

TABLE OF CONTENTS

INTRODUCTION	2
WELCOME	3
LITERATURE	4
This month's selected articles	4
Immunogenicity	5
Methods	5
Animal models	6
Biomarkers	6
Systemic Lupus Erythematosus	7
Rheumatoid Arthritis	8
Inflammatory Bowel Diseases	9
Multiple Sclerosis	10
Hemophilia	10
Opinions/Commentaries/Across diseases reviews	11
REGULATION	12
EMA	12

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 rheumatism (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 November 2015 **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 - in particular, we would like to point out the EMA Scientific Guidelines on immunogenicity open for comment.

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

LITERATURE

This month's selected articles

1. In this paper, Patakas et al. decipher the mode of action of Abatacept, a CTL4-Ig molecule that interacts with the CD80/CD86 co-stimulation molecules. They show that Abatacept does not induce T cell tolerance but inhibits T cell activation, which results in reduced functionality of antigen presenting cells

[Abatacept inhibits T cell priming by inducing of a unique transcriptional profile that reduces their ability to activate antigen presenting cells.](#)

Patakas A, Ji RR, Weir W, Connolly SE, Benson RA, Nadler SG, Brewer JM, McInnes IB, Garside P.
Arthritis Rheumatol. 2015 Oct 16

2. This paper show that the prevalence of ADA is 15% with golimumab a full human anti-TNF very close to the that observed with adalimumab and associated with low serum level

[Immunogenicity, drug trough levels and therapeutic response in patients with rheumatoid arthritis or ankylosing spondylitis after 24-week golimumab treatment.](#)

Chen DY, Chen YM, Hung WT, Chen HH, Hsieh CW, Chen YH, Huang WN, Hsieh TY.
Ann Rheum Dis. 2015 Oct 6

Immunogenicity

[B cell epitopes on infliximab identified by oligopeptide microarray with unprocessed patient sera.](#)

Homann A, Röckendorf N, Kromminga A, Frey A, Jappe U.
J Transl Med. 2015 Oct 29;13(1):339.

Methods

[Monitoring antibody aggregation in early drug development using Raman spectroscopy and perturbation-correlation moving windows.](#)

Gómez de la Cuesta R, Goodacre R, Ashton L.
Anal Chem. 2014 Nov 18;86(22):11133-40.

[Predicting accelerated aggregation rates for monoclonal antibody formulations, and challenges for low-temperature predictions.](#)

Brummitt RK, Nesta DP, Roberts CJ.
J Pharm Sci. 2011 Oct;100(10):4234-43.

[High-resolution analysis of the murine MHC class II immunopeptidome.](#)

Sofron A, Ritz D, Neri D, Fugmann T.
Eur J Immunol. 2015 Oct 23.

[Effects of surfaces and leachables on the stability of biopharmaceuticals.](#)

Bee JS, Randolph TW, Carpenter JF, Bishop SM, Dimitrova MN.
J Pharm Sci. 2011 Oct;100(10):4158-70.

[Fusion protein technologies for biopharmaceuticals: Applications and challenges.](#)

Berger S, Lowe P, Tesar M.
MAbs. 2015 May 4;7(3):456-60.

[Quantification of a bifunctional drug in the presence of an immune response: a ligand-binding assay specific for 'active' drug.](#)

Staack RF, Jordan G, Viert M, Schäfer M, Papadimitriou A, Heinrich J.
Bioanalysis. 2015 Oct 20.

Animal models

[Fc Receptor-mediated Effector Function Contributes to the Therapeutic Response of Anti-TNF Monoclonal Antibodies in a Mouse Model of Inflammatory Bowel Disease.](#)

McRae BL, Levin AD, Wildenberg ME, Koelink PJ, Bousquet P, Mikaelian I, Sterman AS, Bryant S, D'Haens G, Kamath R, Salfeld J, van den Brink GR.

J Crohns Colitis. 2015 Oct 1.

