ANTI-BIOPHARMACEUTICAL IMMUNIZATION- THE PROBLEM

A major limitation to the use of **biopharmaceuticals products (BPs)** is the development of **anti-drug antibodies (ADA)** in a subset of patients. **ADA** may decrease the efficacy of **BPs** by neutralizing them or modifying their clearance, and they may be associated with **BP-specific hypersensitivity** reactions. **ADA** may also cross-react with closely related endogenous counterparts of **BPs** thereby compromising important physiological functions.

Given this scenario, the prediction, prevention and cure of **anti-drug (AD) immunogenicity** are thus major goals in **biopharmaceutical** drug development and patient safety.

Many factors contribute to the immunogenicity of **BPs**. Some are related to the product itself, others to its mode of administration and still others to the underlying disease or the characteristics of patients. Elucidating the significance of these factors and their specific contribution to immunogenicity requires a varied approach including: the development, evaluation and standardization of new tools for predicting and measuring **AD immunization**, the testing of new concepts originating from basic immunology that have not yet been translated into clinical practice, the development of synthetic predictive models condensing in a comprehensive form all that is known about **AD immunization** and their validation in a clinical setting. Improvements in our understanding of **AD immunization** should also lead to the production of guidelines for drug development and the clinical care of patients.

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.'

www.imi.europa.eu

ABIRISK FOCUS AND OUTCOME

ABIRISK Project aims to provide an integrated approach to **AD immunization**, bringing together, in an extensive and coordinated manner, a large network of clinicians from various specialties with broad experience in the care of patients treated with various type of **BPs** and developing **ADA**, biologists familiar with the immune monitoring of patients, scientists specialized in the mechanisms of immunogenicity, methodologists and biostatisticians. In addition the collaboration with a large network of private pharmaceutical industries under European Federation of Pharmaceutical Industries and Associations (EFPIA), will ensure direct transfer of the experimental findings into **BP development** and patient management.

Collectively, this group will critically evaluate the immunogenicity of existing **BPs** for **Hemophilia A**, **Multiple Sclerosis**, and **Inflammatory Diseases**, and develop standardized **ADA assays**, including **Neutralizing Antibody (NAb) Assays**, for each **BP**. Novel integrated approaches to characterize **AD lymphocyte responses** will be used to provide insight into the basic mechanisms by which **BPs** drive immune cell activation. The predictive value of existing as well as new tools used for prediction of protein drug immunogenicity will be explored and evaluated, including T cell assays, *in silico* prediction, *in vitro* generated **BP-derived agretopes** generated by processing in human dendritic cells, measurement of peptide affinity for HLA class II molecules, modulation of dendritic cell function and activation by **BPs**, human *in vitro* mononuclear leukocytes assays, use of artificial lymph nodes, animal models, and generation of post-translational modifications and aggregates and characterizing them in various models.

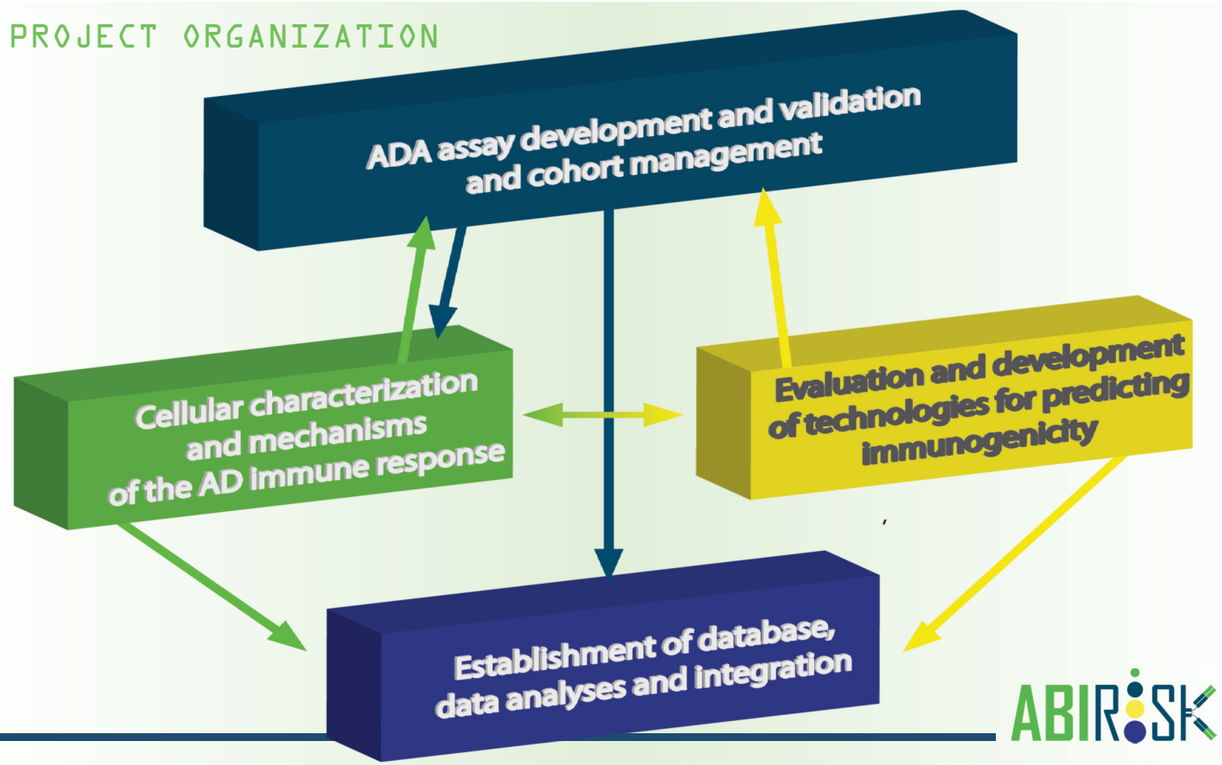
Collection and integration of immunogenicity-related data and clinical relevance will be assembled into a single immunogenicity databank that will be used to describe the natural history of the occurrence of **ADA**, identify common and disease-specific/drug-specific variables associated with immunogenicity/outcomes, develop models that will predict occurrence of **ADA**, presence or absence of subsequent clinical outcomes, derive predictive signatures for immunogenicity phenotypes (**ADA** or **NAb**) and immunogenicity-related-events, and evaluate the operating characteristics of the predictive signatures.

