



2010 Call for proposals

Innovative Medicines Initiative

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Table of Contents

GENERAL PRINCIPLES	2
CALL TOPICS 2010	6
1. IMPROVING THE EARLY PREDICTION OF DRUG INDUCED LIVER INJURY IN MAN	7
2. IMMUNOGENICITY: ASSESSING THE CLINICAL RELEVANCE AND RISK MINIMIZATION OF ANTIBODIES TO BIOPHARMACEUTICALS	13
3. IMMUNOSAFETY OF VACCINES – NEW BIOMARKERS ASSOCIATED WITH ADVERSE EVENTS (EARLY INFLAMMATION, AUTOIMMUNE DISEASES AND ALLERGY)	19
4. IMPROVING THE PRECLINICAL MODELS AND TOOLS FOR TUBERCULOSIS MEDICINES RESEARCH	24
5. TRANSLATIONAL ENDPOINTS IN AUTISM	28
6. DEVELOPMENT OF PERSONALIZED MEDICINE APPROACHES IN DIABETES	33
7. FOSTERING PATIENT AWARENESS ON PHARMACEUTICAL INNOVATION.	38

GENERAL PRINCIPLES

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-competitive¹ 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 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 2010 Call for proposals will have 7 topics addressing three of these strategic pillars:

- Predictivity of Efficacy Evaluation
- Predictivity of Safety Evaluation
- Education and Training

Before submitting an Expression of Interest, the various Call Documents, such as *IMI JU Rules for submission, evaluation and selection of Expressions of Interest, Rules for Participation, the IMI Intellectual Property Policy*, etc., shall be considered carefully. These documents are published on the IMI website www.imi.europa.eu at the time of the 2010 Call launch.

The size of each consortium should be adapted to the scientific goals and the expected key deliverables.

DURATION OF THE PROJECTS

The indicative duration of each project is 5 years.

FUNDING OF THE PROJECTS

The total available financial contribution from the IMI JU to participants eligible for funding will be up to EUR 114 million, matching the in-kind contribution by the research based companies that are members of the European Federation of Pharmaceutical Industries and Associations (EFPIA).

¹ 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.

GENERAL PRINCIPLES



An indicative range for the IMI JU financial support to the Applicant Consortium would be between EUR 5-20 million for the topics addressing the two following strategic pillars: Predictivity of Efficacy Evaluation & Predictivity of Safety Evaluation.

An indicative range for the IMI JU financial support to the Applicant Consortium would be up to EUR 5 million for the Education & Training related topic.

The Applicant Consortia shall keep in mind that the budget of each Expression of Interest should be adapted to the scientific goals and the expected key deliverables of the project.

SYNOPSIS OF CALL AND EVALUATION PROCESS

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

Each topic included in the 2010 Call for proposals is associated with a group of pharmaceutical companies that are members of EFPIA² (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' contributions³ 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, Small and medium sized enterprises (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, as outlined in topic texts below.

Each EoI submitted will be reviewed by independent experts according to predefined evaluation criteria. The Applicant Consortia with the higher 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 according to predefined evaluation criteria.

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.

For full details applicants shall refer to the *IMI JU Rules for submission, evaluation and selection of Expressions of Interest* published on the IMI JU website www.imi.europa.eu at the launch of the 2010 Call.

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

³ In kind contribution is e.g. personnel, clinical research, equipment, consumables.

ELIGIBILITY TO PARTICIPATE IN PROJECTS AND TO RECEIVE FUNDING FROM THE IMI JU

Criteria of eligibility to participate in IMI projects and the criteria to receive funding from IMI JU are specified under the *Rules for participation* published on the IMI JU website www.imi.europa.eu at the launch of the 2010 Call.

The IMI JU 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 (excluding subcontracting costs and the costs of resources made available by third parties which are not used on the premises of the beneficiary) applies⁴. For full details Applicant Consortia are invited to refer to the *Rules for Participation* (www.imi.europa.eu).

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

IMI INTELLECTUAL PROPERTY POLICY

The IMI Intellectual Property Policy (IMI IP policy, www.imi.europa.eu) has been developed to be aligned with the objectives of the IMI JU to ensure knowledge creation, together with its swift dissemination and exploitation, and fair reward of innovation.

The IMI IP Policy sets out inter alia basic principles regarding ownership of Background and Foreground, access rights depending on the entity and the purpose, and dissemination.

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.

The IP policy does not foresee all details and does not aim to answer to all possible practical situations participants may be faced with. Flexibility is provided for participants to establish the most appropriate agreements (e.g. the project agreement) serving each individual project objectives, and considering the wider IMI objectives.

Applicant Consortia are invited to read carefully the Guidance Note on the IMI IP Policy (www.imi.europa.eu) whose purpose is to explore ways to handle related issues and pitfalls that participants may encounter during the preparation, negotiation and completion phases of the Grant Agreement and Project Agreement.

PROJECT AGREEMENT

⁴ Funding rules related to indirect costs are currently under discussion. Therefore, the applicable rules might be subject to a modification following a decision of the IMI Governing Board in this regard.

GENERAL PRINCIPLES



Innovative Medicines Initiative

All participants of a selected IMI project are requested to negotiate and sign a project agreement between them before the grant agreement is signed with the IMI JU.

The Project Agreement is a private agreement which the participants of an IMI project conclude amongst themselves to implement the provisions of the Grant Agreement and to regulate internal issues related to work organisation and objectives for each participant, consortium governance, intellectual property, financial and other matters.



Innovative Medicines Initiative

CALL TOPICS 2010

1. IMPROVING THE EARLY PREDICTION OF DRUG INDUCED LIVER INJURY IN MAN

BACKGROUND

Many different classes of therapeutic medicines licensed for clinical use are known to cause Drug Induced Liver Injury (DILI) in man, and the cumulative DILI burden on professional health services coupled with patient well-being and/or mortality is high. Prior to licensing, DILI observed during clinical trials or preclinical safety evaluation in *in vivo* animal species may lead to serious delays in drug development, and termination of entire project portfolios. In addition, DILI is an important and leading cause of withdrawal, cautionary labelling and restricted usage of licensed drugs.

Some drugs cause dose-dependent, reproducible "Type A" DILI (e.g. paracetamol), which can be replicated readily in various animal species and therefore is evident during pre-clinical safety testing. However, by far the most common pattern of DILI observed in man is idiosyncratic. This occurs only in certain susceptible patients and is not overtly dose dependent. The incidence of idiosyncratic DILI caused by some drugs can be high as 1 in 100 patients (e.g. chlorpromazine), but more typically lower at 1 in 10,000 patients (e.g. halothane). Idiosyncratic DILI is of major concern because it is not predictable from pre-clinical safety assessment studies and typically is not evident until late clinical trials or after regulatory approval.

Numerous promising new technologies and approaches have been described or are being developed which replicate many of the key biological processes implicated in both Type A and idiosyncratic DILI. These range from simple cell systems to complex *in vivo* models, and may have the potential to enhance prediction and risk assessment of DILI in man if used during drug discovery and/or pre-clinical development.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

For academic groups, an important restriction has been lack of access to valuable hepatotoxic reference compounds, which are known by the pharmaceutical industry to cause DILI and which led to termination of development (from preclinical safety testing in animals to late clinical trials).

Within individual pharmaceutical companies, efforts to develop best practice assays have been hampered by the complexity of the science, uncertainty about which of the many potentially useful model systems justify possible investment, and lack of clarity on the most effective strategy for DILI detection.

For this reason, only a coordinated and collaborative approach of activities between multiple institutions will permit significant progress towards tackling DILI.

OVERALL OBJECTIVES

The primary goal of this project is to identify new assays and models, which can be used during drug discovery and early non-clinical development to support design, ranking and selection of drugable candidates that have low propensity to cause DILI in man.

The successful proposal will have as objectives:

- to identify and validate an improved panel of in vitro “best practice assays” for predicting DILI in the human population (major objective)
- to explore and understand the relationship between in vitro assay signals and DILI in vivo, in preclinical test species and in man (supportive)
- to develop and validate novel Systems Modelling approaches that integrate multiple preclinical data types to improve prediction of DILI in man (supportive)
- to enhance shared understanding, between academia, pharma and regulatory agencies, of the value and limitations of new and existing approaches for DILI hazard identification and risk assessment (supportive)

EXPECTED KEY DELIVERABLES

New technologies:

- a panel of improved and/or novel in vitro assays which enhance prediction of DILI in man.
- novel in vivo preclinical models for measuring safety of candidate drugs and decision-making within drug discovery and early non-clinical development.
- industrial and regulatory acceptance of the added value of incorporating early screening tests as part of the safety evaluation of novel drug candidates.
- understanding the most appropriate use of preclinical approaches for replacement, refinement and reduction of animals during safety assessment of new drugs.

