ABIRISK

EXTERNAL NEWSLETTER

ISSUE 15 - SEPTEMBER 2016

WWW.ABIRISK.EU

Dear colleagues, dear friends and supporters of ABIRISK,

we are pleased to present you the fifteenth 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.'

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PROJECT NEWS

NEW ABIRISK PROJECT COORDINATOR

We are pleased to announce that **Sebastian Spindeldreher** (ABIRISK Partner 30 Novartis Pharma AG), is taking over the project coordinator role from **Dan Sikkema** (ABIRISK Partner 1 GlaxoSmithKline Research & Development Limited-GSK), who decided to pursue new opportunities outside of GSK and therefore can't contribute the project any longer. **Sebastian** has been involved in the project from the very beginning as co-author of the IMI call, deputy coordinator and co-leader of work package 3.
Despite taking the role as project coordinator, **Sebastian** will stay co-leader of WP3. We wish Dan all the best for his professional and private live and Sebastian success in his new role.

ABIRISK 2016 Steering Committee Meeting

ABIRISK
EXECUTIVE PROJECT MANAGEMENT TEAM AND STEERING COMMITTEE MEETING
SEPTEMBER 21st-22nd 2016 - IPSEN - LES ULIS, FRANCE

On the **21st and 22nd September 2016**, the **2016 Steering Committee Meeting of ABIRISK Project** was held in Paris (France) at the **IPSEN Innovation Centre (ABIRISK Partner 37)**.

ABIRISK 2016 Steering Committee Meeting was organized mainly for the Principal Investigators of the project and about 40 participants attended the meeting in Paris.

The meeting started with the Executive Project Management Team (EPMT) meeting. **EPMT meeting** was focused on main issues, objectives and expectations for the ABIRISK Project in the reference period. Particular attention was dedicated to discuss and share important items related to the optimization of the ABIRISK budget management and project sustainability.

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In order to increase awareness and improve the visibility to the **ABIRISK project** aims, objectives and expectations as well to the most important results achieved from the project so far, the first day of the 2016 ABIRISK Steering Committee meeting was closed by the **Symposium "Immunogenicity Management"** opened also to all IPSEN collaborators.

The ABIRISK Symposium Program was opened by the presentation of **Marc Pallardy** (ABIRISK Managing Entity; ABIRISK Partner 2 Institut National de la Santé et de la Recherche Médicale – INSERM) focused on the problem of the anti-biopharmaceutical immunization, the ABIRISK focus, outcome and the project organization. Marc' presentation was followed by **Florian Deisenhammer** (ABIRISK Partner 18 Medizinische Universität Innsbruck) talk titled **"Clinical consequences of anti-drug antibodies in autoimmune diseases and hemophilia A"** and **Bernard Maillère** (ABIRISK Partner 5 Commissariat à l'énergie atomique et aux énergies alternative - CEA) presentation titled **"How to predict immunogenicity of therapeutic proteins"**.
The **ABIRISK Symposium** was closed by the presentation of **Matthieu Allez** (ABIRISK Partner 12 Groupe d'Etudes Therapeutiques des Affections Inflammatoires du Tube Digestif – GETAID) titled **"How to manage immunogenicity in the clinic"**.

The second day of the meeting was fully dedicated to the **Steering Committee meeting**. The Steering Committee meeting started with a general update on the most important project news of the period including also the management of the amendments n. 5 and 6 to the project, and the fourth periodic report. The rest of the Steering Committee meeting was dedicated to the presentation of the scientific achievements reached in the period as well as on the planned activities for the next reporting period of the project that was followed by the discussion and formal vote on the project budget modifications.

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ABIRISK presented at key immunogenicity meetings

At the **32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)**, held in London, UK, on 14-17 September 2016, **Marsilio Adriani (ABIRISK Partner 8 University College London - UCL)** gave an oral presentation entitled **"Immunological profile of peripheral blood mononuclear cells (PBMCs) as a tool to understand the development of anti-drug immune responses in multiple sclerosis."**

The ECTRIMS Congress offered comprehensive and exciting scientific and teaching programmes. Themes included disease mechanisms, prognostic markers, developments in imaging, approaches to early treatment, the latest clinical trial results, and emerging targets for modulation of the innate immune system, neuroprotection and repair. While Multiple Sclerosis (MS) was the main focus, there were talks on other inflammatory demyelinating CNS diseases. There was a special section of the programme for MS nurses and symposia sponsored by the European Charcot Foundation and industry. The meeting was also partner with the Annual Conference of Rehabilitation in MS (RIMS).

UPCOMING EVENTS

THIRD ANNUAL DISPLAY OF ANTIBODIES

Lisboa, Portugal - 31th October/1st November 2016

Display of antibodies is the engine responsible for the proliferation of novel constructs that are advancing into clinical studies. This meeting will showcase the latest technologies and applications including antibody generation, targeting ion channels and GPCRs, engineering antibodies against immunotherapy targets, phenotypic screening and enhancing developability. Learn how the experts have made significant progress and uncover innovative approaches for improving library design and biophysical properties of biologics, as well as gain insight from a heightened understanding of the immune system.

