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INTRODUCTION

A growing number of medicines are based on biological molecules such as proteins and monoclonal antibodies. These novel drugs have resulted in new, more effective treatments for a number of serious conditions. Yet sometimes these medicines trigger a response from the patient's immune system, which can decrease the effectiveness of the drug or cause severe side effects.

The aim of the IMI-founded ABIRISK project **"Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Re to Minimize the Risk",** is to shed new light on the factors behind this immune response. The project, which represents the first concerted effort to solve this problem, officially kicked off March 1st, 2012. ABIRISK project will aid in the creation of new, safer **biopharmaceuticals (BPs)** and also generate tools to determine how individual patients are likely to respond to them both in clinical trials and after release to the market.

The ABIRISK consortium (presently made up of thirty-five partners, twenty-four of which are academic institutions, nine are EFPIA member companies and two are small and medium enterprises, with thirteen countries represented), has been designed to meet all of these requirements in order to target three types of disorders: **Hemophilia A, Multiple sclerosis and Inflammatory diseases: inflammatory rheumatisms (including rheumatoid arthritis) and inflammatory bowel diseases.**

ABIRISK Project will collect data both retrospectively from patients suffering from various types of diseases and treated with various BPs at European centers with a high level of experience in clinical research and will prospectively recruit additional patients in dedicated studies during the 5 years of this program. Guidelines and Standard Operating Protocols for the study of anti-drug immunization will be established and used to standardize the collection of prospective data from these patients.

ABIRISK Project thus represents a unique opportunity to create an interdisciplinary task force of clinical centers especially designed to study immune responses against biopharmaceuticals.

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WELCOME

Dear Reader,

We would like to welcome you to the March 2015 issue of the **ABIRISK Scientific Newsletter**. The Scientific Newsletter gives you a monthly update on the most relevant literature related to ABIRISK topics published around the globe, both inside and outside ABIRISK consortium.

This month, we chose to draw your attention to a paper published by N. Gupta *et al* in Science Translational Medicine, in which they describe a novel strategy to prevent anti-drug immune responses in Hemophilia A upon induction of central and peripheral tolerance during fetal life.

In addition, you will find in this issue some regulatory news on biopharmaceuticals

We look forward to your visit on **ABIRISK** website for more information and updates on the program.

Enjoy reading !

Best wishes

The ABIRISK management team

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LITERATURE

This month's selected article

Advert immune responses may occur against some protein therapeutics. This is the case in patients with genetic disorders such as hemophilia A, hemophilia B, Willebrand disease or Pompe disease, when they receive exogenous factor VIII, factor IX, Willebrand factor or alpha-glucosidase. The development of neutralizing antibodies to Protein Therapeutics represents a major clinical complication and a problem of public health. In such pathologies, in utero induction of immune tolerance to Protein Therapeutics would represent a major step to improve the clinical management of the patients as well as their quality of life and reduce associated societal costs.

The article published by N Gupta et al describes a novel strategy to prevent anti-drug immune responses upon induction of central and peripheral tolerance during fetal life. The strategy exploits the fact that maternal immunoglobulins G (IgG) are transferred to the circulation of the fetus through the placenta via the neonatal Fc receptor. The results demonstrate that the materno-fetal transfer of a protein fused to the Fc fragment of the IgG generates specific and long-lasting tolerance in newborn mice. Using transgenic mice expressing a monoclonal T-cell receptor specific for hemagglutinin, the authors demonstrate that tolerance is associated with an increase in central and peripheral regulatory T cells specific for the administered antigen. The scientists then bring the proof-of-concept for the validity of their approach in the murine pre-clinical model of severe hemophilia A, a rare hemorrhagic disorder linked to the X chromosome and resulting from the absence of functional pro-coagulation factor VIII. The transplacental transfer of factor VIII fragments fused to the IgG Fc fragment reduced in a drastic manner the neutralizing anti-factor VIII immune response on the offspring upon treatment with therapeutic FVIII later in life. Tolerance was mediated by the induction of factor VIII-specific regulatory T cells.