New data and knowledge:

- relationship between novel and validated assays generated within the scope of the project and relevance to man.
- uptake of “best practice” principles, standards and procedures.
- availability of data generated through timely publications, presentation of data and web-based access.
- publication of findings contributing to biological mechanisms underlying DILI, susceptibility to DILI, and inter-individual variability within different patient populations at risk.
- computational quantitative structure-toxicity models that identify substructures associated with high DILI risk
- systems biology models which integrate various data types allowing improved DILI hazard identification and risk assessment.

Biological samples:

- availability of tissue and bio-fluid samples to support and help identify improved DILI biomarkers and DILI mechanisms.

CONSORTIUM

EFPIA Participants

(as of 1 September 2010)

Abbott, AstraZeneca, Bristol-Myers Squibb, Glaxo-SmithKline, Johnson&Johnson, Lundbeck, Novartis, Orion, Pfizer, Sanofi-Aventis, Servier, UCB.

Applicant Consortium

(to be selected on the basis of the submitted expression of interest)

The Applicant Consortium is expected to be a multi-disciplinary body and to enable effective communication between key stakeholder groups (academia; SME technology service providers and regulatory agencies). The consortium will have experience and expertise in:

- providing an integrated approach to ensure appropriate interpretation of in vivo relevance of in vitro findings,
- building and interrogate useful risk assessment models,
- developing and working with cell systems,
- mathematical modelling.

Participation of SMEs is considered to be especially important for evaluation and validation of in vitro models, and for provision of cells which will be utilized in these models

Whilst it is acknowledged that regulatory acceptance of new assays and risk assessment tools arising from the work may not be a realistic short term goal, it is an important long term objective and needs to be considered as the work progresses. Therefore Regulatory bodies will be invited to participate and to offer input as data is generated.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution on the defined deliverables in synergy with the EFPIA consortium.

The below architecture for the full proposal is a suggestion, different innovative project designs are welcome, if properly justified.

Work Package 1.

Pharma, academia and SMEs will jointly contribute to the overall evaluation of evidence-based scientific data, in order to select the most promising in vitro and in vivo models for evaluation and to select opportunities for development and evaluation of new models. Key sources of scientific information arising from in-house data contributed by participating companies, and expertise from academic partners and SMEs, will be assessed collectively.

EFPIA Contribution:

- Data that aids in selection of the most appropriate compounds and models systems to be studied e.g. details of assays to assess mitochondrial toxicity, BSEP inhibition, phospholipidosis, steatosis, and metabolite mediated toxicity.
- Reagents or expertise, e.g. antibodies for use as tools, assay formats applicable both in pre-clinical and clinical settings, and novel cell systems arising from stem cell technology.

Work Package 2-3 and 5.1: In vitro predictive assays for DILI.

This work package should build on the many novel and potentially useful model systems and analytical endpoints that have been described or are currently being developed.

- These may include well characterised models (e.g. cultured hepatocytes or hepatocyte derived cell lines) as well as emerging models (e.g. co-cultures which include hepatocytes and non-parenchymal cells; bioreactors; stem cell derived human culture systems).
- Model systems that maintain differentiated cell polarity, 3D cell architecture and enable inter-cellular interactions plus long term culture models may be especially desirable, although simpler models may also be appropriate.
- Mechanistically driven emerging approaches that can provide insight into currently intractable issues (e.g. immune-mediated mechanisms), and that take account of potential individual susceptibility factors (e.g. use of iPSC) derived from patients who have developed DILI, to explore the impact of genetically determined susceptibility), are especially desirable.
- Justification of model systems and endpoints for investigation will be required, based on pre-defined objective criteria which include: relevant biology; tractability; ability to address known DILI mechanisms; target cell types; relevance to man; throughput, amenability to scale up and automation; potential cell access and/or ethical issues (especially for human cells).
- Optimisation of biology; assessment of biological and mechanistic relevant endpoints; standardisation of protocols; analysis of appropriately annotated reference compounds (hepatotoxic and non-hepatotoxic, including marketed drugs), so that DILI positive and negative predictivity can be determined and structure-toxicity relationships can be explored.
- The work packages should address multiple DILI mechanisms, including but not restricted to: mitochondrial injury; reactive metabolite formation; biliary transport inhibition; and immune mechanisms.
- When selecting endpoints, emerging knowledge of processes involved in human liver development, function and repair processes will need to be considered. For some models, assessment of multiple physiologically-relevant endpoints (e.g. via high content cell imaging; 'omic profiling) may add significant value, as may a combination of endpoints.
- Studies that explore the impact of inter-species variability (between animals and man), and potential inter-individual variability in man (e.g. due to differences in energy source, oxygen tension, hormonal factors, glutathione status, genetics etc.), are an integral component of this initiative.
- For assays that meet pre-defined validation criteria, evaluation of reproducibility (within- and between-laboratory) will be needed.

EFPIA Contribution:

Experimental support of in vitro assay evaluation and validation and more specifically:

- Supply of test compounds
- Intellectual support to experimental design
- Experimental support of assay evaluation, assay scale up, automation and cross-validation, especially where this requires complex instrumentation or technology (e.g. high content cell biology; high throughput assays).

Work Package 4 and 5.2: In vivo preclinical models.

This work package should cover the following points:

- In vivo studies in preclinical species, undertaken with selected drugs known to cause DILI in man and non-hepatotoxic drugs. These will provide improved insights into DILI mechanisms and DILI hazard/risk assessment that complement information provided by in vitro assays. Such work may also enable development and validation of preclinical models that provide improved prediction of DILI in man, when compared with standard regulatory safety studies.
- The work is expected to require repeat dose safety studies undertaken using selected compounds in animal strains used in regulatory safety studies within pharma, and also evaluation of promising new models (e.g. humanized mice; knockout or humanised/transgenic mice; animals with humanised immune systems; human disease models). The studies may also explore impact on DILI of variables known to occur in man, e.g. underlying disease, diet, gut microbiome, concomitant medications etc.
- It is anticipated that evaluation of conventional indices of overt liver injury (microscopic tissue histopathology, and serum liver markers e.g. ALT, bilirubin etc.) will be combined with evaluation of compound-induced biological effects indicative of early stages of liver dysfunction or tissue adaptation, incorporating methodologies such as LC-MS, gene expression profiling, protein expression profiling and metabolomic/metabonomic profiling.
- Evaluation of drug specific immune responses (antibody or cell mediated) are encouraged, since preclinical models that reproduce immune mediated DILI continue to be a major unmet need.

EFPIA Contribution:

Repeat dose preclinical safety studies, and more specifically

- Study design and live phase of studies
- Sample analysis by conventional clinical chemistry analysis and liver histology
- Additional evaluations when considered appropriate (e.g. immunohistochemistry, gene expression analysis; metabonomic analysis; ex vivo immune assays).

Work Package 6-7: Correlation & statistical analysis, Systems modelling.

This work package should include:

- Data analysis and interpretation, including statistics and bioinformatics, of the data generated in work packages 2 to 5.
- Mathematically derived, physiologically-based Systems Models, which integrate multiple data types obtained from in vitro and in vivo assays with data on compound uptake and clearance in vivo, and/or other parameters, have the potential to improve markedly DILI hazard identification and risk assessment. Use of the data generated in the project to build and test such models is therefore encouraged.
- Modelling that builds on approaches used currently to predict drug doses in man and drug-drug interactions may be most productive.
- Successful models should accurately describe differences in DILI observed between doses, between species and between in vitro and in vivo.

EFPIA Contribution:

Data analysis and informatics

Work Package 8: Communication and publication.

Proactive data and knowledge sharing between the key stakeholder groups (which will include for example academia, pharma, and regulatory agencies) will be required to provide shared understanding of new progress in DILI hazard identification and risk assessment.

EFPIA Contribution:

Data and scientific expertise

Work Package 9: Project Management.

This work package will address the strategy and implementation of the project management encouraging regular meetings and interaction between sub-groups and teams, to coordinate the work effort.

- Each work package should have a work package leader who will be responsible for ensuring the deliverables are planned in conjunction with an Executive Committee and Steering Committee.
- Each work package will encompass different workloads throughout the duration of the project. Progress will be monitored through regular project meetings involving all participants.

