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INTRODUCTION

A growing number of medicines are based on biological molecules such as proteins and monoclonal antibodies. These novel drugs have resulted in new, more effective treatments for a number of serious conditions. Yet sometimes these medicines trigger a response from the patient's immune system, which can decrease the effectiveness of the drug or cause severe side effects.

The aim of the IMI-founded ABIRISK project **"Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Relevance to Minimize the Risk",** is to shed new light on the factors behind this immune response. 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 (BPs)** 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.

The ABIRISK consortium (presently made up of thirty-five partners, twenty-four of which are academic institutions, nine are EFPIA member companies and two are small and medium enterprises, with thirteen countries represented), has been designed to meet all of these requirements in order to target three types of disorders: **Hemophilia A, Multiple sclerosis and Inflammatory diseases: inflammatory rheumatisms (including rheumatoid arthritis) and inflammatory bowel diseases.**

ABIRISK Project will collect data both retrospectively from patients suffering from various types of diseases and treated with various BPs at European centers with a high level of experience in clinical research and will prospectively recruit additional patients in dedicated studies during the 5 years of this program. Guidelines and Standard Operating Protocols for the study of anti-drug immunization will be established and used to standardize the collection of prospective data from these patients.

ABIRISK Project thus represents a unique opportunity to create an interdisciplinary task force of clinical centers especially designed to study immune responses against biopharmaceuticals.

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WELCOME

Dear Reader,

We would like to welcome you to **March 2014** issue of the **ABIRISK Scientific Newsletter**. The Scientific Newsletter gives you a monthly update on the most relevant literature related to ABIRISK topics published around the globe, both inside and outside ABIRISK consortium.

This month, we chose to highlight a proof of concept study conducted by Gavasso and colleagues in Norway and published in Plos One, demonstrating the possible use of phosphorylation of Stat1 protein as a surrogate marker of anti-IFNβ neutralizing antibodies effect on INFβ treatment in multiple sclerosis patients.

We are also very pleased to have inserted in the Literature Immunogenicity section, a link to publication by the group of Anna Fogdell-Hahn, from the ABIRISK partner Karolinska Institute in Sweden !

In addition as usual, you will find in this issue some news from the regulatory field of Biotherapeutics, and in particular the consultation is open for the Draft Scientific guideline: Concept paper on the revision of the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins

We look forward to your visit on **ABIRISK** website for more information and updates on the program.

Enjoy reading !

Best wishes

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The ABIRISK management team

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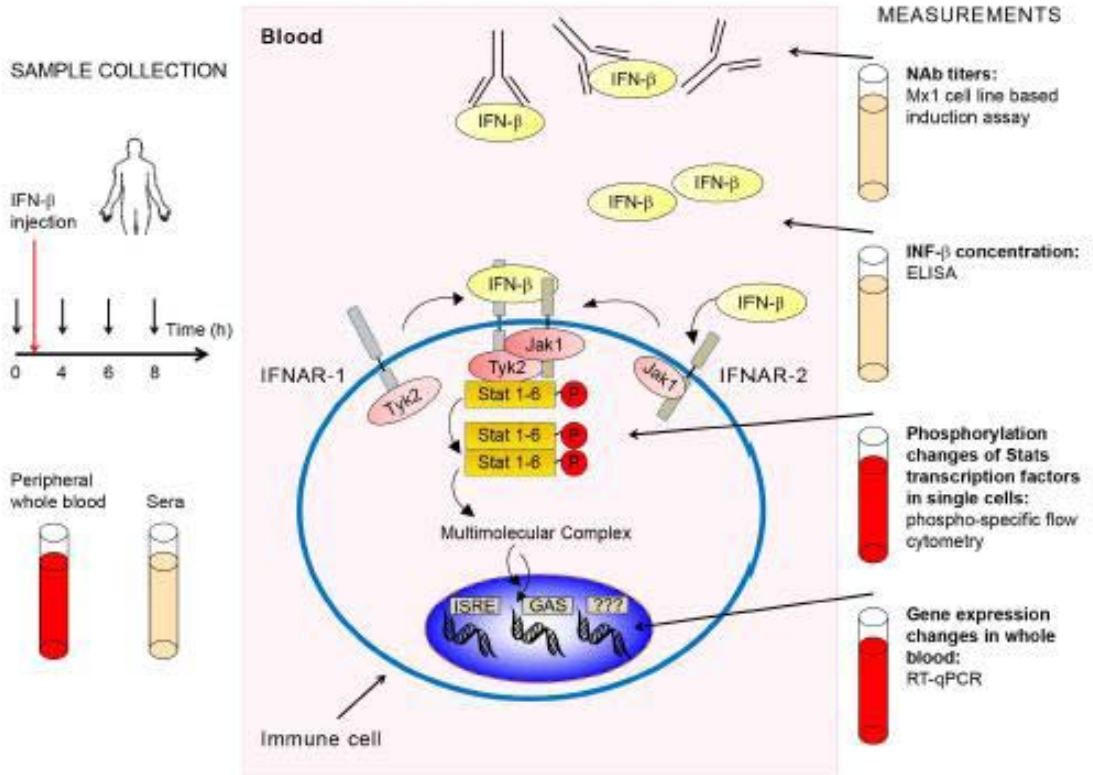
LITERATURE

