TABLE OF CONTENTS

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

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.

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

WELCOME

Dear Reader,

We would like to welcome you to the June 2016 **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.

From now on, we will draw your attention to a selection of articles each month that we think make a difference in their respective fields.

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

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

LITERATURE

This month's selected article

This month, a large consensus elected this article, which stands as a milestone paper that will change the treatment of haemophilia in the next years dramatically from every second day i.v. protein substitution to weekly to monthly s.c. injection of a FVIII mimetic antibody :

Factor VIII-Mimetic Function of Humanized Bispecific Antibody in Hemophilia A.
Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, Fukazawa N, Yoneyama K, Yoshida H, Nogami K.
N Engl J Med. 2016 May 26;374(21):2044-53.

Commentary :
Bispecific antibody mimicking factor VIII.
Nogami K.
Thromb Res. 2016 May;141 Suppl 2:S34-5.

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

Immunogenicity

Posttranslational Modifications and the Immunogenicity of Biotherapeutics.
Jefferis R.
J Immunol Res. 2016;2016:5358272.

Adalimumab trough serum levels and anti-adalimumab antibodies in the long-term clinical outcome of patients with Crohn's disease.
Bodini G, Giannini EG, Savarino V, Del Nero L, Pellegatta G, De Maria C, Baldissarro I, Savarino E.
Scand J Gastroenterol. 2016 May 20:1-6.

Response to: 'Comparing the immunogenicity of the etanercept biosimilar SB4 with the innovator etanercept: another consideration' by Marshall et al.
Emery P, Vencovský J, Ghil J, Kang JW.
Ann Rheum Dis. 2016 May 4

Optimizing Treatment with TNF Inhibitors in Inflammatory Bowel Disease by Monitoring Drug Levels and Antidrug Antibodies.
Steenholdt C, Bendtzen K, Brynskov J, Ainsworth MA.
Inflamm Bowel Dis. 2016 Apr 29.

Methods

An Immunoinhibition Approach to Overcome the Impact of Pre-existing Antibodies on Cut Point Establishment for Immunogenicity Assessment of Moxetumomab Pasudotox.
Schneider AK, Vainshtein I, Roskos LK, Chavez C, Sun B, Liang M.
J Immunol Methods. 2016 May 21.

Quantifying Trace Amounts of Aggregates in Biopharmaceuticals Using Analytical Ultracentrifugation Sedimentation Velocity: Bayesian Analyses and F Statistics.
Wafer L, Kloczewiak M, Luo Y.
AAPS J. 2016 May 16.

Generation of a Highly Specific Monoclonal Anti-Infliximab Antibody for Harmonization of TNF-Coated Infliximab Assays.
Van Stappen T, Brouwers E, Tops S, Geukens N, Vermeire S, Declerck PJ, Gils A.
Ther Drug Monit. 2015 Aug;37(4):479-85.

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

Animal models

Animal Models of Rheumatoid Arthritis (I): Pristane-Induced Arthritis in the Rat.
Tuncel J, Haag S, Hoffmann MH, Yau AC, Hultqvist M, Olofsson P, Bäcklund J, Nandakumar KS, Weidner D, Fischer A, Leichsenring A, Lange F, Haase C, Lu S, Gulko PS, Steiner G, Holmdahl R.
PLoS One. 2016 May 26;11(5):e0155936

Animal models of inflammatory bowel disease: how useful are they really?
Kolios G.
Curr Opin Gastroenterol. 2016 May 19.

Biomarkers

Rheumatoid factor, not antibodies against citrullinated proteins, is associated with baseline disease activity in rheumatoid arthritis clinical trials.
Aletaha D, Alasti F, Smolen JS.
Arthritis Res Ther. 2015 Aug 26;17:229.

stimating disease activity using multi-biomarker disease activity scores in patients with rheumatoid arthritis treated with abatacept or adalimumab.
Fleischmann R, Connolly SE, Maldonado MA, Schiff M.
Arthritis Rheumatol. 2016 Apr 25.

