Innovative Medicines Initiative

IMI Highlights

May 2013

FOREWORD

The Innovative Medicines Initiative (IMI) is a public-private partnership (PPP) between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). With a budget of €2 billion, the mission of IMI is to strengthen the competitiveness of the pharmaceutical sector in Europe with the objective of facilitating and accelerating the development of better and safer medicines for the benefit of patients and society. Today, more than 4 500 scientists collaborate under the IMI umbrella.

The strong interest elicited recently all over the world by the IMI programme to tackle anti-microbial resistance and the creation of the European Lead Factory demonstrates that IMI effectively contributes to restoring European leadership in this critically important sector.

Since 2009, IMI consortia have been developing new tools and methods to improve the assessment of drug actions and implementing new education and training programmes. This booklet, based on excerpts of our most recent Annual Activity Report, highlights the progress of IMI's activities and its projects.

The first achievements presented herein are certainly encouraging. Their effective translation into standards of care will require further innovative approaches, taking advantage of the neutral trusted party represented by IMI. To help achieve this goal, IMI recently launched new projects focusing on defining the real effectiveness and risk/benefit evaluation of drugs and vaccines. This effort will be further amplified in coming years with close attention paid to priorities defined by regulatory authorities, and unmet needs expressed by patients and caregivers, thereby establishing a solid foundation for a renewed public-private partnership under Horizon 2020, the forthcoming framework programme for Research and Innovation of the European Commission.

Trust is the essential key for IMI's long-term success. It is the single most important element for ensuring fruitful collaboration between the many stakeholders inside IMI projects, and the efficient governance of the partnership as a whole.

I express my appreciation for the support and constructive criticism received from IMI's Governing Board, IMI's Scientific Committee members, IMI's States Representative Group and the EFPIA Research Directors Group.

Last but not least, I express my deep gratitude to the staff of the Executive Office who have been instrumental in making IMI a fruitful public-private partnership.

Michel Goldman, MD, PhD

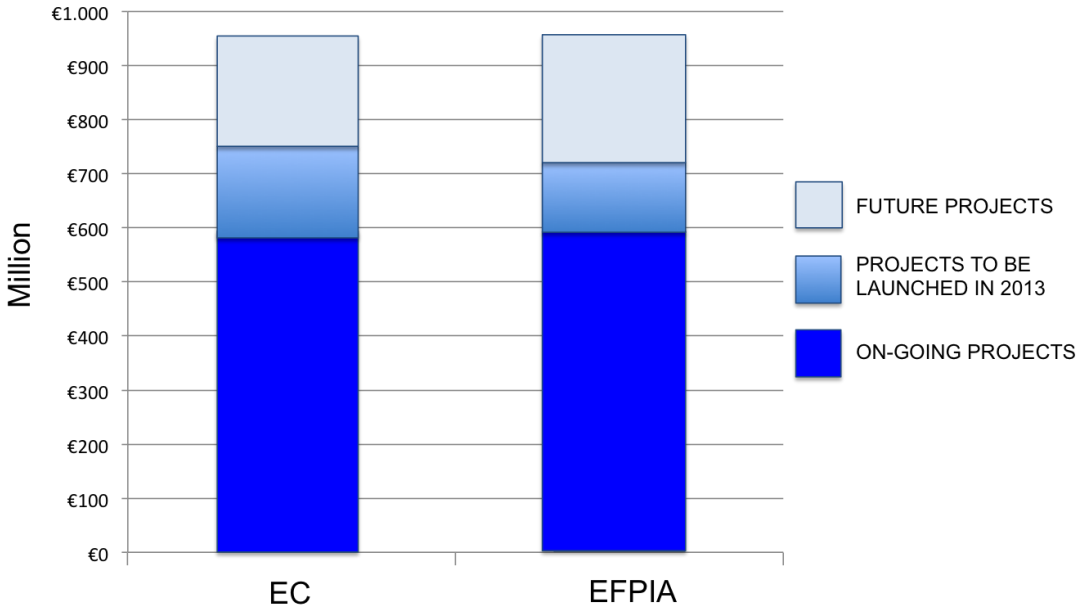
Executive Director

Innovative Medicines Initiative

WHERE DO WE STAND?

IMI projects are conducted by consortia comprising pharmaceutical companies, academic institutions, small and medium-sized enterprises (SMEs), patient organisations, and regulatory agencies. These projects are focused on non-competitive research in areas of high medical need and are based on the principle of open innovation.

As of May 2013, **40 projects** are up and running with a budget of €1.2 billion. They are financed jointly by resources from the European Commission (EC) and from large pharmaceutical companies that are members of EFPIA. As shown in the figure below, the public and private investments are well matched.

