



# Innovative Medicines Initiative

# 2009

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**2009**

**Call Topics**

**14-09- 2009**

## Innovative Medicines Joint Undertaking (IMI JU) 2009 Call for proposals

### Call topics

The Innovative Medicines Initiative Joint Undertaking (IMI JU) is a unique pan-European public private partnership aiming to foster collaboration between all relevant stakeholders including large and small biopharmaceutical and healthcare companies, regulators, academia and patients.

The aim of IMI is to support pre-competitive<sup>1</sup> pharmaceutical research and development to foster the development of safe and more effective medicines for patients through removing identified bottlenecks in the drug development process and enhance Europe's competitiveness by ensuring that its biopharmaceutical sector remains a dynamic high-technology sector.

The IMI Research Agenda [http://www.imi.europa.eu/sra\\_en.html](http://www.imi.europa.eu/sra_en.html) describes the research bottlenecks in the drug development process and identifies four strategic pillars: Predictivity of safety evaluation, Predictivity of efficacy evaluation, Knowledge management and Education and Training.

The IMI 2009 Call for proposal will have 9 topics addressing two of these strategic pillars:

#### - Predictivity of Efficacy Evaluation

The IMI 2009 Call topics around efficacy encompass oncology, diabetes, inflammation and infectious diseases. The ultimate aim of the efficacy topics is to develop more predictive pre-clinical models and validate novel translatable biomarkers and imaging agents, to increase the efficiency with which effective medicines can be delivered to the patient population most likely to benefit from treatment. Although there are already efforts ongoing within academia and industry in all of these areas, IMI offers the opportunity for pre-clinical and clinical scientists from academia, Small & Medium sized Enterprises (SMEs) and industry as well as patient advocacy groups to come together to collaborate and tackle these areas of pre-competitive research more efficiently and effectively.

#### - Knowledge Management

Improving Knowledge Management is an essential component of IMI that provides the data-pooling and data processing infrastructure to support IMI collaborations in Europe.

Gaps in information technology, lack of platforms to analyze large amounts of information in an integrated and predictive way is another major pre-competitive barrier in the current biomedical R&D process. In particular, the predictivity of preclinical studies to anticipate clinical safety and clinical efficacy, as well as the overall assessment of patient benefits and risks with regulatory authorities is affected by this barrier. Leveraging scientific and technological advances around these bottlenecks could, potentially, boost Europe's biomedical R&D base, and accelerate the discovery and development of better innovative medicines.

### Call and evaluation process

A short overview of the IMI JU Call process is presented below. For full details applicants are referred to the *IMI JU Rules for submission, evaluation and selection of Expressions of Interest* which will be published on the IMI JU website [www.imi.europa.eu](http://www.imi.europa.eu) at the launch of the 2009 Call.

The IMI JU supports research activities following open and competitive Calls for proposals, independent evaluation and the conclusion of Project- and Grant Agreements.

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<sup>1</sup> In the present context 'pre-competitive pharmaceutical research and development' should be understood as research on the tools and methodologies used in the drug development process.

## Introduction

Each topic included in the 2009 Call for proposals is associated with a group of pharmaceutical companies that are members of EFPIA<sup>2</sup> (herein after called the 'EFPIA Consortia') and which are committed to collaborate with public and private organizations eligible for funding by the IMI JU. The EFPIA members will provide 'in kind' contributions<sup>3</sup> to support their activities within the research projects.

The IMI JU applies a two stage Call process where in the first stage 'Applicant Consortia' (i.e. formed by academia, SMEs, patient organizations, non EFPIA companies, etc.) are invited to submit, to the IMI JU, an Expression of Interest (Eoi) in response to a Call topic.

In preparing their Eois the Applicant Consortia should carefully consider the research contribution that an EFPIA Consortium will make to a given project as well as the expectations from the Applicant Consortia. These are outlined in sections 5 and 8 of the topic texts.

Each Expression of Interest submitted will be reviewed by independent experts according to predefined evaluation criteria. The "Applicant Consortia" with the highest ranked Eoi will be invited to jointly develop a Full Project Proposal together with the EFPIA Consortium associated to the corresponding topic. The Full Project Proposal will then be subject to a final review by independent experts.

Only Full Project Proposals that have been favourably reviewed in the evaluation process can be selected for funding. These projects will then be invited by the IMI JU to conclude a Grant Agreement governing the relationship between the selected project consortium and the IMI JU.

### **Eligibility to participate in projects and to receive funding from the IMI**

Criteria of eligibility to participate in IMI projects and the criteria to receive funding from IMI JU are specified under the *Rules for participation* which will be published on the IMI JU website [www.imi.europa.eu](http://www.imi.europa.eu) at the launch of the 2009 Call.

The IMI financial contribution will be based on the reimbursement of the eligible costs. The following funding rates apply to the legal entities eligible for funding: For research and technological development activities up to 75 % of the eligible costs and for other activities (including management and training activities) up to 100 % of the eligible costs charged to the project. For indirect costs (overheads), a flat rate of 20 % of total eligible direct costs applies.

The total available financial contribution from the IMI JU to participants eligible for funding will be EUR 76.8 million, matching the in-kind contribution by the research based companies that are members of EFPIA.

The research based companies that are members of EFPIA shall not be eligible to receive financial contributions from the IMI JU.

### **IMI IP Policy**

IMI Intellectual Property Policy (IMI IP policy, [www.imi.europa.eu](http://www.imi.europa.eu)) has been developed to be aligned with the objectives of the IMI JU by allowing the wide access to research findings for use in the drug development process. In submitting an Eoi the "Applicant Consortia" fully understand the principals laid out in the IMI IP policy that will apply to all research projects conducted under the IMI JU.

### **General**

Before submitting Eoi the various Call document, such as rules for participation, rules for submission, etc., should be considered carefully. These documents will be available on the IMI website at the time of the 2009 Call launch.

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<sup>2</sup> European Federation of Pharmaceutical Industries and Associations (<http://www.efpia.org/>)

<sup>3</sup> In kind contribution is e.g. personnel, clinical research, equipment, consumables.

## IMI Efficacy Pillar

In the Efficacy Pillar the areas of cancer, infectious diseases and inflammation are seen as priorities for this year.

In **Oncology** the focus is foreseen on the following fields:

1. The development, evaluation and qualification of imaging biomarkers of tumor cell proliferation and death, and of the invasive phenotype is one area with the focus to create a network of imaging centers allowing clinical validation of imaging biomarkers across multiple sites.
2. Another field in the area of cancer is the search for new tools for target validation to improve drug efficacy, including improved models and integrated bioinformatics to generate testable hypotheses (systems biology).
3. A third field are molecular biomarkers for the acceleration of cancer therapy development and refining of patient care focusing on the characterization of predictive, prognostic and pharmacodynamic biomarkers and the standardization of analytical methods and data retention and sharing.

### 1. Oncology – Target Validation

0	Topic Code	IMI_Call_2009_1
1	Topic Title	<b>New tools for target validation to improve drug efficacy</b>
2	Project Description	<p><b>Background</b></p> <p>There is a huge cancer burden in Europe. In 2006 there were an estimated 3,191,600 new cases of cancer diagnosed, and 1,703,000 deaths from cancer (Ferlay J., et al., <i>Annals of Oncology</i>, <b>18</b>: 581-592, 2007). While it is widely recognised that major advances have been made both in the understanding of the disease and also in the treatment of many forms of cancer, a large number of anticancer drugs still fail due to a lack of efficacy in late stage (post-phase IIb) trials. There are a variety of reasons for these failures. One major reason is considered to be the failure to appropriately validate potential drug targets at the start of the drug discovery process.</p> <p><b>Problem Statement</b></p> <p>Improvements in our understanding of the underlying biology of cancer and the development of new models for target validation is essential to support the significant advances required to improve the quality of this first key phase of drug discovery. Historically targets have been inappropriately selected or validated due to using reductionist models which do not represent the complexity of tumours <i>in situ</i>, which led to failure in the clinical setting. In order to improve the likelihood of success it is essential to better validate potential drug targets by:</p> <ol style="list-style-type: none"> <li>1. Improving <i>in vitro</i> models of the human disease, through the development of complex, reproducible and robust models that more closely mimic the cellular organisation of tumours (e.g. in three dimensions) and the cellular heterogeneity within human malignancies</li> <li>2. Cross validating, in a reciprocal way, these novels, complex <i>in vitro</i> models against relevant <i>in vivo</i> models which more closely reflect characteristics of human cancer pathology, particularly tumours arising in transgenic mice.</li> </ol>

3. Using a systems biology-based approach to integrate and compare ‘omics data derived from the novel models and the public databases, to generate testable *in silico* models of the biochemical circuitry associated with potential drug targets.

### **The need for a collaborative approach**

There are already significant efforts ongoing within academia and industry to address the development and validation of novel models to support target identification and validation. However, these efforts are often fragmentary, for example with respect to expertise within *in vitro* cell biology and *in vivo* models of cancer, and they have often lacked a pharmacological perspective. IMI offers the opportunity to integrate the innovative thinking and resources of independent experts in this field to significantly advance this field on a scale greater than the sum of each individuals own efforts. The opportunity for pre-clinical scientists from academia, SMEs and industry to come together to share already existing data and expertise to tackle these areas of pre-competitive research more efficiently is unprecedented in this arena. The focus is to develop transferable platforms to increase the efficiency with which effective medicines can be delivered to a patient population most likely to benefit from treatment. In addition to efforts conducted within the framework of this project, dissemination through such consortium will benefit the global scientific community.

### **Key Objectives to be addressed**

The development of improved *in vitro* and *in vivo* models to support target identification and target validation with greater predictive capacity to the human disease.

### **High Level Plan**

**Package 1: Development of complex *in vitro* cellular models for the validation of potential drug targets and their cross-validation with well characterized *in vivo* models of pathology (80% of the resources should be applied against this package)**

*In vitro* and *in vivo* models are essential to the initiation of drug discovery process as they are used to validate new therapeutic targets and rank novel therapeutic agents with respect to efficacy prior to progression to other preclinical studies. However, cancers are often highly heterogeneous at the molecular and cellular level and display variable clinical responses to therapies. The complex context in which a potential drug target operates within a biochemical circuitry requires that *in vitro* models for target validation reflect, as closely as possible, the three dimensional organisation of tumours and aspects of their cellular heterogeneity, for example with respect to host-tumour cell interactions. Whilst there are some prior examples of the successful use of predictive reductionist models for target validation, there are many instances where hypotheses supported by simplistic, reductionist cellular models (such as homogeneous cell lines growing as monolayers on plastic) have failed in the clinic.

Recent advances in this field include the development of:

- (i) 3D cultures on extra cellular matrices
- (ii) Primary short term explants
- (iii) Tissue slices

The material for these assays has also been derived from relevant animal models – see below. These models clearly advance closer to the human disease state, however they require further characterisation and validation before they can be used in a decision making capacity during the drug discovery process.

Complex *in vitro* models representing the cellular heterogeneity of human tumours should permit analyses of the heterogeneity of response following target inhibition. Recently, although somewhat controversially, it has been suggested that residual disease may be due to cells expressing some properties of normal stem cells. The development of complex *in vitro* models to permit analysis of a heterogeneous response to target inhibition, including analysis of molecular markers representative of a stem cell signature, would be pertinent.

In developing an *in vitro* model(s) suitable to support target validation and later compound ranking, it is essential to consider aspects such as the relevance to the disease, validation with a variety of mechanistic agents and gold standards, stability, robustness, reproducibility and manipulability of models. Therefore validation with challenges such as the selective use of RNA interference techniques and the use of drugs and chemicals should also be addressed. Innovative methods to permit 'omics analyses of the tumour cells grown in complex models may have to be developed.

### **Integration of vivo models**

Early validation of potential drug targets using complex *in vitro* models requires comparison with appropriate *in vivo* models, where the aspects of complexity provided by host-tumour interactions are present. The *in vivo* models should have characteristics closely representative of human tumours, for example defined by histology and 'omics methods. A dynamic reciprocity of investigations between *in vivo* and *in vitro* models is an essential element of the programme.

A major issue is the availability of *in vivo* models that 1) represent the complexity of the human disease, 2) display key molecular genotypes and phenotypes closely reflecting the disease, 3) support investigation of host-tumour interactions and 4) which enable the successful translation of hypotheses from pre-clinical drug discovery into man.

Transgenic mouse models of cancer, and some fresh tumour implant models to immune-deprived mice, are emerging which may fulfil this role more appropriately than *in vivo* xenograft models.

(i) *Transgenic mouse models*. As new transgenic mouse models emerge which more closely represent the histopathology, molecular pathology and other characteristics (e.g. patterns of metastases) of the major human tumour pathologies, their utility in target validation should be examined. The use of transgenic models for large scale pharmacological testing is recognised as largely impractical but their use in proof of principle experiments for drug testing and in establishing primary cultures and/or tissue slices and fragments is attractive.

(ii) *Primary human tumour explants*. These have been investigated but their advantage offered over xenograft models is not yet fully understood, and their success is likely to depend on further validation, in the same ways as described for transgenic models.

Applicants are invited to bring forward innovative, complex *in vitro* and complementary *in vivo* models which address the key objective of target validation, balancing complexity with the practical requirements necessary to support novel drug discovery programmes at the target validation stage.

		<p><b>Package 2: Integrated bioinformatics of multivariate data in order to generate testable hypotheses (20% of effort).</b></p> <p>The data accumulated from genomic and proteomic analyses of clinical human tumour samples, held in both public and industrial hands, should be used to validate the models described above. In addition, the data generated in the models themselves should permit the modelling and testing of the interactions between multiple signalling pathways, the activity of transcription factors, changes in intermediary metabolism and the impact of host-tumour interactions on the molecular circuitry of normal and tumour cells. This should provide hypotheses regarding the nature of nodal points that drive malignancy and the position of a potential drug target in this circuitry. Indicators suggesting those proteins or pathways to which certain malignant pathologies become “addicted” in order to survive, proliferate and metastasise, will suggest strategies of intervention. Testable hypotheses may also emerge implicating “synthetic lethal” strategies, targeting more than one locus in order to collapse a network unique to a tumour cell. Clearly validation of such an approach will be required using appropriate cellular models where perturbation of key pathways by chemical tools, dominant negatives or RNAi strategies is relatively facile.</p> <p>This <i>in silico</i> work will better describe tumour signalling networks as they exist in complex model systems and should lead to improved drug targeting strategies. Additionally, it has the potential to indicate potential mechanism of drug resistance because of redundancies in pathways, and to improve the alignment of tumour models to human disease. It should better develop patient stratification hypotheses in oncology by generating ideas regarding potential biomarkers of drug sensitivity.</p>
3	Key Deliverables of the Project	<p>The key project goal is to develop robust tools and approaches to improve target validation and thus the attrition profile for oncology products, preventing unnecessary progression of targets with a low chance of success.</p> <p><b>Package 1: Development of novel <i>in vitro</i> and <i>in vivo</i> models of disease with improved predictive capacity for target validation</b></p> <ul style="list-style-type: none"> <li>▪ Development and validation of the next generation of <i>in vitro</i> and <i>in vivo</i> models with greater predictive capacity for the clinic.</li> <li>▪ Alignment of models with molecular profiles obtained from high quality human tumour samples to assess their relevance and applicability.</li> <li>▪ Establishment of the limits of manipulability of the new, complex model systems for target validation and drug testing using new methods and technologies.</li> </ul> <p><b>Package 2: Integrated bioinformatics of multivariate data in order to generate testable hypotheses (20% of effort)</b></p> <ul style="list-style-type: none"> <li>▪ Systems biology descriptions of tumour biochemical circuitry in novel models (compared to human tumours) capable of describing the context of novel targets and generating hypotheses to be tested in models of target validation</li> </ul> <p><b>General</b></p> <ul style="list-style-type: none"> <li>▪ Ability to more effectively identify and validate targets and to identify successful drug candidates reducing the number of studies required and increasing probability of success.</li> </ul>

