Innovative Medicines Initiative

IMI JU SCIENTIFIC PRIORITIES FOR 2014

For integration in the Annual Work Plan for IMI2 in 2014 (revising the Annual Implementation Plan for IMI1 in 2014)

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The Scientific Priorities for 2014 reflect the principles of the Council Regulation on the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, specifically:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including mid-caps, from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender matters are considered). Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The Scientific Research Agenda (SRA) for IMI2 (see http://www.imi.europa.eu/content/imi-2) sets out the framework that underpins the development of specific projects or research programmes to be prioritised for funding.
12 key health priorities have been identified on the bases of the WHO Priority Medicines Report, and it is anticipated that throughout the lifetime of IMI2, many of these health priorities will be addressed. The SRA furthermore identifies data and knowledge management as key enabling technologies and education and training and excellence in clinical trial implementation as key implementation strategies.

The SRA places the research objectives of IMI2 under four major research axes:

1. target validation and biomarker research (efficacy and safety);
2. adoption of innovative clinical trial paradigms;
3. innovative disease prevention, interception and treatment solutions;
4. patient-tailored adherence programmes.

The activities generated from the priorities areas will be designed considering relevant differentiating enablers for early and effective patient access to innovative prevention and treatment solutions (Medicines Adaptive Pathway to Patients-MAPPs-[1]):

- target validation based on human biology;
- stratified medicine, precision medicine;
- innovation in clinical trials for new drugs and therapeutic modalities;
- data generation and interpretation (knowledge management);
- prevention, disease interception, patient adherence (incl. societal acceptance of vaccines);
- patient-centric approach – effect on medical practice and outcomes (health/disease management);
- regulatory framework (including pharmacovigilance);
- reimbursement/patient access.

[1] Press release: European Medicines Agency launches adaptive licensing pilot project: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/03/news_detail_002046.jsp&mid=WC0b01ac058004d5c1

Using the framework of the SRA, the 2014 Priorities for the design of the first IMI2 Call topics have been selected on the basis of their potential to foster a first batch of high impact initiatives, in areas where the maximum number of stakeholders can join forces. In particular five therapeutic areas (including rare forms of diseases) and cross-cutting themes have been identified:

1) metabolic disorders;
2) neuro-degeneration;
3) prevention and treatment of immune-mediated disease, and advancement in prophylactic and therapeutic vaccines for infectious & non-infectious diseases;
4) infection control including incentives for reinvestment in antimicrobials, antivirals, and vaccines;
5) translational Safety.

In addition to these priority areas, EFPIA and/or other industries active in health care may propose further priorities under one or more of the 12 key health priorities or based on emerging needs which are identified in the Scientific Research Agenda. Topics will be selected based on the level of unmet need, the need for a public-private partnership to make a difference, the extent to which the science is capable of delivering a high impact over the next decade, and the synergies/complementarity with similar initiatives.

To implement these Scientific Priorities, IMI2 will initiate competitive Calls for proposals and any other necessary procedure to evaluate proposals and award funding to projects[2]. Each priority may be implemented via the launch of one or more topics, which might generate one or more multi-stakeholder projects, potentially including (or driven by) other non EFPIA industry partners, or tailor-made projects for specific stakeholder groups. These details will be worked out as part of the maturation of the individual topics.

All proposals must conform to the conditions set out in the H2020 Rules for Participation (http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/rules_participation/h2020-rules-participation_en.pdf) and the Commission Delegated Regulation with regard to IMI2 (add weblink), unless they are supplemented in the call text.

In recognition of the opening of the US National Institutes of Health's programmes to European researchers, any legal entity established in the United States of America is eligible to receive IMI2 funding to support its participation in projects supported under the Societal Challenge `Health, demographic change and well-being' of H2020.

The proposals will be evaluated against the evaluation criteria (including scoring and threshold) and according to the evaluation procedure described in the call text.

For topics including clinical trials/studies/investigations, a specific template for essential information is available under
http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-phc-2014-single-stage/1600139-essential_information_for_clinical_studies_en.pdf

Consortia will be requested to disseminate research data based on the basis of open access.

[2] Please see Annex Statutes of the IMI2 Joint Undertaking paragraph (f) and (g)

1.1. Metabolic disorders

Activities in this priority area should seek progress towards novel diagnostic and treatment paradigms for early onset and progression of diabetes (type 1 and type 2) and its complications, and for early diagnosis and development of novel experimental medicine approaches to efficacious diabetes treatment, considering also health system sustainability of treatment intervention.

