



EXTERNAL NEWSLETTER

ISSUE 9 - MARCH 2015

WWW.ABIRISK.EU

Dear colleagues, dear friends and supporters of ABIRISK,

*we are pleased to present you the ninth 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 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.
www.imi.europa.eu

ABIRISK GENERAL ASSEMBLY 17th-18th MARCH - 2015

On the 16th, 17th and 18th of March 2015, the **Fourth General Assembly of ABIRISK Project** was held in Brussels (Belgium) at Pfizer Limited Headquarter. ABIRISK Fourth General Assembly has been organized only for the partners of the project and about 100 participants attended the meeting in Brussels.

The meeting started with ABIRISK Work Packages sub-meetings and the ABIRISK Executive Project Management Team. The first day of the ABIRISK General Assembly started with the ABIRISK Steering Committee meeting followed by the update on main project successes, issues and challenges for the third year of the project, an update on activity around Hemophilia (presented by **Johannes Oldenburg**, ABIRISK Partner 14 Universitaetsklinikum Bonn), data base demonstration, and an update on the clinical trials.



The Poster Session



Alessandro Sette Presentation

The second day of the ABIRISK General Assembly was completely dedicated to science and it started with the presentation of **Alessandro Sette** (La Jolla Institute for Allergy & Immunology - ABIRISK Scientific Advisory Board Member) titled **"Experimental and computational approaches to prediction of immunogenicity"**. Alessandro Sette presentation was followed by two sessions of oral presentations as well as of poster sessions. All scientific sessions were focused on the most important scientific achievements obtained so far by the ABIRISK Consortium members. Amongst speakers, several young

scientists have had the opportunity to present recent data generated by their belonging groups in the area of ABIRISK interests. More important, lots of discussions amongst ABIRISK partners as well as with ABIRISK Scientific Advisory Board members have taken place during all scientific sessions.



The ABIRISK Project consortium during Forth General Assembly of ABIRISK Project in Brussels - March 2015

PROJECT NEWS

ABIRISK presented at key immunogenicity meetings

At the **7th Open Scientific European Immunogenicity Platform (EIP) Symposium on Immunogenicity of Biopharmaceuticals** (Lisbon, Portugal, 23-25 February 2015) several ABIRISK Partners were invited to present data related to ABIRISK Project.

Presentation of **Sebastian Spindeldreher**, (ABIRISK Partner 30 Novartis Pharma AG) titled **"Aggregation of Human Recombinant Monoclonal Antibodies Enhances Their Presentation by Dendritic Cells In Vitro"** was part of **Session 1: "Aggregates and immune complexes"** of the EIP meeting whereas presentations of **Florian Deisenhammer**, (ABIRISK Partner 18 Medizinische Universität Innsbruck) **"Clinical relevance of IFN γ Nabs"** and **Paul Creeke** (ABIRISK Partner 23 Queen Mary and Westfield, University of London)/ **Thomas Luft** (ABIRISK Partner 18 Medizinische Universität Innsbruck) **"Lessons learned from ADA assay validation within the ABIRISK program"** were involved in **Session 2: "ADA investigations in different clinical settings"**.

Finally, presentation of **Tim Hickling** (ABIRISK Partner 29 Pfizer Limited) **"A framework for immunogenicity data integration and prediction: Applying mathematical modeling to immunogenicity of biopharmaceuticals"** was involved in **Session 8: "New technologies for immunogenicity assays/prediction"** of the meeting.



UPCOMING EVENTS

PEGS - The Essential Protein Engineering Summit is the premier event for antibody and protein science research and the biologics industry, with more than 1,800 participants in attendance from over 30 countries. Join the meeting in **Boston** this **May 4-8, 2015** to share insight and best practices with colleagues, connect and form new collaborations during copious networking opportunities, learn from world-renowned thought leaders, discover industry trends and find solutions to current challenges. PEGS is knowledge-sharing at its best.



