SCIENTIFIC NEWSLETTER — ABIRISK — APRIL 2016

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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 April 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

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LITERATURE

This month's selected articles

1. Important for the community to read the deliverables of this workshop with all the presentations included :

Workshop on immunogenicity assessment of biotechnology-derived therapeutic proteins,
European Medicines Agency, London, UK, From: 09-Mar-2016, To: 09-Mar-2016 (updated)

2. This paper rightly highlights reproducibility issues in research:

Reproducibility and conflicts in immune epitope data.
Vita R, Vasilevsky N, Bandrowski A, Haendel M, Sette A, Peters B.
Immunology. 2016 Mar;147(3):349-54.

3. With its central pragmatic approach in testing an anti-infliximab/biosimilar positive control through utilisation of biobank samples and available assays the publication has been useful in reinforcing the space industry must occupy towards immunogenicity assay standardisation :

Harmonization of Infliximab and Anti-Infliximab Assays Facilitates the Comparison Between Originators   and Biosimilars in Clinical Samples.
Gils A, Van Stappen T, Dreesen E, Storme R, Vermeire S, Declerck PJ.
Inflamm Bowel Dis. 2016 Apr;22(4):969-75.

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Immunogenicity

Assessing the Immunogenicity of Biopharmaceuticals.
Pineda C, Castañeda Hernández G, Jacobs IA, Alvarez DF, Carini C.
BioDrugs. 2016 Apr 20

Methods

Generation and characterization of a unique panel of anti-adalimumab specific antibodies and their application in therapeutic drug monitoring assays.
Bian S, Stappen TV, Baert F, Compernolle G, Brouwers E, Tops S, Vries A, Rispens T, Lammertyn J, Vermeire S, Gils A.
J Pharm Biomed Anal. 2016 Mar 15;125:62-67

Validation of a sample pretreatment protocol to convert a drug-sensitive into a drug-tolerant anti-infliximab antibody immunoassay.
Van Stappen T, Brouwers E, Vermeire S, Gils A.
Drug Test Anal. 2016 Mar 16.

Immunogenicity screening assay development for a novel human-mouse chimeric anti-CD147 monoclonal antibody (Metuzumab).
Mi L, Li W, Li M, Chen T, Wang M, Sun L, Chen Z.
J Immunol Methods. 2016 Mar 2. pii: S0022-1759(16)30038-2

Molecular modeling of antibodies for the treatment of TNFα-related immunological diseases.
Pierri CL, Bossis F, Punzi G, De Grassi A, Cetrone M, Parisi G, Tricarico D.
Pharmacol Res Perspect. 2016 Jan 15;4(1):e00197

se
BIITE: A Tool to Determine HLA Class II Epitopes from T Cell ELISpot Data.
Boelen L, O'Neill PK, Quigley KJ, Reynolds CJ, Maillere B, Robinson JH, Lertmemongkolchai G, Altmann DM, Boyton RJ, Asquith B.
PLoS Comput Biol. 2016 Mar 8;12(3):e1004796..

Animal models

Methods of Inducing Inflammatory Bowel Disease in Mice.
Bang B, Lichtenberger LM.
Curr Protoc Pharmacol. 2016 Mar 18;72:5.58.1-5.58.42

Development of a tail vein transection bleeding model in fully anaesthetized haemophilia A mice - characterization of two novel FVIII molecules.
Johansen PB, Tranholm M, Haaning J, Knudsen T.
Haemophilia. 2016 Mar 3.

Establishment and evaluation of a transgenic mouse model of arthritis induced by overexpressing human tumor necrosis factor alpha.
Li G, Wu Y, Jia H, Tang L, Huang R, Peng Y, Zhang Y.
Biol Open. 2016 Mar 14. pii: bio.016279.

Biomarkers

A Personalized Approach to Biological Therapy Using Prediction of Clinical Response Based on MRP8/14 Serum Complex Levels in Rheumatoid Arthritis Patients.
Nair SC, Welsing PM, Choi IY, Roth J, Holzinger D, Bijlsma JW, van Laar JM, Gerlag DM, Lafeber FP, Tak PP.
PLoS One. 2016 Mar 30;11(3):e0152362.

Dicer and microRNA expression in multiple sclerosis and response to interferon therapy.
Magner WJ, Weinstock-Guttman B, Rho M, Hojnacki D, Ghazi R, Ramanathan M, Tomasi TB.
J Neuroimmunol. 2016 Mar 15;292:68-78.

Biosimilars

A randomised Phase l pharmacokinetic study comparing SB4 and etanercept reference product (Enbrel®) in healthy subjects.
Lee Y, Shin D, Kim Y, Kang J, Gauliard A, Fuhr R.
Br J Clin Pharmacol. 2016 Mar 11.

