

## TABLE OF CONTENTS

<b>INTRODUCTION</b>	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	7
Inflammatory Bowel Diseases	8
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-funded **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 July 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*

## LITERATURE

## This month's selected articles

1. A paper worth reading because it looks at a relatively long follow-up period and enhances awareness of anti-TNF ADA, a field which seems still a little underdeveloped :

[Influence of Immunogenicity on the Efficacy of Long-Term Treatment with TNF  \$\alpha\$  Blockers in Rheumatoid Arthritis and Spondyloarthritis Patients.](#)

Arstikyte I, Kapleryte G, Butrimiene I, Venalis A.  
Biomed Res Int. 2015;2015:604872

2. This article verify that there is not only a difference in the frequency of patients becoming ADA positive dependent on what IFNbeta product is used, but also qualitative difference. For patients treated with IFNbeta-1a almost half of the patients positive for NABs have high titers NAb, whereas for patients treated with IFNbeta-1b only 22% of patients positive for Nabs had high titers :

[Frequency and magnitude of interferon  \$\beta\$  neutralizing antibodies in the evaluation of interferon  \$\beta\$  immunogenicity in patients with multiple sclerosis.](#)

Grossberg SE, Oger J, Grossberg LD, Gehchan A, Klein JP.  
J Interferon Cytokine Res. 2011 Mar;31(3):337-44.

3. Here it is stated that immunogenicity testing is required for biosimilars by both FDA (at least two comparative trials, one pre- and one post-marketing) and EMA (must be assessed during the safety trial). Would be interesting to see if cases come up where the immunogenicity is much higher and what impact that will have on the decision of approval :

[Inflammatory diseases: Integrating biosimilars into clinical practice.](#)

Feldman SR.  
Semin Arthritis Rheum. 2015 Jun;44(6 Suppl):S16-21.

4. This paper addresses the question of the settings to introduce for predicting HLA class II epitopes in allergens and bacterial antigens. While predictive algorithms exist for many alleles, the authors propose to focus the prediction to few alleles only and to introduce poorly stringent cut-offs. This is sufficient to capture 50% of the T cell epitopes:

[Development and validation of a broad scheme for prediction of HLA class II restricted T cell epitopes.](#)

Paul S, Lindestam Arlehamn CS, Scriba TJ, Dillon MB, Oseroff C, Hinz D, McKinney DM, Carrasco Pro S, Sidney J, Peters B, Sette A.  
J Immunol Methods. 2015 Jul;422:28-34.

## Immunogenicity

### [Anti-drug antibodies: B-cell Immunity against therapy.](#)

Fogdell-Hahn A.

Scand J Immunol. 2015 Jun 22.

### [Serum concentration of anti-TNF antibodies, adverse effects and quality of life in patients with inflammatory bowel disease in remission on maintenance treatment.](#)

Brandse JF, Vos LM, Jansen J, Schakel T, Ponsioen CI, van den Brink GR, D'Haens GR, Löwenberg M.

J Crohns Colitis. 2015 Jun 26

### [Influence of Immunogenicity on the Efficacy of Long-Term Treatment with TNF \$\alpha\$ Blockers in Rheumatoid Arthritis and Spondyloarthritis Patients.](#)

Arstikyte I, Kapleryte G, Butrimiene I, Venalis A.

Biomed Res Int. 2015;2015:604872.

### [Practical guidance on immunogenicity to biologic agents used in the treatment of psoriasis: What can be learnt from other diseases?](#)

Lambert J, Nast A, Nestle FO, Prinz JC.

J Dermatolog Treat. 2015 Jun 25:1-8.

### [Epitope characterization of the ADA response directed against a targeted immunocytokine.](#)

Stubenrauch K, Künzel C, Vogel R, Tuerck D, Schick E, Heinrich J.

J Pharm Biomed Anal. 2015 Jun 5;114:296-304.