Immunology 2015 (the American Association of Immunologists Annual Meeting) will be held in New Orleans from **8th to 12th May, in New Orleans**

Join the meeting for the world's leading annual all-immunology event to:

- Find the latest developments in your field
- Hear lectures by the world's most prominent immunologists and POSTER presentations by scientists at every career stage
- Network with colleagues from more than 40 countries, and
- See the newest tools and techniques to benefit your research!



FOCIS 2015 will take place in **San Diego, USA** from **24th to 27th June**.

FOCIS (Federation of Clinical Immunology Societies) 2015 is an international meeting in translational immunology that gives a competitive edge in your career.

This meeting, focusing on molecular pathways and their implications in human disease, will allow you to stay ahead of the curve with leading clinicians and researchers delivering the latest breakthroughs across immune-mediated diseases.

NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT**Assays and strategies for immunogenicity assessment of biological agents**

Nencini F, Pratesi S, Petroni G, Matucci A, Maggi E, Vultaggio A.

Drug Dev Res. 2014 Nov;75 Suppl 1:S4-6.

Some patients with chronic inflammatory diseases either do not respond to or lose their initial responsiveness to Tumor Necrosis Factor (TNF) inhibitor therapy. In these patients, the clinical response after switching to another anti-TNF drug suggests that lack of response is not related to the therapeutic target itself but immunogenicity.

All biologics are potentially immunogenic and can induce the development of antidrug antibodies (ADAs). ADA formation is associated with lower serum drug levels, infusion reactions, and loss of response. Analytical methods for ADA detection include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), surface plasmon resonance, and electrochemiluminescence.

Currently, RIA and ELISA are the preferred methods due to a combination of reproducibility, sensitivity, and cost but have some limitations. There is no single available assay that has all pros and no cons, and therefore the use of more methods for the assessment of samples is a high priority.

Natalizumab exerts a suppressive effect on surrogates of B cell function in blood and CSF

Warnke C, Stettner M, Lehmensiek V, Dehmel T, Mausberg AK, von Geldern G, Gold R, Kümpfel T, Hohlfeld R, Mäurer M, Stangel M, Straeten V, Limmroth V, Weber T, Kleinschnitz C, Wattjes MP, Svenningsson A, Olsson T, Hartung HP, Hermsen D, Tumani H, Adams O, Kieseier BC.

Mult Scler. 2014 Nov 12. pii: 1352458514556296. [Epub ahead of print]

Natalizumab for multiple sclerosis (MS) increases the risk of progressive multifocal leukoencephalopathy (PML). The aim of this study was to assess the effect of natalizumab on cellular composition and functional B cell parameters including patients with natalizumab-associated PML (n=37). Cellular composition by flow cytometry, levels of immunoglobulin (Ig)G/IgM by immunonephelometry, and oligoclonal bands by isoelectric focusing were studied in blood and cerebrospinal fluid.

Results reported in this study showed that in MS patients treated with natalizumab without PML (n=59) the proportion of CD19+ B cells was higher in blood, but lower in cerebrospinal fluid compared with MS patients not treated with natalizumab (n=17). The CD4/CD8-ratio in cerebrospinal fluid was lower, and IgG and IgM levels as well as the IgG index dropped in longitudinal samples during natalizumab therapy. Oligoclonal bands persisted, but the total amount of the intrathecally produced IgG fraction, and the polyclonal intrathecal IgG reactivity to measles, rubella, and zoster declined. At the time of diagnosis of PML patients with natalizumab-associated PML had low total IgG levels in blood and cerebrospinal fluid. In conclusion, this study reported that natalizumab impacts B and T cell distribution and exerts an inhibitory effect on surrogates of B cell function in periphery and in cerebrospinal fluid, potentially contributing to the increased risk of developing PML.