Oncology – Target Validation

		<ul style="list-style-type: none"> <li>▪ Ability to design smaller, stratified clinical studies which deliver early signals of efficacy</li> <li>▪ Access to validated standardised models across Europe</li> <li>▪ Integrated approach to target validation and possible patient stratification across academia and industry</li> <li>▪ Access to a well managed extensive sample (and data) collection of tumour tissue from animal models and patients</li> <li>▪ Standardised and validated protocols and data analysis methods across sites.</li> </ul>
4	EFPIA Participants in the Project	AstraZeneca, Bayer Healthcare, Boehringer-Ingelheim, Novartis, Orion, Pfizer, F. Hoffmann - La Roche AG, Servier, Sigma-Tau, Wyeth.
5	Role of EFPIA Participants in the Project	<p>The EFPIA participants will contribute:</p> <p><b>Pre-clinical</b></p> <ul style="list-style-type: none"> <li>• Pre-clinical models including cell lines, transgenic animals and associated 'omics data.</li> <li>• Pharmacology data from pre-clinical studies.</li> <li>• Biochemical assays that could be replicated for model development and validation and know-how in assay development (including high technology platforms such a High Content Screening imaging).</li> <li>• Know-how on the development of complex cellular models.</li> <li>• Supplies of NCEs and marketed compounds.</li> </ul> <p><b>Clinical</b></p> <ul style="list-style-type: none"> <li>• Tumour and surrogate tissue samples and the associated clinical data. Data from clinical studies exploring efficacy endpoints using both single agents and combinations and either NCEs or marketed drugs.</li> <li>• Omic data on specific human pathologies.</li> <li>• Clinical supplies of registered agents.</li> <li>• Regulatory authority contacts and interactions.</li> </ul> <p><b>General</b></p> <ul style="list-style-type: none"> <li>• Active participation by working with the applicant consortium and supervising the EFPIA participant funded positions accordingly to achieve the key deliverables.</li> </ul>



## Oncology – Target Validation

		<ul style="list-style-type: none"> <li>• General preclinical and clinical oncology expertise.</li> <li>• Know-how in statistical analysis of genomic and clinical study data.</li> <li>• Expertise in bioinformatics, systems biology and algorithms for modelling the perturbation of complex systems</li> <li>• Know-how in sample and data management.</li> </ul>
6	Indicative duration of the project	The indicative duration of the project is 5 years.
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate for the EFPIA in-kind contribution to this project is EUR 8 million.
8	Indicative expectations from the “Applicant Consortium”	<p>The Applicant Consortium should aim to bring forward innovative approaches to address all the major objectives outlined in the call. In summary these are :</p> <p><b>Package 1:</b></p> <p>To develop high quality and complimentary platforms to support improved target identification, target validation and potential patient stratification by developing novel in vitro and in vivo pre-clinical models reflecting the complexity and heterogeneity of human tumours, demonstration of the models’ equivalence to human pathology and demonstrating their performance in target validation using appropriate positive negative controls.</p> <p><b>Package 2:</b></p> <p>Establish a systems biology description of tumours and their models which are capable of validating and identifying novel targets and generating hypotheses to be tested in models of target validation.</p>

## 2. Oncology - Molecular Biomarkers

0	Topic Code	IMI_Call_2009_2
1	Topic Title	<b>Molecular biomarkers - accelerating cancer therapy development and refining patient care</b>
2	Project Description	<p><b>Background</b></p> <p>New, targeted, therapies promise radical improvements in delivery of cancer therapy. Regrettably, such drugs are taking longer to develop with decreasing success and increasing costs. At the same time, it is evident that the heterogeneity of individual tumours presents a diagnostic dilemma for the physician charged with designing a patient's treatment. Ideally, treatment should be personalised to give a patient the most appropriate therapy for their disease, with minimal chance of adverse events, as soon as the disease is diagnosed.</p> <p>It is widely accepted that detailed molecular characterisation of high quality tumour tissue can provide invaluable information to support our fundamental understanding of disease and the influence of heterogeneity on response to therapy. In order to bring effective novel agents more rapidly to registration and into clinical practice, however, there is also a need to identify novel, more sensitive biomarkers that can :</p> <ul style="list-style-type: none"> <li>• Support patient stratification for inclusion in trials thereby excluding subjects with tumours unlikely to respond to the drug in question and subsequently reducing the size of clinical study required to detect a positive response</li> <li>• Provide the basis for 'companion diagnostics' in routine clinical practice, allowing identification of the most appropriate therapy at the right dose for the patient and reducing exposure to potential side-effects of treatment.</li> </ul> <p>Predictive, prognostic and pharmacodynamic biomarkers will benefit cancer patients through their utility at all stages of drug development and routine therapy.</p> <p><b>Problem Statement</b></p> <p>This project seeks to characterize molecular biomarkers to advance our fundamental understanding of tumours (breast, prostate, ovary, lung and/or colon) and their responses to treatment. The primary objective is to exploit molecular biomarkers that will enable the use of less invasive approaches to tumour investigation, thereby reducing patient distress, improving compliance and lowering the risk of procedural and therapeutic complications. Analysis of markers in circulating tumour cells (CTCs), as well as circulating tumour DNA/RNA, may provide an opportunity to assess unique molecular biomarkers originating from both primary tumours and metastases. Preference should be given to biomarkers that are ready for clinical qualification or validation. Where necessary, the biomarkers and approaches developed should find regulatory support through active collaboration with the European regulatory authorities.</p>

**The need for a collaborative approach**

The focus of this project is intended to be on biomarkers that reflect the management of the disease independent of the therapy modality and/or those that are informative in ‘standard of care’ therapies. The complex nature of the challenge presented will require an integrated approach by pre-clinical and clinical scientists to develop sensitive assay techniques to allow identification of suitable biomarkers. Investigation and qualification of markers in the clinical setting will require access to patients undergoing routine cancer care as well as to tissue samples from existing bio banks. Conducting this research in the framework of a collaborative approach will

- Facilitate an integrated approach combining knowledge and expertise from both academic and industrial scientists ensuring the most innovative and practical approaches are explored
- Facilitate the complex collaboration required both to conduct research on technology development and to collect the clinical data and samples needed for qualification of the markers.
- Facilitate participation of regulatory authorities in a dialogue on validation of biomarkers as surrogate markers.

**Key Objectives to be addressed**

In the three work packages described below, the goal is to use biomarkers to describe tumour heterogeneity and assess its influence on response to therapy. Furthermore, innovative approaches for biomarker assessment in the peripheral circulation will be investigated in order to assess the potential of circulating tumour cells and/or nucleic acids to serve as a surrogate for invasive biopsies. Preference should be given to biomarkers that are ready for clinical qualification or validation.

Within all three work packages, standardisation of analytic methods and systems for data storage and transfer must be addressed, so that the biomarkers chosen may be qualified or validated at multiple centres in Europe.

**High Level Plan**

**Package 1: Identification and qualification of markers predictive of response to therapy**

Since solid tumours are usually polyclonal, their heterogeneity has a major influence on the success of targeted therapies. There is therefore a need to identify a panel of biomarkers can be used to define those tumours most likely to respond to a particular therapy. These biomarkers should reflect the management of the disease independent of the therapy modality and/or those that are informative in ‘standard of care’ therapies. Candidate biomarker measurement should indicate the full effect of the intervention (therapy) upon the disease and so permit use of the biomarker in all phases of patient management.

The biomarkers may be established or novel, but those selected must be characterized to the point that they can be used in a prognostic, predictive and/or pharmacodynamic setting both in clinical trials and in routine cancer medicine.

Qualification of markers in patients undergoing standard therapy will be required to support the utility of the biomarker panel in decision making during drug development. Paired biopsies taken prior to and during treatment will be used for analysis of biomarkers in tumour tissue. The biopsies should also be fully characterized using conventional (immuno)-histological procedures, to ensure an accurate description of tumour phenotype, tumour staging etc.

**Package 2: Investigation of circulating tumour cells and nucleic acids as potential biomarkers**

It has been shown that cells are released from solid tumours and that these can be detected in the peripheral circulation. Biomarkers analysed in the paired biopsy study described in Package 1 should be measured in parallel in circulating tumour cells (CTCs). The goals of the CTC part of this package are to establish (1) the feasibility of assessing the selected biomarkers in the CTC population and (2) to compare the phenotype of CTC with the characteristics of the bulk tumour. There is at present no consensus as to how best to isolate and quantify CTCs. Preference should be given to methods that are likely to provide an unselected population of CTCs, so that an accurate comparison of the circulating cell population with the characteristics of the patient’s primary tumour and metastases is possible.

The peripheral blood of tumour patients generally also contains variable amounts of free DNA originating largely from cancer cells. Sequence analysis of this material can therefore provide information on the mutational status of the primary tumour and/or metastases. In the case that mutations or epigenetic markers (e.g. methylation) are included in the biomarker panel, these should be assessed in circulating DNA to allow a comparison with analysis of the tumour biopsy material.

**Package 3:**

**Investigation of cancer stem cells as potential biomarkers.**

While the existence of cancer ‘stem’ or ‘progenitor’ cells has been demonstrated, the significance of these in disease progression, response to therapy and disease management is not well understood.

In order to improve our understanding of the genetic and phenotypic comparison of stem cells with the parent tumour and fully assess their potential for supporting the drug discovery process it is essential develop methodologies to support the isolation and *in vitro* expansion of stem cells, and the testing of stem cell-specific biomarkers.

Consideration should be given to the inclusion of appropriate markers for ‘stem’ or ‘progenitor’ cells in the analysis of the paired biopsies and CTCs.

**Overlap with other Biomarker Programmes**

- Several agencies, support collaborative programmes in biomarker research. For example, the Biomarkers Consortium (Foundation for the National Institutes of Health, USA), the International Cancer Biomarker Consortium and projects funded by the Framework Programs of the European Community. The FP6 programme of the EU includes, among others, the following programs that may address relevant technologies:

		<ul style="list-style-type: none"> <li>○ “Integrated technologies for in-vivo molecular imaging”</li> <li>○ “Translational and Functional Onco-Genomics”</li> <li>○ “Novel molecular diagnostic tools for the prevention and diagnosis of pancreatic cancer”</li> <li>○ “Translating molecular knowledge into early breast cancer management (TRANS-BIG)”</li> </ul> <ul style="list-style-type: none"> <li>● Applicants are therefore encouraged to consider these similar programmes and to concentrate on research topics that are outside the scope of competing programmes to avoid duplication of research efforts.</li> </ul>
3	Key Deliverables of the Project	<p>The key deliverables of the projects are:</p> <ul style="list-style-type: none"> <li>● Innovative, sensitive, specific and accurate methods to detect biomarkers from limited quantities of tissue collected by less invasive methods, suitable for use in routine clinical laboratories.</li> <li>● Qualified biomarkers that advance our understanding of tumour heterogeneity; especially favoured are those relevant to breast, lung, prostate, ovarian and/or colon cancer</li> <li>● New sensitive, specific and accurate methods to detect and characterize circulating tumour cells and an understanding of their utility in assessment of prognostic, predictive and/or pharmacodynamic markers</li> <li>● Novel methods for identification and quantification of cancer stem cells and an understanding of their utility as prognostic, predictive and/or pharmacodynamic markers</li> <li>● A consortium of academic groups, pharmaceutical and diagnostic companies is sought that can work together and with Regulatory Authorities to deliver biomarkers that identify individualised treatments to increase life expectancy, decrease the cost of health care and minimise patient pain and discomfort. Preference should be given to biomarkers that are ready for clinical qualification or validation.</li> <li>● Establishment of uniform SOPs and analytical standards for accepted biomarkers that conform to expectations of the regulatory authorities.</li> <li>● An education and training plan for dissemination of relevant skills among the collaborating sites.</li> </ul>
4	EFPIA Participants in the Project	AstraZeneca, Bayer Schering Pharma, Eli Lilly, GSK, Johnson & Johnson, Merck KGaA, Orion, Pfizer, F. Hoffmann-La Roche AG, Boehringer-Ingelheim
5	Role of EFPIA Participants	<p><b>Pre-clinical</b></p> <ul style="list-style-type: none"> <li>● Data from pre-clinical studies on biomarkers and their qualification.</li> </ul>

	<p>in the Project</p>	<ul style="list-style-type: none"> <li>• Know-how in assay development and biochemical engineering.</li> <li>• Cell selection &amp; culture methods</li> <li>• Supplies of NCEs (IP dependent) and marketed compounds.</li> </ul> <p><b>Clinical</b></p> <ul style="list-style-type: none"> <li>• Tumour and surrogate tissue samples and the associated clinical data.</li> <li>• Candidate pharmaco-dynamic markers and/or predictive biomarkers that could be replicated or validated in prospective clinical studies.</li> <li>• Data from clinical studies exploring efficacy endpoints using both single agents and combinations and subjects treated with NCEs (dependent on IP) and marketed drugs.</li> <li>• ‘Omic’ data from normal and disease tissue.</li> <li>• Clinical supplies of registered agents.</li> <li>• Clinical trial management expertise and support.</li> <li>• Regulatory authority contacts and interactions.</li> </ul> <p><b>General</b></p> <ul style="list-style-type: none"> <li>• General preclinical and clinical oncology expertise.</li> <li>• Know-how in statistical analysis of genomic and clinical study data.</li> <li>• Know-how in bioinformatics.</li> <li>• Know-how in sample and data management.</li> </ul>
6	Indicative duration of the project	The indicative duration of the project is 5 years.
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate for the EFPIA in-kind contribution to this project is EUR 10 million.
8	Indicative expectations from the “Applicant Consortium”	The Applicant Consortium, consisting of preclinical and clinical scientists should aim to develop improved tools for predicting efficacy of cancer therapeutics, especially during the clinical stages of drug development.

		<p>The Applicant Consortium is expected to address all areas outlined in the Call, taking into consideration synergies with the EFPIA participants. In summary these are :</p> <ul style="list-style-type: none"><li>• To develop innovative, sensitive, specific and accurate methods to detect biomarkers from limited quantities of tissue collected by less invasive methods, suitable for use in routine clinical laboratories.</li><li>• To identify and validate biomarkers that advance our understanding of tumour heterogeneity; especially favoured are those relevant to breast, lung, prostate, ovarian and/or colon cancer.</li><li>• Develop new sensitive, specific and accurate methods to detect and characterize circulating tumour cells and an understanding of their utility in assessment of prognostic, predictive and/or pharmacodynamic markers.</li><li>• Develop novel methods for identification and quantification of cancer stem cells and an understanding of their utility as prognostic, predictive and/or pharmacodynamic markers.</li><li>• To develop techniques for the evaluation of circulating tumour DNA, RNA or protein.</li></ul>
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### 3. Oncology – Imaging Biomarkers

0	Topic Code	IMI_Call_2009_3
1	Topic Title	<b>Imaging biomarkers for anticancer drug development</b>
2	Project description	<p><b>Background:</b></p> <p>Imaging has already proved useful for cancer research in providing biomarkers to support early drug development. Unfortunately the best-qualified available imaging biomarkers currently cover only a small range of important phenotypes (e.g.: FDG PET for glycolysis and Warburg effect; DCE-MRI for perfusion and endothelial permeability; and "anatomic" imaging for macroscopic growth, local invasion and distant metastasis). As the field advances, EFPIA research now covers a vast range of targeted anticancer agents, affecting a wide range of phenotypes within the "six hallmarks of cancer" (Hanahan &amp; Weinberg, 2000). While a number of putative imaging biomarkers have been reported in the literature to support these additional phenotypes, most have only been used in a small number of studies, and are therefore not well-qualified to support "go/no-go" decisions in drug development.</p> <p><b>Problem statement</b></p> <p>In order to improve the efficiency of the current drug development process there is a need to develop a broader range of well-qualified imaging biomarkers for assessing response to new drugs in early clinical development.</p> <p>In particular it will be relevant to</p> <ul style="list-style-type: none"> <li>• Accelerate new medicines through the trials and approvals process, so that patients can benefit sooner from discoveries in our laboratories;</li> <li>• Ensure that drug development resources are concentrated on the most effective new drugs, and not wasted on ineffective approaches;</li> <li>• Avoid the exposure of cancer patients in clinical trials to ineffective drugs and doses;</li> <li>• Identify the patient population who will most benefit from each new drug.</li> </ul> <p>We propose here to broaden our range of well-qualified imaging biomarkers in the areas of proliferation, cell death, and invasion.</p> <p><b>The need for a collaborative approach</b></p> <p>These goals can only be achieved in collaboration because:</p> <ul style="list-style-type: none"> <li>• EFPIA members have enormous experience in drug development (including how best to make "go / no-go" decisions) and have great insight into the pharmacologies likely to be investigated most thoroughly in man over the next decade (novel drug targets).</li> <li>• Academic cancer centres work with large patient populations.</li> </ul>



- Academic centres and diagnostic imaging companies have insight into the best emerging imaging biomarkers.
- Imaging CROs have expertise in standardising multicentre imaging trials

**Key objectives to be addressed**

This project comprises two packages, A and B. On completion of package A (approximately 90% of the allocated funding) we will have available a combination of imaging biomarkers which:

- Reflect the balance between to tumour cell proliferation on the one hand, and tumour cell senescence, starvation, and death on the other hand;
- Are qualified for evaluating the efficacy of new anticancer drugs;
- Are usable in multicentre trials in typical Phase 1/2 populations.

