Innovative Medicines Initiative attempts to address this gap by providing more homogeneous groupings for research in new drug development and clinical trials.

Speaker 2: Shitij Kapur, UK
Title: NEWMEDS Innovative Medicine Initiative – Accomplishments and Lessons from a Pre-Competitive Consortium.
Shitij Kapur, MBBS, PhD, FMedSci
King’s College London and the Institute of Psychiatry, Psychology and Neuroscience

There have been remarkable advances in genetics, molecular biology and imaging technologies and every year nearly 15,000 articles relating to schizophrenia and depression are published. Despite these notable advances, there have been few truly innovative new medications that have made it to the clinic. The EU Innovative Medicines Initiative attempts to address this gap through a series of consortia.

NEWMEDS was one of the first (initial application 2008) initiatives and it identified three major challenges: i) a lack of pathophysiology-accurate animal models guiding the drug discovery; ii) a lack of tools and tests in healthy volunteers that can provide early indication of efficacy; and iii) the reliance of clinical trials on symptom-based DSM-categories which inevitably lead to biologically heterogeneous groups of patients. To overcome these limitations, NEWMEDS brought together a consortium of expertise from seven leading universities, two SMEs, and ten EFPIA partners. The purpose of the project was not to develop new drugs – but to develop new methods. Therefore, the focus was on new “pre-competitive” insights, methodologies and analytical methods the NEWMEDS.

Over its lifetime the NEWMEDS consortium: a) developed standardised animal models that focus on reliable cross-species endophenotypes (e.g. cognitive function) based on touch-screen technology which is analogous to what is used in clinical testing; b) develop IMRI and PET based paradigms which may serve as early or surrogate markers to provide guidance for drug development – compatible with cross-species translation and developed new machine-learning methods of image analysis (Pipir); c) examined a set of genetic abnormalities (CNVs) closely linked with Schizophrenia (15q11, 15q13), validated their impact on human populations and developed homologous animal models that are now available to others; d) amassed the largest depression treatment cohort to look for pharmacogenetic biomarkers to stratify response to antidepressant treatments, but, did not find major stratifiers – however this exercise did lead to a simple tool for assessing the clinical utility of any future biomarkers (www.depressiontools.org); and e) by bringing together the largest multi-industry clinical database in Schizophrenia and Depression – identified how trials could be shorter and more efficient. But also identified how trials inadvertently enrol duplicate patients and built a potential solution for this problem (DupCheck - www.dupcheck.org).

While the NEWMEDS consortium itself has come to an end it provided several important lessons about the organisation of these consortia: especially the importance of long-term commitment, consistency of personnel involved, the necessity of focussed objectives and procedural flexibility. The IMI continues to be using this mechanism for a range of projects in Autism (EU-AIMS), Pain (EuroPain) and Cognition (PharmaCog).

Drug development in Psychiatry still remains a challenge. Since 2008 when this project was started, several major companies have disinvested from psychiatry highlighting the complexity of challenges in this area. Given this, such “pre-competitive” consortia are even critical to make the advances to make the field attractive enough for commercial interests to then explore them.

The talk will provide more details about NEWMEDS, lessons learnt and some thoughts about the challenges and solutions for drug development in Psychiatry.

Speaker 3: Tetsuya Suhara, Japan
Title: Japan PPPs Perspective

Abstract
CINP is a leading organization in the field of CNS drugs. As Public Private Partnerships for CNS drug innovation activity, we have discussed in Japan on three topics 1. Imaging biomarkers, 2. Stratification factors, 3. How to share the clinical study data with Academia, Industry and Regulators. Working group 1 focused on imaging biomarkers those can be useful for decision making in drug development. The idea of three pillars to ensure the steps to get clinical POC has been reported form Pfizer. Pillar 1 means the evidence reaching the target site, pillar 2 means the evidence of binding to the pharmacological target and pillar 3 means the evidence of pharmacological action in the brain. The imaging biomarker can be used whether the candidate drug fulfill pillar 2, using receptor occupancy. Using common terminology to express the developing stage would be useful in PPP setting, since different company used different terminology in each company. During our discussion, we thought more precise classification would be needed to explain the stage of the candidate drugs. We propose tier as an alternative of pillar, [Tier 1;target exposure, Tier 2; target binding/engagement, Tier 3a; mechanism-related change, Tier 3b; functional modulation, Tier 4; patient stratification, Tier 5 Disease-related change]. Future needs of imaging biomarkers will be discussed in relation to the various imaging methods. Working group 2 focused stratification factors using the data on randomized double-blind clinical trials of conventional antidepressants vs placebo that have been conducted so far in Japan. Working group 3 focused how to share the clinical study data with Academia. Although majority of the pharmaceutical companies have disclosed not only an initiation/completion of their sponsored clinical trials but also the results through the public domain like clinical trial.gov., the details of the disclosed data have been limited. Working group 3 aimed to create a system to construct a database which unifies all clinical data obtained in the sponsored clinical studies in order to facilitate the pharmaceutical products of the next-generation.