EFPIA Contribution:

Project Management

Glossary: ALT: aspartate alanine transferase; BSEP: bile salt export pump; DILI: Drug-Induced Liver Injury; IP: Intellectual Property; iPSC: Inducible Pluripotent Stem Cells; LC-MS liquid chromatography-mass spectrometry; SME: small-medium enterprise;

2. IMMUNOGENICITY: ASSESSING THE CLINICAL RELEVANCE AND RISK MINIMIZATION OF ANTIBODIES TO BIOPHARMACEUTICALS

BACKGROUND

The induction of an unwanted immune response to a biological drug can lead to the formation of Anti-Drug Antibodies (ADA) and immunogenicity is now widely recognized as a central feature of protein therapeutics. To assess immunogenicity a risk-based approach is adopted involving assay development/validation strategies and evaluation and stratification of clinical results. Recently published regulatory guidelines on immunogenicity testing (EMA/CHMP/BMWP/14327/2006) outline strategies aimed to standardize assay development and validation. Implementation of these guidelines is expected to facilitate data interpretation and lead to improved detection of ADA.

It is now known that even fully human compounds can induce the formation of ADA, and that the likelihood of a patient developing an immune response is dependent on multiple factors, including the intrinsic properties and mode of action of the compound, route and duration of administration, type of disease, age and genetic background of the patients, and concomitant treatment.

Due to the high variability in antibody responses observed, a comprehensive analysis of immunogenicity data and its relationship to safety and efficacy parameters across multiple products is needed in order to obtain a better understanding of the conditions and factors that are most likely to promote the development of clinically relevant antibodies.

Although a large amount of information is available within individual pharmaceutical companies, patient registries and academic institution, data are currently not being shared, making such an analysis not attainable. In addition, various companies have invested significant effort towards the development of tools that can be used to predict clinical immunogenicity. These technologies have not yet been evaluated and standardized across the industry, and their outcomes, including correlation to actual observed immunogenicity and clinical sequelae, is available only within individual companies.

To address these issues and drive the development in this field forward, a greater collaboration between individual companies and academia is needed.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

In order to significantly influence the way predictive and clinical immunogenicity data is generated and interpreted it is essential to foster collaboration between pharmaceutical industry, academia and regulators.

Reaching consensus on immunogenicity terminology, clinical relevance of ADA, assay strategies, predictive value of preclinical tools and guidelines will require sharing of

expertise and data sets in order to gain sufficient information to drive recommendations in this complex field.

OVERALL OBJECTIVES

The overall aim of this project is three-fold:

- Investigation of the clinical relevance of biopharmaceutical-associated immunogenicity in order to increase patient safety, and optimize drug development.
- Evaluation of the predictive value of existing tools and newly developed *ex vivo* methods, along with investigations into the immunological mechanisms that form the basis of the development of anti-drug antibodies. An increased understanding of these tools and mechanisms will result in improvements of existing and development of innovative predictive technologies. In addition, this work may ultimately lead to the identification of patient stratification markers, and reduce the risk of immunogenicity.
- Provide data-driven feed-back to regulators and healthcare professionals and to develop medical professional educational materials.

EXPECTED KEY DELIVERABLES

- Establishment of a database to house the selected biopharmaceutical products' longitudinal information relevant to immunogenicity, including prediction data, patient characteristics, exposure, clinical outcomes, pharmacokinetics, *ex vivo* data to get a better understanding of the underlying immune response, assays for ADA detection and characterization and the anti-drug antibody responses.
- Improved understanding of the clinical relevance of ADA, with special focus on pre-existing, non-neutralizing, low titer and transient antibodies.
- Evaluation of different technologies for detection of ADA.
- Comprehensive statistical analyses of the gathered information in order to assess the correlation of prediction tools with immunogenicity assay results and clinical outcomes.
- Evaluation of the relevance of the different factors used in the risk-based approach, (such as route of administration, level and frequency of dosing, disease population etc.) to immunogenicity and potential identification of patient stratification markers.
- Better understanding of the value of prediction tools.
- Identify early activation biomarkers as potential predictors of immunogenicity.
- Data driven feed-back to health authorities regarding factors influencing the clinical relevance of immunogenicity.
- Education and training material for dissemination to health care professionals.

CONSORTIUM

EFPIA Participants

(as of 27th September 2010)

GlaxoSmithKline, Novartis, Pfizer, Astra Zeneca, Sanofi Aventis, Merck Serono, NovoNordisk, Bayer Schering Pharma

Applicant Consortium

(to be selected on the basis of the submitted expression of interest)

The Consortium should include the necessary expertise to:

- set up a central database that will store information pertaining to drug type, patient, immunogenicity (prediction tools, assay and clinical results), and clinically relevant safety and efficacy data for various selected marketed biopharmaceuticals.
- to thoroughly evaluate and interpret the data.
- to perform in vitro and ex vivo immunology studies
- to perform genotyping studies

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution on the defined deliverables in synergy with the EFPIA consortium.

The below architecture for the full proposal is a suggestion, different innovative project designs are welcome, if properly justified.

Workpackage 1: Identification and description of immunogenicity relevant data.

Three task forces may be formed in this Workpackage:

- an immunogenicity expert task force with members from academia, patient registers, and pharmaceutical companies,
- a clinical task force with clinicians from academia and industry and
- a predictive immunogenicity task force with members from academia, SMEs and pharmaceutical companies. These task forces should lead an effort to provide clear definitions around terms and concepts related to immunogenicity, its prediction and associated clinical events (e.g. transient response, pre-existing ADA).

Representatives from these task forces should:

- liaise with other experts in the field through interactions with various associations, e.g., EIP, AAPS and AAI and regulatory agencies to reach broader consensus on terminology and concepts,
- be responsible for identification, and selection of parameters/ tools that might be critical to successful data analyses and interpretation, including evaluation and selection/prioritization of the available prediction tools, and translation of immunogenicity data generated by different assays into a more standardized format,
- evaluate and select the available immunogenicity and clinical data from selected marketed biopharmaceuticals for entry into the database.

EFPIA Contribution:

Experts to participate on each of the three task forces.

Workpackage 2: Evaluation and development of predictive immunogenicity tools.

The aim of package 2 is

- to investigate the predictive value of existing tools and to further elucidate the immunological mechanisms which underlie the development of anti-drug antibodies. The predictive tools can come from the EFPIA companies and the public consortium. The increased understanding of the immunological mechanism will finally allow improvement of existing as well as establishment of innovative predictive technologies and to identify potential stratification markers, leading on the long run to the development of less immunogenic compounds.
- In order to assess and develop the prediction tools, a representative set of marketed biopharmaceuticals will be selected. This set may include various TNF-alpha blockers, IFN- beta compounds and clotting factors as a certain amount of immunogenicity data is already available in the public domain and patient samples may be available or obtainable for these biopharmaceuticals.
- The main focus of this package will be on those prediction tools that deal with the interactions between T helper and antigen presenting cells, as these interactions are important to the development of anti-drug antibody responses. One of these prediction tools is the Human Artificial Lymph Node System. The most relevant in silico and in vitro prediction tools will be applied to the selected biotherapeutic drugs in order to identify potential T cell epitopes.
- Furthermore patient derived blood samples will be used to detect T cell epitopes ex vivo from patients treated with the selected biotherapeutics.
- The genotype of genes currently presumed to be important for immune reactions to biotherapeutic proteins will also be determined from these patients.

EFPIA Contribution:

- Provide expertise in the selection and prioritization of prediction tools with an emphasis on those dealing with interactions between T helper and antigen presenting cells.
- Provide certain proprietary prediction tools including in silico and in vitro for evaluation.
- Provide expertise in immunogenicity assay development, validation, and data interpretation.
- Provide scientific input for innovative approaches to further assay methodologies and ADA characterization.
- Scientific input regarding innovative approaches to immunogenicity prediction technologies.

Workpackage 3: Establishment of a database for clinical and predictive immunogenicity and patient-related safety and efficacy data

- A database will be set-up containing predictive and clinical immunogenicity as well as patient-related data from post marketing safety programs of a selected set of marketed biopharmaceuticals. Patient registries will be the main data source, and data from individual pharmaceutical companies will be used to supplement the database where possible.
- If needed, the data will be handled through an Honest Broker System to remove patient identifiers and maintain product and data confidentiality.

- As assay methodologies vary for each product, detailed information about the assays will be entered into the database and the clinical impact of ADA resulting from the different assay techniques will be assessed. The collection of ADA data in a partly blinded manner from different drug projects with significant numbers of treated patients will enable the statistical evaluation of the clinical impact of different ADA categories (e.g., pre-existing vs. newly formed ADA, high vs. low titer, neutralizing vs. non-neutralizing, transient vs. persistent) at different time points and for different drug classes (e.g., monoclonal antibodies, recombinant proteins).
- Furthermore, some marketed drug candidates will be included where patients are still on treatment with the selected biotherapeutic and available to provide blood samples in order to apply the prediction tools.
- The resulting information will be entered into the database, thus allowing establishment of a link between prediction and clinical immunogenicity data.
- The database will contain data from predictive tools (*in silico*, *in vitro*, and *in vivo*) and patient longitudinal information related to product, patient, and clinical factors.

