Boosting Drug Development through Public-Private Partnerships: The IMI Model

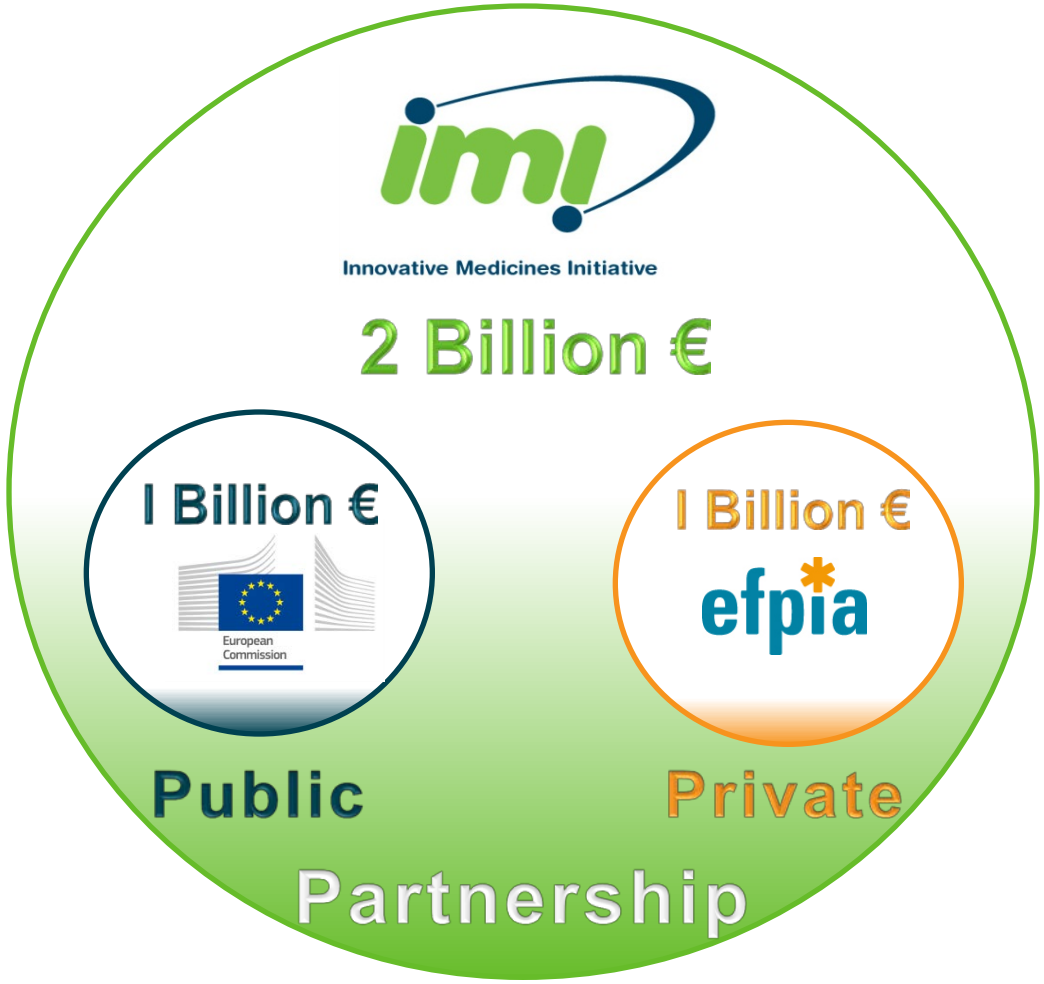
Hugh Laverty

Senior Scientific Project Manager

Key Hurdles in Pharma R&D

- Disease heterogeneity
- Lack of predictive biomarkers for drug efficacy/ safety
- Insufficient pharmacovigilance tools
- Unadapted clinical designs
- Societal bottlenecks
- Lack of incentive for industry

