SCIENTIFIC NEWSLETTER — ABIRISK

AUGUST 2015

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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 Re 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.

WELCOME

Dear Reader,

We would like to welcome you to the August 2015 **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.

From now on, we will draw your attention to a selection of articles each month that we think make a difference in their respective fields.

In addition, you will find in this issue some regulatory news on biopharmaceuticals

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

LITERATURE

This month's selected articles

1. During a large period of time starting with the famous human Th1-Th2 paradigm in 1991, T cells were classified in multiple subsets, including Th1 Th2, TH9, TFh, Th17 and Treg. As illustrated by this paper and others, subsets are not fixed and T cells appear to be much more flexible than expected. They could evolved from inflammatory cells to regulatory cells. A direct implication is that the same T cell epitope could either promote inflammation or regulation. T cell epitopes are also not embedded in fixed subsets :

   Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation.
   Gagliani N, Vesely MC, Iseppon A, Brockmann L, Xu H, Palm NW, de Zoete MR, Licona-Limón P, Paiva RS, Ching **T**, Weaver C, Zi X, Pan X, Fan R, Garmire LX, Cotton MJ, Drier Y, Bernstein B, Geginat J, Stockinger B, Esplugues E, Huber S, Flavell RA.
   Nature. 2015 Jul 9;523(7559):221-5.

2. In this article there are examples of samples that are positive in RIA and nonfunctional and non-persistent. These 3 were negative in functional assay and had detectable drug levels. Very unusual for mAbs drugs, but an example of what we see for interferon beta:

   Time Course and Clinical Implications of Development of Antibodies Against Adalimumab in Patients With Inflammatory Bowel Disease.
   Steenholdt C, Frederiksen MT, Bendtzen K, Ainsworth MA, Thomsen OØ, Brynskov J.
   J Clin Gastroenterol. 2015 Jul 9.

3. An essential paper for anyone working with assay development and validation:

   Recommendations for the development and validation of confirmatory anti-drug antibody assays.
   Jani D, Marsden R, Mikulskis A, Gleason C, Klem T, Krinos Fiorotti C, Myler H, Yang L, Fiscella M.
   Bioanalysis. 2015 Jul;7(13):1619-31.

4. The role of aggregates in the immunogenicity of biologics is a major concern. A recent US FDA guidance on the issue suggests that a gap in knowledge exists regarding the type and size of aggregates involved in the immunogenicity of biologics. In this work, the authors generated and classified aggregates of two therapeutic antibodies based on size and conformation. Despite the fact that immunogenicioty was tested in a murine model this paper gives informations on the putative role of the size of the aggregates in the immunogenic potential of aggregates:

   The Effect of Small Oligomeric Protein Aggregates on the Immunogenicity of Intravenous and Subcutaneous Administered Antibodies.
   Fathallah AM, Chiang M, Mishra A, Kumar S, Xue L, Middaugh R, Balu-Iyer SV.
   J Pharm Sci. 2015 Jul 30.

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Immunogenicity

Time Course and Clinical Implications of Development of Antibodies Against Adalimumab in Patients With Inflammatory Bowel Disease.
Steenholdt C, Frederiksen MT, Bendtzen K, Ainsworth MA, Thomsen OØ, Brynskov J.
J Clin Gastroenterol. 2015 Jul 9.

Antibody-drug conjugates nonclinical support: from early to late nonclinical bioanalysis using ligand-binding assays.
Kumar S, King LE, Clark TH, Gorovits B.
Bioanalysis. 2015 Jul;7(13):1605-17.

Immunogenicity assessment of monoclonal antibody products: A simulated case study correlating antibody induction with clinical outcomes.
Knezevic I, Kang HN, Thorpe R.
Biologicals. 2015 Jul 25.

