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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 August 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. There is a scaring paucity of evaluation of the socio-economic impact of NAB. This paper addresses this issue and should encourage others to do similar, not only in the field of IFNb

   The Cost of Relapsing-Remitting Multiple Sclerosis Patients Who Develop Neutralizing Antibodies during Interferon Beta Therapy.
   Paolicelli D, Iannazzo S, Santoni L, Iaffaldano A, Di Lecce V, Manni A, Lavolpe V, Tortorella C, D'Onghia M, Direnzo V, Puma E, Trojano M.
   PLoS One. 2016 Jul 8;11(7):e0159214.

2. Ettinger et al demonstrate the immunodominant T cell response to a single peptide from FVIII in an inhibitor positive subject. They show that this epitope is also recognized by two other patients with inhibitors. Additionally, TCR sequencing demonstrated that all high-avidity clones and 94% of all clones expressed the same TCRB gene. The authors suggest the limited breadth of the immune response should facilitate the induction of tolerance. Additional note: In silico predictions for this epitope were: IEDB ('weak' binder – top 7%), EpiVax ('strong' binder – top 1%).

   T cells from three Hemophilia A subjects recognized the same HLA-restricted FVIII epitope with a narrow TCR repertoire.
   Ettinger RA, Paz P, James EA, Gunasekera D, Aswad F, Thompson AR, Matthews DC, Pratt KP.
   Blood. 2016 Jul 28.

3. It is the second paper which shows the absence of immunogenicity of tocilizumab the anti-IL6R mAb, one of the best treatments of RA. And the reason for this remains a myster

   Immunogenicity of tocilizumab in patients with rheumatoid arthritis.
   Sigaux J, Hamze M, Daien C, Morel J, Krzysiek R, Pallardy M, Maillere B, Mariette X, Miceli-Richard C.
   Joint Bone Spine. 2016 Jun 28. pii: S1297-319X(16)30101

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Immunogenicity

Incidence, characterization, and clinical impact analysis of peginterferon beta1a immunogenicity in patients with multiple sclerosis in the ADVANCE trial.
White JT, Newsome SD, Kieseier BC, Bermel RA, Cui Y, Seddighzadeh A, Hung S, Crossman M, Subramanyam M.
Ther Adv Neurol Disord. 2016 Jul;9(4):239-49.

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.
AAPS J. 2016 Jul 22.

Infliximab and CT-P13 immunogenicity assessment in PLANETAS and PLANETRAS main and extension studies: utility of laboratory methods description.
Meacci F, Manfredi M, Infantino M, Grossi V, Benucci M.
Ann Rheum Dis. 2016 Jul 11. pii: annrheumdis-2016-210078.

Methods

Classification model of amino acid sequences prone to aggregation of therapeutic proteins.
Marczak M, Okoniewska K, Grabowski T.
In Silico Pharmacol. 2016 Dec;4(1):6.

Preexisting Antibodies to an F(ab')2 Antibody Therapeutic and Novel Method for Immunogenicity Assessment.
Ruppel J, Brady A, Elliott R, Leddy C, Palencia M, Coleman D, Couch JA, Wakshull E.
J Immunol Res. 2016;2016:2921758.

Is an in vitro whole blood cytokine assay useful to detect the potential risk of severe infusion reaction of monoclonal antibody pharmaceuticals?
Iwata Y, Harada A, Hara T, Kubo C, Inoue T, Tabo M, Ploix C, Manigold T, Hinton H, Mishima M.
J Toxicol Sci. 2016;41(4):523-31.

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Biomarkers

Identification of baseline gene expression signatures predicting therapeutic responses to three biologic agents in rheumatoid arthritis: a retrospective observational study.
Nakamura S, Suzuki K, Iijima H, Hata Y, Lim CR, Ishizawa Y, Kameda H, Amano K, Matsubara K, Matoba R, Takeuchi T.
Arthritis Res Ther. 2016 Jul 19;18:159.

Serum tocilizumab trough concentration can be used to monitor systemic IL-6 receptor blockade in patients with rheumatoid arthritis: a prospective observational cohort study.
Kneepkens EL, van den Oever I, Plasencia CH, Pascual-Salcedo D, de Vries A, Hart M, Nurmohamed MT, Balsa A, Rispens T, Wolbink G.
Scand J Rheumatol. 2016 Jul 20:1-8.