Innovative Medicines Initiative:
Joining Forces in the Healthcare Sector

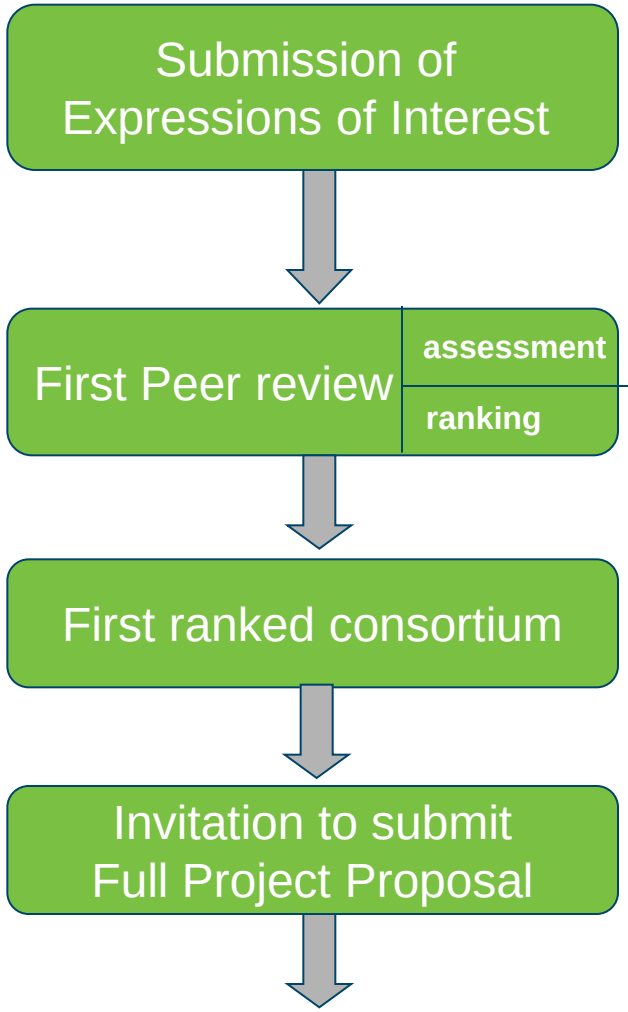


Key Concepts

- "Non-competitive" collaborative research for EFPIA companies
- Open collaboration in public-private consortia (data sharing, wide dissemination of results)
- Competitive calls to select partners of EFPIA companies (IMI beneficiaries)

Building an IMI Project (1/2)

Competition between applicants' consortia
(potential IMI beneficiaries)



- By applicants' consortia (academics, SMEs, Patient org….)
- Independ. experts + EFPIA coordin.
- Independ. experts
- Approved by IMI Governing Board
- to first ranked applicants' consortium + EFPIA consortium

Building an IMI Project (2/2)

Joint Preparation of Full Project Proposal

- By full project consortium (first ranked applicants' consortium + EFPIA consortium)
- Independent experts
- by IMI Governing Board

A Typical IMI Consortium

Private Investment *in kind* (€ 1 billion)

EU Public Funding *cash* (€ 1 billion)

OPINION

Public-private partnerships need honest brokering

Michel Goldman

Given the current challenges in research and development, it's increasingly apparent that collaboration between large pharmaceutical companies, academic teams and biotechnology enterprises is essential for converting basic biomedical discoveries into lifesaving medicines. But these partnerships work best when a neutral third party helps foster them.

A trickling pipeline of new products at many pharmaceutical companies has led to a paradigm shift in the industry's research and development (R&D) strategy. Indeed, the integrated R&D model in which every step of drug development is conducted in-house has proved largely inefficient in delivering the novel therapies needed to address major health challenges. Therefore, this model is being progressively replaced by open innovation networks that allow the leveraging of external pools of knowledge, especially in universities and biotechnology companies[1].

The pharmaceutical industry realizes that the best approach is to apply an open innovation concept to precompetitive research that encourages companies to share expertise. These principles were the cornerstones of the Critical Path Initiative launched by the US Food and Drug Administration in 2004, which led to the creation of the Critical Path Institute, an Arizona-based nonprofit dedicated to fostering collaborations between industry, academia and regulators[2].

Across the pond, the Innovative Medicines Initiative (IMI), a public-private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations, is a prototypic example of an organization created to support open innovation and pre-competitive research in the pharmaceutical sector. It has raised awareness about the principles of open collaboration and has launched several education and training programs for scientists from industry or academia interested in drug development and

> "A neutral organizer is key to ensure the sustainability of public-private partnerships and to restore trust in and among the stakeholders committed to the development of innovative therapies."

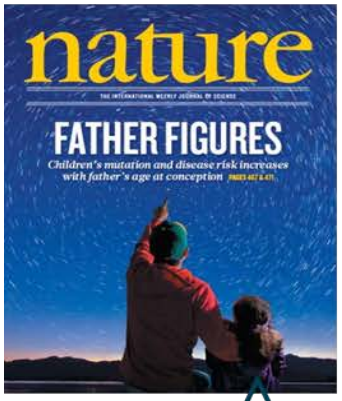
transparent competition, rather than through preexisting connections. For this reason, IMI organizes a competitive process to identify the best partners to match with the pharmaceutical companies that, for their part, invest considerable resources in the projects, propose the research topics and most often coordinate the projects.

This leading role of industry, which distinguishes IMI from most other public-private partnerships, guarantees the optimal exploitation of the knowledge created and its dissemination by the research consortia. As an example, within one of the IMI consortia for diabetes, the optimal exploitation of the first human beta cell line useable for the development of antidiabetic drugs[4] was made possible by the partnership between the academic team that made the basic discovery, a small enterprise that commercializes the cell product and the large pharmaceutical enterprises that will develop drug screening assays relying on this innovative tool.

Ensuring that consortia operate in a balanced manner in terms of intellectual property and allocation of resources requires a neutral party that can act as a referee whenever needed. To address this need, IMI facilitates consortium agreements by playing the role of impartial broker. A key mission of a neutral body such as IMI is, of course, to ensure the sound management and allocation of public funds in the interest of both industry and society. Here, IMI develops performance indicators suited to measure the added value of public-private partnerships[5]. As an example, IMI is closely