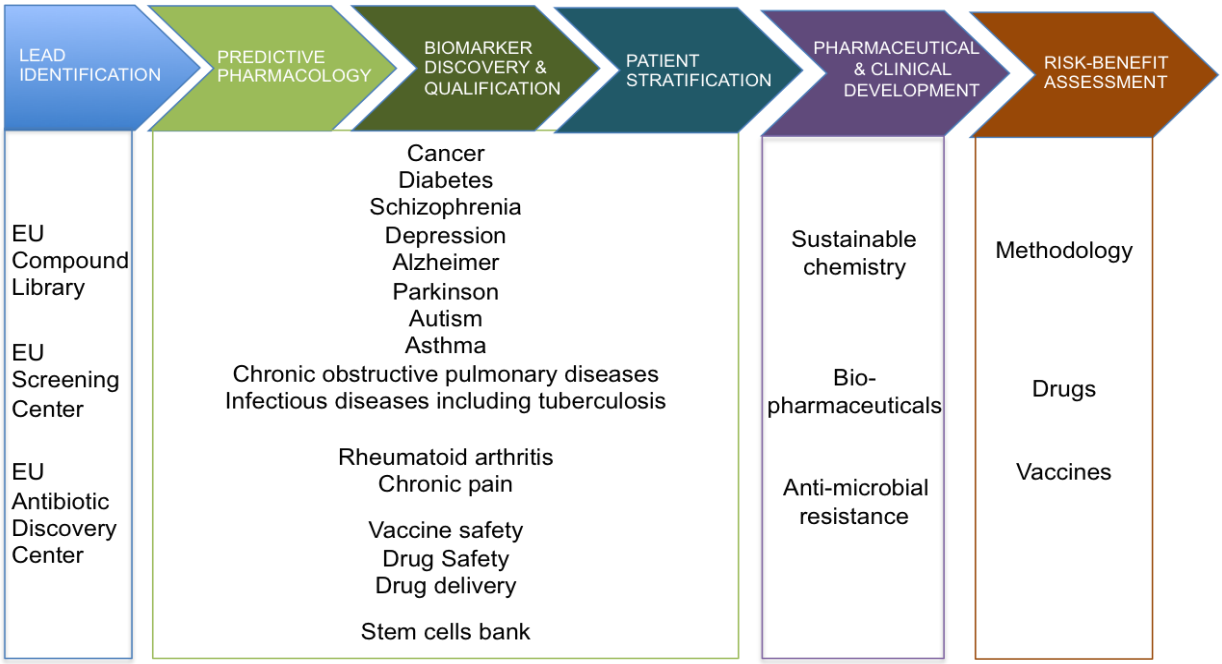


Public funding is often allocated to academic institutions and other non-profit organisations but SMEs are also well represented among beneficiaries. Indeed, **112 SMEs** receiving **18.9% of public funding** are currently engaged in IMI projects.

Since IMI was launched, a series of measures have been taken to facilitate the submission of proposals and accelerate the launch of the projects. Indeed, the **average time to grant** from the initial submission of Expressions of Interest to the signature of Grant Agreements has been decreased to 185 days for the 6th Call for proposals, which is in line with the target proposed by the European Commission for the forthcoming Horizon 2020 Framework Programme.

As envisioned in the initial IMI Strategic Research Agenda developed in 2007, most projects from the first IMI Calls for proposals focused on the early stages of the drug development and education and training.

The figure on the next page represents a mapping of current IMI activities according to the value chain of drug development and scientific or disease areas.



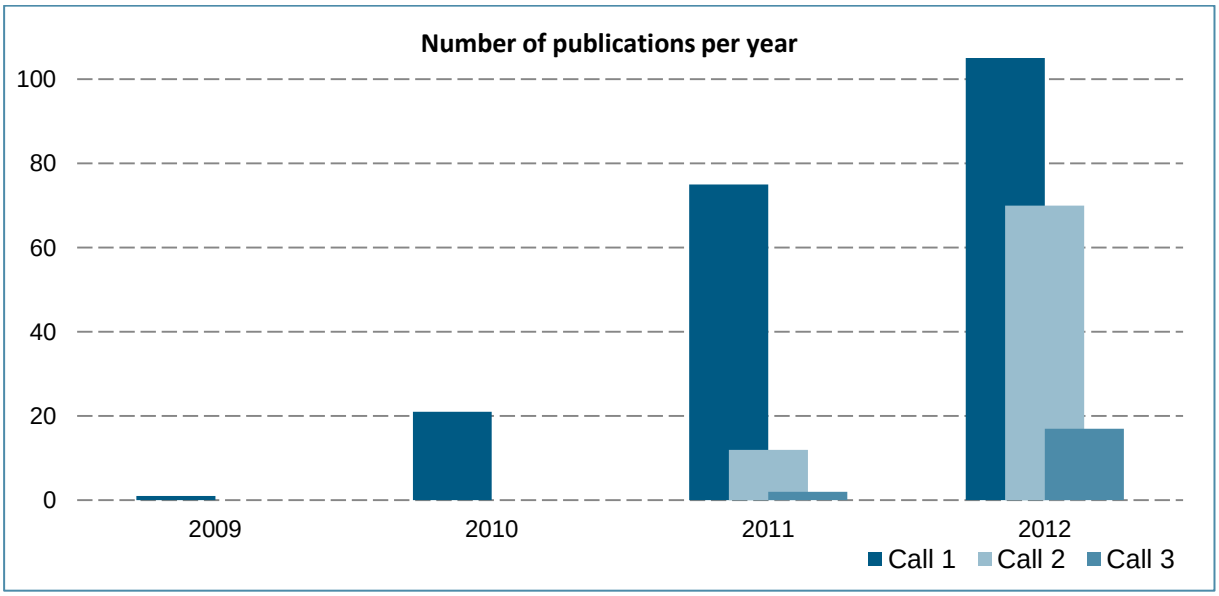
Although most IMI projects are still less than three years old, the analysis of their publications and their impact beyond the scientific literature publications already provides evidence that IMI is an efficient PPP that fosters **European scientific leadership** in medical sciences by building **collaborative intelligence networks**, develops **innovative tools for drug development**, creates **new business opportunities** and **educates scientists and citizens** to accelerate drug development.