This month's selected article

In multiple sclerosis (MS) IFNβ-treated patients, dissecting what leads to the formation of anti-IFNβ neutralizing antibodies (NAbs) from what is the consequence of reduced treatment effect remains a challenge. However, it is possible to measure the grade of biological relevance the presence of different titres of NAbs has at the cellular level. Using a phospho-specific flow cytometry approach (phosphoflow), Gavasso *et al.* previously identified pStat1 as a possible biomarker of anti-IFNβ NAbs impact on immune cells responsiveness *ex vivo* (Multiple Sclerosis 2012).

In this proof of concept study, published in PloS One in March, blood samples were taken before and 4, 6 and 8 hours after IFNβ injection, from MS patients who had been treated for 1-5 years and were either negative, low/medium or high IFNβ NAbs positive. IFNβ- specific NAbs, IFNβ serum concentration, gene expression and phosphorylation of Stats were assessed as depicted in the workflow below :



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Principal Component (PCA) and Statistical analyses revealed that the phosphorylation of Stat1 was clearly blocked by anti-IFNβ NAbs. Phosphorylation status assessment was more reliable than gene expression. Moreover, PCA could separate high NAb-positive from medium positive and negative patients. The authors rightly concluded that "Measurements of pathway-specific activation levels of signalling molecules after in vivo IFNβ injection are possible, and phosphorylation patterns of Stat proteins are clearly affected by NAbs."

In light of this paper, assessment of phosphorylation patterns of Stat proteins might be a better way to measure biological relevance of NAbs compared to Mx1 *in vivo* expression, since Stat phosphorylation exhibited both less individual variation and less variation with time after injection.

Deficient phosphorylation of stat1 in leukocytes identifies neutralizing antibodies in multiple sclerosis patients treated with interferon-Beta.
Gavasso S, Mosleth EF, Marøy T, Jørgensen K, Nakkestad HL, Gjertsen BT, Myhr KM, Vedeler C.
PLoS One. 2014 Feb 19;9(2):e88632. doi: 10.1371/journal.pone.0088632. eCollection 2014.

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Immunogenicity

! ABIRISK PUBLICATION !

Human leukocyte antigen genes and interferon Beta preparations influence risk of developing neutralizing anti-drug antibodies in multiple sclerosis.
Link J, Lundkvist Ryner M, Fink K, Hermanrud C, Lima I, Brynedal B, Kockum I, Hillert J, Fogdell-Hahn A.
PLoS One. 2014 Mar 7;9(3):e90479.

Trough s-infliximab and antibodies towards infliximab in a cohort of 79 IBD patients with maintenance infliximab treatment.

Marits P, Landucci L, Sundin U, Davidsdottir L, Nilsson J, Befrits R, Wikström AC, Eberhardson M.

J Crohns Colitis. 2014 Jan 30.

Methods

Innovative Use of LC-MS/MS for Simultaneous Quantitation of Neutralizing Antibody, Residual Drug, and Human Immunoglobulin G in Immunogenicity Assay Development.

Jiang H, Xu W, Titsch CA, Furlong MT, Dodge R, Voronin K, Allentoff A, Zeng J, Aubry AF, Desilva BS, Arnold ME.

Anal Chem. 2014 Feb 17.

Analyzing Subvisible Particles in Protein Drug Products: a Comparison of Dynamic Light Scattering (DLS) and Resonant Mass Measurement (RMM).

Panchal J, Kotarek J, Marszal E, Topp EM.

AAPS J. 2014 Feb 26.

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Animal models

Interleukin-6 Receptor Blockade Enhances CD39+ Regulatory T Cell Development in Rheumatoid Arthritis and in Experimental Arthritis.

Thiolat A, Semerano L, Pers YM, Biton J, Lemeiter D, Portales P, Quentin J, Jorgensen C, Decker P, Boissier MC, Louis-Plence P, Bessis N.

Arthritis Rheumatol. 2014 Feb;66(2):273-83.

Interleukin-10 produced by B cells is crucial for the suppression of Th17/Th1 responses, induction of T regulatory type 1 cells and reduction of collagen-induced arthritis.

Carter NA, Rosser EC, **Mauri C.**

Arthritis Res Ther. 2012 Feb 8;14(1):R32

Biomarkers

A1.25 B-Cell profile in RA patients treated with two different biological therapeutic targets: anti-TNF and anti-IL6R. a cross-sectional study.