Nature Medicine
18: 341, 2012

Key Figures of 37 On-going Projects



EU-AIMS contribution to autism

508 Academic & research teams

341 EFPIA teams

92 SMEs

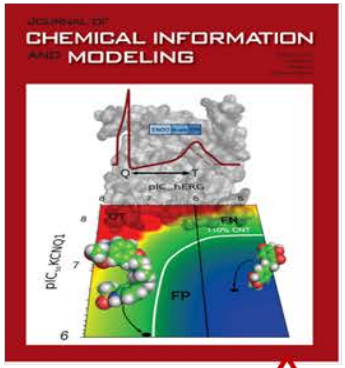
10 regulators

17 patient org

€ 600 mln EFPIA 'n kind contribution

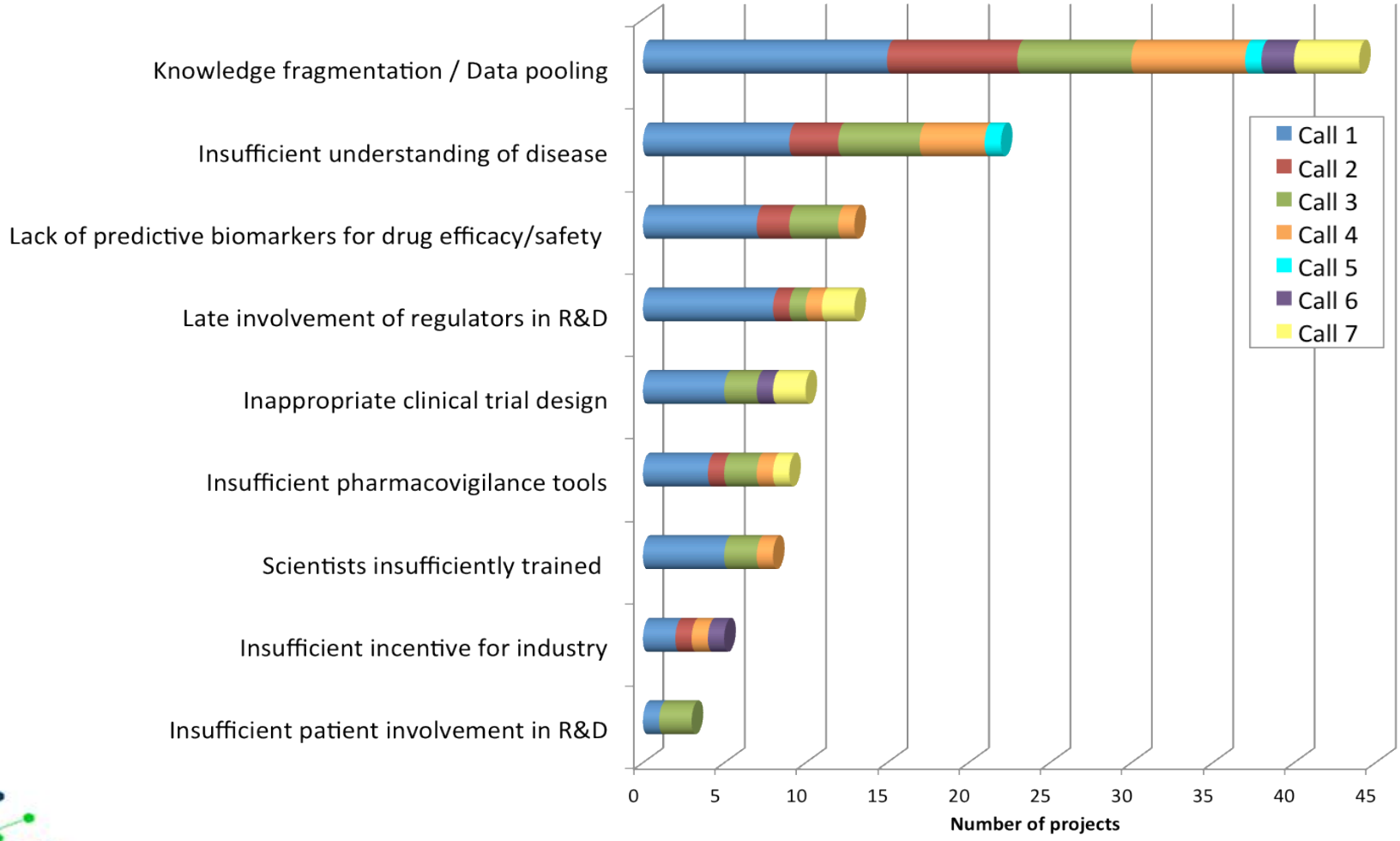
€ 603 mln *IMI JU cash contribution*

~ 3500 researchers
> 200 publications



eTOX contribution to cardiotoxicity

Projects Address Hurdles in R&D



Regulator involvement in IMI projects (Call 1-4)

Regulatory Agencies are consortium members of 4 IMI projects

PROTECT, PharmaTrain, EU2P, OrBiTo

Regulatory Agencies are on the Advisory Boards of 12 projects

MARCAR, SUMMIT, PHARMA-COG, U-BIOPRED, PROactive, DDmore, EHR4CR, ABIRISK, EU-AIMS, DIRECT, EUPATI, EMIF

How Does IMI Improve R&D Productivity?

- **Establishment of robust validated models for drug development**
  e.g. first human β cell line - diabetes, Tg models - AD, translatable challenge models – AD, chronic pain
- **Elimination of poorly predictive pre-clinical models**
- **Novel biomarkers**
  e.g. AD, pain
- **Novel targets**
  e.g. pain
- **More effective approaches to predict adverse drug effects and late attrition (discussed at early stages with regulators)**
  e.g. in silico model to predict cardiac toxicity, translational biomarkers - cardio, renal and hepatotoxicity

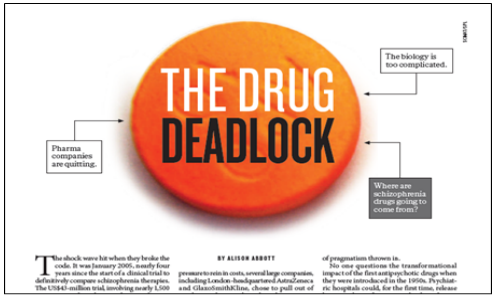
How Does IMI Improve R&D Productivity?

