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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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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 the third 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 review by Wiendl and Gross in Nature Reviews Neurology on the unexpected mechanisms of action of daclizumab in Multiple Sclerosis patients.
In addition , you will find our usual update on regulation within the Immunogenicity field.

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

Enjoy reading !

Best wishes

The ABIRISK management team

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LITERATURE

This month's selected article

IL-2/IL-2 receptor (IL-2R) interactions are central to T cell differentiation, activation and expansion. Two functional forms of IL-2 receptor exist, one of which being the high affinity receptor, a trimer composed of the IL-2Rß, IL-2Rγc and IL-2Rα (also known as CD25) chains, and primarily expressed by activated T cells. As antigen-specific activated T cells are known to play a major role in the immunopathogenesis of multiple sclerosis disease (MS), disrupting the IL-2/IL-2Rα pathway has been proposed as a new therapeutic approach in MS.

Daclizumab, a humanized IgG1 monoclonal antibody directed against IL-2Rα originally developed and commercialized for prevention of renal allograft rejection, is currently under clinical investigation in MS patients. To date, several clinical trials, including recent randomized double blind comparator studies have established that daclizumab strongly inhibited disease activity and slowed disease progression in patients with MS, with a fairly good tolerability and safety profile.

Interestingly in the present paper, Wiendl and Gross not only review the efficacy and safety data collected through the different clinical studies, but also discuss novel putative mechanisms of action of daclizumab associated with its observed efficacy. When contemplating the use of daclizumab for MS treatment, it was initially postulated that disrupting the IL-2/IL-2R pathway on activated T cells would suppress IL-2-mediated expansion of autoreactive T cell populations, thus resulting in disease amelioration. In fact, a growing body of evidence now supports the hypothesis of the immune balance being ameliorated or restored through enhancement of endogenous mechanisms of immune tolerance, rather than through neutralization of the expansion of deleterious activated T cells.

These so far identified mechanisms involve expansion and stimulation of immune regulatory $CD56^{bright}$ natural killer cells - the most prominent NK cell population in the cerebrospinal fluid, reduction of early T-cell activation through inhibition of IL-2 -mediated cross presentation by dendritic cells, and reduction of the of proinflammatory LTi cells.

Modulation of IL-2Rα with daclizumab for treatment of multiple sclerosis.
Wiendl H, Gross CC.
Nat Rev Neurol. 2013 Jun 4.

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Immunogenicity

Inhibitor development in previously treated Haemophilia A patients: a systematic review, meta-analysis and meta-regression.

Xi M, Makris M, Marcucci M, Santagostino E, Mannucci P, Iorio A.

J Thromb Haemost. 2013 Jun 26.

Allergological in vitro and in vivo evaluation of patients with hypersensitivity reactions to infliximab.

Matucci A, Pratesi S, Petroni G, Nencini F, Virgili G, Milla M, **Maggi E**, **Vultaggio A.**

Clin Exp Allergy. 2013 Jun;43(6):659-64.

The timing of serum infliximab loss, or the appearance of antibodies to infliximab (ATI), is related with the clinical activity in ATI-positive patients with rheumatoid arthritis treated with infliximab.

Plasencia C, Pascual-Salcedo D, Alcocer P, Bonilla MG, Villalba A, Peiteado D, Arribas F, Díez J, Lopez-Casla MT, Martín-Mola E, Balsa A.

Ann Rheum Dis. 2013 Jun 5.

Early development of anti-natalizumab antibodies in MS patients.

Oliver-Martos B, Orpez-Zafra T, Urbaneja P, Maldonado-Sanchez R, Leyva L, Fernández O.

J Neurol. 2013 Jun 14.

Methods

Comparison of Techniques for Monitoring Infliximab and Antibodies Against Infliximab in Crohn's Disease.

Steenholdt C, Ainsworth MA, Tovey M, Klausen TW, Thomsen OO, Brynskov J, Bendtzen K.

Ther Drug Monit. 2013 Jun 12.

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Evaluating the inter and intra batch variability of protein aggregation behaviour using Taylor dispersion analysis and dynamic light scattering.

Hulse WL, Gray J, Forbes RT.

Int J Pharm. 2013 Jun 7.

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Animal methods

Prolonged effect of a new O-glycoPEGylated FVIII (N8-GP) in a murine saphenous vein bleeding model.
Pastoft AE, Ezban M, Tranholm M, Lykkesfeldt J, Lauritzen B.
Haemophilia. 2013 Jun 4.

Tolerance induction in hemophilia A animal models: battling inhibitors with antigen-specific immunotherapies.
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Immune status following alemtuzumab treatment in human CD52 transgenic mice.
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J Neuroimmunol. 2013 Jun 4.

The minipig as an alternative non-rodent model for immunogenicity testing using the TNFα blockers adalimumab and infliximab.
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J Immunotoxicol. 2013 Jun 5.

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Effects of Interferon β-1a and Interferon β-1b Monotherapies on Selected Serum Cytokines and Nitrite Levels in Patients with Relapsing-Remitting Multiple Sclerosis: A 3-Year Longitudinal Study.
Stępień A, Chalimoniuk M, Lubina-Dąbrowska N, Chrapusta SJ, Galbo H, Langfort J.
Neuroimmunomodulation. 2013 May 24;20(4):213-222.

