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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 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.

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WELCOME

Dear Reader,

We would like to welcome you to the October 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

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LITERATURE

This month's selected articles

1) Characterizing PK in preclinical studies is essential for determining whether a drug will survive through development. For monoclonal antibodies, predicting human PK from mouse studies can be complicated by species differences and immunogenicity. The study by Myzithras et al. addresses both of these issues by using SCID mice transgenic for the human FcRn receptor. Whilst the transgenic FcRn mouse had already proven to provide more consistently translatable data, this is the first report investigating mAb PK in the combined model. The study demonstrates that for Humira (Adalimumab) a more accurate prediction of human PK parameters was achieved in the SCID background :

Utility of immunodeficient mouse models for characterizing the preclinical pharmacokinetics of immunogenic antibody therapeutics.
Myzithras M, Bigwarfe T, Li H, Waltz E, Ahlberg J, Giragossian C, Roberts S.
MAbs. 2016 Sep 6:0.

2) An attractive approach of engineering to improve activity, stability and synthesis of biopharmaceuticals. Reduction of ADA recognition was also observed but antigenicity reduction does not entail the lack of immunogenicity. New specificities might be stimulated by the modified variants **:**

Enhancing the pharmaceutical properties of protein drugs by ancestral sequence reconstruction.
Zakas PM, Brown HC, Knight K, Meeks SL, Spencer HT, Gaucher EA, Doering CB.
Nat Biotechnol. 2016 Sep 26.

3) Pursuing the idea of adding target to the assay in order to reduce drug interference needs more attention :

An innovative and highly drug-tolerant approach for detecting neutralizing antibodies directed to therapeutic antibodies.
Sloan JH, Conway RG, Pottanat TG, Troutt JS, Higgs RE, Konrad RJ, Qian YW.
Bioanalysis. 2016 Oct;8(20):2157-68.

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Immunogenicity

Long-term treatment with adalimumab in psoriatic arthritis: serum adalimumab concentration, immunogenicity and the link with clinical response.
Chimenti MS, Triggianese P, Narcisi A, Marinari B, Teoli M, Faleri S, Arcese A, Perricone R, Costanzo A.
J Int Med Res. 2016 Sep;44(1 suppl):48-52.

Anti-Drug Antibodies, Drug Levels, Interleukin-6 and Soluble TNF Receptors in Rheumatoid Arthritis Patients during the First 6 Months of Treatment with Adalimumab or Infliximab: A Descriptive Cohort Study.
Eng GP, Bouchelouche P, Bartels EM, Bliddal H, Bendtzen K, Stoltenberg M.
PLoS One. 2016 Sep 8;11(9):e0162316.

Clinical Use of Measuring Trough Levels and Antibodies against Infliximab in Patients with Pediatric Inflammatory Bowel Disease.
Choi SY, Kang B, Lee JH, Choe YH.
Gut Liver. 2016 Sep 9.

Comparisons of Serum Infliximab and Antibodies-to-Infliximab Tests Used in Inflammatory Bowel Disease Clinical Trials of Remicade®.
Marini JC, Sendecki J, Cornillie F, Popp JW Jr, Black S, Blank M, Gils A, Van Stappen T, Hamann D, Rispens T, Thérien L, Chun K, Shankar G.
AAPS J. 2016 Sep 6.

Biomarkers

T cell subpopulations in juvenile idiopathic arthritis and their modifications after biotherapies.
Maggi L, Cosmi L, Simonini G, Annunziato F, Cimaz R.
Autoimmun Rev. 2016 Sep 15

Serological markers associated with disease activity in patients with rheumatoid arthritis treated with rituximab.
Conigliaro P, Triggianese P, Chimenti MS, Lucchetti R, Kroegler B, Perricone R.
J Int Med Res. 2016 Sep;44(1 suppl):53-57.

Metabolomic profiling predicts outcome of rituximab therapy in rheumatoid arthritis.
Sweeney SR, Kavanaugh A, Lodi A, Wang B, Boyle D, Tiziani S, Guma M.
RMD Open. 2016 Aug 16;2(2):e000289.