On completion of package B (an exploratory high-risk high-potential work package with 10% of the funding) we will have candidate imaging biomarkers of the invasive phenotype.

**High-level plan**

**Package A: Imaging biomarkers of tumour cell proliferation and death (90% of funding)**

Based on a critical assessment of confounds, gaps in understanding, strengths and weaknesses, the applicant consortium will propose a combination of imaging biomarkers which assess balance between tumour cell proliferation and cell death. Consortia are free to propose any imaging biomarkers, or combinations of imaging biomarkers, and any qualification plan, to meet the needs. As examples, some imaging biomarkers which have previously been described in the literature needing further evaluation in the phase 1 setting for include: molecular imaging markers of proliferation (e.g. FLT, FMAU); molecular imaging markers of apoptosis; MRI markers of necrosis and death (e.g.  $v_e$ , ADC). In addition, consortia may wish to incorporate imaging biomarkers of angiogenesis, hypoxia, tumour metabolism, and/or interaction of tumour cells with stromal cells and microenvironment, if a compelling case can be made that these assess changes in tumour cell death and proliferation. These example biomarkers are provided as a general guide only: it is not necessary or desirable to include all, and many other relevant imaging biomarkers could also be considered. It may be that this work package can be delivered with a combination of as few as 2-5 imaging biomarkers. The work plan will likely involve an imaging science / image analysis work stream followed by a clinical imaging work stream and a preclinical imaging work stream running in parallel, and should include elements performed in applicants' laboratories together with elements performed In EFPIA members' laboratories (see section 5). The clinical imaging work stream will likely address reproducibility, changes in the imaging biomarker with disease progression and response to intervention, and robust multicentre deployment in appropriate patients. The preclinical imaging work stream will likely address imaging–pathology correlation and changes in the imaging biomarker in response to a range of appropriate interventions in appropriate animal models.

**Package B: An imaging biomarker of the invasive phenotype (10% of funding)**

The applicant consortium will propose a programme of imaging biomarker research to assess the invasive phenotype. Consortia are free to propose any imaging biomarkers, or combinations of imaging biomarkers, and any biomarker discovery strategy to meet the needs. As a general guide, biomarkers of matrix (perhaps pH or MMP activity), novel combinations of existing biomarkers, tumour-associated macrophages, or novel imaging biomarkers of cryptic metastasis, may merit consideration. The work plan will likely involve an imaging science / image analysis work stream followed by a preclinical and clinical imaging deployment, and should include elements performed in applicants' laboratories together with elements performed in EFPIA members' laboratories (see section 5). The preclinical imaging work stream will likely address imaging–pathology correlation and changes in the imaging biomarker in response to appropriate interventions in appropriate animal models.

**Points to consider**

1. Proposals may include any imaging modality, but must be amenable to use in typical Phase 1/2 populations (e.g. metastatic or primary tumour in liver, lung or visceral locations). Imaging biomarkers that can only be measured in special anatomic locations not often encountered in Phase 1 (e.g. brain, skin) will not be of interest. Use of the imaging biomarker in tumours previously treated with radiotherapy should be considered. Proposals could consider PET and/or SPECT, and/or physiologic biomarkers from MRI and/or CT. Structural MRI and CT are unlikely to be of interest in isolation. Other imaging modalities (e.g. optical/fluorescence, ultrasound, or MRS) have significant limitations (difficulty with small tumours, difficulty with deep tumours, difficulty in quantitation etc), and should only be included if accompanied by compelling strategies to overcome the limitations.
2. Central to the proposal should be qualification and risk-management. Qualification is not the same as Validation, but it does include the accumulation of evidence linking the biomarker to the underlying biology, and to the clinical outcome, in a variety of settings. Specifically imaging-histopathology correlation should be addressed, and the potential confounds and risks of false-positive or false-negative with a range of anticancer drugs must be considered.
3. Proposals may focus on biomarkers suitable for a broad range of tumours, or may focus on some specific cancers. However if the focus is on specific cancers, these must be common cancers, to give the widest possible benefit to cancer patients in Europe.
4. Image analyses must be considered, including robust algorithms capable of addressing issues of tumour heterogeneity in the setting of a prospective controlled trial. The project must address how the result of any high-dimensional analyses can be collapsed to a single scalar and used in power calculations.
5. Use of the imaging biomarker in widely available animal models such as xenografts must also be addressed, because animal imaging studies with new drug are often performed to help risk-manage the clinical programme. Studies in animals should not however be proposed, unless they are consistent with the principles of Reduction, Refinement and Replacement, and applicants should familiarise themselves with EFPIA's position (see: <http://www.efpia.org/Content/Default.asp?PageID=499> and [http://www.animalresearchforlife.eu/Non-invasive Imaging techniques help reduce and refine animal studies.pdf](http://www.animalresearchforlife.eu/Non-invasive%20Imaging%20techniques%20help%20reduce%20and%20refine%20animal%20studies.pdf) ).

6. Much previous academic work on imaging biomarkers has been single-centre. Significant differences in acquisition and analysis protocols, and vendor platform differences, mean that data are difficult to compare between centres in multicentre trials. Thus there is a need to standardise techniques and to define variability in imaging markers. Standardisation must be addressed so that the imaging biomarkers chosen in package A are made available initially for multicentre trials in at least four to six major cancer centres in Europe according to standard protocols.
7. Imaging biomarkers using novel tracers and ligands (e.g. hyperpolarised MRI/S; novel PET/SPECT tracers; novel MR/CT contrast media; novel microbubbles) historically have posed a serious problem for the anticancer drug developer, the so-called "double IND problem", in that it has been difficult (for regulatory and other reasons) to combine an investigational diagnostic imaging agent and an investigational therapeutic in the same clinical trial. Therefore, novel tracers or contrast media which lack regulatory marketing approval should not be employed, unless drug developers can be assured that these novel tracers/contrast media can be used in their Phase 1/2 trials (including any licences to third-party IPR and a robust regulatory framework for combination of an investigational tracer/contrast agent with an investigational anti-cancer drug).
8. Imaging biomarkers using PET/SPECT tracers have short half-life isotopes (e.g.  $^{18}\text{F}$ , 2 hours) and if used, will need to be produced with appropriate regulatory approval and made available to centres across Europe, with logistic and resource issues addressed.
9. Active participation of Imaging CROs and/or Diagnostic Imaging Companies in the Applicant Consortium is encouraged.
10. Proposals should consider use of the imaging biomarkers as pharmacodynamic biomarkers for early efficacy assessment (imaging biomarker changes after treatment in patient and in animal tumour model), and may also consider use in personalised healthcare (imaging biomarker predicts which patients will respond to treatment).
11. A process for gaining regulatory advice on combining an investigational diagnostic imaging agent and investigational therapeutics in the same clinical trial, and on the regulatory acceptability of imaging biomarker data, is desirable.
12. Proposals must not duplicate work underway elsewhere but may be complementary to programmes funded e.g. by the US Biomarkers Consortium ( <http://www.biomarkersconsortium.org/> )

Definitions (based on Atkinson et al 2001):

*Imaging Biomarker: a measurement from an image, associated with the pathological process and with putative diagnostic/prognostic utility.*

*Validated Imaging Biomarker (Surrogate Endpoint): An imaging biomarker which can definitively substitute for a clinical endpoint in measurements of drug efficacy or toxicity*

*Qualification: The process of accumulating evidence to link a biomarker with underlying biology, and with clinical endpoints. It is a graded evidentiary process, which depends on the intended application.*

Glossary

*ADC: Apparent Diffusion Coefficient, an MRI measurement*

*CRO: Contract Research Organisation or Clinical Research Organisation*

*CT: X-ray Computed Tomography*

*DCEMRI: dynamic contrast-enhanced MRI*

*EFPIA: European Federation of Pharmaceutical Industries and Associations*

*FDG: [<sup>18</sup>F]-2-fluoro-2-deoxy-D-glucose, a PET tracer*

*FLT: [<sup>18</sup>F]-3'-fluoro-3'-deoxy-L-thymidine, a PET tracer*

*FMAU: [<sup>18</sup>F]-1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)thymine, a PET tracer*

*GCP: ICH Good Clinical Practice*

*GMP: ICH Good Manufacturing Practice*

*ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use*

*IND: Investigational New Drug*

*IPR: Intellectual Property Rights*

*K<sup>trans</sup>: transfer constant for contrast agent arriving into a tissue, a DCEMRI measurement*

*MRI/S: Magnetic Resonance Imaging and Spectroscopy*

*MRI: Magnetic Resonance Imaging*

*MRS: Magnetic Resonance Spectroscopy*

*PET: Positron Emission Tomography*

*PK-PD: Pharmacokinetic-Pharmacodynamic*

*PME: Phosphomonoester, an MRS measurement*

*SOP: Standard Operating Procedure*

*SPECT: Single-Photon Emission Computed Tomography*

*tCho: total cholines, an MRS measurement*

*v<sub>e</sub>: volume fraction of the extravascular extracellular space, a DCEMRI measurement*

		<p><b>References</b></p> <p><i>Atkinson Jr, AJ, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework (Commentary). Clinical Pharmacology &amp; Therapeutics (2001) 69: 89–95</i></p> <p><i>Hanahan, D, Weinberg, RA. The Hallmarks of Cancer (Review). Cell (2000) 100: 57–70</i></p>
3	Key Deliverables of the Project	<p><b>Package A: Imaging biomarkers of tumour cell proliferation and death</b></p> <p>At the conclusion of the project we will have imaging biomarker(s) (or combinations of biomarkers):</p> <ul style="list-style-type: none"> <li>• Which assess the amount of, and pharmacodynamic changes in, tumour cell proliferation and death (by necrosis, apoptosis, autophagy or otherwise)</li> <li>• Which are Qualified for use to support drug development "go / no-go" decisions in typical Phase 1/2 studies and also possibly for patient selection/stratification or for personalised healthcare</li> <li>• With robust protocols allowing them to be performed in typical Phase 1/2 populations, including image analysis algorithms which are robust in the presence tumour heterogeneity, even in the setting of a prospective controlled trial</li> <li>• With robust protocols allowing them to be performed in pre-clinical disease models to support PK/PD studies</li> <li>• Which are made routinely available to conduct clinical studies in at least four to six major cancer centres in Europe</li> </ul> <p><b>Package B: An imaging biomarker of the invasive phenotype</b></p> <p>At the conclusion of the project we will have candidate imaging biomarker(s):</p> <ul style="list-style-type: none"> <li>• Which distinguish tumours likely to invade locally, or to metastasise, from those less likely so to do, with evidence that drug-induced change in the biomarker predicts change to a less invasive phenotype</li> <li>• Which are made available for use in preclinical models and in man in typical Phase 1/2 populations</li> </ul>
4	EFPIA Participants in the Project	<p>Amgen, AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck KGaA, Orion, Pfizer, F. Hoffmann-La Roche AG, Sanofi-Aventis.</p>

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5	Role of EFPIA Participants in the Project	<p>It is intended that the EFPIA partners will work closely with the public and SME partners to ensure effective project management and achievement of the deliverables. Specifically the EFPIA partners wish to conduct collaborative research and contribute in most or all of the following areas:</p> <ul style="list-style-type: none"> <li>• Making available imaging laboratories for preclinical and clinical imaging studies;</li> <li>• Collaborating in development of animal models in imaging research, including data on existing imaging agents tested in these models, correlations with histology and outcome;</li> <li>• Providing data from ongoing pre-clinical model development;</li> <li>• Providing data from ongoing clinical studies using existing imaging biomarkers including correlations with histology and outcome;</li> <li>• Providing clinical supplies of imaging agents;</li> <li>• Providing image analysis expertise and biometric support;</li> <li>• Providing clinical trial management support, data management;</li> <li>• Performing histopathology;</li> <li>• Performing clinical statistics;</li> <li>• Providing expertise in medicinal chemistry for development of molecular imaging probes;</li> <li>• Funding contractors or postdoctoral fellows: however this will be at most a minor contribution as EFPIA will mainly contribute 'in-kind' rather cash.</li> </ul>
6	Indicative duration of the project	The indicative duration of the project is 5 years
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate for the EFPIA in-kind contribution to this project is up to EUR 7 million.
8	Indicative expectations from the “Applicant Consortium”	The Applicant Consortium should provide the skills and capabilities necessary to deliver both packages A and B. It is likely to include preclinical and clinical imaging scientists, preclinical cancer researcher(s), clinical research oncologist(s), and specialists in image analysis. Other important skills may include histopathology, radiotracers, GCP and possibly GMP, and the development and operation of SOPs. These skills and capabilities will complement those provided by the EFPIA members (section 5).

		<p>Package A likely will involve approaches which although preceded are insufficiently understood. The focus is on qualification and utilisation of these potential imaging biomarkers as pharmacodynamic response biomarkers, and also possibly as prognostic or predictive biomarkers. These biomarkers should be delivered at 4-6 cancer centres, working to standardised protocols. The consortium would be expected to propose:</p> <ul style="list-style-type: none"><li>• A portfolio of animal and human imaging studies for imaging biomarker evaluation and qualification;</li><li>• If ligand / tracer production is needed, this should be to GMP (or other appropriate standard) for human studies;</li><li>• Clinical Imaging including the image analysis component to GCP;</li><li>• Standardised protocols.</li></ul> <p>Package B is higher risk, in that currently there are no established imaging biomarkers to predict invasion, but if identified would represent a major scientific advance, and high scientific value. The consortium would be expected to propose:</p> <ul style="list-style-type: none"><li>• A portfolio of animal and human imaging studies for imaging biomarker discovery and evaluation</li></ul>
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In **Infectious Diseases** IMI sees a strong need in the identification and development of rapid point of care diagnostic tests for bacterial diagnosis to facilitate conduct of clinical trials and clinical practice with focus on respiratory tract infections (pneumonia, bronchitis etc ).

#### 4. Infectious Diseases - Diagnostic Tools

0	Topic Code	IMI_Call_2009_4
1	Topic title	<b>Identification and Development of Rapid Point of Care Microbiologic Diagnostic Tests to Facilitate Clinical Practice and Conduct of Clinical Trials</b>
2	Project description	<p><b>Background</b></p> <p>For many bacterial, mycobacterial and fungal infections, currently available culture-based diagnostic methods are suited for recovery of the pathogen(s) and provide information on susceptibility or resistance profile. This information can take 2-3 days or longer to become available.</p> <p>The focus of this Topic is to advance methodology for the rapid detection of bacteria, fungi and mycobacteria, and to differentiate them from viral infections where necessary.</p> <p>Progress with rapid detection of viruses is more advanced and believed to require less attention at this time.</p> <p>There is an urgent need for rapid diagnostic tests that can at the point of care identify the pathogen(s) and the presence of markers of resistance. For serious infections and when resistance is present, instituting immediate appropriate therapy early is critical. Therefore, the use of rapid diagnostic tests to confirm the presence of a pathogen and/or a resistance biomarker directly from the clinical specimen and subsequent accurate antimicrobial therapy, can potentially improve clinical outcome and facilitate the efficient conduct of clinical trials.</p> <p>Several rapid, simple tests have been successfully integrated into the diagnosis of infections (i.e., rapid antigen detection tests for diagnosis of meningitis from CSF samples and rapid antigen detection of group A beta haemolytic streptococci from throat specimens). However, other infections have suffered from lack of such advances.</p> <p>With the advent of PCR and more recently real-time detection methods, more sophisticated assays have been developed, especially directly from clinical samples. However some of these technologies are only available for a limited number of pathogens or clinical specimens, or may have a long turnaround time to have an impact on treatment or enrolment decisions, particularly in life-threatening infections. Tests with complex processing or handling by highly trained laboratory personnel diminish the utility of such tests and increase the turnaround time.</p> <p>Existing technologies, such as Septifast from Roche or GeneXpert from Cepheid are useful in certain settings but may not provide information in a timely manner or may not be appropriate for various specimen types.</p> <p>The objective is the development of fast, specific, sensitive, reliable, cost-effective, user-friendly point of care tests that meet the needs of the clinic and have applicability</p>



in clinical investigations.

The development of the desired tests will take into account the environment and needs of the user (e.g., clinician as well as clinical investigations).

There are three main technologies for microbial identification:

- Culture  
Microbial culture is the gold-standard for pathogen identification and testing of susceptibility to antibacterial agents. The technique has little demands on equipment but takes a minimum of 24 hours to deliver a result. Determination of resistance requires additional 24 hours. Besides the time requirement, these tests require skilled personnel and certified laboratories.

