ABIRISK

EXTERNAL NEWSLETTER

ISSUE 16 - DECEMBER 2016

WWW.ABIRISK.EU

Dear colleagues, dear friends and supporters of ABIRISK,

we are pleased to present you the sixteenth 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 **ABIRISK project** consortium is presently made up of **thirty-eight partners, twenty-six** of which are **academic institutions, nine are EFPIA member companies** and **three** are small and medium enterprises **(SMEs).** Thirteen countries are represented: The United Kingdom, France, Italy, Germany, Switzerland, Denmark, Belgium, the Netherlands, Spain, Sweden, Austria, Israel and Czech Republic.

The consortium is co-ordinated by **Novartis Pharma AG (Dr. Sebastian Spindeldreher, 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.'

www.imi.europa.eu

ABIRISK
EXTERNAL NEWSLETTER
ISSUE 16 - DECEMBER 2016
WWW.ABIRISK.EU

PROJECT NEWS

Coral Gables Symposium

5-7th October 2016 Coral Gables, Florida

The **4th Coral Gables Symposium was organized by Eurodiagnotica (ABIRISK Partner 6)** and took place at the Biltmore Hotel, Coral Gables, Miami, USA between October 5-7, 2016.

The principal theme of this year's Coral Gables Symposium was **"Immunogenicity and the Patient: The Future is Yours"**, highlighting the consequences of the immunogenicity of biopharmaceuticals for the patient and the prospects of improving the future for the patient.

An array of distinguished speakers from academia, pharma companies, regulatory agencies and clinical practice created the basis for discussions through talks on a wide range of topics. Each session was concluded with a panel discussion, where all the speakers took questions as a group, allowing for open discussions spanning several topics.

The Symposium started off with a session on Immunogenicity and the Patient, where representatives of the FDA and NIBSC described the risks immunogenicity poses to patients and how these can be pre-assessed for specific patient populations, along with highlights of the newly revised EU guidance on immunogenicity which is to be released by the end of 2016.

This was followed by **a session dedicated to the ABIRISK Consortium, describing its purpose to elucidate the underlying mechanisms of immunogenicity by bringing together a large network of clinicians and scientists to investigate the correlation between patients, clinical factors and the incidence of immunogenicity, and from this data derive predictive signatures.**

ABIRISK: CLINICAL RELEVANCE TO MINIMIZE RISK
Thursday, 6th October, 2016 - 11:30 am - 1:00 pm

Chairs: *Drs. Dan Sikkema & Robin Thorpe*

11:30	ABIRISK: An integrated approach to assess biomarkers to predict immunogenicity. *Dr. Sophie Tourdot, INSERM*
11:50	WP1 - Non-drug related immunogenicity factors in biopharmaceutical therapies. *Professor Florian Deisenhammer, University of Innsbruck*
12:10	WP2 – LEGEND Screen: Identification of factors in patients having adverse reactions to biological drugs. *Dr. Liz Jury, UCL*
12:30	WP3 – Evaluation and development of technologies for predicting immunogenicity. *Dr. Sebastian Spindeldreher, Novartis*
12:50.	General Discussion

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.'
www.imi.europa.eu

The **ABIRISK Dedicated Session**, chaired by **Dan Sikkema** (ABIRISK Partner 1 GlaxoSmithKline Research & Development Limited - GSK) and **Robin Thorpe** (ABIRISK Scientific Advisory Board Member), was opened by the presentation of **Sophie Tourdot** (ABIRISK Partner 2 Institut National de la Santé et de la Recherche Médicale - INSERM; ABIRISK Scientific Project Manager) entitled **"ABIRISK: An integrated approach to assess biomarkers to predict immunogenicity".**

Sophie's talk was followed by **Florian Deisenhammer** (ABIRISK Partner 18 Medizinische Universität Innsbruck - IMU; ABIRISK Work Package 1 co-leader) **"WP1 - Non-drug related immunogenicity factors in biopharmaceutical therapies"** and **Liz Jury** (ABIRISK Partner 8 University College London - UCL) **"WP2 - LEGEND Screen: Identification of factors in patients having adverse reactions to biological drugs"** presentations.

The **ABIRISK Dedicated Session** was closed by **Sebastian Spindeldreher** (ABIRISK project Co-ordinator and WP3 co-leader; ABIRISK Partner 30 Novartis Pharma) presentation titled **"WP3 - Evaluation and development of technologies for predicting immunogenicity".**

The topic of prediction of immune responses to biopharmaceuticals was raised in several talks throughout the Symposium, and a separate session was also dedicated to a systems biology approach to prediction of immunogenicity.

One of the presented methods was based on in silico, in vitro and in vivo assessments, all combined into one multi-scale mechanistic model with immunogenicity prediction as output.