Systemic Lupus Erythematosus

Recent advances and current state of immunotherapy in systemic lupus erythematosus.
Mok MY, Shoenfeld Y.
Expert Opin Biol Ther. 2016 Mar 31.

Efficacy of abatacept in systemic lupus erythematosus: a retrospective analysis of 11 patients with refractory disease.
Danion F, Rosine N, Belkhir R, Gottenberg JE, Hachulla E, Chatelus E, Pugnet G, Pers YM, Mariette X, Sibilia J, Seror R; Club Rhumatismes et Inflammation section of the French Society of Rheumatology.
Lupus. 2016 Mar 24.

Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study.
Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, Illei GG, Drappa J, Wang L, Greth W; CD1067 study investigators.
Ann Rheum Dis. 2016 Mar 23. pii: annrheumdis-2015-208562.

Drugs In Early Clinical Development For Systemic Lupus Erythematosus.
Postal M, Sinicato NA, Appenzeller S, Niewold TB.
Expert Opin Investig Drugs. 2016 Mar 7.

Rheumatoid Arthritis

Suppression of normal immune responses after treatment with rituximab.
Kado R, Sanders G, McCune WJ.
Curr Opin Rheumatol. 2016 May;28(3):251-8.

Effect of age at rheumatoid arthritis onset on clinical, radiographic, and functional outcomes: The ESPOIR cohort.
Krams T, Ruyssen-Witrand A, Nigon D, Degboe Y, Tobon G, Fautrel B, Berenbaum F, Cantagrel A, Constantin A.
Joint Bone Spine. 2016 Mar 15.

The impact of disease activity and tumor necrosis factor-α inhibitor therapy on cytokine levels in juvenile idiopathic arthritis.
Walters HM, Pan N, Lehman TJ, Adams A, Kalliolias GD, Zhu YS, Santiago F, Nguyen J, Sitaras L, Cunningham-Rundles S, Walsh TJ, Toussi SS.
Clin Exp Immunol. 2016 Mar 2016

Comparative Effectiveness of Infliximab and Adalimumab in Crohn's Disease and Ulcerative Colitis.
Ananthakrishnan AN, Cagan A, Cai T, Gainer VS, Shaw SY, Savova G, Churchill S, Karlson EW, Kohane I, Liao KP, Murphy SN.
Inflamm Bowel Dis. 2016 Apr;22(4):880-5.

Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update.
Goswami RP, Basu K, Das S, Mondal S, Ghosh P, Ghosh A.
Ann Rheum Dis. 2016 Mar 29

Treat-to-target as an approach in inflammatory arthritis.
Smolen JS.
Curr Opin Rheumatol. 2016 May;28(3):297-302.

Comparison of the clinical effectiveness of tumour necrosis factor inhibitors and abatacept after insufficient response to tocilizumab in patients with rheumatoid arthritis.
Akiyama M, Kaneko Y, Kondo H, Takeuchi T.
Clin Rheumatol. 2016 Mar 12

Comparative efficacy of tocilizumab, abatacept and rituximab after non-TNF inhibitor failure: results from a multicentre study.
Pascart T, Philippe P, Drumez E, Deprez X, Cortet B, Duhamel A, Houvenagel E, Flipo RM.
Int J Rheum Dis. 2016 Mar 27

Vaccinations for rheumatoid arthritis.
Friedman MA, Winthrop K.
Curr Opin Rheumatol. 2016 May;28(3):330-6.

Inflammatory Bowel Diseases

Selective biologics for ulcerative colitis and Crohn's disease - clinical utility of vedolizumab.
Petkau JM, Eksteen B.
Biologics. 2016 Mar 9;10:33-52.

The Risk of Relapse after Anti-TNF Discontinuation in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis.
Gisbert JP, Marín AC, Chaparro M.
Am J Gastroenterol. 2016 Mar 22

Association of Vitamin D Level With Clinical Status in Inflammatory Bowel Disease: A 5-Year Longitudinal Study.
Kabbani TA, Koutroubakis IE, Schoen RE, Ramos-Rivers C, Shah N, Swoger J, Regueiro M, Barrie A, Schwartz M, Hashash JG, Baidoo L, Dunn MA, Binion DG.
Am J Gastroenterol. 2016 Mar 8.

Biologic agents for IBD: practical insights.
Danese S, Vuitton L, Peyrin-Biroulet L.
Nat Rev Gastroenterol Hepatol. 2015 Sep;12(9):537-45.

