

TABLE OF CONTENTS

INTRODUCTION	2
WELCOME	3
LITERATURE	4
This month's selected article	4
Immunogenicity	5
Methods	5
Biomarkers	5
Animal models	6
Biosimilars	6
Rheumatoid Arthritis	7
Inflammatory Bowel Disease	9
Multiple Sclerosis	9
Hemophilia	10
Opinions/Commentaries/ Across diseases reviews	10
REGULATION	11
EMA	11

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 Reactions 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.
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WELCOME

Dear Reader,

We would like to welcome you to the November 2016 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.

Each month we draw your attention to a selection of articles 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 article

Neutralizing capacity of monoclonal and polyclonal anti-natalizumab antibodies: the immune response to antibody therapeutics preferentially targets the antigen binding site.

van Schie KA, Kruithof S, van Schouwenburg PA, Vennegoer A, Killestein J, Wolbink G, Rispens T.
J Allergy Clin Immunol. 2016 Oct 4.

Continuous work of this group (unfortunately not ABIRISK members) on exploring characteristics of ADA mostly against mAbs. In this case confirming that probably all Natalizumab ADA are actually neutralizing underlining its clinical relevance.



Immunogenicity

Risks of inhibitors from recombinant factor VIII: a quarter of a century to reach the conclusion.

Burnouf T, Strengers PF.

J Thromb Haemost. 2016 Oct;14(10):2073-2074.

Effect of growth hormone and IgG aggregates on dendritic cells activation and T-cells polarization.

Gallais Y, Szely N, Legrand FX, Leroy A, Pallardy M, Turbica I.

Immunol Cell Biol. 2016 Oct 7.

Methods

Robust factor selection in early cell culture process development for the production of a biosimilar monoclonal antibody.

Sokolov M, Ritscher J, MacKinnon N, Bielser JM, Brühlmann D, Rothenhäuser D, Thanei G, Soos M, Stettler M, Souquet J, Broly H, Morbidelli M, Butté A.

Biotechnol Prog. 2016 Sep 30.

Analytical and Clinical Evaluation of an Immunoassay for Estimating Immunogenicity of Infliximab and Etanercept in Indian Population.

Ghia C, Akerkar S, Sabnis S, Rao U, Rambhad G.

J Assoc Physicians India. 2016 Sep;64(9):14-17.

Biomarkers

CD40-Mediated NF-κB Activation in B Cells Is Increased in Multiple Sclerosis and Modulated by Therapeutics.

Chen D, Ireland SJ, Remington G, Alvarez E, Racke MK, Greenberg B, Frohman EM, Monson NL.

J Immunol. 2016 Oct 26.

B cells of multiple sclerosis patients induce autoreactive proinflammatory T cell responses.

Fraussen J, Claes N, Van Wijmeersch B, van Horssen J, Stinissen P, Hupperts R, Somers V.

Clin Immunol. 2016 Oct 4. pii: S1521-6616(16)30163-2.



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[Repeated decrease of CD4+ T-cell counts in patients with rheumatoid arthritis over multiple cycles of rituximab treatment.](#)

Lavielle M, Mulleman D, Goupille P, Bahuaud C, Sung HC, Watier H, Thibault G.
Arthritis Res Ther. 2016 Oct 28;18(1):253.

[Interferon-β therapy specifically reduces pathogenic memory B cells in multiple sclerosis patients by inducing a FAS-mediated apoptosis.](#)

Rizzo F, Giacomini E, Mechelli R, Buscarinu MC, Salvetti M, Severa M, Coccia EM.
Immunol Cell Biol. 2016 Oct;94(9):886-894

[Alemtuzumab treatment alters circulating innate immune cells in multiple sclerosis.](#)

Gross CC, Ahmetspahic D, Ruck T, Schulte-Mecklenbeck A, Schwarte K, Jörgens S, Scheu S, Windhagen S, Graefé B, Melzer N, Klotz L, Arolt V, Wiendl H, Meuth SG, Alferink J.
Neurol Neuroimmunol Neuroinflamm. 2016 Oct 12;3(6):e289.

Animal models

[Multiple sclerosis animal models: A clinical and histopathological perspective.](#)

Kipp M, Nyamoya S, Hochstrasser T, Amor S.
Brain Pathol. 2016 Oct 28.

Biosimilars

[Efficacy, safety and immunogenicity of biosimilars in inflammatory bowel diseases: A systematic review.](#)

Martelli L, Peyrin-Biroulet L.
Curr Med Chem. 2016 Oct 14

[Clinical Outcomes Following a Switch from Remicade® to the Biosimilar CT-P13 in Inflammatory Bowel Disease Patients: A Prospective Observational Cohort Study.](#)

Smits LJ, Derikx LA, de Jong DJ, Boshuizen RS, van Esch AA, Drenth JP, Hoentjen F.
J Crohns Colitis. 2016 Nov;10(11):1287-1293.