Immunogenicity assessment of biotherapeutic products: An overview of assays and their utility.
Wadhwa M, Knezevic I, Kang HN, Thorpe R.
Biologicals. 2015 Jul 2

Methods

The use of an interferon-gamma release assay as a biomarker of response to anti-TNF-alpha treatment.
Cacciapaglia F, Buzzulini F, Arcarese L, Ferraro E, Afeltra A.
Drug Dev Res. 2014 Nov;75 Suppl 1:S50-3.

Multiparameter Flow Cytometric Assays to Quantify Effector and Regulatory T-Cell Function in Multiple Sclerosis.
Sinha S, Crawford MP, Ortega SB, Karandikar NJ.
J Mult Scler (Foster City). 2015 Jan;2(1)

Development of an ELISA based competitive binding assay for the analysis of drug concentration and anti-drug antibody levels in patients receiving adalimumab or infliximab.
Hock BD, Stamp LK, Hayman MW, Keating PE, Helms ET, Barclay ML.
Ther Drug Monit. 2015 Jul 24.

Surface plasmon resonance-based methodology for anti-adalimumab antibody identification and kinetic characterization.
Real-Fernández F, Cimaz R, Rossi G, Simonini G, Giani T, Pagnini I, Papini AM, Rovero P.
Anal Bioanal Chem. 2015 Jul 26

Animal models

[Reduction of inflammation and preservation of neurological function by anti-CD52 therapy in murine experimental autoimmune encephalomyelitis.](#)
Turner MJ, Pang PT, Chretien N, Havari E, LaMorte MJ, Oliver J, Pande N, Masterjohn E, Carter K, Reczek D, Brondyk W, Roberts BL, Kaplan JM, Siders WM.
J Neuroimmunol. 2015 Aug 15;285:4-12.

[Integrated pharmacokinetic, pharmacodynamic and immunogenicity profiling of an anti-CCL21 monoclonal antibody in cynomolgus monkeys.](#)
Dudal S, Subramanian K, Flandre T, Law WS, Lowe PJ, Skerjanec A, Genin JC, Duval M, Piequet A, Cordier A, Jarai G, Van Heeke G, Taplin S, Krantz C, Jones S, Warren AP, Brennan FR, Sims J, Lloyd P.
MAbs. 2015 Jul 31:0.

Biomarkers

[Clinical parameters and biomarkers for anti-TNF treatment prognosis in rheumatoid arthritis patients.](#)
Cuchacovich M, Bueno D, Carvajal R, Bravo N, Aguillón JC, Catalán D, Soto L.
Clin Rheumatol. 2014 Dec;33(12):1707-14.

[Peripheral blood biomarkers in multiple sclerosis.](#)
D'Ambrosio A, Pontecorvo S, Colasanti T, Zamboni S, Francia A, Margutti P.
Autoimmun Rev. 2015 Jul 28.

[Effect of IFN β-1b on CXCR4-dependent chemotaxis in T cells from multiple sclerosis patients.](#)
Wostradowski T, Gudi V, Pul R, Gingele S, Lindquist JA, Stangel M, Lindquist S.
Clin Exp Immunol. 2015 Jul 25.

Systemic Lupus Erythematosus

[Genetics and novel aspects of therapies in systemic lupus erythematosus.](#)
Relle M, Weinmann-Menke J, Scorletti E, Cavagna L, Schwarting A.
Autoimmun Rev. 2015 Jul 9

[The mechanistic impact of CD22 engagement with epratuzumab on B cell function: Implications for the treatment of systemic lupus erythematosus.](#)
Dörner T, Shock A, Goldenberg DM, Lipsky PE.
Autoimmun Rev. 2015 Jul 23. pii: S1568-9972(15)00162-7.

Rheumatoid Arthritis

Efficacy and Safety of Tabalumab, an Anti-B-Cell-Activating Factor Monoclonal Antibody, in a Heterogeneous Rheumatoid Arthritis Population: Results From a Randomized, Placebo-Controlled, Phase 3 Trial (FLEX-O).
Genovese MC, Silverman GJ, Emery P, Gupta RC, Gill A, Veenhuizen M, Xie L, Komocsar WJ, Berclaz PY, Lee C.
J Clin Rheumatol. 2015 Aug;21(5):231-8.

