



Innovative Medicines Initiative

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## INDICATIVE TOPICS FOR THE IMI 4TH CALL FOR PROPOSALS (2011)

**All information below is indicative and subject to change. Final information about the IMI 4th Call topics will be communicated after approval by the IMI Governing Board.**

### CLUSTER A: EU MEDICAL INFORMATION SYSTEM

#### 1. BUILDING UP A EUROPEAN MEDICAL INFORMATION SYSTEM TO IMPROVE HEALTHCARE AND FACILITATE RESEARCH IN AREAS SUCH AS EXTREME PHENOTYPES AND DISEASE MANAGEMENT AND OUTCOMES

Electronic Health Records (EHR) contain an enormous wealth of medical information that has the potential to significantly improve healthcare and advance medical research. Industry believes that technological advances and broad implementation of EHRs in Europe are necessary to realize this potential. At the present time, the European healthcare information environment is fragmented by lack of legal and technical standards, cost effective platforms, and sustainable business models. Thus, even though a considerable amount of relevant patient health information does exist, it typically resides in a variety of systems in a fragmented way in different locations thereby inhibiting ready and efficient access from a central place. Direct applications of a linked-up network of such data sources across Europe are numerous. Of particular relevance to the project presented here are the elucidation at the molecular level of diseases and drug response using an extreme phenotype approach, insight into geographical disparities in disease management and outcome and evaluation of treatment benefit/risk ratio. The extreme phenotype approach is based on the concept that individuals at the extreme of the distribution of a particular trait have a high probability of having a mono- or oligogenic predisposition to this trait, and that these genetic abnormalities can now be elucidated at the molecular level using breakthrough technologies like exome sequencing and direct comparison of the extremes. This information can then be applied to understand less extremes variations in the phenotype, for diagnostic purposes and to develop innovative therapeutics for the condition under evaluation.

Real-world data on treatment effectiveness and safety are increasingly needed by a number of stakeholders requiring further systematically collected in-depth information spanning a range of populations from different geographic areas on a large scale.

#### Need for public-private collaborative approach

Healthcare organisations and the pharmaceutical industry in Europe share a common goal: improve patient outcomes by delivering the best possible personalised treatments and innovative medicines. The development and implementation of a European Medical Information System (EMIS) that provides access to comprehensive and in-depth data on a large scale for addressing the above research topics requires a massive effort that spans a number of contributors and experts from Pharma industry, healthcare organisations, academia and other third parties throughout Europe.

The proposed project will complement and will be coordinated with ongoing IMI projects, most notably the 2009 Knowledge Management Project call EHR4CR as well as the 2008 call PROTECT

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## 2. TRANSLATIONAL STUDY KNOWLEDGE MANAGEMENT & SERVICES

Translational research (TR) in drug discovery and development requires sharing of knowledge between pre-clinical and clinical activities in order to derive new insights into disease presence, progression, drug response and drug toxicity. This translational philosophy is at the heart of the IMI pre-competitive mission between the EC and the European Pharmaceutical Industry. As expected, such TR involves significant knowledge management challenges. In particular these challenges include access, management, integration and analytics across diverse data types. These information challenges are too broad to be addressed in a single IMI call but instead will require the coordinated EFPIA steer onto a wide range of public-private partnerships (PPP) investments across the EC.

While the scientific community develops a knowledge management (KM) strategy, it is clear there is a need for focused KM provision for existing and future IMI calls incorporating both preclinical and clinical data to ensure they maximize their potential. The proposal here is to establish a European physical infrastructure and service to

- a) provide the necessary supporting capability for IMI calls and other EU translational projects
- b) aid the coordination across the various related bio-medical infrastructure and standards activities pertinent to this complex domain.

### **Need for public-private collaborative approach**

The challenges involved in building and supporting a translational platform, and associated content, can only be addressed through a collaborative public-private partnership approach, requiring industry know-how, experience and problem understanding combined with academic/SME expertise in methodology and standards development. In addition a key role for the public consortium is that of the Not-For-Profit honest broker and service provider, with a mandate to support relevant translational studies across the EU, not just IMI.