EFPIA Contribution:

- Provide expertise toward defining a common data set for inclusion in the database.
- Provide clinical expertise in the different disease areas appropriate to the selected biopharmaceuticals.
- Provide expertise in interpreting and standardizing existing immunogenicity data.
- Where available, provide EFPIA participating company clinical trial and registry data for certain biopharmaceuticals.
- HLA typing of clinical samples may be available.

Workpackage 4: Data Analyses and Integration.

- Analyses of the data should lead to an improved understanding of the factors most likely to be associated with immunogenicity-related adverse events. Importantly the variables affecting both the incidence and severity of impact on patient safety will be investigated. Analytic studies may be conducted within drug, within drug classes, across disease states, etc. Results from these analyses as well as information from other sources, such as reported clinical case studies and industry- and academic-led research will be integrated into the final analyses and report.
- The results and conclusions will be used to substantiate the “risk-based approach to immunogenicity” outlined in the EMA (European Medicine Agency) guideline on Immunogenicity.
- Education and training materials will be prepared for health care professionals about immunogenicity and what it means for patient safety and management.

EFPIA contribution:

- Provide bioinformatics, statistical, and epidemiological expertise for the analyses of relationships between laboratory and assay results versus clinical outcomes
- Provide clinical and preclinical expertise toward the interpretation of results

Work Package 5: Project management and communication.

The workpackage should cover all aspects of project management and coordination, including dissemination and communication strategy. The results of the project will be disseminated in the form of publications, meeting presentations, and via the consortium’s website.

IMMUNOGENICITY



Innovative Medicines Initiative

EFPIA contribution:

- Partners will contribute rigorous project management and leadership expertise
- Co-author publications and training materials and make presentations in regulatory and public forums.

3. IMMUNOSAFETY OF VACCINES – NEW BIOMARKERS ASSOCIATED WITH ADVERSE EVENTS (EARLY INFLAMMATION, AUTOIMMUNE DISEASES AND ALLERGY)

BACKGROUND

Vaccines are generally recognized as the most efficient and the least expensive way to fight infectious disease in developed as well as developing countries. However, in contrast to anti-infective drugs, vaccines are generally employed for prophylaxis and therefore mostly administered to healthy subjects (infants, adults, elderly and, during the H1N1 pandemic, pregnant women have been also vaccinated on large scale) with administration most generally by the parenteral route.

Vaccine safety, particularly the potential for adverse events involving the immune system, is of particular concern for pharmaceutical companies making vaccines as well as for regulatory health authorities that oversee this industry.

It is accepted that local early inflammation, fever and injection site pain are common adverse events after vaccination. On the other hand, rarer events such as hypersensitivity or anaphylaxis following vaccination are more serious events and it is difficult to predict who is at risk for these events.

The increasing reliance on antigen-adjuvant combinations in modern vaccines will drive increased interest in understanding immune response parameters in the next decades. The use of new adjuvants as well as the advent of new delivery systems aimed at stimulating the immune system to protect against infectious diseases may give rise to real or imaginary concerns regarding the safety of these new vaccines. In addition, new approaches in the area of therapeutic vaccination that will address cancer as well as other chronic disorders will also require a better understanding of the action of these new delivery systems and adjuvants.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

There is a clear need for the harmonization, standardization and optimization of both reporting and grading of early adverse events following vaccination, particularly those linked to early inflammation. This will evolve only as practices evolve in the clinical development of human vaccines and engaging regulatory authorities to develop guidelines as initiated by the Brighton collaboration.

There is the need to share knowledge and to provide guidelines and guidance throughout the whole vaccine community to assess the safety of new vaccines, particularly new adjuvanted vaccines that will be accepted by the public, manufacturers and regulators.

In order to foster better understanding of the aetiology of autoimmune diseases and their possible link with previous events including infections and vaccination data have to be collected and organized in a comprehensive manner.

For these goals a strict collaboration between vaccine companies and academic partners will be of extreme importance. In fact in the last few years the vaccine field has become one of the most important for innovative medicines

OVERALL OBJECTIVES

The three main objectives of the project are the following:

- the characterization of early inflammation induced by vaccines currently on the market and the identification and validation of biomarkers of early inflammation and allergic responses.
- the identification and validation of early biomarkers of autoimmunity and their use to help identifying population at risk of developing autoimmunity
- the analysis of the incidence and epidemiology of autoimmune disease in the general population and the link to genetic background or previous events in the life of patients, including severe effects, such as anaphylactic shock.

EXPECTED KEY DELIVERABLES

- Innovative biomarkers and assessment methods to accurately describe vaccine induced inflammation
- Validation of acceptable type/level of inflammation after administration of vaccine
- Validation of new and reliable in vivo (animal models) or in vitro (cell culture) models predicting early inflammation and potential exacerbations of latent autoimmunity induced by vaccines
- Harmonization of guidelines to identify and record early clinical symptoms after vaccination
- Early biomarkers of autoimmunity and allergy “qualified for use” to predict potential risk of revealing chronic disorders at time of vaccination
- Identification of early biomarkers of potentially at risk individuals which could allow adopting a more personalized vaccination strategy
- Large databases of samples from recipients of current vaccines, innovative tools and adequate IT/Knowledge management structure allowing to determine the link between occurrence of autoimmune and allergic disorders and new biomarkers/historical events in the general population that will serve as a baseline for future vaccines
- A better understanding of the frequency of more common autoimmune diseases (namely those claimed to be revealed/exacerbated by vaccines) in the general population
- New general guidelines approved by Regulatory Authorities to evaluate the immuno-safety of vaccines.

CONSORTIUM

EFPIA Participants

(as of 1st September 2010)

Novartis, Sanofi-Aventis, GSK, Astra Zeneca

Applicant Consortium

(to be selected on the basis of the submitted expression of interest)

The applicant consortium is expected to have experience and expertise to propose new innovative approaches on the way to evaluate the immunosafety of vaccines and should:

- Include experts not only in vaccinology but also in the clinical and preclinical identification and assessment of biomarkers for inflammatory diseases and autoimmunity.
- Have demonstrable experience in conducting pan-European clinical trials, establishing and maintaining biobanks, sample and data management, bioinformatics and mathematical modeling.
- Closely associate Regulatory authorities (FDA/EMA) as well as experts in infectivology and cohorts of patients suffering from autoimmune diseases.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution on the defined deliverables in synergy with the EFPIA consortium.

The below architecture for the full proposal is a suggestion, different innovative project designs are welcome, if properly justified.

Workpackage 1: Definition of biomarkers of vaccine-induced inflammation.

Most vaccines induce local or systemic early adverse effects due to early inflammation. This workpackage should:

- Characterize, clinically and pre-clinically, the different types of early inflammation induced by vaccines and compare them to the inflammation induced by natural diseases to identify what type and what level of inflammation is needed for the efficacy of vaccine and what inflammation should be considered as a show-stopper. The safety of vaccines in recipients who have/had previous inflammation, infection, chronic disorder is also in the scope (risk of exacerbation of early symptoms).
- New biomarkers of early inflammation should be identified and qualified for use to be accepted by regulatory authorities and to be used by all companies making vaccines with standardized protocols to evaluate and measure them.

EFPIA contribution:

- Make available to the public consortium marketed vaccines.
- Harmonize and standardize evaluation of early adverse effects linked to innate or specific immunity induced by vaccines and share them with public consortium.
- Make available bio samples from internal bio banks (sera, cells ...).
- General immunological and toxicological expertise's regarding inflammation.

- Standardize immunoassays used to evaluate the safety of vaccines (evaluation of cytokines, inflammatory proteins ...) and transfer to public consortium.

Workpackage 2: Establishment of reliable in vivo animal models and in vitro models predicting early inflammation, autoimmune diseases and allergy.

This workpackage should deliver innovative approaches to identify biomarkers based on pre-clinical studies (animal and in vitro models). The goals are:

- to establish markers for assessment of clinical inflammation following vaccination and that allow understanding of its magnitude with respect to natural disease;
- to set up preclinical models that support prediction of inflammatory response following vaccination. In addition, there is a need for better animal models of autoimmunity capable of studying any potential link between early inflammation observed after vaccination and potential exacerbation in patients with "silent" autoimmunity.
- These models, after being reviewed by a panel of experts and validated by regulatory authorities would be used, when appropriate, by all manufacturers to assess the safety of new vaccines.