Synergies will have to be created with several ongoing EU-wide and global initiatives including ongoing IMI projects such as SUMMIT, IMIDIA and DIRECT. All these efforts are already generating large scale sequencing data, and are performing genome-wide association studies (GWAS), and metabolomic and epigenomic studies in a large number of patients to identify new targets and biomarkers for prediction of disease progression and drug response.

IMI2's activities will build on the progress made through each of these initiatives, continuing to grow the science base required to support a personalised/precision medicine approaches for diabetes.

Activities in this area planned for 2014 will focus for example on one or more of the following:

- Predictive biomarkers, targets and pathways involved in insulin resistance and disease progression in the pre-diabetic stage of the cardio-metabolic continuum should be identified. Of relevance will be early non-glucose-related biomarkers for disease initiation and progression to complications and renal failure, and cardiovascular mechanisms as independent risk factors for type 2 diabetes.

- Tools and methods for the monitoring of key markers of glucose metabolism and diabetes complications using nanotechnologies should be defined.

- Data should be generated to allow a molecular definition of diagnosis criteria, and the determination of the best time point for pharmacological intervention to prevent disease progression to overt diabetes and complications.

- The interactions of immune cells (T-cells) with pancreatic ß-cells should be defined, and the development of early predictive biomarkers for the immunodestruction of ß-cells should be sought. This should lead to a better understanding of common and rarer immune mechanisms in type 1 diabetes and other auto-immune diseases, paving the way towards a molecular taxonomy of type 1 diabetes.

- Reliable and generally accepted outcome parameters and clinical trial designs for immune therapy in type 1 diabetes patients should be established. This might include comparative experimental clinical trials with different immune-modulatory drugs for a tailor-made, immune-modulating therapy of type 1 diabetes, and the definition of the efficacy parameters, regulatory rules and a roadmap for immune-modulating therapy in newly-diagnosed type 1 diabetes patients.

1.2. Neurodegeneration

Given the healthcare burden that neurodegenerative diseases pose, together with the current disinvestment by major pharmaceutical companies, joint and urgent action from public and private sectors is essential.

The focus will be on the early and correct diagnosis of neurodegenerative diseases, the development of more preventative treatment approaches, the development of innovative patient focused endpoints, trial designs, and simulation and analytical approaches to devise new clinical trial paradigms both pre-and post-marketing. This will be critical to assess outcomes (good and bad) in small patient populations, thus balancing the needs for regulation (efficacy/safety) and HTA (Health Assessment Agencies) agencies (effectiveness/safety), as well as the risk and cost for pharmaceutical companies while responding to the urgent patient needs in this area.

A framework for scaling the collection of biomarker and clinical data is already in place, at least for some neurodegenerative conditions, with successful implementation of worldwide efforts such as the Alzheimer's Disease NeuroImaging Initiative (ADNI) and other European initiatives. These include IMI's EMIF-AD project, the Joint Programme – Neurodegenerative Disease Research (JPND), the Centre of Excellence Network (CoEN) and UK Dementias Platform supported by the UK's Medical Research Council (MRC) and the German Centre for Neurodegenerative diseases (DZNE) and others. Any new activities undertaken in IMI2 will collaborate with such initiatives and data resources available from academia across Europe to ensure synergies are maximised, and efforts are not duplicated.
Furthermore, important learnings should be generated by tackling alternative neurodegenerative and aging-related diseases with a high societal burden such as ophthalmic indications.

Activities in this area foreseen for 2014 will focus among other possible neurodegenerative conditions for example on one or more of the below:

- Age-related macular degeneration (AMD) is a serious neurodegenerative condition and leading cause of progressive blindness in patients of middle age and older. Outcome measures, biomarkers and composite endpoints that may be used in efficacy and safety trials for AMD, should be identified, and validation and regulatory agreement in principle should be sought.
- Health economic models and ways of monitoring therapy for AMD after marketing authorisation is granted should also be developed.

1.3. Prevention and treatment of immune-mediated disease

Autoimmune diseases cover over 100 distinct diseases and syndromes, together affecting approximately 5% of the population of Europe, with two-thirds of the patients being female. The burden of autoimmune disease crosses medical and scientific boundaries, and requires cross-functional collaboration by scientists and physicians with interests in diseases of widely differing organ systems. Activities should seek to identify therapeutic opportunities and design and implement clinical strategies, which will transform the diagnosis and management of autoimmune diseases.