Subcutaneous abatacept in rheumatoid arthritis: current update.
Keystone E, Alkhalaf A, Makkawy M.
Expert Opin Biol Ther. 2015 Aug;15(8):1221-30.

Basics of Drug Development in Rheumatology.
Mina-Osorio P.
Arthritis Rheumatol. 2015 Jul 2

Advances in the treatment of polyarticular juvenile idiopathic arthritis.
Webb K, Wedderburn LR.
Curr Opin Rheumatol. 2015 Sep;27(5):505-10.

Atacicept combination with rituximab in rheumatoid arthritis: randomised Atacicept for redUction of siGns and symptoms in rheUmatoid arthritiS Trial.
van Vollenhoven RF, Wax S, Li Y, Tak PP.
Arthritis Rheumatol. 2015 Jul 2

Are All Biologics the Same? Optimal Treatment Strategies for Patients With Early Rheumatoid Arthritis: Systematic Review and Indirect Pairwise Meta-Analysis.
Albert DA.
J Clin Rheumatol. 2015 Jul 29.

Immunogenetics of rheumatoid arthritis: Understanding functional implications.
Messemaker TC, Huizinga TW, Kurreeman F.
J Autoimmun. 2015 Jul 24.

The use of a multi-biomarker disease activity score as an inclusion criterion in rheumatoid arthritis clinical trials may enhance patient recruitment.
van Vollenhoven RF, Bolce R, Hambardzumyan K, Saevarsdottir S, Forslind K, Petersson IF, Sasso EH, Hwang CC, Segurado OG, Geborek P.
Arthritis Rheumatol. 2015 Jul 20.

Interleukin-34 in rheumatoid arthritis: potential role in clinical therapy.
Zhang F, Ding R, Li P, Ma C, Song D, Wang X, Ma T, Bi L.
Int J Clin Exp Med. 2015 May 15;8(5):7809-15. eCollection 2015.

Intra-articular etanercept treatment in inflammatory arthritis: A randomized double-blind placebo-controlled proof of mechanism clinical trial validating TNF as a potential therapeutic target for local treatment.
Aalbers C, Gerlag D, Vos K, Vervoordeldonk M, Landewé R, Tak PP.
Joint Bone Spine. 2015 Jul 15.

A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy.
Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Baranauskaite A, Tseluyko V, Zhdan VM, Stasiuk B, Milasiene R, Barrera Rodriguez AA, Cheong SY, Ghil J.
Ann Rheum Dis. 2015 Jul 6.

Ten-year drug survival of anti-TNF agents in the treatment of inflammatory arthritides.
Biggioggero M, Favalli EG.
Drug Dev Res. 2014 Nov;75 Suppl 1:S38-41.

Inflammatory Bowel Diseases

Circulating Interleukin 6 and Albumin, and Infliximab Levels Are Good Predictors of Recovering Efficacy After Dose escalation Infliximab Therapy in Patients with Loss of Response to Treatment for Crohn's Disease: A Prospective Clinical Trial.
Suzuki Y, Matsui T, Ito H, Ashida T, Nakamura S, Motoya S, Matsumoto T, Sato N, Ozaki K, Watanabe M, Hibi T.
Inflamm Bowel Dis. 2015 Jul 24.

Anti-tumour Necrosis Factor Treatment with Adalimumab Induces Changes in the Microbiota of Crohn's Disease.
Busquets D, Mas-de-Xaxars T, López-Siles M, Martínez-Medina M, Bahí A, Sàbat M, Louvriex R, Miquel-Cusachs JO, Garcia-Gil JL, Aldeguer X.
J Crohns Colitis. 2015 Jul 4.