CP03: Depression

Speaker: George Papakostas, USA and Hong-Jin Jeon, Republic of Korea

Abstract
Major Depressive Disorder (MDD) is a serious, debilitating, life-shortening illness that affects many persons of all ages and backgrounds. All FDA-approved antidepressants used as monotherapies have shown only modest benefits. In fact, in acute (6-8 week) studies, typically with relatively uncomplicated, non-chronic forms of MDD, remission rates range between remission rates range between 30.0-35.0%. To make matters worse, as currently delivered, none of these pharmacologic and
non-pharmacologic treatments have been shown to result in rapid symptom resolution (defined as a sizeable and statistically significant treatment effect versus placebo that is apparent as early as 24 to 72 hours post-initiation of therapy), despite the tremendous need for rapid antidepressant therapies that would allow for meaningful clinical improvements within the context of very short hospital admissions for TRD patients. The goal of the NIMH-funded RAPID (rapidly acting treatments for major depressive disorder) program is explore treatments that could meet this need. This lecture will review current options for treatment-resistant depression, as well as the rational and structure of the RAPID program and its components.

**PL04 Imaging: Multimodal human brain imaging of the serotonergic transmitter system**

**Chair**: Siegfried Kasper, Austria

**Speaker**: Gitte Moos Knudsen, Denmark

**Abstract**

Over the last decade, the availability of suitable Positron Emission Tomography (PET) radioligands has enabled new vivo imaging of the serotonin (5-HT) system in humans. The combination of high-resolution PET and structural magnetic resonance brain imaging (MRI) with novel quantification methods (1) allows for generation of population based brain atlases showing the 5-HT receptors and transporters in the brain in great detail. Access to 5-HT imaging (MRI) with novel quantification methods (high-resolution PET and structural magnetic resonance brain imaging with novel quantification methods) allows for meaningful clinical improvements within the context of very short hospital admissions for TRD patients. The goal of the NIMH-funded RAPID (rapidly acting treatments for major depressive disorder) program is explore treatments that could meet this need. This lecture will review current options for treatment-resistant depression, as well as the rational and structure of the RAPID program and its components.

An example of how multimodality imaging approaches can benefit science will be given here: Healthy volunteers underwent three-week intervention with either placebo or the selective serotonin reuptake inhibitor (SSRI) fluoxetine and were scanned before and after with fMRI and the 5-HT4 receptor radioligand [11C]SB207145 PET. The intervention did not result in any significant group-differences in emotional face processing with fMRI. This, however, changed when taking the SSRI intervention associated changes in central 5-HT levels, as measured with the 5-HT4 receptor radioligand [11C]SB207145 PET (2), into account: The greater the increase in central 5-HT levels, the lower the threat-related amygdala reactivity (3). This provides direct evidence that individual changes in brain 5-HT levels are linked to threat-related amygdala reactivity.

Although historically mostly being used separately, magnetic resonance imaging (MRI) and positron emission tomography (PET) offer two complementary techniques for in vivo investigation of the brain. With the recent development of combined MR-PET equipment that allows for simultaneous acquisition of the signals, a powerful tool has been made available to tap different physio-chemical properties of the brain condition. This is particularly promising assessment of pharmacological or non-pharmacological interventions because one can then assess the regional and temporal effects of, e.g., hemodynamics and neurotransmitter related outcome measures.

Simultaneous fMRI-PET studies have captured effects of regional differences in pharmacologically induced endogenous brain neurotransmitter levels of dopamine (4) or pain induced changes in opioids (5) corresponding to observed changes in regional cerebral blood flow. The relationship between pharmacologically induced changes in receptor occupancies and regional blood flow changes remains, however, to be better understood.

In conclusion, a particular promising exploitation of simultaneous PET-MRI is its ability to capture neurotransmission specific networks within the brain and to investigate how those are related to the associated changes in regional metabolism and blood flow. This presents a completely novel opportunity to assess pharmacological effects on the human brain in vivo.

**References**

D. N. Greve et al., Neuroimage. 92, 225 (2014).

M. E. Haahr et al., Mol. Psychiatry 19, 427 (2014).

P. M. Fisher et al., Neuropsychopharmacology (2015).

C. Y. Sander et al., Proc. Natl. Acad. Sci. U. S. A 110, 11169 (2013).

H. Y. Wey et al., Neuroimage. 102 Pt 2, 275 (2014).

---

**Tuesday 5th July 2016**

**08.45 – 09.30**

**PL05 Schizophrenia / Dopamine:**

**Chair**: Anthony Phillips, Canada

**Speaker**: Anthony Grace, USA

**Title**: Dopamine Neuron Regulation and its Implications for the Treatment and Prevention of Schizophrenia

**Abstract**

Substantial evidence shows a role for the dopamine system in schizophrenia. However, studies indicate that it is not the dopamine neurons themselves that are responsible for these pathological states, but instead the disorder appears to arise due to a disruption of dopamine neuron regulation by afferent inputs. Dopamine neurons recorded in vivo are known to exhibit multiple functional activity states, including baseline tonic firing and phasic activation in response to salient stimuli. Phasic burst firing is believed to be the behaviorally relevant “signal” of the dopamine neuron, whereas the level of tonic discharge represents the “gain” or the level of amplification of this signal. This tonic gain is differentially regulated by multiple brain regions, with the ventral hippocampus playing a major role. Using the MAM developmental disruption model of schizophrenia in rats, we found that parvalbumin interneuron loss in the hippocampus leads to abnormally high tonic dopamine neuron firing, causing the system to be hyper-responsive to phasic stimuli. This would lead to over- or misinterpretation of external events. Restoring GABAAergic balance in the hippocampus by a selective GABA A alpha 5 positive allosteric modulator restores baseline dopamine neuron firing and behavioral responses to amphetamine. In contrast, this drug is not effective if the rats are pre-treated with a D2 blocking antipsychotic drug, which has implications for the failure of novel target compounds in clinical trials.