The proposed work will build on the knowledge base and infrastructure present within the EU from ongoing research-based initiatives e.g. Eumusc.net, EMEUNET, EUSTAR, ERS/ELF, ECCO, BILAG, EUVAS and Euro Lupus OMERACT, as well as relevant IMI projects (BTCURE, PRECISESADS), which together have aggregated substantive information on disease phenotypes, biomarkers and other factors associated with disease progression in many autoimmune disorders in order to guide better patient treatments.

For some conditions, like multiple sclerosis (MS), while disease modifying therapies have been available for 20 years, there has been limited progress in evaluating the real world outcomes and impact of treatment. Similarly there is a limited amount of long term data to support the impact of the approved therapeutic approaches in terms of disability and quality of life.
There are efforts at national and international levels to capture real world data, however up to now there have been only limited efforts to improve, expand and link up this data in a way that would enable the use of real world evidence to develop tools to guide health professionals in how and when to use treatments and support their management decisions to optimise outcomes (personalised medicine).

<u>Activities in this area foreseen for 2014 will focus for example on one or more of the below:</u>

- Database efforts across Europe should be further expanded and coordinated leading to a European knowledge platform in MS and its treatment. This should aim to expand and enhance the collection of real world MS data in Europe, explore the use of real world data in innovative regulatory pathways, and develop models for disease risk assessment for better decision making.

- Tools and measures to assist in personalised medicine decision making should be developed and advanced. These should include magnetic resonance imaging (MRI) and other techniques for assessment of brain function, patient reported outcomes (PROs), cognition, adherence, and clinical measures. This will require also developing relevant education in MS with specialist certification courses for healthcare professionals (nurses, neurologists, radiologists, etc.) and pharmaceutical industry professionals.

1.4. Infection control including incentives for reinvestment in antimicrobials, antivirals, and vaccines

Vaccination is one of the most valuable and cost-effective public health measures to prevent and control the spread of viral/bacterial infectious diseases responsible for high mortality and morbidity. It at least saves three million lives every year globally. Changes in society both nationally and internationally have led to the need for research & development on vaccines to address the changing risks and immunological characteristics of the whole lifespan. This requires innovative solutions to understand and measure the maturation of the immune system, and to tackle emerging/unmet medical needs. Research is also needed to better understand drivers underpinning inconsistent utilisation of available immunisation measures, as a rise in the numbers of people hesitating to use vaccines undermines individual and societal public health and exacerbates the challenges of maintaining the financial sustainability of healthcare systems. Furthermore this is a priority area where research to reduce the use of experimental animals is highly relevant.

In the field of vaccines a number of large research infrastructures already exist such as CIMT/CIC (T-cell Immunity), and EU-funded OPTIMALVAC/EMVDA (malaria vaccines) and TRANSVAC (vaccines in general) among others. This provides an excellent opportunity to drive collaboration between these existing initiatives, bringing together industry and public research organisations and maximising synergies. The benefits could be even further enhanced by linking to other European infrastructures such as biobanks and IT infrastructures.

Activities in this area planned for 2014 will focus for example on one or more of the below:

- Alternative approaches to the current animal tests required for lot release testing of established vaccines have been under development in both the public and private sectors for years, and some progress has been made. However, validation of these methods by comparison with the immunisation-challenge potency tests has been very difficult, time consuming and not always successful, for, amongst other reasons, the poor reproducibility of the in vivo tests. Therefore, the development of analytical methods, in vitro models demonstrating functionality of immune responses, and bioinformatics, to generate a set of consistency tests that will allow improved monitoring of vaccine quality during production and final formulation should be sought.

1.5. Translational safety

There is still a critical need for tools and methods that will facilitate the monitoring of safety issues, contributing to the safety of patients beyond the launch of new products. A better understanding of toxicological findings for human risk assessment has to be built for example via a retrospective review of clinical side effects and their relationship to non-clinical safety data. Better preclinical models representing human biology for predicting safety issues, and understanding the molecular causes underlying it, are needed to reduce attrition in the development of novel drugs and enable the development of safety biomarkers for the management of risks in humans.

Activities in the area will build on progress and success from the portfolio of IMI projects on safety, from other relevant European and global initiatives to create synergies (e.g. US Critical Path Institute and NIH driven projects) and from data management initiatives.

