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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,

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

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LITERATURE

This month's selected article

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 TNRF1. 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 TNFbNFR2 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.

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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

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