Although culture-based methods are suited for recovery of the pathogen, these methods can suffer from poor sensitivity and are not rapid. Due to many factors, pathogen recovery rates by culture are low and therefore confirming microbiologic diagnosis in only a fraction of the patients investigated.

- Nucleic Acid Testing (NAT)  
NAT is well established for the detection of viruses because of high sensitivity of the technology. Requirements for equipment, infrastructure and operator skill are usually high. Tests can be performed within hours. Detection of resistance via identification of gene mutations is possible but may depend on recovery of the pathogen adding an additional 24 hours to the turnaround time.

- Immunological tests  
Rapid immunologic tests (Point of Care) are available for some microbial diseases. These tests can usually be performed easily and rapidly, but do not amplify the target. Immunologic tests are fast but may require a confirmation by standard technologies. Immunologic tests also may be less sensitive than NAT. In some cases cross reactivity of the detecting antibodies may result in lower specificity. There are currently a limited number of tests available for detection of resistance markers (e.g. Circa Beta Test) but requires culture (colonies) prior to testing.

#### **Problem statement**

The development of rapid diagnostic tests to detect pathogens, resistance markers, and guide timely use of appropriate therapy has been identified by many sources and opinion leaders as a clear unmet medical need. In clinical practice, rapid diagnostic tests at point of care can avoid useless antibacterial treatment in case of viral infection and can allow selection of appropriate antimicrobial treatment for specific pathogens.

In pharmaceutical drug development, conduct of clinical trials is inefficient due to lack of rapid diagnostic tools, particularly when a therapeutic agent targets a certain pathogen or is active for a particular resistance phenotype. Often, many patients are enrolled and randomized in clinical trials with only a small fraction having the desired bacteriological diagnosis. Therefore, clinical investigations for new antimicrobials must be able to identify a pathogen of interest at the point of care for immediate correct patient stratification.

Use of a rapid method to identify the target population would allow conduct of smaller and more efficient trials, therefore exposing fewer patients to an investigational agent

with higher probability of demonstrating treatment benefit. As a consequence, research and development efforts in antimicrobial agents will be expedited.

The following disease entities are identified as high priority: pneumonia (hospital acquired, ventilator associated, and community acquired pneumonia), serious skin infections, bloodstream infections, bacterial sinusitis, bacterial bronchitis, otitis media, and tuberculosis.

### **The need for a collaborative approach**

The diversity of bacterial, fungal and mycobacterial pathogens with highly variable genetic resistance mechanisms, the ability of these pathogens to infect virtually all human organ systems, as well as an insufficient number of patients with disease at a single geographical location requires a pan-European research approach.

### **Key objectives to be addressed**

An ideal diagnostic test should have the following characteristics:

- Detection time around 30 minutes up to 2 hours directly from clinical specimens
- Equal or higher sensitivity and specificity than Rapid Immunologic Tests
- Ability to detect bacterial pathogens and associated resistance markers directly from clinical specimens
- Integrated system (sample preparation + reaction + detection) on one reaction matrix. Easy test to conduct with little sample handling. Convenient assay read-out with appropriate interpretation system
- Modest investment into equipment

Improvements are needed in the following areas:

- Tests that accurately and rapidly discern high quality clinical specimens that are likely to contain pathogen of interest, allowing an immediate decision at the bed side to obtain another specimen.
- Tests those are less complex than currently available technologies, not requiring sophisticated processing and automation with the possibility of readouts that can be easily conducted at the point of care.
- Test that can detect genetic elements, antigens, or other biomarkers to simultaneously identify the specific pathogen and its associated resistance profile directly from clinical specimens.
- Tests that are sensitive and specific enough to enrich for certain patient populations (when positive) and to exclude patients (when negative) from enrolment in clinical trials
- Provide diagnosis based on “panel” testing for multiple pathogens usually associated with a given disease entity (e.g. Gram-negative and Gram-positive panel for bacteraemia)

		Note that the development of a final product(s) is not in the scope of this Topic.
3	Key deliverables of the project	<p>The project is expected to deliver:</p> <ul style="list-style-type: none"> <li>• Novel assays that improve specimen quality and enhance detection of pathogens and resistance markers.</li> <li>• Tests that enable the conduct of smaller, more efficient trials. Test should be simple, rapid [results available in 2 hour or less] and easily incorporated in multi-centre (e.g., rapid Group A strep tests) studies without the requirement of highly sophisticated equipment or specialized lab personnel.</li> </ul> <p>Priority should be given for development of tests that can assist in rapid diagnosis of pneumonia, serious skin infections, bloodstream infections, bacterial sinusitis, bacterial bronchitis, otitis media, or tuberculosis.</p> <p><b>Package 1:</b> Screening/assessment program for best available technology based on the requirements for the following packages and development of generic platform(s)  <u>Deliverables:</u> For most promising technologies, proof of concept is shown.</p> <p><b>Package 2:</b> Rapid tests that can identify with accuracy the appropriateness of the obtained clinical specimens at point of care to allow an immediate decision to obtain a second sample. This is particularly important for bacterial respiratory tract infections, such as pneumonia.  <u>Deliverables:</u> Feasibility for such a test is shown with existing or new parameters.</p> <p><b>Package 3:</b> Rapid, accurate, and simple tests for direct detection and differentiation of Gram-positive and Gram-negative bacterial species and to provide diagnosis of resistance markers (e.g., methicillin, vancomycin, presence of ESBLs etc.)  <u>Deliverables:</u> Feasibility for such a test is shown on the chosen platform.</p> <p><b>Package 4:</b> Rapid, accurate and simple tests for rapidly distinguishing bacterial or fungal from viral etiologic agents with particular emphasis on respiratory infections (e.g. bronchitis, pneumonia).  <u>Deliverables:</u> Feasibility for such a test is shown on the chosen platform.</p> <p><b>Package 5:</b> Rapid, accurate and simple test for the direct detection of TB and its resistant forms at the same time. This is important for the correct patient selection for treatment and clinical investigations.  <u>Deliverables:</u> Feasibility for such a test is shown on the chosen platform.</p>
4	EFPIA participants in the project	AstraZeneca, GSK, Johnson & Johnson, MSD, Novartis, Sanofi-Aventis
5	Role of EFPIA participants in the project	<p>The contribution from the EFPIA consortium is expected to include all aspects of the following areas:</p> <ul style="list-style-type: none"> <li>• Scouting available technologies</li> <li>• Technical evaluation/validation of technology candidates and comparisons vs. gold standard methods (culture or PCR)</li> <li>• Coordinate different research projects and audit the progress</li> </ul>

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		<ul style="list-style-type: none"> <li>• Access to well characterized samples as available</li> <li>• Evaluation/validation of the diagnostic tests</li> </ul>
6	Indicative duration of the project	The indicative duration of the project is up to 5 years.
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate for the EFPIA in-kind contribution to this project is EUR 9.8 million.
8	Indicative expectations from the "Applicant Consortium" (e.g. SME's, academia, patient organisations, regulators and non-EFPIA companies)	<p>The Applicant Consortium is expected to address all 5 packages in their Expression of Interest.</p> <p>Ideally, Package 1 should be finished before packages 3-5 can start. Package 2 is independent from this time line.</p> <p>The Applicant Consortium is expected to address applicability of the diagnostic technology in clinical trials as well as in clinical practise.</p>

In **Inflammation chronic immune mediated diseases** (IMDs) are the focus for 2009. The goal is to get a better understanding of aberrant adaptive immunity mechanisms in human chronic IMDs by comparative human T-cell and B-cell biology. To identify common denominators and differentiating factors between autoimmune diseases, the primarily tackled diseases will be Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) & Inflammatory Bowel Disease (IBD). The establishment of a pan-European network for Immuno-Pathology and Translational Biomarker research should facilitate translational research in chronic IMD in order to bridge the gap between animal models and humans.

## 5. Inflammation - Aberrant Adaptive Immunity

0	Topic code	IMI_Call_2009_5
1	Topic title	<b>Understanding aberrant adaptive immunity mechanisms in human chronic Immune-Mediated Diseases: Rheumatoid Arthritis, Systemic Lupus Erythematosus &amp; Inflammatory Bowel Disease</b>
2	Project description	<p><b>Background</b></p> <p>Immune-mediated diseases (IMDs) remain as some of the most intractable diseases to manage, most have no cure and are limited to palliative and symptom-controlling measures. A wide range of various conditions has been identified which affect millions of patients worldwide; in the developed world one out of three is estimated to be chronically affected at a certain time of his / her life span. IMDs manifest from organ specific such as in Graves-Basedow disease to systemic such as in Rheumatoid Arthritis (RA) and Systemic Lupus Erythematosus (SLE). Aside from a handful of diseases of high frequency and with a huge economic burden (e.g. Asthma, RA), there are a large number of rarer but often more aggressive and even life threatening conditions such as SLE, systemic vasculitis and scleroderma. These especially are currently poorly managed with the primary armament being a range of agents including high dose corticosteroids, cyclophosphamide and azathioprine all of which have significant limitations and none of which has been systematically studied and developed for the life threatening condition. Overall, the situation is generally one of symptomatic care at worst, with lately some limited inroads made into disease modification and little evidence of cure.</p> <p><b>Problem Statement</b></p> <p>While these highly diverse diseases vary widely in their symptoms, organ / tissue involvement, gender distribution, genetic susceptibility, severity, co-morbidities, influence by environmental triggers, and response rate to current treatment their <b>chronic</b> nature and <b>immune-mediated</b> pathologies strongly suggests that an aberrant, innate and <b>adaptive immunity</b> may be a common denominator. Relatively recent clinical studies in IMDs using T and B cell-directed biological therapies have provided strong evidence of the adaptive immune components being a central part of the pathology. Specifically, use of a soluble CTLA4-Ig fusion protein (ORENCIA®, abatacept, Bristol-Mayers Squibb) and a depleting anti-CD20 monoclonal antibody (Rituximab, Mabthera®, Roche / Genentech) strongly argue the case for T and B-cell components in several IMDs. However, despite these innovative and encouraging findings we do not currently understand many disease-relevant aspects e.g. the relative contribution of auto-antibodies / B-cell trafficking / B-cell cytokines or B cell antigen-presenting cell function to the pathology of IMDs. Similarly, despite arguably a longer and more extensive history of T cell-focused research in IMDs and the</p>

success of CTLA4-Ig and cyclosporin in the clinic, significant unanswered questions remain as to the underlying reason(s) for breaking peripheral tolerance, the generation and breadth of pathogenic T cell populations, the *non-redundant* mechanisms underlying homing and recruitment of pathogenic T cells and even regarding CTLA4-Ig itself, how this molecule affects adaptive immune mechanisms, in a human disease setting to produce clinical benefit .

### **The need for a collaborative approach**

Research on IMDs suffers from a significant gap between immuno-inflammatory analyses and understanding of disease patho-physiology (i.e. what targets and pathways contribute / link to what phenotypical appearance with what incidence and penetrance).

While basic research approaches on pathological mechanisms of IMDs are underway, the primary interest to bring generated basic and clinical findings to immediate application in man (drug discovery and development aspect) is still missing. In addition, the heterogeneous appearance at onset and various diagnostic criteria make it especially difficult to access patients in early stages in sufficient number to support robust and comparative results on a broader scale.

Therefore, a collaborative approach has the highest likelihood of creating the necessary breakthroughs in the fields of:

- Basic and clinical science (novel targets, pathways and biomarkers)
- Translation of basic and clinical science into new drug development approaches

### **Key objectives to be addressed**

There is a fundamental need to use recent advancements and new insight into successfully modulating the T- and B-cell compartment in some pathological conditions, to further improve our basic and especially **applied** understanding of the adaptive immune processes in IMDs on a broader scale. The overall aim is thereby to improve our current existing treatment modalities further and especially to discover new ways of tackling those disease and / or conditions that respond partially or are still untreatable by finding commonalities and differences that can be used as new starting points for more effective, selective and better tolerated interventions.

For the above reason, the project concentrates on comparative T cell and B-cell biology and all other disease relevant cell types (activation, migration, homing, effector function, interaction with resident cells, tolerance, characterization and functional involvement of subtypes) exclusively in two human disease groups or complexes where these cell types are thought / known to play an essential role:

- I) Rheumatoid Arthritis and related diseases of this type (including SLE, scleroderma, vasculitis etc.)
- II) Inflammatory Bowel Disease (IBD), Chron's disease and ulcerative colitis.

This selection of diseases is made to allow for sufficient focus of specialized experts and getting together a critical mass without being too narrow and having ample room for comparative studies. Furthermore those diseases seem specifically suited to extend the research into immune triggered patho – mechanisms that are at the borderline of immunological research today i.e.: immune mediated / induced bone / cartilage destruction and gut barrier function / tolerance induction

		<p><b>High Level Plan</b></p> <p>Currently two different research strategies are envisaged. However, proposals with an innovative strategy to tackle the problem are strongly encouraged. The decision whether to move forward with strategy 1, 2 or a novel one will depend on the relative scientific attractiveness of the proposals.</p> <p><b>Strategy 1:</b> Comparative and mechanistic studies of human T- and B-cell biology in RA, RA-like diseases and IBD to define aberrant immune cell function, common denominators and differentiating factors between autoimmune diseases.</p> <p><b>Strategy 2:</b> Proposals in the field of RA, RA-like diseases and IBD that include a) systematic and preferably longitudinal description and mechanisms of adaptive immunity in the different stages of the disease and b) categories of patients who respond to distinct treatments (i.e. currently available biologic therapies targeting key cytokines or cellular mediators of inflammation).</p> <p><b>Novel Strategy:</b> Additional innovative proposals in the field of RA, RA-like diseases and IBD not covered by strategies 1 and 2.</p> <p>All three strategies pivot around the need to further understand adaptive immune cell function firstly in RA, and secondly in other RA-like diseases and IBD...</p> <p>The current project represents a unique opportunity to</p> <ul style="list-style-type: none"> <li>• Increase the basic understanding of the nature of chronic inflammatory diseases and risk factors associated with disabling co-morbidities to these diseases</li> <li>• Identify and validate new targets, pathways and biomarkers with pathobiological significance that serve as a starting point for future drug development</li> <li>• Unravel and qualify molecular signatures of chronic inflammatory diseases predictive of long-term disease outcome, risk of progression, risk of co-morbidity, or response to treatment to guide and accelerate the development of tailored medicines with superior risk/benefit ratios and the basic scientific level.</li> </ul> <p><b>Link to other EU initiatives</b></p> <p>This topic is closely linked to the IMI 2009 Call topic 6 ‘Translational Research in Chronic Immune-Mediated Disease: bridging between animal models and humans’. The IMI JU may explore and facilitate the setting up of a common steering committee during negotiations for grant agreements in order to guarantee scientific and technological exchange between topic 5 and 6.</p>
3	Key deliverables of the project	<p>Overall these activities should lay the foundation to drive forward IMD research in Europe beyond the period of this project and to develop solutions to pre-clinical, challenges in the area of immunology (organ – resident cell biology).</p>

Inflammation – Aberrant Adaptive Immunity

		<p>Improved scientific understanding of aberrant adaptive immune function, resident organ cell type pathology and T- / B-cell phenotypes specific to different forms of IMDs (strategy 1) related rheumatologic diseases in a broader sense (strategy 2) and RA specifically is expected. The key deliverables of the three strategies in the short to medium term (5 years) are:</p> <ul style="list-style-type: none"> <li>- New therapeutic targets specific to one or several of these autoimmune diseases</li> <li>- New candidate biomarkers to specifically differentiate the various autoimmune diseases at immunological level and to follow a potential future successful treatment</li> <li>- New pathways and mechanisms of clinical relevance to one or several IMDs</li> </ul>
4	EFPIA participants in the project	AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Novartis, Novo Nordisk, F. Hoffmann-La Roche AG, UCB, and Wyeth.
5	Role of EFPIA participants in the project	<p>The EFPIA participants will contribute:</p> <ul style="list-style-type: none"> <li>• Technical input and resources related to assays and application of relevant screening technologies. For example access to high-content biology instrumentation and data processing capabilities, high-throughput confocal imaging, high-speed fluorescent cell scanning/sorting instruments.</li> <li>• Supply of relevant pharmacological tools. For example research tool compounds, antibodies, siRNA and other biopharmaceuticals.</li> <li>• Bioinformatics / informatics support (for example gene expression databases, pathway analysis applications and data processing).</li> <li>• IMD Steering-group support</li> </ul> <p>EFPIA partners will also contribute to the projects by providing immunological expertise and disease context (e.g. preclinical <i>in vitro</i> and <i>in vivo</i> model systems, clinical expertise and pathology data).</p>
6	Indicative duration of the project	The indicative duration of the project is 5 years.
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate for the EFPIA in-kind contribution to this project is EUR 7.5 million.