[Generation and preclinical characterization of an antibody specific for SEMA4D.](#)

Fisher TL, Reilly CA, Winter LA, Pandina T, Jonason A, Scrivens M, Balch L, Bussler H, Torno S, Seils J, Mueller L, Huang H, Klimatcheva E, Howell A, Kirk R, Evans E, Paris M, Leonard JE, Smith ES, Zauderer M.

MAbs. 2015 Oct 2:0.

[Evaluation of the toxicology and pharmacokinetics of recombinant factor VIII Fc fusion protein in animals.](#)

Dumont JA, Loveday KS, Light DR, Pierce GF, Jiang H.

Thromb Res. 2015 Jul 23.

Biomarkers

[Relationship between baseline/early changes in c-reactive protein and interleukin-6 and clinical response to tocilizumab for rheumatoid arthritis.](#)

Wang J, Devenport J, Low J, Yu D, Hitraya E.

Arthritis Care Res (Hoboken). 2015 Oct 16.

[Lymphocytosis as a response biomarker of natalizumab therapeutic efficacy in multiple sclerosis.](#)

Signoriello E, Lanzillo R, Brescia Morra V, Di Iorio G, Fratta M, Carotenuto A, Lus G.

Mult Scler. 2015 Oct 9.

[Biomarkers in Remission According to Different Criteria in Patients with Rheumatoid Arthritis.](#)

Yilmaz-Oner S, Ozen G, Can M, Atagunduz P, Direskeneli H, Inanc N.

J Rheumatol. 2015 Oct 15.

[Combination of B cell biomarkers as independent predictors of response in patients with rheumatoid arthritis treated with rituximab.](#)

Tony HP, Roll P, Mei HE, Blümner E, Straka A, Gnuegge L, Dörner T.

Clin Exp Rheumatol. 2015 Oct 30.

[Serum 14-3-3 \$\eta\$ level is associated with severity and clinical outcomes of rheumatoid arthritis, and its pretreatment level is predictive of DAS28 remission with tocilizumab.](#)

Hirata S, Marotta A, Gui Y, Hanami K, Tanaka Y.
Arthritis Res Ther. 2015 Oct 9;17:280

[IgA rheumatoid factor as a serological predictor of poor response to tumour necrosis factor \$\alpha\$ inhibitors in rheumatoid arthritis.](#)

Sakthiswary R, Shaharir SS, Mohd Said MS, Asrul AW, Shahril NS.
Int J Rheum Dis. 2014 Nov;17(8):872-7.

[Upregulation of integrin expression on monocytes in multiple sclerosis patients treated with natalizumab.](#)

Dallari S, Franciotta D, Carluccio S, Signorini L, Gastaldi M, Colombo E, Bergamaschi R, Elia F, Villani S, Ferrante P, Delbue S.
J Neuroimmunol. 2015 Oct 15;287:76-9.

[Higher expression of IL-12R \$\beta\$ 2 is associated with lower risk of relapse in relapsing-remitting multiple sclerosis patients on interferon- \$\beta\$ 1b therapy during 3-year follow-up.](#)

Milosevic E, Dujmovic I, Markovic M, Mesaros S, Rakocevic G, Drulovic J, Stojkovic MM, Popadic D.
J Neuroimmunol. 2015 Oct 15;287:64-70.

Systemic Lupus Erythematosus

[Systemic lupus erythematosus exacerbation following cessation of belimumab treatment.](#)

Furer V, Zisman D, Pokroy-Shapira E, Molad Y, Elkayam O, Paran D.
Scand J Rheumatol. 2015 Oct 29:1-4.

[Remission in SLE: closing in on the target.](#)

van Vollenhoven RF, Voskuyl A, Morand E, Aranow C.
Ann Rheum Dis. 2015 Oct 28.

[Belimumab in systemic lupus erythematosus.](#)

Vilas-Boas A, Morais SA, Isenberg DA.
RMD Open. 2015 Mar 3;1(1):e000011.