## Methods

### [Using simple models to describe the kinetics of growth, glucose consumption, and monoclonal antibody formation in naive and infliximab producer CHO cells.](#)

López-Meza J, Araíz-Hernández D, Carrillo-Cocom LM, López-Pacheco F, Rocha-Pizaña MD, Alvarez MM.

Cytotechnology. 2015 Jun 20

### [Rational Design of Biobetters with Enhanced Stability.](#)

Courtois F, Schneider CP, Agrawal NJ, Trout BL.

J Pharm Sci. 2015 Jun 10.

[Effects of blood processing and sample storage on the stability of biotherapeutics and anti-drug antibodies.](#)

Andisik M, DeStefano L, Stefan C, Gathani M, Laurino K, Lai VCh, Rajadhyaksha M, Torri A, Shao W.  
Bioanalysis. 2015 Jun;7(11):1325-35.

### Animal models

[Antigen-Specific Tolerogenic Dendritic Cells Ameliorate the Severity of Murine Collagen-Induced Arthritis.](#)

Ning B, Wei J, Zhang A, Gong W, Fu J, Jia T, Yang SY.  
PLoS One. 2015 Jun 24;10(6):e0131152.

### Biomarkers

[Blood-based identification of non-responders to anti-TNF therapy in rheumatoid arthritis.](#)

Thomson TM, Lescarbeau RM, Drubin DA, Laifenfeld D, de Graaf D, Fryburg DA, Littman B, Deehan R, Van Hooser A.  
BMC Med Genomics. 2015 Jun 3;8:26.

[A cohort of anti-TNF treated Danish patients with inflammatory bowel disease, used for identifying genetic markers associated with treatment response.](#)

Bank S.  
Dan Med J. 2015 May;62(5). pii: B5087.

[Infliximab and etanercept have distinct actions but similar effects on cytokine profiles in rheumatoid arthritis.](#)

Takeshita M, Suzuki K, Kikuchi J, Izumi K, Kurasawa T, Yoshimoto K, Amano K, Takeuchi T.  
Cytokine. 2015 Jun 18. pii: S1043-4666(15)00162-3.

[Can measuring urinary biomarkers improve the management of lupus nephritis?](#)

Rahman A.  
Arthritis Res Ther. 2012 Dec 19;14(6):127.

## Systemic Lupus Erythematosus

[A fully human monoclonal antibody with novel binding epitope and excellent neutralizing activity to multiple human IFN- \$\alpha\$  subtypes: a candidate therapy for systemic lupus erythematosus.](#)

Du P, Xu L, Qiu W, Zeng D, Yue J, Wang S, Huang P, Sun Z.

MAbs. 2015 Jun 5:0.

[A Phase II study of the efficacy and safety of rontalizumab \(rhuMAb interferon- \$\alpha\$ \) in patients with systemic lupus erythematosus \(ROSE\).](#)

Kalunian KC, Merrill JT, Maciuga R, McBride JM, Townsend MJ, Wei X, Davis JC Jr, Kennedy WP.

Ann Rheum Dis. 2015 Jun 2

[Upcoming biological therapies in systemic lupus erythematosus.](#)

Sciascia S, Talavera-Garcia E, Roccatello D, Baldovino S, Mengatti E, Cuadrado MJ.

Int Immunopharmacol. 2015 May 28.

[The evolution of drug discovery in systemic lupus erythematosus.](#)

Wallace DJ.

Nat Rev Rheumatol. 2015 Jun 30.

[Efficacy and safety of rituximab in Japanese patients with systemic lupus erythematosus including lupus nephritis who are refractory to conventional therapy.](#)

Tanaka Y, Takeuchi T, Miyasaka N, Sumida T, Mimori T, Koike T, Endo K, Mashino N, Yamamoto K.

Mod Rheumatol. 2015 Jun 9:1-27

## Rheumatoid Arthritis

[Safety of biologic therapies for the treatment of juvenile idiopathic arthritis.](#)

Horneff G.