The role of integrin antagonists in the treatment of inflammatory bowel disease.
Beniwal-Patel P, Saha S.
Expert Opin Biol Ther. 2014 Dec;14(12):1815-23.

IgE antibodies and skin tests in immediate hypersensitivity reactions to infliximab in inflammatory bowel disease: impact on infliximab retreatment.
Fréling E, Peyrin-Biroulet L, Poreaux C, Morali A, Waton J, Schmutz JL, Guéant JL, Barbaud A.
Eur J Gastroenterol Hepatol. 2015 Jul 15

Positioning Therapy for Ulcerative Colitis.
Grinspan A, Kornbluth A.
Curr Gastroenterol Rep. 2015 Aug;17(8):454.

Adalimumab for the treatment of pediatric Crohn's disease.
Nuti F, Fiorino G, Danese S.
Expert Rev Clin Immunol. 2015 Sep;11(9):963-72

First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis.
Kobayashi T, Suzuki Y, Motoya S, Hirai F, Ogata H, Ito H, Sato N, Ozaki K, Watanabe M, Hibi T.
J Gastroenterol. 2015 Jul 11.

Effects of Concomitant Immunomodulator Therapy on Efficacy and Safety of Anti-TNF Therapy for Crohn's Disease: A Meta-analysis of Placebo-controlled Trials.
Jones JL, Kaplan GG, Peyrin-Biroulet L, Baidoo L, Devlin S, Melmed GY, Tanyingoh D, Raffals L, Irving P, Kozuch P, Sparrow M, Velayos F, Bressler B, Cheifetz A, Colombel JF, Siegel CA.
Clin Gastroenterol Hepatol. 2015 Jun 30

Therapeutic drug monitoring is predictive of loss of response after de-escalation of infliximab therapy in patients with inflammatory bowel disease in clinical remission.
Amiot A, Hulin A, Belhassan M, Andre C, Gagniere C, Le Baleur Y, Farcet JP, Delchier JC, Hüe S.
Clin Res Hepatol Gastroenterol. 2015 Jun 29.

Safety of vedolizumab in the treatment of Crohn's disease and ulcerative colitis.
Hagan M, Cross RK.
Expert Opin Drug Saf. 2015 Jul 3:1-7.

Could therapeutic drug monitoring of anti-TNF-α be useful to consider a de-escalation of treatment?
Flamant M, Roblin X.

Expert Opin Biol Ther. 2015 Jul 20:1-3.
Optimizing Biologic Agents in Ulcerative Colitis and Crohn's Disease.
O'Toole A, Moss AC.
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Biomarkers of Inflammation in Inflammatory Bowel Disease.
Sands BE.
Gastroenterology. 2015 Jul 9. pii: S0016-5085(15)00938-5.

Multiple Sclerosis

Circulating CCR7+ICOS+ Memory T Follicular Helper Cells in Patients with Multiple Sclerosis.
Fan X, Jin T, Zhao S, Liu C, Han J, Jiang X, Jiang Y.
PLoS One. 2015 Jul 31;10(7):e0134523.

Genetic variants associated with autoimmunity drive NFκB signaling and responses to inflammatory stimuli.
Housley WJ, Fernandez SD, Vera K, Murikinati SR, Grutzendler J, Cuerdon N, Glick L, De Jager PL, Mitrovic M, Cotsapas C, Hafler DA.
Sci Transl Med. 2015 Jun 10;7(291):291ra93.

Alemtuzumab in Multiple Sclerosis: Mechanism of Action and Beyond.
Ruck T, Bittner S, Wiendl H, Meuth SG.
Int J Mol Sci. 2015 Jul 20;16(7):16414-39

Effect of high dose vitamin D intake on interleukin-17 levels in multiple sclerosis: A randomized, double-blind, placebo-controlled clinical trial.
Toghianifar N, Ashtari F, Zarkesh-Esfahani SH, Mansourian M.
J Neuroimmunol. 2015 Aug 15;285:125-8.

