ABIRISK

EXTERNAL NEWSLETTER

ISSUE 11 - SEPTEMBER 2015

WWW.ABIRISK.EU

Dear colleagues, dear friends and supporters of ABIRISK,

we are pleased to present you the eleventh 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.'

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PROJECT NEWS

ABIRISK 2015 STEERING COMMITTEE MEETING

On the **5th and 6th October 2015**, the **2015 Steering Committee Meeting of ABIRISK Project** was held in Vienna (Austria) at the **Austria Center Vienna.**

ABIRISK 2015 Steering Committee Meeting was organized mainly for the Principal Investigators of the project and about 40 participants attended the meeting in Copenhagen.

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. 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 management of the third periodic report that was followed by the discussion and formal vote on the new project budget. The rest of the Steering Committee meeting was dedicated to the presentation of the scientific and dissemination achievements reached in the period as well as on the plan for the next phase of the project.

In order to increase awareness and improve the visibility to the international scientific community on **ABIRISK project** aims, objectives and expectations, the 2015 ABIRISK Steering Committee meeting was organized in the same location and in coincidence with the **4th European Congress of Immunology (ECI).** To the same aim, the ABIRISK Consortium organized the **Satellite Symposium on Immunogenicity of Biopharmaceuticals** that was held just before the open ceremony of the ECI.

The ABIRISK Symposium Program included the presentation of **Florian Deisenhammer**, (ABIRISK Partner 18 Medizinische Universität Innsbruck) titled **"Drug immunogenicity - what does it mean for treatment of patients?".** Florian' talk was followed by **Claudia Mauri** (ABIRISK Partner 8 University College London) presentation titled **"Global immunophenotyping as a tool to predict immunogenicity in autoimmune disorders".**

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The ABIRISK Symposium was closed by the presentation of **Bernard Maillère** (ABIRISK Partner 5 Commissariat à l'énergie atomique et aux énergies alternative) titled **"CD4+ T cell response to biopharmaceuticals in healthy donors as a tool of prediction of immunogenicity".**

About one hundred of ECI participants attended the ABIRISK Symposium and, more important, lots of discussions amongst ABIRISK Symposium participants have taken place after each presentation as well as at the end of the ABIRISK Symposium .

The ABIRISK Symposium

ABIRISK presented at key immunogenicity meetings

At the **4th European Congress of Immunology** (ECI - Vienna, Austria, 6-9 September 2015) several ABIRISK Partners presented data related to ABIRISK Project.
ABIRISK Partner 3 Università di Firenze submitted three abstracts on behalf of the ABIRISK Consortium two of which were selected for oral presentations in the "Drug Immunogenicity and Biomarkers of Efficacy" session (***Detection of cell sensitization to infliximab in treated patients without anti-drug antibodies*** *by A. Vultaggio, F. Nencini, S. Pratesi, A. Matucci, E. Maggi* and ***Identification of T cell response to infliximab peptides in treated patients*** *by S. Pratesi, F. Nencini, E. Maggi, A. Matucci, A. Vultaggio).*

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In addition the following posters were presented at the ECI on behalf of ABIRISK Consortium:

PARTNER	TITLE
3- Università di Firenze UNIFI	**Anti-infliximab antibodies production and clinical consequences: adverse reaction and loss of response** A. Matucci, A. Vultaggio, F. Nencini, S. Pratesi, E. Maggi
17-Karolinska Institutet KI	**Descriptive analysis of differences in testing of antibodies against interferon beta and natalizumab in European multiple sclerosis patients - data from ABIRISK** J. Link, R. Ramanujam, M.Auer, S. Hässler, D. Bachelet, C. Sievers, PE Jensen, C. Warnke, K.Ingenhoven, D. Buck, B. Hemmer, V. Grummel, B. Kieseier, HP Hartung, P. Soelberg Soerensen, N. Fissolo, M.Comabella, X. Montalban, R. Lindberg, T. Derfuss, F. Deisenhammer, C. Mbogning, P. Broët, A. Lawton, J. Davidson, P. Dönnes, A.Fogdell-Hahn on behalf of ABIRISK Consortium
5-Commissariat à l'Energie Atomique et aux Energies Alternatives -CEA	**Comprehensive analysis of the CD4 T cell epitopes of chimeric therapeutic antibodies Infliximab and Rituximab identified in healthy donors and immunized patients** Moustafa Hamze, Sylvain Meunier, Amélie Goudet Abdelaziz Gdoura, Natacha Szely, Marc Pallardy, Franck Carbonnel, Xavier Mariette, Corinne Miceli-Richard and Bernard Maillère.
27-DRK-Blutspendedienst Baden-Württemberg - Hessen gemeinnützige GmbH - DRK-BSD	**FVIII tolerization in a hemophilic mouse model** P. Milanov, P. Quade-Lyssy, S. Roth[1], E. Seifried, A. Pashov, S. Lacroix-Desmazes, J. Schüttrumpf, J. Schwäble
2- Institut National de la Santé et de la Recherche Médicale - INSERM	**Effect of protein aggregates from therapeutic proteins on dendritic cells maturation: Examples of Rituximab and Somatropin** Y Gallais, N Szely, F-X Legrand, A Leroy, M Pallardy and I Turbica
2- Institut National de la Santé et de la Recherche Médicale - INSERM	**Risk factors of anti-drug antibodies occurrence in multiple sclerosis** Delphine Bachelet* (INSERM), Signe Hässler (INSERM)*, Cyprien Mbogning (INSERM), Jenny Link (KI), Ryan Ramanujam (KI), Michael Auer (IMU), Poul Erik Hyldgaard Jensen (RegionH), Clemens Warnke (UKD), Kathleen Ingenhoven (UKD), Dorothea Buck (TUM-Med), Verena Grummel (TUM-Med), Bernd Kieseier (UKD), Bernard Hemmer (TUM-Med), Hans Peter Hartung (UKD), Per Soelberg Sorensen (RegionH), Florian Deisenhammer (IMU), Pierre Dönnes (Scicross), Julie Davidson (GSK), Anna Fogdell-Hahn (KI) and Philippe Broët (INSERM), on behalf of ABIRISK Consortium **these authors contributed equally to the work*

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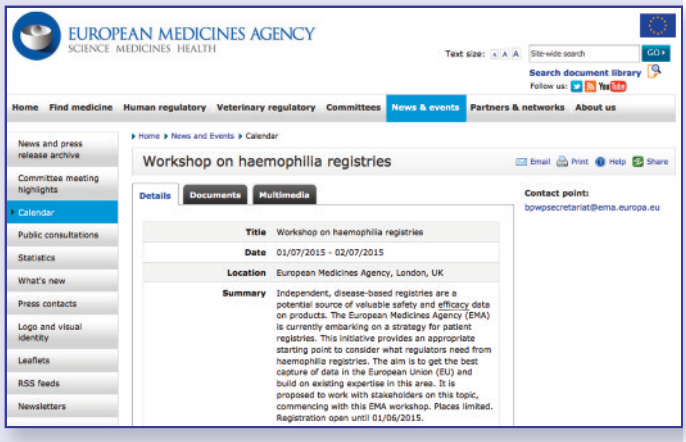
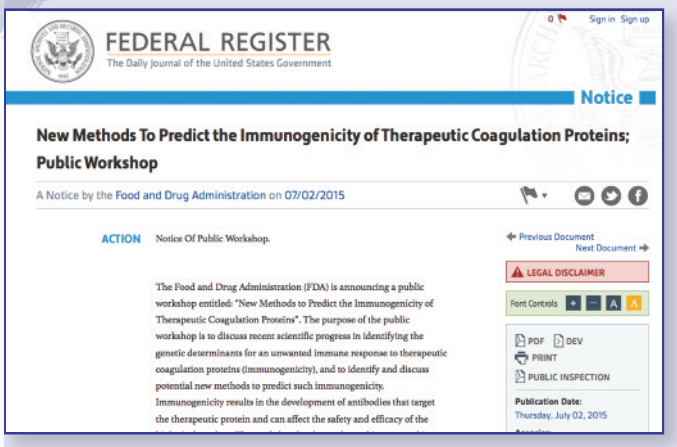
At the **Workshop on Haemophilia Registries**, taking place at the **European Medicines Agency (EMA)** in London on 1-2 July 2015, **Christine Keipert** (ABIRISK Partner 15 Paul-Ehrlich-Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel) was invited to give a talk about *"Registries - quantity vs quality. An overview of the situation in Europe"*. Christine's presentation was included in the registry session where it was aimed to consider how, on the basis of current experiences, the benefit of data collected in registries to public health can be improved.