Importantly this IMI service provision call should be closely coordinated with the ESFRI infrastructure investment proposals as part of the Biological and Medical Science (BMS) infrastructure business cases, particularly EATRIS (Translational data), but also ECRIN (clinical data), ELIXIR (biological data) and EuroBioImaging (biomolecular/medical imaging data). These investments by EU member states will progress over the next 4 years and have scope well beyond this IMI proposal. However standards and infrastructures resulting from these investments should be adopted where possible into this platform. In addition where appropriate it may be advisable to coordinate funding opportunities across IMI KM services and ESFRI.

## CLUSTER B: CHEMISTRY, MANUFACTURING AND CONTROL

### 3. DELIVERY AND TARGETING MECHANISMS FOR BIOLOGICAL MACROMOLECULES

Therapeutic modalities based on macromolecules of biological origin, e.g., proteins, peptides and oligonucleotides, have a huge pharmacological potential due to their highly selective mode of action, and some of them have activity against targets that are considered non “druggable” by more traditional small organic molecules. Similarly, therapeutic oligonucleotide medicines for the most part interfere with gene translation and transcription and are currently being evaluated for treatment of diseases with currently “undruggable” molecular targets, although the target selectivity is usually very high for both peptide and oligonucleotide based drugs, dose related adverse events are not uncommon. There is still room for improvement in therapeutic margins to minimize the potential for off target effects via strategies focused on improved delivery and dose reduction.

Widespread application of many potential macromolecular therapeutics have been very limited due to pharmacokinetic and drug disposition limitations at both the tissue and cellular level. For example, double-stranded oligonucleotides that make use of the intracellular RNA interference (RNAi) mechanism such as siRNAs and miRNAs, and single-stranded antisense oligonucleotides (ASO) that specifically modulate mRNA expression or protein function have emerged as very promising disease-modulating pharmacological molecules. However, unlike protein-based molecules, these nucleic acid-based compounds have the inherent issue of biological instability and low tissue bioavailability. Therefore, their success in developing future innovative medicines will heavily depend on improvements in both chemistries and delivery technologies that can address these limitations.

Macromolecular drugs with intracellular targets will only be effective after systemic administration if they avoid degradation, hepatic/reticuloendothelial system uptake and renal excretion, traverse the microvascular endothelium, cross target cell membranes and escape degradation in the endosome-lysosome system. Subverting these barriers has contributed to the requirement for large doses, and low therapeutic margins have been observed in both animal experiments and clinical trials. As a result, biological drugs may have issues of therapeutic ratio that could be mitigated by improvements in selective delivery.

#### **Need for public-private collaborative approach**

Innovative strategies for chemical stabilization and cellular delivery of biological macromolecules can only be developed and tested with availability of broad expertises and appropriate resources. This can only be delivered by a cross-functional/cross-institutional consortium of academic, SME, regulatory and industrial scientists to foster a better understanding of drug development, molecular and cellular biology of cellular uptake mechanisms of macromolecules, protein and nucleic acid chemistry, manufacturing of biological macromolecules; and nanotechnologies. There are also patient interest groups, particularly for rare diseases, who would press for and encourage this approach to the delivery problem.

#### 4. IN VIVO PREDICTIVE BIOPHARMACEUTICALS TOOLS FOR ORAL DRUG DELIVERY

Pharmaceutical product design during drug development is a critical step in facilitating the translation of pre-clinical research to human trials. The science of biopharmaceutics, which provides the link between API physicochemical properties, solid state form, dosage form design and bioavailability, has an integral role throughout the development process.

Biopharmaceutical properties are used to guide formulation design and choice of delivery system, however profiling dosage form performance under conditions which are relevant to in vivo conditions remains a significant challenge for development scientists.

