ABIRISK

EXTERNAL NEWSLETTER

Dear colleagues, dear friends and supporters of ABIRISK,

we are pleased to present you the fourth 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)

PROJECT NEWS

WATCH OUT FOR THE RELEASE OF TERMS AND DEFINITIONS DOCUMENT

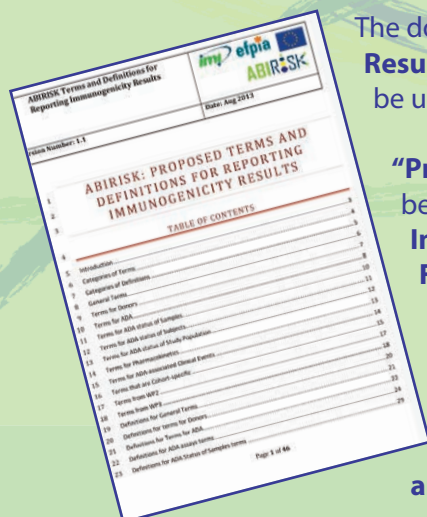**Proposed Terms and Definitions for Reporting Immunogenicity Results**

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.**

PLEASE LET US KNOW YOUR COMMENTS AND SUGGESTIONS!!!

THANKS IN ADVANCE FOR YOUR KIND COLLABORATION!!!

ABIRISK PRESENTED AT KEY IMMUNOTOXICOLOGY MEETINGS

Marc Pallardy (INSERM, ABIRISK Managing Entity) was invited to present **ABIRISK Project** at the **49th Congress of the European Societies of Toxicology - EUROTOX 2013** (Interlaken, Switzerland, 1-4 September 2013).

The scientific programme of **EUROTOX 2013** included 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.

The **EUROTOX meetings** offer a unique opportunity for toxicologists with different backgrounds, coming from a variety of countries, to meet and network with friends, colleagues and leaders in the different disciplines.

UPCOMING EVENTS

JANUARY

KEYSTONE SYMPOSIUM: INFLAMMATORY DISEASES: RECENT ADVANCES IN BASIC AND TRANSLATIONAL RESEARCH AND THERAPEUTIC TREATMENTS

Chronic inflammatory diseases represent a major threat to the health of our society. In the past several years, there have been advancements in understanding the immunological basis for inflammatory diseases and in identifying the cellular components and molecular pathways underlying their pathogenesis. Systems approaches have been taken in translational research of human patients. In addition, new biological and small molecule drugs have been tested with different degrees of success. The goal of this meeting is review these advances and to provide a single forum for basic, clinical and industrial experts to consider opportunities for further development of concepts, systems and therapeutics.
This will be achieved by: 1) covering multiple types of inflammatory diseases that affect multiple organs; 2) gathering basic scientists, translational researchers and pharmaceutical investigators in the same setting; and 3) featuring roundtable discussion on future improvements in animal models and approaches to study human diseases and drug responses. This meeting will foster discussion on common pathways in inflammatory diseases, common methodology in studying human diseases and common challenges in designing the best medicine and clinical trials.
17th-22nd, 2014 - Vancouver, Canada

2ND IMMUNOGENICITY AND IMMUNOTOXICITY CONFERENCE

The conference will cover important progress made in the areas of therapeutic protein immunogenicity and immunotoxicity evaluation such as protein aggregation, clinical relevance and assessment of immunogenicity, mitigation of immunogenicity-related risks, biosimilar development, and immunotoxicity evaluation strategies. The Immunogenicity and Immunotoxicity Conference will provide guests with a better understanding of the ongoing research for tools to mitigate risks associated with the immunogenicity of therapeutic proteins. Guests will get an up-to-date understanding of the mechanisms and consequences of protein aggregation and insights on how to prosecute state-of-the-art assessment of the clinical immunogenicity of therapeutic proteins.
29th-31st, 2014 - San Diego, USA

FEBRUARY

EUROPEAN IMMUNOGENICITY PLATFORM (EIP) IMMUNOGENICITY OF BIOPHARMACEUTICAL SYMPOSIUM

Over the past years, the EIP open symposium became the yearly rendez-vous of industry players, regulators and scientist in the field of immunogenicity.