Predictors of response to anti-TNF therapy in RA patients with moderate or high DAS28 scores.
Atzeni F, Bongiovanni S, Marchesoni A, Filippini M, Caporali R, Gorla R, Cavagna L, Favalli EG, Saccardo F, Sarzi-Puttini P.
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Polymorphic alleles in Exon 1 of the CTLA4 gene do not predict the response to abatacept.
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Clin Exp Rheumatol. 2013 May 28.

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Hartung HP, Steinman L, Goodin DS, Comi G, Cook S, Filippi M, O'Connor P, Jeffery DR, Kappos L, Axtell R, Knappertz V, Bogumil T, Schwenke S, Croze E, Sandbrink R, Pohl C.

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Joint Bone Spine. 2013 May 31.

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Mechanisms of disease for the clinician: systemic lupus erythematosus.
Frieri M.
Ann Allergy Asthma Immunol. 2013 Apr;110(4):228-32

Recent progress in conventional and biologic therapy for systemic lupus erythematosus.
Wofsy D.
Ann Rheum Dis. 2013 Apr;72 Suppl 2:ii66-8

Recent insights into the genetic basis of systemic lupus erythematosus.
Rullo OJ, Tsao BP.
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Clin Pharmacokinet. 2013 Jun 11.

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Hochberg MC, Berry S, Broglio K, Rosenblatt L, Nadkarni A, Trivedi D, Hebden T.

Curr Med Res Opin. 2013 Jun 10

Monotherapy with tocilizumab or TNF-alpha inhibitors in patients with rheumatoid arthritis: efficacy, treatment satisfaction, and persistence in routine clinical practice

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Clin Rheumatol. 2013 May 24

Efficiency of adalimumab, etanercept and infliximab in rheumatoid arthritis patients: dosing patterns and effectiveness in daily clinical practice.

Ramírez-Herráiz E, Escudero-Vilaplana V, Alañón-Plaza E, Trovato-López N, Herranz-Alonso A, Morell-Baladrón A, Sanjurjo-Sáez M.

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Ann Rheum Dis. 2013 May 30.

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Treatment choices of paediatric rheumatologists for juvenile idiopathic arthritis: etanercept or adalimumab?

Anink J, Otten MH, Gorter SL, Prince FH, van Rossum MA, van den Berg JM, van Pelt PA, Kamphuis S, Brinkman DM, Swen WA, Swart JF, Wulffraat NM, Dolman KM, Koopman-Keemink Y, Hoppenreijs EP, Armbrust W, Ten Cate R, van Suijlekom-Smit LW.

Rheumatology (Oxford). 2013 Jun 4

Long-Term Safety and Efficacy of Rilonacept in Patients with Systemic Juvenile Idiopathic Arthritis (sJIA).

Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ, Wallace CA, Onel KB, Foell D, Wu R, Biedermann S, Hamilton JD, Radin AR.

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Immunomodulators in Inflammatory Bowel Disease: An Emerging Role for Biologic Agents.

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Novel targets for inflammatory bowel disease therapeutics.

Löwenberg M, D'Haens G.

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Forni D, Cagliani R, Pozzoli U, Colleoni M, Riva S, Biasin M, Filippi G, De Gioia L, Gnudi F, Comi GP, Bresolin N, Clerici M, Sironi M.

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Multiple Sclerosis

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Filippini G, Del Giovane C, Vacchi L, D'Amico R, Di Pietrantonj C, Beecher D, Salanti G.

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Differential microRNA expression in blood in multiple sclerosis.
Søndergaard HB, Hesse D, Krakauer M, Sørensen PS, Sellebjerg F.
Mult Scler. 2013 Jun 17.

Role of regulatory T cells in pathogenesis and biological therapy of multiple sclerosis.
Buc M.
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Future of coagulation factor replacement therapy.
Peyvandi F, Garagiola I, Seregni S.
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MARCH1-mediated MHCII ubiquitination promotes dendritic cell selection of natural regulatory T cells.
Oh J, Wu N, Baravalle G, Cohn B, Ma J, Lo B, Mellman I, Ishido S, Anderson M, Shin JS.
J Exp Med. 2013 Jun 3;210(6):1069-77

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Opinions/Commentaries

Antibodies to watch in 2013: Mid-year update.
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Rescue therapy: ciclosporin or infliximab?
Rizzello F, Praticò C, Calabrese C, Gionchetti P.
Expert Rev Clin Immunol. 2013 Jun;9(6):503-5.

Continuous downstream processing of biopharmaceuticals.
Jungbauer A.
Trends Biotechnol. 2013 Aug;31(8):479-92.

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REGULATION

EMA

Opinion/decision on a Paediatric Investigation Plan (PIP): Humira,adalimumab
Updated
July 2013

Scientific guideline: Draft guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome
July 2013
Draft- Consultation open
Deadline 15th January 2014

EMA IBS guideline.pdf

Orphan designation: Octocog alfa (liposomal) for the treatment of Haemophilia A
Updated
July 2013

Human medicines European public assessment report (EPAR): NovoSeven, eptacog alfa (activated)
Revision: 27, Authorised
July 2013

Human medicines European public assessment report (EPAR): RoActemra, tocilizumab
Revision: 11, Authorised
July 2013

Human medicines European public assessment report (EPAR): Orencia, abatacept
Revision: 15, Authorised
July 2013

FDA

Biological License Application Approvals : Rixubis, Coagulation Factor IX (Recombinant)
For treatment of Haemophilia B
June 2013

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Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring
FDA Guidance for Industry
August 2013

FDA Monitoring guideline.pdf

OTHER NEWS

Announcement

Teva and Lonza Announce Mutual Decision to Discontinue Biologics Joint Venture
July 2013

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