Hernández D, Valor L, de la Torre I, Del Río T, Martinez L, Naredo E, González C, Lopez-Longo J, Monteagudo I, Montoro M, Carreño L.

Ann Rheum Dis. 2014 Mar 1;73 Suppl 1:A10-1.

IL2/IL21 region polymorphism influences response to rituximab in systemic lupus erythematosus patients.

Márquez A, Dávila-Fajardo CL, Robledo G, Rubio JL, de Ramón Garrido E, García-Hernández FJ, González-León R, Ríos-Fernández R, Barrera JC, González-Escribano MF, García MT, Palma MJ, del Mar Ayala M, Ortego-Centeno N, Martín J.

Mol Biol Rep. 2013 Aug;40(8):4851-6.

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Predictive Factors of Response to Biological Disease Modifying Antirheumatic Drugs: Towards Personalized Medicine.

Daïen CI, Morel J.

Mediators Inflamm. 2014;2014:386148.

Systemic Lupus Erythematosus

Lupus clinical development: will belimumab's approval catalyse a new paradigm for SLE drug development?

Runkel L, Stacey J.

Expert Opin Biol Ther. 2014 Feb 3.

Therapeutic targeting of the BAFF/APRIL axis in systemic lupus erythematosus.

Stohl W.

Expert Opin Ther Targets. 2014 Feb 13.

Systemic lupus erythematosus: a therapeutic challenge for the XXI century.

Ugarte-Gil MF, Alarcón GS.

Clin Rheumatol. 2014 Feb 28.

In-/off-label use of biologic therapy in systemic lupus erythematosus.

Gatto M, Kiss E, Naparstek Y, Doria A.

BMC Med. 2014 Feb 17;12:30.

Arthritis

Switching of biologic disease modifying anti-rheumatic drugs in patients with rheumatoid arthritis in a real world setting.

Meissner B, Trivedi D, You M, Rosenblatt L.

J Med Econ. 2014 Feb 27.

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The early clinical course of infliximab treatment in rheumatoid arthritis: results from the REMARK observational study.

Westhovens R, van Vollenhoven RF, Boumpas DT, Brzosko M, Svensson K, Bjorneboe O, Meeuwisse CM, Srinivasan S, Gaudin P, Smolen JS, Rahman MU, Nelissen RL, Vastesaeger N.

Clin Exp Rheumatol. 2014 Feb 11.

A1.54 Development of a novel bispecific therapeutic for rheumatoid arthritis.

Ferrari M, Onuoha S, Sblattero D, Pitzalis C.

Ann Rheum Dis. 2014 Mar 1;73 Suppl 1:A23.

Applying biologic therapies to the management of patients with rheumatoid arthritis.

Epstein AA, Kremer JM, Siegel E.

Semin Arthritis Rheum. 2014 Feb;43(4):577.

Safety, effectiveness, and pharmacokinetics of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to 4 years.

Kingsbury DJ, Bader-Meunier B, Patel G, Arora V, Kalabic J, Kupper H.

Clin Rheumatol. 2014 Feb 2.

Inflammatory Bowel Disease

Novel concepts in inflammatory bowel disease.

Moran GW, Dubeau MF, Kaplan GG, Panaccione R, Ghosh S.

Br Med Bull. 2014 Feb 5.

Subcutaneous golimumab therapy for ulcerative colitis.

Lowe AW, Moseley RH.

Gastroenterology. 2014 Jan;146(1):1-2.

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When combination therapy isn't working: Emerging therapies for the management of inflammatory bowel disease.

Krishnareddy S, Swaminath A.

World J Gastroenterol. 2014 Feb 7;20(5):1139-1146.

Moving towards disease modification in inflammatory bowel disease therapy.

Allen PB, Peyrin-Biroulet L.

Curr Opin Gastroenterol. 2013 Jul;29(4):397-404.

Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis.

Panaccione R, Ghosh S, Middleton S, Márquez JR, Scott BB, Flint L, van Hoogstraten HJ, Chen AC, Zheng H, Danese S, Rutgeerts P.

Gastroenterology. 2014 Feb;146(2):392-400.e3.

Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis.

Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, Elmunzer BJ, Saini SD, Vijan S, Waljee AK.

Aliment Pharmacol Ther. 2014 Feb 9.

Adalimumab for Crohn's disease: Long-term sustained benefit in a population-based cohort of 438 patients.

Peters CP, Eshuis EJ, Toxopeüs FM, Hellemons ME, Jansen JM, D'Haens GR, Fockens P, Stokkers PC, Tuynman HA, van Bodegraven AA, Ponsioen CY; On behalf of the North Holland GUT club.

J Crohns Colitis. 2014 Jan 31. pii: S1873-9946(14)00016-6.

Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in adult patients naïve to anti-TNF therapy: An indirect treatment comparison meta-analysis.

Thorlund K, Druyts E, Mills EJ, Fedorak RN, Marshall JK.

J Crohns Colitis. 2014 Jan 31. pii: S1873-9946(14)00014-2.

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Early Trough Levels and Antibodies to Infliximab Predict Safety and Success of Re-initiation of Infliximab Therapy.

Baert F, Drobne D, Gils A, Casteele NV, Hauenstein S, Singh S, Lockton S, Rutgeerts P, Vermeire S.

Clin Gastroenterol Hepatol. 2014 Jan 28. pii: S1542-3565(14)00141-4.

Crohn's disease: a review of treatment options and current research.

Bandzar S, Gupta S, Platt MO.

Cell Immunol. 2013 Nov-Dec;286(1-2):45-52.

New biologic therapeutics for ulcerative colitis and Crohn's disease.

Mozaffari S, Nikfar S, Abdolghaffari AH, Abdollahi M.

Expert Opin Biol Ther. 2014 Feb 6.

In vitro assessment of the effects of vedolizumab binding on peripheral blood lymphocytes.

Wyant T, Yang L, Fedyk E.

MAbs. 2013 Nov 1;5(6):842-50.

Multiple Sclerosis

Atorvastatin Added to Interferon Beta for Relapsing Multiple Sclerosis: 12-Month Treatment Extension of the Randomized Multicenter SWABIMS Trial.

Kamm CP, El-Koussy M, Humpert S, Findling O, Burren Y, Schwegler G, Donati F, Müller M, Müller F, Slotboom J, Kappos L, Naegelin Y, Mattle HP; SWABIMS Study Group.

PLoS One. 2014 Jan 30;9(1):e86663.

Treatment satisfaction, adherence and behavioral assessment in patients de - escalating from natalizumab to interferon beta.

Zecca C, Riccitelli GC, Calabrese P, Pravatà E, Candrian U, Guttmann CR, Gobbi C.

BMC Neurol. 2014 Feb 28;14(1):38.

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An update on new and emerging therapies for relapsing-remitting multiple sclerosis.

Weinstock-Guttman B.

Am J Manag Care. 2013 Nov;19(17 Suppl):s343-54.

Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results.

Butzkueven H, Kappos L, Pellegrini F, Trojano M, Wiendl H, Patel RN, Zhang A, Hotermans C, Belachew S; on behalf of the TYSABRI Observational Program (TOP) Investigators.

J Neurol Neurosurg Psychiatry. 2014 Feb 14.

Hemophilia

Rates of Inhibitor Development in Previously Untreated Patients with Severe Hemophilia A Treated with Plasma-Derived or Recombinant Factor VIII: No Proof of Difference or Proof of No Difference?

Messori A, Fadda V, Maratea D, Trippoli S.

Semin Thromb Hemost. 2014 Mar;40(2):269-70.

Response to "Rates of Inhibitor Development in Previously Untreated Patients with Severe Hemophilia A Treated with Plasma-Derived or Recombinant Factor VIII: No Proof of Difference or Proof of No Difference?".

Franchini M, Mengoli C.

Semin Thromb Hemost. 2014 Mar;40(2):271-2.

Basic immunology

Circadian Clock Proteins and Immunity.

Curtis AM, Bellet MM, Sassone-Corsi P, O'Neill LA.

Immunity. 2014 Feb 20;40(2):178-186.

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Opinions/Commentaries

Biosimilar safety considerations in clinical practice.

Choy E, Allen Jacobs I.

Semin Oncol. 2014 Feb;41 Suppl 1:S3-S14.

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REGULATION

EMA

Scientific guideline: Concept paper on review and update of European Medicines Agency guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products
Draft: consultation open
Consultation end date : 31 May 2014

Scientific guideline: Concept paper on the revision of the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins
Draft consultation open
Consultation start date 25/03/2014
Consultation end date 30/06/2014

Concept paper on
the revision of the gu

Scientific guideline: Draft guideline on the investigation of subgroups in confirmatory clinical trials
Draft : consultation open
Consultation end date : 31 July 2014

Work plan for the Gastroenterology Drafting Group 2014
Updated
February 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Secukinumab, Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
February 2014

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Work plan for the Rheumatology-Immunology Working Party 2014
Updated
February 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Simponi, Golimumab, Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
February 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Humira, Adalimumab, Therapeutic area: Immunology-Rheumatology-Transplantation/Dermatology/Gastroentology-Hepatology
Updated
February 2014

Human medicines European public assessment report (EPAR): Avonex, interferon beta-1a
Revision: 18, Authorised
February 2014

Human medicines European public assessment report (EPAR): Enbrel, etanercept
Revision: 39, Authorised
February 2014

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