At the **U.S. Food and Drug Administration (FDA) workshop entitled,** *"New Methods to Predict the Immunogenicity of Therapeutic Coagulation Proteins"* (17-18 September 2015, Bethesda, Maryland) several ABIRISK Partners were invited to present data related to the ABIRISK Project. The goal of the workshop was to discuss recent scientific progress in identifying the genetic determinants for an unwanted immune response to therapeutic coagulation proteins (immunogenicity), and to identify and discuss potential new methods to predict such immunogenicity. The workshop aimed to address what patients, healthcare professionals and regulators may do with this information to improve patient outcomes.

Dan Sikkema (Project Coordinator, ABIRISK Partner 1 GlaxoSmithKline Research & Development Limited) presented the ABIRISK Consortium and participated in the Panel Discussion *"Preclinical Assessments of Immunogenicity: Are they useful? Can they inform clinical trials"*, **Timothy Hickling** (ABIRISK Partner 29 Pfizer Limited) participated in the Panel Discussion *"What do we do with the genetic information: Are pharmacogenomic GWAS studies even possible?"* and **Johannes Oldenburg** (ABIRISK Partner 14 Universitaetsklinikum Bonn) was part of the program steering committee and chaired a session on registry initiatives of Anti-Drug Antibodies in Haemophilia and led the panel discussion on Genetic Determinants of Immunogenicity.



Anna Fogdell-Hahn (ABIRISK Partner 17 Karolinska Institutet) was invited to give a keynote lecture as part of the **Pfizer Immunogenicity Research Forum** (15-16 September 2015, Nice, France). Anna' lecture was entitled *"Exchanging experience of immunogenicity across different disease areas"* and it was focused on most important items related to the immunogenicity of biopharmaceuticals as well as on how the ABIRISK Project is contributing in improving the knowledge in the field.

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UPCOMING EVENTS

2015 AAPS ANNUAL MEETING AND EXPOSITION
Orlando, USA, 25-29, October 2015

The 2015 AAPS ANNUAL MEETING is focused on seven themes:
Big Data: Find out how to make more informed decisions about appropriate clinical candidates, optimize dosing regimens and accelerate drug development with cutting-edge techniques such as microdialysis combined with molecular imaging or highly sensitive bioanalysis methods.

Drug Delivery Technology: The range of topics include drug absorption enablement; peptide delivery; delivery to the brain; personalized medicine and more. Learn about the challenges and opportunities that impact all drug delivery formats: oral, parenteral, ocular, transdermal, 3-D printed and more.

Impurities: Examine the challenges of identifying and controlling impurities such as heavy metal and mutagenic impurities to assure purity and potency of the final delivery system.

Microdialysis, Imaging, Target Site: Discuss how using cutting-edge techniques such as microdialysis and molecular imaging link site specific drug concentration and effects and facilitate more informed decisions about appropriate clinical candidates, accelerated drug development and optimized dosing regimens.

Modeling: Sessions examine the application of quantitative model-based drug development, with a specific focus on innovative translational strategies. Modeling approaches such as physiologically-based pharmacokinetic modeling, quantitative systems pharmacology, site-of-action models, and drug and disease modeling and more.