Rheumatoid Arthritis

[Eosinophilia predicts poor clinical outcomes in recent-onset arthritis: results from the ESPOIR cohort.](#)

Guellec D, Milin M, Cornec D, Tobon GJ, Marhadour T, Jousse-Joulin S, Chiochia G, Vittecocq O, Devauchelle-Pensec V, Saraux A.

RMD Open. 2015 Jul 15;1(1):e000070.

[Vitamin D in rheumatoid arthritis-towards clinical application.](#)

Jeffery LE, Raza K, Hewison M.

Nat Rev Rheumatol. 2015 Oct 13.

[Efficacy and safety of subcutaneous golimumab in methotrexate-naïve patients with rheumatoid arthritis: 5-year results of the GO-BEFORE trial.](#)

Emery P, Fleischmann RM, Strusberg I, Durez P, Nash P, Amante E, Churchill M, Park W, Pons-Estel B, Han C, Gathany TA, Xu S, Zhou Y, Leu JH, Hsia EC.

Arthritis Care Res (Hoboken). 2015 Oct 16.

[Biological treatment in systemic juvenile idiopathic arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent.](#)

Woerner A, Uettwiller F, Melki I, Mouy R, Wouters C, Bader-Meunier B, Quartier P.

RMD Open. 2015 Apr 30;1(1):e000036.

[Short-term efficacy reliably predicts long-term clinical benefit in rheumatoid arthritis clinical trials as demonstrated by model-based meta-analysis.](#)

Wang Y, Zhu R, Xiao J, Davis JC Jr, Mandema JW, Jin JY, Tang MT.

J Clin Pharmacol. 2015 Oct 30.

[Late-onset neutropenia after treatment with rituximab for rheumatoid arthritis and other autoimmune diseases: data from the AutoImmunity and Rituximab registry.](#)

Salmon JH, Cacoub P, Combe B, Sibilia J, Pallot-Prades B, Fain O, Cantagrel A, Dougados M, Andres E, Meyer O, Carli P, Pertuiset E, Pane I, Maurier F, Ravaud P, Mariette X, Gottenberg JE.

RMD Open. 2015 Jun 30;1(1):e000034.

[Should rheumatoid arthritis patients preferentially be treated with tocilizumab after rituximab failure?](#)

Verschueren P.

Rheumatology (Oxford). 2015 Oct 9.

[ROUTINE-a prospective, multicentre, non-interventional, observational study to evaluate the safety and effectiveness of intravenous tocilizumab for the treatment of active rheumatoid arthritis in daily practice in Germany.](#)

Iking-Konert C, von Hinüber U, Richter C, Schwenke H, Gürtler I, Kästner P, Klapperich B, Peters MA, Burmester GR.

Rheumatology (Oxford). 2015 Oct 29.

[Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial.](#)

Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Kelman A, Dimonaco S, Mitchell N.

Ann Rheum Dis. 2015 Oct 28.

[Immunological evaluation of rheumatoid arthritis patients treated with itolizumab.](#)

Aira LE, Hernández P, Prada D, Chico A, Gómez JA, González Z, Fuentes K, Viada C, Mazorra Z.

MAbs. 2015 Oct 15:0.

[Levels of interleukin-1 beta can predict response to tocilizumab therapy in rheumatoid arthritis: the PETITE \(predictors of effectiveness of tocilizumab therapy\) study.](#)

Okano T, Inui K, Tada M, Sugioka Y, Mamoto K, Wakitani S, Koike T, Nakamura H.

Rheumatol Int. 2015 Oct 5.

Inflammatory Bowel Diseases

[Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease - algorithm for practical management.](#)

Ding NS, Hart A, De Cruz P.