Biosimilars

Biosimilar Medicines Group - 14th Annual Medicines for Europe Conference (April 28-29, 2016 - London, UK).
Hodgkinson L.
Drugs Today (Barc). 2016 May;52(5):309-12.

A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab.
Kaur P, Chow V, Zhang N, Moxness M, Kaliyaperumal A, Markus R.
Ann Rheum Dis. 2016 Jul 27

'Lower anti-drug antibodies with etanercept biosimilar: can Ctrough explain the differences?'
Shah CA.
Ann Rheum Dis. 2016 Jul 7.

Response to: 'Lower anti-drug antibodies with etanercept biosimilar: Can Ctrough explain the differences' by Shah.
Emery P, Vencovský J, Ghil J, Kang JW.
Ann Rheum Dis. 2016 Jul 19.

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Animal models

Ingested (oral) rituximab inhibits EAE.
Brod SA.
Cytokine. 2016 Sep;85:177-83.

Recombinant soluble IFN receptor (sIFNAR2) exhibits intrinsic therapeutic efficacy in a murine model of Multiple Sclerosis.
Suardíaz M, Clemente D, Marin-Bañasco C, Orpez T, Guerrero-Hurtado I, Pavía P, Pinto-Medel MJ, de Castro F, Leyva L, Fernández O, Oliver B.
Neuropharmacology. 2016 Jul 21.

Adjuvants- and vaccines-induced autoimmunity: animal models.
Ruiz JT, Luján L, Blank M, Shoenfeld Y.
Immunol Res. 2016 Jul 14.

In Vivo Expansion of Activated Foxp3+ Regulatory T Cells and Establishment of a Type 2 Immune Response upon IL-33 Treatment Protect against Experimental Arthritis.
Biton J, Khaleghparast Athari S, Thiolat A, Santinon F, Lemeiter D, Hervé R, Delavallée L, Levascot A, Roga S, Decker P, Girard JP, Herbelin A, Boissier MC, Bessis N.
J Immunol. 2016 Jul 29.

Systemic Lupus Erythematosus

1.

Recent advances in the biologic therapy of lupus: the 10 most important areas to look for common pitfalls in clinical trials.
Medina-Rosas J, Al-Rayes H, Moustafa AT, Touma Z.
Expert Opin Biol Ther. 2016 Jul 29:1-14.

Therapeutic monitoring of the immuno-modulating drugs in systemic lupus erythematosus.
Mok CC.
Expert Rev Clin Immunol. 2016 Jul 22:1-7.

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Belimumab decreases flare rate and hinders the expected damage progression in patients with active systemic lupus erythematosus.
Iaccarino L, Bettio S, Reggia R, Zen M, Frassi M, Andreoli L, Gatto M, Piantoni S, Nalotto L, Franceschini F, Larosa M, Fredi M, Punzi L, Tincani A, Doria A.
Arthritis Care Res (Hoboken). 2016 Jul 7.

Post-hoc analysis of the Phase II/III APRIL-SLE study: Association between response to atacicept and serum biomarkers including BLyS and APRIL.
Gordon C, Wofsy D, Wax S, Li Y, Pena Rossi C, Isenberg D.
Arthritis Rheumatol. 2016 Jul 7.

Arthritis

Room for more IL-6 blockade? Sarilumab for the treatment of rheumatoid arthritis.
June RR, Olsen NJ.
Expert Opin Biol Ther. 2016 Jul 27.

BAFF inhibition does not significantly impair immunization responses in patients with rheumatoid arthritis.
Bingham CO 3rd, Winthrop KL, Yang L, Lee C, Komocsar WJ.
Arthritis Res Ther. 2015 Nov 30;17:347..

Understanding inflammation in juvenile idiopathic arthritis: How immune biomarkers guide clinical strategies in the systemic onset subtype.
Swart JF, de Roock S, Prakken BJ.
Eur J Immunol. 2016 Jul 27.

Secukinumab for rheumatology: development and its potential place in therapy.
Koenders MI, van den Berg WB.
Drug Des Devel Ther. 2016 Jun 24;10:2069-80

Drug survival of adalimumab in patients with rheumatoid arthritis over 10 years in the real-world settings: high rate remission together with normal function ability.
Iannone F, Sinigaglia L, Favalli EG, Sarzi-Puttini P, Atzeni F, Caporali R, Codullo V, Ferraccioli G, Gremese E, Carletto A, Giollo A, Govoni M, Bergossi F, Galeazzi M, Cantarini L, Salaffi F, Di Carlo M, Bazzani C, Pellerito R, Sebastiani M, Ramonda R, Lapadula G.
Clin Rheumatol. 2016 Jul 14.