8	<p>Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)</p>	<p>The Applicant Consortium is expected to:</p> <ul style="list-style-type: none"> <li>a) Address extrinsic factors and intrinsic signalling pathways (in a comparative way between RA, RA like diseases and IBD) mediating the susceptibility, prognosis, drug efficacy and safety of patients mediated and influenced by these T- and B-cells and organ resident cells.</li> <li>b) Address potential gender differences (such as changes in disease-related, adaptive immunity in pregnancy – induced temporary remission) and genetic and environmental factors that manifest in these T- and B-cells / organ resident cells and contribute to the disease.</li> <li>c) Identify very early diagnostic and predictive markers at first disease manifestation and early stage of disease in these cell types.</li> <li>d) Addressing co-morbidity and severity mediated by T- and B-cells and organ resident cells.</li> </ul> <p>It is expected that all proposals include point a) plus one or several of b) –d) in addition.</p> <p>Proposals should be based on:</p> <ul style="list-style-type: none"> <li>a) Direct investigations of patients and patient materials with chronic rheumatological and other chronic IMDs including accurate clinical data matching the sample collection timing.</li> <li>b) A multi-disciplinary approach to support the understanding of T and B-cell / organ resident cell function in IMDs.</li> <li>c) Experimental research programmes in systems – in vivo, ex-vivo and in vitro (in that order of priority).</li> </ul> <p>It is expected that the applicants are in a position to provide clinical samples and specimens required to address the above questions. This project thereby exclusively focuses on investigations in human biology.</p>
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## 6. Inflammation – Translational Research

0	Topic Code	IMI_Call_2009_6
1	Topic title	<b>Translational Research in Rheumatoid arthritis (RA) and RA like diseases: bridging between animal models and humans</b>
2	Project description	<p><b>Background</b></p> <p>Chronic inflammatory diseases affect millions of people causing substantial individual suffering, disability, and premature mortality and hence such immune-mediated diseases (IMDs) represent a significant burden in both social and economic terms.</p> <p>Rheumatoid arthritis, in adult and pediatric variants, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, and other less frequent diseases like vasculitides are all heterogeneous, chronic IMDs with recurrent disease patterns fluctuating between quiescent periods interrupted by flares of symptoms. The aetiology of these diseases involves complex contributions of environmental factors and multiple susceptibility genes.</p> <p>Research on the complex and heterogeneous nature of IMDs has revealed some patterns, including clustering of specific risk associated HLA haplotypes, dysfunctional regulation of adaptive and innate immune cell subsets, and production of auto-antibodies and inflammatory mediators such as cytokines and interleukins, among which TNF-<math>\alpha</math>, IL-1, IL-6, and IFN's play key roles.</p> <p>However, in depth understanding of the aetiology and pathogenic mechanisms driving chronic inflammatory diseases is limited.</p> <p><b>Problem Statement</b></p> <p>A first bottleneck for the development of therapies for inflammatory diseases is the lack of good predictive models. Disease heterogeneity is probably the main factor responsible for the inter-patient differences in clinical benefits and side effects of various drugs.</p> <p>A second bottleneck in the treatment of chronic inflammatory diseases (like rheumatoid arthritis) is the lack of commonly qualified disease biomarkers that ultimately translate from animal models to patients.</p> <p><b>The need for a collaborative approach</b></p> <p>Research on IMDs suffers from a significant gap between immuno-inflammatory analyses and true understanding of disease patho-physiology (i.e. what targets and pathways contribute / link to what phenotypical appearance with what incidence and penetrance). This provides an opportunity for cross fertilization of different disciplines in immunology and translational medicine.</p> <p>Although several important IMDs are contemplated to fall within the scope of this topic, <b>this project will focus on rheumatoid arthritis (RA) and RA like diseases</b>, both early-onset and established disease. This selection is made to allow for a critical mass of specialized experts. Furthermore RA seems specifically suited to extend the research into immune triggered pathological mechanisms that are at the borderline of immunological research today i.e.: immune mediated/induced bone/cartilage destruction and – due to the current low predictability of the available animal models would profit most from any advancement here.</p>

Such a collaborative approach on RA and RA like diseases will have the highest likelihood of creating the necessary breakthroughs in the fields of:

- Basic science (novel targets, pathways and biomarkers)
- Translational medicine (new and predictive animal models and validated biomarkers in animals and man)
- Translation of basic and clinical science into new drug development approaches

### **Key Objectives to be addressed**

The aim of the project is to drive forward the understanding of the underlying principles RA and RA like diseases and develop solutions to translational and clinical development bottlenecks to the delivery of safe and effective therapies.

The key objectives are:

1. Identification and characterisation of pathophysiological mechanisms and biomarkers in animal models of RA and RA like diseases that correlate with human disease progression
2. Identification of pre-clinical and clinical mechanisms and biomarkers that enable diagnosis of early-stage RA and RA like diseases
3. Identification of pre-clinical and clinical biomarkers that accurately predict treatment responses in RA and RA like diseases

This is expected to result in:

- Qualified animal models based on their approximation to the clinical condition and predictive value in RA and RA like diseases
- Identification of underlying mechanisms of early disease and disease progression (e.g. biomarkers supporting an early diagnosis of disease as well as those which indicate delayed disease progression in response to drug treatment), including structural cartilage and bone damage
- Markers indicative of prognosis/ long-term disease outcome.

### **High-level plans**

Two complementary packages are foreseen:

#### **Package 1: Improved animal models with increased 'predictive value' in RA and RA like diseases**

The scope of Package 1 is to fully characterise translational (pre-clinical) models of human RA and RA like diseases in three dimensions: 'phenotype', biomarker and genetic profiles.

Animal model pathways may be different from those in human disease and modulating them in animals may not predict results in humans. Despite these limitations, animal models of RA and RA like diseases have been traditionally useful

to dissect molecular mechanisms of disease pathogenesis in the corresponding human diseases. Thus, they will continue to play a key role as the first-line model system in the development of novel therapeutic approaches. However, improving their predictability is the key to success.

Key questions addressed by this work package:

1. What defines a 'good animal model' in RA and RA like diseases (for the purpose of identifying risk of early disease and response to drug treatment)? Define criteria to select the most appropriate model(s) for each disease (spontaneous versus induced models; monophasic versus relapsing, etc); this may be achieved by comparing biological phenotype, biomarker and genotype profiles for available models of RA and RA like diseases cf. the clinical condition.
2. Pharmacological characterisation of the response in 'best models' of RA and RA like diseases using drugs proven to be effective in the clinic and compare these with the responses in man. Establishing of a correlation of clinical phenotypes with changes in biomarker profile is foreseen. Marketed compounds will be used as benchmarks.
3. Analysis of targets/compounds that looked promising in animal models but which failed to exhibit adequate efficacy in man. Identification of the main factors leading to false positives. Establishing of a correlation of clinical phenotypes with changes in biomarker profile is foreseen.

Extensive characterisation of animal models for RA and RA like diseases will likely require the collection of appropriate biosamples from all pre-clinical models of RA. Storage and analysis of these samples will be integrated with the information obtained in Package 2 (please see below) in order to identify and qualify biomarkers which are relevant for early disease diagnosis, predictive of disease progression and prognosis/outcome of disease.

### **Package 2: Biobanking and Translational Biomarkers**

The overall goal of Package 2 is to establish a pan-EU biobank of both pre-clinical (from animal models for RA and RA like diseases) and equivalent clinical samples from patients with RA and RA like diseases.

This will enable direct comparison of profiles from animal models (Package 1) with the profile of human samples; it also allows reverse-translation of results from human samples to those from animal models in response to drug treatment. This is expected to support the refinement of existing (or development of improved) animal models of RA and RA like diseases.

The success of this project is therefore closely linked to the establishment of a pan-EU biobank of longitudinally collected specimens from patients with early stage and established RA and RA like diseases and matched controls (age, sex, demographics).

The biobank should as a minimum include collection of whole blood, serum, plasma, and urine samples for genetic fingerprinting, gene expression profiling as well as assessment of protein and metabolite levels with state of the art technologies in the fields of genomics, proteomics, and metabonomics. However, as many RA and RA like disease processes are localised to the specific organs (e.g. synovium and synovial fluid), tissue biopsies should also be prioritised and subjected to histology and other relevant techniques.

		<p>A complementary clinical database of demographic, medication, disease activity, disease duration, comorbidities, dietary status, and treatment outcome information linked to the individual samples must be an integrated part of this biobank.</p> <p><b>Link to other EU initiatives</b></p> <p>This topic is closely linked to IMI 2009 topic on <i>"Understanding aberrant adaptive immunity mechanisms in human chronic Immune-Mediated Disease"</i>. The IMI JU may explore and facilitate the setting up of a common steering committee during negotiations for grant agreements in order to guarantee scientific and technological exchange between topic 5 and 6.</p>
3	Key deliverables of the project:	<p><b>Package 1:</b></p> <ul style="list-style-type: none"> <li>• Identification of animal models which best represent the underlying features of early and established RA (this will primarily be based on information in the public domain, expanded to include – where available - other models which may have been developed by EFPIA participants)</li> <li>• Definition of the type of specimen required / to be collected from each model as well as selected time points for sample collection</li> <li>• Characterisation of the response (in selected 'best models') to gold standards of treatments, including biologics or surrogate compounds; this will include 'phenotype', biomarker and genetic profiling (for translational mapping to the response in humans).</li> <li>• Validation of imaging, serum/plasma/urine biomarker endpoints and/or novel clinical measures with respect to their utility for assessing pharmacodynamic responses across models</li> <li>• Identification and qualification of pharmacodynamic endpoint to support translation from animals to humans and vice versa</li> </ul> <p><b>Expected Outcomes</b></p> <ul style="list-style-type: none"> <li>• Hierarchy of 'best models' (i.e. most closely resembling clinical condition)</li> <li>• Translational gaps identified (based on medico-scientific literature)</li> <li>• Alignment on 'best pre-clinical models' of RA and RA like diseases</li> <li>• Alignment on translational gaps (profile and properties of pre-clinical models vs. clinical condition)</li> </ul> <p><b>Package 2</b></p> <ul style="list-style-type: none"> <li>• Definition of the specimen collections to be obtained from each study collective (e.g. serum/plasma/urine/tissues), collection time points, sample aliquots, and technical aspects of collection (e.g. barcoding, SOPs for collection).</li> <li>• Establishment of storage facilities (with temperature monitoring)</li> <li>• Collection of an appropriate number of samples from patients, patient subgroups, and controls that enables sufficient power in the statistical analyses</li> </ul>

		<p>This will be accomplished by:</p> <ul style="list-style-type: none"> <li>• Establishment of a network of institutions, including academic and clinical practitioners, that will participate in sample collection from both patients and appropriate matched controls</li> <li>• Identification of competent assay service providers to analyse the collected samples with relevant technologies within genomics, proteomics, metabonomics</li> <li>• Obtain approval from relevant authorities (e.g. ethics committees and institutional review boards)</li> <li>• Use of biostatistical expertise to optimise data analysis and ‘translational’ correlations, including analysis of the collected data in relation to clinical information of demographics, medication, disease activity, disease duration, co-morbidities, dietary status, and treatment outcome</li> </ul> <p><b>Expected Outcomes:</b></p> <ul style="list-style-type: none"> <li>• Ability to correlate ‘phenotype’ and ‘markers’ in both pre-clinical models and disease state, and correlate pre-clinical cf. clinical profiles (‘translational modelling’)</li> <li>• Identification and validation of at least one novel biomarker or a combination of biomarkers predictive of underlying mechanisms of early disease development (diagnosis of disease), disease progression, prognosis/long-term disease outcome</li> </ul>
4	EFPIA participants in the project	Almirall, AstraZeneca, Boehringer Ingelheim, Johnson & Johnson, Novartis, Novo Nordisk, F. Hoffmann-La Roche AG, UCB and Wyeth.
5	Role of EFPIA participants in the project	<p>The EFPIA participants will contribute to:</p> <p><b>Package 1</b></p> <ul style="list-style-type: none"> <li>• Information about animal models of RA and RA like diseases (e.g. transgenic mouse strains/ models of interest)- as needed to complement that in the public domain</li> <li>• Supplies of registered agents and pharmacological tools (incl. compounds giving false positive results in animal models)</li> <li>• Image and biomarker analysis, expertise, and support</li> <li>• Scientific and medical expertise and support in the field of chronic inflammation in general, in particular within RA and RA like diseases</li> <li>• Project management and oversight</li> </ul>

		<p><b>Package 2</b></p> <ul style="list-style-type: none"> <li>• Clinical trial and data management expertise and support in the establishment of procedures and ethical standards for the biobank and integrated clinical database</li> <li>• Clinical trial and regulatory expertise and support in obtaining approval from relevant authorities</li> <li>• Medical and trial management expertise and support in the establishment of a network of academic institutions that will participate in the sample collection and coordinate input from other key stakeholders, e.g. patient organisations and other European biobank networks</li> <li>• Clinical trial management expertise and support in the establishment of storage facilities and collection of samples</li> <li>• Scientific and technical expertise and support in the sample analysis (staff, laboratories, costs of reagents and materials)</li> <li>• Scientific, medical, statistical, programming, and data management expertise and support in the data analysis</li> </ul>
6	Indicative duration of the project	The indicative duration of the project is up to 5 years.
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate for the EFPIA in-kind contribution to this project is EUR 12 million, equally divided between the two packages.
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	<p>The Applicant Consortium is expected to propose projects in the framework of <b>Package 1</b> (Improved animal models with increased predictive value for RA and RA like diseases) and <b>Package 2</b> (Biobanking and Translational Biomarkers) that would:</p> <ul style="list-style-type: none"> <li>• Increase the basic understanding of the nature of RA and RA like diseases and risk factors associated with disabling co-morbidities to these diseases.</li> <li>• Qualify translational animal models of RA and RA like diseases predictive of response to treatment in order to guide and accelerate the development of novel medicines.</li> <li>• Unravel and qualify molecular signatures of RA and RA like diseases predictive of long-term disease outcome, risk of progression, risk of co-morbidity, or response to treatment to guide and accelerate the development of tailored medicines with superior benefit/risk ratios.</li> <li>• Facilitate accelerated development of novel, safer, and more efficacious treatments for patients with chronic inflammatory diseases and hence increase benefit for the patients as well as society.</li> </ul>

<p><b>Specific Requirements for Package 2</b></p> <ul style="list-style-type: none"><li>• Close coordination and adherence to ethical standards and procedures (informed consent, personal data protection, sample ownership, transfer of samples and data across boundaries, intellectual property rights, and publications) developed from the initiatives such as the EuroBioBank (<a href="http://www.eurobiobank.org">www.eurobiobank.org</a>) or the Biobanking and Biomolecular Resources Research Infrastructure (<a href="http://www.bbmri.eu">www.bbmri.eu</a>) is required. In addition, qualified storage facilities that adhere to these ethical standards and ensure long-term preservation of sample integrity and quality will need to be identified.</li><li>• For animal model research, adherence to recent European Council guidance on accommodation and care of animals is required (<a href="http://www.coe.int/t/e/legal_affairs/legal_co-operation/biological_safety_use_of_animals/laboratory_animals/Revision%20of%20Appendix%20A.asp#TopOfPage">www.coe.int/t/e/legal_affairs/legal_co-operation/biological_safety_use_of_animals/laboratory_animals/Revision%20of%20Appendix%20A.asp#TopOfPage</a>.)</li></ul>
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## IMI Knowledge Management Pillar

In the **Knowledge Management Pillar** the focus for 2009 lies on standardization, free access, interoperability and exchange of data relevant for drug discovery and development, including databases for drug/disease models and small molecules and a frame for access and exchange of clinical/healthcare data.

