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## 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 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 **January 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.

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 very well thought review on new functions of B cells in autoimmunity especially on secretion of cytokines which can be important for immunization against biologics

[Cytokine-producing B cells: a translational view on their roles in human and mouse autoimmune diseases.](#)

Lino AC, Dörner T, Bar-Or A, Fillatreau S.  
Immunol Rev. 2016 Jan;269(1):130-44

2. In this study, Ternant et al. show that both allotypes of the therapeutic antibody and of the recipients influence the PK of therapeutic antibody because of allotypic variations of binding to FcRn

[IgG1 Allotypes Influence the Pharmacokinetics of Therapeutic Monoclonal Antibodies through FcRn Binding.](#)

Ternant D, Arnoult C, Pugnière M, Dhommée C, Drocourt D, Perouzel E, Passot C, Baroukh N, Mulleman D, Tiraby G, Watier H, Paintaud G, Gouilleux-Gruart V.  
J Immunol. 2015 Dec 18.

3. This work provides some important information on the mechanism of action of Multiple Sclerosis and other demyelinating CNS diseases therapies, another challenge for the autoimmune nature of MS, which could not be proven so far

[Rituximab induces clonal expansion of IgG memory B-cells in patients with inflammatory central nervous system demyelination.](#)

Maurer MA, Tuller F, Gredler V, Berger T, Lutterotti A, Lünemann JD, Reindl M.  
J Neuroimmunol. 2016 Jan 15;290:49-53.

## Immunogenicity

### [Infliximab-induced autoantibodies: a multicenter study.](#)

Vaz JL, Fernandes V, Nogueira F, Arnóbio A, Levy RA.  
Clin Rheumatol. 2015 Dec 17.

### [Aggregation risk prediction for antibodies and its application to biotherapeutic development.](#)

Obrezanova O, Arnell A, de la Cuesta RG, Berthelot ME, Gallagher TR, Zurdo J, Stallwood Y.  
MAbs. 2015;7(2):352-63.

### [The Role of Aggregates of Therapeutic Protein Products in Immunogenicity: An Evaluation by Mathematical Modeling.](#)

Yin L, Chen X, Tiwari A, Vicini P, Hickling TP.  
J Immunol Res. 2015;2015:401956.

### [Small amounts of sub-visible aggregates enhance the immunogenic potential of monoclonal antibody therapeutics.](#)

Ahmadi M, Bryson CJ, Cloake EA, Welch K, Filipe V, Romeijn S, Hawe A, Jiskoot W, Baker MP, Fogg MH.  
Pharm Res. 2015 Apr;32(4):1383-94.

## Methods

### [Indirect assessment of neutralizing anti-drug antibodies utilizing pharmacokinetic assay data.](#)

Vettermann C, Ortiz J, Lee S, Sanchez S, Victor HP, Ma M, Heath T, Gupta S.  
J Immunol Methods. 2015 Dec 19.

### [Enhanced Detection of Antigen-Specific CD4+ T Cells Using Altered Peptide Flanking Residue Peptide-MHC Class II Multimers.](#)

Holland CJ, Dolton G, Scurr M, Ladell K, Schauenburg AJ, Miners K, Madura F, Sewell AK, Price DA, Cole DK, Godkin AJ.  
J Immunol. 2015 Dec 15;195(12):5827-36.

### [Cytokine release assays for the prediction of therapeutic mAb safety in first-in man trials--Whole blood cytokine release assays are poorly predictive for TGN1412 cytokine storm.](#)

Vessillier S, Eastwood D, Fox B, Sathish J, Sethu S, Dougall T, Thorpe SJ, Thorpe R, Stebbings R.  
J Immunol Methods. 2015 Sep;424:43-52.

[Agreement in assessment of infliximab and adalimumab levels in rheumatoid arthritis: interlaboratory and interassay comparison.](#)

Valor L, Hernández-Flórez D, de la Torre I, Llinares F, Rosas J, Yagüe J, Garrido J, Naredo E.  
Clin Exp Rheumatol. 2015 Sep-Oct;33(5):617-23.

[Comparison of Two Different Techniques to Assess Adalimumab Trough Levels in Patients with Crohn's Disease.](#)

Bodini G, Giannini EG, Furnari M, Marabotto G, Baldissarro I, Del Nero L, Assandri L, Moscatelli A, Savarino V, Savarino E.  
J Gastrointest Liver Dis. 2015 Dec;24(4):451-6.

[Clinical laboratory application of a reporter-gene assay for measurement of functional activity and neutralizing antibody response to infliximab.](#)

Pavlov IY, Carper J, Lázár-Molnár E, Delgado JC.  
Clin Chim Acta. 2015 Dec 12;453:147-153.

### Biosimilars

[The Tortoise and the Hare: Evolving Regulatory Landscapes for Biosimilars.](#)

Konara CS, Barnard RT, Hine D, Siegel E, Ferro V.  
Trends Biotechnol. 2016 Jan;34(1):70-83.

