

# News and EFIS

## The Innovative Medicines Initiative moves translational immunology forward

The Innovative Medicines Initiative (IMI) was established in 2008 as a public-private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations with the mission to promote the development of novel therapies through collaborative efforts based on the concept of pre-competitive research. Several consortia supported by IMI are dedicated to immuno-inflammatory disorders, immune-based biopharmaceuticals and vaccines. Herein, we present the key principles underlying IMI, briefly review the status of projects related to translational immunology, and present future topics of interest to immunologists.

### Introduction

Over the last decades, advances in experimental and clinical immunology have resulted in a number of innovative therapies based on immunological products or immunological targets. Indeed, monoclonal antibodies — such as trastuzumab, cetuximab, bevacizumab, rituximab — that target tumor antigens or critical receptors for tumor development are now part of the standard care for common cancers while antibodies targeting inhibitory immune receptors such as CTLA-4 and PD1 are being developed to enhance anti-tumor responses [1]. In parallel, biological agents targeting TNF, IL-6, and IL-1 have been introduced in the portfolio of anti-inflammatory agents for rheumatic disorders and inflammatory bowel diseases [2–5]. Biologicals targeting the IL-23/IL-17 pathway [6] and Janus kinase inhibitors [7] also show promise for the control of these diseases as well as psoriasis. Multiple sclerosis is another disorder in which significant therapeutic advances have been achieved by biologicals (e.g. IFN- $\beta$ , natalizumab) or chemicals (e.g. fingolimod, teriflunomide) which interfere with the activation, differentiation or trafficking of T lymphocytes [8, 9].

As far as antibody-mediated diseases are concerned, beside rituximab, belimumab that neutralizes B-lymphocyte stimulator (BLyS/BAFF) was recently approved by the US Food and Drug Administration (FDA) for the treatment of systemic lupus erythematosus [10].

The development of these new treatments was made possible by combining genomics-based target discoveries, use of relevant models *in vitro* or in animals, and proof-of-concept translational studies in patients. These major successes illustrate the critical importance of close collaboration between multiple stakeholders from public and private sectors to move immunotherapies forward. Several public-private partnerships (PPP) have been established over the last years to foster such collaborations with the goal to reinvigorate the development of innovative drugs. The largest one is the Innovative Medicines Initiative (IMI) that supports partnerships between large pharmaceutical companies, academic institutions, small and medium-size enterprises, patients' associations and regulatory agencies. Herein, we present key features of IMI, focusing on on-going projects and future calls for proposals of interest to the community of immunologists.

### Key features of IMI

IMI is a public-private partnership between the European Commission and the pharmaceutical industries' members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) [11]. IMI's key mission is to enhance the competitiveness of the pharmaceutical sector in Europe for the benefit of patients and scientists by supporting pharmaceutical research and development. IMI was launched in 2008 with a total budget of €2 billion to be spent over a 10-year period, making the IMI the largest PPP in life sciences. To fulfill its mission, IMI supports public-private consortia that are responsible for the implementation of Research and Development (R&D) as well as Education and Training programs. IMI research topics were initially focused on the development of new tools and methods for the prediction of drug safety or efficacy but more recently they also address key issues related to drug licensing and market access. All IMI activities and projects are based on two cornerstones: precompetitive research and open innovation. The precompetitive space can be simply defined as the field in which large companies agree to collaborate and invest jointly because the

results of this research do not provide a direct, immediate commercial advantage [12]. Open innovation defines new modes of collaboration between large firms and academic teams or small biotech companies, based on extensive sharing of expertise, knowledge and data for the benefit of all partners [13].

EFPIA pharmaceutical companies invest in IMI in the form of in-kind contributions by committing internal human resources or providing access to data sets and infrastructure and sometimes in the form of direct monetary contributions. This industry investment is matched by funds from the European Union to support the other members of the IMI consortia, including academic teams, small and medium-sized enterprises (SMEs), patients' organizations, and regulatory agencies. IMI provides a neutral platform for aligning the perspectives of these stakeholders regarding healthcare priorities. Furthermore, the IMI Executive Office exerts a critical role of "honest broker" to facilitate consortium agreements [14].

A two-stage process is used to assemble the public-private IMI consortia. As shown in Figure 1, after pharmaceutical companies belonging to EFPIA agree on a given topic, a Call is launched to select their partners receiving funds from the European Union. This selection is primarily based on recommendations from independent experts who assess expressions

of interest (EoI) submitted by consortia of applicants eligible for public funding. The first ranked applicant consortium is then invited to prepare a full project proposal together with the EFPIA consortium. This full project proposal undergoes a final peer-review by independent experts before approval.

