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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 October 2015 **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. This study from colleagues of ABIRISK highlights the risk of immunogenicity resulting from the unwanted targeting of a therapeutic antibody to human dendritic cells

[Contribution of enhanced engagement of antigen presentation machinery to the clinical immunogenicity of a human IL21 receptor-blocking therapeutic antibody.](#)

Xue L, Hickling T, Song R, Nowak J, Rup B.  
Clin Exp Immunol. 2015 Sep 24.

2. A special issue addressing the question of extrapolation of immunogenicity from 1 compound to its biosimilars

[The immunogenicity of biosimilar infliximab: can we extrapolate the data across indications?](#)

Ben-Horin S, Heap GA, Ahmad T, Kim H, Kwon T, Chowers Y.  
Expert Rev Gastroenterol Hepatol. 2015 Sep;9 Suppl 1:27-34.

## Immunogenicity

[Characterisation of a Novel Anti-CD52 Antibody with Improved Efficacy and Reduced Immunogenicity.](#)

Holgate RG, Weldon R, Jones TD, Baker MP.

PLoS One. 2015 Sep 15;10(9):e0138123.

[Contribution of enhanced engagement of antigen presentation machinery to the clinical immunogenicity of a human IL21 receptor-blocking therapeutic antibody.](#)

Xue L, Hickling T, Song R, Nowak J, Rup B.

Clin Exp Immunol. 2015 Sep 24.

## Methods

[Identification of suitable reference genes for peripheral blood mononuclear cell subset studies in multiple sclerosis.](#)

Oturai DB, Søndergaard HB, Börnsen L, Sellebjerg F, Christensen JR.

Scand J Immunol. 2015 Sep 23.

[Remediating agitation-induced antibody aggregation by eradicating exposed hydrophobic motifs.](#)

Clark RH, Latypov RF, De Imus C, Carter J, Wilson Z, Manchulenko K, Brown ME, Ketchem RR.

MAbs. 2014;6(6):1540-50.

[Role of benzyl alcohol in the unfolding and aggregation of interferon  \$\alpha\$ -2a.](#)

Bis RL, Singh SM, Cabello-Villegas J, Mallela KM.

J Pharm Sci. 2015 Feb;104(2):407-15.

[Quantitative measurement of the target-mediated internalization kinetics of biopharmaceuticals.](#)

Vainshtein I, Roskos LK, Cheng J, Sleeman MA, Wang B, Liang M.

Pharm Res. 2015 Jan;32(1):286-99.

## Biosimilars

[Comparison of immunogenicity test methods used in clinical studies of infliximab and its biosimilar \(CT-P13\).](#)

Kim JS, Kim SH, Kwon B, Hong S.

Expert Rev Clin Immunol. 2015 Sep;11 Suppl 1:33-41.

[Comparison of the pharmacokinetics and safety of three formulations of infliximab \(CT-P13, EU-approved reference infliximab and the US-licensed reference infliximab\) in healthy subjects: a randomized, double-blind, three-arm, parallel-group, single-dose, Phase I study.](#)

Park W, Lee SJ, Yun J, Yoo DH.

Expert Rev Clin Immunol. 2015 Sep;11 Suppl 1:25-31.

[Biosimilar monoclonal antibodies: the scientific basis for extrapolation.](#)

Schellekens H, Lietzan E, Faccin F, Venema J.

Expert Opin Biol Ther. 2015 Nov;15(11):1633-46

[An update on biosimilar drugs for inflammatory bowel disease.](#)

Schreiber S.

Expert Rev Gastroenterol Hepatol. 2015 Sep;9 Suppl 1:1-3.

[The Pharmacokinetics of Biologics: A Primer.](#)

Mould DR.

Dig Dis. 2015 Sep 14;33 Suppl 1:61-69.

[Scientific rationale behind the development and approval of biosimilar infliximab \(CT-P13\) in Europe.](#)

Müller-Ladner U, Hong S, Oh C, Taylor P.