### 7. Knowledge Management – Drug/Disease Modelling

0	Topic Code	IMI_Call_2009_7
1	Topic title	<b>Drug/Disease Modelling: Library &amp; Framework (DDMLF)</b>
2	Project description	<p><b>Background</b></p> <p>Modelling and Simulation (M&amp;S) are an important discipline across all stages of pharmaceutical drug development. M&amp;S tasks range from target feasibility analysis in early drug discovery, over the characterisation of drug/disease properties in drug development, to the prediction and optimisation of clinical trials. The crucial advantage of the use of M&amp;S is the fact that it allows informed decision-making at all stages, that would otherwise not be possible.</p> <p>Models that are used in the context of drug discovery and development range from <i>mechanistic models</i>, describing the underlying biology and physiology in varying levels of detail to <i>empirical models</i>, which simply try to describe the observed data, without an underlying assumption about the biological or physiological mechanisms. Even though models can be very different from one another and are always developed for a specific purpose, the common denominator of all models is that they all can be represented in terms of mathematical functions that relate certain model inputs to certain model outputs. In this call the expression <i>drug (and/or) disease model</i> is equivalent to the word <i>model</i> in the sense that the considered models represent the behaviour of a drug in the context of a disease. Models facilitate learning, as they integrate information from a wide array of sources in order to describe and predict the behaviours of complex biological systems.</p> <p>Models thus provide both a method of storage and a communication framework for knowledge about the impact of drugs and diseases on biological systems.</p> <p><b>Problem Statement</b></p> <p>Significant gaps exist in the way knowledge is integrated within and across different phases of drug development. Thus, identification of opportunities for compound differentiation, as well as the assessment of risks and attrition points, proves difficult.</p> <p>Assembling existing information and building knowledge within the context of pharmaceutical development needs to be applied consistently, but currently happens inadequately owing to the complexity of integrating disease processes and drug action.</p> <p>Models are a convenient medium for storing knowledge. However, the M&amp;S process typically takes place in an <i>ad hoc</i> manner, not allowing for potential reuse of models</p>

and analysis methods. Further, a large number of software packages are used in the pharmaceutical industry, many of which implement proprietary formats for representing models and data, rendering it complex and time-consuming to use a single model to perform all relevant analyses, since recoding of the model and the data is required each time.

This has resulted not only in a large duplication of effort across the research and development (R&D) process, but also in a limitation of access to this knowledge for public bodies who may be able to use it in innovative ways.

### **The need for a collaborative approach**

Currently, as part of the drug development process, newly-developed models, methods, and methodologies are shared with the scientific community through publication or interaction with regulatory bodies.

However, such sharing across organizations, whether academia, pharmaceutical bodies, or regulators, relies on standardization. The adoption of common standards across all stakeholders is a prerequisite for the successful integration of shared knowledge. Only widely-accepted and widely-implemented standards have the power to impact the long-term development of methodologies, tools, and applications.

The approach proposed will ensure that the standards required support the interests of public institutions, which are the primary source for the development of models, methods, and methodologies, and industry, who are the most intensive users of these developments, are equally addressed. Knowledge can thus be shared between public and private groups in a consistent manner.

This will lead to an increase in the speed of distribution and review of new approaches. A common framework, coupled with standards, will reduce the time taken to develop and qualify innovative new methodologies by others in the field.

A consortium of industry, academia and other third parties is the only practical approach of successfully realising these stated objectives. The stakeholders in this equation are:

- Industry, which use software, methods and methodologies to facilitate the development of safe and effective new compounds.
- Academia, who develop innovative new methods and methodologies to enhance the range and predictability of models.
- Solution Providers, from both academia and the private sector (ranging from SMEs to established enterprise software providers), who develop software.
- Regulators, who use software, methods and methodologies to verify findings submitted by industry in support of license applications.

### **Key objectives to be addressed by Drug/Disease Modelling: Library & Framework (DDMLF)**

To improve the existing environment for M&S activities, related to drug discovery and development, the participants advocate that the components of pharmacometric and mechanistic (biologically plausible) modelling: data, models (code), metadata (descriptions), analysis results and inferences, should evolve from a common ontology, and be developed and shared among all stakeholders.

To facilitate the development of novel theoretical concepts on mechanism-based PK-PD modelling, particularly in relation to the modelling of drug effects on disease processes and disease progression a wide range of concepts will need consideration and incorporation into the project:

- Physiologically-based PK modelling for prediction of target exposure.
- Receptor theory for prediction of in vivo concentration-effect relationships.
- Dynamic systems analysis for characterisation of time dependent signal transduction processes and homeostatic feedback mechanisms.
- Disease systems analysis for the characterisation of disease processes and disease progression.
- Hierarchical description of models in order to allow for the description and combination of various sub-models (modules) to generate a more complete model.

### High-level plans

The availability of a public and freely available **library** for drug/disease models would streamline the re-use and **sharing of existing models and code** and thus accelerate the drug development process, while ultimately improving accuracy in the interpretation of efficacy and safety findings.

To facilitate this, the participants are pioneering the development of a **modelling library** and a **software “framework”** to enable exchangeability and interoperability of both the existing information (data and models) and future methods and applications in this area.

The library should include, but not be restricted to, models describing pharmacokinetics (PK), pharmacodynamics (PD), physiology-based PK (PBPK), dynamic biological systems and pathways, disease processes and progression, and interactions between them, and should be portable, shareable and publicly available.

The framework will be designed to save significant time and effort by eliminating the need to hand-translate models between different platforms. It is also expected to act as a catalyst for the development of new and innovative methods and applications in this discipline, and to encourage faster adoption of more efficient and relevant modelling methodologies in drug discovery and development.

Both the library and the framework will depend on the development and subsequent adoption of common standards. Standards would have to be developed to provide consistency to definitions and syntax across methods and applications (**a standard modelling mark-up language**) as well as to facilitate the description of drug and disease models by end users (**a standard model description and coding language**). Such standards would promote and facilitate the sharing of models and data, as well as the evaluation and qualification of models in a consistent and transparent manner.

Collaboration between stakeholders (academia, industry, regulators, patients, and healthcare providers) is another major goal of this proposal, and will be greatly facilitated by the development of the library, the interoperability framework and the common standards which underpin them. With all stakeholders speaking the same

language and using tools that can readily interact, collaboration becomes easier. The availability of a shareable **library of knowledge**, fulfilling a key public need, would in addition encourage the adoption of standards. Ultimately by supporting these standards new and existing tools would facilitate their easier integration into the framework.

A further opportunity relates to the current regulatory drive for the development of common standards for data used in the submission of new drugs for approval. Regulators currently perform re-analyses of data used in modelling, and common standards would significantly reduce the amount of time and resources required for such review activities.

An example for an interoperable and extensible framework is given in Figure 1, which illustrates an intended workflow between the model library and numerous application interfaces.

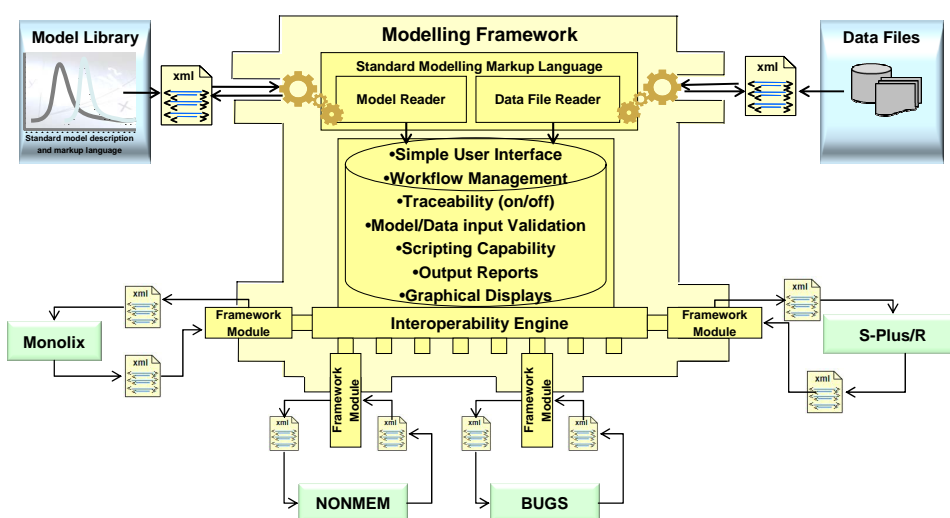


Figure 1: Proposed framework concept diagram. Monolix, NONMEM, BUGS and S-Plus/R are commonly-used software tools in the pharmacometric domain.

The work will be organised into various packages (described in section 3) which will address the delivery of the overall library and framework in a consistent and reliable manner.

**Prototype / Example:**

It is anticipated that examples from various therapeutic areas will be utilized to prove the implementation of the concept:

1. **Diabetes:** A recent example of modelling efforts undertaken to gain information from the different glucose challenges that exist in clinical drug development, is the integrated glucose-insulin model developed by Jauslin et al (2007). By integrating drug effects and disease progression from other models, this model might be used as a tool to simulate the outcome of clinical trials, optimise clinical trial designs and support decisions for, or against, further development of drug candidates.
2. **Oncology:** Another area of primary interest is likely to be oncology, with integration of early in silico preclinical cell cycle and angiogenesis models to inform decision making during the clinical investigation process to model disease progression as elucidated through surrogate endpoints (e.g. change in tumour size) predicting long term outcome (survival, time to clinical worsening).

Other therapeutic areas worthy of focus include **inflammation** and **neurodegenerative disease**.

Such modelling activities are most likely to be successful if they are conducted as common efforts between different pharmaceutical companies and universities, via a common disease model platform that shares the state-of-the-art information generated using multiple tools in a particular disease area. The drug/disease model library and framework offers an ideal way of facilitating this.

Various stakeholders will benefit from this project:

- **Industry:** Qualification, support, and maintenance of a streamlined environment that is robust, auditable, flexible and scaleable; encourage good data analytical practice; promotion and simplification of the re-use of data to accelerate drug development.
- **Academia:** Open source, free-to-use framework software; enablement of more effective and more rapid dissemination of relevant methodologies to the broader community; facilitation of communication and knowledge sharing between relevant stakeholders; enabling of more effective training in modelling techniques and tools in the pharmaceutical sector.
- **Regulatory authorities:** Enhancement of evaluation and acceptance of drug and disease models, and use in decision-making; better assessment of regulatory advice on dosing and dose individualisation; quantitative evaluation of pooled safety and efficacy data across compounds; facilitation of interchange of generated knowledge (data and models) between submissions; improvement of cycle time for review of new drug applications.
- **Health care providers:** Improvement in delivery of personalised medical care, through simulation of clinical scenarios, for example; communication and sharing of integrated knowledge (disease and therapeutic models) with the medical community.

Ultimately, these capabilities will provide an opportunity to better and more efficiently apply modern quantitative techniques to assess the properties of drugs, disease and disease progression and to differentiate the pharmacological properties of both new and established drugs, enabling more accurate predictions of their efficacy and safety.

**Differentiation of DDMLF from existing initiatives in the area:**

**The Virtual Physiological Human (VPH) (<http://www.vph-noe.eu>)**

The VPH initiative pursues similar targets: predicting disease progression, optimizing drug treatment and, consequently, improving patient health care. However, the areas explored and the methods applied are very different from the DDMLF initiative.

While the VPH tries to understand the underlying biology of a disease/treatment process, the DDMLF aims to provide the means to utilize any existing information (biological and non-biological) to optimize the drug development process for an enhanced chance of success (thus reducing attrition).

		<p>In areas where standards and languages cover similar entities and processes, the DDMLF will build upon already developed ontologies, and will adopt and progress them as necessary, potentially resulting in a universally applicable model-based framework capable of covering any quantitative drug-development problem by linking relevant technologies with one another.</p> <p><b>CDISC (<a href="http://www.cdisc.org/">http://www.cdisc.org/</a>)</b></p> <p>The primary aim of the <b>Clinical Data Interchange Standards Consortium (CDISC)</b> is to develop and support global platform-independent data standards that enable clinical information system interoperability. The DDMLF aims to promote clinical data standards for the interchange of model-related clinical data, lacking in current CDISC specifications, and there is thus a high degree of synergy between these projects.</p> <p><b>Other mark-up languages – SBML, CellML, SEDML</b></p> <p>Other mark-up languages are in development. Although none fulfils the pharmaceutical industry requirement for a standard model markup language by themselves, elements of these projects may well lend themselves to incorporation into the DDMLF project. Three prominent examples are <b>SBML (Systems Biology Markup Language)</b>, an XML-based standard which describes models for biochemical reaction networks, <b>CellML</b>, an open language for describing biological models, but with a more general scope than SBML, and <b>SEDML (Simulation Experiment Description Markup Language)</b>, an XML based format to allow for the definition of simulation experiments using models. All of these have since grown into wider applicability.</p> <p>The consortium is expected to consider and adapt to overlaps and synergies with external initiatives identified during the process, to prevent the duplication of deliverables.</p>
3	Key deliverables of the project	<p>The following work packages (WPs) are target-oriented individual blocks of deliverables. Independent parallel or sequential development of those packages may be feasible but needs to build on package interrelations to enhance consistency and timely delivery of the overall project.</p> <p><b>Package 1: Model Library</b></p> <p>A public and freely available infrastructure for a drug/disease model library oriented towards the storage and retrieval of drug/disease models, comprising (but not limited to) pharmacometric, statistical/empirical, PBPK, hierarchical, and mechanistic (systems biology type) models.</p> <p><b>Package 2: Interoperability Framework</b></p> <p>An environment to enable integration of existing applications and methodologies, as well as to improve the efficiency of integration of new methods.</p> <p><b>Package 3: Standard Model Description and Coding Language</b></p> <p>A unified, human-readable (i.e. non-XML), language for drug/disease model description, which builds the foundation of the user-to-system interaction to describe any quantitative drug development problem.</p>

**Package 4: Standard Modelling Markup Language**

A comprehensive set of common standards that enable the storage and system-to-system interchange of data, models, and related metadata to facilitate interoperability.

**Package 5: Application/Module I Integration**

Provides the means to integrate existing software applications by adopting standards, application programming interface, and the modelling language by means of the Interoperability Framework. Examples of applications envisaged to be included are NONMEM, R/S-PLUS, MATLAB (including Monolix and SBTOOLBOX2) and WinBUGS, which effectively cover the spectrum of modelling tasks currently required in an industrial setting.

**Package 6: Application/Module II Integration**

Provides the means to generate new software applications which build upon the deliverables above, and integrate into a healthcare provider as well as drug development context.

**Package 7: Public Instance of the Modelling Framework**

Provides an IT infrastructure that hosts the project website to supply project documentation, integrates a data warehouse with web access to store models and code (versioned), and provides a forum / wiki for communication.

**Package 8: Documentation**

Provides the documentation and lectures on language/style sheets/tools required to manage the technical aspects of the project.

**Package 9: Training and Education**

Provides lectures and material to be used as tools for training in drug/disease M&S.

**Package 10: Project Management**

Provides project management to ensure proper functioning of the project, to facilitate effective communications within the consortium, to make sure contractual duties are carried out and intellectual property is handled appropriately.

**Interrelations between work packages**

Figure 2 illustrates relationships and dependencies between the work package projects and represents guidance on the sequence in which components of the project will be delivered, as well as milestones to be achieved, and subsequent work packages can build upon.

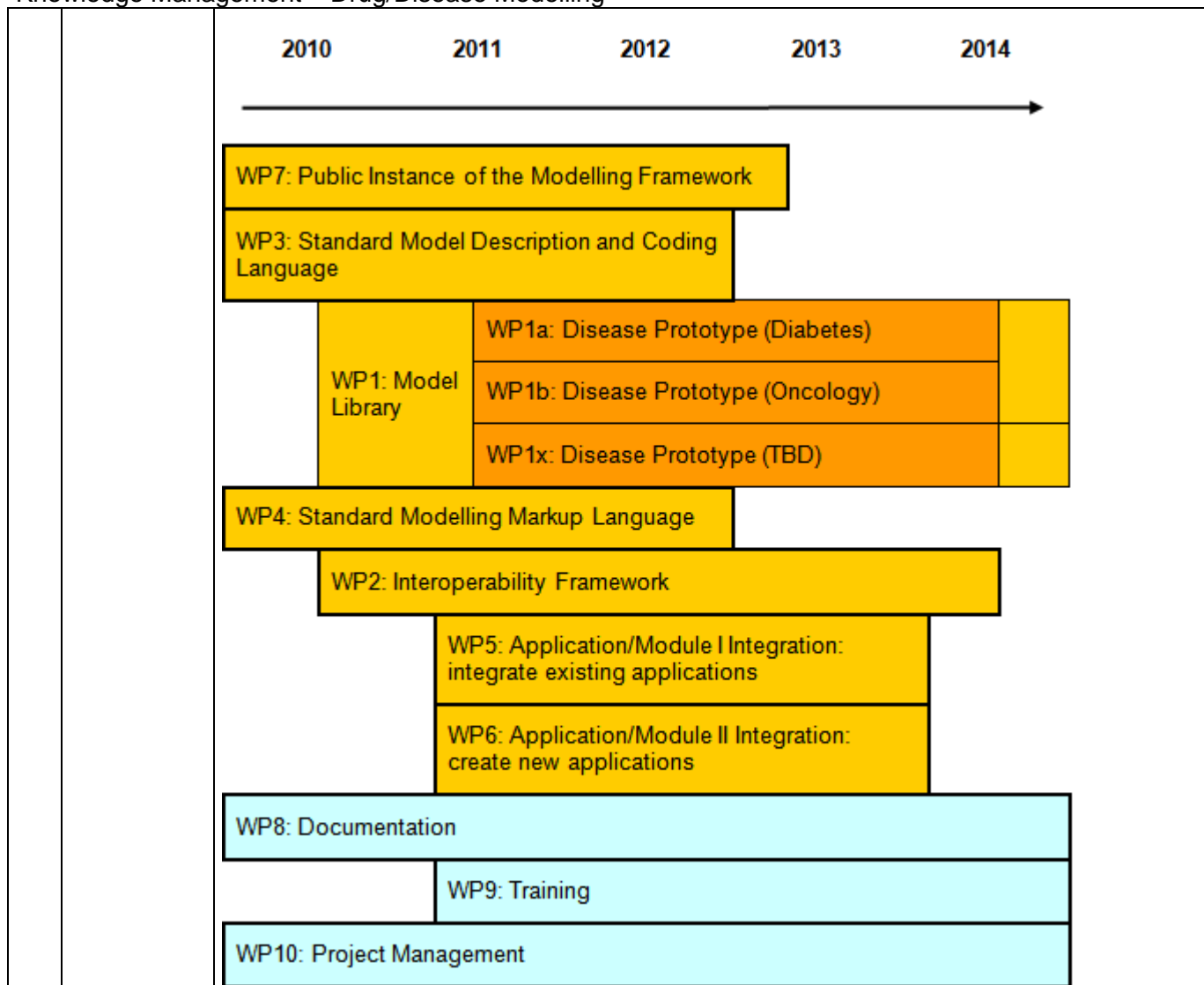


Figure 2: Relationships between work packages.