RESEARCH PERFORMANCE AND MAPPING OF IMI COLLABORATIVE NETWORKS

The scientific publications produced by IMI projects are closely monitored and analysed in collaboration with Thomson Reuters. Key figures from the most recent report are presented in the following pages.

Number of publications

- By the end of January 2013, a total of **320 publications** resulting from IMI projects had been identified. As shown in the next figure, publication output has increased each year since 2009, with a substantial increase between 2010 and 2011. In 2012, the publication output was more than double the number identified for 2011. It is expected that publication output will continue to grow non-linearly as the number of funded projects increases and those projects yield results for publication.

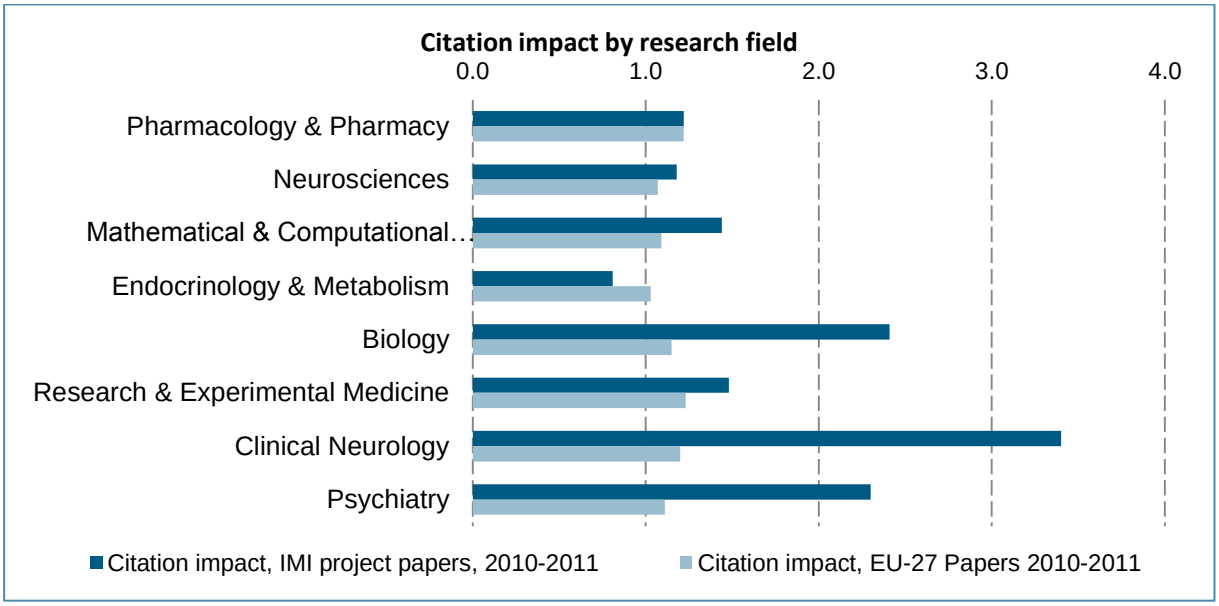


Quality of the journals

- IMI project publications have been published in a total of **119 journals** to date, of which 95 are ranked in the top quartile of journals (by Journal Impact Factor) in their specific research fields.
- **82.7%** of IMI project publications have been published in **well-regarded journals**, including *Nature*, *JAMA*, *PNAS* and *Nature Genetics*.