Expert Opin Drug Saf. 2015 Jul;14(7):1111-26

[Clinical utility of random anti-TNF drug level testing and measurement of anti-drug antibodies on long-term treatment response in rheumatoid arthritis.](#)

Jani M, Chinoy H, Warren RB, Em Griffiths C, Plant D, Fu B, Morgan AW, Wilson AG, Isaacs JD, Hyrich KL, Barton A; BRAGGSS.

Arthritis Rheumatol. 2015 Jun 24

[Clinical Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies Approved to Treat Rheumatoid Arthritis.](#)

Ternant D, Bejan-Angoulvant T, Passot C, Mulleman D, Paintaud G.

Clin Pharmacokinet. 2015 Jun 28

[Long-Term Safety, Efficacy, and Quality of Life with Intravenous Abatacept in Juvenile Idiopathic Arthritis: Up to 7 Years of Treatment.](#)

Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Pérez N, Silva CA, Abud-Mendoza C, Burgos-Vargas R, Gerloni V, Melo-Gomes JA, Saad-Magalhaes C, Chavez-Corrales J, Huemer C, Kivitz A, Blanco FJ, Foeldvari I, Hofer M, Huppertz HI, Deslandre CJ, Minden K, Punaro M, Block AJ, Giannini EH, Martini A; Pediatric Rheumatology Collaborative Study Group (PRCSG); Paediatric Rheumatology International Trials Organization (PRINTO).

Arthritis Rheumatol. 2015 Jun 19.

[Effectiveness and survival-on-drug of certolizumab pegol in rheumatoid arthritis in clinical practice: results from the national Swedish register.](#)

Chatzidionysiou K, Kristensen LE, Eriksson J, Askling J, van Vollenhoven R, For The Artis Group.

Scand J Rheumatol. 2015 Jun 18:1-7.

[Clinical Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies Approved to Treat Rheumatoid Arthritis.](#)

Ternant D, Bejan-Angoulvant T, Passot C, Mulleman D, Paintaud G.

Clin Pharmacokinet. 2015 Jun 28. [Epub ahead of print]

Pardeo M, Pires Marafon D, Insalaco A, Bracaglia C, Nicolai R, Messia V, De Benedetti F.

J Rheumatol. 2015 Jun 1.

## Inflammatory Bowel Diseases

[Vedolizumab: first global approval.](#)

Poole RM.

Drugs. 2014 Jul;74(11):1293-303.



[Seasonal variability of vitamin D and bone metabolism in infliximab-treated paediatric Crohn's disease.](#)

Szabó D, Hosszú É, Arató A, Müller KE, Béres N, Lakatos PL, Papp M, Dezsőfi A, Szabó AJ, Szűcs D, Veres G.  
Dig Liver Dis. 2015 May 19.

[Infliximab-Related Infusion Reactions Systematic Review.](#)

Lichtenstein L, Ron Y, Kivity S, Ben-Horin S, Israeli E, Fraser GM, Dotan I, Chowers Y, Confino-Cohen R, Weiss B.  
J Crohns Colitis. 2015 Jun 19.

[Predicting the Durability of Biological Therapy in Pediatric Crohn's Disease: Do the Immunomodulators Matter?](#)

Aloi M, Cucchiara S.  
Clin Gastroenterol Hepatol. 2015 Jun 16

[Next-Generation Therapeutics for IBD.](#)

Löwenberg M, D'Haens G.  
Curr Gastroenterol Rep. 2015 Jun;17(6):444.

[Randomised clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis.](#)

Rutgeerts P, Feagan BG, Marano CW, Padgett L, Strauss R, Johanns J, Adedokun OJ, Guzzo C, Zhang H, Colombel JF, Reinisch W, Gibson PR, Sandborn WJ; PURSUIT-IV study group.  
Aliment Pharmacol Ther. 2015 Jun 29.