Positioning Therapy for Ulcerative Colitis.
Grinspan A, Kornbluth A.
Curr Gastroenterol Rep. 2015 Aug;17(8):29

Multiple Sclerosis

Therapeutic strategies targeting B-cells in multiple sclerosis.
Milo R.
Autoimmun Rev. 2016 Mar 9. pii: S1568-9972(16)30054-4.

Disrupted balance of T cells under natalizumab treatment in multiple sclerosis.
Kimura K, Nakamura M, Sato W, Okamoto T, Araki M, Lin Y, Murata M, Takahashi R, Yamamura T.
Neurol Neuroimmunol Neuroinflamm. 2016 Mar 3;3(2):e210.

Natalizumab in relapsing-remitting multiple sclerosis.
Outteryck O.
Expert Rev Neurother. 2016 Mar 23

Response to interferon-beta treatment in multiple sclerosis patients: a genome-wide association study.
Mahurkar S, Moldovan M, Suppiah V, Sorosina M, Clarelli F, Liberatore G, Malhotra S, Montalban X, Antigüedad A, Krupa M, Jokubaitis VG, McKay FC, Gatt PN, Fabis-Pedrini MJ, Martinelli V, Comi G, Lechner-Scott J, Kermode AG, Slee M, Taylor BV, Vandenbroeck K, Comabella M, Boneschi FM; Australian and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene), King C.
Pharmacogenomics J. 2016 Mar 22.

HLA genes as modifiers of response to IFN-β-1a therapy in relapsing-remitting multiple sclerosis.
Mazdeh M, Taheri M, Sayad A, Bahram S, Omrani MD, Movafagh A, Inoko H, Akbari MT, Noroozi R, Hajilooi M, Solgi G.
Pharmacogenomics. 2016 Mar 29

ALAIN01-Alemtuzumab in autoimmune inflammatory neurodegeneration: mechanisms of action and neuroprotective potential.
Ruck T, Afzali AM, Lukat KF, Eveslage M, Gross CC, Pfeuffer S, Bittner S, Klotz L, Melzer N, Wiendl H, Meuth SG.
BMC Neurol. 2016 Mar 10;16(1):34.

Effect of interferon-β1b on CXCR4-dependent chemotaxis in T cells from multiple sclerosis patients.
Wostradowski T, Gudi V, Pul R, Gingele S, Lindquist JA, Stangel M, Lindquist S.
Clin Exp Immunol. 2015 Nov;182(2):162-72.

Long-term persistence with injectable therapy in relapsing-remitting multiple sclerosis: an 18-year observational cohort study.
Zhornitsky S, Greenfield J, Koch MW, Patten SB, Harris C, Wall W, Alikhani K, Burton J, Busche K, Costello F, Davenport JW, Jarvis SE, Lavarato D, Parpal H, Patry DG, Yeung M, Metz LM.
PLoS One. 2015 Apr 13;10(4):e0123824.

Therapeutic protein-drug interaction assessment for daclizumab high-yield process in patients with multiple sclerosis using a cocktail approach.
Tran JQ, Othman AA, Wolstencroft P, Elkins J.
Br J Clin Pharmacol. 2016 Mar 17.

Pharmacokinetics of daclizumab high-yield process with repeated administration of the clinical subcutaneous regimen in patients with relapsing-remitting multiple sclerosis.
Tran JQ, Othman AA, Mikulskis A, Wolstencroft P, Elkins J.
Clin Pharmacol. 2016 Feb 11;8:9-13.

Hemophilia

Neutralisation of factor VIII inhibitors by anti-idiotypes isolated from phage-displayed libraries.
Schmidt A, Brettschneider K, Kahle J, Orlowski A, Becker-Peters K, Stichel D, Schulze J, Braner M, Tampé R, Schwabe D, Königs C.
Thromb Haemost. 2016 Mar 24;116(1).

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Opinions/Commentaries/Across diseases reviews

Suppression of normal immune responses after treatment with rituximab.
Kado R, Sanders G, McCune WJ.
Curr Opin Rheumatol. 2016 May;28(3):251-8.

REGULATION

EMA

Human medicines European public assessment report (EPAR): Remsima, infliximab
Revision: 7, Authorised

Opinion/decision on a Paediatric investigation plan (PIP): -, PEGylated recombinant factor VIII
Therapeutic area: Haematology-Hemostaseology (updated)

Human medicines European public assessment report (EPAR): MabThera, rituximab
Revision: 36, Authorised

Referral: Article 20 procedures, Tysabri, natalizumab (updated)

Human medicines European public assessment report (EPAR): Avonex, interferon beta-1a
Revision: 26, Authorised

Human medicines European public assessment report (EPAR): Kogenate Bayer, octocog alfa
Revision: 27, Authorised