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UPCOMING EVENTS

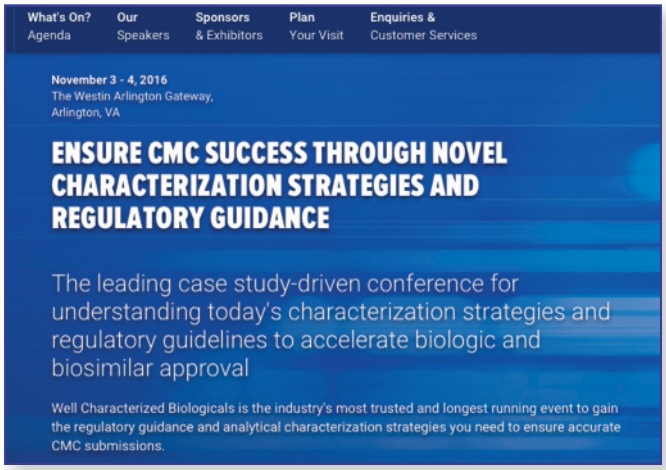
WELL CHARACTERIZED BIOLOGICALS

Arlington, VA, USA - 3rd October/4th November 2016

Ensure CMC success through novel characterization strategies and regulatory guidance

The leading case study-driven conference for understanding today's characterization strategies and regulatory guidelines to accelerate biologic and biosimilar approval

Well Characterized Biologicals is the industry's most trusted and longest running event to gain the regulatory guidance and analytical characterization strategies you need to ensure accurate CMC submissions.



NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

Circulating T cells to infliximab are mainly detectable in treated patients developing anti-drug antibodies and hypersensitivity reactions

Vultaggio A, Petroni G, Pratesi S, Nencini F, Cammelli D, Milla M, Prignano F, Annese V, Romagnani S, Maggi E, Matucci A; ABIRISK Consortium

Clin Exp Immunol. 2016 Aug 29. doi: 10.1111/cei.12858. [Epub ahead of print]

Antibodies recognizing infliximab (IFX) may develop in a proportion of treated patients leading to loss of response or hypersensitivity reactions (HRs). T cell response to IFX has been poorly investigated.

The aim of this paper was addressed to detect IFX-specific T cells in treated patients with inflammatory diseases developing, or not, anti-drug antibodies (ADA) and to correlate the presence of specific T cells with the clinical outcomes of the treatment. Co-culture system of IFX-loaded dendritic cells and purified autologous CD4+ T cells was used to detect memory T cells in 32 ADA+ and 39 ADA- IFX-treated patients and control groups. The cytokine profile of IFX-specific T cells was also studied in culture supernatants.

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NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

IFX-specific cell proliferation was detected mainly in cells from ADA+ patients, irrespective to their different diseases. HRs patients displayed higher T cell proliferation than non-responder and tolerant patients. A mixed (IFN-γ, IL-13, IL-10) cytokine profile was shown in cells from ADA+ patients, while IL-10 was the most frequently detected cytokine in the supernatants of cultures from ADA- patients. IgE+ADA+ patients with previous HRs exhibited a more pronounced type-2 profile than IgE-ADA+ patients.

This work provides evidence that IFX-specific circulating T cells are mainly detectable in ADA+ patients with HRs, regardless of their disease. The IFX-induced cytokine pattern partially correlates with the ADA isotype.

Effect of growth hormone and IgG aggregates on dendritic cells activation and T-cells polarization
Gallais Y, Szely N, Legrand FX, Leroy A, Pallardy M, Turbica I, on behalf of the ABIRISK Consortium
Immunol Cell Biol. 2016 Oct 7. doi: 10.1038/icb.2016.100. [Epub ahead of print]

Patients treated with therapeutic biological products (BP) frequently develop anti-drug antibodies (ADA) with potential neutralizing capacities leading to loss of clinical response, or serious side effects. BP aggregates have been suggested to promote immunogenicity thus enhancing ADA production. Dendritic cells (DC) are key effectors in T-cell and B-cell fates and the subsequent generation of immunogenicity. The objective of this work was to determine if BP aggregates can participate to DC maturation and T-cell activation.

The authors of this manuscript compared aggregates from three different proteins: human growth hormone (hGH), Rituximab, a chimeric anti-CD20 antibody and a serum-purified human IgG1. All three proteins underwent a stir stress, generating comparable populations of aggregated particles. Maturation of human monocyte-derived DC (moDC) upon exposure to native BPs or aggregates was evaluated in vitro.

Results showed that hGH aggregates induced an increased expression of moDC co-stimulation markers, and augmented levels of IL-6, IL-8, IL-12p40, CCL2, CCL3, CCL4 and CXCL10. Both antibodies aggregates were also able to modify DC phenotype but cytokine and chemokine productions were seen only with IL-6, IL-8, IL-12p40 and CXCL10. Aggregates-treated moDC enhanced allogenic T-cell proliferation and cytokines production suggesting Th1 polarization with hGH, and mixed T-cell responses with antibodies aggregates.