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[Subcutaneous Ustekinumab Provides Clinical Benefit for Two-Thirds of Patients With Crohn's Disease Refractory to Anti-Tumor Necrosis Factor Agents.](#)

Wils P, Bouhnik Y, Michetti P, Flourie B, Brixi H, Bourrier A, Allez M, Duclos B, Grimaud JC, Buisson A, Amiot A, Fumery M, Roblin X, Peyrin-Biroulet L, Filippi J, Bouguen G, Abitbol V, Coffin B, Simon M, Laharie D, Pariente B; Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID).

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[Therapeutic innovations in Inflammatory bowel diseases.](#)

Vanhove W, Nys K, Vermeire S.

Clin Pharmacol Ther. 2015 Oct 28.

[BIOLOGIC THERAPY IN IMMUNE MEDIATED INFLAMMATORY DISEASE: BASIC SCIENCE AND CLINICAL CONCEPTS.](#)

Molinelli E, Campanati A, Ganzetti G, Offidani A.
Curr Drug Saf. 2015 Oct 14.

[Tacrolimus or infliximab for severe ulcerative colitis: short-term and long-term data from a retrospective observational study.](#)

Minami N, Yoshino T, Matsuura M, Koshikawa Y, Yamada S, Toyonaga T, Madian A, Honzawa Y, Nakase H.
BMJ Open Gastroenterol. 2015 Feb 20;2(1):e000021.

Multiple Sclerosis

[Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis.](#)

Kappos L, Wiendl H, Selmaj K, Arnold DL, Havrdova E, Boyko A, Kaufman M, Rose J, Greenberg S, Sweetser M, Riester K, O'Neill G, Elkins J.
N Engl J Med. 2015 Oct 8;373(15):1418-28

[Emerging immunopharmacological targets in multiple sclerosis.](#)

Farjam M, Zhang GX, Ciric B, Rostami A.
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[Alemtuzumab for multiple sclerosis: Long term follow-up in a multi-centre cohort.](#)

Willis MD, Harding KE, Pickersgill TP, Wardle M, Pearson OR, Scolding NJ, Smee J, Robertson NP.
Mult Scler. 2015 Oct 29.

[Proinflammatory GM-CSF-producing B cells in multiple sclerosis and B cell depletion therapy.](#)

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Sci Transl Med. 2015 Oct 21;7(310):310ra166.

Hemophilia

[The anti-CD20 monoclonal antibody rituximab to treat acquired haemophilia A.](#)

D'arena G, Grandone E, Di Minno MN, Musto P, Di Minno G.

Blood Transfus. 2015 Sep 3:1-7.

[In vivo induction of regulatory T cells for immune tolerance in hemophilia.](#)

Wang X, Terhorst C, Herzog RW.

Cell Immunol. 2015 Oct 9.

[T cell response to FVIII.](#)

Jacquemin M, Saint-Remy JM.

Cell Immunol. 2015 Sep 26.

Opinions/Commentaries/Across diseases reviews

[Biologic efficacy optimization-a step towards personalized medicine.](#)

Kiely PD.

Rheumatology (Oxford). 2015 Sep 30.

[Leukocyte integrins: role in leukocyte recruitment and as therapeutic targets in inflammatory disease.](#)

Mitroulis I, Alexaki VI, Kourtzelis I, Ziogas A, Hajishengallis G, Chavakis T.

Pharmacol Ther. 2015 Mar;147:123-35.

REGULATION

EMA

[Scientific guideline: Draft guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins, draft: consultation open](#)

Consultation start date [01/10/2015](#)

Consultation end date [31/01/2016](#)

[Opinion/decision on a Paediatric investigation plan \(PIP\): PEGylated recombinant factor VIII](#)

Updated
October 2015

[Human medicines European public assessment report \(EPAR\): Avonex, interferon beta-1a](#)

Revision: 24, Authorised
October 2015

[Human medicines European public assessment report \(EPAR\): Humira, adalimumab,](#)

Revision: 41, Authorised
October 2015

[Pharmaceutical industry](#)

Updated
October 2015