# TABLE OF CONTENTS

**INTRODUCTION** 2  
**WELCOME** 3  
**LITERATURE** 4  
  - This month's selected articles 4  
  - Immunogenicity 5  
  - Methods 5  
  - Animal models 6  
  - Biosimilars 7  
  - Biomarkers 7  
  - Systemic Lupus Erythematosus 7  
  - Arthritis 8  
  - Inflammatory Bowel Diseases 9  
  - Multiple Sclerosis 10  
  - Hemophilia 11  
  - Basic immunology 12  
**REGULATION** 14  
**EMA** 14
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 Response 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.
Dear Reader,

We would like to welcome you to the March 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.

This month again we are drawing 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
LITERATURE

This month’s selected articles

1. A holistic consideration on the topic of immunecomplexes which I have been able to share with multiple disciplines from bioanalytists, toxicologists and clinicians. This one review is an excellent starting point for anyone embarking on or indeed refining an immunogenicity risk assessment, a thoroughly useful document:

Immunogenicity to Biotherapeutics - The Role of Anti-drug Immune Complexes.
Krishna M, Nadler SG.

2. An interesting discussion highlighting the difficulty to compare immunogenicity of biosimilars with the initial product:

Reporting of potential immunogenicity with biologic drugs: clarity and accuracy required.
Moots R, Balsa A, Wolbink G.

Response to: 'Reporting of potential immunogenicity with biologic drugs: clarity and accuracy required' by Moots et al.
Emery P, Vencovský J, Ghil J.
Ann Rheum Dis. 2016 Feb 17

3. The third version of the IEDB. Born in 2004, this outstanding database continues to be active and to provide us with new epitope sequences and innovative tools of prediction:

The immune epitope database (IEDB) 3.0.
Nucleic Acids Res. 2015 Jan;43(Database issue):D405-12.

4. This study confirms the previously observed heterogeneous nature of Relapsing Remitting Multiple Sclerosis and suggests that stratification of patients by the means of biomarkers can be informative for prognosis and treatment response:

Cytokine profiles show heterogeneity of interferon-β response in multiple sclerosis patients.
Immunogenicity

The role of previously untreated patient studies in understanding the development of FVIII inhibitors.
Carcao M, Re W, Ewenstein B.

The Impact of Methylprednisolone Pulses during Relapses of Multiple Sclerosis on the Kinetics of Anti-Interferon-Beta Antibodies.
Eur Neurol. 2016;75(1-2):82-8

Presence of antidrug antibodies correlates inversely with the plasma tumor necrosis factor (TNF)-α level and the efficacy of TNF-inhibitor therapy in psoriasis.
Kui R, Gál B, Gaál M, Kiss M, Kemény L, Gyulaï R.

Engineering less immunogenic and antigenic FVIII proteins.
Pratt KP.

High level of anti-drug antibodies after intra-articular injection of anti-TNF.
Zufferey P, Perreau M, So A.

Immunogenicity of Therapeutic Protein Aggregates.
Moussa EM, Panchal JP, Moorhys BS, Blum JS, Joubert MK, Narhi LO, Topp EM.

Methods

Chen YQ, Pottanat TG, Carter QL, Troutt JS, Konrad Rj, Sloan JH.
J Immunol Methods. 2016 Feb 10
Aggregation Kinetics for IgG1-Based Monoclonal Antibody Therapeutics.
Singla A, Bansal R, Joshi V, Rathore AS.
AAPS J. 2016 Feb 22

Targeting inflammatory bowel diseases by nanocarriers loaded with small and biopharmaceutical anti-inflammatory drugs.
Beloqui A, Coco R, Préat V.

Artificial antigen presenting cells expressing HLA class II molecules as an effective tool for amplifying human specific memory CD4+ T cells.

Establishment of a cell model for screening antibody drugs against rheumatoid arthritis with ADCC and CDC.

Reproducibility and conflicts in immune epitope data.
Vita R, Vasilevsky N, Bandrowski A, Haendel M, Sette A, Peters B.
Immunology. 2016 Mar;147(3):349-54.

Animal models

Waiving in vivo studies for monoclonal antibody biosimilar development: national and global challenges.
MAbs. 2016 Feb 6:0.

Characterization of a genetically engineered mouse model of hemophilia A with complete deletion of the F8 gene.