Citation impact

- The **average citation impact** for IMI project research is **1.55** for the 2-year period, 2010-2011, where world average is 1.0. For comparison, the EU's average citation impact relative to world baseline for the same 2-year period in similar research fields was 1.14.
- IMI-supported research published in Biology, Clinical Neurology and Psychiatry journals is exceptionally well-cited with average citation impact well above the European and world benchmarks. This performance is driven by multiple highly-cited papers, as well as publications identified as a 'hot papers' in the Thomson Reuters databases.

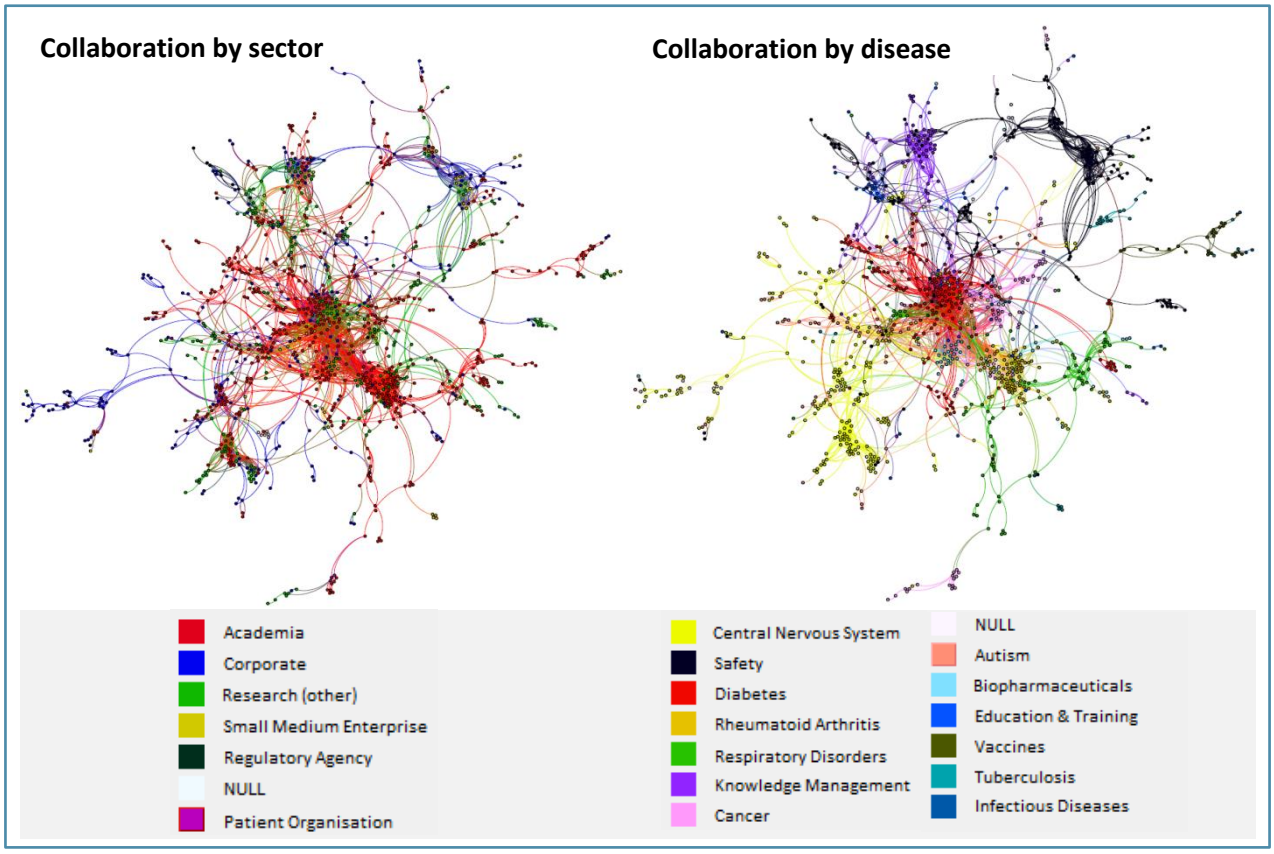


Performance of academic scientists engaged in IMI projects

- Of the **385 publishing academic-based researchers**:
  - 23% have published at least one 'hot paper';
  - 20% have an h-index of at least 10;
  - the majority have published most frequently in top-quartile journals.