Interferon-Beta Therapy of Multiple Sclerosis Patients Improves the Responsiveness of T Cells for Immune Suppression by Regulatory T Cells.
Trinschek B, Luessi F, Gross CC, Wiendl H, Jonuleit H.
Int J Mol Sci. 2015 Jul 17;16(7):16330-46.

Interferon Beta-1a (AVONEX®) as a Treatment Option for Untreated Patients with Multiple Sclerosis (AXIOM): A Prospective, Observational Study.
Kleinschnitz C, Niemczyk G, Rehberg-Weber K, Wernsdörfer C.
Int J Mol Sci. 2015 Jul 6;16(7):15271-86

Hemophilia

A new recombinant factor VIII: from genetics to clinical use.
Kannicht C, Kohla G, Tiemeyer M, Walter O, Sandberg H.
Drug Des Devel Ther. 2015 Jul 23;9:3817-9.

Assessment of the frequency of regulatory T cells (CD4+CD25+CD127-) in children with hemophilia A: relation to factor VIII inhibitors and disease severity.
El-Asrar MA, Hamed AE, Darwish YW, Ismail EA, Ismail NA.
Blood Coagul Fibrinolysis. 2015 Jul 29

Safety of PEGylated recombinant human full-length coagulation factor VIII (BAX 855) in the overall context of PEG and PEG conjugates.
Stidl R, Fuchs S, Bossard M, Siekmann J, Turecek PL, Putz M.
Haemophilia. 2015 Jul 29.

Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with haemophilia A.
Nolan B, Mahlangu J, Perry D, Young G, Liesner R, Konkle B, Rangarajan S, Brown S, Hanabusa H, Pasi KJ, Pabinger I, Jackson S, Cristiano LM, Li X, Pierce GF, Allen G.
Haemophilia. 2015 Jul 27.

Half-life extended factor VIII for the treatment of hemophilia A.
Tiede A.
J Thromb Haemost. 2015 Jun;13 Suppl 1:S176-9.

Basic immunology

HUMORAL IMMUNITY. **T cell help controls** the **speed** of the **cell cycle** in **germinal center B cells**.
Gitlin AD, Mayer CT, Oliveira TY, Shulman Z, Jones MJ, Koren A, Nussenzweig MC.
Science. 2015 Aug 7;349(6248):643-6.

IMMUNOLOGY. An **interactive reference framework** for **modeling** a **dynamic immune system**.
Spitzer MH, Gherardini PF, Fragiadakis GK, Bhattacharya N, Yuan RT, Hotson AN, Finck R, Carmi Y, Zunder ER, Fantl WJ, Bendall SC, Engleman EG, Nolan GP.
Science. 2015 Jul 10;349(6244):1259425.

REGULATION

EMA

Human medicines European public assessment report (EPAR): ReFacto AF, moroctocog alfa
Revision: 29, Authorised
July 2015

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol
Revision: 14, Authorised
July 2015

European Medicines Agency workshop on the development of new medicinal products for the treatment of ulcerative colitis and Crohn's disease
European Medicines Agency, London, From: 29-Jun-2015, To: 29-Jun-2015
Updated
July 2015

Human medicines European public assessment report (EPAR): Advate, octocog alfa
Revision: 21, Authorised
July 2015

Opinion/decision on a Paediatric investigation plan (PIP): RoActemra, tocilizumab
Updated
July 2015

Opinion/decision on a Paediatric investigation plan (PIP): Humira, adalimumab
Updated
July 2015

Opinion/decision on a Paediatric investigation plan (PIP): Recombinant single-chain coagulation factor VIII
Updated
July 2015

Human medicines European public assessment report (EPAR): Extavia, interferon beta 1-b
Revison: 16, Authorised
July 2015

Opinion/decision on a Paediatric investigation plan (PIP): RoActemra, tocilizumab
Updated
July 2015