[Biosimilars in IBD: from theory to practice.](#)

Danese S, Bonovas S, Peyrin-Biroulet L.
Nat Rev Gastroenterol Hepatol. 2016 Oct 12.



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[GP2015, a proposed etanercept biosimilar: Pharmacokinetic similarity to its reference product and comparison of its auto-injector device with pre-filled syringes.](#)

von Richter O, Skerjanec A, Afonso M, Sanguino Heinrich S, Poetzl J, Woehling H, Velinova M, Koch A, Kollins D, Macke L, Wuerth G.

Br J Clin Pharmacol. 2016 Oct 27.

[The EGALITY study: A confirmatory, randomised, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, versus the originator product in patients with moderate to severe chronic plaque-type psoriasis.](#)

Griffiths CE, Thaci D, Gerdes S, Arenberger P, Pulka G, Kingo K, Weglowska J; EGALITY study group., Hattebuh N, Poetzl J, Woehling H, Wuerth G, Afonso M.

Br J Dermatol. 2016 Oct 27.

[Biosimilars in rheumatic diseases: structural and functional variability that may impact clinical and regulatory decisions.](#)

Lakhanpal A, Brahn E.

Clin Rheumatol. 2016 Oct 6.

Rheumatoid Arthritis

[Comparisons of the outcomes between early and late tocilizumab treatment in systemic juvenile idiopathic arthritis.](#)

Pacharapakornpong T, Vallibhakara SA, Lerkvaleekul B, Vilaiyuk S.

Rheumatol Int. 2016 Oct 31.

[Defining the optimal biological monotherapy in rheumatoid arthritis: A systematic review and meta-analysis of randomised trials.](#)

Tarp S, Furst DE, Dossing A, Østergaard M, Lorenzen T, Hansen MS, Singh JA, Choy EH, Boers M, Suarez-Almazor ME, Kristensen LE, Bliddal H, Christensen R.

Semin Arthritis Rheum. 2016 Sep 14.

[Emerging Therapies for Rheumatoid Arthritis.](#)

Kalden JR.

Rheumatol Ther. 2016 Jun;3(1):31-42. Review.



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Rituximab for Rheumatoid Arthritis.

Cohen MD, Keystone E.

Rheumatol Ther. 2015 Dec;2(2):99-111. Review.

The dimeric form of HLA-G molecule is associated with the response of early rheumatoid arthritis (ERA) patients to methotrexate.

Rizzo R, Farina I, Bortolotti D, Galuppi E, Padovan M, Di Luca D, Govoni M.

Clin Rheumatol. 2016 Oct 24

Spotlight on sirukumab for the treatment of rheumatoid arthritis: the evidence to date.

Lazzerini PE, Capecci PL, Guidelli GM, Selvi E, Acampa M, Laghi-Pasini F.

Drug Des Devel Ther. 2016 Sep 26;10:3083-3098. Review.

Mechanism of action of methotrexate in rheumatoid arthritis, and the search for biomarkers.

Brown PM, Pratt AG, Isaacs JD.

Nat Rev Rheumatol. 2016 Oct 27.

Use of tumor necrosis factor-alpha inhibitors in children and young adults with juvenile idiopathic arthritis or rheumatoid arthritis.

Lee WJ, Briars L, Lee TA, Calip GS, Suda KJ, Schumock GT.

Pharmacotherapy. 2016 Oct 25.

Comparative effectiveness of biologics for the management of rheumatoid arthritis: systematic review and network meta-analysis.

Alfonso-Cristancho R, Armstrong N, Arjunji R, Riemsma R, Worthy G, Ganguly R, Kleijnen J.

Clin Rheumatol. 2016 Oct 10

Anti-IL6-R Tocilizumab for Severe Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to anti-TNF therapy. A multicenter study of 25 patients.

Calvo-Río V, Santos-Gómez M, Calvo I, González-Fernández MI, López Montesinos B, Mesquida M, Adán A, Victoria Hernández M, Maíz O, Atanes A, Bravo B, Modesto C, Díaz-Cordovés G, Palmou-Fontana N, Loricera J, González-Vela MC, Demetrio-Pablo R, Hernández JL, González-Gay MA, Blanco R.

Arthritis Rheumatol. 2016 Oct 1.



Inflammatory Bowel Disease

Recent trends and future directions for the medical treatment of ulcerative colitis.