Initial lymphocyte count and low BMI may affect fingolimod-induced lymphopenia

Warnke C, Dehmel T, Ramanujam R, Holmen C, Nordin N, Wolfram K, Leussink VI, Hartung HP, Olsson T, Kieseier BC. *Neurology*. 2014 Dec 2;83(23):2153-7

The main objective of this study was to assess whether pretreatment-lymphocyte counts, treatment before fingolimod, age, sex, or body mass index (BMI) affects the risk of fingolimod-induced lymphopenia in patients with relapsing-remitting multiple sclerosis (RRMS). Data were obtained from a German multicenter, single-arm, open-label study of patients with RRMS treated with fingolimod, and findings were validated in an independent Swedish national pharmacovigilance study. Four hundred eighteen patients with RRMS from Germany and 438 patients from Sweden were included. Results reported in this study showed that a nadir $\leq 0.2 \times 10^9$ lymphocytes/L was reached in 15% (95% confidence interval [CI] 12%-17%) of all 856 patients. Patients with lower starting lymphocyte counts (below 1.6×10^9 /L) and patients with BMI lower than 18.5 kg/m² (women only) were at higher risk of developing lymphopenia with values $\leq 0.2 \times 10^9$ /L in the combined analysis, increasing the risk in these subgroups to 26% (95% CI 20%-31%) or 46% (95% CI 23%-71%), respectively. In the German cohort, infection rates were similar in patients who developed severe lymphopenia and those who did not. Findings of this study suggest that patients with low baseline lymphocyte counts and underweight women in which fingolimod treatment will be initiated should possibly be monitored more closely.

Cerebrospinal fluid JC virus antibody index for diagnosis of natalizumab-associated progressive multifocal leukoencephalopathy

Warnke C, von Geldern G, Markwerth P, Dehmel T, Hoepner R, Gold R, Pawlita M, Kümpfel T, Mäurer M, Stangel M, Wegner F, Hohlfeld R, Straeten V, Limmroth V, Weber T, Hermesen D, Kleinschnitz C, Hartung HP, Wattjes MP, Svenningsson A, Major E, Olsson T, Kieseier BC, Adams O. *Ann Neurol*. 2014 Dec;76(6):792-801

Progressive multifocal leukoencephalopathy (PML), caused by JC virus (JCV), can occur in patients receiving natalizumab for multiple sclerosis (MS). JCV detection by quantitative polymerase chain reaction (qPCR) in cerebrospinal fluid (CSF), or brain biopsy, is required for probable or definite diagnosis of PML. However, in some patients only low levels of JCV DNA (<100 copies/ml) are present in CSF, making the diagnosis challenging. The main objective of this study was to assess the complementary value of a CSF JCV antibody index (AIJCV) in the diagnosis of natalizumab-associated PML. AIJCV was assessed in 37 cases of natalizumab-associated PML and 89 MS-patients treated with natalizumab without PML. Sera and CSF were tested in a capture enzyme-linked immunosorbent assay, using JCV-VP1 fused to glutathione S-transferase as antigen. Albumin levels and total immunoglobulin G concentration were determined by immunonephelometry, and the AIJCV was calculated as published. Results reported in this study showed that twenty-six of 37 (70%) patients with natalizumab-associated PML exhibited an AIJCV > 1.5 , whereas this was seen in none of the controls ($p < 0.0001$). At time of the first positive qPCR for JCV DNA, 11 of 20 (55%) patients with natalizumab-associated PML had an AIJCV > 1.5 . JCV DNA levels of <100 copies/ml were seen in 14 (70%) of these 20 patients, of whom 8 (57%) demonstrated an AIJCV > 1.5 . Findings of this study suggest that determination of the AIJCV could be an added tool in the diagnostic workup for PML and should be included in the case definition of natalizumab-associated PML.

RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Interferon-Beta: Neutralizing Antibodies, Binding Antibodies, Pharmacokinetics and Pharmacodynamics, and Clinical Outcomes.

Deisenhammer F.

