ABIRISK

EXTERNAL NEWSLETTER

ISSUE 14 - JUNE 2016

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Dear colleagues, dear friends and supporters of ABIRISK,

we are pleased to present you the fourteenth 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

Coral Gables Symposium 2016

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

Coral Gables Symposium offers a unique opportunity to participate in informal discussions with thought leaders from academia, industry, regulatory agencies and clinical practice as well as influence future approaches to the major challenges confronting those active in the field.

Coral Gables Symposia 2016 will provide a unique forum for thought leaders to address the principal concerns regarding **immunogenicity and the patient.** In particular, how an understanding of the immune response to biopharmaceuticals can benefit the patient both in terms of optimizing therapy, mitigating side effects, and improving outcome.

The overall theme of the 2016 Symposium will be:

Immunogenicity and the patient: The Future is Yours

A whole Session of the 4th Coral Gables Symposium will be dedicated to the ABIRISK Project.

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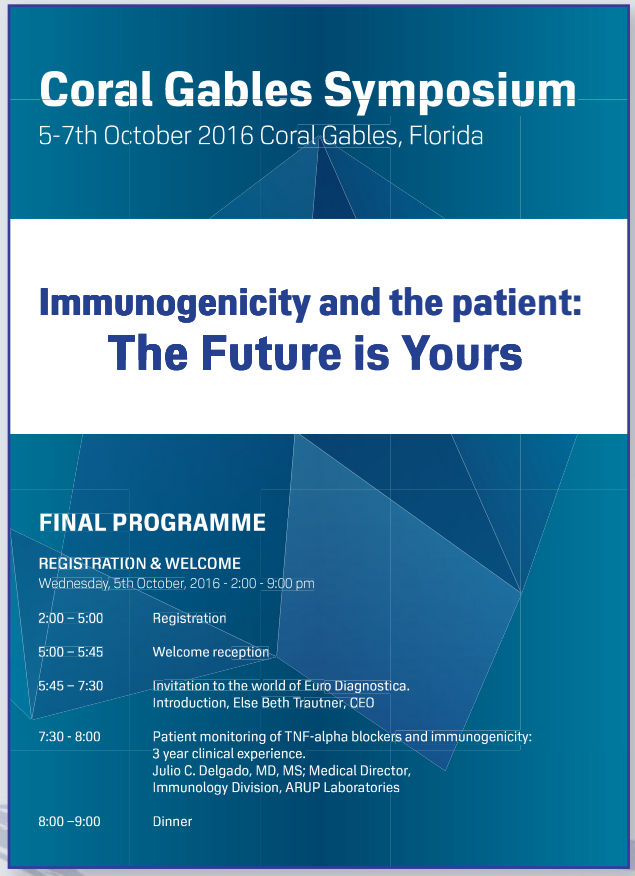
The Session will be entitled **"ABIRISK: CLINICAL RELEVANCE TO MINIMIZE RISK"** and will be chaired by **Dan Sikkema** (ABIRISK Coordinator; ABIRISK Partner 1 GlaxoSmithKline Research & Development Limited - GSK) and **Robin Thorpe** (ABIRISK Scientific Advisory Board Member).

The Session will be 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 will be 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"**, **Liz Jury** (ABIRISK Partner 8 University College London – UCL) **"WP2 – LEGEND Screen: Identification of factors in patients having adverse reactions to biological drugs"** and **Sebastian Spindeldreher** (ABIRISK Partner 30 Novartis Pharma; ABIRISK Work Package 3 co-leader) **"WP3 – Evaluation and development of technologies for predicting immunogenicity"** presentations.



Click to register!

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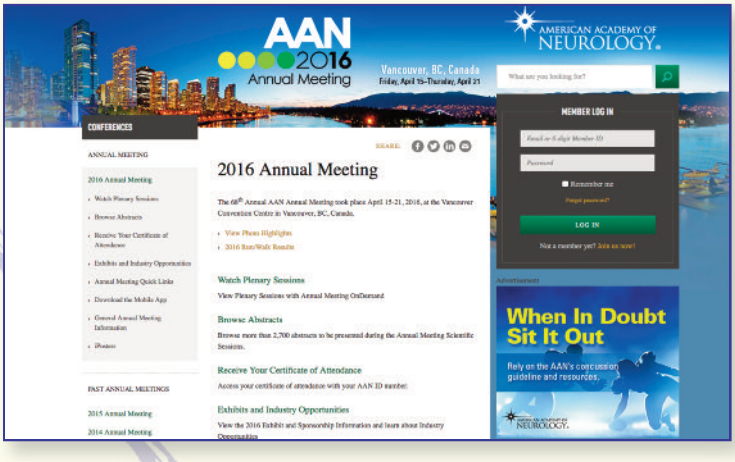
ABIRISK presented at key immunogenicity meetings