High throughput modern drug discovery approaches yield highly potent and selective molecules but it is clear from experience across the industry that molecules identified as hits from such screens are becoming increasingly difficult to formulate due to poor molecular properties such as hydrophobicity and low aqueous solubility. In response to this, formulation science and technology has delivered a number of diverse approaches such as nanosized materials and stabilised amorphous systems to overcome the obstacles of low solubility and dissolution rate limitations which would otherwise impede drug development. However, our ability to select the optimal approach based on in vitro characterisation is limited by the basic nature of the predictive biopharmaceutics tools available. When the challenges associated with oral drug delivery are considered in this context, the current in vitro characterisation tools, such as conventional dissolution systems, simply do not replicate the rapidly changing dynamic environment of the gut lumen. Additionally, the physiological variability and complexity observed on meal ingestion cannot be accurately reproduced. The lack of predictive biopharmaceutical tools also limits our ability to fully utilise the power of biomodelling software to predict formulation performance. Often, in vivo testing in preclinical species is required to confirm formulation performance and predictive tools would have a direct contribution to minimizing the use of animals in accordance the 3R (Replacement, Reduction, Refinement) principles. Accurate predictive tools would also impact our ability to tailor product design through modified-release technologies and optimise PK/PD relationships to improve clinical safety and efficacy. The use of predictive tools to understand and evaluate how changes in drug product processing or manufacture impact clinical performance is a key component of the Quality by Design (QbD) concept. There is a clear opportunity to embed the use of predictive tools in a regulatory framework and reduce the significant economic burden of empirical testing (both in terms of manufacturing multiple batches and clinical assessment) when developing the QbD design space for commercialisation of drug products. Drug development costs can also be reduced through the use of the Biopharmaceutical Classification System (BCS) to facilitate the replacement of in vivo bioequivalence studies with in vitro testing for a limited number of drugs (BCS class I). It would be desirable to further extend the BCS based biowaiver provision through a better of understanding of the predictive tools, especially in combination with the enhanced knowledge generated by applying QbD. Finally, work done so far in this area has focused almost exclusively on the physiological conditions in "average", young, healthy volunteer populations and the influence of disease state, age and concomitant medication on in vivo performance of formulations in true patient populations has been largely neglected.

##### **Need for public-private collaborative approach**

Combining industry experience and resources with academic expertise is essential to improve our understanding of the biopharmaceutics of oral drug delivery and to develop predictive tools which can be used to drive a more efficient product development process and deliver significant clinical benefits through rational product design. A pre-competitive PPP initiative would bring together expertise across multi-disciplinary areas and providing the resources for pooling information on formulation characterisation and clinical product performance to create an industry-leading knowledge base for biopharmaceutics.

## 5. GREEN CHEMISTRY – DELIVERING MEDICINES FOR THE 21<sup>ST</sup> CENTURY

The pharmaceutical industry is devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. In addition, pharmaceutical companies are also committed to bringing key medicines to the patient with minimum impact on the environment. The concept of Green Chemistry provides an ideal framework upon which to develop a synthetic capability to meet the needs of sustainability in the 21st century through a benign by design approach.

In addition to the obvious challenge of 'bulk' material consumption (i.e., mass efficiency) and cost as resources become scarce, there are also concerns related to reagents and catalysts commonly used in synthetic approaches. Precious metals such as platinum and rhodium are annually becoming scarcer. With increasing use, the economically viable reserves of these materials could be exhausted in as few as 30 years. Synthetic methodologies which offer 'green' alternatives, such as through more cost effective and sustainable catalytic approaches, synthetic biology/biotransformations, flow chemistry, and natural product extraction may result in more sustainable practices but require a long term commitment to develop. In addition, newly discovered transformations may assist in the generation of molecular diversity in drug candidates.

Because Pharma shares common synthetic approaches, many member companies have been able to agree on the transformations most in need of improvement to achieve a long-term sustainability benefit. These results have been published. Improvements to these transformations offer an ideal starting point for an IMI project.

The potential benefits of investments in synthetic capability on the discovery and development of new medicines are far-reaching. Some key areas are listed below:

- Cost effective, sustainable access to existing classes of medicines
- Access to new modalities through novel transformations
- The compression of development/manufacture timescales

### Need for public-private collaborative approach

Improving the sustainability of manufacturing processes is critical to ensuring the economic competitiveness of Europe's chemical and pharmaceutical manufacturing base while improving environmental quality in the region. Public-private collaboration provides European universities, institutions, and industries with an opportunity to develop an integrated, long-lasting, and leading position in „green“ research and development, while providing researchers with the skills and training required to meet future industry challenges.