Expert Rev Clin Immunol. 2015 Sep;11 Suppl 1:5-14.

[A scientific update on biosimilar infliximab \(CT-P13\) in rheumatic diseases.](#)

Taylor P.

Expert Rev Clin Immunol. 2015 Sep;11 Suppl 1:1-4.

[Biosimilars in immune-mediated inflammatory diseases: initial lessons from the first approved biosimilar anti-tumour necrosis factor monoclonal antibody.](#)

Isaacs JD, Cutolo M, Keystone EC, Park W, Braun J.

J Intern Med. 2015 Sep 25.



## Animal models

[A novel human truncated IL12rβ1-Fc fusion protein ameliorates experimental autoimmune encephalomyelitis via specific binding of p40 to inhibit Th1 and Th17 cell differentiation.](#)

Guo W, Wang C, Wang X, Luo C, Yu D, Wang Y, Chen Y, Lei W, Gao X, Yao W.  
Oncotarget. 2015 Sep 4.

## Biomarkers

[Adalimumab and etanercept serum \(anti\)drug levels are not predictive for successful dose reduction or discontinuation in rheumatoid arthritis.](#)

van Herwaarden N, Bouman CA, van der Maas A, van Vollenhoven RF, Bijlsma JW, van den Hoogen FH, den Broeder AA, van den Bemt BJ.  
Ann Rheum Dis. 2015 Sep 4.

[Heightened Expression of CD39 by Regulatory T Lymphocytes Is Associated with Therapeutic Remission in Inflammatory Bowel Disease.](#)

Gibson DJ, Elliott L, McDermott E, Tosetto M, Keegan D, Byrne K, Martin ST, Rispens T, Cullen G, Mulcahy HE, Cheifetz AS, Moss AC, Robson SC, Doherty GA, Ryan EJ.  
Inflamm Bowel Dis. 2015 Aug 31

[Immune- and miRNA-response to recombinant interferon beta-1a: a biomarker evaluation study to guide the development of novel type I interferon- based therapies.](#)

Coenen M, Hinze AV, Mengel M, Fuhrmann C, Lüdenbach B, Zimmermann J, Dykstra V, Fimmers R, Viviani R, Stingl J, Holdenrieder S, Müller M, Hartmann G, Coch C.  
BMC Pharmacol Toxicol. 2015 Sep 22;16(1):25

[Impact of baseline anti-cyclic citrullinated peptide-2 antibody concentration on efficacy outcomes following treatment with subcutaneous abatacept or adalimumab: 2-year results from the AMPLE trial.](#)

Sokolove J, Schiff M, Fleischmann R, Weinblatt ME, Connolly SE, Johnsen A, Zhu J, Maldonado MA, Patel S, Robinson WH.  
Ann Rheum Dis. 2015 Sep 10

## Systemic Lupus Erythematosus

[Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study.](#)

Isenberg DA, Petri M, Kalunian K, Tanaka Y, Urowitz MB, Hoffman RW, Morgan-Cox M, Iikuni N, Silk M, Wallace DJ.

Ann Rheum Dis. 2015 Sep 3. pii: annrheumdis-2015-207653.

[Efficacy, pharmacokinetic and pharmacodynamic profile of belimumab for systemic lupus erythematosus.](#)

Jordan NP, D'Cruz DP.

Expert Opin Drug Metab Toxicol. 2015 Oct;11(10):1635-45.

[Low-dose interleukin-2 selectively corrects regulatory T cell defects in patients with systemic lupus erythematosus.](#)

von Spee-Mayer C, Siegert E, Abdirama D, Rose A, Klaus A, Alexander T, Enghard P, Sawitzki B, Hiepe F, Radbruch A, Burmester GR, Riemekasten G, Humrich JY.

Ann Rheum Dis. 2015 Aug 31.

[Elevated BlyS levels in patients with systemic lupus erythematosus: Associated factors and responses to belimumab.](#)

Roth DA, Thompson A, Tang Y, Hammer AE, Molta CT, Gordon D.

