IMI- Putting Ideas Into Practice
Key Figures of 37 on-going Projects

- **514 Academic & research teams**
- **347 EFPIA teams**
- **91 SMEs**
- **7 regulators**
- **22 patient orgs**

**Financial Contributions:**
- **€603 mln IMI JU cash contribution**
- **€600 mln EFPIA ‘n kind contribution**

**Projects:**
- ~ 3500 researchers
- > 220 publications

**R&D Productivity Improvements**
Bibliometric Output so Far

By August 2012

Number of Web of Science publications

EU-AIMS contribution to autism

eTOX contribution to cardiotoxicity

Data & analysis: Thomson Reuters (Custom Analytics & IP Solutions)
**Establishment of robust validated models for drug development**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>Translatable sleep deprivation model developed</td>
</tr>
<tr>
<td>Disease</td>
<td>Characterized multiple Tg mice models</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>Sleep deprivation model validation on-going</td>
</tr>
<tr>
<td></td>
<td>Menthol model validation on-going</td>
</tr>
<tr>
<td></td>
<td>UVB irradiation model validation on-going</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>New animal models developed, multiple models evaluated</td>
</tr>
<tr>
<td>Depression</td>
<td>Translatable imaging methodology develop</td>
</tr>
<tr>
<td>Autism</td>
<td>Developed animal model that mimics nonsyndromathic autism</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Developed new animal models that mimic T1 and T2 diabetes, multiple models evaluated</td>
</tr>
<tr>
<td></td>
<td>Tg mice developed</td>
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<tr>
<td></td>
<td>Developed human B cell line</td>
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<tr>
<td>Asthma</td>
<td>2 new animal models developed FCA/HDM and CT &amp; MRI imaging of chronic HDM model</td>
</tr>
<tr>
<td></td>
<td>Evaluated and harmonized multiple animal models</td>
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Science

The consortium has developed an animal model replicating a nonsyndromic autism and demonstrated that the condition can be reversed with specific therapy. This new development is of great importance for clinical development of new treatments for autism.

October 5th 2012

Shared Synaptic Pathophysiology in Syndromic and Nonsyndromic Rodent Models of Autism


The consortium has developed an animal model replicating a nonsyndromic autism and demonstrated that the condition can be reversed with specific therapy.
## Development of novel biomarkers for drug development

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>novel biomarkers that follow disease progression in Tg mice</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>translatable imaging biomarkers of brain activation related to chronic pain</td>
</tr>
<tr>
<td>Schizophrenia/Depression</td>
<td>clinical imaging biomarkers&lt;br&gt;clinical and molecular biomarker candidates for antidepressant response&lt;br&gt;surrogate proteomic biomarkers for efficacy prediction</td>
</tr>
<tr>
<td>Diabetes</td>
<td>candidate lipodomic and metabolomic biomarkers&lt;br&gt;novel genetic markers identified</td>
</tr>
<tr>
<td>Asthma</td>
<td>genetic, proteomic, metabolomic, breathomic biomarker candidates – validation on-going</td>
</tr>
<tr>
<td>Safety</td>
<td>novel early non genotoxic carcinogen biomarkers identified&lt;br&gt;potential biomarkers of drug induced injury of liver, kidney and vascular system</td>
</tr>
</tbody>
</table>
Development of liver injury alert algorithm for real time patient assessment and comparison with the efficacy of the routine examination.

The new strategy was much more efficient in identifying potential liver injury incidents, 12x more cases were identified than with the standard strategy.

The cases identified with the centralized strategy were much milder allowing for timely intervention.