At the **68th Annual American Academy of Neurology (AAN) Meeting**, held in Vancouver, Canada, on 15-21 April 2016, **Signe Hässler** (ABIRISK Partner 2 Institut National de la Santé et de la Recherche Médicale - INSERM) gave an oral presentation entitled **"Vitamin D and immunogenicity of IFNβ in multiple sclerosis patients: a case-control study".**
Signe's presentation was included in the Session **"Neuroepidemiology: Movement Disorders, MS, and Stiff Person Syndrome".**
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.

Florian Deisenhammer (ABIRISK Partner 18 Medizinische Universität Innsbruck - IMU) has been invited to give a talk at the **Essential Protein Engineering Summit - PEG**, held in Boston, MA, on 25-29 April 2016.
The summit featured experts from pharma, academia, and government sharing information, case studies, and best practices covering a vast area of biologic drug development and provided in-depth coverage of protein and engineering, immunotherapy oncology, expression, analytical, immunogenicity, and therapeutics.

Florian' talk, entitled **"Linear epitope mapping, binding strength, and neutralization of interferon-beta using patient-derived monoclonal antibodies: Results from ABIRISK"**, was included in the Session **"Immunogenicity: Regulatory and Clinical Case Studies"** of the meeting, focused on case studies of clinical candidates of biological therapies in order to learn the most clinically relevant information for immunogenicity, and also share insights from regulators on winning approaches for ensuring safety of biologic drugs.

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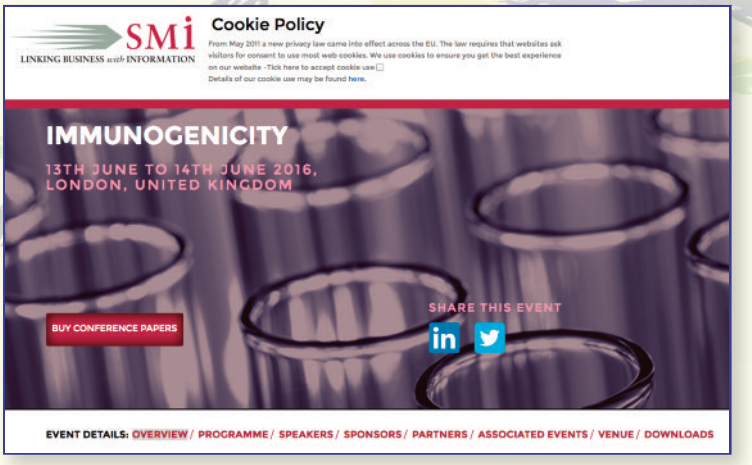
Enrico Maggi (ABIRISK Partner 3 Università di Firenze – UNIFI) presented some ABIRISK data at the **7th Drug Hypersensitivity Meeting of the European Academy of Allergology and Clinical Immunology (EAACI)**, held in Malaga, Spain, on 21–23 April 2016.

Enrico's presentation was included in the Symposium **"Hypersensitivity to chemotherapy and biologicals agents".**

The Drug Hypersensitivity Meeting is an interdisciplinary meeting, bringing together researchers and physicians from different disciplines to exchange their most up-to-date data in this continually evolving field and to transfer it to clinical practice. It is the leading event of its kind, attracting up to 400 physicians and researchers from all over the world.

Dan Sikkema (ABIRISK Coordinator; ABIRISK Partner 1 GlaxoSmithKline Research & Development Limited – GSK) was invited to give a talk entitled **"A Harmonised Approach to Interpretation and Reporting of Clinical Immunogenicity Data"** to the **Immunogenicity Workshop**, held in London, UK, on 13–14 June 2016.



The Immunogenicity Workshop was mainly focused on two topics:

1) Biologics immunogenicity as the major concern for the field of science, due to its impact on safety and efficacy and;

2) Immunogenicity of an antigen in the context of vaccine development .

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UPCOMING EVENTS

INTERNATIONAL CONGRESS OF IMMUNOLOGY

Melbourne, Australia - August 21 - 26, 2016

The International Congress of Immunology (ICI) is the largest global event in the field of immunology. It is held every three years under the auspices of the International Union of Immunological Societies (IUIS). Rio de Janeiro (Brazil), Kobe (Japan) and Milan (Italy) hosted the three previous events, each with an attendance of >5,000 delegates.

