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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 May 2015 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.

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

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LITERATURE

This month's selected articles

1. Immunogenicity of biosimilars is an very important issue and a future challenge:

Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima.
Ben-Horin S, Yavzori M, Benhar I, Fudim E, Picard O, Ungar B, Lee S, Kim S, Eliakim R, Chowers Y.
Gut. 2015 Apr 20.

2. Association of immune responses with HLA class II molecules points out the importance of HLA molecules in the control of immunogenicity but also raises the question of the mechanistic reasons of this genetic link :

Immunogenicity to infliximab is associated with HLA-DRB1.
Billiet T, Vande Casteele N, Van Stappen T, Princen F, Singh S, Gils A, Ferrante M, Van Assche G, Cleynen I, Vermeire S.
Gut. 2015 Apr 15.

3. Therapeutic drug monitoring, measuring clinically relevant ADA, cost effective individualised therapies are all hot topics currently. Bendtzen provides a sound overview to these topics :

Immunogenicity of Anti-TNF-α Biotherapies: I. Individualized Medicine Based on Immunopharmacological Evidence.
Bendtzen K.
Front Immunol. 2015 Apr 8;6:152.

Immunogenicity of Anti-TNF-α Biotherapies: II. Clinical Relevance of Methods Used for Anti-Drug Antibody Detection.
Bendtzen K.
Front Immunol. 2015 Apr 8;6:109.

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Immunogenicity

Standardizing terms, definitions and concepts for describing and interpreting unwanted immunogenicity of biopharmaceuticals: Recommendations of the innovative medicines initiative **ABIRISK** consortium.
Rup B, Pallardy M, Sikkema D, Albert T, Allez M, Broet P, Carini C, Creeke P, Davidson J, De Vries N, Finco D, Fogdell-Hahn A, Havrdova E, Hincelin-Mery A, Holland MC, Erik P, Jensen H, Jury EC, Kirby H, Kramer D, Lacroix-Desmazes S, Legrand J, Maggi E, Maillère B, Mariette X, Mauri C, Mikol V, Mulleman D, Oldenburg J, Paintaud G, Ross Pedersen C, Ruperto N, Seitz R, Spindeldreher S, Deisenhammer F; **ABIRISK** Consortium.
Clin Exp Immunol. 2015 May 8.

The effect of antidrug antibodies on the sustainable efficacy of biologic therapies in rheumatoid arthritis: practical consequences.
Keiserman M, Codreanu C, Handa R, Xibillé-Friedmann D, Mysler E, Briceño F, Akar S.
Expert Rev Clin Immunol. 2014 Aug;10(8):1049-57

Therapeutic outcomes, assessments, risk factors and mitigation efforts of immunogenicity of therapeutic protein products.
Yin L, Chen X, Vicini P, Rup B, Hickling TP.
Cell Immunol. 2015 Mar 14;295(2):118-126.

Combination of C-reactive protein, infliximab trough levels and stable but not transient antibodies to infliximab are associated with loss of response to infliximab in inflammatory bowel disease.
Roblin X, Marotte H, Leclerc M, Del Tedesco E, Phelip JM, Peyrin-Biroulet L, Paul S.
J Crohns Colitis. 2015 Apr 19

Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial.
Baert F, Kondragunta V, Lockton S, Vande Casteele N, Hauenstein S, Singh S, Karmiris K, Ferrante M, Gils A, Vermeire S.
Gut. 2015 Apr 10.

The quintessence of immunogenicity reporting for biotherapeutics.
Shankar G, Arkin S, Devanarayan V, Kromminga A, Quarmby V, Richards S, Subramanyam M, Swanson S.
Nat Biotechnol. 2015 Apr 7;33(4):334-6.

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Methods

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Gene expression of cultured human chondrocytes as a model for assessing neutralization efficacy of soluble TNFα by TNFα antagonists.
Barlič A, Žigon S, Blejec A, Kregar Velikonja N.
Biologicals. 2015 Apr 4.

Animal models

Projecting human pharmacokinetics of monoclonal antibodies from nonclinical data: comparative evaluation of prediction approaches in early drug development.
Wang J, Iyer S, Fielder PJ, Davis JD, Deng R.
Biopharm Drug Dispos. 2015 Apr 13.

A New Approach for the Treatment of Arthritis in Mice with a Novel Conjugate of an Anti-C5aR1 Antibody and C5 Small Interfering RNA.
Mehta G, Scheinman RI, Holers VM, Banda NK.
J Immunol. 2015 Apr 27. pi

Biomarkers

Effect of prednisone on type I interferon signature in rheumatoid arthritis: consequences for response prediction to rituximab.
de Jong TD, Vosslamber S, Blits M, Wolbink G, Nurmohamed MT, van der Laken CJ, Jansen G, Voskuyl AE, Verweij CL.
Arthritis Res Ther. 2015 Mar 23;17(1):78

Expression of GM-CSF in T Cells Is Increased in Multiple Sclerosis and Suppressed by IFN-β Therapy.
Rasouli J, Ciric B, Imitola J, Gonnella P, Hwang D, Mahajan K, Mari ER, Safavi F, Leist TP, Zhang GX, Rostami A.
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Low Baseline Interleukin-17A Levels Are Associated with Better Treatment Response at 12 Weeks to Tocilizumab Therapy in Rheumatoid Arthritis Patients.
Lee SJ, Park W, Park SH, Shim SC, Baek HJ, Yoo DH, Kim HA, Lee SK, Leee YJ, Park YE, Cha HS, Park JK, Lee EY, Lee EB, Song YW.
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Association of HLA-DRB1 haplotypes with rheumatoid arthritis severity, mortality, and treatment response.
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miRNA in multiple sclerosis: search for novel biomarkers.
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Mult Scler. 2015 Apr 28.

