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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 Relevance 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,

Welcome to the second issue of the **ABIRISK Scientific Newsletter**. The Scientific Newsletter gives you a monthly update on the most relevant literature related to ABIRISK areas of research published around the globe, both inside and outside the ABIRISK consortium.

This month, we chose to highlight a piece of work in the field of hemophilia by Kitazawa and colleagues, who produced a bispecific antibody to factors IXa and X that restores factor VIII hemostatic activity *in vivo*.

In addition, you will also find in this issue updates on international regulation on production and use of biopharmaceuticals and reminders about some November/December scientific meetings that could be of interest to you.

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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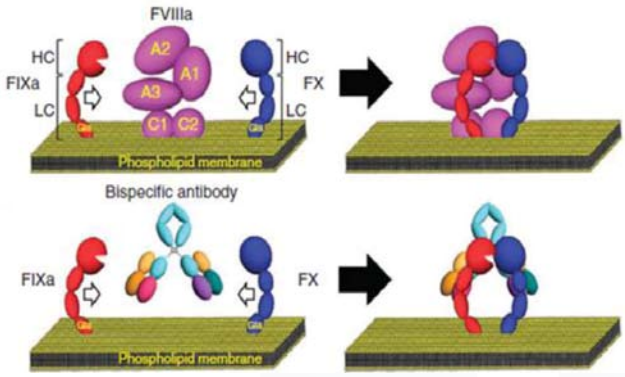
LITERATURE

This month's selected article

A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model.
Kitazawa T, Igawa T, Sampei Z, Muto A, Kojima T, Soeda T, Yoshihashi K, Okuyama-Nishida Y, Saito H, Tsunoda H, Suzuki T, Adachi H, Miyazaki T, Ishii S, Kamata-Sakurai M, Iida T, Harada A, Esaki K, Funaki M, Moriyama C, Tanaka E, Kikuchi Y, Wakabayashi T, Wada M, Goto M, Toyoda T, Ueyama A, Suzuki S, Haraya K, Tachibana T, Kawabe Y, Shima M, Yoshioka A, Hattori K.
Nat Med. 2012 Sep 30.

Exogenous supplementation of FVIII is the current common approach to treating the bleeding disorder Haemophilia A. However this replacement therapy comes up against two major obstacles: 30% of patients will develop inhibitors during the course of treatment, and the short half-life of the product necessitates repeated administrations meaning frequent venous access for FVIII injection, particularly hard to manage in paediatric patients.

To overcome these two drawbacks, Kitazawa and colleagues set out to generate a humanized bi-specific antibody that would act as FVIIIa cofactor in promoting the spatial interaction between FIXa and FXa. Their idea was based on the observation that the distance between the two binding sites of a human IgG is comparable to the distance between the FIXa- and FXa-binding sites of FVIIIa :



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Humanized antibodies have been shown to elicit inhibitors with a low incidence. Bearing no common amino acid sequence with FVIII, such agent would not be recognized either by existing neutralizing antibodies in previously FVIII-treated patients. Moreover, the subcutaneous route of administration could be envisaged.

The screening of some 40, 000 bi-specific antibodies lead to the selection of hBS23, which displayed in vitro coagulation activity in FVIII-deficient plasma, even in the presence of FVIII-specific inhibitors.
Haemostatic activity of hBS23 was further demonstrated in vivo, in a nonhuman primate model of acquired haemophilia A. Pharmacokinetic studies in cynomolgus monkeys gave evidence for a high bioavailability (84%) and a 14 days half-life of hBS23 after subcutaneous administration.

As discussed by the authors, the bi-specific antibody hBS23 may require further optimization in several ways before reaching the clinical stage. Yet, it represents a new perspective for treatment of Haemophilia A, which could theoretically overcome the major current shortcomings: biotherapeutics bioavailability and immunogenicity.

