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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 Relevance 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 January 13 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, alongside with some news from the Regulatory field.

This month we chose to highlight a report by van Schouwenburg et al. on the assessment of clinical relevance of anti-Adalimumab antibodies in Rheumatoid Arthritis patients, using their recently described 'pH-shift-anti-Idiotype Antigen binding test'.

We are also very pleased to announce on page 9 the publication in *Haemophilia* of a paper by **partner Inserm UMR872 on behalf of ABIRISK consortium.** Sébastien Lacroix-Desmazes' team explored the early cellular mechanisms involved in FVIII inhibitors generation and confirmed that FVIII alone is not sufficient to trigger a danger signal on antigen presenting cells to initiate an immune response.

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 article

Long-term measurement of anti-adalimumab using pH-shift-anti-idiotype antigen binding test shows predictive value and transient antibody formation.
van Schouwenburg PA, Krieckaert CL, Rispens T, Aarden L, Wolbink GJ, Wouters D.
Ann Rheum Dis. 2013 Jan 7

Drug interference in Anti-Drug Antibodies (ADA) assays remains a major issue when determining patients' ADA status. Indeed most methods routinely used in the clinic will only detect free ADA, but not those in complex with the drug present in the serum of treated patients. Hence, a patient would be found positive for ADA only if ADA production exceeds drug through levels. To overcome this hurdle, drug wash-out periods prior to testing are observed but they can complicate or even hinder a comprehensive follow-up of patients' immunization status.

Several groups have therefore attempted to set up new ADA assays that will allow for the detection of both free and complexed ADA, mainly based on acid dissociation and neutralization of the complexes in the presence of a solid phase drug. Likewise, Wolbink and Wouters group recently described a new method for anti-adalimumab antibodies detection. Called 'pH-shift-anti-Idiotype Antigen binding test' or *PIA*, the assay is based on acid dissociation and prevention of complexes re-association by addition of excess fluid phase F(ab) fragments of rabbit anti-idiotype antibodies (van Schouwenburg et al., J Immunol Methods 2010).

In the current publication, van Schouwenburg and colleagues set out to take advantage of their new method to investigate the clinical relevance of complexed anti-adalimumab antibodies (AAA) in rheumatoid (RA) patients. Sera were obtained in the first 3 years of treatment from 99 RA patients enrolled in a prospective observational cohort, receiving 40 mg adalimumab every other week subcutaneaously. Of note, a total of 20 patients saw their dose increase to 40 mg adalimumab each week. Sera were tested with both new (PIA) and standard (ABT) AAA assays.

Results showed that PIA was able to detect AAA in more patients (54% vs 29%) and at earlier time points than ABT: AAA could be detected in 94% of patients in the first 28 weeks of treatment. Use of PIA also revealed that 32% patients had transient AAA production.

However the clinical relevance of measuring AAA with PIA proved to be limited as there was no statistically significant difference in the number of patients reaching sustained remission when comparing PIA positive and PIA negative individuals. Nevertheless patients with positive PIA at 28 weeks were found to have an increased risk of developing clinical non-response du to immunogenicity-related low drug through levels, indicative of PIA predictive value.

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Immunogenicity

The polygenic nature of inhibitors in hemophilia A: results from the Hemophilia Inhibitor Genetics Study (HIGS) Combined Cohort.
Astermark J, Donfield SM, Gomperts ED, Schwarz J, Menius ED, Pavlova A, **Oldenburg J**, Kessing B, Dimichele DM, Shapiro AD, Winkler CA, Berntorp E.
Blood. 2012 Dec 6.

Hydrolysis of factor VIII mediated by catalytic antibodies occurs in haemophilia A patients with or without factor VIII inhibitors.
Grosbois SS, Brionne MF, de Longcamp AL, Gautier P, V Kaveri S, Borel-Derlon A, Repessé Y.
Haemophilia. 2012 Dec 6

Management of patients with long-term inhibitors: is immune tolerance an underestimated life-long solution?
Di Minno G, Coppola A.
Haemophilia. 2013 Jan;19 Suppl 1:18-23.

Inhibitors: our greatest challenge. Can we minimize the incidence?
Kruse-Jarres R.
Haemophilia. 2013 Jan;19 Suppl 1:2-7

The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis.
Garcês S, Demengeot J, Benito-Garcia E.
Ann Rheum Dis. 2012 Dec 6.

Characterization and quantitation of aggregates and particles in interferon-β products: Potential links between product quality attributes and immunogenicity.
Barnard JG, Babcock K, Carpenter JF.
J Pharm Sci. 2012 Dec 11.

Methods

Validation of an automated method for compounding monoclonal antibody patient doses: Case studies of Avastin (®) (bevacizumab), Remicade (®) (infliximab) and Herceptin (®) (trastuzumab).
Peters BJ, Capelle MA, Arvinte T, van de Garde EM.
MAbs. 2012 Dec 19;5(1).