The discovery of green chemistry methodologies is often long-term (> 3 years), and beyond the timeframe required to progress a medicine to market. As a result, Pharma R&D typically focuses on the implementation of public sector developed methodologies rather than the 'in-house' discovery of fundamentally new transformations. Universities and Research Institutes possess the talent, time, and patience to develop general methodologies which can be applied cross-industry, due to the commonality of Pharma R&D problems. Basic research is required to achieve true 'step change' results in green chemistry that will deliver environmental health and safety benefits across Pharma and complementary industries, while spurring innovative approaches to molecular discovery and development.

Public-private collaboration provides European universities, institutes, and industries with an opportunity to develop an integrated, long-lasting, and leading position in 'green' research and development, while providing researchers with the skills and training required to meet future industry challenges. With sustainability being a key focus of many EU member country and world economies, this green chemistry focus has the potential to develop a key talent base important to economic development, while delivering innovative solutions to strengthen the EU pharmaceutical industry. As a result, this public-private partnership offers a true 'win-win' potential.

Finally, there is a significant need to engage medicinal chemists in green chemistry, so that new graduates enter industry with a 'Benign by Design' approach to chemistry. This is important for both the R&D impacts of making early supplies and for the long term impacts of



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successful medicine production. A public education system emphasizing green chemistry is needed to appropriately train graduates for a future in which resources are scarcer.



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## CLUSTER C: TECHNOLOGY AND MOLECULAR DISEASE UNDERSTANDING

### 6. STEM CELLS FOR DRUG DISCOVERY AND SAFETY ASSESSMENT

Human inducible pluripotent stem cells (iPS) and their derivatives present an emergent system with the potential to replicate drug responses in man, addressing disease mechanisms, and predict both efficacy and safety.

Both academia and industry share a common interest to develop improved in vitro biological systems, in particular those relevant to man (e.g. derived from human tissue), in order to improve the assessment of safety and efficacy during drug development. Human primary cells are available in limited amounts and demonstrate high batch-to-batch variations. Stem cells, and their cellular derivatives, produced in sufficient amounts can be used to develop more physiological, more relevant assays. Moreover, a sustained source of human derived lines, through iPS cells, will help overcome the batch-to-batch variability observed thus far. Further, the ability to phenotype differentiated cell types derived from patient specific iPS will improve the ability to link disease properties back to the physiology of specific cells. This issue is particularly acute for diseases of the central nervous system. While it is possible to obtain cells from biopsies in diseases like diabetes, cardiovascular disease and cancer, this cannot be done for CNS diseases. As a consequence, understanding of the molecular basis of diseases like depression, bipolar disorders, and schizophrenia have lagged behind.

Finally, linking the iPS back to genotype of patients will aid in the exploration of the genetic link between patient and disease, and will allow phenotyping of disease relevant cell types for which the genetic makeup is known. Besides the immediate scientific advancement, this project will ensure the sustainable application of the acquired knowledge by fostering the implementation of a centre for the long-term maintenance of the cell lines and standardized assay performance beyond the timeframe supported by this grant.

#### Need for public-private collaborative approach

The use of iPS cells in drug discovery requires several pre-requisites which can only be tackled by a collaboration including all stakeholders. These aspects are, for example:

- Establish framework for ethical and legal aspects for the use of iPS cells for research purposes (efficacy and toxicity).
- Establish a biobank for iPS lines including quality control.
- Establish and make accessible iPS lines from different ethnicities and patients with defined genotypes/phenotypes affecting drug efficacy and side effects.
- Establish standardized biological assays with stem derived cell types addressing disease biology, response to treatment and toxicity assessment.

Hence, pharmaceutical industry and academia are the main drivers of the scientific effort, but the inclusion of patient groups to address ethical questions, of SMEs to access cutting edge technology in this fast developing field and of regulators to ultimately facilitate the acceptance of biological systems and assays are pivotal for concerted progress and success of this endeavour.

