

# The Innovative Medicines Initiative (IMI)

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## IMI Efficacy Calls



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## Diabetes Calls: Islet cell research Surrogate markers for vascular endpoints

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- **Islet Cell Research:** Improving Beta Cell Function and Identification of Biomarkers for Treatment Monitoring in Diabetes
- **Surrogate Markers for Vascular Endpoints:** Surrogate Markers for Micro- and Macrovascular Hard Endpoints to Shorten Clinical Trials in Diabetes

- **Focus**
  - Beta cell dynamics in vitro and in vivo
  - Cross talk of beta cells with other cell types in islets and with other tissues or organs
- **EFPIA Participants (n=10)**
  - Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, Roche, Sanofi Aventis, Servier, Solvay

- **Beta cell dynamics in vitro and in vivo**
  - Origin, source and function of novel beta cells
  - Conditions for beta cell proliferation and differentiation from precursor cells
  - Genetic and genomic studies for identification of biomarkers
  - Beta cell apoptosis: its mechanisms, prevention, measurement
- **Novel technologies, tools, approaches**
  - Novel animal models or in silico tools
  - Novel biomarkers for beta cell function and islet regeneration
  - Non-invasive technologies for monitoring beta cell mass
    - Imaging, nanotechnologies, biomarkers

- **Cross talk with beta cells and other cell types**
  - Abnormalities with alpha cell function, alpha/beta cell ratio
  - Interaction between islet cells and gastrointestinal tract
- **Key deliverables**
  - Generation of tools
  - Identification and validation of biomarkers and novel mechanism and targets for diagnosis and therapy
  - Knowledge on
    - mechanism of beta cell loss in type 1 and type 2 diabetes
    - beta cell proliferation and differentiation

# Surrogate Markers for Vascular Endpoints I



- **Focus**
  - To find ways to shorten clinical trials on hard vascular endpoints in diabetes
  - Retrospective: Analyse data in already performed or ongoing clinical trials
  - Prospective approach: Perform novel trials to search and validate the surrogate markers
- **EFPIA Participants (n=8)**
  - Boehringer Ingelheim, Eli Lilly, Novartis, Novo Nordisk, Pierre Fabre, Roche, Servier, Solvay

# Surrogate Markers for Vascular Endpoints II



- **Analysing data in already performed studies**
  - Genotype, phenotype, biomarkers, outcomes
  - Surrogate markers for micro- and macrovascular endpoints
  
- **Novel prospective studies**
  - Preclinical biomarkers and surrogate endpoints in animal studies
  - Develop in silico tools to reduce animal experiments
  - Validate surrogate markers obtained from earlier studies
  - Perform novel biomarker and genomic analysis to be validated by hard endpoints

# Surrogate Markers for Vascular Endpoints III



- **Key deliverables**

- Validated, industry-relevant, clinically meaningful and agency -acceptable biomarkers
- Validated genotypes of type 1 and type 2 diabetic patients, who are prone to develop micro- or macrovascular complications
- Novel assays (biochemical, imaging etc)
- Novel in silico models, which reduce the need of animal studies
- New tools for the development of therapies
- A model for clinical research collaboration between key stakeholders



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**THANK YOU VERY MUCH**

# The Innovative Medicines Initiative (IMI)

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**Brain disorders**  
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Lundbeck



Bruxelles , April 30<sup>th</sup> 2008

# General considerations for Psychiatric disorders, Neurodegeneration and Pain



- **Issues, Needs, Background**

- Management of these diseases are unsatisfactory
- Pathophysiological processes and etiologic factors these diseases remain elusive
- As a consequence, safe therapies that effectively relieve core symptoms or delay disease progression are a major challenge.

- **Scope**

- Gain greater **insight into pathways and mechanisms** underlying Psychiatric disorders, Neurodegenerative disorders and Pain.
- Develop **translatable** efficacy, pharmacodynamic and pharmacokinetic pain measures and models in animals and humans
- Establish and validate **human models**
- Develop robust markers for **patient stratification**



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# Psychiatric disorders

- **Issues and Background**

- Pathophysiological processes and etiologic factors within psychiatric disorders remain elusive.
- As a consequence, safe therapies that effectively relieve core symptoms or delay disease progression are a major challenge.