[Efficacy and safety of certolizumab pegol for Crohn's disease in clinical practice.](#)

Moon W, Pestana L, Becker B, Loftus EV Jr, Hanson KA, Bruining DH, Tremaine WJ, Kane SV.  
Aliment Pharmacol Ther. 2015 Jun 17.

[Intravenous Versus Subcutaneous Anti-TNF-Alpha Agents for Crohn's Disease: A Comparison of Effectiveness and Safety.](#)

Liu J, Sylwestrzak G, Ruggieri AP, DeVries A.  
J Manag Care Spec Pharm. 2015 Jul;21(7):559-66.

[Biological therapy for ulcerative colitis: an update.](#)

Seo GS, Chae SC.  
World J Gastroenterol. 2014 Oct 7;20(37):13234-8.

## Multiple Sclerosis

[A Network Meta-Analysis of Efficacy and Evaluation of Safety of Subcutaneous Pegylated Interferon Beta-1a versus Other Injectable Therapies for the Treatment of Relapsing-Remitting Multiple Sclerosis.](#)

Tolley K, Hutchinson M, You X, Wang P, Sperling B, Taneja A, Siddiqui MK, Kinter E.  
PLoS One. 2015 Jun 3;10(6):e0127960.

[Alemtuzumab in multiple sclerosis: an update.](#)

Gross RH, Krieger S.  
Neurodegener Dis Manag. 2015 Jun;5(3):225-32.

[Comparative efficacy of alemtuzumab and established treatment in the management of multiple sclerosis.](#)

Babji R, Perumal JS.  
Neuropsychiatr Dis Treat. 2015 May 18;11:1221-9.

[PEGylated IFN \$\beta\$ -1a in the treatment of multiple sclerosis.](#)

Khan UT, Tanasescu R, Constantinescu CS.  
Expert Opin Biol Ther. 2015 Jul;15(7):1077-84.

## Hemophilia

[Reflections on the FranceCoag report on inhibitory antibodies to factor VIII in patients with severe hemophilia](#)

[A](#)

Berntorp E, Iorio A.  
Blood. 2015 Jun 11;125(24):3816-7.

[Efficacy, Safety, and Pharmacokinetics of Beractocog Alfa in Patients Previously Treated for Hemophilia A.](#)

Hyun SY, Park SY, Lee SY, Kook H, Paik SH, Jang IJ, Lee KS.  
Yonsei Med J. 2015 Jul;56(4):935-43

Opinions/Commentaries/Across diseases reviews

[Clinical trial development for biosimilars.](#)

Alten R, Cronstein BN.

Semin Arthritis Rheum. 2015 Jun;44(6S):S2-S8. doi: 10.1016/j.semarthrit.2015.04.002. Review.

## REGULATION

### EMA

[Scientific guideline: Concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant granulocyte-colony stimulating factor](#)

Draft: consultation open

Consultation start date 27/07/2015

Consultation end date 31/10/2015

[Opinion/decision on a Paediatric investigation plan \(PIP\): Voncento, Human coagulation factor VIII / von Willebrand factor](#)

Updated June 2015

[Human medicines European public assessment report \(EPAR\): Enbrel, etanercept](#)

Revision: 45, Authorised

June 2015

[Human medicines European public assessment report \(EPAR\): Cimzia, certolizumab pegol](#)

Revision: 14, Authorised

June 2015

[Opinion/decision on a Paediatric investigation plan \(PIP\): RoActemra, tocilizumab](#)

Updated June 2015

[Opinion/decision on a Paediatric investigation plan \(PIP\): Humira, adalimumab](#)

Updated June 2015

[Opinion/decision on a Paediatric investigation plan \(PIP\): -, Recombinant single-chain coagulation factor VIII](#)

Updated June 2015

[Opinion/decision on a Paediatric investigation plan \(PIP\): RoActemra, tocilizumab](#)

June 2015