ABIRISK

EXTERNAL NEWSLETTER

ISSUE 3 - SEPTEMBER 2013

WWW.ABIRISK.EU

Dear colleagues, dear friends and supporters of ABIRISK,

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

ABIRISK External 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 Project 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 **biopharmaceutical products** 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 the European Federation of Pharmaceutical Industries and Associations (EFPIA), will ensure direct transfer of the experimental findings into **biopharmaceutical product** development and patient management. Collectively, this group will critically evaluate the immunogenicity of existing **biopharmaceutical products** for **Hemophilia A, Multiple Sclerosis,** and **Inflammatory Diseases.** The **ABIRISK consortium**, constituting unique task forces for each of these complementary contributions, should improve our ability to predict immunogenicity and to minimize the risk of immunization against **biopharmaceutical products**.

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 milion funding over 5 years from 1st March 2012.

The list of ABIRISK partners and more information on the project can be found on the website (www.abirisk.eu)

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.'

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PROJECT NEWS

PROPOSED TERMS AND DEFINITIONS FOR REPORTING IMMUNOGENICITY RESULTS

Many terms and definitions pertaining to immunogenicity, in particular those used for reporting anti-drug antibodies results, have been in common use throughout the medical and scientific and pharmaceutical communities. However, various disease areas and scientific disciplines have used different terms or have defined the same terms in different ways.

One of the first goals of the **ABIRISK consortium** was to provide clear definitions around terms and concepts related to immunogenicity, its prediction and associated clinical events.

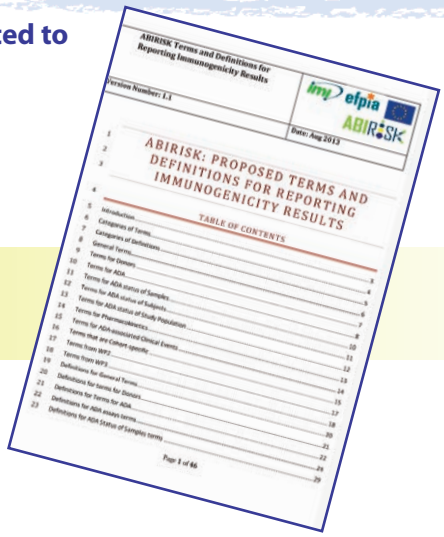
Beyond the reporting of anti-drug antibodies data, **ABIRISK** will also be reporting data on cellular and pharmacogenomic markers of immunogenicity and results from predictive immunogenicity methods.

Agreement on terms and definitions to describe and implement these new and emerging aspects of immunogenicity science will also be an outcome of the **ABIRISK goals.**

The document **"Proposed Terms and Definitions for Reporting Immunogenicity Results"** has been recently finalized by **ABIRISK Consortium members** and it will be updated throughout the whole course of the **ABIRISK Project.**

"Proposed Terms and Definitions for Reporting Immunogenicity Results" will be presented and distributed to key international organizations **(e.g. European Immunogenicity Platform-EIP, AAPS Therapeutic Protein Immunogenicity Focus Group, Ligand Binding Assay Bioanalytical Focus Groups etc.)** asking for their comments and suggestions to further improve it.

To the same aim, as readers of ABIRISK External Newsletter, **you are kindly requested to assess our document (just click on the specific icon on the right to access the document and download it) and post your comments and suggestions at: newsletter@abirisk.eu.**


ABIRISK Terms and Definitions for Reporting Immunogenicity Results

Version Number: 1.1

Date: Aug 2013

ABIRISK: PROPOSED TERMS AND DEFINITIONS FOR REPORTING IMMUNOGENICITY RESULTS

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ALL YOUR COMMENTS AND SUGGESTIONS WILL BE TAKEN INTO CONSIDERATION AND WELL APPRECIATED!

THANKS IN ADVANCE FOR YOUR KIND COLLABORATION!!!

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ABIRISK NEW PARTNERS

The ABIRISK Consortium would like to welcome **SciCross** and **Assistance Publique-Hôpitaux de Paris (AP-HP)** as a new full ABIRISK partners of the Consortium.
Dr. Pierre Dönnes, SciCross owner, will be the Principal Investigator in charge for this SME. **SciCross** has extensive experience in building complex databases, containing data from both clinical and non-clinical studies. **SciCross** will be deeply involved in WP4 "Establishment of a data base, data analyses and integration" activities, providing clinical, analytic and informatics support to facilitate creation of the ABIRISK database.
Dr. Mohcine Benbijja will be the Principal Investigator in charge for **AP-HP**. **AP-HP** is the public hospital system of the city of Paris and its suburbs and the largest hospital system in Europe. Linked with the University of Paris, **AP-HP** has vast experience in EU project management. Close collaboration with investigators, researchers and clinical research units ensures follow up of clinical trials sponsored by **AP-HP** when **AP-HP** acts as coordinator. In ABIRISK Project, **AP-HP** will be the sponsor of the prospective rheumatoid arthritis cohort in France.