EFPIA contribution:

- Share relevant animal models or in vitro model used in the companies to evaluate immunosafety of vaccines.
- Harmonize and standardize preclinical tests used to evaluate the safety of vaccines.
- Standardize immunoassays (evaluation of cytokines, inflammatory proteins...) and transfer to public consortium.

Workpackage 3: Definition of early biomarkers of autoimmunity to predict potential risk of revealing chronic disorders at time of vaccination.

Autoimmune diseases can appear in different populations (infants, adults, elderly) and there is currently a lack of early biomarkers to predict the occurrence of autoimmunity later in life. To address this need the workpackage should:

- compare cohorts of patients with different autoimmune disorders at different chronological stages of the diseases with controls to identify possible biomarkers for the risk of autoimmune disease. This could be achieved by a consortium of clinicians and experts in autoimmunity together with bioinformaticians.

EFPIA contribution:

- Make available bio samples from internal bio banks (sera, cells ...).
- Provide support and expertise in data management and biostatistics
- Standardize immunoassays (evaluation of cytokines, inflammatory proteins...) and transfer to public consortium.
- Know how in statistical analysis of genomic and pre clinical or clinical study data
- Know how in bioinformatics - Know how in sample and data management

Workpackage 4: Understanding of the frequency of more common autoimmune diseases (namely those claimed to be revealed/exacerbated by vaccines) in the general population.

The goal is to define the incidence and epidemiology of early reactions and autoimmune diseases in the general population.

Vaccination is an event that occurs at different stages of life not taking into account the history of inflammation of the recipients of the vaccines. The impact of genetic aspects together with previous immunomodulating processes such as infectious diseases, allergies, stress, immunosuppression, other than vaccines, on the occurrence of inflammatory processes linked to autoimmune diseases, is largely unknown. In order to

improve the understanding of the inflammations leading to autoimmune disorders in the general population, this workpackage will:

- follow different populations (infants, children, adults and elderly) immunized with different vaccines currently on the market. Samples (plasma, blood cells) from these subjects should be collected at the time of immunization and at later time points, depending on the type of vaccine and namely during the development of the immune response to be capable to establish: correlations between new biomarkers identified in objectives 1 and 2, history of the recipients of the vaccines and the occurrence of autoimmune diseases/early adverse effects. Different types of clinical studies could be considered: retrospective and prospective studies (horizontal or longitudinal).
- Consideration should be given to the creation of large databases in different academic centres and the availability of innovative mathematical tools/models capable to perform all the relevant analyses and correlations. Epidemiologists, clinicians and family doctors familiar with the administration of vaccines, should collect samples and collaborate with specialists in biostatistics and bioinformatics.

EFPIA contribution:

- Provide support and expertise in data management and biostatistics
- Standardize immunoassays and transfer to public consortium

Workpackage 5: Creation of Databases.

In order to determine the link between occurrence of autoimmune disorders and new biomarkers/historical events in the general population that will serve as a baseline for future vaccines this workpackage should:

- Create large databases of human samples,
- Develop innovative tools and an adequate IT/Knowledge management structure.

EFPIA contribution:

Provide support and expertise in data management and biostatistics

Workpackage 6: Preparation of Guidelines.

This workpackage should aim to the preparation of new general guidelines approvable by Regulatory Authorities to evaluate the immuno-safety of vaccines.

EFPIA contribution:

Expertise in preparing guidelines.

Work Package 7: Project management and communication.

The workpackage should cover all aspects of project management and coordination, including dissemination and communication strategy.

4. IMPROVING THE PRECLINICAL MODELS AND TOOLS FOR TUBERCULOSIS MEDICINES RESEARCH

BACKGROUND

Tuberculosis (TB) remains one of the most devastating infectious diseases across the world. Indeed, current therapies are not satisfactory because they are based on the combined administration of several compounds for prolonged periods and do not efficiently address drug-resistance. Therefore, there is a clear need for new, more effective and affordable treatments that should shorten and simplify the treatment of active TB, provide safer and more efficacious treatments for drug-resistant TB, and simplify treatment of TB/HIV co-infections by eliminating drug-drug interactions.

Clinical trials in TB are extremely challenging due to the length of treatments with combinations of antibacterial drugs, poor adherence to treatments, and long periods of follow up in order to assess cure of patients. In this context, uncertainty about the optimal combination of drugs and doses needed to effectively treat patients is a major risk of efficacy failure. In order to address this bottleneck it is essential to develop an integrated set of predictive pre-clinical tools to facilitate the selection of optimal combinations of drugs and dosages.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

As a poverty-related disease, TB is considered as a paradigm for pre-competitive research and public-private partnership in the health sector. Although several large-scale initiatives focusing on clinical R&D and regulatory science are currently ongoing across the world (like Critical Path to TB Drug Regimens or CPTR), none of them addresses in a comprehensive manner the development of pre-clinical tools and their clinical predictive value.

The traditional focus in industry has been on process oriented mechanisms where emphasis was put on measurable outputs (i.e. candidates and clinical assets at different stages of development). This has also led in time to short-comings with regard to the basic understanding of the biology of TB and a clear lack of tools that can support the discovery of the next generation therapeutics or “not-so-low” hanging fruit.

While the product oriented philosophy is still sorely needed, this has to be complemented by a mid-long term view focusing on innovative tool development.

The pooling and cross-fertilization of resources and expertise in the public and private sectors and a joint collaborative effort are critical to achieve successfully this objective.

OVERALL OBJECTIVES

This topic offers a unique opportunity to create a European wide strategy to overcome key bottlenecks in the development of anti-TB drugs. To achieve this objective the successful proposal is expected to:

- develop an integrated set of pre-clinical in vitro and in vivo models that provide critical data to design optimized clinical studies in TB patients.

EXPECTED KEY DELIVERABLES

- Identification of in vitro and in vivo models for pre-clinical studies on TB therapies.
- Optimization, standardization and validation of those models for drug discovery.
- Development of a predictive mathematical model able to integrate data generated, and to provide accurate estimates of efficacious exposures in patients.
- The ultimate goal is to deliver a reliable prediction of efficacious regimens containing new agents as a critical parameter for optimal design of phase II clinical trials.

CONSORTIUM

EFPIA Participants

(as of 1st September 2010)

GlaxoSmithKline (lead company), Sanofi-Aventis (deputy), Pfizer, AstraZeneca and Johnson&Johnson/Tibotec.

These companies are involved in TB Alliance and CPTR and there will be opportunity for collaboration and support with both initiatives (e.g. compound sourcing, clinical trial data; reinforce current regulatory guidelines, collaboration with other companies outside EFPIA).

AstraZeneca and Pfizer have also agreed to contribute from their non-European TB Units. As an open initiative, it is expected that other EFPIA companies may consider joining this initiative at a later stage (Novartis, Otsuka, Eli Lilly, etc.).

Applicant Consortium

(to be selected on the basis of the submitted expression of interest)

The Applicant Consortium is expected to have ability for interdisciplinary and inter-sectorial work and to cover the following critical fields:

- Microbiology of TB. Cellular Biology and Immunology related with TB.
- Enabling technologies (e.g. imaging, biomarkers).
- Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution on the defined deliverables in synergy with the EFPIA consortium.

The below architecture for the full project proposal is a suggestion, different innovative project designs are welcome, if properly justified.

Overall, the EFPIA partners will provide investigative new and standard antitubercular compounds under appropriate MTA agreements, travel expenses, facilities for regular meetings, laboratory costs for visiting scientists, data repositories, website, and 10 FTEs for development of the following areas:

Workpackage 1: *In vitro* and *ex vivo* models.

This workpackage should aim to the development and validation of innovative culture systems that can assess *in vitro* dose-response relationships for measuring activity against:

- intra- and extracellular bacteria either actively growing or in non-growing state.
- bacteria found in histological lesions from human patients (e.g. artificial human granulomas).
- *ex vivo* system to assess the antibacterial activity of drug combinations in the presence of human effector cells (e.g. *ex vivo* whole blood bactericidal assays).

EFPIA contribution:

EFPIA partners will perform experiments in house using *in vitro* models of tuberculosis and will provide support and advice to set up and run activities in the public laboratories. Specifically, Pfizer will provide expertise on the whole blood bactericidal assays.

Workpackage 2: Animal models of tuberculosis.

This workpackage should aim to the development and validation of innovative animal models to estimate curative drug exposure in animals against *M. tuberculosis* in different physiological and histological conditions:

- *in vivo* models showing human-like granulomas
- *in vivo* models for actively replicating intracellular bacteria
- *in vivo* models for assessment of compounds capable of killing non-growing *M. tuberculosis*.