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Immunogenicity

Models for assessing immunogenicity and efficacy of new therapeutics for the treatment of haemophilia.
Saint-Remy JM, Reipert BM, Monroe DM.
Haemophilia. 2012 Jul;18 Suppl 4:43-7.

Stratification of Antibody-Positive Subjects by Antibody Level Reveals an Impact of Immunogenicity on Pharmacokinetics.
Zhou L, Hoofring SA, Wu Y, Vu T, Ma P, Swanson SJ, Chirmule N, Starcevic M.
AAPS J. 2012 Oct 9.

Characterization of anti-natalizumab antibodies in multiple sclerosis patients.
Lundkvist M, Engdahl E, Holmén C, Movérare R, Olsson T, Hillert J, Fogdell-Hahn A.
Mult Scler. 2012 Oct 8.

Low infliximab serum trough levels and anti-infliximab antibodies are prevalent in rheumatoid arthritis patients treated with infliximab in daily clinical practice: results of an observational cohort study.
van der Maas A, van den Bemt BJ, Wolbink GJ, van den Hoogen FH, van Riel PL, den Broeder AA.
BMC Musculoskelet Disord. 2012 Sep 24;13(1):184.

Minimizing immunogenicity of biopharmaceuticals by controlling critical quality attributes of proteins.
van Beers MM, Bardor M.
Biotechnol J. 2012 Oct 2

Plasma trough levels of adalimumab and infliximab in terms of clinical efficacy during the treatment of psoriasis.
Takahashi H, Tsuji H, Ishida-Yamamoto A, Iizuka H.
J Dermatol. 2012 Oct 5.

Methods

Improved analytical methods for the detection and quantification of neutralizing antibodies to biopharmaceuticals.
Tovey MG, Lallemand C.
Bioanalysis. 2012 Sep;4(17):2179-90.

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Challenges of developing and validating immunogenicity assays to support comparability studies for biosimilar drug development.
Cai XY, Thomas J, Cullen C, Gouty D.
Bioanalysis. 2012 Sep;4(17):2169-77.

PAAQD: Predicting immunogenicity of MHC class I binding peptides using amino acid pairwise contact potentials and quantum topological molecular similarity descriptors.
Saethang T, Hirose O, Kimkong I, Tran VA, Dang XT, T Nguyen LA, Le TK, Kubo M, Yamada Y, Satou K.
J Immunol Methods. 2012 Oct 8.

Biomarkers

Discovery of serum proteomic biomarkers for prediction of response to infliximab (a monoclonal anti-TNF antibody) treatment in Rheumatoid Arthritis: an exploratory analysis.
Ortea I, Roschitzki B, Ovalles JG, Longo JL, de la Torre I, González I, Gómez-Reino JJ, González A.
J Proteomics. 2012 Sep 20. pii: S1874-3919(12)00655-0

Predictive factors of rituximab response in rheumatoid arthritis: Results from a french university hospital.
Couderc M, Mathieu S, Pereira B, Glace B, Soubrier M.
Arthritis Care Res. 2012 Oct 8.

Systemic Lupus Erythematosus

Abatacept in the treatment of lupus.
Hoi AY, Littlejohn GO.
Expert Opin Biol Ther. 2012 Oct;12(10):1399-406

Rheumatoid Arthritis

Association of Rheumatoid Arthritis Risk Alleles with Response to Anti-TNF Biologics: Results from the CORRONA Registry and Meta-analysis.
Pappas DA, Oh C, Plenge RM, Kremer JM, Greenberg JD.
Inflammation. 2012 Sep 25.

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The efficacy of biologic agents in patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor inhibitors: a systematic review.
Moots RJ, Naisbett-Groet B.
Rheumatology. 2012 Sep 1

IBD

Comparative Effectiveness of Anti-TNF Agents for Crohn's Disease in a Tertiary Referral IBD Practice.
Patil SA, Rustgi A, Langenberg P, Cross RK.
Dig Dis Sci. 2012 Sep 27

Multiple Sclerosis

Natalizumab use in pediatric patients with relapsing-remitting multiple sclerosis.
Arnal-Garcia C, García-Montero MR, Málaga I, Millán-Pascual J, Oliva-Nacarino P, Ramió-Torrentà L, Oreja-Guevara C.
Eur J Paediatr Neurol. 2012 Sep 26. pii: S1090-3798(12)00196-1.