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Biomarkers in Search of Precision Medicine in IBD.
Boyapati RK, Kalla R, Satsangi J, Ho GT.
Am J Gastroenterol. 2016 Sep 27.

Biosimilars

A multicentre randomised controlled trial to compare the pharmacokinetics, efficacy and safety of CT-P10 and innovator rituximab in patients with rheumatoid arthritis.
Yoo DH, Suh CH, Shim SC, Jeka S, Cons-Molina FF, Hrycaj P, Wiland P, Lee EY, Medina-Rodriguez FG, Shesternya P, Radominski S, Stanislav M, Kovalenko V, Sheen DH, Myasoutova L, Lim MJ, Choe JY, Lee SJ, Lee SY, Kwon TS, Park W.
Ann Rheum Dis. 2016 Sep 13.

Infliximab biosimilars are safe, effective, and cheap, UK audit shows.
White C.
BMJ. 2016 Sep 21;354:i5084.

The design of clinical trials to support the switching and alternation of biosimilars.
Faccin F, Tebbey P, Alexander E, Wang X, Cui L, Albuquerque T.
Expert Opin Biol Ther. 2016 Sep 27:1-9.

Infliximab Biosimilar (CT-P13; Infliximab-dyyb): A Review in Autoimmune Inflammatory Diseases.
Blair HA, Deeks ED.
BioDrugs. 2016 Sep 20.

Biosimilar Monoclonal Antibodies for Inflammatory Bowel Disease: Current Comfort and Future Prospects.
Gecse KB, Lakatos PL.
Drugs. 2016 Sep 15.

Nonclinical Evaluation of PF-06438179: A Potential Biosimilar to Remicade® (Infliximab).
Derzi M, Johnson TR, Shoieb AM, Conlon HD, Sharpe P, Saati A, Koob S, Bolt MW, Lorello LG, McNally J, Kirchhoff CF, Smolarek TA, Leach MW.
Adv Ther. 2016 Sep 1.

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Animal models

Computational and functional analysis of biopharmaceutical drugs in zebrafish: Erythropoietin as a test model.
Guarienti M, Giacopuzzi E, Gianoncelli A, Sigala S, Spano P, Pecorelli S, Pani L, Memo M.
Pharmacol Res. 2015 Dec;102:12-21.

The bispecific antibody aimed at the vicious circle of IL-1β and IL-17A, is beneficial for the collagen-induced rheumatoid arthritis of mice through NF-κB signaling pathway.
Wu Q, Wang Y, Wang Q, Yu D, Wang Y, Song L, Liu Z, Ye X, Xu P, Cao H, Li D, Ren G.
Immunol Lett. 2016 Sep 9.

Systemic Lupus Erythematosus

Off-label use of rituximab for systemic lupus erythematosus in Europe.
Rydén-Aulin M, Boumpas D, Bultink I, Callejas Rubio JL, Caminal-Montero L, Castro A, Colodro Ruiz A, Doria A, Dörner T, Gonzalez-Echavarri C, Gremese E, Houssiau FA, Huizinga T, Inanç M, Isenberg D, Iuliano A, Jacobsen S, Jimenéz-Alonso J, Kovács L, Mariette X, Mosca M, Nived O, Oristrell J, Ramos-Casals M, Rascón J, Ruiz-Irastorza G, Sáez-Comet L, Salvador Cervelló G, Sebastiani GD, Squatrito D, Szücs G, Voskuyl A, van Vollenhoven R.
Lupus Sci Med. 2016 Sep 6;3(1):e000163.

Efficacy and Safety of Epratuzumab in Moderately to Severely Active Systemic Lupus Erythematosus: Results from the Phase 3, Randomized, Double-blind, Placebo-controlled Trials, EMBODY™ 1 and EMBODY™ 2.
Clowse ME, Wallace DJ, Furie RA, Petri MA, Pike MC, Leszczyński P, Neuwelt CM, Hobbs K, Keiserman M, Duca L, Kalunian KC, Galateanu C, Bongardt S, Stach C, Beaudot C, Kilgallen B, Gordon C; EMBODY Investigator Group.
Arthritis Rheumatol. 2016 Sep 6.