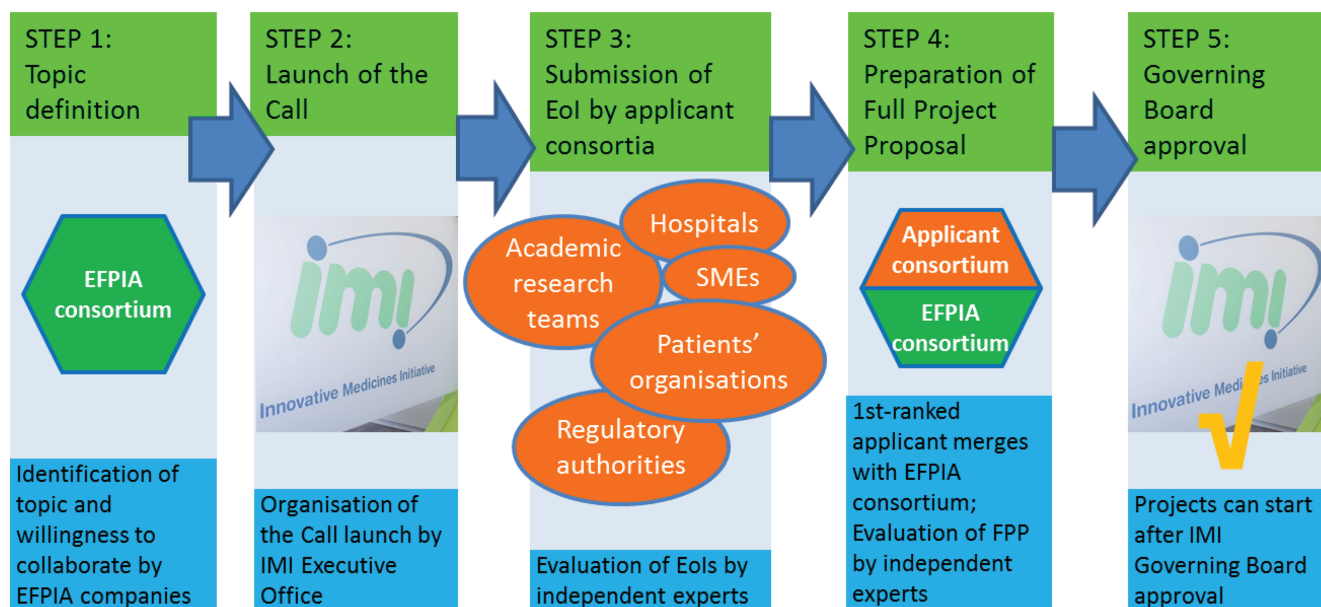
Currently, there are 40 on-going projects in IMI and more are to come in the near future. Even though IMI projects are relatively young, with the first project launched in May of 2009, there is already evidence that the IMI collaborative model is successful in removing traditional barriers between various private and public stakeholders and improving drug development processes [15]. The key figures of projects of immunological nature are presented in Table 1.

### Supporting personalized medicine in rheumatic disorders

Translation of discoveries regarding the basic mechanisms of disease into targeted and stratified therapies is especially challenging for immuno-inflammatory disorders because of the multitude of potential molecular targets, the different phenotypic expressions of the disorders, and the genetic factors influencing the response to therapies [16, 17]. The objective of the BTCure consortium, gathering 33 partners from 15 different countries

(www.btcure.eu), is to facilitate translational research in the field of rheumatoid arthritis (RA) by sharing and integrating data from basic immunology studies, animal models, clinical investigations, and powerful knowledge management tools. Animal models of RA are standardized and used to develop novel biomarkers and imaging tools suitable for pre-clinical assessment of novel therapeutic strategies. In parallel, new inventories of clinical cohorts, registries, and biobanks from academic and industrial partners are built and integrated. The collected materials are used to decipher immune mechanisms and predisposing factors to the disease using large-scale multiplex technologies and up-to-date bioinformatics. A pan-European cohort of patients with risk factors for developing RA will be constituted with the aim of offering early treatment options for patients with a high risk of developing the disease. In parallel, efforts towards personalization of RA treatment will be pursued through the development of novel biomarkers predictive of the response to therapies.

