# TABLE OF CONTENTS

## INTRODUCTION  
INTRODUCTION 2

## WELCOME  
WELCOME 3

## LITERATURE  
LITERATURE 4

- This month's selected articles 4
- Immunogenicity 5
- Methods 6
- Biomarkers 7
- Biosimilars 8
- Animal models 9
- Systemic Lupus Erythematosus 9
- Rheumatoid Arthritis 9
- Inflammatory Bowel Disease 11
- Multiple Sclerosis 11
- Hemophilia 12
- Basic immunology 13
- Opinions/Commentaries/ Across diseases reviews 13

## REGULATION  
REGULATION 14

- EMA 14
- FDA 15
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.
Dear Reader,

We would like to welcome you to the December 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
LITERATURE

This month’s selected articles

1. This retrospective analysis shows the potential for reduction of ADA response with the restoration of clinical effect when dosing methotrexate or azathioprine to patients who developed ADA to Adalimumab after starting on mono-therapy for IBD. This effect had previously been observed with Infliximab. In the present study, although only half the small number of patients treated with immunomodulators benefitted through reduction of ADA, this observation indicates the potential for use of immunomodulators as a treatment for ADA. Further work is needed to understand which patients are most likely to benefit and by which mechanism(s) the effect manifests:

Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab.
Aliment Pharmacol Ther. 2016 Nov 16

2. The study further underlines the uselessness of Vit D supplementation in MS. As we know, Vit D is a biomarker of UV (mostly sunlight) exposure and is decreased in ALL chronic medical conditions (from chronic heart to chronic joint diseases) and therefore most likely related to reduced mobility. Vit D supplementation is cosmetics of Vit D serum levels and totally misleading the patients in their hope the disease is getting better if they take Vit D:

Immune regulatory effects of high dose vitamin D3 supplementation in a randomized controlled trial in relapsing remitting multiple sclerosis patients receiving IFNβ; the SOLARIUM study.

3. vitamin D do have something to do with the risk of MS. One hypothesis of how vitamin D influence risk for MS is the influence vitamin D has on early life ability to deal with infections. If that would be the case it would be hard to repair by supplementary later in life.

Neonatal vitamin D status and risk of multiple sclerosis: A population-based case-control study.
Neurology. 2016 Nov 30
Immunogenicity

**Occurrence of Anti-Drug Antibodies against Interferon-Beta and Natalizumab in Multiple Sclerosis: A Collaborative Cohort Analysis.**

**Prediction of short- and medium-term efficacy of biosimilar infliximab therapy. Do trough levels and antidrug antibody levels or clinical and biochemical markers play a more important role?**
J Crohns Colitis. 2016 Nov 12

**Successful desensitization to natalizumab using a 1-solution protocol.**
Pérez-Rodríguez E, Hernández-Pérez MÁ, Martínez-Tadeo JA.

**The cross-reactivity of binding antibodies with different interferon beta formulations used as disease-modifying drugs in multiple sclerosis patients.**

**Inhibition of interleukin-5 induced false positive anti-drug antibody responses against mepolizumab through the use of a competitive blocking antibody.**
Liao K, Meyer E, Lee TN, Loercher A, Sikkema D.

**Evaluating Immunogenicity Risk Due to Host Cell Protein Impurities in Antibody-Based Biotherapeutics.**
Jawa V, Joubert MK, Zhang Q, Deshpande M, Hapuarachchi S, Hall MP, Flynn GC.
Methods

Strategies to Determine Assay Format for the Assessment of Neutralizing Antibody Responses to Biotherapeutics.

LC-MS/MS strategies for therapeutic antibodies and investigation into the quantitative impact of antidrug-antibodies.

Detection of anti-infliximab antibodies is impacted by antibody titer, infliximab level and IgG4 antibodies: a systematic comparison of three different assays.

Validation of a Drug-Resistant Anti-Adalimumab Antibody Assay to Monitor Immunogenicity in the Presence of High Concentrations of Adalimumab.
Bian S, Ferrante M, Gils A.

Physiologically-based modeling to predict the clinical behavior of monoclonal antibodies directed against lymphocyte antigens.
Glassman PM, Balthasar JP.
MAbs. 2016 Nov 28:0

Optimization on Fc for Improvement of Stability and Aggregation Resistance.
Bioanalysis. 2016 Dec;8(23):2457-2474.