Dynamic tracking of functional gene modules in treated juvenile idiopathic arthritis.
Du N, Jiang K, Sawle AD, Frank MB, Wallace CA, Zhang A, Jarvis JN.
Genome Med. 2015 Oct 24;7:109.

Biosimilars

Biosimilars in rheumatology: understanding the rigor of their development.
Goel N, Chance K.
Rheumatology (Oxford). 2016 May 30.

European Experience of Infliximab Biosimilars for the Treatment of Inflammatory Bowel Disease.
Lakatos P.
Gastroenterol Hepatol (N Y). 2016 Feb;12(2):119-21.

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

Pharmacology and metabolism of infliximab biosimilars - A new treatment option in inflammatory bowel diseases.
Włodarczyk M, Fichna J, Sobolewska-Włodarczyk A.
Pharmacol Rep. 2016 Apr 26

Clinical experience with infliximab biosimilar Remsima (CT-P13) in inflammatory bowel disease patients.
Jahnsen J.
Therap Adv Gastroenterol. 2016 May;9(3):322-9.

A randomized, controlled trial of efficacy and safety of Anbainuo, a bio-similar etanercept, for moderate to severe rheumatoid arthritis inadequately responding to methotrexate.
Chen XX, Li ZG, Wu HX, Zhao DB, Li XF, Xu JH, Tao Y, Yang NP, Hu SX, Huang AB, Jiang LD, Wang GC, Zhang X, Bao CD.
Clin Rheumatol. 2016 May 16.

Biosimilars in Inflammatory Bowel Disease: Facts and Fears of Extrapolation.
Ben-Horin S, Casteele NV, Schreiber S, Lakatos P.
Clin Gastroenterol Hepatol. 2016 May 20.

Systemic Lupus Erythematosus

IL-10-producing forkhead box protein 3-negative regulatory T cells inhibit B-cell responses and are involved in systemic lupus erythematosus.
Facciotti F, Gagliani N, Häringer B, Alfen JS, Penatti A, Maglie S, Paroni M, Iseppon A, Moro M, Crosti MC, Stölzel K, Romagnani C, Moroni G, Ingegnoli F, Torretta S, Pignataro L, Annoni A, Russo F, Pagani M, Abrignani S, Meroni P, Flavell R, Geginat J.
J Allergy Clin Immunol. 2016 Jan;137(1):318-21.

Arthritis

Circulating CD4+ T-cell number decreases in rheumatoid patients with clinical response to rituximab.
Piantoni S, Scarsi M, Tincani A, Airò P.
Rheumatol Int. 2015 Sep;35(9):1571-3

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

Complete clinical remission with tocilizumab in two infants with systemic juvenile idiopathic arthritis: a case series.
Maritsi DN, Onoufriou M, Vartzelis G, Eleftheriou D.
Scand J Rheumatol. 2016 May 24:1-2

Monitoring serum etanercept levels in juvenile idiopathic arthritis: a pilot study.
Alcobendas R, Rodríguez-Vidal A, Pascual-Salcedo D, Murias S, Remesal A, Diego C, Merino R.
Clin Exp Rheumatol. 2016 Apr 28.

Inflammatory Bowel Diseases

Biologic therapies in ulcerative colitis: primi inter pares?
Allocca M, Fiorino G, Gilardi D, Preatoni P, Papa A, Peyrin-Biroulet L, Danese S.
Curr Drug Targets. 2016 May 27.

The impact of updated NICE guidelines on biologic treatment of ulcerative colitis: reflections on past practices, the changing present and implications for the future.
Samaan MA, Irving PM.
Expert Opin Biol Ther. 2016 May 31:1-3.

Cost-effectiveness of adalimumab, infliximab or vedolizumab as first-line biological therapy in moderate-to-severe ulcerative colitis.
Yokomizo L, Limketkai B, Park KT.
BMJ Open Gastroenterol. 2016 May 3;3(1):e000093.

Safety of vedolizumab in the treatment of Crohn's disease and ulcerative colitis.
Hagan M, Cross RK.
Expert Opin Drug Saf. 2015;14(9):1473-9.