As a last activity of the Symposium, an appreciated Q&A session with all the representatives from the regulatory agencies was held. Requirements on time periods for immunogenicity testing during clinical development and post-market surveillance was discussed as one of many topics, as well as the FDAs position to encourage new technologies for biosimilar immunogenicity testing as opposed to using assays filed with the innovator drug.

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.'
www.imi.europa.eu

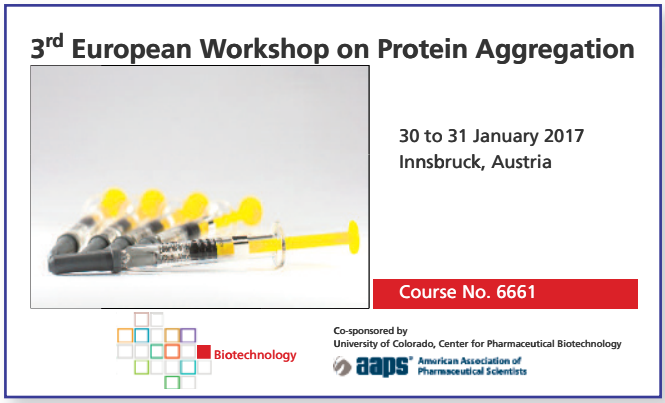
ABIRISK
EXTERNAL NEWSLETTER
ISSUE 16 - DECEMBER 2016
WWW.ABIRISK.EU

UPCOMING EVENTS

3rd EUROPEAN WORKSHOP ON PROTEIN AGGREGATION AND IMMUNOGENICITY

Innsbruck, Austria - 30th-31st January 2017

The course is designed for all scientists involved in the production and formulation of therapeutic proteins, working in Pharmaceutical and Biopharmaceutical Industry or at suppliers of analytical equipment or at service companies contributing, e.g. to analytical characterization of therapeutic protein drug products.



The seminar offers the opportunity to students to presenttheir latest results in poster format, and the display of advanced analytical technology to suppliers in an industrial exhibition.

61st ANNUAL MEETING OF THE SOCIETY OF THROMBOSIS AND HEMOSTASIS RESEARCH

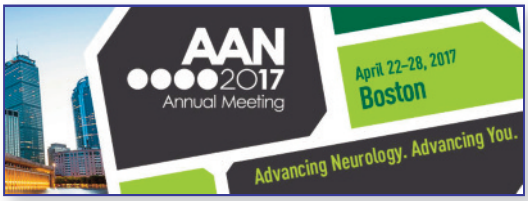
Basel, Switzerland - 15th-18th February 2017

The **GTH 2017 Annual Meeting** has been organized based on the theme from individual patients to pathophysiological insights.

The educational and scientific program will provide state-of-the-art sessions and plenary lectures given by experts as well as a platform for the presentation of original research in the field of thrombosis and hemostasis. In addition, there will be the possibility to attend satellite symposia organized by pharmaceutical companies and to visit their booths.

ANNUAL MEETING AMERICAN ACADEMY OF NEUROLOGY

Boston, USA - 22nd-28th April 2017



The **69th AAN Annual Meeting** will take place **April 22 through 28, 2017**, at the Boston Convention and Exhibition Center.
The **AAN Annual Meeting** is the world's largest gathering of neurologists, bringing together more than 10,000 neurology professionals across the globe to network, discuss cutting-edge research, and take part in top-rated education programming across a wide variety of topics.

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.'
www.imi.europa.eu

ABIRISK
EXTERNAL NEWSLETTER
ISSUE 16 - DECEMBER 2016
WWW.ABIRISK.EU

NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

Serum cotinine does not predict neutralizing antibodies against Interferon-beta in an Austrian MS-cohort

Michael Auer, Harald Hegen, Thomas Luft, Gabriel Bsteh, Anna Fogdell-Hahn, Amy Loercher and Florian Deisenhammer; on behalf of the ABIRISK consortium
J Interferon Cytokine Res. 2016 Dec;36(12):667-670. Epub 2016 Oct

Previous epidemiologic studies showed an increased risk of neutralizing antibody (NAb) development against Interferon beta in multiple sclerosis patients who smoke.
Cotinine is an easily detectable metabolite of nicotine and, therefore, can be used as an objective surrogate marker for smoking status.
The authors of this study measured cotinine levels in NAb-positive and NAb-negative patients to find a potential association of nicotine consumption and NAb development. Cotinine was measured in 37 patients with known smoking status and in 123 patients with unknown smoking status, all of whom were routinely tested for NAb. Cotinine was detected by an enzyme-linked immunosorbent assay, inhibition assay. The study compared cotinine levels by NAb status and tested for the strength of association between cotinine and NAb status.
Authors found a discrepancy between smoking status stated by patients and status defined by cotinine levels in 7 of 37 patients. In both cohorts, together with and without previously known smoking status (n=160), we found 34% and 39% smokers, respectively, as defined by cotinine levels in NAb-negative and NAb-positive patients (P=0.511).
In the analysis reported in this manuscript, smoking was not associated with higher risk of NAb development. Moreover, smoking habits stated by patients do not always correlate with cotinine levels.