Mapping collaborations

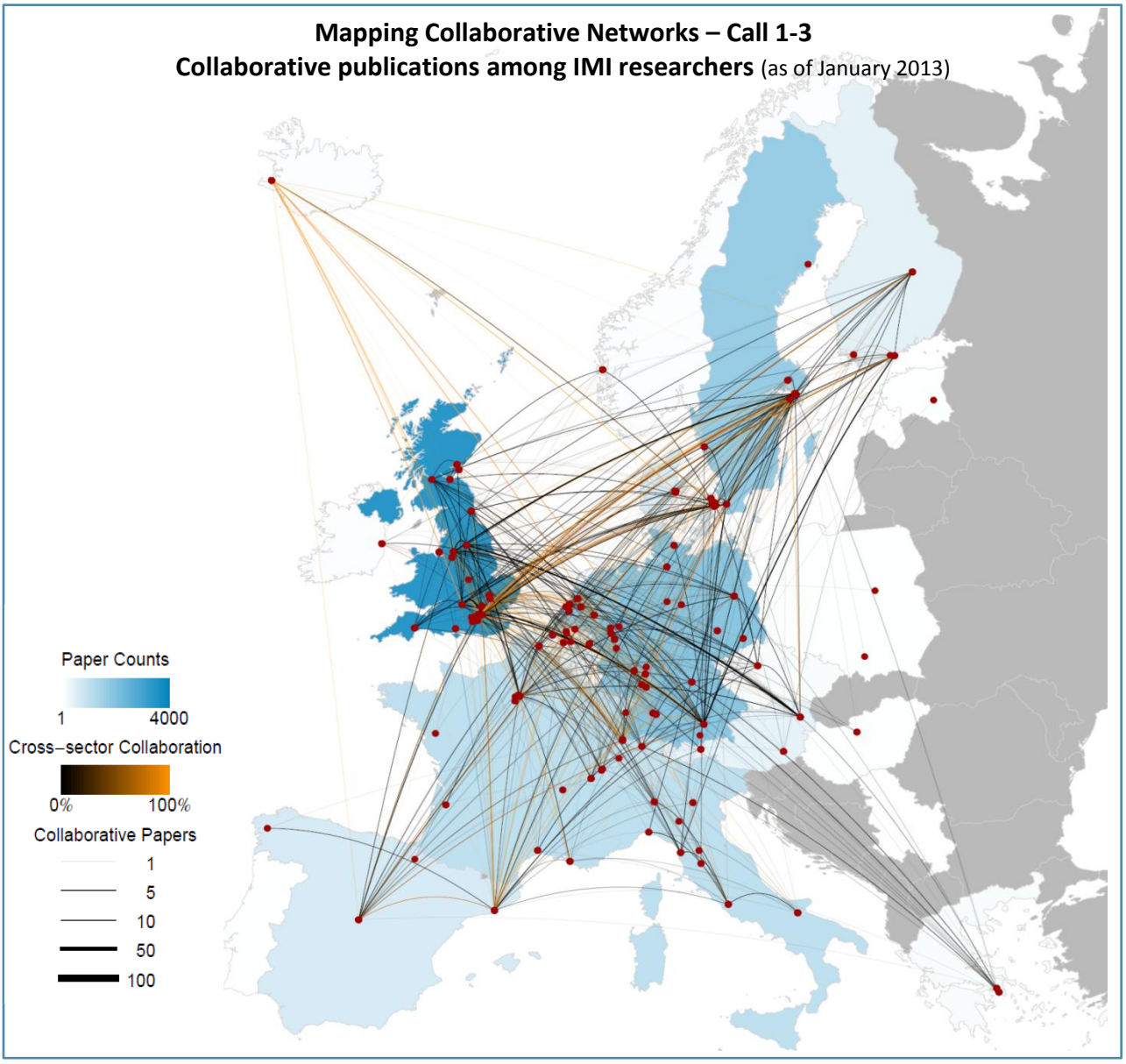
Collaboration analysis was performed on the basis of co-authorship between IMI-supported researchers as well as between co-authors. For this purpose 3 477 individual researchers participating in IMI projects from the first 3 Calls for proposals were identified.



Figures illustrate patterns and frequency of collaborative activities. Each individual is represented as a single node coloured with respect to the sector of their organisation (left pane) or according to the disease in which their project is active (right pane). Lines between researchers are instances where the co-authorship has occurred in a published work. The distance between the nodes correlates to the frequency of co-authorship.

- As expected, co-authorship is more common among researchers in the same sector than among researchers in different sectors. However, there are also substantial co-authorship activities among researchers from different sectors, accounting for 40% of all co-authorship activities during the IMI lifetime so far.

IMI facilitates widespread collaborations between researchers involved in IMI projects. These collaborations are illustrated in the figure below, which is based on data on all IMI participants in Europe from the first 3 Calls for proposals and includes more than 13 000 publications published since May 2009 by those researchers. It should be noted that this map focuses on "within-EU collaboration" and that some papers have authors based outside EU.



This map of collaborations shows:

- ***Total number of publications from each partner country***
  Maps are shaded from white to dark blue based on output. Countries with no contributing output are shaded grey.
- ***Frequency of collaboration between affiliations***
  Lines connecting countries or cities indicate co-authorship, with thicker lines indicating a higher number of co-authored papers.
- ***Visualisation of cross-sector nature of the collaborations***
  If both collaborating partners are from the same sector, the line is black. If they are from different sectors, the line is orange. As the data are aggregated, either by country or by city, the proportion of cross-sector collaborations will therefore vary between these two extremes.