- **Needs**

- Systematic research into human disease biology
- Biomarker identification linked to disease pathophysiology
- Translation of sensitive markers into preclinical models

- **Scope**

- Development of platforms that translate efficacy of novel therapeutic approaches into measures for clinical assessment including experimental medicines paradigm , such as
  - Blood/CSF markers
  - Neuroimaging
  - Electrophysiological read-outs

# Goals & Related Project Plans



- **Improving Understanding of Disease Biology & Treatment Effects**

- Transcription patterns - correlation between human blood and brain. Advancement of the disease biology understanding.
- Correlation of blood markers (metabolites, gene transcription) with disease states and treatment response
- Identify marker profiles that predict treatment response

- **Improving animal models**

- Improved understanding of disease biology and associated markers  
leading to improved animal models
- Focus on read-outs relevant as endpoints in clinical studies
- PK/PD modelling – confirmation of pharmacology in humans vs animals

- **Improving dose selection**

- Establish tools to obtain clinically relevant target occupancy – support dose selection and relate to relevant read-outs e.g., functional neuroimaging



- **Identify relevant markers to segment patient populations**
  - Identify blood markers related to distinct phenotypes, including intermediate phenotypes: used for early signs of clinical efficacy
  - Identify blood markers that predict treatment response: to enrich study populations
  - Validate pharmacodynamic markers to support regulatory submissions
  - Use transcription markers to guide genotyping.
  - Use markers to identify novel treatment targets
  - Link transcription patterns to phenotype
  - Experimental medicine models



- **Improve animal models**

- Establish animal models that share marker changes identified in humans. Focus on 'translatable' read-outs, e.g. blood markers, neuroimaging, EPs, EEG
- Develop models of PK/PD relationships on pharmacodynamic markers

- **Improve dose selection**

- Establish functional neuroimaging read-outs that correlate with target occupancy and clinical efficacy to facilitate dose selection
- Establish preclinical in vivo validation of clinical neuroimaging read-outs

# Participants EFPIA



- AstraZeneca
- Eli Lilly
- GSK
- Johnson & Johnson
- Lundbeck
- Novartis
- Orion Pharma
- Pfizer
- Pierre Fabre
- Roche
- Servier
- Solvay
- Wyeth

- All companies are committed to deliver in-kind contributions
- Level of in-kind contributions remains to be determined, depending on proposals
  
- **‘In kind’ contributions**
  - ‘Omics platform’ and neuroimaging expertise
  - Translatable’ animal models (e.g. transgenic animals, preclinical models)
  - Markers/samples/patients from ongoing EFPIA-company sponsored pre-clinical and clinical studies
  - Mathematical modelling/handling of data
  - Development of PET ligands
  - Project management: Close interaction with public partners to ensure effective management and systematic and co-ordinated approach to ensure goal completion



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# Neurodegeneration

# The challenge to delivering successful medicines in the field of Neurodegeneration



- **Issues, Needs, Background**

- Clinical outcome studies in Neurodegenerative disorders are notoriously long and expensive
- Positive proof of efficacy or futility is often not identified until late in development

- **Scope**

- to validate biomarkers, novel pharmacodynamic models and develop more predictive animal models

# Key areas addressed by research proposal



- **Healthy Volunteer/Pharmacodynamic model development**
  - Novel approaches to well described models : e.g. scopolamine challenge, sleep deprivation, diurnal vigilance
  - Innovative model design/validation to deliver the next generation of HVT models
- **Pharmacodynamic marker development**
  - identify pharmacodynamic markers acutely altered by drug activity (i.e within 4-6 weeks)
  - Exploit pharmacological tools available from EFPIA partners to identify :
    - those markers with utility across a variety of different therapeutic classes, or across indications, such as biochemical, functional or imaging markers for atrophy, brain degeneration or reduced activity in defined brain regions
    - Markers with utility to support translation from pre-clinical models to HVT (young and elderly) to patients
- **Pre-clinical model development**
  - Develop pre-clinical models to support early drug screening by capitalising on the consortium's pre-clinical and clinical expertise to develop pre-clinical models in parallel to the clinic, using fully translatable endpoints.