Systemic lupus erythematosus: Epratuzumab not effective in phase III trials.
Onuora S.
Nat Rev Rheumatol. 2016 Sep 22.

A Review of Clinical Trials of Belimumab In The Management of Systemic Lupus Erythematosus.
Garcia A, De Sanctis JB.
Curr Pharm Des. 2016 Aug 31.

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One year in review 2016: systemic lupus erythematosus.
Adinolfi A, Valentini E, Calabresi E, Tesei G, Signorini V, Barsotti S, Tani C.
Clin Exp Rheumatol. 2016 Jul-Aug;34(4):569-74.

The role of autophagy in the pathogenesis of systemic lupus erythematosus.
Liu X, Qin H, Xu J.
Int Immunopharmacol. 2016 Sep 24;40:351-361.

Efficacy and safety of an interleukin 6 monoclonal antibody for the treatment of systemic lupus erythematosus: a phase II dose-ranging randomised controlled trial.
Wallace DJ, Strand V, Merrill JT, Popa S, Spindler AJ, Eimon A, Petri M, Smolen JS, Wajdula J, Christensen J, Li C, Diehl A, Vincent MS, Beebe J, Healey P, Sridharan S.
Ann Rheum Dis. 2016 Sep 26.

Rheumatoid Arthritis

Targeting GM-CSF in rheumatoid arthritis.
Avci AB, Feist E, Burmester GR.
Clin Exp Rheumatol. 2016 Jul-Aug;34(4 Suppl 98):39-44.

The role of methotrexate as combination therapy with etanercept in rheumatoid arthritis: Retrospective analysis of a local registry.
Becciolini A, Biggioggero M, Favalli EG.
J Int Med Res. 2016 Sep;44(1 suppl):113-118.

Tocilizumab as monotherapy or combination therapy for treating active rheumatoid arthritis: a meta-analysis of efficacy and safety reported in randomized controlled trials.
Teitsma XM, Marijnissen AK, Bijlsma JW, Lafeber FP, Jacobs JW.
Arthritis Res Ther. 2016 Sep 22;18(1):211.

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Inflammatory Bowel Disease

Adalimumab or infliximab as monotherapy, or in combination with an immunomodulator, in the treatment of Crohn's disease.
Cosnes J, Sokol H, Bourrier A, Nion-Larmurier I, Wisniewski A, Landman C, Marteau P, Beaugerie L, Perez K, Seksik P.
Aliment Pharmacol Ther. 2016 Sep 26

Switching from Remicade® to Remsima® is safe and feasible: a prospective, open-label study.
Buer LC, Moum BA, Cvancarova M, Warren DJ, Medhus AW, Høivik ML.
J Crohns Colitis. 2016 Sep 22.

Biological Therapy in Pediatric Inflammatory Bowel Disease: A Systematic Review.
Corica D, Romano C.
J Clin Gastroenterol. 2016 Sep 15.

Integrin antagonists as potential therapeutic options for the treatment of Crohn's disease.
McLean LP, Cross RK.
Expert Opin Investig Drugs. 2016;25(3):263-73.

Therapeutic drug monitoring in inflammatory bowel disease.
Jossen J, Dubinsky M.
Curr Opin Pediatr. 2016 Oct;28(5):620-5.

Integrins and adhesion molecules as targets to treat inflammatory bowel disease.
Bravatà I, Allocca M, Fiorino G, Danese S.
Curr Opin Pharmacol. 2015 Dec;25:67-71.

B Cell-Activating Factor (BAFF)-Targeted B Cell Therapies in Inflammatory Bowel Diseases.
Uzzan M, Colombel JF, Cerutti A, Treton X, Mehandru S.
Dig Dis Sci. 2016 Sep 21.

