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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.
WELCOME

Dear Reader,

We would like to welcome you to the May 2013 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 highlight a publication by Liang et al. in Journal of Biological Chemistry, reporting on the first crystal structure resolution at 2.6Å of an anti-TFNα therapeutic antibody (infliximab) in complex with its target.

We would also like to draw your attention to a study on page 7 (see reference marked ***), in which many members of ABIRISK consortium took part outside the ABIRISK project and which demonstrated for the first time a role of CD84 in prediction RA biotherapy efficacy.

In addition, you will find in this issue some recent news from the European regulatory field.

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
Therapeutic anti-TNFα antibody infliximab was originally approved by the US FDA for the treatment of Crohn's disease. Its indications were soon to be extended to other diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and other inflammatory skin conditions. Taken together, anti-TNFα biotherapeutics (infliximab, adalimumab, etanercept, golimumab and certolizumab pegol) have been successfully used for TNFα-related diseases for over 10 years, but the precise mechanism of action by which anti-TNFα antibodies exert their high efficacy remains unclear. Previous crystallographic studies have depicted the molecular basis of TNFα interactions with its receptor TNFR2, and that of TNFβ with TNFR1. In the present paper, Liang et al. further report on the crystal structure of TNFα in complex with the therapeutic anti-TNFα antibody infliximab Fab fragment at 2.6Å, shedding light on to the molecular mechanisms underlying TNFα blockage.

The new crystal structures exhibited a 3:3 molar ratio for TNFα and infliximab Fab, as it was previously observed for both TNFα-TNFR1 and TNFβ-NFR2 complexes, indicative of the formation of an aggregated network for the inhibition of membrane-associated TNFα. Most importantly, the comparison of TNFα-infliximab Fab and TNFα-TNFR1 interfaces revealed an overlap of the receptor binding site with the antibody binding site on TNFα molecule, providing a structure-based rational for a spatial competition between infliximab and the TNF receptor for TNFα binding. Moreover, infliximab high measured avidity (4.2 pM) could be correlated with the 30 pairs of interaction found at the infliximab Fab-TNFα interface, and with a total buried region (1,977 Å²) higher than typical protein-protein interfaces (1,560–1,700 Å²).

Additionally, a large conformational change was observed in the E-F loop when TNFα binds the antibody. Since the E-F loop is the most divergent portion between TNFα and TNFβ, the authors suggest that this conformational change participate in the specificity of infliximab for TNFα.

Efficacy of monoclonal antibody therapy of TNFα-related inflammatory diseases often remains hindered by the apparition of inhibitors in a high number of patients. Crystal studies such as the one presented here give critical insights into the interaction of biotherapeutics with their targets at the molecular level. This may be key in designing further humanized therapeutic antibodies with limited inhibitors induction capacity, without altering their high specificity and avidity.

Structural basis for treating TNFα-associated diseases with the therapeutic antibody Infliximab.
J Biol Chem. 2013 Mar 15
Immunogenicity

**Factor VIII genotype characterization of haemophilia A affected patients with transient and permanent inhibitors: a comprehensive Argentine study of inhibitor risks.**
Rossetti LC, Szurkalo I, Radic CP, Abelleyro MM, Primiani L, Neme D, Candela M, Bianco RP, de Tezanos Pinto M, Larripa IB, De Brasi CD.

**Product-dependent anti-factor VIII antibodies.**
Butenas S, Krudysz-Amblo J, Rivard GE, G Mann K.
*Haemophilia*. 2013 Apr 4

**Polymorphic miRNA-mediated gene contribution to inhibitor development in haemophilia A.**
Bafunno V, Santacroce R, Chetta M, Peyvandi F, Sessa F, Chinni E, Longo V, Margaglione M.

**Methods**

**Generation and Characterization of Fully Human Monoclonal Antibodies Against Human Orai1 for Autoimmune Disease.**

**Nanomolar to subpicomolar affinity measurements of antibody-antigen interactions and protein multimerizations: fluorescence-assisted HPLC.**
Rispens T, Heer PO, Derksen NI, Wolbink G, van Schouwenburg PA, Kruithof S, Aalberse RC.
*Anal Biochem*. 2013 Mar 7

**Is the tiered immunogenicity testing of biologics the adequate approach in preclinical development?**
Sauerborn M.

**Nijmegen-Bethesda Assay to Measure Factor VIII Inhibitors.**
Duncan E, Collecutt M, Street A.  

**Animal models**

*Protection from articular damage by passive or active anti-tumour necrosis factor (TNF)-α immunotherapy in human TNF-α transgenic mice depends on anti-TNF-α antibody levels.*  
Semerano L, Biton J, Delavallée L, Duvallet E, Assier E, Bessis N, Bernier E, Dhellin O, Grouard-Vogel G, Boissier MC.  

*Prevention of arthritis by locally synthesized recombinant antibody neutralizing complement component c5.*  

*Adjuvant facilitates tolerance induction to factor VIII in hemophilic mice through a Foxp3-independent mechanism that relies on IL-10.*  
Oliveira VG, Agua-Doce A, Curotto de Lafaille M, Lafaille JJ, Graca L.  

**Biomarkers**

*Clinical predictors of an optimal response to natalizumab in multiple sclerosis*  
Sargento-Freitas J, Batista S, Macario C, Matias F, Sousa L.  

***Genome-Wide Association Study and Gene Expression Analysis Identifies CD84 as a Predictor of Response to Etanercept Therapy in Rheumatoid Arthritis.***  
Mahurkar S, Moldovan M, Suppiah V, O'Doherty C.

