carmen Moreno (CM) described the capabilities of the Department of child and adolescent psychiatry (Hospital, G.U. Gregorio Maranon). The group has a large catchment area with over 800,000 children and adolescents and access to purpose built inpatient facilities at the hospital. The group’s research, led by Prof. Arango, focuses on schizophrenia, autism spectrum disorders and diagnostic overlap with an emphasis on translational research with strong clinical implications. CM also described the work of Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) with the mission of improving clinical care and mental health generated by translational research in psychiatry and neuroscien (www.cibersam.es). Funded by a FP7 grant they are currently creating a Roadmap for Mental Health Research in Europe attempting to integrate and coordinate research in all EU countries (www.roamer-mh.org).

c) ECNPExperimental Medicine Network: The Würzburg Perspective

Jürgen Deckert - Würzburg, Germany

There are several research priorities relevant to experimental medicine at the Centre of Mental Health, University Würzburg. These include a translational medicine approach to elucidating mechanisms of depression and anxiety in humans using both human and animal models. These are supported by a number of key technology platforms including high throughput genotyping, clinical epidemiology, a specialist behavioural unit, a virtual reality suite and fMRI facilities. Studies focus on combining and individualizing various therapies (pharmacotherapy, behavioural therapy, virtual
reality, psychotherapy and transcranial magnetic stimulation (TMS)) using e.g. fMRI and (epi)genetics to maximise patient therapeutic response.

d) ECNPExperimental Medicine Network: The Aristotle University of Thessaloniki Perspective

Georgios Papazisis – Thessaloniki, Greece

Research collaborations have been established between the Department of Pharmacology/Clinical Pharmacology, Department of Toxicology, the 2nd Department of Psychiatry, Laboratory of General Biology and Genetics located within at the School of Medicine. A number of animal models have been established including a rat hypoxic-ischemic encephalopathy model, the rat elevated plus maze, open field maze, olfactory social memory and rota rod tests to support research in psychiatric and neurological disorders. A push-pull super fusion technique has also been established to determine tissue levels of neurotransmitters in specific rat brain regions. Current patient studies include a pharmacogenetic study to determine the influence of ABCB1 genotypes on the therapeutic response to antipsychotics in schizophrenic patients.

e) Translational matching of gene-imaging data and improvement of target identification / validation

Jeffrey Glennon – Nijmegen, The Netherlands

There are four core research areas linking three centres, Donders Institute for Brain, Cognition and Behavior Department of Cognitive Neuroscience and the Karakter Child and Adolescent Psychiatry Centre, at the University Nijmegen Medical Center. These are:

1. Translational mapping of neurochemistry / imaging / behaviour in psychiatric traits between clinical populations and animal models.
2. Translation of pharmacological & non-pharmacological therapies in autism, ADHD, impulse / compulsive control, conduct disorder.
3. Creation (bioinformatics) and functional validation of targets from genetic networks in psychiatric traits / disorders.

The overall aims of these collaborations are to:

1. Establish predictive neural, genetic and molecular markers of impulsivity/compulsivity end phenotypes in paediatric and adult populations with a focus on impulsivity, compulsivity and decision making.
2. Optimize and develop animal models for pharmaceutical screening and proof-of-concept studies.
3. Build and validate a translational biomarker endophenotype database united by machine learning analysis.
4. Provide pilot efficacy data in clinical populations to support future large scale clinical trials according to these strategies.


<table>
<thead>
<tr>
<th>f) Experimental Psychopharmacology, Maastricht University and Cambridge Cognition</th>
<th>Wim Riedel – Maastricht, The Netherlands and Cambridge UK.</th>
</tr>
</thead>
</table>

Wim Riedel (WR) has two roles, one as professor Experimental Psychopharmacology at the University of Maastricht and the second as Vice President of Science, Cambridge Cognition. WR described the research in psychopharmacology at the University of Maastricht which has focused on developing models of aggression, hypoxia, hyperventilation, sleep deprivation, physical exhaustion, heat stress, water depletion, scopolamine, tryptophan and histamine depletion, 5-HT agonist challenge and methylphenidate challenge. They have also developed biomarkers using naturalistic driving tests, cognitive tests, eye movements and EEG. More recently they have developed preclinical models of Alzheimer’s Disease (AD). Cambridge Cognition has established a product for cognitive testing (CANTAB) which is widely used in academia, industry and primary care. They are developing tools for home and remote cognitive testing on various emerging test platforms such as the iPAD. WR also outlined a proposed new model of cohort building to support the development of new treatments for AD and the recent new guidelines provided by the FDA relating to the prevention and treatment of AD.