Activities in this area planned for 2014 will focus for example on one or more of the below:

- The concordance of toxicity of pharmaceuticals in humans and in animals should be re-assessed. While an extensive arsenal of biomarkers for renal and hepatic safety has been already generated, during clinical studies and particularly during early or adaptive licensing it will be important to monitor early for changes and trends in those biomarkers.

- Identification and/or further validation of known and suggested new safety biomarkers representing different types of molecules, e.g. proteins and enzymes, but also nuclei-acids, might also be sought. One goal will be the characterisation of biomarkers which are easily translatable across preclinical species and human patients. A further goal will be the search for/evaluation of biomarkers for organs other than the liver and kidney, e.g. heart, pancreas, gastro-intestinal tract, brain etc.

- A key component of these activities might be the development of devices to automatically monitor for metabolic changes while being minimally invasive, and the use of contemporary communication technology to aggregate/monitor information in real time. The use of automated biomarkers will also be used in combination with the knowledge management work to understand and optimise real world medicine use more broadly. Points of care for automated safety monitoring will help minimise and provide early detection of drug-drug interactions and unanticipated consequence of treating patients with multiple conditions.

- New platforms should be developed reflecting human organ physiology (e.g. 3D, or organ-on-chip models, single cell-type or co-culture) to predict toxicity and safety during early drug development. In particular, liver, renal and cardiac safety might be studied using induced pluripotent stem (iPS) cells from subjects with a variety of phenotypes to understand better which patient subpopulations are at risk from rare safety issues. These models will be validated based on existing compound libraries and safety databases. Assessment of such new models will include evaluation of the limitations of such models with respect to *in vivo* organ function, which thereby will define their applicability.

- Molecular targets and pathways (through e.g. integrated 'omics' approaches) underlying toxic phenotypes of drugs failed for safety reasons should be identified. One goal will be the development of *in vitro* models representing these pathways which can be employed in early safety testing. This should lead to a reduced and refined use of animals, including the possibility for better prediction of suitable toxicology species.

- Since toxicological phenotypes are the result of both the hazard and the dose, a further activity should include the evaluation and optimisation of existing or new toxicokinetic models with the aim of predicting adaptive and adverse changes based on *in vitro* assay results and modelled exposure data. Of relevance may also be studies of the pharmacokinetic interactions caused by mechanism-based, time-dependent and metabolite- mediated inhibition of drug metabolism and transport as well as relevant pharmacogenetic studies. This will be important to anticipate and study adverse drug interactions, understand variability in the metabolism and disposition of drugs and their metabolites, and guide future revisions of regulatory guidance on drug-drug interaction studies.

- A systematic annotation of observed toxic phenotypes, and the integration of various types of both newly generated and already available data into existing data management structures should be also achieved, with potential consolidation into fewer database formats to allow flexible public and private use.

1.6. Other Priorities derived from the SRA: 1- Psychiatric diseases

More than a quarter of all Europeans are estimated to experience at least one form of mental disorder during their lives. Although several treatments are available, positive response is limited, and for most mental disorders, treatment algorithms are based on trial and error.

Activities are needed for a better understanding of the disease biology and potential biomarkers of psychiatric disorders, which will be the key to increasing rates of diagnosis and treatment success, and to the development of more targeted medicines. Attention should be paid to new techniques for the functional assessment of the human brain.

Activities will build on early successes and progress in ongoing IMI projects (NEWMEDS and EU-AIMS) and will seek synergies with other national, European and global initiatives on mental health.

Activities in this area planned for 2014 will focus for example on one or more of the below:

- A systematic analysis of genetic and environmental factors contributing to different psychiatric disorder categories in a trans-diagnostic way should be considered. This should be the basis for (back)-translational work, taking advantage of new instruments of research and patient characterisation, to allow the establishment of trajectories for the development of psychiatric disorders.
- A taxonomy which better reflects the neurobiological mechanisms of psychiatric disorders and is better suited for developing new and efficacious drugs to treat mental disorders should be developed. This activity will link to ongoing projects on disease taxonomy already implemented by IMI.
- A framework for translation of research on clinically relevant neuropsychiatric endo-phenotypes for regulatory agencies should also be built.
- This might also include the development of surrogate endpoints and markers for efficacy and patient stratification, and for identification of endo-phenotypes of potentially disruptive disorders in ‘at-risk’ patients.