The potential use of expression profiling: implications for predicting treatment response in rheumatoid arthritis.
Smith SL, Plant D, Eyre S, Barton A.
Ann Rheum Dis. 2013 Mar 13

The 158VV Fc gamma receptor 3A genotype is associated with response to rituximab in rheumatoid arthritis: results of an Italian multicentre study.

Circulating microRNAs as biomarkers for disease staging in multiple sclerosis

Combined Serological, Genetic, and Inflammatory Markers Differentiate Non-IBD, Crohn's Disease, and Ulcerative Colitis Patients.
Inflamm Bowel Dis. 2013 May;19(6):1139-4

Systemic Lupus Erythematosus

New therapeutics in systemic lupus erythematosus.
Paz Z, Tsokos GC.

Abstracts of the 10th International Congress on SLE. April 18-21, 2013. Buenos Aires, Argentina
**Rheumatoid Arthritis**

**Biological Therapies for Rheumatoid Arthritis: Progress to Date.**
*BioDrugs*. 2013 Apr 5

**Inflammatory Bowel Disease**

**TGF-beta signaling manipulation as potential therapy for IBD.**
Marafini I, Zorzi F, Codazza S, Pallone F, Monteleone G.
*Curr Drug Targets*. 2013 Mar 13

**Review article: the role of anti-TNF in the management of ulcerative colitis - past, present and future.**
Danese S, Colombel JF, Peyrin-Biroulet L, Rutgeerts P, Reinisch W.

**Adherence to Anti-TNF Therapy in Inflammatory Bowel Diseases: A Systematic Review.**
Lopez A, Billioud V, Peyrin-Biroulet C, Peyrin-Biroulet L.

**Preoperative use of anti-TNF therapy and postoperative complications in inflammatory bowel diseases: A meta-analysis.**
Billioud V, Ford AC, Tedesco ED, Colombel JF, Roblin X, Peyrin-Biroulet L.

**Multiple Sclerosis**

**Pharmacodynamic Consequences of Administration of VLA-4 Antagonist CDP323 to Multiple Sclerosis Subjects: A Randomized, Double-Blind Phase 1/2 Study.**

**Efficacy and safety of interferon beta-1b sc in older RRMS patients-a posthoc analysis of the BEYOND study.**
*J Neurol.* 2013 Mar 17

**The Outlook for Alemtuzumab in Multiple Sclerosis.**
Williams T, Coles A, Azzopardi L. 
*BioDrugs.* 2013 Apr 5.

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**Hemophilia**

*A novel B-domain O-glycoPEGylated FVIII (N8-GP) demonstrates full efficacy and prolonged effect in hemophilic mice models.*

**Immune tolerance induction in haemophilia A patients with inhibitors by treatment with recombinant factor VIII: a retrospective non-interventional study.**
Rivard GE, Rothschild C, Toll T, Achilles K. 
*Haemophilia.* 2013 May;19(3):449-55

**Progress towards inducing immunologic tolerance to factor VIII.**
Scott DW, Pratt KP, Miao CH. 
*Blood.* 2013 Mar 15

**Innovative coagulation factors: albumin fusion technology and recombinant single-chain factor VIII.**
Schulte S. 

**Bringing new therapy options to the hemophilia community.**
Bensen-Kennedy D. 

**Haemophilia care in Europe - a survey of 35 countries.**
O'Mahony B, Noone D, Giangrande PL, Prihodova L. 
*Haemophilia.* 2013 Apr 4.
Basic immunology

**Tumor Necrosis Factor-α Blocks Differentiation and Enhances Suppressive Activity of Immature Myeloid Cells during Chronic Inflammation.**
Sade-Feldman M, Kanterman J, Ish-Shalom E, Elnekave M, Horwitz E, Baniyash M.

**Germinal center B cells govern their own fate via antibody feedback.**

Opinions/Commentaries/Across diseases reviews

**Challenges and approaches for the development of safer immunomodulatory biologics.**

**Biosimilars in IBD: hope or expectation?**
*Gut.* 2013 Mar 16

**Drug targets in the cytokine universe for autoimmune disease.**
Liu X, Fang L, Guo TB, Mei H, Zhang JZ.

**Clinical targeting of the TNF and TNFR superfamilies.**
Croft M, Benedict CA, Ware CF.
*Nat Rev Drug Discov.* 2013 Feb;12(2):147-68

**Monoclonal antibodies in neuroinflammatory diseases.**
Klotz L, Wiendl H.
*Expert Opin Biol Ther.* 2013 Mar 22

**Biologic therapy for autoimmune diseases: an update.**
Rosman Z, Shoenfeld Y, Zandman-Goddard G.
*BMC Med.* 2013 Apr 4;11:88

**Building a wall against biosimilars**
REGULATION

EMA

Opinion/decision on a Paediatric Investigation Plan (PIP): Mabthera, Therapeutic area: Immunology-Rheumatology-Transplantation/Oncology
Updated
April 2013

Human medicines European Public Assessment Report (EPAR): MabThera, rituximab
Revision: 28, Authorised
April 2013

Human medicines European Public Assessment Report (EPAR): Humira, adalimumab
Revision: 33, Authorised
April 2013

Opinion/decision on a Paediatric Investigation Plan (PIP): pegylated human recombinant factor VIII (BAX 855)
May 2013

Opinion/decision on a Paediatric Investigation Plan (PIP): Benlysta, Belimumab
Updated
May 2013

Opinion/decision on a Paediatric Investigation Plan (PIP): Sarilumab
May 2013

Scientific guideline: Draft guideline on similar biological medicinal products, draft: consultation open
May 2013