As future advances in the field of rheumatic disorders clearly require new diagnostic criteria based on their biological and molecular etiology, IMI just launched a new call for projects aiming at the definition of a new taxonomy of systemic lupus erythematosus and rheumatoid arthritis (Table 2).



**Figure 1.** Building an IMI consortium: Key steps. EoI: Expression of interest.

**Table 1.** On-going IMI projects in the field of immunology: Facts and figures.**BTCURE<sup>a)</sup>**

Core objective: Deciphering disease-causing factors and disease progression mechanisms in rheumatoid arthritis to develop targeted therapies

Starting date: 01/04/2011

Duration: 5 years

Total budget: €37.0 Million

EFPIA company coordinator: UCB

Managing entity: Karolinska Institutet, Sweden

Website: [www.btcure.eu](http://www.btcure.eu)

**U-BIOPRED**

Core objective: Understanding and stratifying the different types of severe asthma

Starting date: 01/10/2009

Duration: 5 years

Total budget: €22.3 Million

EFPIA company coordinator: Novartis

Managing entity & project coordination: Academic Medical Center, Amsterdam, The Netherlands

Website: [www.ubiopred.eu](http://www.ubiopred.eu)

**ABIRISK**

Core objective: Predicting and monitoring immune responses against biopharmaceuticals

Starting date: 01/03/2012

Duration: 5 years

Total budget: €34.9 Million

EFPIA company coordinator: GlaxoSmithKline

Managing entity: INSERM, France

Website: [www.abirisk.eu](http://www.abirisk.eu)

**BIOVACSAFE**

Core objective: Identification of predictive biomarkers for vaccine immunosafety

Starting date: 01/03/2012

Duration: 5 years

Total budget: €30.2 Million

EFPIA company coordinator: Novartis

Managing entity: University of Surrey, UK

Website: [www.biovacsafe.eu](http://www.biovacsafe.eu)

<sup>a)</sup> Acronym of IMI consortium conducting the project.

**Building a new classification of asthma**

Bronchial asthma, especially in its severe form, represents another complex disease for which the heterogeneity of the

molecular mechanisms involved results in poor predictability of therapeutic outcome and efficacy of candidate drugs. There is an urgent need for new targeted drugs, a goal that requires a more detailed characterization and classification of patients, as recently underlined

following the report of the results of the clinical trial with mepolizumab, an anti-IL-5 monoclonal antibody [18]. This is the main goal of the U-BIOPRED project conducted by 40 partners from different horizons, including six patient organizations ([www.ubiopred.european-](http://www.ubiopred.european-)

**Table 2.** Topics of immunological nature in on-going and future IMI Calls for Proposals.

Topic	Expected budget	Call launch	Deadline for submission <sup>a)</sup>
New classification for systemic lupus erythematosus, rheumatoid arthritis and related connective tissue disorders	€20 M	17 December 2012	19 March 2013
Correlates of protection for influenza vaccines <sup>b)</sup>	tbd	June 2013**	tbd

<sup>a)</sup> Deadline for the submission of expressions of interest;

<sup>b)</sup> Topic and timelines are indicative and subject to approval by IMI founding members; tbd: to be defined.

lung-foundation.org). The U-BIOPRED consortium is sub-phenotyping patients with severe refractory asthma by taking advantage of a sophisticated systems biology approach. Important features of the project include data pooling and linkage to preclinical models. By generating a 'handprint' — a combination of biomarkers based on genetic data, results from tissue samples, blood tests, breathing tests, clinical findings and patient-reported symptoms — the project aims to develop a new classification of severe asthma that would permit the prediction of disease progression and response to existing or experimental treatments. Along this line, the U-BIOPRED consortium already reached consensus regarding an algorithm for disease diagnostic [19].

### Assessing benefits and risks of biopharmaceuticals and vaccines

Several recent cases of drug-induced adverse events discovered after market authorization demonstrate the urgent need to reconsider in-depth the methods used to assess risks and benefits of medicines. This is clearly a top-priority in terms of public health, as well as from an industrial standpoint, in view of the high economical cost of late-stage drug failures. IMI has launched several collaborative projects aimed at renewing the approaches to drug safety and risk-benefit assessment and facilitating the dialog with the regulators and patients at an early stage of drug development.