<table>
<thead>
<tr>
<th>g) Human Psychopharmacology research at Utrecht University</th>
<th>Joris Verster – Utrecht, The Netherlands</th>
</tr>
</thead>
</table>

Human psychoharmacology research at Utrecht University focuses on the effects of therapeutic drugs and drugs of abuse on cognitive and psychomotor functioning, memory, daily activities (driving, work performance), and quality of life. Joris Verster highlighted their work on experimental medicine and drug safety in real-life situations such as driving. The department has 30 years experience in evaluating the effects of drugs on driving behaviour on the road and have developed standard operating procedures for conducting on-the-road driving tests and the measurement of the standard deviation of lateral position (SDLP). The group have developed and maintained a unique database of the effects of hypnotic and other drugs on driving behaviour.

<table>
<thead>
<tr>
<th>h) Centre for Innovative Research in Psychiatry and Psychotherapy</th>
<th>Markus Leweke – Heidelberg, Germany.</th>
</tr>
</thead>
</table>

Markus Leweke described how the Centre for Innovative Research in Psychiatry and Psychotherapy (CIPP) has embarked on a number of large scale infrastructure projects to establish a state-of-the-art
experimental medicine and treatment centre. Current funding provides for: (i) an outpatient centre to facilitate research in diagnostics and therapy, virtual reality applications, and neuropsychological and behavioural assessment; (ii) a 6 bed unit to enable Phase 0-II clinical trials (iii) an imaging centre with MR, PET and MEG facilities and (iv) laboratories to support the development of genomic, proteomics, lipidomics and CSF biomarkers and bio-banking. As well as focusing on psychiatric disorders for adults, a new interdisciplinary treatment centre for adolescent-specific disorders will be established.

2. Industry perspectives on experimental medicine

| a) Neuroscience Experimental Medicine | Darrel Pemberton – Beerse, Belgium. |
| Janssen Research and Development | |

Janssen Research and Development is a major contributor to research in basic and clinical neuroscience. It has a significant portfolio of treatments for psychiatric disorders. It has recently focused its discovery research efforts in two main areas, Alzheimer’s disease and mood disorders. Darrel Pemberton highlighted some advances in EM and the utility of biomarkers from a pharma perspective. EM models allow for rapid progress into humans, moving the focus of efficacy signal detection to Phase 0 – Phase 2a providing a “rapid decision” approach. It can also provide early verification of target engagement and provide a better understanding of disease pathophysiology. The selection of homogeneous proof of concept sub-populations using biomarkers and informatics, validated clinical and sub-clinical traits is seen as critical to the development of precision medicine approaches. For mood disorders biomarkers that can confirm a diagnosis of major depressive disorder is seen as an important adjunct to clinical assessment which may reduce placebo responses in clinical trials. Moreover biomarkers and EM models that provide an early detection of efficacy can shift compound attrition to the early stages of clinical development. A wish list of biomarkers for Janssen would include diagnostic biomarker for the early detection of efficacy and safety in MDD and prognostic biomarkers of TRD. Darrel’s experience with previous networks suggests that support from a professional project management organisation would significantly improve involvement and overall scientific productivity.

| a) Experimental Medicine – A Lundbeck perspective | Birgitte Søgaard– Copenhagen, Denmark. |

Careful consideration needs to be given to development of biomarkers in particular what the biomarker is being developed for. Simply mimicking the symptoms that are seen in patient populations in healthy volunteer models may lead to the same issues that have arisen from the use of animal models. Moreover these models will not help us find new targets for psychiatric diseases. In recent years Lundbeck have built a biobank of bloods samples from patient populations, with the aim of looking into markers for patient segmentation. There are clear subgroups in depression and
inflammation definitely plays a role and Lundbeck have been able to reproduce markers in several populations suggesting that these markers are robust. However, it is not yet possible to predict treatment response based on blood markers.

PET is proving to be very useful and is informing early phase MAD studies and selection of doses. It would be useful to be able to combine PET and EEG and to use EM for more exploratory studies but they should be guided by patient studies.

The meeting concluded with a review session, objectives for 2013-2014 and a number of action points. The formation and development of the network was fully supported with a focus on the development of experimental models to elucidate disease mechanisms and to support drug discovery. The main therapeutic areas of interest are: Alzheimer’s Disease, mood disorders, schizophrenia and cognition with a focus on human EM models with back translation from patient studies. The standardisation of commons tools, outcome measures and tasks across disorders are seen as crucial elements in the development of biomarkers that can be reliably deployed across centres and used with confidence in early phase drug development studies. A common goal across the network should be methods for stratifying patients for enriching studies and better matching them to treatments potential through the development of companion diagnostics. The network should seek to develop the ability to conduct multi-centred studies utilising fMRI/phMRI, PET, EEG, MEG. It is important that the network begins to influence the agenda for Horizon 2020 not only focussing on funds to support studies but also to fund a training network for medics to provide them with specialist training in experimental medicine studies.

The group agreed to re-convene at the ECNP meeting in Barcelona. At the Barcelona meeting a steering group will be formed to set objectives for 2014.

Post meeting note: ECNP experimental medicine meeting (2) - Monday 7 October from 08.00-09.00 in room Y3.

References:
