Novel Methods leading to New Medications in Depression and Schizophrenia

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coordinator of NEWMEDS

Stakeholder meeting, Brussels June 14th 2010

Innovative Medicines Initiative

NEWMEDS – the work leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (IMI)

”The ugly duckling” or ?

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Who are the key contacts in NEWMEDS?

Coordinator: H Lundbeck A/S, Copenhagen, Dr Tine Bryan Stensbøl

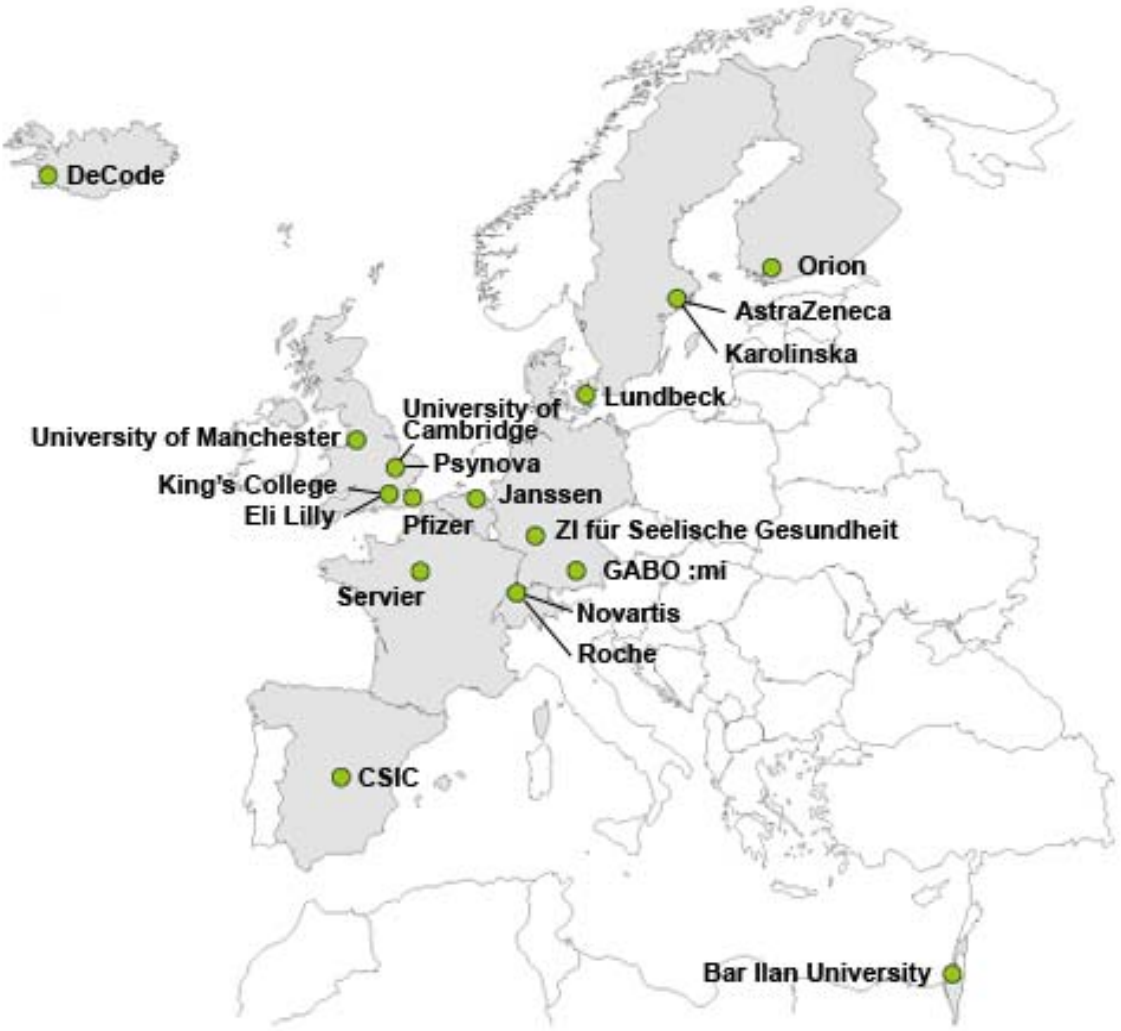
Leader of the Managing Entity: King's College London, London, Prof Shitij Kapur

Project Office: GABO:milliarium mbH & Co. KG, Munich, Kathrin Stoller

www.newmeds-europe.com

NEWMEDS – the work leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (IMI)

The Consortium members are spread all over Europe



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What is the intention of NEWMEDS?

NEWMEDS brings together top scientists from academic institutions with a wide range of expertise, and partners them with nearly all major pharmaceutical companies.

NEWMEDS will focus on developing new animal models which use brain recordings and behavioral tests to identify innovative and effective methods that translate the underlying biology of schizophrenia and depression from animal to man.

NEWMEDS will develop standardised paradigms, acquisition and analysis techniques to apply brain imaging, especially fMRI and PET imaging to drug development.

NEWMEDS will examine how proteomic markes may provide a tool for stratifying patients in schizophrenia and whether this information can validated in animal models of schizophrenia.

NEWMEDS will examine how new genetic findings (duplication and deletion or changes in genes) influence the response to various drugs and whether this information can be used to choose the right drug for the right patient.

Finally, NEWMEDS will try and develop new approaches for shorter and more efficient trials of new medication – trials that may require fewer patients and give faster results.

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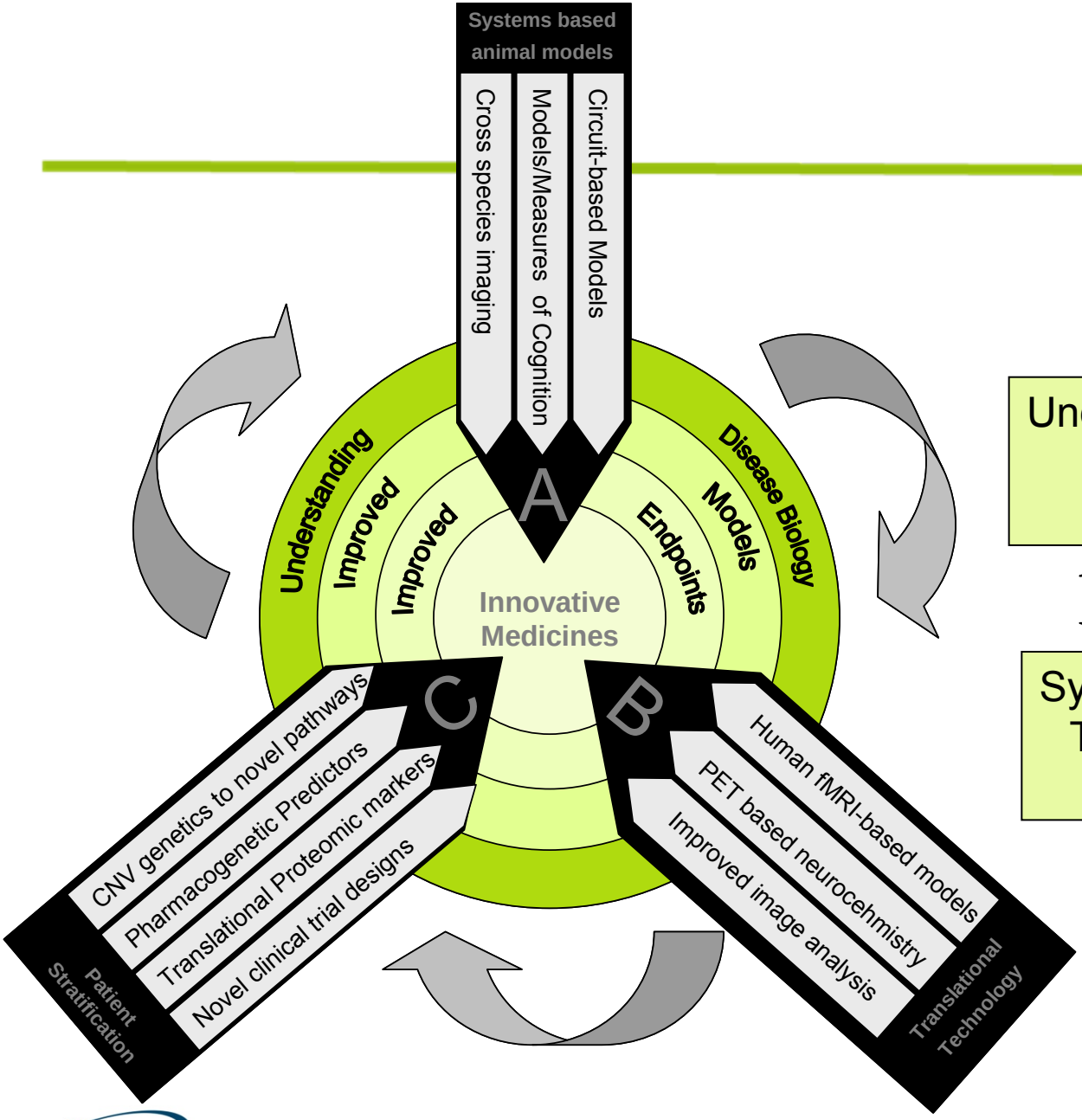

Understanding disease biology
Improve Models
Improve Endpoints

Systems based animal model
Translational technologies
Patient stratification

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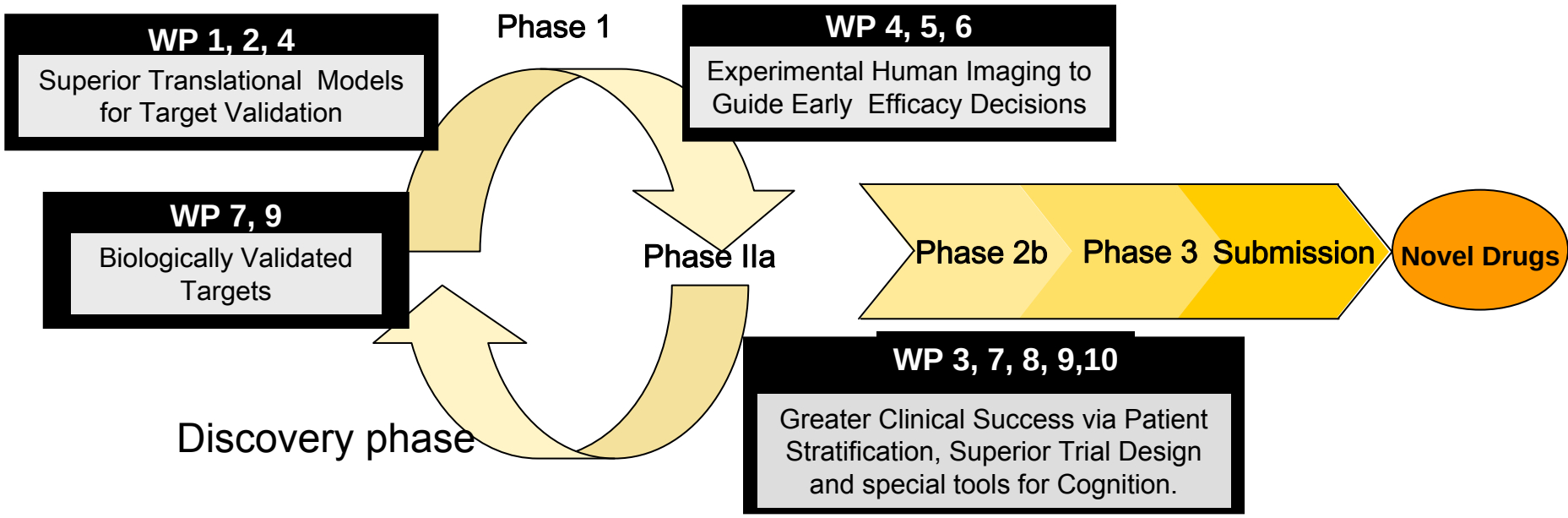
The Development of a drug and expected outcome of NEWMEDS



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Key data for NEWMEDS

Start date:	**1 September 2009**
Runtime:	**5 years**
Structure:	**11 Workpackages**
Clusters:	**System based animal models** **Translational Technology** **Patient Stratification**

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NEWMEDS Workpackage Leads

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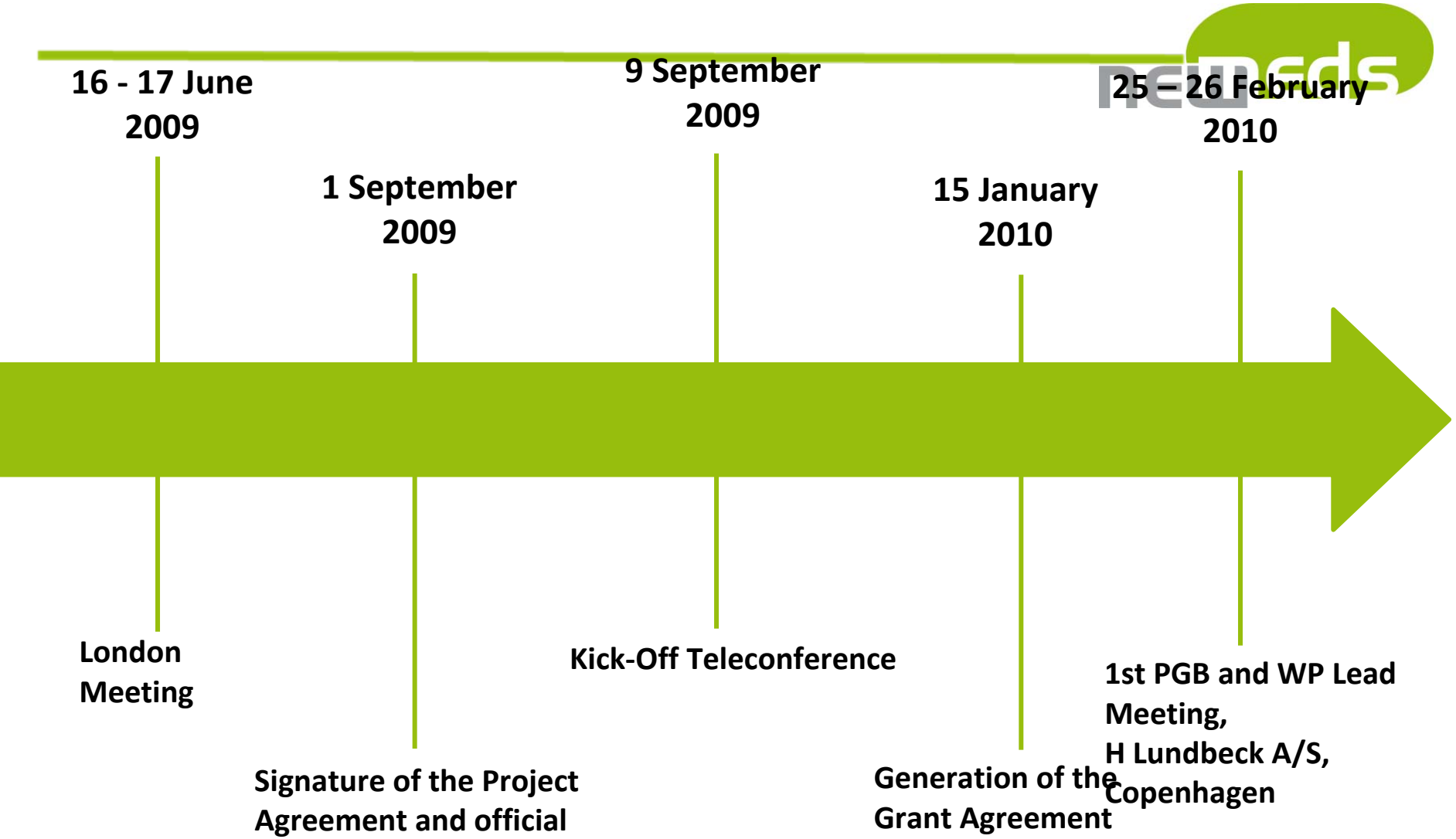
How time flies!



