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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.
Dear Reader,

We would like to welcome you to the December 2014 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 draw your attention to a basic immunology paper published in Science by Marchingo et al., proposing a new a quantitative paradigm for activation, expansion and contraction of the T cell compartment, which might help manipulating the immune response strength for therapeutic purposes.

In addition, you will find in this issue some regulatory news on biopharmaceuticals from the European Medicines Agency.

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
To date, T cells are believed to undergo an obligatory 3-steps signaling activation pathway, which leads to proliferation: 1) T cell receptor signal, 2) co-stimulation signal through molecules expressed by antigen presenting cells, 3) signal induced via cytokines and other immunomodulatory molecules present in the T cell milieu. Proliferation is soon followed by subsequent contraction of the extended T cell population through cell death.

Based on B cell compartment homeostasis recent reports, Marchingo and colleagues re-investigated here the current paradigm on activation, expansion and contraction of the T cell compartment. The authors hypothesized that T cell proliferation and death is programmed by the resulting sum of the strength of the 3 signal types (see figure below). The combination of these signals hence determines the cell Division Destiny (DD) : a cell divides for a series of generations then return to a quiescent non-dividing state.

Making use of existing or newly created elegant transgenic mouse models (allowing for instance the in vivo tracking of cell division upon antigen stimulation or the control of cytokine signal) alongside mathematical predictive models, the authors showed that a combination of different co-stimulatory and cytokine signals provide many alternative paths to generate T cell responses of similar magnitude: no single particular signal seemed mandatory, but rather multiple small arithmetic effects on DD culminated in large geometric differences in cell population expansion.
Moreover, the authors could establish that cell DD is regulated in a two-stage manner: signal 1 and a series of signal 2 and 3 initially program DD before the very first cell division, and in a second phase, DD can be altered by further exposure to signal 3.

Taken together, these results suggest that the magnitude of a T cell response can be quantitatively predicted from the sum of the stimulatory signals.

Immunogenicity

**Assays and strategies for immunogenicity assessment of biological agents.**

**Measurement of Anti-TNF Agents and anti-Drug Antibodies Serum Levels in Patients with Inflammatory Bowel Disease.**
Guerra I, Chaparro M, Bermejo F, Gisbert JP.
Curr Drug Metab. 2014 Nov 5

**Prevalence of TNF-α Blocker Immunogenicity in Psoriatic Arthritis.**
J Rheumatol. 2014 Nov 15.

**Immunogenicity of Antibody Drug Conjugates: Bioanalytical Methods and Monitoring Strategy for a Novel Therapeutic Modality.**
Hock MB, Thudium KE, Carrasco-Triguero M, Schwabe NF.

**Methods**

**Detection of Adalimumab and Anti-Adalimumab Levels by ELISA: Clinical Considerations.**

**New treatments for inflammatory rheumatic disease.**
Selmi C, Generali E, Massarotti M, Bianchi G, Sciré CA.

**PEGylation and its impact on the design of new protein-based medicines.**
Ginn C, Khalili H, Lever R, Brocchini S.
Development of assay platforms for in vitro screening of Treg modulating potential of pharmacological compounds.
Pedersen AE, Holmstrøm K, Jørgensen F, Jensen SS, Gad M.

Animal models

Immunoglobulin heavy-chain-binding protein (BiP): a stress protein that has the potential to be a novel therapy for rheumatoid arthritis.
Panayi GS, Corrigall VM.

Collagen II antibody-induced arthritis in Tg1278TNFko mice: optimization of a novel model to assess treatments targeting human TNF in rheumatoid arthritis.

Biomarkers

Prognostic biomarkers of IFNb therapy in multiple sclerosis patients.


CD98 is a potential target for ablating B cell clonal expansion and autoantibody in multiple sclerosis.
Cantor JM.
**Modulating effects of WT1 on interferon-β-vitamin D association in MS.**

**The Use of an Interferon-Gamma Release Assay as a Biomarker of Response to Anti-TNF-Alpha Treatment.**

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**Systemic Lupus Erythematosus**

**Profile of epratuzumab and its potential in the treatment of systemic lupus erythematosus.**
Al Rayes H, Touma Z. Drug Des Devel Ther. 2014 Nov 17;8:2303-2310

**Clinical, laboratory and health-related quality of life correlates of Systemic Lupus Erythematosus Responder Index response: a post hoc analysis of the phase 3 belimumab trials.**

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**Rheumatoid Arthritis**

**Usefulness of monitoring of B-cell depletion in rituximab-treated rheumatoid arthritis patients in order to predict clinical relapse: a prospective observational study.**

**Response to Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis for Function and Pain is Affected by Rheumatoid Factor.**
Efficacy and safety of pateclizumab (anti-Lymphotoxin-¿) compared to adalimumab in rheumatoid arthritis: a head-to-head phase 2 randomized controlled study (The ALTARA Study).