Immunology is a vigorous discipline, continually delivering advances in basic and clinical research that affect the lives of billions worldwide. Vaccines save lives, especially among children, and anti-inflammatory drugs improve the quality of life of sufferers of autoimmune diseases such as arthritis, lupus and multiple sclerosis, in particular among the elderly. We are witnessing the emergence of new immunotherapeutic drugs, antibodies and cell-based therapies that promise to revolutionise the treatment of cancer, autoimmunity, allergy and immune deficiencies, and to improve the outcomes of transplantation.

These are exciting times for immunologists, and the ICI 2016 in Melbourne will provide the ideal environment to share new findings, report clinical advances, explore new career opportunities, and establish collaborations amongst scientist, industry and non-for-profit organisations. It will also provide the ideal venue to host public lectures and engage with the media to report new advances to the general public.

The main theme for ICI 2016 is **"Immunotherapy: Harnessing the Power of the Immune System".** This is a timely motto, as we witness the emergence of amazing new immunotherapeutic strategies revolutionising the treatment of cancer, autoimmunity, allergy and immune deficiencies and transplant outcomes. Advances in discovery and development of vaccines for infectious diseases will remain a major focus of the Congress, as will the emerging fields of microbiome-host interactions, new innate cell subsets and immunoregulatory pathways. Progress in immunology is to a large extent driven by new technology, and advances in imaging from the molecular to whole-animal levels, single-cell analysis and deep sequencing will also be showcased in the program. Without forgetting that new advances in immunology are required to save and improve human lives in developing and in developed countries, and among disadvantaged communities such as indigenous populations.

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NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

Bagging survival tree procedure for variable selection and prediction in the presence of nonsusceptible patients

Cyprien Mbogning and Philippe Broët

BMC Bioinformatics. 2016 Jun 7;17(1):230.

For clinical genomic studies with high-dimensional datasets, tree-based ensemble methods offer a powerful solution for variable selection and prediction taking into account the complex interrelationships between explanatory variables. One of the key component of the tree-building process is the splitting criterion. For survival data, the classical splitting criterion is the Logrank statistic. However, the presence of a fraction of nonsusceptible patients in the studied population advocates for considering a criterion tailored to this peculiar situation.


BMC Bioinformatics

Open Access

METHODOLOGY ARTICLE

Bagging survival tree procedure for variable selection and prediction in the presence of nonsusceptible patients

Cyprien Mbogning[1,2*] and Philippe Broët[1,2,3,4]

Abstract

Background: For clinical genomic studies with high-dimensional datasets, tree-based ensemble methods offer a powerful solution for variable selection and prediction taking into account the complex interrelationships between explanatory variables. One of the key component of the tree-building process is the splitting criterion. For survival data, the classical splitting criterion is the Logrank statistic. However, the presence of a fraction of nonsusceptible patients in the studied population advocates for considering a criterion tailored to this peculiar situation.

Results: We propose a bagging survival tree procedure for variable selection and prediction, where the survival tree-building process relies on a splitting criterion that explicitly focuses on time-to-event survival distribution among susceptible patients.

A simulation study shows that our method achieves good performance for the variable selection and prediction. Different criteria for evaluating the importance of the explanatory variables and the prediction performance are reported. Our procedure is illustrated on a genomic dataset with gene expression measurements from early breast cancer patients.

Conclusions: In the presence of nonsusceptible patients among the studied population, our procedure represents an efficient way to select event-related explanatory covariates with potential higher-order interaction and identify homogeneous groups of susceptible patients.

Keywords: Bagging, Survival tree, High-dimensional data, Nonsusceptible individuals, Genomic

Then authors of this manuscript propose a bagging survival tree procedure for variable selection and prediction where the survival tree-building process relies on a splitting criterion that explicitly focuses on time-to-event survival distribution among susceptible patients.

A simulation study shows that the proposed method achieves good performance for the variable selection and prediction. Different criteria for evaluating the importance of the explanatory variables and the prediction performance are reported. The proposed procedure is illustrated on a genomic dataset with gene expression measurements from early breast cancer patients.

The authors conclude that in the presence of nonsusceptible patients among the studied population, the proposed procedure represents an efficient way to select event-related explanatory covariates with potential higher-order interaction and identify homogeneous groups of susceptible patients.

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NEW PUBLICATIONS PRODUCED BY ABIRISK PROJECT

Anti-infliximab Antibodies with Neutralizing Capacity in Patients with Inflammatory Bowel Disease: Distinct Clinical Implications Revealed by a Novel Assay

Roni Weisshof, Bella Ungar, Alexandra Blatt, Aviva Dahan, Sigal Pressman, Matti Waterman, Uri Kopylov, Shomron Ben-Horin, and Yehuda Chowers, on behalf of the ABIRISK consortium

Inflamm Bowel Dis. 2016 Jul;22(7):1655-61.