Deliverable A Development of translational models based on systems and circuits that translate to clinical endpoints

WP1. **Animal models of schizophrenia and depression based on circuit dysfunction led by *Prof. Dr. Artegas (CSIC) and Michael Spedding (Servier)***

- Validation of animal models of schizophrenia based on pyramidal cell electrophysiology and models of depression based on circuit (prefrontal-amygdala-hippocampal) dysfunction.
- Identification of the molecular and cellular basis of circuit dysfunction to identify new targets.

Highlights Q210: Publications in preparation

- Effects of PCP on midbrain thalamic neurons. Reversal by clozapine. N. Santana, E. Troyano, G. Mengod, P. Celada, F. Artigas in prep
- Role of 5□HT receptors on the PCP□induced disruption of cortical activity and its reversal by clozapine. L. Kargieman, P. Celada, F. Artigas in prep
- Joint session abstract for SfN San Diego to be submitted before May 13, 2010

WP2. **Animal models that model the clinical endpoints of cognitive impairment associated with schizophrenia led by *Prof. Trevor Robbins (UCAM) and Mark Tricklebank (E.Lilly)***

- Develop a battery of biologically and statistically validated tests of cognition that provide the preclinical rodent analogue of the impairments observed in schizophrenia.
- Using this battery, define the experimental manipulations that best model the deficits seen in schizophrenia.
- Examine the portability of the battery to different EFPIA labs and test established and emerging compounds for CIAS.

Highlights Q210 :

- Two UCAM Post□docs hired
- Analysis of object recognition started: details of testing conditions across EFPIA
- partners and UCAM obtained. Data requested.
- Meta□analysis proposals refined and awaiting data from EFPIA collaborators

Deliverable A Development of translational models based on systems and circuits that translate to clinical endpoints

WP3. Development of a computerised cognitive battery that is optimal for international cognitive clinical trials and preclinical back-translation led by *Shon Lewis (KCL) and Pfizer (Donna Palumbo)*

- Provide a comparison and validation of MCCB, Cog-State Computerised Battery and CANTAB and evaluate MCCB in three distinct European linguistic groups.
- Evaluate the sensitivity of these scales to a pharmacological challenges using a single dose experimental strategy.
- Evaluate the concept and trial designs for combined pharmacological plus cognitive remediation therapy trials.

Highlights Q210

- The study of cognitive enhancer and cognitive training combination has been adopted (accepted) by the Mental Health Research Network.
- In March, two Research Assistant appointments were made at the Manchester site.
- MMCB training programmes have been obtained and disseminated to both sites so that MCCB training can begin. Arrangements are being made for the delivery of training using the CogState package at both the IOP and Manchester sites, to be undertaken at the earliest opportunity.

Deliverable B Development of functional and molecular neuroimaging for drug discovery

WP4 Cross-species and cross-modal (fMRI and EEG) models for early drug discovery led by *Prof. Meyer-Lindenberg (CIMH) and Adam Schwarz(E.Lilly)*

- Development of a method to undertake cross-modal imaging using simultaneous fMRI and EEG
- Develop a cross-species (rodent-human) method of evaluating the same perturbation (e.g. ketamine) using identical methods (fMRI-EEG) .
- Development of a standardised 'discovery' panel of fMRI activation tests that tap into cognitive, reward and affective mechanisms.
- The implementation of this battery across different laboratories along with its validation using existing and emerging pharmacological probes.

Highlights Q210

- SOP for rodent neuroimaging quality control delivered/uploaded to milliarium and
- first rat rCBV EPI images with ketamine challenge
- Measured 14 human subjects for the test/retest study
- Developed Matlab Code for ICC analyses

Deliverable B Development of functional and molecular neuroimaging for drug discovery

WP5 **Cross-species neurochemical imaging using PET and micro-PET with a focus on transmitter release and modulation led by *Eric Wong (AZ) and Christer Haldin (Karolinska)***

- Development of a PET imaging approach that is sensitive to changes in endogenous serotonin (using 5-HT1B) and norepinephrine (using α2C)
- Development of micro-PET equivalents that can be used for early preclinical drug discovery and can then be translated into experimental human experiments.

