TABLE OF CONTENTS

INTRODUCTION 2
WELCOME 3
LITERATURE 4
   This month's selected article 4
   Immunogenicity 5
   Methods 5
   Animal models 6
   Biomarkers 7
   Systemic Lupus Erythematosus 7
   Rheumatoid Arthritis 8
   Inflammatory Bowel Diseases 9
   Multiple Sclerosis 10
   Hemophilia 11
   Basic immunology 11
   Opinions/Commentaries/Across diseases reviews 12
REGULATION 13
   EMA 13
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 January 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.

This month, we chose to highlight a review by Pandey and Sauna on the potential use of pharmacogenetic factors in the predicting and circumventing unwanted therapeutic protein immunogenicity.

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
In this review, Pandey and Sauna discuss potential pharmacogenetic determinants of immunogenicity, how these can be measured, and also present clinical examples in the field of Haemophilia where such pharmacogenetic approach to predicting and circumventing immunogenicity may prove to be useful.

Three main pharmacogenetic criteria are highlighted: 1) the sequence homology between the endogenous protein and its therapeutic counterpart; 2) the number of MHC class II binding epitopes that can be derived from the therapeutic protein; 3) the presence of a functional CD4 T cell repertoire specific for those epitopes in one taken individual:

All these parameters are measurable and taken together should allow the tailoring of therapeutic protein with reduced immunogenicity and/or the identification of patient populations at higher risk of developing unwanted immunogenicity and resistance to treatment.

Pharmacogenetics and the Immunogenicity of Protein Therapeutics.
Pandey GS, Sauna ZE.
Immunogenicity

Interferon-Beta: Neutralizing Antibodies, Binding Antibodies, Pharmacokinetics and Pharmacodynamics, and Clinical Outcomes,
Deisenhammer F.
J Interferon Cytokine Res. 2014 Dec;34(12):938-945.

Epitope mapping via selection of anti-FVIII antibody-specific phage-presented peptide ligands that mimic the antibody binding sites.
Thromb Haemost. 2014 Dec 18;113(2).

Antibody dissociation rates are predictive of neutralizing antibody (NAb) course: A comparison of interferon beta-1b-treated patients with transient versus sustained NAbs.
Gibbs E, Karim ME, Oger J; the Steering Committee of the BENEFIT study; the Steering Committee of the BENEFIT study.

In vitro and in vivo modifications of recombinant and human IgG antibodies.
MAbs. 2014 Sep 3;6(5):1145-54.

Methods

In-depth determination and analysis of the human paired heavy- and light-chain antibody repertoire.
DeKosky BJ, Kojima T, Rodin A, Charab W, Ippolito GC, Ellington AD, Georgiou G.

Recombinant H22(scFv) blocks CD64 and prevents the capture of anti-TNF monoclonal antibody.
Hristodorov D, Mladenov R, Brehm H, Fischer R, Barth S, Thepen T.

Generation of a highly specific monoclonal anti-infliximab antibody for harmonization of TNF-coated infliximab assays.
Van Stappen T, Brouwers E, Tops S, Geukens N, Vermeire S, Declerck PJ, Gils A.
Ther Drug Monit. 2014 Dec 18.
Pharmacokinetics and Pharmacokinetic-Pharmacodynamic Relationships of Monoclonal Antibodies in Children.
Edlund H, Melin J, Parra-Guillen ZP, Kloft C.

Fc fusion as a platform technology: potential for modulating immunogenicity.
Levin D, Golding B, Strome SE, Sauna ZE.

Isolation of high affinity, neutralizing anti-idiotypic antibodies by phage and ribosome display for application in immunogenicity and pharmacokinetic analyses.
Chin SE, Ferraro F, Groves M, Liang M, Vaughan TJ, Dobson CL.

Animal models

A modified immune tolerant mouse model to study the immunogenicity of recombinant human interferon beta.
Abdolvahab MH, Brinks V, Schellekens H.

Assessment of the Immunogenicity of Mechanically Induced Interferon Aggregates in a Transgenic Mouse Model.
Human P, Ilsley H, Roberson C, Grovender E, Van Antwerp B, Fogt E, Zilla P.

B-cell inhibition by cross-linking CD79b is superior to B-cell depletion with anti-CD20 antibodies in treating murine collagen-induced arthritis.

Protective effect of a germline, IL-17-neutralizing antibody in murine models of autoimmune inflammatory disease.
Dallenbach K, Maurer P, Röhn T, Zabel F, Kopf M, Bachmann MF.
Biomarkers

**Immunological biomarkers identifying natalizumab-treated multiple sclerosis patients at risk of progressive multifocal leukoencephalopathy.**

**Systemic Lupus Erythematosus**

**Evaluation of epratuzumab as a biologic therapy in systemic lupus erythematosus.**
Rao V, Gordon C.

**Belimumab for the treatment of systemic lupus erythematosus.**
Jordan N, D’Cruz DP.

**Ofatumumab: a novel treatment for severe systemic lupus erythematosus.**
Thornton CC, Ambrose N, Ioannou Y.

**Current role of rituximab in systemic lupus erythematosus.**
Mok CC.

**Biologicals for the treatment of systemic lupus erythematosus: current status and emerging therapies.**
Leone A, Sciascia S, Kamal A, Khamashta M.

**Safety of off-label biologicals in systemic lupus erythematosus.**
Aringer M, Smolen JS.
Alternatively activated dendritic cells derived from systemic lupus erythematosus patients have tolerogenic phenotype and function.
Wu HJ, Lo Y, Luk D, Lau CS, Lu L, Mok MY.