Immune therapy of multiple sclerosis - future strategies.
Meuth SG, Göbel K, Wiendl H.
Curr Pharm Des. 2012;18(29):4489-97.

Daclizumab Therapy for Multiple Sclerosis.
Bielekova B.
Neurotherapeutics. 2012 Oct 5.

B cells and antibodies in multiple sclerosis pathogenesis and therapy.
Krumbholz M, Derfuss T, Hohlfeld R, Meinl E.
Nat Rev Neurol. 2012 Oct 9

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Hemophilia

Characterisation of the post-translational modifications of a novel, human cell line-derived recombinant human factor VIII.
Kannicht C, Ramström M, Kohla G, Tiemeyer M, Casademunt E, Walter O, Sandberg H.
Thromb Res. 2012 Oct 8.

Successful immune tolerance induction consisting of high-dose factor VIII rich in von Willebrand factor and pulsed intravenous immunoglobulin: a case report.
Kubisz P, Plamenova I, Holly P, Stasko J.
J Med Case Rep. 2012 Oct 11;6(1):350.

Use of Haemate(®) P as immune tolerance induction in patients with severe haemophilia A who failed previous induction attempts: a multicentre observational study.
Rothschild C, D'oiron R, Borel-Derlon A, Gruel Y, Navarro R, Negrier C.
Haemophilia. 2012 Oct 8.

Basic immunology

Regulatory B cells control T-cell autoimmunity through IL-21-dependent cognate interactions.
Yoshizaki A, Miyagaki T, Dilillo DJ, Matsushita T, Horikawa M, Kountikov EI, Spolski R, Poe JC, Leonard WJ, Tedder TF.
Nature. 2012 Oct 14

Targeting IL-17 and T(H)17 cells in chronic inflammation.
Miossec P, Kolls JK.
Nat Rev Drug Discov. 2012 Oct;11(10):763-76.

Opinions/Commentaries

How I treat inhibitors in haemophilia.
Makris M, Hay CR, Gringeri A, D'Oiron R.
Haemophilia. 2012 Jul;18 Suppl 4:48-53.

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Thirty years of preclinical safety evaluation of biopharmaceuticals: did scientific progress lead to appropriate regulatory guidance?
Kooijman M, J K van Meer P, H M Moors E, Schellekens H.
Expert Opin Drug Saf. 2012 Sep;11(5):797-801.

REGULATION

EMA

European Medicines Agency invites feedback on the draft guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis
October 12

Orphan designation (EU/3/12/1030) granted by the European Commission to Novo Nordisk A/S, Denmark, for vatreptacog alfa (activated) for the treatment of haemophilia A.
September 12

Concept paper on the need for revision of the guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis
September 12

Reflection paper on immune tolerance induction in haemophilia-A patients with inhibitors, draft: consultation open
August 12

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CONFERENCES & MEETINGS

November

Internal Congress of Neuroimmunology	4-8, Boston, Massachusetts, USA	http://www.isni2012.org/
ACR/ARHP joint meeting	10-14, Washington D.C, USA	http://www.nxtbook.com
European workshop on immune-mediated autoimmune diseases	28-30, Noordwijk aan Zee, The Netherlands	http://www.ewimid.com

December

Antibody engineering and antibody therapeutics	2-6, San Diego, California, USA	http://www.ibclifesciences.com
2012 Advances in inflammatory bowel diseases	13-15, Hollywood, Florida, USA	http://www.advancesinibd.com
European workshop on immune-mediated autoimmune diseases	28-30, Noordwijk aan Zee, The Netherlands	http://www.ewimid.com

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