EFPIA contribution:

EFPIA partners will perform experiments in house using rodent models of tuberculosis and will provide support and advice to set up and run activities in the public laboratories. Specifically, GlaxoSmithKline R&D, Diseases of the Developing World Medicines Development Campus and AstraZeneca India, TB Unit, will perform PK/PD studies in state-of-the-art BioSafety Level 3 (BSL3) facilities that provide total containment of mycobacteria. Sanofi-Aventis will perform studies using the Zebrafish model of TB.

Workpackage 3: Standardized enabling technologies.

This workpackage should contribute to the development of new standardized enabling technologies to measure biological effects of treatments with combinations of antitubercular drugs *in vitro* and *in vivo*, using the models developed in the previous WPs and leading the way to translation in the clinic. Possible candidate technologies and tools are:

- imaging technologies for *in vitro* bactericidal response to treatments

TUBERCULOSIS



Innovative Medicines Initiative

- imaging technologies for non-invasive measurement of *in vivo* therapeutic response in animal models
- novel biomarkers to predict cure (e.g., absence of relapse).

EFPIA contribution

EFPIA partners will provide support and advice to set up and run activities in the public laboratories.

Workpackage 4: Mathematical PK/PD model for prediction of efficacious dose regimens in patients.

This workpackage should deliver statistical support and new mathematical PK/PD models that, using the data generated by the set of selected standardized techniques, provide accurate estimates of clinically efficacious exposures of drug combinations.

EFPIA contribution

EFPIA partners will provide support and advice to set up and run activities in the public laboratories.

Work Package 5: Project management and communication.

The workpackage should cover all aspects of project management and coordination, including dissemination and communication strategy.

EFPIA contribution

EFPIA partners will contribute rigorous project management and leadership expertise.

5. TRANSLATIONAL ENDPOINTS IN AUTISM

BACKGROUND

Autism spectrum disorders (ASD) are a family of heterogeneous neuro-developmental disorders characterized by deficits in (a) social interaction, (b) communication, and (c) unusual repetitive behaviours. It is estimated that 1% of all children is diagnosed with autism, representing nearly 5.5 million patients in the EU. Epidemiological studies suggest the prevalence rate of autism is increasing 10-17 percent annually for which there is no obvious explanation.

Present pharmacological approaches for the treatment of autism are based on drugs that ameliorate behavioural symptoms with a high impact on individual functioning. However, no medication is available that can change the core symptoms of autistic disorders and improve the long-term outcome of the disease.

Recent pre-clinical developments have brought major excitement to the field. Using animal models of monogenetic diseases leading to ASD, key behavioural and neuro-anatomical phenotypes have shown to be responsive to drug intervention. Examples include mGlu5 receptor antagonists for Fragile X syndrome (one of the most common identified causes of ASD), sirolimus for tuberous sclerosis, statins for neurofibromatosis Type 1, and insulin-like growth factor-1 (IGF-1) for RETT syndrome. These approaches are currently in translation to the clinic, offering novel perspectives for the control of ASD even in adolescence or adulthood, a concept that was not generally believed only a few years ago.

Recent genetic studies have identified several candidate genes that may confer susceptibility to ASD. Several of these genes are linked to synaptic function. Mouse models recapitulating these mutations exhibit defects in behaviour and in synaptic physiology supporting the importance of corresponding proteins in ASD. Furthermore, common biological pathways for brain development and plasticity across ASD are starting to be identified.

While various pharmaceutical companies have initiated clinical trials investigating new drugs in ASD patients, advances in neuro-imaging technologies have demonstrated the ability to quantify physiological and anatomical parameters underlying social cognitive impairments in ASD patients. Indeed, non-invasive approaches including event related potentials and eye-tracking are being applied to early diagnoses and have the potential to be further developed as tools to define translational biomarkers for drug discovery and development. In parallel, efforts have been made to generate large clinical sample sets, genomic and neurobiological data.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

Notwithstanding the advances mentioned here above, considerably more research is needed to translate these efforts and developments into registered drugs.

Thus, to produce a real impact on this field, a united effort of a variety of stakeholders including industry, academia and regulators is urgently needed.

Such a concerted effort of key players will allow a road map for possible new therapies for a disease that only started to emerge recently as a viable treatable condition.

OVERALL OBJECTIVES

This topic offers a unique opportunity to create a European wide strategy for ASD treatment where a 'guidance' structure is currently absent.

Therefore, the successful proposal will fulfil the following objectives:

- to develop and validate translational approaches for the advancement of novel therapies to treat ASD
- to set new standards in research and clinical development to aid the drug discovery process
- to identify and develop expert clinical sites across Europe to run clinical studies and trials and so create an interactive platform for ASD professionals and patients.

EXPECTED KEY DELIVERABLES

- The establishment of an integrated approach using cellular assays, animal models and translational biomarkers to enable drug discovery and development in ASD.
- The development of animal models with a close link to the neurobiology of ASD and that supports translation from animals to patients.
- The validation of biomarkers that aid the drug discovery process to predict pharmacodynamic responses to drug, to allow patient stratification and support regulatory submissions.
- An integrated clinical and preclinical research approach for ASD built on academia and industry strengths across Europe.
- The promotion of an educational program to increase awareness/ make the knowledge on all aspects of ASD accessible to a wider public, involving patient organizations.

CONSORTIUM

EFPIA Participants

(as of 1st September 2010)

F. Hoffmann-La Roche, Pfizer, Eli Lilly, Novartis, Sigma Tau, Johnson&Johnson

Applicant Consortium

(to be selected on the basis of the submitted expression of interest)

The Applicant Consortium is expected to provide both pre-clinical and clinical expertise and ability for interdisciplinary and inter-sectorial work and to cover the following critical fields:

- Scientific and clinical expertise and leadership in ASD including a broad multidisciplinary dimension.
- Innovative project design
- Clinical trial expertise
- Regulatory expertise
- Data management and integration expertise
- Involvement of Patient organisations
- Educational program to create awareness
- Professional project management (involvement of SMEs with specialized expertise is welcome)

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution on the defined deliverables in synergy with the EFPIA consortium.

The below architecture for the full proposal is a suggestion, different innovative project designs are welcome, if properly justified.

Work Package 1: In vitro systems development.

This work package will take advantage of emerging advances in the field of autism genetics and aim to develop in vitro model systems for new target identification, validation and prosecution.

Proposed model systems ideally include cellular readouts of neuronal and synaptic structure and function including 1) In vitro primary embryonic neuronal cultures; 2) In vitro slice preparations and 3) embryonic and induced pluripotent stem (iPS) cells.

The work package should:

- Define phenotypes (anatomical and functional) at the synaptic, cellular and circuitry levels to define shared common deficits amongst different ASD candidate genes and possibly epigenetic mechanisms leading to ASD.
- Assess the reliability and reproducibility of assays and models within and between collaborating laboratories.
- Use anatomical, biochemical and/or electrophysiological approaches and endpoints to assist in the biological validation and translation of ASD cellular models from *in vitro* systems to animals and to man.
- Use the most promising assays and models to assess pharmacological agents for their ability to ameliorate cellular deficits identified within ASD cellular model systems.

EFPIA contribution:

Lead: Pfizer - Participants: Roche, Novartis, Johnson&Johnson, Eli Lilly

In vitro technologies expertise and experiments

Neuro-anatomical and electrophysiological expertise and experiments

Work Package 2: Animal model development.

This workpackage should deliver recommendations on the most appropriate animal behavioural endpoints for use in genetic and/or environmental disease models relevant to ASD.

The work package should:

- Identify objective, quantitative, statistically validated and, wherever possible, translational measures of i.e. cognitive, affective and social behaviour in ASD animal models that most closely resemble symptoms of ASD.

- Assess the reliability and reproducibility of assays and models within and between collaborating laboratories.
- Use i.e. anatomical, biochemical and/or electrophysiological approaches to assist the biological validation and translation of the behavioural measures and ASD models.
- Use the most promising assays and models to assess pharmacological agents for their ability to ameliorate ASD-like behavioural deficits.

EFPIA contribution:

Lead: Johnson&Johnson - participants: Roche, Eli Lilly, Pfizer, Sigma Tau

- Behavioural Supply and generation of transgenic animals
- Methods, expertise and experiments
- Supplies of pharmacological tools

Work Package 3: Translational research development.