Lupus. 2015 Sep 18.

[Safety, Pharmacokinetics and Pharmacodynamics of Epratuzumab in Japanese Patients with Moderate-to-Severe Systemic Lupus Erythematosus: Results from a Phase 1/2 Randomized Study.](#)

Tsuru T, Tanaka Y, Kishimoto M, Saito K, Yoshizawa S, Takasaki Y, Miyamura T, Niuro H, Morimoto S, Yamamoto J, Lledo-Garcia R, Shao J, Tatematsu S, Togo O, Koike T.

Mod Rheumatol. 2015 Sep 18:1-19.

## Rheumatoid Arthritis

[Comparing Effects of Biologic Agents in Treating Patients with Rheumatoid Arthritis: A Multiple Treatment Comparison Regression Analysis.](#)

Tvete IF, Natvig B, Gåsemyr J, Meland N, Røine M, Klemp M.

PLoS One. 2015 Sep 10;10(9):e0137258.



[Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis.](#)

Miserocchi E, Modorati G, Berchicci L, Pontikaki I, Meroni P, Gerloni V.  
Br J Ophthalmol. 2015 Sep 22.

[Evaluation of safety, efficacy and post-cessation efficacy durability of tocilizumab in patients with active rheumatoid arthritis.](#)

Ahmadzadeh A, Farahmand AN, Gachkar L.  
Int J Rheum Dis. 2015 Sep 19.

[Certolizumab pegol plus methotrexate 5-year results from the rheumatoid arthritis prevention of structural damage \(RAPID\) 2 randomized controlled trial and long-term extension in rheumatoid arthritis patients.](#)

Smolen JS, van Vollenhoven R, Kavanaugh A, Strand V, Vencovsky J, Schiff M, Landewé R, Haraoui B, Arendt C, Moutian I, Carter D, van der Heijde D.  
Arthritis Res Ther. 2015 Sep 10;17:245.

[Clinical outcomes in a cohort of Colombian patients with rheumatoid arthritis treated with Etaner, a new biologic type rhTNFR:Fc.](#)

Santos-Moreno PI, Sánchez G, Gomez D, Castro C.  
Clin Exp Rheumatol. 2015 Sep 7.

[RENACER Study: Assessment of 12-month efficacy and safety of 168 certolizumab-PEGol rheumatoid arthritis treated patients from a Spanish multicenter National database.](#)

Torrente-Segarra V, Urruticoechea Arana A, Sánchez-Andrade A, Tovar JV, Muñoz A, Martínez A, González JA, Fernández M, Vázquez N, Corominas H, García-Díaz S, Acosta-Pereira A, Ruiz Martín JM, Lamua Riazuelo JR, Expósito R, Ruiz Vilchez D, Veiga Cabello R, Carlos Fernández J, Noguera Pons JR, Patricia Garrido Puñal N, Giralte Celiméndiz P, Cortés Verdú R, Aragón Díez A, Tomás Roura C, Moll Turudi C, Taverner Torrent D, Rivas Santirso FJ, Lerma Garrido JJ, García Portales R, Ordoñez Palau S, Paredes González-Albo S, Gracia Pérez A, Conesa Mateos A, Calvo Alén J, Graña Gil J, Navarro Alonso MP, Martínez Blasco MJ.  
Mod Rheumatol. 2015 Sep 29:1-18.

## Inflammatory Bowel Diseases

[Vedolizumab: an  \$\alpha 4\beta 7\$  integrin antagonist for ulcerative colitis and Crohn's disease.](#)

Cherry LN, Yunker NS, Lambert ER, Vaughan D, Lowe DK.  
Ther Adv Chronic Dis. 2015 Sep;6(5):224-33.

[Review article: pharmacological aspects of anti-TNF biosimilars in inflammatory bowel diseases.](#)

Papamichael K, Van Stappen T, Jairath V, Gecse K, Khanna R, D'Haens G, Vermeire S, Gils A, Feagan BG, Levesque BG, Vande Casteele N.