There are already several consortia working on the use of stem cells for research, either based on cells from embryonic (hESC) or adult (iPS) origin. The current proposal will be however unique, since its main focus lies on patient-derived iPS, the corresponding differentiated cell types and their application in drug discovery. This project will thus be able to mimic patient's responses and enable personalized medicine by population-relevant testing of efficacy and toxicity. Also, iPS-derived cells will be unique tools to address disease biology and response to drug treatment for diseases for which there are no animal models available. With this, the outcome of our efforts would facilitate a paradigm shift in drug discovery and safety assessment.

## 7. PROTEIN/PROTEIN INTERACTIONS (UBIQUITIN LIGATION IN HEALTH AND DISEASE)

The field of protein ubiquitination is rapidly becoming an area of considerable interest for both academic and drug discovery activities. The recent approval of bortezomib for the treatment of multiple myeloma has validated inhibition of ubiquitination as a viable mechanism for the treatment of human disease. However, bortezomib remains the only current exemplar of therapies in this area and despite its early clinical promise in the treatment of cancer the drug also comes with limitations in that it also is associated with a broad toxicity and drug resistance, suggesting more selective inhibitors will be required for future therapies.

Considerable efforts in this emergent field has led to a rapidly accumulating data set identifying novel therapeutic targets within the ubiquitin family in a number of diseases including: cancer (CARP2, Hdm2, SCF), neurodegeneration (Parkin, TRIM11, UCH-L1), metabolic disease (Praj1, MuRF1, SCF), immune diseases ((Hrd1, TRAF6, SLIM) and viral infection (NEDD4, TRIM). Despite this, the ability to drug these new targets remains relatively poor due to a lack of understanding of the wider target class and available tools such as recombinant proteins, structural information, assay platforms, inhibitor chemotypes and target associated biology.

### **Need for public-private collaborative approach**

The biological understanding for this target class lies largely in the academic community although a number of small start up companies have been crystallised. These companies will be adept at developing new platform technologies to allow access to selected members of the ubiquitin family of proteins, but will largely lack access to the sophisticated and scalable chemistry, crystallography and assay platforms that are common in large pharmaceutical organisations which will allow a wider target class approach. Taking a combined consortia approach gathering academia, SME and pharma will allow more rapid progress on a broader front through accelerating and coordinating the exchange of key complimentary platforms and expertise as well as the rapid expansion of target class understanding in this relatively novel and expanding scientific area.

## **8. TOWARDS A GREATER UNDERSTANDING OF OPTIMISATION OF KINETICS OF BINDING IN DRUG DISCOVERY**

The understanding of kinetics (and thermodynamics) of binding are of increasing importance in drug discovery. Recent reports suggest that compounds with slow off-rate -such as maraviroc, tiotropium or singulair- are more likely to succeed in development, however, it would seem that such properties are normally found serendipitously and realised late. However, it is possible to say with some confidence that the ability to design compounds with different kinetics should impact development attrition of small molecules. For instance, slow off compounds will have lower doses / greater efficacy whilst reducing the overall drug burden and bringing about greater selectivity, hence reducing toxicity.

Given the potential value of this, it is somewhat surprising that there are few reports of systematic screening and analysis of compound SAR and translation to in vivo effects. Ideally, we would like this information to be generated in project time scales so it could have a greater impact on compound design.

This proposal would seek to address simultaneously the three areas which currently hinder progress in the area. Firstly, by using previously studied systems, we would seek to understand the molecular interactions that lead to changes in kinetics. Secondly, we would seek to develop higher throughput methods of measurement to increase our ability to establish "structure-kinetic relationships". Lastly, we would seek to understand the relationship between in vitro kinetics and in vivo effects to establish how assay data would transfer through to the clinical setting and allow better prediction of responses in patients.

### **Need for public-private collaborative approach**

This proposal aims to bring together leading European academic and industrial communities from structural, pharmacological and chemical fields. In view of the resources and expertise needed for addressing SAR paradigms in a systematic manner, the assembling of a pre-competitive consortium involving several large pharma companies together with academic partners and SME appear as the best strategy to design and conduct robust studies on SAR at a pre-clinical pharmacological level.