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Effectiveness and safety of tocilizumab in achieving clinical and functional remission, and sustaining efficacy in biologics-naive patients with rheumatoid arthritis: The FIRST Bio study.
Ishiguro N, Atsumi T, Harigai M, Mimori T, Nishimoto N, Sumida T, Takeuchi T, Tanaka Y, Nakasone A, Takagi N, Yamanaka H.
Mod Rheumatol. 2016 Jul 14:1-10

Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of ASP2408, a Potent Selective T-Cell Costimulation Modulator After Single and Multiple Ascending Doses in Healthy Volunteers and RA Patients.
Zhu T, Keirns J, Howieson C, Kaibara A, Goldwater R, Kivitz AJ, Chindalore V, Cohen S, Santos V, Akinlade B, Kernstock R, Delgado-Herrera L, Blahunka PC, Karrer EE, Garg JP, Samberg N, Zeiher BG.
Clin Pharmacol Drug Dev. 2016 Jan 26.

Canakinumab for the treatment of active systemic juvenile idiopathic arthritis.
Orrock JE, Ilowite NT.
Expert Rev Clin Pharmacol. 2016 Aug;9(8):1015-24

Inflammatory Bowel Disease

Ustekinumab for the treatment of Crohn's disease.
Hansen T, Targownik LE.
Expert Rev Gastroenterol Hepatol. 2016 Jul 28:1-6.

CT-P13 (Inflectra™, Remsima™) monitoring in patients with inflammatory bowel disease.
Schulze K, Koppka N, Lutter F, Brandhorst G, Schreiber S, Helwig U.
Biologicals. 2016 Jul 16.

Systematic review: genetic biomarkers associated with anti-TNF treatment response in inflammatory bowel diseases.
Bek S, Nielsen JV, Bojesen AB, Franke A, Bank S, Vogel U, Andersen V.
Aliment Pharmacol Ther. 2016 Jul 15.

Advances in the development of new biologics in inflammatory bowel disease.
Ungar B, Kopylov U.
Ann Gastroenterol. 2016 Jul-Sep;29(3):243-8.

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Safety of Long-Term Treatment With Certolizumab Pegol in Patients with Crohn's Disease, Based on a Pooled Analysis of Data From Clinical Trials.
Loftus EV Jr, Colombel JF, Schreiber S, Randall CW, Regueiro M, Ali T, Arendt C, Coarse J, Spearman M, Kosutic G.
Clin Gastroenterol Hepatol. 2016 Jul 24.

Pharmacokinetics and Exposure-Response Relationship of Golimumab in Patients with Moderately-to-Severely Active Ulcerative Colitis: Results from Phase 2/3 PURSUIT Induction and Maintenance Studies.
Adedokun OJ, Xu Z, Marano CW, Strauss R, Zhang H, Johanns J, Zhou H, Davis HM, Reinisch W, Feagan BG, Rutgeerts P, Sandborn WJ.
J Crohns Colitis. 2016 Jul 20.

Next-Generation Therapeutics for Inflammatory Bowel Disease.
Dulai PS, Sandborn WJ.
Curr Gastroenterol Rep. 2016 Sep;18(9):51.
.
Current approaches for optimizing the benefit of biologic therapy in ulcerative colitis.
Sofia MA, Rubin DT.
Therap Adv Gastroenterol. 2016 Jul;9(4):548-59.

Multiple Sclerosis

Effectiveness and safety of natalizumab in real-world clinical practice: Review of observational studies.
van Pesch V, Sindic CJ, Fernández O.
Clin Neurol Neurosurg. 2016 Jul 14;149:55-63.

Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study.
Gold R, Radue EW, Giovannoni G, Selmaj K, Havrdova E, Stefoski D, Sprenger T, Montalban X, Cohan S, Umans K, Greenberg SJ, Ozen G, Elkins J.
BMC Neurol. 2016 Jul 26;16:117.