In the field of biopharmaceuticals, major concerns include the development of anti-drug antibodies that might cause hypersensitivity reactions or interfere with drug efficacy and the induction of cytokine release syndromes [20]. The ABIRISK project aims to provide an integrated approach to anti-drug immunization by bringing together a large network of clinicians, industry and academic scientists with expertise in the mechanisms of adverse drug reactions, in immune monitoring and in biostatistics ([www.abirisk.eu](http://www.abirisk.eu)). Concretely, this consortium critically evaluates the immunogenicity of existing biopharmaceuticals for hemophilia A, multiple sclerosis and inflammatory disorders and develops standardized assays for each of them. Different approaches and tools are used to consider the multiple factors responsible for the induction of anti-drug B-cell and T-cell

responses. The data collected are input into a single databank that will be exploited to generate predictive signatures of drug immunogenicity and immunogenicity-related events. Major attention is paid to the reproducibility and standardization of immunogenicity assays and elaboration of guidelines for drug development and clinical care of patients, upon consultation with regulatory agencies.

Although vaccines have proved to be remarkably efficient in controlling major infectious diseases, public adherence to immunization programs is insufficient due to recurrent allegations regarding vaccine safety. In order to restore public confidence in immunization programs, it is essential to develop new approaches to measure the real risks associated with vaccine administration and to monitor vaccine safety throughout the development process and during the post-marketing period. IMI supports two projects dedicated to vaccine safety. The first one is conducted by the BIOVACSAFE consortium ([www.biovacsafe.eu](http://www.biovacsafe.eu)) that includes 19 partners among which are major vaccine manufacturers, academic teams, small businesses and non-governmental organizations. The BIOVACSAFE project is dedicated to the development and validation of tools and methods to monitor early inflammatory, allergic and autoimmune responses. In parallel, the public-private consortium gathers data on the incidence of autoimmune diseases in the general population and the links of such diseases with genetic and environmental factors, in order to specify the background against which the effects of vaccines must be assessed.

A second project dedicated to vaccines is currently planned for launch in 2013 with the objective of creating an efficient and sustainable framework for rapid and integrated assessment of post-approval benefit and risk of vaccines. It is indeed mandatory to ensure integration of data regarding vaccine coverage, effectiveness and safety. The pioneering work under the Vaccine Safety Data Link project in the US [21] and the first European experiences gathered by the Vaccine Adverse Event Surveillance and Communication (VAESCO) and I-MOVE projects [22–24] have paved the way for a broader and sustainable, readily available framework for combined benefit/risk measurements that are based on standardized, automated, and validated processes. In order to ensure sharing and transparency

of the collected data, attention will be paid to establish clear governance rules that meet the interests of the multiple stakeholders, namely vaccine manufacturers, regulatory agencies, public health institutes, healthcare organizations, academia, owners of patient-level health information, experts in the use of electronic health records and data linkage, and experts in measuring the outcomes of vaccination. Furthermore, policy makers and experts in ethics are also expected to play important roles in this consortium.

Finally, a project dedicated to correlates of protection induced by vaccination [25] is currently under discussion after European vaccine manufacturers expressed their willingness to work alongside academics and public health institutes to build validated and clinically relevant correlates of protection for influenza vaccines. To reach this goal, (i) experts in assay development, validation and standardization are needed to provide the tools, (ii) regulatory input is critical to ensure that the assays meet European regulatory expectations, (iii) clinical centers and public health agencies are essential for validation of the novel surrogate markers of protection, and (iv) academic research is required to advance our understanding of B-cell and T-cell assays. Indeed, this project represents an excellent case for the IMI public-private collaborative model (Table 2).

### Concluding remarks

By fostering collaboration between large pharmaceutical industries, academic teams, and biotechnology companies, IMI is supporting translational immunology and innovative approaches for the treatment of immune-based disorders and the development of safe and efficient vaccines. The neutral platform provided by IMI facilitates balanced agreements between the different stakeholders and the dialog with regulatory authorities that is critical to ensure that the results obtained lead to the introduction of new pharmaceuticals in agreement with the standard of care. It is our hope that the community of European immunologists will provide major contributions to the new ecosystem that is needed to reach the ultimate objective of IMI, namely to align the interests of industry and society for the benefit of patients. To find out more

about IMI and calls for proposals, visit the IMI website (<http://www.imi.europa.eu>).