This workpackage should develop objective markers linked to ASD to translate electrophysiological, imaging and pharmacological outcome measures from animal to man and back to animal. The work package should:

- Identify objective markers of neuron-anatomical changes in animal models of ASD using histological preparations and in vivo imaging outcome measures i.e. fMRI, PET, SPECT, and their susceptibility to pharmacological challenges.
- Define phenotypes in animal models using fluid and electrophysiological markers i.e. ERP, EEG/MEG to define shared common signatures amongst different ASD candidate genes and their susceptibility to pharmacological treatments.
- Confirm defined translational end-points from the animal studies in ASD patients as well as from ASD patients in animal models i.e. ERP, EEG, fMRI, DTI, PPI, CEB.

EFPIA contribution:

Lead: Roche - Participants: Eli Lilly, J&J, Novartis, Pfizer

- Biofluid biomarker development and experiments
- Imaging expertise, methods and experiments
- Translational behavioural procedures and experiments

Work Package 4: Clinical research development.

The objective of this workpackage should be to facilitate and enhance scientific collaboration and exchange across Europe for ASD professionals – clinicians and researchers from both private and public sectors - and to significantly promote research and development of drugs for ASD.

The work package should:

- facilitate the implementation of Clinical Research to assess interventional pharmacological studies with PHARMA and Academic sites.
- Develop and align the infrastructure necessary to validate diagnostic, biochemical, electrophysiological and imaging markers among others, that will help to identify the disease at an early stage and improve treatment outcome and initiate pharmacogenomic assessment (“bio banking”) from ongoing trials possibly linking to other libraries i.e. AGRE.
- Assess Standards of care of ASD patients in Europe. Conduct a study assessing quality of life of patients; this study will be an observational naturalistic long term study in ASD patients to collect data on current access to care, diagnostic assessment and treatment paradigms chosen including the relationship between treatments regimens prescribed.
- develop standardized assessments including outcome measures, treatment and long term follow up criteria across Europe, that are based on learnings from

clinical and translational research (link to work packages 1-3) and recommendation of standards for scientific exchange which benefits patients and their families.

- develop an educational program to increase awareness/make the knowledge in ASD accessible to a wider public (establish symposia/ training courses for scientists/ physicians, patients and their families).

EFPIA contribution:

Lead: Novartis - Participant: Roche, Eli Lilly, Pfizer

- Clinical and neuropsychological expertise and experiments
- Imaging and electrophysiological expertise and experiments
- Experience, expertise and data from relevant clinical trials - past and present
- Clinical trials supplies and logistics

Work Package 5: Data handling, management and integration.

The workpackage should provide the strategy and implementation for efficient handling, management and integration of all data produced by the project activities.

EFPIA contribution

- Data management
- Criteria for cross validation of assays and outcome measures

Work Package 6: Project management and communication.

The workpackage should cover all aspects of project management and coordination, including dissemination and communication strategy. The applicant consortium is expected to contribute with a dedicated professional project management office.

EFPIA contribution

- Rigorous project management/leadership expertise

Glossary: CEB: conditioned eye blink response; CNV: copy number variation; CSF: cerebrospinal fluid; EEG: electroencephalogram; ERP: evoked related potentials; DTI: diffusion tensor imaging; MEG: magnetencephalogram PPI: Pre-pulse inhibition

6. DEVELOPMENT OF PERSONALIZED MEDICINE APPROACHES IN DIABETES

BACKGROUND

Diabetes is a major threat for public health worldwide. It is estimated that 8.6% of the European adult population suffer from the disease and this number is expected to grow to over 10% by 2025. In 90-95% of the cases patients have type 2 diabetes, a form that is more and more often encountered in young adults with the potential risk to develop end-organ damages.

The optimal management of type 2 diabetes should take into consideration the heterogeneity of the disorder which requires individualized therapies tailored to patient's individual needs. Unfortunately, this personalized approach is currently not applied efficiently for several reasons including:

- the lack of predictive "stratification markers" especially in the very early stages of diabetes.
- the limited value of existing response markers to monitor disease progression.

So far, the attempts to stratify type 2 diabetic patients according to their genotype did not lead to significant therapeutic breakthroughs. On the other hand, certain phenotypic characteristics hold strong promise to develop personalized therapy for well-defined subpopulations of patients.

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

A pooled large accessible data collection from well described phenotypes of specific diabetes populations is needed to build the foundation for a retrospective data mining and a systems biology description and subsequent biomarker candidates generation to monitor and stratify for 'early' or 'pre-diabetes' and diabetes progression to end-organ manifestation.

Patient samples have been collected and stored in the past by academia and industry but only if they are brought together a sufficient number of samples will be available to generate statistically significant data sets, i.e. to retrospectively assess potential biomarkers. In order to prospectively qualify the selected biomarkers in clinical trials, access to well defined patient populations as well as clinical development skills can only be warranted if academic and industry resources are brought together.

A number of different data mining tools do exist for data processing and biomarker candidate generation which, however, are not available in a single place. Integration of resources and innovation in the fields of diabetes, patient phenotyping, systems biology, data mining and clinical research require a joined cross-functional and cross-institutional effort.

The opportunity is for scientists from academia, SME and industry to build, share and process large data banks from well phenotyped patients, to generate new biomarker candidates on the basis of systems biology and data mining, to develop new diagnostic tools for patient stratification and response markers, and to qualify selected biomarkers.

The global scientific community will benefit from this joint endeavour since it will increase the understanding of the pathophysiology of the disease by integrating different types of parameters in a single data repository.

OVERALL OBJECTIVES

The ultimate goal is to develop robust disease stratification and response tools to overcome current bottlenecks in drug development for diabetes and to improve patient care through a personalized / stratified therapeutic strategy.

PART 1 of the project (patients' phenotypes) will make use of available as well as newly developed resources, technologies, infrastructures and knowledge management tools to enhance our understanding of the disease and identify potentially relevant biomarkers.

- The consortium will build a systems biology approach generating a broad data set for individual patients using disease-relevant technologies (clamp, MRI, PET, etc.).
- Data mining technologies applied to available patient data resources (retrospective studies) will be used to identify novel biomarker candidates for patients stratification (from disease onset) and monitoring disease progression.
- Standardized protocols will be developed for both basic (e.g. Hb1Ac, fasting plasma glucose, oral glucose tolerance test, etc...) and deep/specific (e.g. MRI, PET, clamp, etc...) phenotyping.

PART 2 of the project will be based on the knowledge generated in PART1, with a view to assess the value of hypotheses and potential biomarkers in prospective clinical trials with innovative design concepts.

Consensus will be sought with regulatory authorities regarding approval criteria for biomarkers, corresponding diagnostic tests and stratification methods.

NB. Part 2 of the project will start during the indicative time frame planned for this project (i.e. duration of 5 years) but will likely extend beyond the end of this period.

EXPECTED KEY DELIVERABLES

Overall:

- Integrated approach for patients' stratification based on patients' phenotype
- New mechanistic hypotheses on the pathogenesis of the disease
- Identification of novel biomarker candidates to monitor disease progression
- Design of clinical studies for the qualification of biomarkers
- Enabled design of specific clinical studies for early proof of efficacy and safety of new treatment modalities.

PART 1

- Patient samples and data: high quality European data bank from patients at risk to develop diabetes or with established diabetes at risk to develop diabetic complications to generate relevant phenotypical data sets. Co-segregating

parameters will be included to define sub-phenotypes to explore the development of diabetes or the response to different therapies.

- Systems biology platform: To be established by integrating clinical data, biological data, genomics, metabonomics and other relevant data.
- Data mining: Application and development of novel data mining tools and algorithms to generate stratification and response biomarker candidates (i) describing patients at risk of diabetes and in early stages of disease as well as for disease progression, (ii) to derive a personalized treatment strategy and (iii) potentially identify new drug development targets.
- Development of biomarker assays: Confirmation (according to industry standards) and qualification of new or already known biomarkers for personalized therapy in well defined sub-populations. Quantification of patient metabolism and target variability.

PART 2

- Prospective clinical trials: Validation of biomarker candidates in prospective clinical trials (potential scenarios depending on the biomarker candidate types to be tested)
- Assessment of response (or lack of response) to established therapies (targeting extensively characterized mechanisms, for instance incretin pathway) in well defined sub-populations.

CONSORTIUM**EFPIA Participants**

(as of 1st September 2010)

Sanofi-Aventis, Eli Lilly, Novartis, Servier

Applicant Consortium

(to be selected on the basis of the submitted expression of interest)

The Applicant Consortium is expected to provide both pre-clinical and clinical expertise and ability for interdisciplinary and inter-sectorial work in order to:

- build a large high quality EU database from phenotyped patients
- develop a diabetes specific systems biology platform
- identify, evaluate and qualify biomarker candidates
- perform phenotyping, genetic and metabolic assays
- develop and validate new biomarker tools and corresponding predictive biomarker assays
- have experience in conducting clinical trials
- provide and develop novel clinical trial design concepts (adaptive clinical trial designs).