Humanizing glycosylation pathways in eukaryotic expression systems.
Khan AH, Bayat H, Rajabibazl M, Sabri S, Rahimpour A.
Biomarkers

**Infliximab Selectively Modulates the Circulating Blood Monocyte Repertoire in Crohn's Disease.**
Slevin SM, Dennedy MC, Connaughton EP, Ribeiro A, Ceredig R, Griffin MD, Egan LJ.
Inflamm Bowel Dis. 2016 Dec;22(12):2863-2878.

**Natalizumab treatment leads to an increase in circulating CXCR3-expressing B cells.**
Saraste M, Penttilä TL, Airas L.

**Serum level of reactive oxygen metabolites (ROM) at 12 weeks of treatment with biologic agents for rheumatoid arthritis is a novel predictor for 52-week remission.**
Nakajima A, Aoki Y, Sonobe M, Takahashi H, Saito M, Nakagawa K.

**Serological markers in diagnosis of pediatric inflammatory bowel disease and as predictors for early tumor necrosis factor blocker therapy.**
Olbjørn C, Cvancarova Småstuen M, Thiis-Evensen E, Nakstad B, Vatn MH, Perminow G.

**2016 White Paper on recent issues in bioanalysis: focus on biomarker assay validation (BAV) (Part 1 - small molecules, peptides and small molecule biomarkers by LCMS).**

**2016 White Paper on recent issues in bioanalysis: focus on biomarker assay validation (BAV): (Part 3 - LBA, biomarkers and immunogenicity).**
Bioanalysis. 2016 Dec;8(23):2475-2496.
2016 White Paper on recent issues in bioanalysis: focus on biomarker assay validation (BAV): (Part 2 - Hybrid LBA/LCMS and input from regulatory agencies).

Bioanalysis. 2016 Dec;8(23):2457-2474.

Biosimilars

Bioequivalence, safety and immunogenicity of BI 695501, an adalimumab biosimilar candidate, compared with the reference biologic in a randomized, double-blind, active comparator phase I clinical study (VOLTAIRE®-PK) in healthy subjects.


Biosimilars: The US Regulatory Framework.
Christl LA, Woodcock J, Kozlowski S.

Monoclonal Antibody and Fusion Protein Biosimilars Across Therapeutic Areas: A Systematic Review of Published Evidence.
Jacobs I, Petersel D, Shane LG, Ng CK, Kirchhoff C, Finch G, Lula S.

Demonstration of physicochemical and functional similarity between the proposed biosimilar adalimumab MSB11022 and Humira®.
Magnenat L, Palmese A, Fremaux C, D'Amici F, Terlizzese M, Rossi M, Chevalet L.
MAbs. 2016 Nov 17:0.

Biosimilars for the Treatment of Chronic Inflammatory Diseases: A Systematic Review of Published Evidence.
Jacobs I, Petersel D, Isakov L, Lula S, Lea Sewell K.
Animal models

Immunogenicity of Murine mPEG-Red Blood Cells and the Risk of Anti-PEG Antibodies in Human Blood Donors.
Le Y, Toyofuku WM, Scott MD.

Systemic Lupus Erythematosus

New insights into the immunopathogenesis of systemic lupus erythematosus.
Tsokos GC, Lo MS, Reis PC, Sullivan KE.

Cross-talk between iNKT cells and monocytes triggers an atheroprotective immune response in SLE patients with asymptomatic plaque.
Smith, E; Croca, S; Waddington, K; Sofat, R; Griffin, M; Nicolaides, A; Isenberg, D; Ines Pineda Torra, Anisur Rahman and Elizabeth C. Jury
Science Immunology 02 Dec 2016. Vol. 1, Issue 6

Safety, pharmacokinetics, and pharmacodynamics of RSLV-132, an RNase-Fc fusion protein in systemic lupus erythematosus: a randomized, double-blind, placebo-controlled study.

Rheumatoid Arthritis

Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study.
Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab.

Comparative usability study for a certolizumab pegol autoinjection device in patients with rheumatoid arthritis.
Domańska B, VanLunen B, Peterson L, Mountian I, Schiff M.

