

Dear colleagues, dear friends and supporters of ABIRISK,

we are pleased to announce the launch of the first issue of the external newsletter of **Anti-Biopharmaceutical Immunization: prediction and analysis of clinical relevance to minimize the risk - ABIRISK - Project**.

This newsletter will be filled with interesting information mainly for all groups external to the ABIRISK consortium that may have an interest in our research and progress. Please don't hesitate to forward this mail to anyone who could also be interested in reading it. If they want to receive their own newsletter in the future they can write at newsletter@abirisk.eu. If you're not interested in receiving our newsletter anymore, you can unsubscribe via mail. In order to contribute to the contents of the newsletter, please send news, photos and other material related to ABIRISK areas of research at newsletter@abirisk.eu We hope you will enjoy reading our latest news.

Best regards,
The ABIRISK management team

THE ABIRISK PROJECT

ABIRISK is an Innovative Medicine Initiative 3rd Call project on Anti-Biopharmaceutical Immunization. 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 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.

ABIRISK is a public private consortium of thirty-five partners, twenty-four of which are academic institutions, nine are European Federation of Pharmaceutical Industries and Associations (EFPIA) member companies and two are small and medium enterprises (SMEs), with thirteen countries represented. **ABIRISK** consortium has been designed to meet all of the 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)**. The consortium is co-ordinated by GlaxoSmithKline (Dr. Daniel Sikkema, Project coordinator) and Institut National de la Santé et de la Recherche Médicale (INSERM; Prof. Marc Pallardy, Managing entity), and will receive over €30 million funding over 5 years from 1st March 2012.



ABIRISK Project Consortium

ABIRISK aims to provide an integrated approach to **anti-drug immunization**, bringing together, in an extensive and coordinated manner, a large network of clinicians from various specialties with broad experience in the care of patients treated with various type of **biopharmaceuticals** and developing **anti-drug antibodies**, biologists familiar with the immune monitoring of patients, scientists specialized in the mechanisms of immunogenicity, methodologists and biostatisticians. In addition the collaboration with a large network of private pharmaceutical industries under EFPIA, will ensure direct transfer of the experimental findings into **biopharmaceutical product development** and **patient management**.

ABIRISK will investigate the correlation between patient and clinical factors and the incidence of immunogenicity. A major goal is to further elucidate the underlying mechanisms of immunogenicity and this may result in more science-based regulatory guidelines, which may reduce the regulatory burden for immunogenicity testing and save time and resources in the **biopharmaceutical drug development** process.

ABIRISK COMMUNICATION TOOLS

PRESS RELEASE

Updating the original version generated by IMI Communication Office, **ABIRISK kick-off meeting fact sheet** has been created to promote ABIRISK project to broad audience mainly through institutional websites of ABIRISK partners, highlighting that the project has been started.

PROJECT BROCHURE

Official **ABIRISK Brochure** has been created and distributed to ABIRISK partners to disseminate information about the project in any suitable occasion (meetings, congresses, workshops, exhibition, shows or open forum, etc.) to broad audiences.

SCIENTIFIC NEWSLETTER

The **ABIRISK Scientific Newsletter**, an update on ABIRISK topics-related literature and international regulation, is sent to all consortium members and key opinion leaders in the different ABIRISK fields each month, posted on ABIRISK website and advertised on LinkedIn in several Immunogenicity-focused groups.



PROJECT WEBSITE

The main source for information on the project is ABIRISK website (www.abirisk.eu) where you will find the list of ABIRISK partners and their contact, more detailed information on the project, recent news on the project, all ABIRISK publications and press release, and the ABIRISK Scientific Newsletter.

PROJECT NEWS

ABIRISK new partner

The **ABIRISK Consortium** would like to welcome **Chaim Sheba Medical Center**, originally a close collaborator to partner RAMBAM, as a new full ABIRISK partner of the Consortium. **Dr Shomron Ben-Horin** will be the Principal Investigator in charge for this institution.

ABIRISK presented at the EUCRAF meeting

ABIRISK has been presented at the **EUCRAF 3rd Annual Biopharmaceuticals Workshop** held in Freiburg on 7-8 February 2013. The focus of this meeting was on the most important regulatory activities in European biopharmaceuticals that have taken place over the past years and scientific news on immunogenicity requirements. Sessions on pharmacovigilance, ATMPs, biosimilar monoclonal antibodies, drug-diagnostic co-development and HTA in the context of development were also included in the meeting programme. The focus on ABIRISK objectives and current status of the project was included in **Dr Paul Chamberlain** (NDA Advisory Board) presentation titled "Essentials to know in 2013 on immunogenicity of therapeutic proteins. An update on most recent occurrences, regulatory activities and scientific progress".

UPCOMING EVENTS

Coral Gables Symposium 2013-Prediction of Immunogenicity: The Future in View" on April 24th-26th 2013

Coral Gables Symposia provide a **unique forum for thought leaders** to address the principal concerns regarding the **immunogenicity of biopharmaceuticals**; in their development, regulation, and clinical use. Coral Gables Symposia provide delegates with a convivial environment designed to foster the exchange of ideas and facilitate the establishment of improved approaches to the major challenges confronting those active in the field.

The 2013 Symposium will focus on the effective prediction of the immunogenicity of biopharmaceutical products and the prediction of the consequences of such immunogenicity on clinical outcome and patient safety. The 2013 Symposium will review the predictive value of available *in silico*, *in vitro*, and *in vivo* approaches to the identification of T-cell epitopes in therapeutic proteins and the effectiveness of de-immunization.