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Letter: detection of infliximab levels and anti-infliximab antibodies - comparison of three different assays.*
Parussini E.
Aliment Pharmacol Ther. 2013 Jan;37(2):281

Letter: detection of infliximab levels and anti-infliximab antibodies - comparison of three different assays: authors' reply.*
Buurman DJ, Vande Casteele N, Sturkenboom MG, Kleibeuker JH, Vermeire S, van der Kleij D, Rispens T, Gils A, Dijkstra G.
Aliment Pharmacol Ther. 2013 Jan;37(2):282.

**Both letters refer to an article by van de Casteele et al., Aliment Pharmacol Ther 2012 (September ABIRISK Scientific Newsletter)*

Biomarkers

Genome-wide association analysis of anti-TNF drug response in patients with rheumatoid arthritis.
Umicevic Mirkov M, Cui J, Vermeulen SH, Stahl EA, Toonen EJ, Makkinje RR, Lee AT, **Huizinga TW**, Allaart R, Barton A, **Mariette X**, Miceli CR, Criswell LA, Tak PP, **de Vries N**, **Saevarsdottir S**, Padyukov L, Bridges SL, van Schaardenburg DJ, Jansen TL, Dutmer EA, van de Laar MA, Barrera P, Radstake TR, van Riel PL, Scheffer H, Franke B, Brunner HG, Plenge RM, Gregersen PK, Guchelaar HJ, Coenen MJ.
Ann Rheum Dis. 2012 Dec 11

Utility of faecal calprotectin analysis in adult inflammatory bowel disease.
Smith LA, Gaya DR.
World J Gastroenterol. 2012 Dec 14;18(46):6782-9

Clinical relevance of differential lymphocyte recovery after alemtuzumab therapy for multiple sclerosis.
Cossburn MD, Harding K, Ingram G, El-Shanawany T, Heaps A, Pickersgill TP, Jolles S, Robertson NP.
Neurology. 2013 Jan 1;80(1):55-61

Predictors of Response to TNF Inhibitors in Rheumatoid Arthritis - Do We Have New Tools for Personalized Medicine?
Simsek I.
Bull NYU Hosp Jt Dis. 2012;70(3):187-90

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Systemic Lupus Erythematosus

Targeting the BLyS-APRIL signaling pathway in SLE.
La Cava A.
Clin Immunol. 2012 Dec 6.

Arthritis

Different effects of biological drugs in rheumatoid arthritis.
Atzeni F, Benucci M, Sallì S, Bongiovanni S, Boccassini L, Sarzi-Puttini P.
Autoimmun Rev. 2012 Dec 3

Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis.
Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, Brik R, McCann L, Kasapcopur O, Rutkowska-Sak L, Schneider R, Berkun Y, Calvo I, Erguven M, Goffin L, Hofer M, Kallinich T, Oliveira SK, Uziel Y, Viola S, Nistala K, Wouters C, Cimaz R, Ferrandiz MA, Flato B, Gamir ML, Kone-Paut I, Grom A, Magnusson B, Ozen S, Sztajnbok F, Lheritier K, Abrams K, Kim D, Martini A, Lovell DJ; PRINTO; PRCSG.
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Burmester GR, Weinblatt ME, McInnes IB, Porter D, Barbarash O, Vatutin M, Szombati I, Esfandiari E, Sleeman MA, Kane CD, Cavet G, Wang B, Godwood A, Magrini F; for the EARTH Study Group.
Ann Rheum Dis. 2012 Dec 12

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Tabalumab, an anti-BAFF monoclonal antibody, in patients with active rheumatoid arthritis with an inadequate response to TNF inhibitors.
Genovese MC, Fleischmann RM, Greenwald M, Satterwhite J, Veenhuizen M, Xie L, Berclaz PY, Myers S, Benichou O.
Ann Rheum Dis. 2012 Dec 25.

The effect of autoimmune arthritis treatment strategies on regulatory T-cell dynamics.
Mijnheer G, Prakken BJ, van Wijk F.
Curr Opin Rheumatol. 2012 Dec 26.

IBD

Clinical experience with adalimumab in anti-TNF-naïve patients with ulcerative colitis.
Aldeguer X, Busquets D.
J Crohns Colitis. 2012 Dec 6.

Anti-TNF, Infliximab And Adalimumab, Can Be Effective In Eosinophilic Bowel Disease: A Report Of Eight Pediatric Cases.
Turner D, Wolters VM, Russell RK, Shakhnovich V, Muise AM, Ledder O, Ngan B, Friesen C.
J Pediatr Gastroenterol Nutr. 2012 Dec 5

Current status of monoclonal antibody therapy for the treatment of inflammatory bowel disease: an update.
Denmark VK, Mayer L.
Expert Rev Clin Immunol. 2013 Jan;9(1):77-92.

IL-23 in Colitis: Targeting the Progenitors.
Tang C, Iwakura Y.
Immunity. 2012 Dec 14;37(6):957-9

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Fatal Neuroinflammation in a Case of Multiple Sclerosis with Anti-Natalizumab Antibodies.
Svenningsson A, Dring AM, **Fogdell-Hahn A**, Jones I, Engdahl E, Lundkvist M, Brännström T, Gilthorpe JD.
Neurology. 2013 Feb 6.