4	EFPIA participants in the project	AstraZeneca, GlaxoSmithKline, Lilly, Merck KGaA, Novartis, Novo Nordisk, Pfizer, F. Hoffmann-La Roche AG, Servier, UCB
5	Role of EFPIA participants in the project	<p>The EFPIA participants will contribute:</p> <ul style="list-style-type: none"> <li>• Facilitation, review and development of:             <ul style="list-style-type: none"> <li>○ a standard model description and coding language for end users</li> <li>○ system-to-system interchange standards, in the form of a standard modelling markup language</li> <li>○ specifications for the drug/disease model library</li> <li>○ scope and content of the framework</li> </ul> </li> <li>• Case studies, data and background information across therapeutic areas throughout the whole development cycle including:</li> </ul>



		<ul style="list-style-type: none"> <li>○ data from ongoing and future non-clinical and clinical trials</li> <li>○ review of literature for quantitative disease descriptions</li> <li>○ extraction of mathematical content from the published scientific literature to inform model-based meta-analyses</li> </ul> <ul style="list-style-type: none"> <li>● IT – infrastructure and services to achieve an auditable and compliant (in terms of 21 CFR Part 11 and Good Practices) framework implementation</li> <li>● Expertise in clinical development (clinical, statistical, data-management, IT and legal) to provide the means of implementing a workflow oriented framework</li> <li>● Expert knowledge of drugs, diseases and disease progression (clinical, biology, epidemiology, etc.)</li> </ul>
6	Indicative duration of the project	The indicative duration of the project is 5 years.
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate for the EFPIA in-kind contribution to this project is up to EUR 9.0 million.
8	Indicative expectations from the “Applicant Consortium” (e.g. SMEs, academia, patient organisations, regulators and non-EFPIA companies)	<p>The Applicant Consortium, should aim to bring forward innovative approaches to address the work packages as outlined above. The contribution from the Applicant Consortium is expected to include all aspects of the following areas:</p> <p><b>Language (WP3, WP4, WP8):</b></p> <ul style="list-style-type: none"> <li>● Define a standard model description and coding language.</li> <li>● Define a standard modelling markup language.</li> <li>● Capture functionality of existing languages, including NONMEM (NMTRAN), Monolix (MLXTRAN), BUGS, R/S, MATLAB (potentially including but not limited to StatsToolbox, OptDesign, SimBio, SBTOOLBOX2 model format), etc.</li> <li>● Capture the various aspects of the drug-disease modelling process: PBPK, receptor theory, dynamical system analysis, disease progression, statistical and data analytical models, etc.</li> <li>● Capture the possibility of describing hierarchical models.</li> </ul> <p><b>Library (WP1, WP7, WP8):</b></p> <ul style="list-style-type: none"> <li>● Development of the model library structure.</li> <li>● Development of a common format (possibly XML-based) for model (and</li> </ul>

associated metadata) description.

- Transcription of currently available disease models into these new structures (library + language).
- Storage of the currently available models in original computer program code to enable re-running the code with minimal additional effort.
- Ability to track changes in models and reuse templates to create models which have only minor variations, as well as link back to historical (in-house) origins of the development of the model.
- Publication of the model library and its content, with non-competitive components shareable and reusable.
- Comprehensive documentation and training material.
- Maintenance of the library and evolution/development of available content for pre-competitive use.

**Framework (WP2, WP4, WP5, WP6, WP7, WP8):**

- Define scope and content of framework.
- Development and implementation of complex data management systems for data-sharing between the various partners in the program.
- Define system-to-system standards.
- Create framework implementation.
- Provide means for application integration.
- Provide maintenance and long term support.

**Training (WP8, WP9):**

- Education and training of PhD students and post doctoral fellows in advanced mathematical M&S, in relation to drug discovery and development oriented research questions.

**Collaborations (WP1, WP9):**

- Successful collaboration with the international pharmaceutical industry in strategic research projects in the area of advanced drug and disease type of modelling.
- Community engagement (academics, training, education, joint with EFPIA)

**Prototype / Examples (WP1, WP8):**

- Development of mechanism-based models for the characterisation of drug effects on disease progression in type 2 diabetes mellitus, oncology, inflammatory, neurodegenerative and other disease areas.

**Project Management (WP10)**

- Project management to ensure proper functioning of the project, to facilitate effective communications within the consortium, to make sure contractual duties are carried out and intellectual property is handled appropriately.

## 8. Knowledge Management – Open Pharmacological Space

0	Topic Code	IMI_Call_2009_8
1	Topic title	<b>Open Pharmacological Space (OPS)</b>
2	Project description	<p><b>Background</b></p> <p>Knowledge of small molecules and the targets that they act upon forms a key pillar of therapeutic intervention for human diseases. Novel bioactive small molecules are identified by screens which take place both within industry and academia. In screening experiments, the choice of small molecule library and the most appropriate targets to screen against are critical to the success of drug discovery. The screening library should encompass the widest possible range of molecular activities (“chemistry space”) represented by the least redundant chemical library. The target should be tractable to small molecule or biopharmaceutical intervention and validated in the disease (“target space”). This makes access to comprehensive catalogues of pharmacological reagents and molecular targets a critical requirement for drug discovery.</p> <p><b>Problem Statement</b></p> <p>Freely available public domain tools and databases to support drug discovery are strong on biological data but tend to lack chemistry data. There are also very few common standards for the integration of data, particularly in the chemistry domain. These issues are making it difficult to effectively utilize public domain resources for the support of drug discovery research (in industry or academia). For example to access and integrate biological and chemistry information to support the disease validation of targets or to derive information to support drug development, e.g. identification of appropriate animal models for pre-clinical studies. This project proposes the development of a set of open access standardized tools that could enhance existing databases to allow comprehensive integration of information on small molecules and their targets. The suggested scope of data considered within this call is illustrated in Figure 1.</p> <p><b>Fig 1. Open Pharmacological Space : Scope</b></p> <p><b>Issues/Dependencies:</b> -Business Interfaces -Ownership</p> <p>This project will enable industrial and academic researchers to use computational methods to select the most relevant small molecule libraries and targets to support</p>

high throughput screening, cross screening and structure activity relationship (SAR) analysis, in support of drug discovery, safety and efficacy studies respectively.

### **Developing OPS Standards and Database Infrastructure**

The public domain contains a great deal of drug discovery relevant information however most of this data is effectively inaccessible. For example, the biomedical literature and patent corpus contains unstructured information on small molecule screening data and target structure activity relationships. Small molecule screens have also been published but are also largely inaccessible due to a lack of a standardized, semantically structured public repository for such data. In both cases, the lack of semantic standards for the representation of these data makes it difficult to reuse and integrate data. A similar situation also exists for information on potential and precedent molecular targets of small molecules – so called “druggable targets”. Although many excellent biological resources are present in the public domain, few are focused on drug discovery and there are few agreed standards for integrating target information with chemistry information.

The open access tool infrastructure proposed in this project aims to improve the accessibility of public domain drug discovery resources by interoperation with existing public domain systems.

### **The need for a collaborative approach**

A collaborative approach on this topic will provide the following benefits:

- Enable the transfer of know-how currently restricted to industry in a way that will improve public resources for drug discovery.
- The collaboration will significantly expand the range of data available whilst maintaining connectivity with existing datasets and resources
- Development of these standardised open resources for drug discovery will improve the structure and utility of results presented in text formats (e.g. publications, patent documents, etc). It will also allow easier curation from unstructured data formats into a structured format (e.g. text mining literature and patents).

### **Key objectives to be addressed**

To achieve the key objectives, to build sustainable informatics resources for drug discovery in the public domain, the following issues need to be addressed:

#### **Development of Robust Standards**

- Robust shared standards and vocabulary are required to enable integration of resources so that they can be queried with web services. Ideally these should be Open Biomedical Ontologies (OBO)-compliant (<http://www.obofoundry.org/>)
- Standards will enable development of workflows and analysis pipelines for transformation and translation of data and for building assertions between data (creation of knowledge)

#### **Development of Robust Web Services**

- Development of open source web services to enable drug discovery, examples include but are not limited to:
  - Services to profile small molecule screening libraries
  - Services to evaluate target tractability
  - Services to integrate target validation information
  - Services to profile compound QSAR properties

#### Development of a Secure Web-Service model

- This project will need to develop service models and infrastructure to allow secure submission and queries with proprietary data (e.g. compounds).

#### Maintenance Plan for Resources

- A realistic maintenance plan will be needed for resources developed during the term of this collaboration.

#### Open Access Resources

- The general guiding principle of this collaboration will be to create open access resources to provide the benefits as stated below.

#### **Benefit**

These resources are expected to significantly increase the public availability of small molecule data and molecular target information, as public and commercial organizations seek to utilize these resources to analyze their own data.

Such a repository would also be able to include small molecule data from chemical companies (providing molecular libraries), the patent and academic literature as well as ad-hoc submissions by research groups. As much of these data are within the public domain, it can be considered pre-competitive.

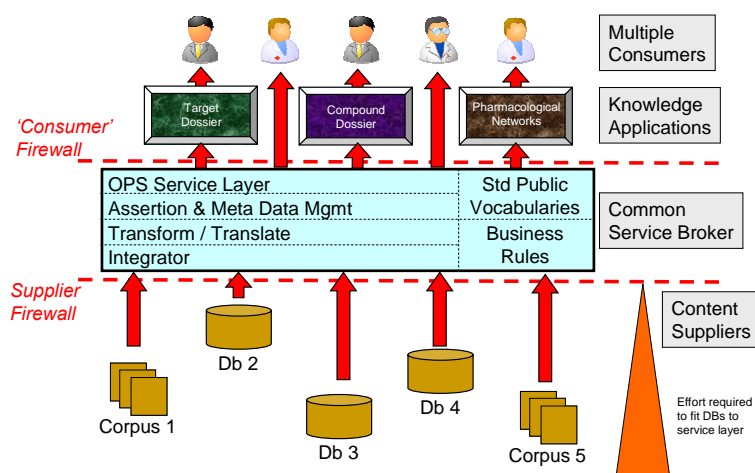
Building such a resource would be advantageous to industry as each company is currently duplicating significant effort in assembling target data, compound data and associated activity data themselves. This effort should address the extraction of these data from patents and journal articles, which is currently performed by many of the member companies on an individual basis. This would help to reduce the duplication of these complex, time-consuming operations across individual pharma companies.

#### **High level plans**

This project requires the identification of sources of target and pharmacological information, and liaison with those data providers to develop standards and mechanisms for data extraction and integration. Ultimately, a knowledgebase would be created that provides the widest range of publicly known drug-like small molecule space available, along with a knowledgebase of known druggable targets. Both resources should be possible to query in an integrated fashion. Additionally, tools for contribution and annotation of datasets by external parties (universities, chemical vendors, pharma) should be provided. Finally, provision should be made for the exploitation of the data, by derivation of models to aid efficacy and safety prediction, as well as the development of innovative visualisation approaches to ensure as many scientists as possible are able to derive value from the data.

		<p><b>Scope</b></p> <p>The work will be organised into two work streams.</p> <ul style="list-style-type: none"> <li>• Workstream 1 will consider the development of open standards and the integration of existing resources, extraction of historical data to enrich existing resources. The project will avoid creating new resources where viable resources already exist, focusing instead on the confederation of existing databases to an open standard. Where no viable resource exists, a new database may be generated or added to the scope of an existing database.</li> <li>• Workstream 2 will address the need to exploit the data and develop innovative algorithms, which address target ID, safety and efficacy questions within drug discovery.</li> </ul>
3	Key deliverables of the project	<p><b>Deliverables will be from two major work streams</b></p> <p>The exact nature of the work streams is flexible and will be agreed with the successful applicant consortium. A possible working model is described below:</p> <ul style="list-style-type: none"> <li>▪ WS1: Development of an OPS service layer and resource integration</li> <li>▪ WS2: Development of exemplar web services</li> </ul> <p>Project Initiation for WS2 may be staggered to allow for implementation of WS1.</p> <p><b>Work Stream 1: Open Target/Drug Pharmacology Service Layer</b></p> <p><b>Develop OPS Service Layer</b></p> <ul style="list-style-type: none"> <li>▪ Define or adopt existing standards in accordance with the research community</li> <li>▪ Construct service layer. Develop APIs to allow development of web services for data access, integration and analysis (Fig 2)</li> </ul> <p><b>OPS Resource Integration</b></p> <ul style="list-style-type: none"> <li>▪ Modify major public data repositories to operate through OPS service layer <ul style="list-style-type: none"> <li>○ Funding modifications for key resources to work to agreed standards will ensure the wider adoption of standards</li> </ul> </li> <li>▪ Integrate Drug Domain Resources <ul style="list-style-type: none"> <li>○ E.g. Bioassay data, Target/Drug interaction, SAR, PK/PD (see figure 1)</li> </ul> </li> <li>▪ Integrate Target Domain Resources <ul style="list-style-type: none"> <li>○ E.g. Druggability and Target Validation information</li> </ul> </li> </ul>

Fig 2. OPS Service Framework



**Work Stream 2: Exemplar Work Packages**

Develop Exemplar Services to test aspects of OPS Service Layer (Fig. 2). Proposals are intended as proof of concept of the functionality of the infrastructure developed by work stream 1. The final content of the services will depend on the consortium, some possible exemplar services are listed below:

**Target Dossier (Data Integration)**

Collate target info across diverse services (e.g. bioactive molecules, druggability, orthology, variation, expression, toxicology).

**Pharmacological Network Navigator (Data Visualisation)**

Develop of innovative visualisation techniques to increase understanding of small molecule-target relationships (e.g. Contrast properties of successful/failed drugs, profile compound libraries).