- **Agreeing development and regulatory submission of key standards for drug development**
  e.g. diagnostic criteria - severe asthma, virtual carotid histology - diabetic macroangiopathy, biomarker qualification strategy
- **Developed new international consensus for definition of severe asthma**
- **New patients reported outcome in COPD**
- **More efficient patient enrolment in clinical trials (localisation of patients for targeted clinical trials)**
  e.g. clinical investigator network - antibiotic development and autism, patient involvement, electronic health records
- **Faster and cheaper clinical trials**
  e.g. schizophrenia, Alzheimer's disease

Closer Look – CNS Disorders

Expected output	NEWMEDS	PharmaCog	EU-AIMS Autism Research in Europe	EuroPain
Mechanistic knowledge	✓	✓	✓	✓
Patient stratification	✓	✓	✓	✓
Standardized model - in vitro -			✓	
Standardized model - in vivo -	✓	✓	✓	✓
Predictive biomarkers - genetic -	✓	✓	✓	
Predictive biomarkers - "omics" -	✓	✓	✓	✓
Predictive biomarkers - "imaging" -	✓	✓	✓	✓
Early involvement of regulators		✓	✓	

Novel Methods leading to New Medications in Depression and Schizophrenia

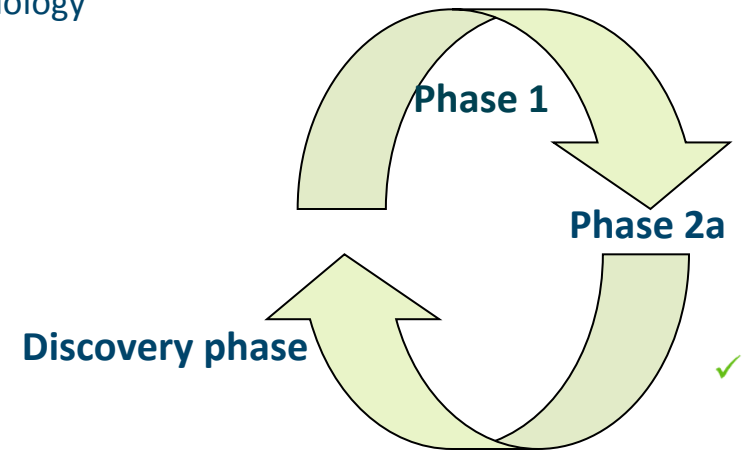


Nature, 11 November 2010

✓Identified phenotypes associated with schizophrenia CNVs (1300 subjects)

✓Developed animal models carrying the CNVs

✓ Developed animal-human imaging methodology

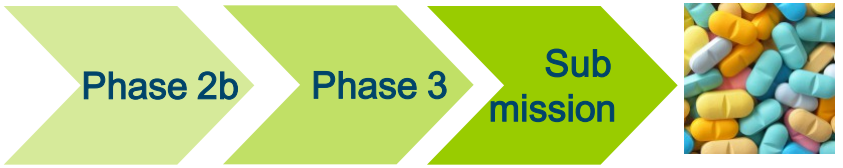


✓ Validated cognitive and electrophysiological batteries in animal models

✓ 14 animal models of schizophrenia evaluated in a proteomic markers panel

✓ 2 Clinical trials initiated

✓ Workshop on Negative symptoms held



✓ The largest databases: schizophrenia trials (> 23,000 patients) and treated depressed populations (2146 DNA samples)

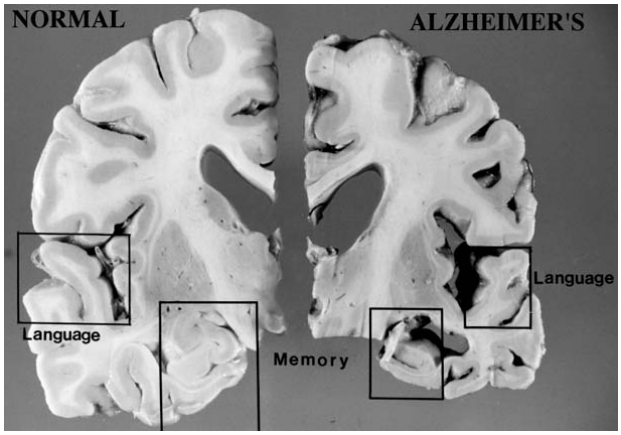
✓ Clinical trials in schizophrenia modified