Role of IL-17-producing lymphocytes in severity of multiple sclerosis upon natalizumab treatment.
Bühler U, Fleischer V, Luessi F, Rezk A, Belikan P, Graetz C, Gollan R, Wolf C, Lutz J, Bar-Or A, Siffrin V, Zipp F.
Mult Scler. 2016 Jul 19.

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Design of TRUST, a non-interventional, multicenter, 3-year prospective study investigating an integrated patient management approach in patients with relapsing-remitting multiple sclerosis treated with natalizumab.
Ziemssen T, Gass A, Wuerfel J, Bayas A, Tackenberg B, Limmroth V, Linker R, Mäurer M, Haas J, Stangel M, Meergans M, Harlin O, Hartung HP.
BMC Neurol. 2016 Jul 12;16(1):98
.

Use of natalizumab in multiple sclerosis: current perspectives.
Gandhi S, Jakimovski D, Ahmed R, Hojnacki D, Kolb C, Weinstock-Guttman B, Zivadinov R.
Expert Opin Biol Ther. 2016 Jul 27:1-12.

Hemophilia

Comparative pharmacokinetics of rVIII-SingleChain and octocog alfa (Advate®) in patients with severe haemophilia A.
Klamroth R, Simpson M, von Depka-Prondzinski M, Gill JC, Morfini M, Powell JS, Santagostino E, Davis J, Huth-Kühne A, Leissinger C, Neumeister P, Bensen-Kennedy D, Feussner A, Limsakun T, Zhou M, Veldman A, St Ledger K, Blackman N, Pabinger I.
Haemophilia. 2016 Jul 19.

Innovating immune tolerance induction for haemophilia.
Batsuli G, Meeks SL, Herzog RW, Lacroix-Desmazes S.
Haemophilia. 2016 Jul;22 Suppl 5:31-5

Rituximab for eradicating inhibitors in people with acquired haemophilia A.
Zeng Y, Zhou R, Duan X, Long D.
Cochrane Database Syst Rev. 2016 Jul 8;7:CD011907.

Potential role of a new PEGylated recombinant factor VIII for hemophilia A.
Wynn TT, Gumuscu B.
J Blood Med. 2016 Jun 20;7:121-8.

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Basic immunology

Down-Regulation of Surface CD28 under Belatacept Treatment: An Escape Mechanism for Antigen-Reactive T-Cells.
de Graav GN, Hesselink DA, Dieterich M, Kraaijeveld R, Weimar W, Baan CC.
PLoS One. 2016 Feb 26;11(2):e0148604

Opinions/Commentaries/ Across diseases reviews

New Alternatives for Autoimmune Disease Treatments: Physicochemical and Clinical Comparability of Biosimilar Etanercept.
Miranda-Hernández MP, López-Morales CA, Perdomo-Abúndez FC, Salazar-Flores RD, Ramírez-Ibanez ND, Pérez NO, Molina-Pérez A, Revilla-Beltri J, Flores-Ortiz LF, Medina-Rivero E.
J Immunol Res. 2016;2016:9697080.

Pharmacokinetics interactions of monoclonal antibodies.
Ferri N, Bellosta S, Baldessin L, Boccia D, Racagni G, Corsini A.
Pharmacol Res. 2016 Jul 18;111:592-599.

Etanercept (SB4): A Review in Autoimmune Inflammatory Diseases.
Burness CB, Duggan ST.
BioDrugs. 2016 Jul 25

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REGULATION

EMA

Scientific guideline: Draft review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products – report on actions taken

Draft : consultation open

WC500211433.pdf

Scientific guideline: Draft guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft: consultation open

WC500211315.pdf

Human medicines European public assessment report (EPAR): Orencia, abatacept
Revision: 22, Authorised

Human medicines European public assessment report (EPAR): Humira, adalimumab
Revision: 48, Authorised

Human medicines European public assessment report (EPAR): Remicade, infliximab
Revision: 46, Authorised

Human medicines European public assessment report (EPAR): Flixabi, infliximab
Revision: 1, Authorised

Referral: Article 31 referrals , **Factor VIII**

Scientific guideline: Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'

Draft : consultation open

WC500210825.pdf

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Workshop on immunogenicity assessment of biotechnology-derived therapeutic proteins - Workshop summary:

WC500209667.pdf

Scientific guideline: Draft guideline on the clinical investigation of medicinal products for the treatment of axial spondyloarthritis - Revision 1,

Draft : consultation open

WC500209471.pdf

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