Naganuma M, Mizuno S, Nanki K, Sugimoto S, Kanai T.

Clin J Gastroenterol. 2016 Oct 3. [Epub ahead of print] Review.

Concurrent immunomodulator therapy is associated with higher adalimumab trough levels during scheduled maintenance therapy.

Bond A, Dodd S, Fisher G, Skouras T, Subramanian S.

Scand J Gastroenterol. 2016 Oct 31:1-5

Effectiveness and safety of vedolizumab for treatment of Crohn's disease: a systematic review and meta-analysis.

Moćko P, Kawalec P, Smela-Lipińska B, Pilc A.

Arch Med Sci. 2016 Oct 1;12(5):1088-1096. Review.

Advances in refractory ulcerative colitis treatment: A new therapeutic target, Annexin A2.

Tanida S, Mizoshita T, Ozeki K, Katano T, Kataoka H, Kamiya T, Joh T.

World J Gastroenterol. 2015 Aug 7;21(29):8776-86.

Multiple Sclerosis

Improved treatment satisfaction after switching therapy to rituximab in relapsing-remitting MS.

de Flon P, Laurell K, Söderström L, Gunnarsson M, Svenningsson A.

Mult Scler. 2016 Oct 25.

Anti-CD20 monoclonal antibodies in multiple sclerosis.

Moreno Torres ID, García-Merino A.

Expert Rev Neurother. 2016 Oct 10.

Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy.

Salzer J, Svenningsson R, Alping P, Novakova L, Björck A, Fink K, Islam-Jakobsson P, Malmeström C, Axelsson

M, Vågberg M, Sundström P, Lycke J, Piehl F, Svenningsson A.

Neurology. 2016 Oct 19.



Safety of monoclonal antibodies for the treatment of multiple sclerosis.

McGinley MP, Moss BP, Cohen JA.
Expert Opin Drug Saf. 2016 Oct 19

Hemophilia

Hemophilia A gene therapy via intraosseous delivery of factor VIII-lentiviral vectors.

Miao CH.
Thromb J. 2016 Oct 4;14(Suppl 1):41. Review.

Therapeutic and routine prophylactic properties of rFactor VIII Fc (efrinoctocog alfa, Eloctate[®]) in hemophilia A.

Chowdary P, Fosbury E, Riddell A, Mathias M.
J Blood Med. 2016 Sep 12;7:187-198. Review.

Different impact of factor VIII products on inhibitor development?

van den Berg HM.
Thromb J. 2016 Oct 4;14(Suppl 1):31. Review.

Opinions/Commentaries/ Across diseases reviews

Therapeutic Targeting of IL-17 and IL-23 Cytokines in Immune-Mediated Diseases.

Fragoulis GE, Siebert S, McInnes IB.
Annu Rev Med. 2016;67:337-53.

Awareness, Knowledge, and Perceptions of Biosimilars Among Specialty Physicians.

Cohen H, Beydoun D, Chien D, Lessor T, McCabe D, Muenzberg M, Popovian R, Uy J.
Adv Ther. 2016 Oct 31

Of patents and patent disputes - the TNF α patent files. Part 1 - Humira.

Storz U.
Hum Antibodies. 2016 Oct 21.



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REGULATION

EMA

Scientific guideline: [ICH E11\(R1\) guideline on clinical investigation of medicinal products in the pediatric population: Step 2b](#), draft: consultation open

Human medicines European public assessment report (EPAR): [Humira](#), adalimumab
Revision: 52, Authorised

Referral: Article 31 referrals, [Factor VIII \(updated\)](#)

Human medicines European public assessment report (EPAR): [Benlysta](#), belimumab
Revision: 15, Authorised

Human medicines European public assessment report (EPAR): [Kogenate Bayer](#), octocog alfa
Revision: 28, Authorised

Human medicines European public assessment report (EPAR): [Tysabri](#), natalizumab
Revision: 24, Authorised

Human medicines European public assessment report (EPAR): [Remsima](#), infliximab
Revision: 8, Authorised

Opinion/decision on a Paediatric investigation plan (PIP): Entyvio, [Vedolizumab](#)
Therapeutic area: Gastroenterology-Hepatology ([updated](#))

Opinion/decision on a Paediatric investigation plan (PIP): NovoEight, [turoctocog alpha](#)
Therapeutic area: Haematology-Hemostaseology ([updated](#))

[EMA workshop on qualification and reporting of physiologically-based pharmacokinetic \(PBPK\) modelling and simulation](#), European Medicines Agency, London, UK, From: 21-Nov-2016, To: 21-Nov-2016