✓*depressiontools.org* → clinical meaningfulness calculator

Advancing Science and Treatment of Alzheimer's Disease

The Objective

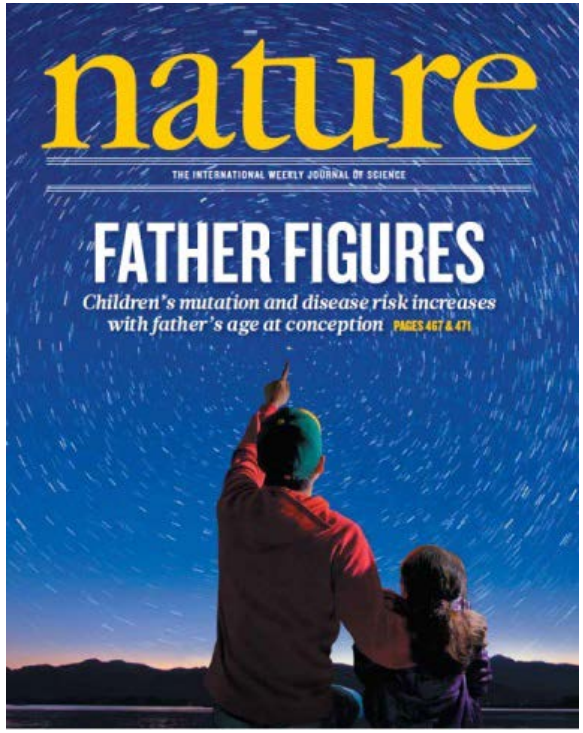
To develop and validate the models required to increase the effectiveness of the drug discovery process in Alzheimer's disease



Progress:

- ✓ Established a translatable challenge model based on sleep deprivation in three different species
- ✓ Development of a translatable, cognition touchscreen methodology for rodents (NEWMEDS)
- ✓ Identified novel biomarkers that follow disease progression in Tg mice
- ✓ Optimized 4 clinical study designs based on literature reviews, protocols and data from EFPIA clinical studies (250 subjects planned)

Developing New Knowledge on Autism Spectrum Disorders



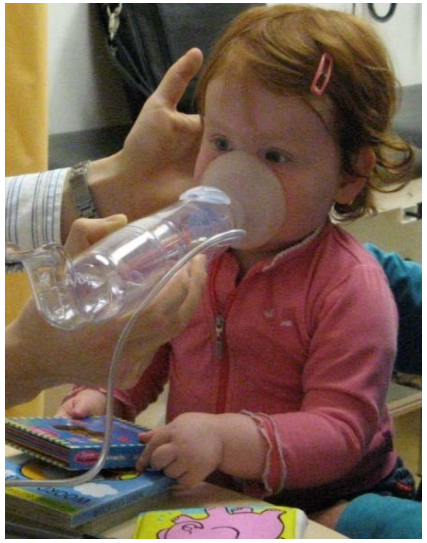
As a man ages, the number of de novo mutations in his sperm increases, and the chance that his child would carry a deleterious mutation that could lead to autism or schizophrenia increases proportionally.

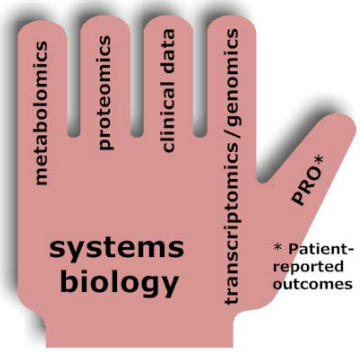
Closer Look – Respiratory Disorders

Expected output	U-BIOPRED	PROactive	PREDICT-TB
Patient stratification	✓		
Standardized model - in vitro -	✓		✓
Standardized model/tools - in vivo -	✓	✓	✓
Predictive biomarkers - genetic -	✓		✓
Predictive biomarkers - "omics" -	✓		✓
Predictive biomarkers - "imaging" -			✓
Patient involvement	✓	✓	
Early involvement of regulators	✓	✓	✓

Unbiased Biomarkers in the Prediction of Respiratory Disease Outcome

U-BIOPRED





The Objective

Developing biomarker profiles from molecular, physiological, and clinical data integrated by into ***handprints*** for the prediction of clinical course, therapeutic efficacy and identification of novel targets in the treatment of severe asthma

Progress

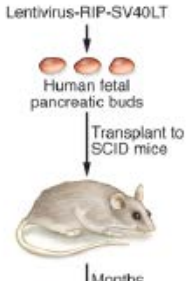
- ✓ Developed an international consensus on diagnostic criteria
- ✓ Creating novel phenotype 'handprints' by combining molecular, histological, clinical and patient-reported data – validation and refining is on-going
- ✓ Two novel animal models have been identified (FCA/HDM, CT & MRI imaging of chronic HDM model)
- ✓ **Preparation and recruitment for cohort clinical study have started, 14 centres across Europe targeting 1025 subjects, to validate the handprints for their predictive efficacy in gold standard and experimental therapeutic intervention**

efpia

Closer Look– Diabetes

Expected output	imidia	SUMMIT	ddmore	DIRECT
Knowledge management tool	✓	✓	✓	✓
Mechanistic knowledge	✓	✓		
Patient stratification		✓		✓
Standardized model - in vitro -	✓			
Standardized model - in vivo -	✓	✓		✓
Predictive biomarkers - genetic -		✓		✓
Predictive biomarkers - "omics" -	✓	✓		✓
Predictive biomarkers - "imaging" -	✓	✓		✓
Early involvement of regulators		✓		

IMIDIA: New knowledge on β cells



Related Commentary, page 3395 Technical advance

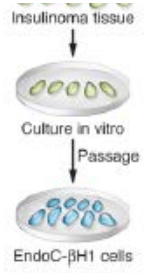
A genetically engineered human pancreatic β cell line exhibiting glucose-inducible insulin secretion