What is new in systemic lupus erythematosus.
Rúa-Figueroa Fernández de Larrinoa I.

Rheumatoid Arthritis

Tocilizumab for treating rheumatoid arthritis: an evaluation of pharmacokinetics/pharmacodynamics and clinical efficacy.
Song SN, Yoshizaki K.

Biological drugs for the treatment of rheumatoid arthritis by the subcutaneous route: interpreting efficacy data to assess statistical equivalence.
Messori A, Fadda V, Maratea D, Trippoli S, Gatto R, De Rosa M, Marinai C.

The 'Switch' study protocol: a randomised-controlled trial of switching to an alternative tumour-necrosis factor (TNF)-inhibitor drug or abatacept or rituximab in patients with rheumatoid arthritis who have failed an initial TNF-inhibitor drug.

Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: Results from the TENDER trial.
Long-term real-life experience with rituximab in adult Finnish patients with rheumatoid arthritis refractory or with contraindication to anti-tumor necrosis factor drugs.

Safety issues and concerns of new immunomodulators in rheumatology.
Selmi C, Ceribelli A, Naguwa SM, Cantarini L, Shoenfeld Y.

The efficacy and safety of certolizumab pegol (CZP) in the treatment of active rheumatoid arthritis (RA): a meta-analysis from nine randomized controlled trials.

Novel multimeric IL-1 receptor antagonist for the treatment of rheumatoid arthritis.
Pasi S, Kant R, Gupta S, Surolia A.
Biomaterials. 2015 Feb;42:121-33.

Therapeutic Vaccination with TNF-Kinoid in TNF Antagonist-Resistant Rheumatoid Arthritis: A Phase II Randomized, Controlled Clinical Trial.

Inflammatory Bowel Diseases

Current and emerging biologics for ulcerative colitis.
Park SC, Jeen YT.

Tailoring treatment to the individual patient: drug monitoring.
Sandborn WJ.
Multiple Sclerosis

**Interferon Beta and Vitamin D Synergize to Induce Immunoregulatory Receptors on Peripheral Blood Monocytes of Multiple Sclerosis Patients.**

**Can we measure long-term treatment effects in multiple sclerosis?**
Sormani MP, Bruzzi P.
Nat Rev Neurol. 2014 Dec 23.

**Pharmacogenomics of interferon-β in multiple sclerosis: What has been accomplished and how can we ensure future progress?**
Carlson RJ, Doucette JR, Knox K, Nazarali AJ.

**IFN-β and multiple sclerosis: From etiology to therapy and back.**

**Switch to natalizumab vs fingolimod in active relapsing-remitting multiple sclerosis.**
Ann Neurol. 2014 Dec 27.

**Divergent effects of type-I interferons on regulatory T cells.**
Piconese S, Picella I, Timperi E, Barnaba V.

**Natalizumab-related anaphylactoid reactions in MS patients are associated with HLA class II alleles.**
**IFN-β and multiple sclerosis: Cross-talking of immune cells and integration of immunoregulatory networks.**
Severa M, Rizzo F, Giacomini E, Salvetti M, Coccia EM.
Cytokine Growth Factor Rev. 2014 Nov 22.

**Hemophilia**

**Factor VIII Antigen, Activity, and Mutations in Hemophilia A.**
Nair PS, Shetty S, Ghosh K.

**A new recombinant factor VIII: from genetics to clinical use.**
Santagostino E.

**The pharmacokinetics of a B-domain truncated recombinant FVIII, turoctocog alfa (NovoEight®), in patients with hemophilia A.**

**Basic immunology**

**T-B-cell entanglement and ICOSL-driven feed-forward regulation of germinal centre reaction.**
Liu D, Xu H, Shih C, Wan Z, Ma X, Ma W, Luo D, Qi H.

**Resident memory T cells in human health and disease.**
Clark RA.
Sci Transl Med. 2015 Jan 7;7(269):269rv1

**Role of dendritic cells in the initiation, progress and modulation of systemic autoimmune diseases.**

**Dietary modulation of the microbiome affects autoinflammatory disease.**
Metabolic control of regulatory T cell development and function.
Zeng H, Chi H.

Opinions/Commentaries/Across diseases reviews

Antibodies to watch in 2015.
Reichert JM.
MAbs. 2014 Nov 19:0.

Advances in biomarkers for paediatric rheumatic diseases.
Consolaro A, Varnier GC, Martini A, Ravelli A.

Biosimilars: are they bioequivalent?
Gomollón F.
REGULATION

The Innovative Medicines Initiative: an engine for regulatory science.
Goldman M, Seigneuret N, Eichler HG.

EMA

Human medicines European public assessment report (EPAR): Tysabri, natalizumab
Revision: 18, Authorised
December 2014

Human medicines European public assessment report (EPAR): Humira, adalimumab
Revision: 37, Authorised
December 2014

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol
Revision: 12, Authorised
December 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Benlysta, belimumab
Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
December 2014

Public summary of the evaluation of a proposed paediatric investigation plan: Belimumab for treatment of systemic lupus erythematosus
December 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Turoctocog alfa pegol
Therapeutic area: Haematology-Hemostaseology
Updated
December 2014
Opinion/decision on a Paediatric Investigation Plan (PIP): Voncento, Human coagulation factor VIII / von Willebrand factor
Therapeutic area: Haematology-Hemostaseology
Updated
December 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): tabalumab
Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
December 2014

Overview of comments received on draft guideline on similar biological medicinal products
December 2014