Aliment Pharmacol Ther. 2015 Sep 13.

[New Insights into the Mechanisms of Action of Anti-Tumor Necrosis Factor- \$\alpha\$  Monoclonal Antibodies in Inflammatory Bowel Disease.](#)

Slevin SM, Egan LJ.

Inflamm Bowel Dis. 2015 Aug 12.

[Assessment of disease related therapeutic protein drug-drug interaction for etrolizumab in patients with moderately to severely active ulcerative colitis.](#)

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J Clin Pharmacol. 2015 Sep 28.

[Is There a Role for Therapeutic Drug Monitoring of Anti-TNF Monoclonal Antibodies in Inflammatory Bowel Disease.](#)

Baert F.

Dig Dis. 2015 Sep 14;33 Suppl 1:70-77.

[Role of Vitamin D in Infliximab-induced Remission in Adult Patients with Crohn's Disease.](#)

Reich KM, Fedorak RN, Madsen K, Kroeker KI.

Inflamm Bowel Dis. 2015 Sep 9.

## Multiple Sclerosis

[Pharmacokinetic considerations in the treatment of multiple sclerosis with interferon- \$\beta\$ .](#)

Hegen H, Auer M, Deisenhammer F.

Expert Opin Drug Metab Toxicol. 2015 Sep 30:1-17.

[Immunologic monitoring during a phase 2a trial of the GNBAC1 antibody in patients with MS.](#)

Zimmermann M, Sanderson NS, Rasenack M, Lalive PH, Lang AB, Curtin F, Lindberg RL, Kappos L, Derfuss T.

Neurol Neuroimmunol Neuroinflamm. 2015 Aug 20;2(5):e144.

[Long-term treatment of relapsing-remitting multiple sclerosis with interferon  \$\beta\$ : how strongly should we encourage patients to adhere to the 'old' therapies?](#)

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[Novel Agents for Relapsing Forms of Multiple Sclerosis.](#)

Straus Farber R, Harel A, Lublin F.  
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[A review of genome-wide association studies for multiple sclerosis: classical and hypothesis-driven approaches.](#)

Bashinskaya VV, Kulakova OG, Boyko AN, Favorov AV, Favorova OO.  
Hum Genet. 2015 Sep 25.

[Natalizumab in the pediatric MS population: results of the Italian registry.](#)

Ghezzi A, Moiola L, Pozzilli C, Brescia-Morra V, Gallo P, Grimaldi LM, Filippi M, G GC; MS Study Group-Italian Society of Neurology.  
BMC Neurol. 2015 Sep 25;15(1):174.

[Short-Term Effect of High-Dose Vitamin D on the Level of Interleukin 10 in Patients with Multiple Sclerosis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial.](#)

Ashtari F, Toghianifar N, Zarkesh-Esfahani SH, Mansourian M.  
Neuroimmunomodulation. 2015 Sep 25

## Hemophilia

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

Klukowska A, Szczepański T, Vdovin V, Knaub S, Jansen M, Liesner R.  
Haemophilia. 2015 Sep 14

[Successful immunoadsorption of life-threatening bleeding in factor VIII inhibitor disease, but no long-term remission with anti-CD20 treatment.](#)

Grahammer F, Fischer KG.  
BMJ Case Rep. 2015 Aug 30;2015.

[Can a "center effect" explain the higher frequency of inhibitors for a second generation recombinant factor VIII product?](#)

van den Berg HM, Ljung R.  
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## Opinions/Commentaries/Across diseases reviews

### [Antibodies to watch in 2015.](#)

Reichert JM.  
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### [Interactive Big Data Resource to Elucidate Human Immune Pathways and Diseases.](#)

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Immunity. 2015 Sep 15;43(3):605-14.

## REGULATION

### EMA

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

Updated  
September 2015

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

Updated  
September 2015

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

Updated  
September 2015

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

Updated  
September 2015