Immunogenicity of Recombinant Human Interferon Beta-1b in Immune-Tolerant Transgenic Mice Corresponds with the Biophysical Characteristics of Aggregates.
Haji Abdolvahab M, Fazeli A, Halim A, Sediq AS, Fazeli MR, Schellekens H
J Interferon Cytokine Res. 2016 Feb 2
**Biosimilars**

Br J Clin Pharmacol. 2016 Feb 25

A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis.

Current status of biosimilars in the treatment of inflammatory bowel diseases.
Park DI.

Key design considerations on comparative clinical efficacy studies for biosimilars: adalimumab as an example.
Lai Z, La Noce A.
RMD Open. 2016 Feb 5;2(1):e000154.

**Biomarkers**

MxA mRNA expression as a biomarker of interferon beta response in multiple sclerosis patients.
Matas E, Bau L, Martínez-Iniesta M, Romero-Pinel L, Mañé-Martínez MA, Cobo-Calvo Á, Martínez-Yélamos S.

Changes in anti-cyclic citrullinated peptide antibodies and rheumatoid factor isotypes serum levels in patients with rheumatoid arthritis following treatment with different biological drugs.

**Systemic Lupus Erythematous**

Abatacept for the Treatment of Systemic Lupus Erythematosus.
Pimentel-Quiroz VR, Alarcón GS, Ugarte-Gil MF.
Expert Opin Investig Drugs. 2016 Feb 15.
Arthritis

**Sarilumab for the treatment of rheumatoid arthritis.**
Cooper S.

**Decreased use of glucocorticoids in biological-experienced patients with rheumatoid arthritis who initiated intravenous abatacept: results from the 2-year ACTION study.**

**The Challenge of Treating Early-Stage Rheumatoid Arthritis: The Contribution of Mixed Treatment Comparison to Choosing Appropriate Biologic Agents.**
Migliore A, Bizzi E, Petrella L, Bruzzese V, Cassol M, Integlia D.
BioDrugs. 2016 Feb 23.

**Effectiveness of two different doses of rituximab for the treatment of rheumatoid arthritis in an international cohort: data from the CERERRA collaboration.**

**A randomised trial evaluating anakinra in early active rheumatoid arthritis.**

**Adalimumab discontinuation in patients with early rheumatoid arthritis who were initially treated with methotrexate alone or in combination with adalimumab: 1 year outcomes of the HOPEFUL-2 study.**
Tanaka Y, Yamanaka H, Ishiguro N, Miyasaka N, Kawana K, Hiramatsu K, Takeuchi T.

**Tocilizumab for treating juvenile idiopathic arthritis.**
Turnier JL, Brunner HI.
A phase III, multicentre, randomised, double-blind, active-controlled, parallel-group trial comparing safety and efficacy of HD203, with innovator etanercept, in combination with methotrexate, in patients with rheumatoid arthritis: the HERA study.

Inflammatory Bowel Diseases

Approach to Optimize Anti-TNF-α Therapy in Patients With IBD.
Komaki Y, Komaki F, Sakuraba A, Cohen R.
Curr Treat Options Gastroenterol. 2016 Feb 12.

The safety of vedolizumab for ulcerative colitis and Crohn’s disease.

Long-Term Follow-Up of Patients Treated with Infliximab for Ulcerative Colitis: Predictive Factors of Response-An Observational Study.

A Retrospective Comparison of Infliximab vs Adalimumab as Induction and Maintenance Therapy for Crohn’s Disease.
Varma P, Paul E, Huang C, Headon B, Sparrow MP.

Effectiveness and Safety of Vedolizumab Induction Therapy for Patients with Inflammatory Bowel Disease.

Etrolizumab for Ulcerative Colitis: The new kid on the block?
Makker J Md, Hommes DW Md.
**Immunomodulators for the treatment of Crohn’s disease in adults: optimal use and prospects for future drug treatments.**
Allen PB, Peyrin-Biroulet L.

**Mechanism of action of anti-TNF therapy in inflammatory bowel disease.**
Levin AD, Wildenberg ME, van den Brink GR.

**Anti-TNF-A Therapy about Infliximab and Adalimamab for the Effectiveness in Ulcerative Colitis Compared with Conventional Therapy: A Meta-Analysis.**
Zhou Z, Dai C, Liu WX.