OUTPUTS OF IMI PROJECTS

In order to illustrate how the IMI public-private partnership contributes to accelerating the development of innovative drugs, the following tables set out the first achievements of IMI's projects in key areas of high medical or industrial relevance.

1. Establishment of robust validated models for drug development

Project acronym	Area	Description of results
PHARMACOG	Alzheimer's disease	Developed a translatable sleep deprivation challenge model that performs well in three pre-clinical species as well as in human volunteers.
		3 transgenic mouse models of Alzheimer's disease (AD) were longitudinally characterised using imaging, cognition, electrophysiological and a biochemical marker battery to assess their translational validity in efficacy prediction.
		Developed and pre-validated translatable rodent touchscreen technology for precisely measuring cognitive dysfunction (in collaboration with NEWMEDS).
EUROPAIN	chronic pain	New surrogate pre-clinical models of neuropathic pain and relevant outcome measures developed and pharmacologically validated across several laboratories: evoked pains (cold), neuronal activity (μENG), and quality of life (anxiety).
		Extensively evaluated multiple translational pain models. Validation of several selected models, such as sleep deprivation model, menthol model, or ultraviolet B (UVB) irradiation model.
NEWMEDS	schizophrenia, depression	Evaluated 14 animal models of schizophrenia in the proteomic biomarker panel developed by the consortium. Identified four preclinical models mimicking serum clinical biomarker signatures of first onset schizophrenia patients.
		Developed a circuit (hippocampal-prefrontal) model of schizophrenia and validated it against currently available agents.
		Developed new imaging techniques via new PET probes, and developed translatable animal-human imaging methodologies (fMRI).
		Developed and pre-validated translatable rodent touchscreen technology for precisely measuring cognitive dysfunction (together with PHARMACOG).
IMIDIA	diabetes	Developed the first fully functional human beta-cell line and completed successful validation of its secretory activity and functional properties by three pharmaceutical company partners – patented.
		Generated the SOFIA mouse – a powerful new tool for the functional imaging of insulin turnover *in vivo*.
SUMMIT	diabetes	Evaluated and characterised nine existing pre-clinical models of diabetic vascular complications. Established new rat model of diabetic vascular complications – patenting ongoing
		Developed new transgenic models by deletion of candidate diabetic nephropathy genes (GWAS).

U-BIOPRED	asthma	Harmonized several animal models and identified two novel ones (FCA/HDM, CT & MRI imaging of chronic HDM model).
EU-AIMS	autism	Developed animal model that mimics nonsyndromic autism.
PREDECT	cancer	Developed *ex vivo* tissue culture model for targeted drug discovery reproducing microenvironment contribution and intra-tumoural heterogeneity.
PREDICT-TB	tuberculosis	Is developing an integrated PK-PD/disease modelling framework which will facilitate the prediction of optimal drug combinations for tuberculosis and the design of clinical studies.

2. Development of biomarkers and other predictive tools for clinical outcome

Project acronym	Area	Description of results
NEWMEDS	schizophrenia, depression	Developed clinical imaging biomarkers - fMRI methods that can be applied in experimental drug development.
		Developed toolbox for the analysis of brain images for a better use in drug development. Publicly available.
		Developed robust surrogate proteomic biomarkers for drug efficacy prediction.
		Characterisation and correlation of genotype-function-phenotype across species in carriers of CNVs linked to schizophrenia.
		Developed clinical meaningfulness calculator for assessment of biomarker candidates' utility in predicting antidepressant response: www.depressiontools.org – publicly available.
		Identified neuropsychological and anthropometric phenotypes associated with schizophrenia CNVs.
PHARMACOG	Alzheimer's disease	Identified novel biomarkers sensitive to disease progression in transgenic mice.
		Demonstrated that cortical resting state EEG is sensitive to the cognitive decline in mild AD patients and might represent a cost-effective and non-invasive marker with which to enrich cohorts of AD patients that decline faster for clinical studies.
EUROPAIN	chronic pain	Developed translatable imaging biomarkers of brain activation related to chronic pain.
		Translational biomarkers (by transcriptomics, lipidomics, microneurography, imaging) developed and validated in pre-clinical species, experimental medicine pain models, and pain patients.
U-BIOPRED	asthma	Developed various 'omics' platforms based on genetic, proteomic, metabolomic, breathomic biomarkers – validation is ongoing.
		Generated a preliminary phenotype 'handprint' by combining molecular, histological, clinical and patient-reported data – validation and refinement is ongoing.
		Established a set of diagnostic criteria on severe asthma providing a stepwise algorithm for diagnosing the disease.