ABIRISK Project will investigate the correlation between patient and clinical factors and the incidence of immunogenicity. A major goal is to further elucidate the underlying mechanisms of immunogenicity and this may result in more science-based regulatory guidelines, which may reduce the regulatory burden for immunogenicity testing and save time and resources in the **BP drug development** process.

ABIRISK ALLIANCE

The **ABIRISK project** consortium is presently made up of thirty-eight partners, twenty-six of which are academic institutions, nine are EFPIA member companies and three are small and medium enterprises (SMEs).
Thirteen countries are represented: The United Kingdom, France, Italy, Germany, Switzerland, Denmark, Belgium, the Netherlands, Spain, Sweden, Austria, Israel and Czech Republic.

PROJECT ORGANIZATION



ABIRISK

Johann Wolfgang Goethe Universität - Klinikum und Fachbereich Medizin - Germany
www.kgu.de

Karolinska Institutet
Sweden
ki.se

Klinikum rechts der Isar der Technischen Universitaet Muenchen - Germany
www.med.tum.de

Medizinische Universität Innsbruck
Austria
www.i-med.ac.at

Paul-Ehrlich-Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel - Germany
www.pei.de

Queen Mary and Westfield - University of London
United Kingdom
www.qmul.ac.uk

Rambam Medical Center
Israel
www.rambam.org.il

Region Hovedstaden
Denmark
www.regionh.dk

Università di Firenze
Italy
www.unifi.it

Universitaetsklinikum Bonn
Germany
www.ukb.uni-bonn.de

Universitätsklinikum Düsseldorf
Germany
www.uniklinik-duesseldorf.de

University College London
United Kingdom
www.ucl.ac.uk

University Hospital Basel
Switzerland
www.unispital-basel.ch

Univerzita Karlova v Praze
Czech Republic
www.cuni.cz

Chaim Sheba Medical Center
Israel
www.eng.sheba.co.il

Assistance Publique-Hôpitaux de Paris
France
www.aphp.fr

SMEs

ALTA Ricerca e Sviluppo in Biotecnologie S.r.l.u
Italy
www.altaweb.eu

Biomonitor A/S
Denmark
www.biomonitor.dk

SciCross AB
Sweden
www.scicross.com

ABIRISK

Project Coordinator

Sebastian Spindeldreher
Novartis Institutes for BioMedical Research (NIBR)
Novartis Pharma AG
4002 Basel
Switzerland
sebastian.spindeldreher@novartis.com

Managing Entity for EU funds

Marc Pallardy
Institut National de la Santé et de la Recherche Médicale
UMR 996, University Paris-Sud
32 rue des Carnets
92140 Clamart
France
marc.pallardy@u-psud.fr

www.abirisk.eu

EUROPEAN COMMISSION

Total cost:
€34.9 million

EFPIA in kind contribution
€9.6 million

Innovative Medicines Initiative

IMI funding:
€18.2 million

ABIRISK

Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Relevance to Minimize the Risk

EUROPEAN COMMISSION

Innovative Medicines Initiative

EFPIA MEMBER COMPANIES

GlaxoSmithKline Research & Development Limited
United Kingdom
www.gsk.com

Bayer Pharma AG
Germany
www.bayer.com

IPSEN Innovation S.A.S
France
www.ipsen.com

Merck KGaA
Germany
www.merckserono.com

Novartis Pharma AG
Switzerland
www.novartis.com

Novo Nordisk A/S
Denmark
www.novonordisk.com

Pfizer Limited
United States
www.pfizer.com

Sanofi-Aventis Research and Development
France
en.sanofi.com

UCB Pharma S.A.
Belgium
www.ucb.com

ACADEMIC INSTITUTES

Institut National de la Santé et de la Recherche Médicale
France
www.inserm.fr

Academisch Medisch Centrum
the Netherlands
www.amc.nl

Leids Universitair Medisch Centrum
the Netherlands
www.lumc.nl

Centre National de la Recherche Scientifique
France
www.cnrs.fr

Commissariat a L'Energie Atomique et aux Energies Alternatives- France
www.cea.fr

DRK-Blutspendedienst Baden-Württemberg – Hessen gemeinnützige GmbH - Germany
www.blutspende.de

Fondazione per l'Istituto di Ricerca in Biomedicina
Switzerland
www.blutspende.de

Fundació Institut de Recerca de L'hospital Universitari Vall D'hebron - Spain
www.vhir.org

Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif - France
www.getaid.org

Istituto Giannina Gaslini
Italy
www.gaslini.org