Tofacitinib Versus Biologic Treatments in Patients With Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Tumor Necrosis Factor Inhibitors: Results From a Network Meta-analysis.
Vieira MC, Zwillich SH, Jansen JP, Smiechowski B, Spurden D, Wallenstein GV.

Tapering biologics in rheumatoid arthritis: a pragmatic approach for clinical practice.
Lenert A, Lenert P.

Denosumab: Targeting the RANKL pathway to treat Rheumatoid Arthritis.
Chiu YG, Ritchlin CT.

Five-year Safety Data from 5 Clinical Trials of Subcutaneous Golimumab in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis.

Comparable Efficacy of Abatacept Used as First-line or Second-line Biological Agent for Severe Juvenile Idiopathic Arthritis-related Uveitis.

Immunosuppressive Activity of Abatacept on Circulating T Helper Lymphocytes from Juvenile Idiopathic Arthritis Patients.
Inflammatory Bowel Disease

**A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of Brodalumab in Patients With Moderate-to-Severe Crohn's Disease.**

**Association Between Low Trough Levels of Vedolizumab During Induction Therapy for Inflammatory Bowel Diseases With Need for Additional Doses Within 6 months.**

**Vedolizumab for the treatment of ulcerative colitis.**
Stallmach A, Schmidt C, Teich N.

**Emerging biologics in inflammatory bowel disease.**
Chan HC, Ng SC.

**Molecular mechanism of action of anti-tumor necrosis factor antibodies in inflammatory bowel diseases.**
Billmeier U, Dieterich W, Neurath MF, Atreya R.

**Biological therapy targeting the IL-23/IL-17 axis in inflammatory bowel disease.**
Verstockt B, Van Assche G, Vermeire S, Ferrante M.

Multiple Sclerosis

**An update on the evidence base for peginterferon β1a in the treatment of relapsing-remitting multiple sclerosis.**
Bhargava P, Newsome SD.
Inebilizumab, a B Cell-Depleting Anti-CD19 Antibody for the Treatment of Autoimmune Neurological Diseases: Insights from Preclinical Studies.

Hemophilia

Regulatory T cells and their potential for tolerance induction in haemophilia A patients.

Anti-factor VIII antibodies in brothers with haemophilia A share similar characteristics.

Extended half-life pegylated, full-length recombinant factor VIII for prophylaxis in children with severe haemophilia A.

Baby hamster kidney cell-derived recombinant factor VIII: a quarter century of learning and clinical experience.

Summary report of the First International Conference on inhibitors in haemophilia A.
Basic immunology

CD8αβ+ γδ T Cells: A Novel T Cell Subset with a Potential Role in Inflammatory Bowel Disease.
Kadivar M, Petersson J, Svensson L, Marsal J.

Opinions/Commentaries/ Across diseases reviews

Effect of IL-17 receptor A blockade with brodalumab in inflammatory diseases.

The challenge of autoinflammatory syndromes: with an emphasis on hyper-IgD syndrome.
vander Meer JW, Simon A.

MIF, a controversial cytokine: a review of structural features, challenges, and opportunities for drug development.
Bloom J, Sun S, Al-Abed Y.
REGULATION

EMA

Scientific guideline: Draft guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products, draft: consultation open

Human medicines European public assessment report (EPAR): ReFacto AF, moroctocog alfa
Revision: 33, Authorised

List of medicinal products under additional monitoring (updated)

Development challenges for medicines for central nervous system disorders

Opinion/decision on a Paediatric investigation plan (PIP): Recombinant humanized anti-MMP9 monoclonal antibody IgG4 (GS-5745)
Therapeutic area: Gastroentology-Hepatology (updated)

Human medicines European public assessment report (EPAR): Remicade, infliximab
Revision: 47, Authorised

Human medicines European public assessment report (EPAR): Simponi, golimumab
Revision: 25, Authorised

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol
Revision: 17, Authorised

Human medicines European public assessment report (EPAR): Flixabi, infliximab
Revision: 2, Authorised

Orphan designation: Human monoclonal IgG1 antibody for the: Treatment of haemophilia A
FDA

Guidance for Industry

Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

2056912fnl.pdf