PROactive	chronic obstructive pulmonary disease (COPD)	Derived and statistically validated a conceptual model for physical activity.
		Developed patient reported outcome tools – validation is ongoing.
SUMMIT	diabetes	Identified a biomarker of extracellular matrix degradation and vascular disease.
		Identified candidate biomarkers from the initial analysis of the lipodomic and metabolomic screening.
		Identified novel genetic markers to be further evaluated.
		Developed a new ultrasound-based method for non-invasive assessment of atherosclerotic plaques - patenting ongoing.
		Generated phenotype definitions for diabetic complications.
EMIF-EMIF-AD	Alzheimer's disease	Will identify new AD biomarkers to facilitate drug development and trial design in predementia AD, taking advantage of the largest single collection of data and samples yet assembled for biomarker analysis
EMIF-EMIF-Metabolic	metabolic syndromes	Will identify new biomarkers predictive of metabolic complications in obesity, taking advantage of the largest single collection of data and samples yet assembled for biomarker analysis
SAFE-T	safety	Evaluated 153 potential biomarker candidates for drug-induced injury of the kidney, liver and vascular system.
		Established generic qualification strategy for new translational biomarkers.
e-TOX	knowledge management, safety	Is building a toxicology information database utilising legacy toxicology reports from pharma partners to develop better *in silico* tools for toxicology prediction of new compounds.
		Assembled a database of public data covering over 170000 compounds linked to 400 targets from 11 000 publications.
		Has built an ontology which maps over 500 000 terms from the toxicology reports to 110 000 preferred terms for use in modelling.
		Developed 83 *in silico* models including a predictive model of cardiac toxicity. Internal pre-validation of all models by the EFPIA companies is on-going.
		Developed a toxicogenomics model for interpretation of transcriptomics and toxicogenomics data in order to predict inter-species toxicological profiles.
MARCAR	safety	Identified novel early non-genotoxic carcinogen (NGC) biomarkers and mechanisms via integrated genome-wide epigenomic and transcriptomic profiling of rodent livers and tumours.
		Exploited EFPIA *in vivo* toxicology studies, tissue archives, and molecular profiling data for >30 reference compounds to study NGC, genotoxic carcinogens and non-hepatocarcinogen controls.
PROTECT	pharmacovigilance	Established the Drug Consumption Databases in Europe using data from European National sources and IMS data – **publicly available.**
		Established the database of adverse drug reactions of centrally authorised medicinal products – **publicly available.**

		Drafted a protocol for the review of graphical/visual representation of benefit-risk scenarios.
RAPP-ID	infectious diseases	Developed a device and protocol related to breath-born aerosol sampling - **patenting ongoing.**
STEMBANCC	stem cells	Will generate a large number of patient-derived induced pluripotent stem (iPS) cell lines, characterise them in terms of their genetic, protein, and metabolic profiles, and make them available to researchers. All cell lines will also undergo a rigorous quality check.

3. Identification of new drug targets

Project acronym	Area	Description of results
EUROPAIN	chronic pain	Identified CXCL5 as novel translatable pain target.
NEWMEDS	schizophrenia, depression	Completed *de novo* CNV analysis implicating specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia.
MARCAR	safety	Identified a sustained liver-specific epigenetic switch within non-genotoxic carcinogens' target genes.
		Gained novel insight into early mechanisms of non-genotoxic carcinogens that might lead to novel target identification.
EU-AIMS	autism	Uncovered NL1 isoform-specific cis-interactions with ionotropic glutamate receptors as a key mechanism for controlling synaptic properties.
BTCure	rheumatoid arthritis	Identified the association with rheumatoid arthritis (RA) of autotaxin, of the two microRNA-221/222 and microRNA-323-3p and of epigenetic changes.
ELF	drug discovery	Will combine a library of as many as 500 000 drug candidates from industry and academia with a high-throughput screening centre, providing to public partners an 'industry-like' discovery platform to translate cutting-edge academic research into high-quality candidate drug molecules on a scale and speed that was not possible previously.

4. Clinical trials- improved design & process

Project acronym	Area	Description of results
NEWMEDS	schizophrenia, depression	The analysis of the combined data from 23 401 schizophrenia patients has resulted in a proposal for a reduction in the length of schizophrenia clinical trials as well as a reduction in the number of patients required to be enrolled.
		Initiated a clinical trial to develop new approach to combining medications with therapy.
PHARMACOG	Alzheimer's disease	Optimised four clinical study designs based on literature reviews, protocols and data from EFPIA clinical studies.
EUROPAIN	chronic pain	Optimising clinical trial design to reduce placebo response.
EU-AIMS	autism	Creation of pan-European network of clinical sites.