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The Applicant Consortium is expected to address all the research objectives and make key contribution on the defined deliverables in synergy with the EFPIA consortium.

The below architecture for the full proposal is a suggestion, different innovative project designs are welcome, if properly justified.

Overall

Workpackage1: Project Management.

The Focus of the workpackage will be alliance management, project management and support.

EFPIA contribution:

Provision of a dedicated project office.

Workpackage 10: Statistical Analysis.

The workpackage will focus on evaluation of novel statistical and clinical trial design concepts and methods for the clinical evaluation of biomarker tools. It is expected that the Applicants will contribute with novel statistical analysis methods (e.g. in adaptive clinical trial designs).

EFPIA contribution:

Clinical statisticians for both retrospective and prospective clinical trial analysis could be provided (but also potentially by specialized SME).

PART1:

Workpackage 2: Database Establishment + Retrospective Hypotheses Testing.

The focus will be on merging of existing data from small/individual cohorts into a large, high quality European data bank from patients at risk to develop diabetes or with established diabetes at risk to develop diabetic complications, to generate relevant phenotypical data sets. Applicants are expected to provide samples and data from patient cohorts.

This database will be the basis for the

- data mining,
- systems biology platform and
- serves as resource for first retrospective assessment of biomarker candidates.

EFPIA contribution:

Provision of samples and data from clinical trials.

Workpackage 3: Phenotype Data Generation.

The focus of the workpackage will be to consolidate / generate a broad data set for individual patients (in line with corresponding legal and ethical guidelines) using highly disease relevant technologies (for example clamp, MRI, PET, etc.).

EFPIA contribution:

EFPIA and the Applicants will share responsibility for the deliverables of the work.

Workpackage 4: Systems Biology.

The focus of the workpackage will be on the establishment of systems biology platforms by integrating clinical data, biological data, genomics, metabonomics and other relevant data. The Applicants will provide expertise, know how, tools and infrastructure.

EFPIA contribution:

Provision of expertise and know how.

Workpackage 5: Data Mining.

The workpackage will focus on the application and development of novel data mining tools and algorithms to generate stratification and response biomarker candidates

- describing patients at risk of diabetes and in early stages of disease as well as for disease progression,
- to derive a personalized treatment strategy and
- potentially identify new drug development targets.

The Applicants are expected to provide experts, tools and tool development resources

EFPIA contribution:

Provision of experts & tools.

Workpackage 6: Biomarker Assay Development.

The workpackage will provide an “Industrialized” confirmation and qualification of new or already known biomarkers for personalized therapy in well defined sub-populations. The applicants should be the main driver for this activity.

- Part 1: application in retrospective trials.
- Part 2: support exploring novel clinical design strategies, e.g. adaptive clinical trial designs.
- Quantification of patient metabolism and target variability.

EFPIA contribution:

Provision of expertise and application support.

PART2:

Workpackage 7: Design of prospective clinical trial(s)

The focus will be on the design of prospective clinical trials for validation of biomarker candidates.

- Potential scenarios will depend on the biomarker candidate types to be tested (example 1: deep phenotyping, e.g. PET, MRI, clamp in ~ 500 patients; example 2: basic phenotyping in ~ 3000 patients).
- The aim will be the assessment of the response (or lack of response) to established therapies (targeting extensively characterized mechanisms, for instance incretin pathway) in well defined sub-populations. The Applicants are expected to provide innovative clinical expertise.

EFPIA contribution:

Provision of resources and expertise for trial design, specific focus on stratification in the context of drug development.

Workpackage 8/9: Execution of prospective clinical trial(s) and interpretation of results.

The workpackage will focus on execution of trials (examples see WP7) where the Applicants are expected to provide direct access to patients and conduct the clinical trial in the role of legal sponsor and key investigator.

EFPIA contribution:

Provision of resources and expertise to conduct multi-centre clinical trials (monitoring, data management, etc.)

7. FOSTERING PATIENT AWARENESS ON PHARMACEUTICAL INNOVATION.

BACKGROUND

Pharmaceutical drug development is a highly regulated, costly, long and complex process that is largely unknown to the lay public. In an era of growing demand and emphasis on both quality and sustainability of healthcare, it is critical to address this major gap in perception and knowledge.

Raising societal awareness in this area would significantly facilitate the translation of innovative therapies into high quality care to respond to unmet medical needs. Indeed, well informed patients and carers have a key role to play in the implementation of patient-centred clinical research strategies and approval processes.

Information to patients and their carers that meet stringent quality principles is critical to ensure reliability of clinical trials and treatment adherence as well as for the successful development of personalized medicine where therapies are tailored to patients' individual needs,

NEED FOR PUBLIC-PRIVATE COLLABORATIVE RESEARCH

Although several patient organisations, pharmaceutical companies and academic research organisations have developed their own information programmes on drug development, these endeavours are rather fragmented, limited in scope and sometimes criticised. Clearly, a broader consolidated approach is needed.

As a public-private partnership, the Innovative Medicines Initiative offers a unique opportunity to bring together experts from the pharmaceutical industry, academia, patient organisations, health professionals, ethical bodies, regulatory authorities and media to jointly work in an open and transparent way on improving the understanding of pharmaceutical research and development among patients, carers and other interested lay people across the European Union.

OVERALL OBJECTIVES

The successful proposal will build innovative education programmes centred on the following themes:

- The complex but crucial nature of biomedical research aiming at therapeutic breakthroughs (i.e. translational medicine), with emphasis on the respective roles of the different stakeholders involved and on the processes leading to drug approval.
- The multiple facets of personalized and predictive medicine.

PATIENT AWARENESS



- Rational approach to drug safety and risk benefit assessment of novel drugs from the perspective of the various stakeholders involved.
- The growing importance of pharmaco-economics and health technology assessment in modern medicine.
- The design and objectives of clinical trials, with emphasis on the respective roles of the different stakeholders involved, in particular patients themselves.
- The synergies between innovative medicines and other strategies to enhance patient-centred chronic disease management.

EXPECTED KEY DELIVERABLES

- Establishment of a multidisciplinary and multilingual network of committed experts including patient advocacy groups to conceive and implement balanced education programs for patients, carers and other lay audiences interested in health policy.
- Establishment of a course programme addressing the objectives above, to be available in a minimum of 6 major European languages.
- Implementation of educational / informational strategies and activities based on novel information and communication technologies, targeting large audiences across Europe.
- Establishment of methods to assess and monitor the understanding and perception of pharmaceutical research and trust in actors and processes linked to the development of new medicines.

CONSORTIUM

EFPIA Participants

(as of 1st September 2010)

Astra Zeneca, GlaxoSmithKline, Roche, Bayer Schering Pharma, Novartis, Genzyme, Novo Nordisk

Applicant Consortium

(to be selected on the basis of the submitted expression of interest)

In order to fulfil the ambitious aim of the project, the Applicant Consortium is expected to gather the multidisciplinary expertise necessary to conceive and implement the educational/informational activities together with patient organizations representative of major disease areas across the European Union.

SUGGESTED ARCHITECTURE OF THE FULL PROJECT PROPOSAL

The below architecture for the full proposal is a suggestion, different innovative project designs are welcome, if properly justified.

The Applicant Consortium is expected to address all the below areas making key contribution on the defined deliverables in synergy with the EFPIA consortium.

The EFPIA participants will contribute by:

- Developing and implementing educational / informational activities together with the other consortium partners.
- Participating in the overall organisation and governance of the project.
- Supporting translation activities.

Work Package 1: Project management.

This workpackage will deliver alliance management, project management, governance and support.

Work Package 2: Network implementation.

The focus of the workpackage will be the

- development of a pan-European network of patient organisations and pharmaceutical companies covering a broad range of disease areas and geographical regions;
- development of processes for linking to additional national and European stakeholders.

Work Package 3: Needs assessment and gap analysis.

The workpackage will provide a detailed analysis of needs and existing programs/information sources.

Work Package 4: Course content development.

The workpackage will

- develop training documents and website material in a language suitable for the general public (i.e. via the involvement of media professionals);
- provide translation of training materials into relevant major European languages.

Workpackage 5: IT-Infrastructure.

The workpackage will develop a robust IT-infrastructure for the content platform.

Workpackage 6: Quality control.

The workpackage will deliver a sustainable infrastructure for the training delivery, including methods for measuring the input and success of the training courses.

Workpackage 7: Future topics.

The aim of this workpackage is

- to propose new concepts for more active involvement of patients in pharmaceutical R&D projects;
- to develop ideas for making training material available to other audiences beyond patient organisations.