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Eur J Immunol. 2015 Feb;45(2):344-55.

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Sennikov SV, Alshevskaya AA, Shkaruba NS, Chumasova OA, Sizikov AE, Lopatnikova JA.
Cytokine. 2015 Mar 27;73(2):288-294.

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The IL-23-IL-17 axis in inflammatory arthritis.
Lubberts E.
Nat Rev Rheumatol. 2015 Apr 28.

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Rheumatoid arthritis: Biological therapy other than anti-TNF.
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Int Immunopharmacol. 2015 Mar 31.

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Takahashi N, Kojima T, Kaneko A, Kida D, Hirano Y, Fujibayashi T, Yabe Y, Takagi H, Oguchi T, Miyake H, Kato T, Watanabe T, Hayashi M, Kanayama Y, Funahashi K, Asai S, Yoshioka Y, Takemoto T, Terabe K, Asai N, Ishiguro N.
J Rheumatol. 2015 Apr 1.

A genome-wide association study identifies a new locus associated with the response to anti-TNF therapy in rheumatoid arthritis.
Julià A, Fernandez-Nebro A, Blanco F, Ortiz A, Cañete JD, Maymó J, Alperi-López M, Fernández-Gutierrez B, Olivè A, Corominas H, Erra A, Acosta-Colman I, Alonso A, López-Lasanta M, Tortosa R, Tornero J, Marsal S.
Pharmacogenomics J. 2015 Apr 21

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Ann Rheum Dis. 2015 Apr 29.

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Echarri A, Ollero V, Barreiro-de Acosta M, Fernández-Villaverde A, Hernández V, Lorenzo A, Pereira S, Carpio D, Castro J; EIGA Group.
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Pharmacotherapy. 2015 Apr;35(4):412-23.

Which patients with inflammatory bowel disease should receive combination therapy?
Cross RK.
Expert Rev Gastroenterol Hepatol. 2015 Apr 25:1-3.

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Yarur AJ, Rubin DT.
Inflamm Bowel Dis. 2015 Apr 21

Efficacy and Safety of Natalizumab and Vedolizumab for the Management of Crohn's Disease: A Systematic Review and Meta-analysis.
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Inflamm Bowel Dis. 2015 Apr 7.

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Vedolizumab for Induction and Maintenance of Remission in Ulcerative Colitis: A Cochrane Systematic Review and Meta-analysis.
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Inflamm Bowel Dis. 2015 May;21(5):1151-9.

Appropriateness and long-term discontinuation rate of biological therapies in ulcerative colitis.
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J Crohns Colitis. 2014 Aug 1;8(8):825-34

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Expert Opin Investig Drugs. 2015 Apr 10:1-8

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Wendt E, Keshav S.
Clin Exp Gastroenterol. 2015 Apr 7;8:119-30.

Multiple Sclerosis

Immunomodulatory therapies for relapsing-remitting multiple sclerosis: monoclonal antibodies, currently approved and in testing.
Craddock J, Markovic-Plese S.
Expert Rev Clin Pharmacol. 2015 May;8(3):283-96.

IFN-β Therapy Regulates TLR7-Mediated Response in Plasmacytoid Dendritic Cells of Multiple Sclerosis Patients Influencing an Anti-Inflammatory Status.
Severa M, Rizzo F, Giacomini E, Annibali V, Gafa V, Romano S, Buscarinu MC, Fornasiero A, Salvetti M, Coccia EM.
J Interferon Cytokine Res. 2015 Apr 29

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The vitamin D controversy (Part 1).
Rieckmann P.
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Alroughani R.
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Efficacy and safety of Alemtuzumab in treatment-naive patients with relapsing-remitting multiple sclerosis: Four-year follow-up of the Care-MS I study.
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Recombinant B domain deleted porcine factor VIII for the treatment of bleeding episodes in adults with acquired hemophilia A.
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Rituximab for treating inhibitors in people with inherited severe hemophilia.
Liu Y, Zhang L, Santoro C, Song J, Rodriguez A, Wang L.
Cochrane Database Syst Rev. 2015 Apr 4

Opinions/Commentaries/Across diseases reviews

Internalization of rituximab and the efficiency of B cell depletion in rheumatoid arthritis and systemic lupus erythematosus.
Reddy V, Cambridge G, Isenberg D, Glennie M, Cragg M, Leandro M.
Arthritis Rheumatol. 2015 Apr 27.

REGULATION

EMA

Workshop on haemophilia registries, European Medicines Agency, London, UK, From: 01-Jul-2015, To: 02-Jul-2015
Outline of the workshop on haemophilia registries

Human medicines European public assessment report (EPAR): Inflectra, infliximab
Revision: 7, Authorised

Human medicines European public assessment report (EPAR): Remsima, infliximab
Revision: 6, Authorised

Report from the European Medicines Agency/European Federation of Pharmaceutical Industries and Associations workshop on the importance of dose finding and dose selection for the successful development, licensing and lifecycle management of medicinal products

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