Serum Cotinine Does Not Predict Neutralizing Antibodies Against Interferon Beta in an Austrian MS Cohort

Regulatory T cells and their potential for tolerance induction in haemophilia A patients

Anja Schmidt and Christoph Königs on behalf of the ABIRISK consortium
Hamostaseologie. 2016 Nov 8;36(Suppl. 2):S5-S12


Regulatory T cells and their potential for tolerance induction in haemophilia A patients

FVIII inhibitors still are the major concern in treatment of haemophilia A patients by FVIII replacement therapy.
Immune tolerance induction to reverse inhibitor formation fails in about 30% of treated patients.
These patients face increased morbidity and mortality producing a need for new therapy strategies in the treatment of FVIII inhibitor-positive patients.
Regulatory T cells are important modulators of the immune response and are also involved in the immune response to FVIII in haemophilia A patients.

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.'
www.imi.europa.eu

ABIRISK
EXTERNAL NEWSLETTER
ISSUE 16 - DECEMBER 2016
WWW.ABIRISK.EU

NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

Additionally, regulatory T cells have been shown to play a role in tolerance induction induced by multiple experimental treatment regimes.
This review summarises the current knowledge on the role of regulatory T cells in the immune response to FVIII and tolerance induction strategies.
Additionally, possible ways to engineer regulatory T cells as therapeutic agent in haemophilia A and current challenges of regulatory T cell therapies are discussed.

Occurrence of anti-drug antibodies against interferon-beta and natalizumab in multiple sclerosis: A collaborative cohort analysis

Bachelet, D, Hässler, C. Mbogning, J. Link, M. Ryner, R. Ramanujam, M. Auer, P.E. Hyldgaard Jensen, N. Koch-Henriksen, C. Warnke, K. Ingenhoven, D. Buck, V. Grummel, A. Lawton, V. Berthou, N. Donnellan, A. Hincelin-Mery, D. Sikkema, M. Pallardy, B. Kieseier, B.Hemmer, H. Hartung, P. Soelberg Sorensen, F. Deisenhammer, P. Dönnes, J. Davidson, A. Fogdell-Hahn, P. Broët
PLoS One. 2016 Nov 2;11(11):e0162752. doi: 10.1371/journal.pone.0162752.

Immunogenicity of biopharmaceutical products in multiple sclerosis is a frequent side effect which has a multifactorial etiology. The authors of this manuscripts study associations between anti-drug antibody (ADA) occurrence and demographic and clinical factors.
Retrospective data from routine ADA test laboratories in Sweden, Denmark, Austria and Germany (Dusseldorf group) and from one research study in Germany (Munich group) were gathered to build a collaborative multi-cohort dataset within the framework of the ABIRISK project.
A subset of 5638 interferon-beta (IFNβ)-treated and 3440 natalizumab-treated patients having data on at least the first two years of treatment were eligible for interval-censored time-to-event analysis. In multivariate Cox regression, IFNβ-1a subcutaneous and IFNβ-1b subcutaneous treated patients were at higher risk of ADA occurrence compared to IFNβ-1a intramuscular-treated patients (pooled HR = 6.4, 95% CI 4.9-8.4 and pooled HR = 8.7, 95% CI 6.6-11.4 respectively).
Patients older than 50 years at start of IFNβ therapy developed ADA more frequently than adult patients younger than 30 (pooled HR = 1.8, 95% CI 1.4-2.3). Men developed ADA more frequently than women (pooled HR = 1.3, 95% CI 1.1-1.6). Interestingly we observed that in Sweden and Germany, patients who started IFNβ in April were at higher risk of developing ADA (HR = 1.6, 95% CI 1.1-2.4 and HR = 2.4, 95% CI 1.5-3.9 respectively).
This result is not confirmed in the other cohorts and warrants further investigations. Concerning natalizumab, patients older than 45 years had a higher ADA rate (pooled HR = 1.4, 95% CI 1.0-1.8) and women developed ADA more frequently than men (pooled HR = 1.4, 95% CI 1.0-2.0). The study confirmed previously reported differences in immunogenicity of the different types of IFNβ. Differences in ADA occurrence by sex and age are reported here for the first time. These findings should be further investigated taking into account other exposures and biomarkers.