Vedolizumab for the treatment of ulcerative colitis.
Shahidi N, Bressler B, Panaccione R.
Expert Opin Biol Ther. 2016;16(1):129-35

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Optimizing biological therapy in Crohn's disease.
Gecse KB, Végh Z, Lakatos PL.
Expert Rev Gastroenterol Hepatol. 2016;10(1):37-45

Multiple Sclerosis

Predictors of Response to Multiple Sclerosis Therapeutics in Individual Patients.
Hegen H, Auer M, Deisenhammer F.
Drugs. 2016 Sep 21.

CD20 therapies in multiple sclerosis and experimental autoimmune encephalomyelitis - Targeting T or B cells?
Agahozo MC, Peferoen L, Baker D, Amor S.
Mult Scler Relat Disord. 2016 Sep;9:110-7.

A placebo randomized controlled study to test the efficacy and safety of GNbAC1, a monoclonal antibody for the treatment of multiple sclerosis - Rationale and design.
Curtin F, Porchet H, Glanzman R, Schneble HM, Vidal V, Audoli-Inthavong ML, Lambert E, Hartung HP.
Mult Scler Relat Disord. 2016 Sep;9:95-100.

Safety and tolerability profile of daclizumab in patients with relapsing-remitting multiple sclerosis: An integrated analysis of clinical studies.
Giovannoni G, Kappos L, Gold R, Khatri BO, Selmaj K, Umans K, Greenberg SJ, Sweetser M, Elkins J, McCroskery P.
Mult Scler Relat Disord. 2016 Sep;9:36-46.

Decreased soluble IFN-β receptor (sIFNAR2) in multiple sclerosis patients: A potential serum diagnostic biomarker.
Órpez-Zafra T, Pavía J, Hurtado-Guerrero I, Pinto-Medel MJ, Rodriguez Bada JL, Urbaneja P, Suardíaz M, Villar LM, Comabella M, Montalban X, Alvarez-Cermeño JC, Leyva L, Fernández Ó, Oliver-Martos B.
Mult Scler. 2016 Sep 9.

Therapeutic efficacy of monthly subcutaneous injection of daclizumab in relapsing multiple sclerosis.
Cohan S.
Biologics. 2016 Sep 12;10:119-38.

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Hemophilia

Combination therapy for inhibitor reversal in haemophilia A using monoclonal anti-CD20 and rapamycin.
Biswas M, Rogers GL, Sherman A, Byrne BJ, Markusic DM, Jiang H, Herzog RW.
Thromb Haemost. 2016 Sep 29;117(1).

Advances in treatment of bleeding disorders.
Peyvandi F, Garagiola I, Biguzzi E.
J Thromb Haemost. 2016 Sep 2.

Extended half-life factor VIII for immune tolerance induction in haemophilia.
Malec LM, Journeycake J, Ragni MV.
Haemophilia. 2016 Sep 19.

Opinions/Commentaries/ Across diseases reviews

Cost-effectiveness of drug monitoring of anti-TNF therapy in inflammatory bowel disease and rheumatoid arthritis: a systematic review.
Martelli L, Olivera P, Roblin X, Attar A, Peyrin-Biroulet L.
J Gastroenterol. 2016 Sep 24.

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REGULATION

EMA

Human medicines European public assessment report (EPAR): ReFacto AF, moroctocog alfa
Revision: 32, Authorised

Human medicines European public assessment report (EPAR): Nordimet, methotrexate
Revision: 0, Authorised

Opinion/decision on a Paediatric investigation plan (PIP): Benlysta, belimumab
Therapeutic area: Immunology-Rheumatology-Transplantation (updated)

Opinion/decision on a Paediatric investigation plan (PIP): Humira, Adalimumab
Therapeutic area: Dermatology/Immunology-Rheumatology-Transplantation/Ophthalmology/Gastroentology-Hepatology (updated)

Human medicines European public assessment report (EPAR): Inflectra, infliximab
Revision: 12, Authorised

Human medicines European public assessment report (EPAR): Inflectra, infliximab
Revision: 12, Authorised

Human medicines European public assessment report (EPAR): Tysabri, natalizumab
Revision: 23, Authorised

Human medicines European public assessment report (EPAR): Humira, adalimumab
Revision: 49, Authorised

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