# The primary aims and impact on both industrial practices and academia



- **Healthy Volunteer/Pharmacodynamic model development**
  - Identification of cognitive impairment models predictive of effective dose range and eventual clinical efficacy
  - Academic and industrial agreement on predictive value to disease states
- **Pharmacodynamic marker development**
  - Identification of markers validated and widely accepted as being suitable
    - for predicting pharmacologically active exposure range within 4-6 weeks dosing
    - For use across pre-clinical species, HVT and/or patient studies
- **Pre-clinical model development**
  - Identification of animal models using fully translatable endpoints and scientifically proven utility in the translation of efficacy from bench to bedside

**Delivery of academically and industrially validated models and markers to revolutionise future drug development.**

# Deliverables

## Neurodegenerative disorders



- **Identification of and pharmacological validation of parallel HVT and preclinical pharmacodynamic models to establish effective exposure ranges and support poc**
  - Characterisation of HVT and preclinical PD models (e.g. sleep deprivation) using clinically validated agents
  - Identify PD endpoints most sensitive to pharmacological intervention in HVT and preclinical models.
  - Identification of model with highest predictive capacity
- **Identification and pharmacological validation of novel in vivo animal models**
  - Development, validation and refinement of pre-clinical models using fully translatable endpoints and increased predictive capacity.
  - Identification and validation of PD markers to support preclinical and early clinical assessment in HVT/disease populations and that translate from bedside to bench

# EFPIA participants



- AstraZeneca
- Boehringer-Ingelheim
- GSK
- Johnson & Johnson
- Eli Lilly
- Lundbeck
- Merck KGaA
- Novartis
- Pfizer
- Pierre Fabre
- Roche
- Servier
- Solvay
- UCB

- **Estimation of “in kind” contributions from EFPIA members**
  - Supply of pharmacological tools/molecules with broad ranging therapeutic targets
  - Access to placebo data (pre-clinical/clinical)
  - Access to Tg mice/in vivo models of disease
  - Increase sample size via access to samples/patients from ongoing EFPIA sponsored pre-clinical (rodent and primate) and clinical studies
  - Access to ‘omics platforms’ and imaging expertise
  - Increase sample size via access to data/subjects from experimental medicine studies exploring HVT models
  - Access to biomarkers identified in EFPIA sponsored studies
  - Close interaction with public partners to ensure effective management and coordination of work to deliver key objectives



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# Pain Research

# What are we trying to solve?



- **Issues, Needs, Background:**

- Examination, diagnosis and treatment of chronic/neuropathic pain according to anatomical pain site or underlying disease is of limited help to patients and their pain.
- Clinical studies generally designed in this manner.
- Rational, mechanism-based approaches to C/NPP are needed
  - to increase treatment efficacy beyond 50 % pain reduction in about 50 % of patients
  - to improve side-effect profiles.

- **Scope:**

- Gain greater insight into pathways and mechanisms mediating different kinds of pain
- Develop translatable efficacy, pharmacodynamic and pharmacokinetic pain measures and models in animals and humans
- Establish and validate human pain models
- Develop robust markers for patient stratification and quantitative pain assessment

# What are we expecting and going to do?



## Project plan outline:

1. Identify mechanisms involved in generating and sustaining pain:
2. Develop more predictive preclinical animal models:
3. Develop models and markers to translate pain outcomes and pharmacology between animals and humans:
4. Objective and quantitative assessments of pain for use in clinical trials:
5. Analyze abuse potential:

# What are we expecting and going to do?



## Project plan outline:

### 1. Identify mechanisms involved in generating and sustaining pain:

- Peripheral and central sensitisation
- Modulation of inflammatory mediators, neuronal activity and neuroplasticity

### 2. Develop more predictive preclinical animal models:

- Mechanisms and end-points translatable between animals and man (linked to clinical electrophysiology and brain imaging)
- Towards *pain-free models of pain*

### 3. Develop models and markers to translate pain outcomes and pharmacology between animals and humans:

- Mechanism-based human models of pain
- Comparison of preclinical and clinical data-bases obtained with established analgesics, negative controls and NCEs

### 4. Objective and quantitative assessments of pain for use in clinical trials:

- Quantitative sensory testing (QST)
- Functional or 'wet' biomarkers that correlate with clinical efficacy
- fMRI, EEG/evoked potentials, MEG or other quantitative physiological responses
- Factors underlying the placebo response in analgesic drug trials