**Review of vedolizumab for the treatment of ulcerative colitis.**
Lau MS, Tsai HH.

**Vedolizumab for induction and maintenance of remission in ulcerative colitis: a Cochrane systematic review and meta-analysis.**
Inflamm Bowel Dis. 2015 May;21(5):1151-9.

**Multiple Sclerosis**

**Long-term adherence of patients with relapsing-remitting multiple sclerosis to subcutaneous self-injections of interferon β-1a using an electronic device: the RIVER study.**

**Recent Advances in Monoclonal Antibody Therapies for Multiple Sclerosis.**
Population Pharmacokinetics of Daclizumab High-Yield Process in Healthy Volunteers and Subjects with Multiple Sclerosis: Analysis of Phase I-III Clinical Trials.
Diao L, Hang Y, Othman AA, Nestorov I, Tran JQ.

Multiparametric flow cytometric analysis of whole blood reveals changes in minor lymphocyte subpopulations of multiple sclerosis patients.

A robust type I interferon gene signature from blood RNA defines quantitative but not qualitative differences between three major IFNβ drugs in the treatment of multiple sclerosis.
Harari D, Orr I, Rotkopf R, Baranzini SE, Schreiber G.

Minocycline added to subcutaneous interferon β-1a in multiple sclerosis: randomized RECYCLINE study.
Eur J Neurol. 2016 Feb 5.

A Randomized Trial Evaluating Various Administration Routes of Natalizumab in Multiple Sclerosis.
Plavina T, Fox EJ, Lucas N, Muralidharan KK, Mikol D.
J Clin Pharmacol. 2016 Feb 2

Hemophilia

T cell response to FVIII.
Jacquemin M, Saint-Remy JM.

Strategies to target long-lived plasma cells for treating hemophilia A inhibitors.
Liu CL, Lyle MJ, Shin SC, Miao GH.
The anti-CD20 monoclonal antibody rituximab to treat acquired haemophilia A.

Prospective surveillance study of haemophilia A patients switching from moroctocog alfa or other factor VIII products to moroctocog alfa albumin-free cell culture (AF-CC) in usual care settings.

Porcine recombinant factor VIII (Obizur; OBI-1; BAX801): product characteristics and preclinical profile.

In vivo induction of regulatory T cells for immune tolerance in hemophilia.

Novel, human cell line-derived recombinant factor VIII (Human-cl rhFVIII, Nuwiq<sup>&reg;</sup>) in children with severe haemophilia A: efficacy, safety and pharmacokinetics.

Design of clinical trials for new products in hemophilia: communication from the SSC of the ISTH.

Reduction of Factor VIII Inhibitor Titers During Immune Tolerance Induction With Recombinant Factor VIIa-Fc Fusion Protein.

Basic immunology

Harnessing the plasticity of CD4(+) T cells to treat immune-mediated disease.
**T cell migration, search strategies and mechanisms.**
Krummel MF, Bartumeus F, Gérard A.

**SHARPIN controls regulatory T cells by negatively modulating the T cell antigen receptor complex.**

**Multifunctional role of the transcription factor Blimp-1 in coordinating plasma cell differentiation.**
Minnich M, Tagoh H, Bönelt P, Axelsson E, Fischer M, Cebolla B, Tarakhovsky A, Nutt SL, Jaritz M, Busslinger M.
News and press releases: EMA confirms recommendations to minimise risk of brain infection PML with Tysabri
February 2016

Referral: Article 20 procedures, Tysabri, natalizumab
Updated
February 2016

Pending EC decision: Humira, adalimumab
Opinion date: 25-Feb-2016

Report: Report of the first European Medicines Agency and the European Generic and Biosimilar Medicines Association (EGA) annual bilateral meeting
February 2016

Human medicines European public assessment report (EPAR): Tysabri, natalizumab
Revision: 21, Authorised
February 2016
Agenda: Agenda - Workshop on immunogenicity assessment of biotechnology-derived therapeutic proteins

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol
Revision: 15, Authorised
February 2016

Scientific guideline: Final guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products
Adopted
February 2016

Scientific guideline: Final guideline on core SmPC for human plasma derived and recombinant coagulation factor VIII products
Adopted
February 2016