Hemophilia is the most appropriate disorder to envisage translation of these observations in patients. Indeed, the birth of a hemophilic baby may be anticipated based on familial history of hemophilia A, and confirmed by simple and antenatal genetic tests. Besides, the risk for a hemophilia A patient to develop a neutralizing anti-

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factor VIII immune response (up to 30% of the patients) may be predicted at the time of diagnosis of hemophilia A in a rather faithful manner. Further, a fusion FVIII-Fc was recently released in the US and should reach the European market in the coming year.

Regulation of immune responses to protein therapeutics by transplacental induction of T cell tolerance.
Gupta N, Culina S, Meslier Y, Dimitrov J, Arnoult C, Delignat S, Gangadharan B, Lecerf M, Justesen S, Gouilleux-Gruart V, Salomon BL, Scott DW, Kaveri SV, Mallone R, **Lacroix-Desmazes S.**
Sci Transl Med. 2015 Feb 18;7(275):275ra21.

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Immunogenicity

The challenging definition of naïve patient for biological drug use.
Biggioggero M, Danova M, Genovese U, Locatelli F, Meroni PL, Pane F, Scaglione F.
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Oldenburg J, **Lacroix-Desmazes S**, Lillicrap D.
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Toward optimal therapy for inhibitors in hemophilia.
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Clinical impact of concomitant immunomodulators on biologic therapy: Pharmacokinetics, immunogenicity, efficacy and safety.
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Comparative immunogenicity assessment: a critical consideration for biosimilar development.
Liu PM, Zou L, Sadhu C, Shen WD, Nock S.
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Methods

Feasibility of immuno-PCR technology platforms as an ultrasensitive tool for the detection of anti-drug antibodies.
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Bioanalysis. 2015 Feb;7(3):285-94.

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Animal models

Natalizumab analogon therapy is effective in a B cell-dependent multiple sclerosis model.
Häusler D, Nessler S, Kruse N, Brück W, Metz I.
Neuropathol Appl Neurobiol. 2015 Jan 13.

Biomarkers

CD19 mRNA quantification improves rituximab treatment-to-target approach: a proof of concept study.
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J Neuroimmunol. 2014 Dec 15;277(1-2):127-33.

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Low expression of CD39 on regulatory T cells as a biomarker for resistance to methotrexate therapy in rheumatoid arthritis.
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Systemic Lupus Erythematosus

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The impact of biological therapy on regulatory T cells in rheumatoid arthritis.
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Vande Casteele N, Gils A.
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IFN-β Treatment Requires B Cells for Efficacy in Neuroautoimmunity.
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Farsani ZS, Behmanesh M, Sahraian MA.
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Hemophilia

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Montalvão SA, Tucunduva AC, Siqueira LH, Sambo AL, Medina SS, Ozelo MC.
Haemophilia. 2015 Feb 24. doi: 10.1111/hae.12646. [Epub ahead of print]

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Basic immunology

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Kang J, Zhu L, Lu J, Zhang X.
J Neuroimmunol. 2015 Feb 15;279C:25-32.

Cytokines as Therapeutic Targets in Rheumatoid Arthritis and Other Inflammatory Diseases.
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Clinical impact of concomitant immunomodulators on biologic therapy: Pharmacokinetics, immunogenicity, efficacy and safety.
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J Clin Pharmacol. 2015 Mar;55 Suppl 3:S60-74.

Secukinumab: first global approval.
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Drugs. 2015 Feb;75(3):329-38.

REGULATION

EMA

Pending EC decision: Humira, adalimumab
Opinion date: 26-Feb-2015

Opinion/decision on a Paediatric Investigation Plan (PIP): Recombinant single-chain coagulation factor VIII
Therapeutic area: Haematology-Hemostaseology
Updated
February 2015

Work plan for the CHMP Biologics Working Party 2015
Updated
February 2015

Orphan designation:Recombinant human monoclonal antibody to human IL-1beta of the IgG1/K class
Updated
February 2015

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Human medicines European public assessment report (EPAR): Inflectra, infliximab
Revision: 6, Authorised
February 2015

Human medicines European public assessment report (EPAR): Simponi, golimumab
Revision: 20, Authorised
February 2015

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