UPCOMING EVENTS

3RD PROIMMUNE MASTERING IMMUNOGENICITY SEPTEMBER 16-17, 2013-BRITISH CONSULATE-GENERAL, BOSTON, MA, USA

ProImmune's Mastering Immunogenicity Conference represents an ideal forum for group leaders in immunogenicity for a two-day summit to discuss the very latest ideas in immunogenicity risk management. This event represents an ideal opportunity to meet scientists in the field of immunogenicity and to discuss advances in technology and strategy.

Florian Deisenhammer (Medizinische Universität Innsbruck, IMU; ABIRISK Partner 18), co-leader of ABIRISK Working Package 1 "Anti-drug antibodies assay development and validation and cohort management", has been invited to give a talk to this Conference.

ProImmune's Mastering Immunogenicity Conference will be a strategic occasion for Florian to make aware other group leaders in the immunogenicity field on ABIRISK aims, objectives and expectations.


3rd Mastering Immunogenicity

Call For Abstracts

September 16-17, 2013
British Consulate-General, Boston MA, USA

Join a select group of leaders in immunogenicity for a two-day summit to discuss the very latest ideas in immunogenicity risk management

ProImmune's 3rd Mastering Immunogenicity Conference will be a focused forum for key people involved in immunogenicity risk management to come together to share knowledge and perspectives, and plan appropriate ways to approach the challenges of unwanted immunogenicity.

We will be keeping the popular format of presentations on current key issues in the field, followed by round-table discussion sessions on day two. This year we plan to have a strong focus on the basic immunogenicity research which needs to be carried out to improve our understanding of immune regulation to biotherapeutics, and review the progress made in correlating data from pre-clinical predictive tools to clinical outcomes. We will also continue our discussions surrounding the benefits that Quality by Design have on reduced immunogenicity, and the subsequent patient benefits as well as the competitive advantages.

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SEPTEMBER

EUROTOX2013
The scientific programme will include toxicology's novel scientific and regulatory discoveries presented in symposia and workshops framed by key note lectures, continuing education courses, poster sessions and an exhibition.
1st-4th, 2013 - Interlaken, Switzerland

GASTRO2013
The Scientific Program will offer a global perspective on gastroenterology and related disciplines while recognizing the special concerns facing the Asian Pacific region. Sessions covering Endoscopy, Hepatology, Gastroenterology and related GI disorders will be presented.
21st-24th, 2013 - Shangai, China

WORLD CONGRESS ON INFLAMMATION
The 11th World Congress on Inflammation will be organized by the Brazilian Society of Immunology (SBI) as its XXXVIII Congress, in collaboration with the International Association of Inflammation Societies. The program concerning basic science, applied biology and clinical research, where state of the art views of the recent advances in the field will be fostered. The congress will take place in the modern convention center of Natal, Northwest Brazil.
21st-25th, 2013 - Natal, Brazil

WORLD CONGRESS OF NEUROLOGY
The congress theme is "Neurology in the Age of Globalization". During the congress will be discussed the major breakthroughs and developments in the field of neurology – from clinical practice to research and technology.
21th-26th, 2013 - Vienna, Austria

OCTOBER

EUROPEAN MEDICINES AGENCY - WORKSHOP ON THE CLINICAL INVESTIGATION OF NEW MEDICINES FOR THE TREATMENT OF MULTIPLE SCLEROSIS
The main goal of the workshop is to make sure that in the revision of the multiple-sclerosis guideline, the European Medicines Agency can take the most up-to-date, state-of-the-art scientific developments in multiple sclerosis into consideration, as well as the positions of experts in the field on the main topics in the guideline.
17th, 2013 - London, UK

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NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

Development of inhibitory antibodies to therapeutic factor VIII in severe hemophilia A is associated with microsatellite polymorphism in the HMOX1 promoter.

Repessé Y, Peyron I, Dimitrov JD, Dasgupta S, Farrokhi Moshai E, Costa C, Borel-Derlon A, Guillet B, D' Oiron R, Aouba A, Rothschild C, Oldenburg J, Pavlova A, Kaveri SV, Lacroix-Desmazes S.
Haematologica. 2013 May 28. [Epub ahead of print]

Induction of heme oxygenase-1 (HO-1), a stress inducible enzyme with anti-inflammatory activity, reduces the immunogenicity of therapeutic factor VIII in experimental hemophilia A. In human, HO-1 expression is modulated by polymorphisms in the promoter of the HO-1-encoding gene (HMOX1).

In the present study, **ABIRISK partner Inserm UMR872** investigated the relationship between polymorphisms in the HMOX1 promoter and factor VIII inhibitor development in severe hemophilia A. This group performed a case-control study on 99 inhibitor-positive patients and 263 patients who did not develop inhibitor within the first 150 cumulative days of exposure to therapeutic factor VIII. Direct sequencing and DNA fragment analysis were used to study (GT)n polymorphism and single nucleotide polymorphisms located at 1135 and 413 in the promoter of HMOX1. This group assessed associations between the individual allele frequencies or genotypes, and inhibitor development.


haematologica
the hematology journal
Early Release Paper
Development of inhibitory antibodies to therapeutic factor VIII in severe hemophilia A is associated with microsatellite polymorphism in the HMOX1 promoter

The results reported in this study demonstrate a higher frequency in inhibitor-positive patients of alleles with large (GT)n repeats (L: n≥30), that are associated with a lesser HO-1 expression [odds ratio (OR) 2.31; 95% CI 1.46-3.66, p<0.001]. Six genotypes (L/L, L/M, L/S, M/M, M/S and S/S) of (GT)n repeats were identified (S: n<21; M: 21≤n<30). The genotype group including L alleles (L/L, L/M and L/S) was statistically more frequent among inhibitor-positive than inhibitor-negative patients, as compared to the other genotypes (33.3% versus 17.1%) [OR 2.21, 95% CI 1.30-3.76, p<0.01].