U-BIOPRED	asthma	Established network of excellence in bronchoscopy in severe asthma.
		Generated central registry of patients with severe asthma which can be utilised for future studies.
BTCure	rheumatoid arthritis	Provided recommendation for terminology to be used to define specific subgroups of RA patients during different phases of disease
EH4CR	knowledge management	Issued guidelines for writing the eligibility criteria for clinical research.
		Developing the protocol feasibility service, demonstrator.
		Identification and assessment of eligible patients through electronic health records (EHRs).
ND4BB - COMBACTE	antibiotics	Will facilitate the creation of clinical investigator networks.
		Aims to develop new clinical study designs.
PREDICT-TB	tuberculosis	Aims to speed up the search and development for new, more effective combinations of treatments to tackle tuberculosis.
U-BIOPRED	asthma	Involving patients in clinical trial design and beyond.
PROactive	COPD	
EUPATI	patient information	

5. 'Big Data' solutions to leverage knowledge

Project acronym	Area	Description of results
Open PHACTS	knowledge management	Integrated 7 pharmacological information sources (>450 M triples) into a publically available platform which is open for developers to build drug discovery applications (Apps). 4 example applications have been published.
EMIF	knowledge management	Will build an integrated, efficient framework for consistent re-use and exploitation of currently available patient-level data to support novel research.
		Access to information on >40 million patients.
eTRIKS	knowledge management	Building a knowledge management platform for collaborative knowledge management for translational projects based on the open source TranSMART system.
		Development and adoption of translational information standards.
		Research and development of new analytics methods and tools.
DDMoRe	knowledge management	Developing various tools for model based drug discovery.
		Development of clinical trial simulator tool – second prototype delivered.

6. Education and Training (E&T) of scientists and citizens

Project acronym	Area	Description of results
EMTRAIN	E&T, networking	Catalogued 4 773 masters, PhD, Continuing Professional Development (CPD) and short courses taught in 21 languages, from 39 countries, covering over 60 scientific, therapeutic and biomedical areas from about 1 000 universities.
		Assembled extensive CPD database of modules/courses recognised by professional bodies whose quality standards align with IMI's.
SafeSciMET	E&T in safety sciences	Successfully completed its first cycle of courses in 2012, with participants giving very positive feedback. More than 170 students participated (55% from EFPIA companies).
		Performed a gap analysis and identified and included new topics courses, in particular 'drug safety of stem cells and other novel therapeutics'.
Eu2P	E&T in pharmaco-vigilance & pharmaco-epidemiology	12 students are currently following the 2-year Master programme covering medicines risk identification and quantification, medicines and public health, medicine risk communication, assessing the benefits of medicines, and regulatory processes.
PHARMATRAIN	E&T in pharmaceutical medicine	Successfully launched the Cooperative European Medicines Development Course (CEMDC), a postgraduate qualification in medicines development that will provide students from Estonia, Hungary, Lithuania, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, and Turkey the very best teaching in the pharmaceutical field.
		317 students have been following various courses (49% from EFPIA companies).
		Signed Memoranda of Understanding (MoUs) with universities of California and Peking.
EUPATI	E&T for patients in therapeutic innovation	Europe's first Patients' Academy on Therapeutic Innovation aiming to provide scientifically reliable information on medicines and R&D, as well as an online public library that will empower patients to engage more effectively in the development and approval of new treatments and become true partners in pharmaceutical R&D.

RELEVANCE FOR REGULATORY AGENCIES

Most IMI projects address questions that can impact regulatory standards, guidance and practice for the benefit of public health. As a matter of fact, the Work Programme 2013 of the **European Medicines Agency** includes specific objectives concerning IMI in relation to biomarker development and safety monitoring.

A number of consortia have already taken steps to obtain advice on qualifying the tools, methodologies and standards they are developing. Indeed, the EU-AIMS consortium has been instrumental in initiating the development of guidelines for the treatment of autism.

OTHER BENEFITS

Other benefits from IMI projects include tools that will result in the **replacement, reduction or refinement (3Rs) of animal use** in drug development, as recognised by the Fund for the Replacement of Animal Research in Medical Experiments[1].

In parallel, the IMI project CHEM21 is developing economical and **environmentally friendly alternatives** to traditional chemical synthesis.

[1] Balls, M. (2012) FRAME and the Pharmaceutical Industry. *ATLA* **40**: 295-300.

Innovative Medicines Initiative

About IMI

IMI is the world's largest public-private partnership in health research and development. IMI is improving the environment for pharmaceutical innovation in Europe by engaging and supporting networks of industrial and academic experts in collaborative research projects.

The European Union contributes €1 billion to the IMI research programme, which is matched by in kind contributions worth at least another €1 billion from the member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

IMI is currently funding 40 projects, many of which are already producing impressive results. The projects focus on new methods and tools that will enable the entire sector to accelerate the development of safer and more effective treatments for patients.

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