[Efficacy And Safety Of The Biosimilar Infliximab CT-P13 Treatment In Inflammatory Bowel Diseases: A Prospective, Multicentre, Nationwide Cohort.](#)

Gecse KB, Lovász BD, Farkas K, Banai J, Bene L, Gasztonyi B, Golovics PA, Kristóf T, Lakatos L, Csontos AA, Juhász M, Nagy F, Palatka K, Papp M, Patai Á, Lakner L, Salamon Á, Szamosi T, Szepes Z, Tóth GT, Vincze Á, Szalay B, Molnár T, Lakatos PL.  
J Crohns Colitis. 2015 Dec 10.

### Animal models

[The Role of Anti-drug Antibodies in the Pharmacokinetics, Disposition, Target Engagement, and Efficacy of a GITR Agonist Monoclonal Antibody in Mice.](#)

Brunn ND, Mauze S, Gu D, Wiswell D, Ueda R, Hodges D, Beebe AM, Zhang S, Escandon E.  
J Pharmacol Exp Ther. 2015 Dec 15.

[The immunogenicity of platelet-derived FVIII in hemophilia A mice with or without pre-existing anti-FVIII immunity.](#)

Chen Y, Schroeder JA, Chen J, Luo X, Baumgartner CK, Montgomery RR, Hu J, Shi Q.  
Blood. 2015 Dec 14.

### Biomarkers

[Abatacept efficacy in rheumatoid arthritis is dependent upon baseline blood B-cell levels.](#)

Gazeau P, Devauchelle-Pensec V, Pochard P, Pers JO, Saraux A, Renaudineau Y, Cornec D.  
Rheumatology (Oxford). 2015 Dec 14.

[Baseline Serum Osteopontin Levels Predict the Clinical Effectiveness of Tocilizumab but Not Infliximab in Biologic-Naïve Patients with Rheumatoid Arthritis: A Single-Center Prospective Study at 1 Year \(the Keio First-Bio Cohort Study\).](#)

Izumi K, Kaneko Y, Hashizume M, Yoshimoto K, Takeuchi T.  
PLoS One. 2015 Dec 23;10(12):e0145468.

[Circulating complexes between tumour necrosis factor-alpha and etanercept predict long-term efficacy of etanercept in juvenile idiopathic arthritis.](#)

Kahn R, Berthold E, Gullstrand B, Schmidt T, Kahn F, Geborek P, Saxne T, Bengtsson AA, Månsson B.  
Acta Paediatr. 2015 Dec 27.

[Investigating CD11c expression as a potential genomic biomarker of response to TNF inhibitor biologics in whole blood rheumatoid arthritis samples.](#)

Smith SL, Eyre S, Yarwood A, Hyrich K, Morgan AW, Wilson AG, Isaacs J; Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate 6, Plant D, Barton A.  
Arthritis Res Ther. 2015 Dec 14;17:359.

[Dysregulation of RasGRP1 in rheumatoid arthritis and modulation of RasGRP3 as a biomarker of TNF \$\alpha\$  inhibitors.](#)

Golinski ML, Vandhuick T, Derambure C, Fréret M, Lecuyer M, Guillou C, Hiron M, Boyer O, Le Loët X, Vittecoq O, Lequerré T.  
Arthritis Res Ther. 2015 Dec 26;17(1):382.

[Serum proteomic analysis identifies interleukin 16 as a biomarker for clinical response during early treatment of rheumatoid arthritis.](#)

Murota A, Suzuki K, Kassai Y, Miyazaki T, Morita R, Kondo Y, Takeshita M, Niki Y, Yoshimura A, Takeuchi T.  
Cytokine. 2016 Feb;78:87-93.

[Serum levels of granzyme B decrease in patients with rheumatoid arthritis responding to abatacept.](#)

Colombo E, Scarsi M, Piantoni S, Tincani A, Airò P.  
Clin Exp Rheumatol. 2015 Dec 1.

### Systemic Lupus Erythematosus

[Population pharmacokinetic analysis of sifalimumab from a clinical phase IIb trial in systemic lupus erythematosus patients.](#)

Zheng B, Yu XQ, Greth W, Robbie GJ.  
Br J Clin Pharmacol. 2015 Dec 13

[Pharmacokinetics and safety of single doses of tabalumab in subjects with rheumatoid arthritis or systemic lupus erythematosus.](#)

Witcher J, Fleischmann R, Chindalore VL, Hansen RJ, Hu L, Radtke D, Voelker J, Gomez E, McColm J.  
Br J Clin Pharmacol. 2015 Dec 9.

### Arthritis

[Abatacept \(CTLA-4Ig\) treatment reduces T cell apoptosis and regulatory T cell suppression in patients with rheumatoid arthritis.](#)

Bonelli M, Göschl L, Blüml S, Karonitsch T, Hirahara K, Ferner E, Steiner CW, Steiner G, Smolen JS, Scheinecker C.  
Rheumatology (Oxford). 2015 Dec 16.