1.7. Other Priorities derived from the SRA: 2- Respiratory diseases

Despite improvements in the way respiratory diseases are managed, they continue to pose a significant burden on patients and healthcare systems. Unlike asthma and other allergic respiratory diseases, chronic obstructive pulmonary disease (COPD) remains a relatively poorly understood disease despite one person dying of COPD every 10 seconds, more than breast and lung cancer combined.
IMI2 activities will have to seek synergy with ongoing initiatives such as The COPD Foundation Biomarker Qualification Consortium, the UK Technology Strategy Board funded ERICA or the Industry-funded ARCADE and ECLIPSE cohort studies, among others. Furthermore the initiatives will build on current relevant activities in IMI (e.g.PROactive).

Activities in this area planned for 2014 will focus for example on one or more of the below:

- A better understanding of what aspects of COPD heterogeneity are relevant for patient-based risk assessment and stratification should be delivered. This should consider an impact on therapeutic strategies and patient management in real life clinical practice. This might include the identification of alterations of pathway regulation associated with poor patient prognosis.

- Rules for subject-specific health risk assessment and patient-oriented stratification with impact on healthcare management (both preventive and therapeutic) should be generated.

- Knowledge acquired by the project should be transferred to clinical practice through well-defined validation strategies and implemented as a fully deployed integrated care scenario.

- The optimisation of the interactions between pharmacological and non-pharmacological interventions in COPD patients might also be relevant.

- The exploration of potential re-orientations of the use of existing drugs for the design of novel therapeutic approaches (i.e. antioxidant therapies) might be also included.

1.8. Other Priorities derived from the SRA: Enabling Technologies and Excellence in Data Management

The increasing volume (terabytes/patient), diversity (clinical, GWAS/RNASeq, eHR, 'omic', cytometry, imaging, pharmacology, pharmacovigilance etc.) and velocity (e.g. real time telemetric monitoring of patients, social media feeds, etc.) of biomedical data create significant opportunities for healthcare R&D. However, common data standards, as well as robust data production and knowledge management (KM) solutions and services will be essential if the full value of these data sets is to be realised in the development of innovative precision medicines.

Furthermore, as healthcare delivery systems change, clinical trials move to more adaptive designs, new monitoring devices become more sophisticated and "live" patient interactions through mobile enabled, social media technology, are implemented, there will be a need to engage with the IT sector. This will be necessary to collaborate on the development of novel

enabling technologies and adaptive therapies to facilitate the efficient capture and interrogation of these data sets to ensure effective healthcare practices for patients.
The IMI2 activities will expand upon work from existing IMI projects including EMIF[3], eTRIKS and EHR4CR as well as other FP7 projects in the area of electronic health records, and will require coordination/collaboration with European biomedical research infrastructures through the European Strategy Forum on Research Infrastructures (ESFRI). They will also take into account policies and guidelines for data gathering and sharing from relevant international initiatives such as the International Rare Diseases Research Consortium, International Human Cancer Genome Consortium and the Global Alliance for Chronic Diseases.

Ethical Legal and Social Aspects (ELSA), will have to be carefully considered and developed as part of all research activities in this area.

Activities in this area planned for 2014 will focus for example on one or more of the below:

- Building on EMIF, a comprehensive, large scale, usable and accessible database should be developed that in the long term will link genotype, clinical and phenotype data for any individual (diseased or non-diseased). This will be essential to maximise opportunities to understand disease. This project will include the generation and coordination of a pan-European, controlled access database (data safe haven) for qualified genetic and health record/patient-level phenotype information to provide longevity and accessibility to data for 1-3 pilot disease areas beyond those already tackled by EMIF.

- Real-time identification of behavioural and physiological patterns that culminate in disease relapse is of great importance: early detection and communication of "red flags" to both patients and providers can prompt help-seeking behaviour and deployment of just-in-time interventions that may prevent relapse episodes, effectively altering one's clinical trajectory. Achieving this objective might involve among others that:
    a) the science of using biosignatures to characterise disease and predict changes in disease state through a series observational studies is developed and validated.

    b) innovation and development of novel biosensors and the associated knowledge management technology is stimulated.

    c) the understanding of the regulatory pathways for using remote assessment in healthcare is enhanced.

    d) standards for Information Exchange that enable seamless integration of sensor, data capture, data management, & analysis technologies are developed.

    e) an open source reference platform is created to enable the collection, storage and analysis of remote assessment data.

[3] The European Medical Information Framework (EMIF) programme was established as part of the 4th IMI Call, as an IMI project composed of the EMIF-Platform (the data and technical part) and 2 research topics (in metabolics and Alzheimer's disease).