QbD, Regulatory Challenges: Programming delves into regulatory and QbD aspects including the critical quality attributes of global regulatory harmonization, designing state of the art formulation research and development to comply with international regulations.

Transporters: Internationally renowned experts examine the role of transporters in traditional and non-traditional biological barriers such as the eyes; the potential use of transporters as "therapeutic targets"; plus novel strategies resulting from advances in bioinformatics, proteomics and pharmacogenomics.

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UPCOMING EVENTS

ACR/ARHP ANNUAL MEETING

San Francisco, USA, 06-11, November 2015

Each year, this event features the latest innovations, science, business and clinical best practices. Get first-hand access to the latest discoveries and research transforming rheumatic disease care. Or, focus on clinical applications that will improve health for your patients today. Take time to join your colleagues to focus on the prevention, diagnosis and treatment of rheumatic disease. Experience personalized learning that allows you to expand your knowledge to new areas of interest and focus on your specialty.

16th ANNUAL IMMUNOGENICITY FOR BIOTHERAPEUTICS MEETING

San Francisco, USA, 06-11, November 2015

Improve drug safety analysis with improved, specific, and accurate immunogenicity information, minimize the time it takes to gain regulatory approval and increase speed to market

7th ANNUAL IMMUNOGENICITY AND BIOASSAY SUMMIT

Baltimore, USA, 17-19, November 2015

SUMMIT FEATURES:
7 FDA Presenters ; Access All 3 Conferences for One Price Network with 250+ Global Attendees; Hear 45+ Scientific Presentations;
Learn from FDA, Industry, and Leading Academic Research Centers; Dedicated Exhibit/Poster Viewing; Choose from 4 Short Courses; Interactive Roundtable Breakouts & Panel Discussions; Dedicated Networking Opportunities

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NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

A Bagged, Partially Linear, Tree-Based Regression Procedure for Prediction and Variable Selection
Mbogning C, Perdry H, Broët P.
Hum Hered. 2015;79(3-4):182-93.

In genomics, variable selection and prediction accounting for the complex interrelationships between explanatory variables represent major challenges. Tree-based methods are powerful alternatives to classical regression models. The authors of this manuscript have recently proposed the generalized, partially linear, tree-based regression (GPLTR) procedure that integrates the advantages of generalized linear regression (allowing the incorporation of confounding variables) and of tree-based models. In this work, the authors use bagging to address a classical concern of tree-based methods: their instability.
The authors of this manuscript present a bagged GPLTR procedure and three scores for variable importance. The prediction accuracy and the performance of the scores are assessed by simulation. The use of this procedure is exemplified by the analysis of a lung cancer data set. The aim of this study is to predict the epidermal growth factor receptor (EGFR) mutation based on gene expression measurements, taking into account the ethnicity (confounder variable) and perform variable selection.

Obtained results show that the procedure performs well in terms of prediction accuracy. The scores differentiate predictive variables from noise variables. Based on a lung adenocarcinoma data set, the procedure achieves good predictive performance for EGFR mutation and selects relevant genes.
The authors concluded that the proposed bagged GPLTR procedure performs well for prediction and variable selection.

Development and validation of an enzyme-linked immunosorbent assay to measure adalimumab concentration
Desvignes C, Edupuganti SR, Darrouzain F, Duveau AC, Loercher A, Paintaud G, Mulleman D.
Bioanalysis. 2015;7(10):1253-60.

Adalimumab is a therapeutic antibody used for treating inflammatory diseases. To understand interindividual PK variability, there is a need to develop and validate an assay to measure serum adalimumab concentrations. In this manuscript an ELISA was developed on microtiter plates coated with TNF-α. Seven nonzero adalimumab standards ranging from 0.05 to 50 mg/l and three quality controls (0.2, 2.5 and 7 mg/l) were tested for their intra and interday precision on six occasions.
The obtained results show that the LOD, LLOQ and ULOQ of the assay were 0.022, 0.073 and 9 mg/l, respectively. The authors concluded that the developed method is accurate, reproducible and may be useful for PK studies and for therapeutic drug monitoring of adalimumab.