In 2 days, participants will enjoy a broad spectrum of presentations and plenty of networking opportunities. Organized under the flag of the European Immunogenicity Platform (EIP), a central meeting place for European biopharmaceutical companies and scientific experts active in the field of immunogenicity. This scientific meeting with plenary lectures and interactive sessions will give everyone the opportunity to meet the experts and discuss novel technologies.

24th-26th, 2014 - Lisbon, Portugal

2014 AAAAI ANNUAL MEETING

Mark your calendars and head to San Diego for the premier event in allergy/immunology. You will be able to earn CME/CE, learn about cutting-edge research and enrich your networking connections at the 2014 AAAAI Annual Meeting, February 28-March 4.

Join thousands of allergist/immunologists, allied health and related healthcare professionals for five full days with hundreds of educational offerings on a variety of topics including: allergic disease; asthma; immunotherapy; food allergy and GI disease; skin disease; PIDD; practice management; new technologies; and health care reform.

28th February-4th March, 2014 - San Diego, USA

NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

In silico calculated affinity of FVIII-derived peptides for HLA class II alleles predicts inhibitor development in haemophilia A patients with missense mutations in the F8 gene.
Pashov AD, Calvez T, Gilardin L, Maillère B, Repessé Y, Oldenburg J, Pavlova A, Kaveri SV, Lacroix-Desmazes S.
Haemophilia. 2013 Oct 14. doi: 10.1111/hae.12276. [Epub ahead of print]

Forty per cent of haemophilia A (HA) patients have missense mutations in the F8 gene. Yet, all patients with identical mutations are not at the same risk of developing factor VIII (FVIII) inhibitors. In severe HA patients, human leucocyte antigen (HLA) haplotype was identified as a risk factor for onset of FVIII inhibitors.

In the present study **ABIRISK Partner INSERM** hypothesized that missense mutations in endogenous FVIII alter the affinity of the mutated peptides for HLA class II, thus skewing FVIII-specific T-cell tolerance and increasing the risk that the corresponding wild-type FVIII-derived peptides induce an anti-FVIII immune response during replacement therapy.

This study investigated whether affinity for HLA class II of wild-type FVIII-derived peptides that correspond to missense mutations described in the Haemophilia A Mutation, Structure, Test and Resource database is associated with inhibitor development.

The study predicted the mean affinity for 10 major HLA class II alleles of wild-type FVIII-derived peptides that corresponded to 1456 reported cases of missense mutations. Linear regression analysis confirmed a significant association between the predicted mean peptide affinity and the mutation inhibitory status (P = 0.006). Significance was lost after adjustment on mutation position on FVIII domains. Although analysis of the A1-A2-A3-C1 domains yielded a positive correlation between predicted HLA-binding affinity and inhibitory status (OR = 0.29 [95% CI: 0.14-0.60] for the high affinity tertile, P = 0.002), the C2 domain-restricted analysis indicated an inverse correlation (OR = 3.56 [1.10-11.52], P = 0.03).

Results reported in this study validate the importance of the affinity of FVIII peptides for HLA alleles to the immunogenicity of therapeutic FVIII in patients with missense mutations.

The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab.
Ungar B, Chowers Y, Yavzori M, Picard O, Fudim E, Har-Noy O, Kopylov U, Eliakim R, Ben-Horin S
Gut. 2013 Sep 16. doi: 10.1136/gutjnl-2013-305259. [Epub ahead of print]

Prevalence of antibodies to infliximab (ATI) is approximately 60% in episodic infliximab treatment and ranges between 6% and 25% in scheduled treatment. The formation of ATI is associated with lower serum infliximab levels, infusion reactions and in most studies with loss of response. There is scant data regarding temporal evolution of ATI and its correlation to clinical response.

The main objective of the present study performed by **ABIRISK Partners Chaim Sheba Medical Center and Rambam Medical Center** was to characterise the temporal evolution of ATI through a prospective observational study of infliximab treated patients with inflammatory bowel disease between 2009 and 2012.
Trough levels of infliximab and ATI were measured before each infusion by anti-λ ELISA. Patients were monitored for disease activity by clinical activity indexes and for dose-intensification or infliximab cessation. The occurrence of transient ATI disappearing spontaneously without intervention was recorded separately. 125 patients were included (98 Crohn's disease, 27 ulcerative colitis, median follow-up 11.5 ± 22 months) and 1119 sera were analysed for infliximab and ATI levels.