About 60% of infliximab (IFX)-treated patients develop antidrug antibodies (ADA), although their clinical significance remains disputed. The aim of this study was to develop an assay for assessing ADA-neutralizing potential, and clinical significance.

An immune assay was devised in which the inhibition of IFX binding to plated-tumor necrosis factor in the presence of patient sera or controls, was assessed and defined as IFX–tumor necrosis factor binding reduction ratio (ITBR). The assay was compared to a bioassay in which tumor necrosis factor-α–induced interleukin-8 secretion from HT-29 cells was assessed after addition of IFX to ADA-containing sera or control sera.

Both assays detected neutralizing antibodies in 39 of 44 ADA-positive sera. The median ITBR was 3.66 (mean 4.9 6 3.2) in 29 ADA-positive patients with loss of response (LOR), and 1.3 (mean 1.9 6 1.3) in 15 patients without LOR (P ¼ 0.001). ADA titers in both groups were similar (median 9.5 and 10.2 mg/mL, respectively P ¼ 0.74). Using an ITBR of 1.65, the sensitivity for LOR detection was 86.2% and the specificity was 66.7%. (positive predictive value 83%; negative predictive value 71.4%; P ¼ 0.001). When early ADA-IFX–sera from IFX-treated patients with or without subsequent LOR were compared, the median ITBRs were 1.1 and 0.57, respectively (P ¼ 0.028).


ORIGINAL ARTICLE

Anti-infliximab Antibodies with Neutralizing Capacity in Patients with Inflammatory Bowel Disease: Distinct Clinical Implications Revealed by a Novel Assay

Roni Weisshof, MD,*† Bella Ungar, MD,† Alexandra Blatt, MSc,* Aviva Dahan, PhD,* Sigal Pressman, PhD,* Matti Waterman, MD,*† Uri Kopylov, MD,† Shomron Ben-Horin, MD,†‡ and Yehuda Chowers, MD*† on behalf of the ABIRISK consortium

In conclusion, the detection of neutralizing antibody activity was superior to antibody quantization by enzyme-linked immunosorbent assay with respect to correlation with clinical LOR, and for prediction of subsequent LOR. These findings may assist in optimizing infliximab therapy in patients with inflammatory bowel disease.

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RECENT PUBLICATIONS GENERATED BY ABIRISK PARTICIPANTS OUTSIDE THE PROJECT

Assessing the Immunogenicity of Biopharmaceuticals.
Pineda C, Castañeda Hernández G, Jacobs IA, Alvarez DF, Carini C.
BioDrugs. 2016 Apr 20

Efficacy of abatacept in systemic lupus erythematosus: a retrospective analysis of 11 patients with refractory disease.
Danion F, Rosine N, Belkhir R, Gottenberg JE, Hachulla E, Chatelus E, Pugnet G, Pers YM, Mariette X, Sibilia J, Seror R; Club Rhumatismes et Inflammation section of the French Society of Rheumatology.
Lupus. 2016 Mar 24

Response to interferon-beta treatment in multiple sclerosis patients: a genome-wide association study.
Mahurkar S, Moldovan M, Suppiah V, Sorosina M, Clarelli F, Liberatore G, Malhotra S, Montalban X, Antigüedad A, Krupa M, Jokubaitis VG, McKay FC, Gatt PN, Fabis-Pedrini MJ, Martinelli V, Comi G, Lechner-Scott J, Kermode AG, Slee M, Taylor BV, Vandenbroeck K, Comabella M, Boneschi FM; Australian and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene), King C.
Pharmacogenomics J. 2016 Mar 22.

Neutralisation of factor VIII inhibitors by anti-idiotypes isolated from phage-displayed libraries.
Schmidt A, Brettschneider K, Kahle J, Orlowski A, Becker-Peters K, Stichel D, Schulze J, Braner M, Tampé R, Schwabe D, Königs C.
Thromb Haemost. 2016 Mar 24;116(1).

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.

Biosimilars in Inflammatory Bowel Disease: Facts and Fears of Extrapolation.
Ben-Horin S, Casteele NV, Schreiber S, Lakatos P.
Clin Gastroenterol Hepatol. 2016 May 20.

Activity of secukinumab, an anti-IL-17A antibody, on brain lesions in RRMS: results from a randomized, proof-of-concept study.
Havrdová E, Belova A, Goloborodko A, Tisserant A, Wright A, Wallstroem E, Garren H, Maguire RP, Johns DR.
J Neurol. 2016 May 3.

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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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