Highlights Q210

Paper published: Fefluramine induced serotonin release decreases [11C]AZ10419369 binding to 5HT1B receptors in the primate brain. Synapse, Finnema et al., 2010

- Accepted abstracts: **Task 1**: SNM (June 2010, Salt Lake City), CINP (June 2010, Hongkong),
- NRM (July 2010, Glasgow), ECNP (August 2010, Amsterdam), EANM (October 2010, Vienna)

WP6 **Advanced image analysis techniques that are purpose-made for drug development decisions led by *Mick Brammer (IOP) and Lori Badura (Pfizer)***

- Develop a multivariate machine-learning whole-brain image analysis method which can be used for drug-classification in preclinical and clinical studies.
- Provide a user-friendly interface (Matlab toolbox) to facilitate the use of the new analysis methods in industry/academia.
- Extend the use of these machine-learning methods for other large variable datasets (e.g. function MRI/genetics; functional MRI/cognition)

Deliverable C Identification of biomarkers for patient stratification and response prediction

WP 7 **Using CNV based genetic alterations to identify markers and targets for new drugs – a focus on schizophrenia led by *Hreinn Steffansson (DeCode) and Michael Didriksen (Lundbeck)***

- Identify the *cis*- and *trans*- effects of schizophrenia associated CNVs on gene expression.
- Using pathway analysis of altered gene expression, identify the biologically relevant biomarkers and new treatment targets.
- Use pathway analysis to generate candidates for patient stratification and response prediction.

Highlights Q210

- Phenotyping effort has been started in Iceland 100 subjects have been evaluated
- Structural MRI measurements in Iceland have been started 60 subjects have been scanned
- Data from EFPIA being sent to deCODE for analysis
-

WP8 **Identifying biomarkers of response for response prediction and patient stratification – a focus on depression led *by Kings College***

- Establish predictors of differential response to noradrenergic vs. serotonergic antidepressants using integrative modelling of clinical and genomic variables.
- Establish genomic signature of treatment resistant depression to provide a target group for the development and testing of novel treatments.
- Develop and test the sensitivity/specificity of prediction of response at individual level

Highlights Q210

- Samples selected
- Imputation and meta analysis of existing samples
- Genotyping commenced

Deliverable C Identification of biomarkers for patient stratification and response prediction

WP9 **Proteomic biomarkers for patient stratification and animal model validation – a convergent approach for Schizophrenia and Depression *led by Sabine Bahn and Gabriel Vargas (Roche)***

- to compare the clinical biomarker signatures of schizophrenia with those of preclinical models commonly used in the drug discovery process to aid the development of novel therapies.
- to integrate the cross species biomarker analysis with other cross species imaging, electrophysiological and cognition efforts (WP 1 -5) by studying the same models with these different platforms and identifying the “best” models of the various features of schizophrenia.
- to use the selected “clinically validated” preclinical models to (a) test the effect of existing and novel antipsychotic drugs on the biomarker fingerprints that overlap with the clinical condition; and (b) identify novel biomarkers and dr targets hypotheses that can support novel drug discovery and development.

Highlights Q210

- Serum biomarker profiling complete on 13 preclinical models
- Brain tissue biomarker profiling pilot study complete for 2 models
- Serum and brain tissue samples from another 4 preclinical models collected for biomarker profiling.

Deliverable C Identification of biomarkers for patient stratification and response prediction

WP10 **Advanced data analysis techniques for shorter and more efficient trials, biomarker identification and placebo-response differentiation co *led by J. Rabinowitz and S. Kapur***

- Identify the optimal duration and optimal scale measures which reduces patient exposure and maximises efficacy information in schizophrenia and depression.
- Develop designs for more efficient trials by combining statistical tests of outcomes and optimising symptom scales.
- Use trajectors of treatment response (rather than simple responder/non-responder status) to identify and link to emerging biomarkers in schizophrenia and depression

Highlights Q210

- Survey of available studies design and measures.
- Process of comparing study data with study reports has begun.
- All JNJ and Lilly data have been received.

Most substantive developments:

- GSK leaving intitative.
- EUFUS and CATIE becoming available for inclusion.

Are we progressing

”The ugly duckling”…we are on our way