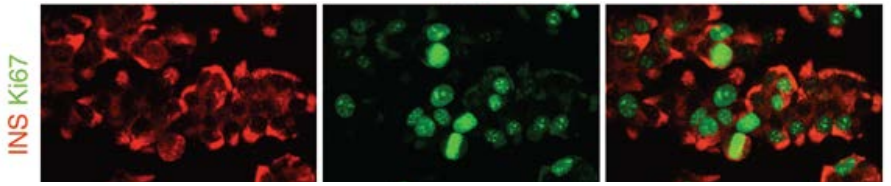
Philippe Ravassard,[1,2,3] Yasmine Hazhouz,[2,4] Séverine Pechberty,[4,5] Emilie Bricout-Neveu,[2,4] Mathieu Armanet,[6,7] Paul Czernichow,[4] and Raphael Scharfmann[5]

Finally! A human pancreatic β cell line

Gordon C. Weir and Susan Bonner-Weir

Section on Islet Cell Biology and Regenerative Medicine, Research Division, Joslin Diabetes Center, and Department of Medicine, Harvard Medical School, Boston, Massachusetts, USA.





The Journal of Clinical Investigation http://www.jci.org Volume 121 Number 9 September 2011

eTOX: In silico toxicology

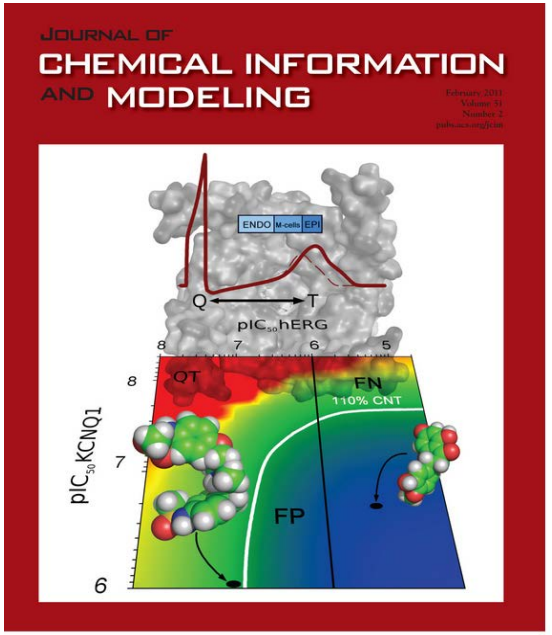
- *Builds a large searchable database containing drug toxicity-related data extracted from relevant pharmaceutical pre-clinical legacy reports*
- *Develops innovative methodological strategies and novel software tools to predict toxicological profiles in silico*

25 Partners

- 13 EFPIA companies
- 8 Public organisations
- 4 SMEs

First achievement

An innovative multi-scale modelling strategy for the prediction of cardiotoxicity has been developed,
successfully tested and published



J. Chem. Inf. Model. 51:483-92 (2011)

eTOX: A key role for SME

Shaping the future of safer innovative drugs in Europe

To the Editor:

An Editorial entitled "Members need only apply" published in the July issue[1] expressed concerns about the input of small- to medium-sized enterprises (SMEs) into the agenda of the Innovative Medicine Initiative (IMI) Joint Undertaking. The editorial argued that the SMEs currently participating in IMI projects do not represent the whole spectrum of companies that make up the innovative biotech space in Europe. We would like to address these criticisms in the context of the eTOX consortium, one of the projects funded following the IMI's first call for proposals in 2008 and specifically singled out for comment in the Editorial.

The eTOX consortium comprises 11 European pharmaceutical companies, 8

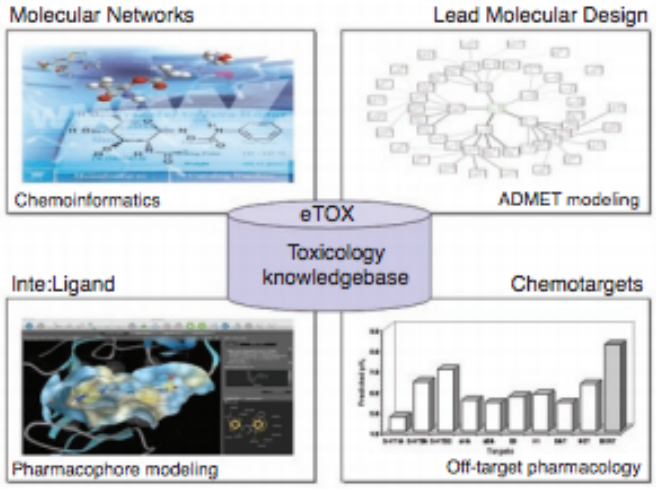


Figure 1 Innovative SME contributions to the integrative *in silico* toxicology approach currently under development within eTOX, an IMI EU project.