Kaplan-Meier analysis showed that 42% of patients remained ATI-free by 4 years of treatment. Most (90%) of the patients who developed ATI did so within the first 12 months of therapy, whereas transient ATI were detected throughout the duration of infliximab therapy (p<0.001). ATI incidence was similar between patients who received infliximab previously (episodic/interrupted therapy patients, n=14) and scheduled therapy patients (n=111). In the scheduled group, combination immunomodulator + infliximab resulted in longer ATI-free survival compared with monotherapy (p=0.003, logrank test). Survival free of clinical loss of response was enjoyed by 51% of patients, and serial measurements showed that ATI development often preceded the onset of clinical flare.

Results reported in this study indicated that, when followed prospectively, most patients who develop ATI do so within the first 12 months of therapy. This incidence is reduced by concomitant immunomodulator even in scheduled therapy patients. In contrast, transient ATI, which are of little clinical significance, can appear haphazardly at any time during treatment. The onset of clinical loss of response may lag behind the appearance of anti-infliximab antibodies.

RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

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.

Monotherapy with tocilizumab or TNF-alpha inhibitors in patients with rheumatoid arthritis: efficacy, treatment satisfaction, and persistence in routine clinical practice.
Kaufmann J, Feist E, Roske AE, Schmidt WA.
Clin Rheumatol. 2013 May 24.

Evaluation of low-dose rituximab for the retreatment of patients with active rheumatoid arthritis: a noninferiority randomised controlled trial.
Mariette X, Rouanet S, Sibilia J, Combe B, Le Loët X, Tebib J, Jourdan R, Dougados M.
Ann Rheum Dis. 2013 May 30.

Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, doubleblind, placebo-controlled trial.
Gold R, Giovannoni G, Selmaj K, Havrdova E, Montalban X, Radue EW, Stefoski D, Robinson R, Riester K, Rana J, Elkins J, O'Neill G; SELECT study investigators.
Lancet. 2013 Jun 22;381(9884):2167-75.

Evaluation of Pre-existing Antibody Presence as a Risk Factor for Posttreatment Anti-drug Antibody Induction: Analysis of Human Clinical Study Data for Multiple Biotherapeutics.
Xue L, Rup B.
AAPS J. 2013 Jun 13.

Serum calprotectin as a biomarker for Crohn's disease.
Meuwis MA, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Piver E, Seidel L, Colombel JF, Louis E; the GETAID (Groupe d'Étude Thérapeutique Des Affections Inflammatoires Digestives).
J Crohns Colitis. 2013 Jul 9.

2012 AAPS National Biotech Conference Open Forum: A Perspective on the Current State of Immunogenicity Prediction and Risk Management.
Rajadhyaksha M, Subramanyam M, Rup B.
AAPS J. 2013 Aug 30.

Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis.
Emery P, Sebba A, Huizinga TW.
Ann Rheum Dis. 2013 Aug 5.

Rituximab-induced T-cell depletion in patients with rheumatoid arthritis: Association with clinical response.
Mélet J, Mulleman D, Goupille P, Ribourtout B, Watier H, Thibault G.
Arthritis Rheum. 2013 Aug 5.

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Taking Crohn's disease personally.
Chowers Y.
Rambam Maimonides Med J. 2013 Apr 30;4(2):e0011.

Early detection of neutralizing antibodies to interferon-beta in multiple sclerosis patients: binding antibodies predict neutralizing antibody development.
Hegen H, Millonig A, Bertolotto A, Comabella M, Giovanonni G, Guger M, Hoelzl M, Khalil M, Killestein J, Lindberg R, Malucchi S, Mehling M, Montalban X, Polman C, Rudzki D, Schautzer F, Sellebjerg F, Sørensen P, Deisenhammer F.
Mult Scler. 2013 Sep 5.

Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials.
Bykerk VP, Cush J, Winthrop K, Calabrese L, Lortholary O, de Longueville M, van Vollenhoven R, Mariette X.
Ann Rheum Dis. 2013 Oct 3

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!