### 5. Analyze abuse potential:

- Imaging technologies: validated cerebral profiles of the positively reinforcing, psychostimulants

# What are we expecting and going to do?

## Deliverables 1



### 1. Mechanisms involved in generating and sustaining pain:

1.1. *Peripheral sensitisation, central sensitisation and neuroplasticity*

1.2. *From bedside to bench -Translation back to animal models*

1.3. *Methods and techniques to analyse the placebo response in clinical trials on pain*

### 2. Preclinical animal model development:

2.1. *Validate novel animal models:*

*mechanism and origin specific, RA, HIV, cancer, diabetic*

2.2. *Objective, quantitative and clinically translatable pain measures:*

2.3. *Development of pain-free animal models of pain (3Rs)*

*(imaging, molecular profiling, collateral behavioural markers)*

2.4. *Eliminating user bias in experimental pain assessment.*

# What are we expecting and going to do?

## Deliverables 2



### **3. Develop models and markers to translate pain outcome and pharmacology between animals and humans:**

- 3.1. Combined use of brain electrophysiology (EEG, MEG) imaging (fMRI, MRS) and molecular profiling (genetics, transcriptomics, proteomics or metabolomics)
- 3.2. *Translatable preclinical/human experimental pain models*, to be used for selection of biomarkers and decision-making concerning patient stratification.

### **4. Objective and quantitative assessments of pain for use in clinical trials:**

- 4.1. Refine and extend *experimental clinical methods of objectively measuring pain*
- 4.2. Investigate *placebo effects* in pain clinical trials by detailed review of placebo data provided by consortium members.

# What are we expecting and going to do?

## Deliverables 3



### **5. Delineate phenotypes of chronic pain patients:**

5.1. *Make different methodologies converge (e. g., genetic linkage, QST, novel methods)*

5.2. *Conduct small-scale, stratified clinical studies, which can deliver reliable early efficacy signals.*

### **6. Brain imaging for objective evaluation of the abuse potential of novel analgesics.**

# EFPIA participants



- AstraZeneca
- Boehringer-Ingelheim
- Eli Lilly
- Esteve
- GSK
- Merck
- Orion Pharma
- Pfizer
- Pierre Fabre
- Sanofi Aventis
- UCB
- Wyeth

# EFPIA contribution



*Pre-clinical and clinical scientific expertise and the sharing of pre-clinical models, human experimental pain data and clinical trial data on non-proprietary compounds.*

- **Clinical trial expertise**
- **Pain clinical trial placebo data**
- **Clinical supply of marketed products**
- **Tool molecules (clinical and pre-clinical)**
- **Clinical and pre-clinical brain imaging facilities**
- **Blood/CSF/biochemical biomarkers**
- **Transgenic mouse strains/models**
- **Animal models of chronic/neuropathic pain**
- **Behavioural measures of chronic/neuropathic pain**

# Expectations from public consortium - general



- **Expected contribution from academic groups and SMEs**
  - Innovative approaches for patient characterization, including intermediate phenotypes, that cross current diagnostic boundaries. Includes established infrastructure to recruit subjects
  - Disease biology understanding
  - Availability of blood samples from well-phenotyped subjects, that are suitable for omics technology
  - Technology platforms (animal models, imaging technologies)
  - Access to animal models that mimic aspects of human disease
  - Innovative approaches to the challenge of pharmacodynamic model/marker development
  - The ability to combine expertise to allow an integrated approach to model/marker development e.g. combining clinical assessment with imaging, EEG/MEG and/or biochemical/genetic assessment
  - The ability to conduct parallel pre-clinical and clinical studies to allow maximum understanding of forward and back translation - Consortia should have both clinical and preclinical groups

# What is expected from the public Consortium?



- **Seek synergies with other related global initiatives:**
  - ADNI
  - Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium ([www.biomarkersconsortium.org](http://www.biomarkersconsortium.org))
  - InnoMed, AdNeuroMed ([www.innomed.addneuromed.com](http://www.innomed.addneuromed.com))
  - US Biomarker consortium
  - CNS Metabolomics consortium
  - P1 Vital