**QSAR Models (Data Analysis & Annotation)**

Draw together knowledge to develop algorithms for QSAR prediction, e.g. Blood Brain Barrier (BBB) penetration

4	EFPIA participants in the project	GSK, AstraZeneca, Pfizer, Lundbeck, Merck KGaA, Eli Lilly, Esteve
5	Role of EFPIA participants in the project	<p>The EFPIA participants will contribute the following to the project:</p> <ul style="list-style-type: none"> <li>• <b>Expertise:</b> Drug discovery expertise and project management and planning support for the project.</li> <li>• <b>Standards and Data Dictionaries:</b> EFPIA companies will contribute information on drug and target nomenclature which will be important for establishing robust standards</li> </ul>

## Knowledge Management – Open Pharmacological Space

		<ul style="list-style-type: none"> <li>• <b>Data:</b> At least three companies will contribute fully curated datasets of druggable targets. Comparison across these datasets will support the development of new methods for predicting druggability. EFPIA companies will also contribute drug discovery data, including pharmacological data, drug-response transcriptomics, target variation data, QSAR models.</li> <li>• <b>Software:</b> EFPIA companies will also contribute directly by development of software modules and web services</li> </ul>
6	Indicative duration of the project	The indicative duration of the project is 3 years.
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate from the EFPIA in-kind contribution to this project is EUR 10 million.
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	<p>The Applicant Consortium should already have a demonstrated track record in the development, integration and analysis of drug discovery data, including small molecule drug data and target data. The Consortium should also include members with experience of robust service level agreements for public data resources. Expertise in large scale data integration and in the development of semantic frameworks for data exchange would also be an advantage. Specific expertise on protein structural analysis and computational chemistry will also be critical.</p> <p>The contribution from the Applicant Consortium is expected to include all aspects of the following areas:</p> <ul style="list-style-type: none"> <li>• <b>Open Standards:</b> Development of standards for the representation of drug discovery data and provision of tools for the deposition of chemical and pharmacological data within the public domain.</li> <li>• <b>Data:</b> Extraction of chemical and pharmacological data from key public resources. Significantly expand the range of data currently available whilst maintaining connectivity with existing datasets and resources. In addition, provision of previously un-published data would be a significant advantage (e.g. existing academic or commercial datasets, proposals for new data generation).</li> <li>• <b>Software:</b> Development of innovative tools for integration, analysis and visualisation of drug discovery data leveraging the infrastructure developed in this project.</li> </ul>



## 9. Knowledge Management – Electronic Health Records (EHR)

0	Topic Code	IMI_Call_2009_9
1	Topic title	<b>Using Electronic Health Records (EHR) to Support and Enhance Medical Research</b>
2	Project description	<p><b>Background</b></p> <p>Electronic Health Records (EHR) contains an increasing wealth of medical information that could significantly advance medical research.</p> <p>Healthcare Organisations and the pharmaceutical industry in Europe both share a common goal: deliver the best possible personalised treatments and innovative medicines to improve patient outcomes. The industry believes that technological advances and broad implementation of EHRs in Europe can achieve this goal and accelerate clinical research.</p> <p>However, the European healthcare information environment is fragmented by lack of legal and technical standards, cost effective platforms, and sustainable business models. This has hindered medical research and clinical development:</p> <ol style="list-style-type: none"> <li>1. Protocols are designed without an understanding of real patient populations; design is sub-optimal</li> <li>2. Information on the location of patients meeting admission criteria is incomplete, slowing patient recruitment</li> <li>3. Recollecting patient data for clinical trials instead of using existing EHRs compromises cost-efficiency</li> <li>4. The present situation requires researchers to carry out studies in an isolated fashion in many locations rather than utilising a unified approach across the different research centres (economies at scale)</li> </ol> <p>The potential gains in efficiency and effectiveness for primary care afforded by rapid and secure access to patient healthcare data in electronic form are widely recognized today across the EU. About half of the member states are currently working on national e-health infrastructures.</p> <p>However, the potential contribution of EHRs to an even wider public health agenda has not been fully recognised. Interoperability of patient data between EHRs and medical research can transform today’s process of drug discovery, development and commercialisation, enable faster access for patients to effective new medications, provide improved patient outcomes, improve medication security and signal detection, and provide a key foundation for targeted (personalized) medicines.</p> <p>In spite of this, the pharmaceutical industry has generally avoided a clear commitment and cooperative effort with key actors in the healthcare arena (physicians and other healthcare professionals, academia, IT vendors, regulators, patients and their families/carers etc.) to explore ways in which the growing adoption of EHR can contribute to medical research.</p>

In addition, while EHR systems are being increasingly deployed across the EU, most of these systems have limited interoperability, even within a primary care setting, often being restricted to a single EHR system in a single site, as opposed to interoperability between multiple EHR systems at different sites, as well as across national borders.

Similarly, demonstrations of interoperability between EHR systems and electronic data capture (EDC) systems used by the pharmaceutical industry in clinical research have been limited to a 1:1, single vendor, single pharmaceutical company context.

Some of the difficulties involved in bridging the gap between primary care and medical research can be grouped as follows:

**Legal & data protection Issues:** The processing of personal data relating to a person's health is particularly sensitive and subject to special protection. The existence of such data in electronic form makes it vulnerable to access by individuals other than those with a legitimate need, e.g. a doctor involved in primary patient care and governed by doctor-patient confidentiality. In general, outside of this primary care context, such data should be used only in an anonymous form. This raises questions about who should perform this aggregation and under what circumstances, as well as questions of data ownership and intellectual property rights, which all remain unanswered.

**Organisational & Governance Issues:** There is a wide range of interested stakeholders (e.g. clinicians, public health authorities, insurers/payers, academic and industrial researchers, IT vendors, pharmaceutical companies, regulatory authorities, patients and caregivers). Each of these stakeholders has different needs and perspectives on the utility of EHR and on the requirements of EHR systems. In general, however, there is limited awareness and/or understanding of these needs between the different stakeholder groups. An attempt to bridge the gap between data hosted within the primary care and the medical research environments suggests an organisational model that independently govern any data transactions between these parties. Such organisation is required for proper governance and to protect the interests of the patients whilst optimising the benefits of medical research via EHR.

**Technical & Semantic Considerations:** Currently, individual, isolated and disparate EHR systems and solutions will prevail without widespread agreement on general IT concepts and specific technical standards. Software tools able to support interoperability and integration between EHR and between EHR entries and EDC for clinical trials and basic research data are urgently needed. In addition to interoperability, using EHRs for seamless, collaborative care and for the various benefits mentioned earlier is only feasible when all those involved in health services can understand and act on this information, even when operating in different languages...

While there is much work being done in this area by many interested parties, a clear demonstration of what can be achieved with an interoperable EHR environment is now required before we can move to the next level of implementation.

Any progress made by organisations such as the NHS' "Connecting for Health" in the UK and those outside the EU need to be identified and evaluated if relevant.

### **Problem statement**

This gap between technology solutions, regional diversity, individual approaches, and the lack of a **common viable model across Europe on how to use EHR information** impedes the advancement of medical research, the improvement of healthcare, and the enhancement of patient safety.

A number of initiatives to date have attempted to bridge this gap, usually by establishing “Trusted Third Parties” to broker data between healthcare, health administration, and medical research in a safe, secure, and ethical manner.

Such initiatives are typically focused on a particular country or region, a specific therapeutic area, and involve a narrow range of stakeholders. These initiatives have achieved a level of success and maturity that warrants the development of a harmonized model across all European countries and regions.

Therefore, the design, development and implementation of a sustainable business model will enable a credible system of health information to be connected at a regional/national level from many data sources to all qualified users of data, such as medical researchers and healthcare providers.

### **The need for collaborative approach**

Along with patients, both the public and private sectors benefit from the accelerated delivery of innovative healthcare as a result of this program. However, public or academic bodies currently hold most data.

To ensure the efficient and secure exchange of healthcare data, so that all benefit through safer, more effective and affordable care, IMI should govern and optimise the interests of both parties for the benefit of the European economy and European patients.

### **Key questions to address**

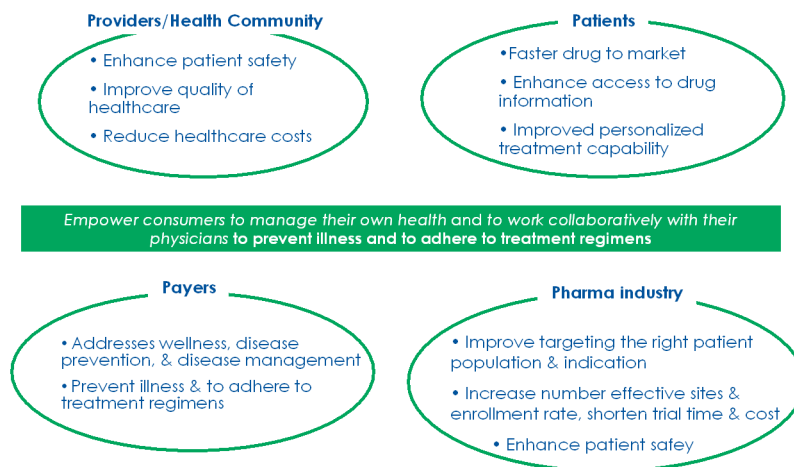
***A sustainable business model for the implementation of EHRs in Europe is required*** to realize the huge benefits that are possible through better health information.

1. How to leverage aggregated EHR data to advance medical research to:
  - a. Improve targeting of patient populations and indications?
  - b. Increase the number of effective sites and enrolment rates, shorten trial times and costs?
  - c. Reduce trial costs by minimising the amount of patient data to be collected?
2. How to achieve safer and more evidence-based diagnoses and treatments for patients?
3. How to align the EHR and health information capabilities of the varying initiatives in different countries, regions, disease areas, and stakeholders (e.g. pooling for a richer data set) to enhance patient safety and speed promising new drugs to market?

4. How to enable the cross-border exchange of knowledge and experiences?
5. How to provide a framework for other areas in Europe (unfamiliar with EHR guidelines and implementation) to enhance the adoption of a similar solution?

Vision: Improve healthcare and accelerate clinical research with EHRs (accessed through sustainable and scalable platforms across Europe) for the efficient and controlled connection of patient data to medical research efforts.

EHRs benefit clinical practice and public health: Coordinated and collaborative initiatives are needed in Europe to support medical research and realise the huge benefits for individual citizens, the healthcare systems, and society in general. For the patient, implementing EHRs can provide easier access to personal medical records, which enables a more holistic approach to healthcare through closer coordination between care providers and the patient. This ultimately results in safer and more evidence-based diagnoses and treatments (provided their records are suitably protected against unauthorised access).



*Four perspectives of potential benefits from the IMI EHR project to establish a sustainable EHR data framework*

### High-level plan

The project is expected to provide the key deliverables outlined below in section 3; including a definition phase (i-iii), a pilot execution and analysis phase (iv), followed by a scale-up implementation phase (v); precise definition of these phases will be established by the full consortium.

3 Key deliverables of the project

- The applicant consortium is expected to bring forward innovative approaches / strategies for the development of:
- i. A business model for electronic healthcare data for medical research purposes, to share and access EHR data, to more efficiently connect patients to research.
    - Through a standardised and scalable platform(s) (may include system, organisation models, standards, processes, technology, etc) that efficiently enable healthcare professionals and medical researchers (e.g. in academia, industry etc.) to share data
    - This platform should ensure:

- i. Information is shared in an ethical and safe way, complying with all necessary legal requirements designed to protect patient rights and interests (e.g. confidentiality).
- ii. In a sustainable and scalable way across European regions and/or countries
- ii. A framework and guidelines for emerging EHR initiatives across Europe that will enable the consistent replication of point (i) above and adoption of best practices as well as support and adoption of recognized global healthcare standards to enable interoperability
- iii. A set of measures that will demonstrate the success of pilot projects and enable their implementation across the European region
- iv. Pilot projects that demonstrate the scalability, security, integrity, and performance of the platform or solution within European regions. These pilot projects may include, but are not limited to:
  1. Accelerated clinical trial patient recruitment
  2. More efficient protocol feasibility
  3. More cost effective clinical trials
- v. Explore feasible opportunities enabled by this platform and describe how to realise the benefits. This may include but is not limited to:
  1. Safety
  2. Outcomes research
  3. Line extensions
  4. Pharmaceutical economics and population health

Proposals are expected to consider the following constraints:

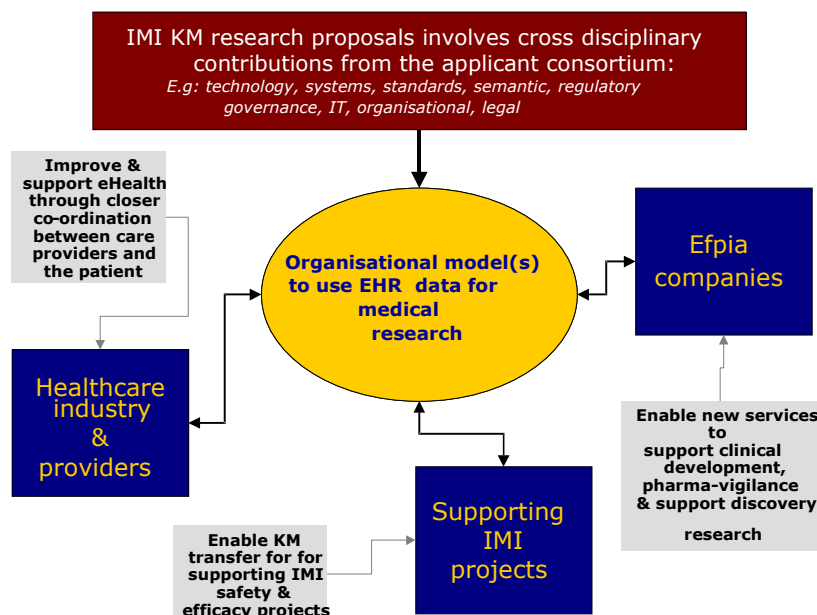
A number of pilot projects are already underway, demonstrating the ability to leverage EHR data for clinical research; these projects typically concern a particular region, therapeutic area, and local stakeholders.

#### **Expected outcome**

The expected outcome of this project will be the **demonstration of the interoperability** of multiple initiatives across different countries, different therapeutic areas, and varying local and national stakeholders.

Moreover, the interoperability between such initiatives (in terms of standards, processes, organisational model) should allow for the **exchange of knowledge**

**and expertise** across these initiatives. And on the basis of best practices and lessons learned within and across these initiatives, a ‘best practices’ **framework** should be developed to allow other regions to effectively adopt such solutions. These are the three components we deem essential toward developing a **sustainable model** for the convergence of clinical research and clinical care across Europe.



**Overview of the objectives of the research proposal for providing EHR data for medical research in EU**

Due to the technical complexity, the broad range of stakeholders, and a significant degree of uncertainty, ambiguity and risk, successful projects within this call for proposals are expected to create a rich environment for interaction and networking across a broad range of functional disciplines in the patient care and medical research settings.

<p>4 EFPIA Participants in the Project</p>	<p>Amgen, AstraZeneca, E Lilly, GSK, J&amp;J, Merck KGaA, F. Hoffmann - La Roche AG and Sanofi Aventis</p>
<p>5 Role of EFPIA participants in the project</p>	<p>The EFPIA participants will contribute:</p> <ul style="list-style-type: none"> <li>• Commitment of subject matter experts, knowledge and expertise in a broad range of functional areas, including but not limited to:             <ul style="list-style-type: none"> <li>○ Clinical trial design</li> <li>○ Clinical trial execution</li> <li>○ Project management</li> <li>○ Clinical data management / Data analysis / Statistics / IT / Data standards</li> <li>○ IT / Knowledge Management</li> </ul> </li> </ul>

Knowledge Management – Electronic Health Records (EHR)

		<ul style="list-style-type: none"> <li>○ Epidemiology / Health outcomes research / Safety</li> <li>○ Business analysis / Strategic planning / Business planning</li> <li>○ Legal, Ethics policy, Data privacy, Intellectual property issues</li> <li>○ Financial control and audit capability</li> <li>● The use or provision of facilities and operational support including but not limited to:             <ul style="list-style-type: none"> <li>○ The cost of salaries, hosting, training, conferences, travel and expenses associated with EFPIA members participating in this program</li> <li>○ Providing infrastructure at the discretion of EFPIA members (e.g. to host meetings and potentially use of specialized hardware, software, datasets etc.)</li> <li>○ Funding for specialized consultancy services at the discretion of EFPIA members, e.g. privacy enhancing technologies, Legal, IT developers</li> </ul> </li> </ul>
6	Indicative duration of the project	The indicative duration of the project is 5 years.
7	Indicative total in kind contribution from the EFPIA companies	The provisional estimate for the EFPIA in-kind contribution to this project is EUR 6 million.
8	Indicative expectations from the “Applicant Consortium” (e.g. SME’s, academia, patient organisations, regulators and non-EFPIA companies)	<p>The contribution from the Applicant Consortium is expected to include commitment of subject matter experts, knowledge and expertise to address the deliverables outlined in section 3 above. Representation from the following areas is recommended:</p> <ul style="list-style-type: none"> <li>● Academia, Healthcare institutions e.g. hospitals, Legal, European legislative experts, Regulatory, Ethics representation, Patient organisations, Small Medium Enterprises, IT, e.g. privacy enhancing techniques etc.</li> </ul> <p>It is recommended that the Applicant Consortium leverage the know-how and expertise from, and connect with existing networks and projects. Examples include, but are not limited to: ESFRI, EHR Roadmap, eHealth for Safety, UK Connecting for Health; ASTEC; FP6-RIDE, FP6-PALLIANET, FP6-SEMANTICHEALTH, FP6-MULTI-KNOWLEDGE, FP6-Q-REC, FP6-C-CARE, WIDENET; or other IST-RTD and national projects, etc.</p>