[1]*Chemotargets, IMIM–Hospital del Mar, and University Pompeu Fabra, Barcelona, Catalonia, Spain.* [2]*Inte:Ligand, Vienna, Austria.* [3]*Lead Molecular Design, Sant Cugat del Vallès, Spain.* [4]*Molecular Networks, Erlangen, Germany.*
e-mail: jmestres@imim.es

Nature Biotechnology, 29: 789, 2011

SAFE-T: Development of novel biomarkers for drug development

SAFE-T

OPEN ACCESS Freely available online

PLOS ONE

Real Time Identification of Drug-Induced Liver Injury (DILI) through Daily Screening of ALT Results: A Prospective Pilot Cohort Study

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

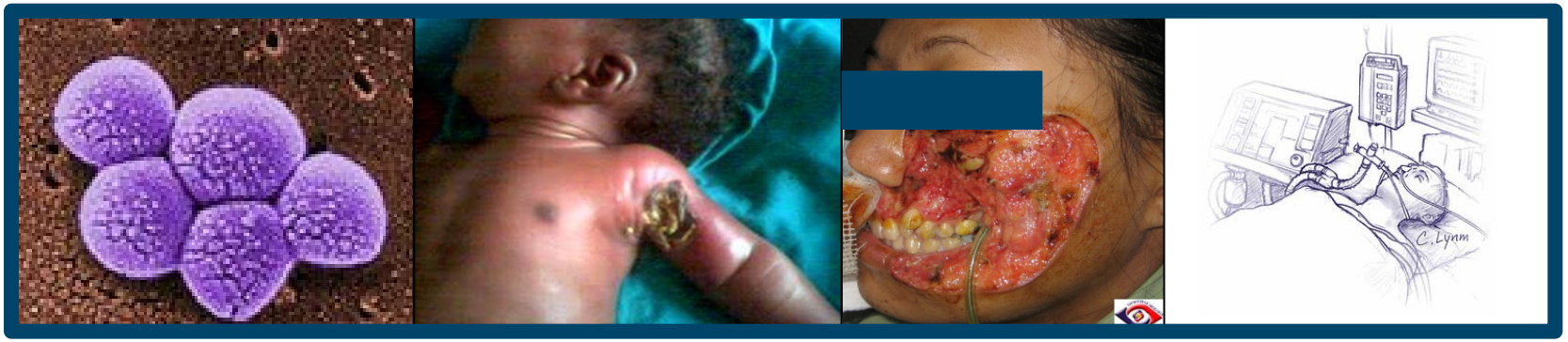
efpia

5th Call: European Lead Factory

budget forecast:
€169m

- ✓ Industry partners will have access to unique high-quality Joint European Compound Library
  - **≥ 300.000 compounds from industry partners – €60m 'in kind' contribution**
  - **200.000 compounds from public partners**
- ✓ Industry-like lead discovery platform available for public projects **-** ***focus on value generation***
- ✓ Addressing **'intractable targets'**
- ✓ 48 high throughput screening projects *per anno*
- ✓ Support in assay development
- ✓ **Sustainable model** for the screening centre to establish independent business entity

6th Call for Proposals 2012
"Combating Antibiotic Resistance"
NEWDRUGS4BADBUGS (ND4BB)



The crisis of no new antibiotics—what is the way forward?

Laura J V Piddock

Antibiotic use not only underpins modern medicine, but has brought huge changes to the world, especially in expectations of survival of children into adulthood. The theme of World Health Day, 2011, was "antimicrobial resistance: no action today and no cure tomorrow". The demise of antibacterial drug discovery brings the spectre of untreatable infections. To prevent this crisis immediate action is needed and a new initiative, Antibiotic Action, has been launched. By bringing together communities who need these drugs with academia, health-care professionals, and pharmaceutical companies, this initiative aims to strengthen and enhance academic-industrial partnerships, bring about revision of costly and laborious processes of licensing and regulation of new antibiotics, and address the economics of antimicrobial drugs (cost of use *vs* profit). A global alliance for antibiotic drug discovery and development would provide a platform for these initiatives.

Published Online
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l.j.v.piddock@bham.ac.uk

The looming crisis

Many articles in medical and scientific journals and the press have documented the problems of rising numbers of antibiotic-resistant bacteria.[1,2] Recently, some articles have revealed the impending catastrophe linked to the failure to develop new antibiotics and its implications for the practice of modern medicine.[3–7] The discovery, development, and widespread use of antibiotics are and others still cause serious global health concerns (eg, *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae*[16]).

Human beings do not live in a sterile world. Food and water can be contaminated and many different events occur that affect sharing of microorganisms between ecosystems and antibiotic-resistance genes between pathogenic and commensal bacteria. Floods, earthquakes, and tsunamis have affected public health