The results presented in this manuscript showed that BP aggregates provoked DC maturation thus driving adaptive T-cell responses and polarization.

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RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Immunogenicity of tocilizumab in patients with rheumatoid arthritis
Sigaux J, Hamze M, Daien C, Morel J, Krzysiek R, Pallardy M, Maillere B, Mariette X, Miceli-Richard C.
Joint Bone Spine. 2016 Jun 28. pii: S1297-319X(16)30101

Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study
Batsuli G, Meeks SL, Herzog RW, Lacroix-Desmazes S.
Haemophilia. 2016 Jul;22 Suppl 5:31-5

Design of TRUST, a non-interventional, multicenter, 3-year prospective study investigating an integrated patient management approach in patients with relapsing-remitting multiple sclerosis treated with natalizumab
Ziemssen T, Gass A, Wuerfel J, Bayas A, Tackenberg B, Limmroth V, Linker R, Mäurer M, Haas J, Stangel M, Meergans M, Harlin O, Hartung HP
BMC Neurol. 2016 Jul 12;16(1):98

Innovating immune tolerance induction for haemophilia
Batsuli G, Meeks SL, Herzog RW, Lacroix-Desmazes S.
Haemophilia. 2016 Jul;22 Suppl 5:31-5

Precision medicine in multiple sclerosis: biomarkers for diagnosis, prognosis, and treatment response
Comabella M, Sastre-Garriga J, Montalban X.
Curr Opin Neurol. 2016 Jun;29(3):254-62.

Key insights to understand the immunogenicity of FVIII products
Goudemand J, Peyvandi F, Lacroix-Desmazes S.
Thromb Haemost. 2016 Aug 31;116(Suppl. 1):S2-S9

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Crowdsourced assessment of common genetic contribution to predicting anti-TNF treatment response in rheumatoid arthritis
Sieberts SK, Zhu F, García-García J, Stahl E, Pratap A, Pandey G, Pappas D, Aguilar D, Anton B, Bonet J, Eksi R, Fornés O, Guney E, Li H, Marín MA, Panwar B, Planas-Iglesias J, Poglayen D, Cui J, Falcao AO, Suver C, Hoff B, Balagurusamy VS, Dillenberger D, Neto EC, Norman T, Aittokallio T, Ammad-Ud-Din M, Azencott CA, Bellón V, Boeva V, Bunte K, Chheda H, Cheng L, Corander J, Dumontier M, Goldenberg A, Gopalacharyulu P, Hajiloo M, Hidru D, Jaiswal A, Kaski S, Khalfaoui B, Khan SA, Kramer ER, Marttinen P, Mezlini AM, Molparia B, Pirinen M, Saarela J, Samwald M, Stoven V, Tang H, Tang J, Torkamani A, Vert JP, Wang B, Wang T, Wennerberg K, Wineinger NE, Xiao G, Xie Y, Yeung R, Zhan X, Zhao C; Members of the Rheumatoid Arthritis Challenge Consortium, Greenberg J, Kremer J, Michaud K, Barton A, Coenen M, Mariette X, Miceli C, Shadick N, Weinblatt M, de Vries N, Tak PP, Gerlag D, Huizinga TW, Kurreeman F, Allaart CF, Louis Bridges S Jr, Criswell L, Moreland L, Klareskog L, Saevarsdottir S, Padyukov L, Gregersen PK, Friend S, Plenge R, Stolovitzky G, Oliva B, Guan Y, Mangravite LM, Bridges SL, Criswell L, Moreland L, Klareskog L, Saevarsdottir S, Padyukov L, Gregersen PK, Friend S, Plenge R, Stolovitzky G, Oliva B, Guan Y, Mangravite LM.
Nat Commun. 2016 Aug 23;7:12460.

A Regulatory Feedback between Plasmacytoid Dendritic Cells and Regulatory B Cells Is Aberrant in Systemic Lupus Erythematosus
Menon M, Blair PA, Isenberg DA, Mauri C.
Immunity. 2016 Mar 15;44(3):683-97.

Ocrelizumab for the treatment of relapsing-remitting multiple sclerosis
Menge T, Dubey D, Warnke C, Hartung HP, Stüve O.
Expert Rev Neurother. 2016 Aug 23

The 11-year long-term follow-up study from the randomized BENEFIT CIS trial
Kappos L, Edan G, Freedman MS, Montalbán X, Hartung HP, Hemmer B, Fox EJ, Barkhof F, Schippling S, Schulze A, Pleimes D, Pohl C, Sandbrink R, Suarez G, Wicklein EM; BENEFIT Study Group.
Neurology. 2016 Aug 10

Drivers of costly treatment strategies in rheumatoid arthritis
Huizinga TW, Gröndal G.
Lancet. 2016 Jul 16;388(10041):213-4

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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!

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