[Safety and Efficacy of Subcutaneous Golimumab in Patients with Active Rheumatoid Arthritis despite Methotrexate Therapy: Final 5-year Results of the GO-FORWARD Trial.](#)

Keystone EC, Genovese MC, Hall S, Bae SC, Han C, Gathany TA, Xu S, Zhou Y, Leu JH, Hsia EC.  
J Rheumatol. 2015 Dec 15.

[Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials.](#)

Lee YH, Bae SC.  
Int J Rheum Dis. 2015 Dec 22.



[Personalized biological treatment for rheumatoid arthritis: a systematic review with a focus on clinical applicability.](#)

Cuppen BV, Welsing PM, Sprengers JJ, Bijlsma JW, Marijnissen AC, van Laar JM, Lafeber FP, Nair SC.  
Rheumatology (Oxford). 2015 Dec 29.

[Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials.](#)

Lee YH, Bae SC.  
Int J Rheum Dis. 2015 Dec 22.

[Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials.](#)

Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JM, Cohen N, Pope TD, Furst DE.  
Rheumatology (Oxford). 2015 Nov 30.

[Subcutaneous tocilizumab for the treatment of rheumatoid arthritis.](#)

Mitchel EL, Jones G.  
Expert Rev Clin Immunol. 2015 Dec 2.

[Time lag between the initiation of adalimumab after methotrexate correlates with the efficacy of adalimumab in rheumatoid arthritis patients.](#)

Kimura N, Suzuki K, Takeuchi T.  
Mod Rheumatol. 2015 Dec 27:1-21.

## Inflammatory Bowel Diseases

[Low Dose Infliximab for Prevention of Postoperative Recurrence of Crohn's Disease: Long Term Follow-Up and Impact of Infliximab Trough Levels and Antibodies to Infliximab.](#)

Sorrentino D, Marino M, Dassopoulos T, Zarifi D, Del Bianco T.  
PLoS One. 2015 Dec 15;10(12):e0144900.

[Pharmacokinetics of Infliximab and Reduction of Treatment for Inflammatory Bowel Diseases.](#)

Williet N, Paul S, Peyrin-Biroulet L, Roblin X.  
Dig Dis Sci. 2015 Dec 15.

[Biologicals in treatment of acute ulcerative colitis.](#)

Ghoshal UC, Verma A.  
Trop Gastroenterol. 2015 Apr-Jun;36(2):80-5.

[Optimization of anti-TNF therapy in patients with Inflammatory Bowel Disease.](#)

Strik AS, Bots SJ, D'Haens G, Löwenberg M.  
Expert Rev Clin Pharmacol. 2015 Dec 17.

### Multiple Sclerosis

[Advances in and Algorithms for the Treatment of Relapsing-Remitting Multiple Sclerosis.](#)

Ingwersen J, Aktas O, Hartung HP.  
Neurotherapeutics. 2015 Dec 23.

[Pharmacogenetic study of long-term response to interferon- \$\beta\$  treatment in multiple sclerosis.](#)

Clarelli F, Liberatore G, Sorosina M, Osiceanu AM, Esposito F, Mascia E, Santoro S, Pavan G, Colombo B, Moiola L, Martinelli V, Comi G, Martinelli-Boneschi F.  
Pharmacogenomics J. 2015 Dec 8.

### Basic immunology

[Immune homeostasis enforced by co-localized effector and regulatory T cells.](#)

Liu Z, Gerner MY, Van Panhuys N, Levine AG, Rudensky AY, Germain RN.  
Nature. 2015 Nov 25. doi: 10.1038/nature16169.

### Opinions/Commentaries/Across diseases reviews

[Antibodies to watch in 2016.](#)

Reichert JM.  
MAbs. 2015 Dec 14:0.

[Third-Kind Encounters in Biomedicine: Immunology Meets Mathematics and Informatics to Become Quantitative and Predictive.](#)

Eberhardt M, Lai X, Tomar N, Gupta S, Schmeck B, Steinkasserer A, Schuler G, Vera J.  
Methods Mol Biol. 2016;1386:135-79.

## REGULATION

### EMA

[Work plan for the Rheumatology-Immunology Working Party 2016](#)

December 2015

[Work plan for the Biosimilar Medicinal Products Working Party 2016](#)

December 2015

[Human medicines European public assessment report \(EPAR\): Avonex, interferon beta-1-a](#)

Revision: 25, Authorised

December 2015

[Orphan designation: Recombinant porcine factor VIII \(B-domain-deleted\) for the: Treatment of haemophilia A](#)

Updated

December 2015

[Human medicines European public assessment report \(EPAR\): Plegridy, peginterferon beta-1a](#)

Revision: 6, Authorised

December 2015

[Human medicines European public assessment report \(EPAR\): Helixate NexGen, octocog alfa](#)

Revision: 28, Authorised

December 2015

[Referral: Article 20 procedures, Tysabri, natalizumab](#)

Updated

December 2015

[Human medicines European public assessment report \(EPAR\): Orencia, abatacept](#)

Revision: 19, Authorised

December 2015