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Effect of Natalizumab on Circulating CD4(+) T-Cells in Multiple Sclerosis.
Börnsen L, Christensen JR, Ratzer R, Oturai AB, Sørensen PS, Søndergaard HB, Sellebjerg F.
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Clinical relevance of differential lymphocyte recovery after alemtuzumab therapy for multiple sclerosis.
Cossburn MD, Harding K, Ingram G, El-Shanawany T, Heaps A, Pickersgill TP, Jolles S, Robertson NP.
Neurology. 2012 Dec 12

Interferon Beta and Glatiramer Acetate Therapy.
McGraw CA, Lublin FD.
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RebiSmart™ (version 1.5) device for multiple sclerosis treatment delivery and adherence.
Lugaresi A.
Expert Opin Drug Deliv. 2012 Dec 20.

Longitudinal interferon-β effects in multiple sclerosis: Differential regulation of IL-10 and IL-17A, while no sustained effects on IFN-γ, IL-4 or IL-13.
Kvarnström M, Ydrefors J, Ekerfelt C, Vrethem M, Ernerudh J.
J Neurol Sci. 2012 Dec 26

T cell vaccination benefits relapsing progressive multiple sclerosis patients: a randomized, double-blind clinical trial.
Karussis D, Shor H, Yachnin J, Lanxner N, Amiel M, Baruch K, Keren-Zur Y, Haviv O, Filippi M, Petrou P, Hajag S, Vourka-Karussis U, Vaknin-Dembinsky A, Khoury S, Abramsky O, Atlan H, Cohen IR, Abulafia-Lapid R.
PLoS One. 2012;7(12):e50478

Hemophilia

Therapeutic factor VIII does not trigger TLR1.2 and TLR2.6 signalling in vitro.
Teyssandier M, André S, Gupta N, Dasgupta S, Bayry J, Kaveri SV, Lacroix-Desmazes S; **The ABIRISK consortium.**
Haemophilia. 2012 Dec 18

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Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A; Treatment Guidelines Working Group The World Federation Of Hemophilia.
Haemophilia. 2013 Jan;19(1):e1-e47

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Distinct characteristics of antibody responses against factor VIII in healthy individuals and in different cohorts of hemophilia A patients.
Whelan SF, Hofbauer CJ, Horling FM, Allacher P, Wolfsegger MJ, **Oldenburg J**, Male C, Windyga J, Tiede A, Schwarz HP, Scheiflinger F, Reipert BM.
Blood. 2012 Dec 12.

Basic immunology

Crystal Structure of the HLA-DM-HLA-DR1 Complex Defines Mechanisms for Rapid Peptide Selection.
Pos W, Sethi DK, Call MJ, Schulze MS, Anders AK, Pyrdol J, Wucherpfennig KW.
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Opinions/Commentaries

Which are the antibodies to watch in 2013?
Reichert JM.
MAbs. 2012 Dec 19;5(1).

Ulcerative colitis: Steroid-refractory ulcerative colitis—ciclosporin or infliximab?
Manreet Kaur & Stephen R. Targan
Nat Rev Gastroenterol Hepatol. 2012 Dec 11

Secukinumab failure in Crohn's disease: the yeast connection?
Colombel JF, Sendid B, Jouault T, Poulain D.
Gut. 2012 Dec 11

Effect of IL-17A blockade with secukinumab in autoimmune diseases.
Patel DD, Lee DM, Kolbinger F, Antoni C.
Ann Rheum Dis. 2012 Dec 19.

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REGULATION

EMA

Human medicines European Public Assessment Report (EPAR): Kineret,anakinra
Revision: 16, Authorised
December 2012

Work plan for the Rheumatology-Immunology Working Party 2013 (updated)
December 2012

WC500100654
EMA.pdf

Paediatric Investigation Plan (PIP): Humira,Adalimumab. Therapeutic area: Immunology-Rheumatology-Transplantation/Dermatology/Gastroentology-Hepatology
Opinion/decision
January 2013

CONFERENCES & MEETINGS

Michael Tovey (BioMonitor, ABIRISK partner 6) is organizing a meeting on the prediction of immunogenicity in Coral Gables Miami in April. The leaders of WP1, 2, & 3 will be giving presentations on the impact of the ABIRISK program on the ability to predict immunogenicity. Please visit www.coralgablessymposia.org for more information and to register.

IMI will hold a workshop entitled 'Applying open innovation to bring personalised medicine to new disease areas' on the afternoon of 20 March in Dublin, Ireland. The workshop will set the stage for an event on Innovation and Patient Access to Personalised Medicine which is organised by the European Alliance for Personalised Medicine (EAPM) under the auspices of the Irish Presidency of the EU CouncilRegistration is free but obligatory via the EAPM event registration page

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