IBD: Tracking TNF and anti-TNF agents in inflamed gut tissue.
Ray K.
Nat Rev Gastroenterol Hepatol. 2015 Apr;12(4):189.

Interleukin-27 as a Novel Therapy for Inflammatory Bowel Disease: A Critical Review of the Literature.
Andrews C, McLean MH, Durum SK.
Inflamm Bowel Dis. 2016 May 26

The role of vedolizumab in patients with moderate-to-severe Crohn's disease and ulcerative colitis.
Shahidi N, Bressler B, Panaccione R.
Therap Adv Gastroenterol. 2016 May;9(3):330-8.

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
Innovative Medicines Initiative

Multiple Sclerosis

Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study.
Havrdová E, Belova A, Goloborodko A, Tisserant A, Wright A, Wallstroem E, Garren H, Maguire RP, Johns DR.
J Neurol. 2016 May 3.

Immunologic profiles of multiple sclerosis treatments reveal shared early B cell alterations.
Dooley J, Pauwels I, Franckaert D, Smets I, Garcia-Perez JE, Hilven K, Danso-Abeam D, Terbeek J, Nguyen AT, De Muynck L, Decallonne B, Dubois B, Liston A, Goris A.
Neurol Neuroimmunol Neuroinflamm. 2016 May 10;3(4)

Hemophilia

A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A.
Peyvandi F, Mannucci PM, Garagiola I, El-Beshlawy A, Elalfy M, Ramanan V, Eshghi P, Hanagavadi S, Varadarajan R, Karimi M, Manglani MV, Ross C, Young G, Seth T, Apte S, Nayak DM, Santagostino E, Mancuso ME, Sandoval Gonzalez AC, Mahlangu JN, Bonanad Boix S, Cerqueira M, Ewing NP, Male C, Owaidah T, Soto Arellano V, Kobrinsky NL, Majumdar S, Perez Garrido R, Sachdeva A, Simpson M, Thomas M, Zanon E, Antmen B, Kavakli K, Manco-Johnson MJ, Martinez M, Marzouka E, Mazzucconi MG, Neme D, Palomo Bravo A, Paredes Aguilera R, Prezotti A, Schmitt K, Wicklund BM, Zulfikar B, Rosendaal FR.
N Engl J Med. 2016 May 26;374(21):2054-64.

Innovative Pharmacological Therapies for the Hemophilias Not Based on Deficient Factor Replacement.
Mannucci PM, Mancuso ME, Santagostino E, Franchini M.
Semin Thromb Hemost. 2016 May 5.

Basic immunology

Antigen processing * Special section: New concepts in antibody therapeutics
Current Opinion in Immunology
Volume 40 , Pages 1-130, June 2016

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

Development and **maintenance** of **intestinal regulatory T cells**.
Tanoue T, Atarashi K, Honda K.
Nat Rev Immunol. 2016 May;16(5):295-309.

AIRE expands: **new roles** in **immune tolerance** and **beyond**.
Anderson MS, Su MA.
Nat Rev Immunol. 2016 Apr;16(4):247-58.

REGULATION

EMA

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol
Revision: 16, Authorised

Pending EC decision: Humira, adalimumab
Opinion date: 26-May-2016

Pending EC decision: Tysabri, natalizumab
Opinion date: 26-May-2016

Pending EC decision: Simponi, golimumab
Opinion date: 26-May-2016

Human medicines European public assessment report (EPAR): Humira, adalimumab
Revision: 45, Authorised

Referral: Article 20 procedures, Tysabri, natalizumab (updated)

Human medicines European public assessment report (EPAR): Tysabri, natalizumab
Revision: 22, Authorised

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

Agenda

Programme - Targeted consultation on development of new medicinal products for the treatment of rheumatoid arthritis

Human medicines European public assessment report (EPAR): Enbrel, etanercept
Revision: 48, Authorised

Scientific guideline:

Concept paper on the revision of the 'Guideline on the environmental risk assessment of medicinal products for human use', **draft: consultation open**

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