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.'
www.imi.europa.eu

ABIRISK
EXTERNAL NEWSLETTER
ISSUE 16 - DECEMBER 2016
WWW.ABIRISK.EU

RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Off-label use of rituximab for systemic lupus erythematosus in Europe
Rydén-Aulin M, Boumpas D, Bultink I, Callejas Rubio JL, Caminal-Montero L, Castro A, Colodro Ruiz A, Doria A, Dörner T, Gonzalez-Echavarri C, Gremese E, Houssiau FA, Huizinga T, Inanç M, Isenberg D, Iuliano A, Jacobsen S, Jimenéz-Alonso J, Kovács L, Mariette X, Mosca M, Nived O, Oristrell J, Ramos-Casals M, Rascón J, Ruiz-Irastorza G, Sáez-Comet L, Salvador Cervelló G, Sebastiani GD, Squatrito D, Szücs G, Voskuyl A, van Vollenhoven R.
Lupus Sci Med. 2016 Sep 6;3(1):e000163.

Predictors of Response to Multiple Sclerosis Therapeutics in Individual Patients
Hegen H, Auer M, Deisenhammer F.
Drugs. 2016 Sep 21.

A placebo randomized controlled study to test the efficacy and safety of GNbAC1, a monoclonal antibody for the treatment of multiple sclerosis - Rationale and design
Curtin F, Porchet H, Glanzman R, Schneble HM, Vidal V, Audoli-Inthavong ML, Lambert E, Hartung
Mult Scler Relat Disord. 2016 Sep;9:95-100.

Safety and tolerability profile of daclizumab in patients with relapsing-remitting multiple sclerosis: An integrated analysis of clinical studies
Giovannoni G, Kappos L, Gold R, Khatri BO, Selmaj K, Umans K, Greenberg SJ, Sweetser M, Elkins J, McCroskery P.
Mult Scler Relat Disord. 2016 Sep;9:36-46.

Decreased soluble IFN-β receptor (sIFNAR2) in multiple sclerosis patients: A potential serum diagnostic biomarker
Órpez-Zafra T, Pavía J, Hurtado-Guerrero I, Pinto-Medel MJ, Rodriguez Bada JL, Urbaneja P, Suardíaz M, Villar LM, Comabella M, Montalban X, Alvarez-Cermeño JC, Leyva L, Fernández Ó, Oliver-Martos B.
Mult Scler. 2016 Sep 9.

Repeated decrease of CD4+ T-cell counts in patients with rheumatoid arthritis over multiple cycles of rituximab treatment
Lavielle M, Mulleman D, Goupille P, Bahuaud C, Sung HC, Watier H, Thibault G.
Arthritis Res Ther. 2016 Oct 28;18(1):253.

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.'
www.imi.europa.eu

ABIRISK
EXTERNAL NEWSLETTER
ISSUE 16 - DECEMBER 2016
WWW.ABIRISK.EU

RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab
Ungar B, Kopylov U, Engel T, Yavzori M, Fudim E, Picard O, Lang A, Williet N, Paul S, Chowers Y, Bar-Giln Shitrit A, Eliakim R, Ben-Horin S, Roblin X.
Aliment Pharmacol Ther. 2016 Nov 16

Inhibition of interleukin-5 induced false positive anti-drug antibody responses against mepolizumab through the use of a competitive blocking antibody
Liao K, Meyer E, Lee TN, Loercher A, Sikkema D.
J Immunol Methods. 2016 Nov 23. pii: S0022-1759(16)30338-6.

Detection of anti-infliximab antibodies is impacted by antibody titer, infliximab level and IgG4 antibodies: a systematic comparison of three different assays
Afonso J, Lopes S, Gonçalves R, Caldeira P, Lago P, Tavares de Sousa H, Ramos J, Gonçalves AR, Ministro P, Rosal, Vieira AI, Coelho R, Tavares P, Soares J, Sousa AL, Carvalho D, Sousa P, da Silva JP, Meira T, Silva Ferreira F, Dias CC, Chowers Y, Ben-Horin S, Magro F; on behalf Portuguese IBD Study Group (GEDII).
Therap Adv Gastroenterol. 2016 Nov;9(6):781-794.

Summary report of the First International Conference on inhibitors in haemophilia A
Lacroix-Desmazes S, Scott DW, Goudemand J, Van Den Berg M, Makris M, Van Velzen AS, Santagostino E, Lillicrap D, Rosendaal FR, Hilger A, Sauna ZE, Oldenburg J, Mantovani L, Mancuso ME, Kessler C, Hay CR, Knoebl P, Di Minno G, Hoots K, Bok A, Brooker M, Buoso E, Mannucci PM, Peyvandi F.
Blood Transfus. 2016 Nov 25:1-9.

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.'
www.imi.europa.eu

ABIRISK
EXTERNAL NEWSLETTER
ISSUE 16 - DECEMBER 2016
WWW.ABIRISK.EU

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 IS VISITED EVERY MONTHS BY OVER 1300 PEOPLE WORLDWIDE!

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.'
www.imi.europa.eu