Michael Tovey (BioMonitor, ABIRISK partner 6) is the principal organizer of the **2013 Symposium at the Biltmore Hotel in Miami, USA**. Beyond Michael, several Working Package leaders of the ABIRISK project will be invited to give presentations to 2013 Symposium on the impact of the ABIRISK program on the ability to predict immunogenicity.

The 2013 Symposium provides a unique opportunity for delegates from academia, industry, regulatory agencies, and clinical practice, to interact with the leading authorities in the field in a relaxed environment at the historic Biltmore Hotel.

MARCH

IMMUNO 2013

10th International Conference on New trends in immunosuppression & immuotherapy
11th-12th, 2013 - Barcelona, Spain

APRIL

Controversies in Rheumatology & Autoimmunity (CORA)

Second CORA congress
4th-6th, 2013 - Budapest, Hungary

Keystone S. "Advances in the knowledge and treatment of autoimmunity"

4th-9^h, Fairmont Chateau Whistler, Whistler, British Columbia, Canada

PEGS 2013 - essential protein & antibody engineering summit

30th April-3rd May, 2013 - Boston, Massachusetts, USA

NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

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. doi: 10.1111/hae.12081. [Epub ahead of print]

As advances in the design and development of complex biologic therapeutic entities (BPs) evolve, the ability to assess, or even predict, the immunogenicity potential of each new product must be considered to avoid loss of clinical responses or adverse effects. The overall objective of ABIRISK is to provide an integrated approach to anti-drug immunization in four major diseases in which BPs provided significant clinical amelioration: multiple sclerosis, rheumatoid arthritis, intestinal bowel diseases and hemophilia (HA). Indeed the administration of therapeutic factor VIII (FVIII) to patients with HA induces the development of inhibitory anti-FVIII IgG in a substantial number of patients.

For an antigen-specific immune response to develop, antigen-presenting cells (APCs) need to mature and procure appropriate co-stimulatory signals to T cells at the time of presentation of the endocytosed antigen. The nature of the danger signals that induce APC maturation, thus initiating the anti-FVIII immune response, are yet ill-characterized and contradictory reports on a direct effect of therapeutic FVIII on APC maturation have been released.

In the present study, **ABIRISK partner Inserm UMR872** investigated whether FVIII could directly triggers Toll-like receptor 2 (TLR2) signaling on APCs. In contrast to zymosan, a known TLR2 agonist, human recombinant FVIII did not induce the maturation of mouse bone marrow macrophages, as analyzed by the levels of cell surface expression of CD80, CD86, CD40 and I-Ab. Furthermore, incubation of FVIII with cells expressing TLR2 paired with TLR1 or TLR6, failed to activate NFκB, whereas NKκB activity was triggered in the presence of zymosan.

The results reported in this study confirm that FVIII alone is insufficient to trigger the maturation of APCs that is required to initiate an immune response.

RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Alemtuzumab more effective than interferon β -1a at 5-year follow-up of CAMMS223 clinical trial

Deisenhammer F, Hegen H.

Neurology. 2012 Sep 4;79(10):1071-2

F8 gene mutation type and inhibitor development in patients with severe hemophilia A: systematic review and meta-analysis.

Gouw SC, van den Berg HM, Oldenburg J, Astermark J, de Groot PG, Margaglione M, Thompson AR, van Heerde W, Boekhorst J, Miller CH, le Cessie S, van der Bom JG.

Blood. 2012 Mar 22;119(12):2922-34.

Anti-drug antibodies

Clemens Warnke, Christina Hermanrud, Malin Lundkvist, Anna Fogdell-Hahn

Drugs and Therapy Studies. Vol 2, No 1 (2012)

Characterization of anti-natalizumab antibodies in multiple sclerosis patients.

Lundkvist M, Engdahl E, Holmén C, Movérare R, Olsson T, Hillert J, Fogdell-Hahn A.

Mult Scler. 2012 Oct 8.

Improved analytical methods for the detection and quantification of neutralizing antibodies to biopharmaceuticals.

Tovey MG, Lallemand C.

Bioanalysis. 2012 Sep;4(17):2179-90.

Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial.

Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA; for the CARE-MS I investigators.

Lancet. 2012 Oct 31

Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial.

Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Miller T, Fisher E, Sandbrink R, Lake SL, Margolin DH, Oyuela P, Panzara MA, Compston DA; for the CARE-MS II investigators.

Lancet. 2012 Oct 31

Addition of an Immunomodulator to Infliximab Therapy Eliminates Anti-Drug Antibodies in Serum and Restores Clinical Response of Patients with Inflammatory Bowel Disease.

Ben-Horin S, Waterman M, Kopylov U, Yavzori M, Picard O, Fudim E, Awadie H, Weiss B, Chowers Y.

Clin Gastroenterol Hepatol. 2012 Oct 24

Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective.

Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X, Marcelli C.
Ann Rheum Dis. 2012 Nov 24.

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.

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.

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, Sztajn bok F, Lheritier K, Abrams K, Kim D, Martini A, Lovell DJ; PRINTO; PRCSG.
N Engl J Med. 2012 Dec 20;367(25):2396-406.

Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis.

De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, Cuttica R, Ravelli A, Schneider R, Woo P, Wouters C, Xavier R, Zemel L, Baildam E, Burgos-Vargas R, Dolezalova P, Garay SM, Merino R, Joos R, Grom A, Wulffraat N, Zuber Z, Zulian F, Lovell D, Martini A; PRINTO; PRCSG.
N Engl J Med. 2012 Dec 20;367(25):2385-95

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.

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.