This is the first association between HMOX1 promoter polymorphism and development of anti-drug antibodies. The results reported in this study pave the way towards modulation of the endogenous anti-inflammatory machinery of hemophilia patients to reduce the risk of inhibitor development.

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Allergological in vitro and in vivo evaluation of patients with hypersensitivity reactions to infliximab.
Matucci A, Pratesi S, Petroni G, Nencini F, Virgili G, Milla M, Maggi E, Vultaggio A.
Clin Exp Allergy. 2013 Jun;43(6) : 659-64.

The administration of biological agents is potentially affected by IgE-mediated infusion reactions.

In the present study, **ABIRISK partner Università di Firenze** evaluated the utility of skin testing in patients who have experienced infliximab (IFX)-related reactions. Thirty patients with previous immediate hypersensitivity reaction to IFX, 20 disease-matched non exposed subjects, 15 IFX-treated disease-matched tolerant patients and 15 IFX non-responder patients were enrolled. Non-isotype-specific and IgE anti-drug antibodies (ADAs) were measured by a double-capture ELISA kit and ImmunoCAP assay, respectively. Prick and intra-dermal tests were carried out with the commercial IFX preparation serially diluted.

Results reported in this study show that skin testing, performed in 23 of 30 reactive patients, resulted positive in 7 of them (30.4%), whereas no positivity was found in other groups of patients. The majority of reactive patients displayed non-isotype-specific ADAs (23/30, 76.6%) and the presence of anti-IFX IgE antibodies was detected in 6 of them (26%). All 6 IgE-positive reactive patients showed skin testing positivity. One reactive ADAs-positive patient who resulted skin test positive, with no detectable serum IFX-specific IgE ADAs, was also found. Skin testing positivity was associated with severe and early reactions (within the 3rd dose). No unexpected adverse reactions to skin testing were recorded.

This study shows that about 30% of reactive patients display skin testing positivity. They usually develop severe reactions, mainly during the first administrations of IFX. The specificity and the safety of skin testing procedure for this biological agent are also confirmed.

RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Genome-Wide Association Study and Gene Expression Analysis Identifies CD84 as a Predictor of Response to Etanercept Therapy in Rheumatoid Arthritis.
Cui J, Stahl EA, Saevarsdottir S, Miceli C, Diogo D, Trynka G, Raj T, Mirkov MU, Canhao H, Ikari K, Terao C, Okada Y, Wedrén S, Askling J, Yamanaka H, Momohara S, Taniguchi A, Ohmura K, Matsuda F, Mimori T, Gupta N, Kuchroo M, Morgan AW, Isaacs JD, Wilson AG, Hyrich KL, Herenius M, Doorenspleet ME, Tak PP, Crusius JB, van der Horst-Bruinsma IE, Wolbink GJ, van Riel PL, van de Laar M, Guchelaar HJ, Shadick NA, Allaart CF, Huizinga TW, Toes RE, Kimberly RP, Bridges SL Jr, Criswell LA, Moreland LW, Fonseca JE, de Vries N, Stranger BE, De Jager PL, Raychaudhuri S, Weinblatt ME, Gregersen PK, Mariette X, Barton A, Padyukov L, Coenen MJ, Karlson EW, Plenge RM.
PLoS Genet. 2013 Mar;9(3):e1003394

Pre-Existing Biotherapeutic-Reactive Antibodies: Survey Results Within the American Association of Pharmaceutical Scientists.
Xue L, Fiscella M, Rajadhyaksha M, Goyal J, Holland C, Gorovits B, Morimoto A.
AAPS J. 2013 Apr 2

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Personalized medicine: predicting responses to therapy in patients with RA.
van den Broek M, Visser K, Allaart CF, Huizinga TW.
Curr Opin Pharmacol. 2013 Apr 8

Roles of the ubiquitin peptidase USP18 in multiple sclerosis and the response to interferon-β treatment.
Malhotra S, Morcillo-Suárez C, Nurtdinov R, Rio J, Sarro E, Moreno M, Castilló J, Navarro A, Montalban X, Comabella M.
Eur J Neurol. 2013 May 22

Baseline Gene Expression Signatures in Monocytes from Multiple Sclerosis Patients Treated with Interferon-beta.
Bustamante MF, Nurtdinov RN, Río J, Montalban X, Comabella M.
PLoS One. 2013 Apr 18;8(4):e60994.

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.

ABIRISK WEBSITE has been visited by a monthly average of over 7 hundred people worldwide in the last 12 months!

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