Tocilizumab (Actemra, Intravenous): For the Treatment of Signs and Symptoms of Active Polyarticular Juvenile Idiopathic Arthritis in Patients Two Years of Age and Older Who Have Responded Inadequately to Previous Therapy With Disease-Modifying Antirheumatic Drugs and Systemic Corticosteroids [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Aug.

Sustained remission with etanercept tapering in early rheumatoid arthritis.

Impact of biologics with and without concomitant MTX and at reduced doses in older rheumatoid arthritis patients.

Epigenetics in rheumatoid arthritis.

**Inflammatory Bowel Diseases**

Human Gut Dendritic Cells Drive Aberrant Gut-specific T-cell Responses in Ulcerative Colitis, Characterized by Increased IL-4 Production and Loss of IL-22 and IFNγ.

Safety considerations when using anti-TNFα therapy to treat Crohn's disease.
**Vedolizumab for inflammatory bowel disease: Changing the game, or more of the same?**
Raine T.

**Ulcerative colitis: current pharmacotherapy and future directions.**
Bezzio C, Furfaro F, de Franchis R, Maconi G, Asthana AK, Ardizzone S.

**Letter: comparative efficacy of biological therapy in patients with ulcerative colitis.**

**Letter: comparative efficacy of biological therapy in patients with ulcerative colitis - authors' reply.**
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**Advances in IBD genetics.**
Van Limbergen J, Radford-Smith G, Satsangi J.

**Multiple Sclerosis**

**A phase IIa randomised clinical study of GNbAC1, a humanised monoclonal antibody against the envelope protein of multiple sclerosis-associated endogenous retrovirus in multiple sclerosis patients.**

**Multiple sclerosis patients treated with intramuscular IFN-β-1a autoinjector in a real-world setting: prospective evaluation of treatment persistence, adherence, quality of life and satisfaction.**
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In Vivo Maintenance of Human Regulatory T Cells during CD25 Blockade.
Huss DJ, Mehta DS, Sharma A, You X, Riester KA, Sheridan JP, Amaravadi LS, Elkins JS, Fontenot JD.

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Hartung HP, Hermsen D, Tumani H, Adams O, Kieseier BC.

Significant clinical worsening after natalizumab withdrawal: Predictive factors.
Castilló J, Sastre-Garriga J, Rovira A, Montalban X.
Mult Scler. 2014 Nov 12

Hemophilia

Rapid Acquisition of Immunologic Tolerance to Factor VIII and Disappearance of Anti-Factor VIII IgG4 After Prophylactic Therapy in a Hemophilia A Patient With High-titer Factor VIII Inhibitor.
Moorehead PC, Thibeault I, Tuttle A, Grabell J, Dwyre I, Silva M, James P, Lillicrap D.

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Anti-TNF Therapy: Past, Present and Future.
Monaco C, Nanchahal J, Taylor P, Feldmann M.
Int Immunol. 2014 Nov 19

Clinical experience of IL-6 blockade in rheumatic diseases - implications on IL-6 biology and disease pathogenesis.
Davies R, Choy E.
REGULATION

EMA

**EMA response to ECCO position statement on biosimilars.**
Danese S, Gomollon F, Michetti P.

**ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD).**
Danese S, Gomollon F; Governing Board and Operational Board of ECCO.

**Human medicines European public assessment report (EPAR): Simponi, golimumab**
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November 2014

**Human medicines European public assessment report (EPAR): MabThera, rituximab**
Revision: 34, Authorised
November 2014

**Human medicines European public assessment report (EPAR): Inflectra, infliximab**
Revision: 5, Authorised
November 2014

**Human medicines European public assessment report (EPAR): Orencia, abatacept**
Revision: 17, Authorised
November 2014

**Human medicines European public assessment report (EPAR): Enbrel, etanercept**
Revision: 41, Authorised
November 2014
Opinion/decision on a Paediatric Investigation Plan (PIP): Secukinumab. Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
November 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Sirukumab. Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
November 2014