J Interferon Cytokine Res. 2014 Dec;34(12):938-945.

Catch-up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis: Results from the TENDER trial.

De Benedetti F, Brunner H, Ruperto N, Schneider R, Xavier R, Allen R, Brown D, Chaitow J, Pardeo M, Espada G, Gerloni V, Myones B, Frane J, Wang J, Lipman TH, Bharucha KN, Martini A, Lovell D; the Paediatric Rheumatology International Trials Organisation (PRINTO); Pediatric Rheumatology Collaborative Study Group (PRCSG).

Arthritis Rheumatol. 2014 Dec 10.

Therapeutic Vaccination with TNF-Kinoid in TNF Antagonist-Resistant Rheumatoid Arthritis: A Phase II Randomized, Controlled Clinical Trial.

Durez P, Vandepapeliere P, Miranda P, Toncheva A, Berman A, Kehler T, Mociran E, Fautrel B, Mariette X, Dhellin O, Fanget B, Ouary S, Grouard-Vogel G, Boissier MC.

PLoS One. 2014 Dec 17;9(12):e113465.

Switch to natalizumab vs fingolimod in active relapsing-remitting multiple sclerosis.

Kalincik T, Horakova D, Spelman T, Jokubaitis V, Trojano M, Lugaes A, Izquierdo G, Rozsa C, Grammond P, Alroughani R, Duquette P, Girard M, Pucci E, Lechner-Scott J, Slee M, Fernandez-Bolanos R, Grand'Maison F, Hupperts R, Verheul F, Hodgkinson S, Oreja-Guevara C, Spitaleri D, Barnett M, Terzi M, Bergamaschi R, McCombe P, Sanchez-Menoyo J, Simo M, Csepany T, Rum G, Boz C, Havrdova E, Butzkueven H; on behalf of the MSBase Study Group.

Ann Neurol. 2014 Dec 27.

Natalizumab-related anaphylactoid reactions in MS patients are associated with HLA class II alleles.

de la Hera B, Urcelay E, Brassat D, Chan A, Vidal-Jordana A, Salmen A, Villar LM, Alvarez-Cermeño JC, Izquierdo G, Fernández O, Oliver B, Saiz A, Ara JR, Vigo AG, Arroyo R, Meca V, Malhotra S, Fissolo N, Horga A, Montalban X, Comabella M.

Neurol Neuroimmunol Neuroinflamm. 2014 Dec 11;1(4):e47.

A fit-for-purpose strategy for the risk-based immunogenicity testing of biotherapeutics: a European industry perspective.

Kloks C, Berger C, Cortez P, Dean Y, Heinrich J, Bjerring Jensen L, Koppenburg V, Kostense S, Kramer D, Spindeldreher S, Kirby H.

J Immunol Methods. 2015 Jan 17

Regulation of immune responses to protein therapeutics by transplacental induction of T cell tolerance.

Gupta N, Culina S, Meslier Y, Dimitrov J, Arnoult C, Delignat S, Gangadharan B, Lecerf M, Justesen S, Gouilleux-Gruart V, Salomon BL, Scott DW, Kaveri SV, Mallone R, Lacroix-Desmazes S.

Sci Transl Med. 2015 Feb 18;7(275):275ra21.

Significance of low level infliximab in the absence of anti-infliximab antibodies.

Ungar B, Anafy A, Yanai H, Ron Y, Yavzori M, Picard O, Fudim E, Loebstein R, Kopylov U, Chowers Y, Dotan I, Eliakim R, Ben-Horin S.

World J Gastroenterol. 2015 Feb 14;21(6):1907-14.

Alloantibodies to therapeutic factor VIII in hemophilia A: the role of von Willebrand factor in regulating factor VIII immunogenicity.

Oldenburg J, Lacroix-Desmazes S, Lillicrap D.

Haematologica. 2015 Feb;100(2):149-156.

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
1000 people worldwide during 2014!**