This new approach presents a significant improvement in timely identification of DILI cases and will allow faster intervention to prevent from more serious events such as liver failure.
### Schizophrenia
- Combined data analysis of 23,401 schizophrenia patients
- Combined genetic data analysis on 2146 DNA samples

### Autism
- Sequenced 78 Icelandic parent–offspring trios, a total of 219 distinct individuals (44 autistic, 21 schizophrenic offspring) and identified 4933 de novo mutations

### Chronic Pain
- Pooled data from 43 past trials to understand the pain medicines mechanism of action and factors important in placebo response

### Safety
- Building a toxicology information database utilising toxicology legacy reports to develop better in silico tools for toxicology prediction of new chemical entities (1274 reports extracted so far, 2092 were cleared, 3564 are planned in total)
- Exploited EFPIA in vivo mouse and rat toxicology studies, tissue archives and molecular profiling data for >30 reference compounds to study NGC, genotoxic carcinogens and non-hepatocarcinogen controls
Proposed ways to reduce required numbers of patients needed for antipsychotic trials while preserving 90% power (p<.05) based on resampling of data from 34 such trials (n=11,670 patients) data from Astra Zeneca, Janssen, Lilly, Lundbeck, Pfizer.

Samples can be reduced from 79 to 46 patients per arm by targeting trials. In addition, the trial duration can be reduced from 6 to 4 weeks.

Average cost savings € 2,8 million.

Current mix = 70% female; 20% early episode; 40% enriched.

Enriched = prominent positive and negative symptoms.

Early episode = under 3 with 4 or more years of illness.

Note: Per patient cost 6wk study $70,000-$100,000.
### Agreeing development and regulatory submission of key standards for drug development

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td>diagnostic criteria on severe asthma</td>
</tr>
<tr>
<td><strong>Schizophrenia</strong></td>
<td>clinical biomarker meaningfulness calculator for predicting biomarker candidate utility in predicting antidepressant response</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>identified phenotypes associated with schizophrenia CNVs</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>developed non-invasive carotid histology for diabetic macroangiopathy</td>
</tr>
<tr>
<td><strong>generated phenotype definitions for diabetic complications</strong></td>
<td></td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>derived a conceptual model for physical activity</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>established generic qualification strategy for translational biomarkers</td>
</tr>
<tr>
<td></td>
<td>building ontology for preclinical pathology, 3917 terms and 2535 synonyms have been mapped</td>
</tr>
</tbody>
</table>
Development of Patient Reported Outcome tools

**Item pool generation for PROactive**

- Discussion Guide
- Focus Groups WP2B
- Initial Item Pool
- Cognitive debriefing WP2B
- Initial Item Pool
- Reduced Item Pool
- Selection of Activity monitors
- Validation (Validity and usability) WP2D
- Reduced Item Pool
- Selection of Activity monitors
- Initial PROs
- Initial PROs
- Clinical Validation studies WP6 A-C
- Final PROs validated
- Integration in Electronic platform WP3
- Draft PROs
- Final PROs validated

**Activity monitor(s) selection**

- Sources
  - Literature WP2A
  - Experts WP2C
  - Patients WP2B
- Validation (Validity and usability) WP2D
- Selection of Activity monitors
- Initial PROs
- Clinical Validation studies WP6 A-C
- Final PROs validated

**Summary of existing conceptual frameworks and development of the conceptual model**

- Airflow obstruction
- Dynamic hyperinflation
- Pulmonary gas exchange
- Respiratory muscle function
- Peripheral muscle function
- Cardiac function
- Vascular function
- Exercise tolerance
- 'Fear' (personality)
- Mood
- Self efficacy
- Symptoms
- Distress
- Health beliefs
- Self efficacy
- Socio-cultural factors
- HRQoL

**Work Package Deliverable Milestone**
Development of Patient Reported Outcome tools

Discussion Guide
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Sources
- Literature WP2A
- Experts WP2C
- Patients WP2B

Selection of Activity monitors
- Validation (Validity and usability) WP2D
- Chosen Activity monitor

Initial Item Pool

Final PROs validated
## Optimizing clinical trials

| **Antibiotics** | creation of pan-European clinical investigator networks |
| **Autism**     | involving patients in clinical trials and beyond |
| **Asthma**     | established network of excellence in bronchoscopy in severe asthma |
| **COPD**       | generated central registry of patients with severe asthma |
| **Schizophrenia** | proposed reduction in duration of schizophrenia trials |
| **Depression** | developing new approach of combining medication with therapy |
| **Alzheimer’s Disease** | new clinical study designs |
| **Tuberculosis** | aims to improve the development of new more effective treatment combinations for TB |
| **Knowledge Management** | identification of clinical sites through EHR |
THANK YOU