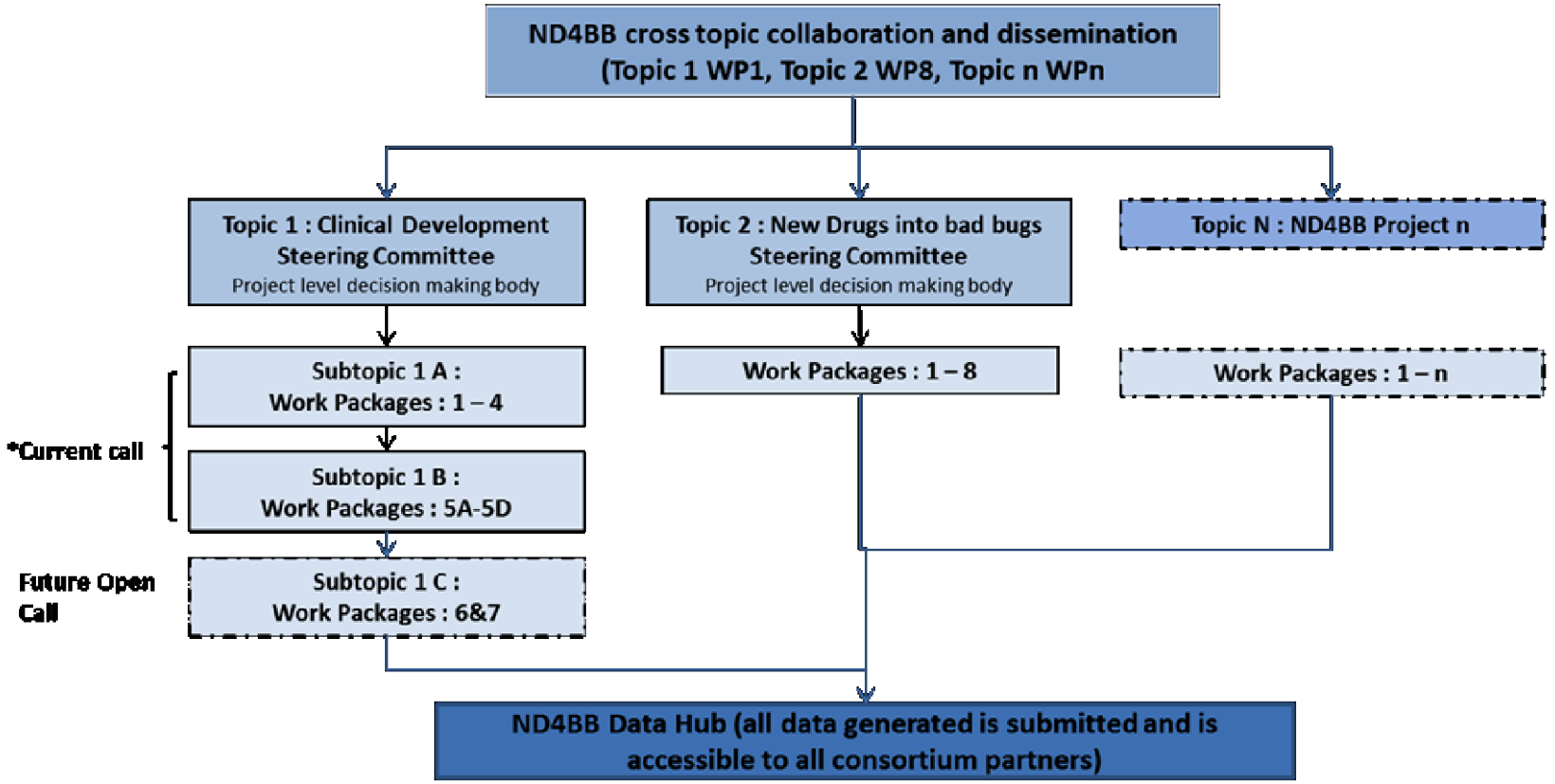
The Broad Picture of the IMI Anti-Microbial Resistance Programme

- As a **public-private partnership** aiming at **removing bottlenecks in drug development, IMI** is the ideal instrument to solve the **scientific challenges**, to provide the necessary **incentives** for industry and to revisit the **regulatory environment** in order to reinvigorate R&D on antibiotics

- The 6th Call is the first Call of **a series of IMI Calls** which will address additional major challenges in the near future

- **First clinical trials** were selected according to **products** that are **ready to be tested** in view of a **rapid introduction in clinical care**

Architecture of the IMI Anti-Microbial Resistance Programme



Topics in current call.

*Note : calls for additional beneficiaries required to implement WP5B&5D will be managed by the Topic 1 consortium as outlined below

Subject to future open calls implemented by the IMI JU office

Call 7 for Proposals

Two topics

- Developing a framework for rapid assessment of vaccination benefit/risk in Europe
- Incorporating relative effectiveness research into development strategies

Budget

- EFPIA contribution: **€13 Million**
- Maximal IMI JU contribution: **€13 Million**

Timelines

- Call launch: July 2012
- Deadline for EoIs submission: 9 October 2012
- Grant agreement signature: Q2 2013

Call 8 for Proposals

Two topics part of the Anti-Microbial Resistance Program:

- Fighting *Staph. aureus* infections: epidemiological studies and clinical trials with a monoclonal antibody
- Discovery and development of new drugs from gram- infections

Four additional topics

- Leveraging emerging technology for pharmacovigilance
- Developing an etiology-based taxonomy for human diseases (Rheumatoid arthritis, Lupus, COPD, Parkinson…)
- Building a European bank to hold and supply iPS stem cells
- Developing combination therapies

Call launch: November 2012

The Future of IMI

Budget to be committed by end of 2013:

- **3 to 4 Calls launched**

Projects started in 2013- 2014 will run until 2018 – 2019

Any future PPP will be part of Horizon 2020 and launched in 2014

A future PPP under Horizon 2020

Moving forward with a PPP in innovative Health research

- **Will be based on experience from IMI**

Criteria to be fulfilled:

- Added value of action at the Union level
- Scale of impact on industrial competitiveness, sustainable growth and socio-economic issues
- Long-term commitment from all partners based on a shared vision and clearly defined objectives
- Scale of the resources involved and the ability to leverage additional investments in research and innovation
- Clear definition of the roles for each of the partners and agreed key performance indicators over the period chosen

- Continued partnership with **EFPIA**
- Plan to enlarging partnership to include **vaccine**, **medical imaging** and **medical information technology** industries

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