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RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Anti-drug antibodies: B-cell Immunity against therapy.
Fogdell-Hahn A.
Scand J Immunol. 2015 Jun 22.

Clinical Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies Approved to Treat Rheumatoid Arthritis.
Ternant D, Bejan-Angoulvant T, Passot C, Mulleman D, Paintaud G.
Clin Pharmacokinet. 2015 Jun 28.

Long-Term Safety, Efficacy, and Quality of Life with Intravenous Abatacept in Juvenile Idiopathic Arthritis: Up to 7 Years of Treatment.
Lovell DJ, Ruperto N, Mouy R, Paz E, Rubio-Pérez N, Silva CA, Abud-Mendoza C, Burgos-Vargas R, Gerloni V, Melo-Gomes JA, Saad-Magalhaes C, Chavez-Corrales J, Huemer C, Kivitz A, Blanco FJ, Foeldvari I, Hofer M, Huppertz HI, Deslandre CJ, Minden K, Punaro M, Block AJ, Giannini EH, Martini A; Pediatric Rheumatology Collaborative Study Group (PRCSG); Paediatric Rheumatology International Trials Organization (PRINTO).
Arthritis Rheumatol. 2015 Jun 19.

Clinical Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies Approved to Treat Rheumatoid Arthritis.
Ternant D, Bejan-Angoulvant T, Passot C, Mulleman D, Paintaud G.
Clin Pharmacokinet. 2015 Jun 28. [Epub ahead of print]
Pardeo M, Pires Marafon D, Insalaco A, Bracaglia C, Nicolai R, Messia V, De Benedetti F.
J Rheumatol. 2015 Jun 1

Infliximab-Related Infusion Reactions Systematic Review.
Lichtenstein L, Ron Y, Kivity S, Ben-Horin S, Israeli E, Fraser GM, Dotan I, Chowers Y, Confino-Cohen R, Weiss B.
J Crohns Colitis. 2015 Jun 19.

Role of coagulation-associated processes on factor VIII immunogenicity in a mouse model of severe hemophilia A.
Gangadharan B, Delignat S, Ollivier V, Gupta N, Mackman N, Kaveri SV, Lacroix-Desmazes S.
J Thromb Haemost. 2014 Dec;12(12):2065-9.

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RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Predictors of disease activity in 857 patients with MS treated with interferon beta-1β.
Hartung HP, Kappos L, Goodin DS, O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Jeffery D, Petkau J, White R, Bogumil T, Beckmann K, Stemper B, Suarez G, Sandbrink R, Pohl C.
J Neurol. 2015 Aug 5.

ABIRISK COMMUNICATION TOOLS

PRESS RELEASE

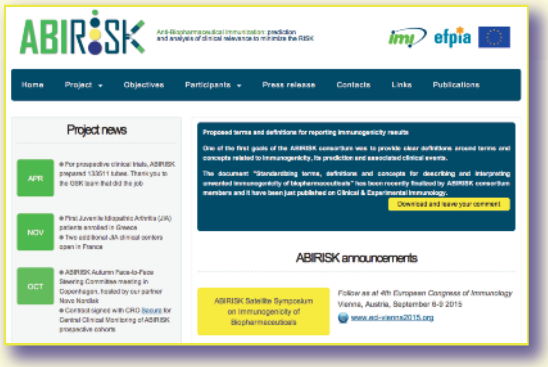
Updating the original version generated by IMI Communication Office, **ABIRISK kick-off meeting fact sheet** has been created to promote ABIRISK project to broad audience mainly through institutional websites of ABIRISK partners, highlighting that the project has been started.

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 1300 people worldwide during the first 8 months of 2015!

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