**Michel Goldman, Angela Wittelsberger and Maria-Teresa De Magistris**

Innovative Medicines Initiative, Executive Office

*Correspondence:* Prof. Michel Goldman, Executive Director, Innovative Medicines Initiative, TO 56, Office 6/4 B-1049 Brussels, Belgium  
e-mail: [michel.goldman@imi.europa.eu](mailto:michel.goldman@imi.europa.eu)

## References

- Weiner, L. M. et al., *Nat. Rev. Immunol.* 2010. 10: 317–327.
- Nelson, A. L. et al., *Nat. Rev. Drug Discov.* 2010. 9: 767–774.
- Feldmann, M. and Maini, R. N., *J. Immunol.* 2010. 185: 791–794.
- Dinarello, C. A. et al., *Nat. Rev. Drug Discov.* 2012. 11: 633–652.
- Chan, A. C. and Carter, P. J., *Nat. Rev. Immunol.* 2010. 10: 301–316.
- Miossec, P. and Kolls, J. K., *Nat. Rev. Drug Discov.* 2012. 11: 763–776.
- Kontzias, A. et al., *Curr. Opin. Pharmacol.* 2012. 12: 464–470.
- Bermel, R. A. and Cohen, J. A., *Lancet Neurol.* 2011. 10: 4–5.
- Chataway, J. and Miller, D. H., *Lancet.* 2011. 6736: 1759–1760.
- Stohl, W. and Hilbert, D. M., *Nat. Biotechnol.* 2012. 30: 69–77.
- Goldman, M., *Clin. Pharmacol. Therap.* 2012. 91: 418–425.
- Woodcock, J., *Clin. Pharmacol. Ther.* 2010. 87: 521–523.
- Melese, T. et al., *Nat. Med.* 2009. 15: 502–507.
- Goldman, M., *Nat. Med.* 2012. 18: 341.
- Laverty, H. et al., *Expert Rev. Pharmacoecon. Outcomes Res.* 2012. 12: 545–548.
- Keith, M. P. et al., *Clin. Pharmacol. Ther.* 2012. 92: 440–442.
- Tsokos, G. C., *N. Engl. J. Med.* 2011. 365: 2110–2121.
- Hashimoto, S. and Bel, E. H., *Lancet* 2012. 380: 626–627.
- Bel, E. H. et al., *Thorax.* 2011. 66: 910–917.
- Hansel, T. T. et al., *Nat. Rev. Drug Discov.* 2010. 9: 325–338.
- Baggs, J. et al., *Pediatrics* 2011. 127 Suppl: S45–53.
- Dieleman, J. et al., *Br. Med. J.* 2011. 343: d3908.
- Andrews, N. et al., *Vaccine* 2012. 30: 3042–3046.
- Valenciano, M. and Ciancio, B., *Euro surveillance: bulletin européen sur les maladies transmissibles = European communicable disease bulletin.* 2012. 17: 1–12.
- Plotkin, S., *Clin Vaccine Immunology* 2010; 17: 1055–1065.

## IMI Calls for Proposals

See the latest IMI Calls for Proposals at <http://www.imi.europa.eu>

Immunological proposal topics and deadlines are outline in Table 2 of the above article.

## ACTERIA Prizes: New Awards in Immunology and Allergology

EFIS is delighted to announce four extraordinary new awards to recognize Europe's young talents in the fields of immunology and allergology:

- ACTERIA Doctoral Thesis Prizes: two prizes
- ACTERIA Early Career Research Prizes: two prizes

Thanks to a recently established partnership with the Fondation ACTERIA – ACTing on European Research in Immunology and Allergology – EFIS will award these four prizes to early career researchers, two each in both biomedical disciplines, for the best doctoral theses defended in the last three years prior to the award nomination deadline and for the best early career research work of investigators with up to 10 years postdoctoral experience. These Prizes carry cash awards of €15 000 and €30 000 each, respectively. In addition, awardees will automatically become eligible for three year research grants of up to €50,000 annually.

Nominations will be accepted exclusively from EFIS-affiliated National Societies so contact your respective National Society with your suggestions. Please note that EFIS-affiliated Societies can submit four nominations, one for each prize in immunology and in allergology.

The ACTERIA Prizes will be awarded for the first time at the 2013 International Congress of Immunology (ICI) in Milan at a special awards ceremony on August 25th, 2013, during which each of the prize winners will be expected to speak and present his or her work. Thereafter, the awards will be presented at the tri annual European Congress of Immunology (ECI) organized by EFIS, starting in 2015 in Vienna.

Deadline for receipt of nominations at EFIS is **February 28th, 2013**.

For further details visit [www.acteria.ch](http://www.acteria.ch)