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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 November 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 draw attention to the work conducted by van Schouwenburg et al. on the functional characterisation of anti-adalimumab antibodies in Rheumatoid arthritis patients.

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

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 article

Adalimumab – a therapeutic monoclonal antibody directed against TNFα – elicits strong anti-drug antibody (ADA) responses in Rheumatoid Arthritis (RA) patients albeit being a fully human recombinant protein. Adalimumab ADA have been found to be anti-idiotypic, i.e. directed to the TNFα binding site of the drug. Hence, most adalimumab ADA are neutralizing antibodies (NAbs).

In this paper, van Schouwenburg and colleagues sought to investigate whether the anti-idiotypic ADA response to adalimumab is confined to various epitopes or a single dominant one within the adalimumab complementary determining region (CDR), and explore the diversity of the anti-adalimumab B cell repertoire.

To this aim, antigen-specific memory B cells were isolated and cloned from the peripheral blood of 2 adalimumab ADA positive RA patients. A total of 16 clones were obtained, 8 of IgG1, 7 of IgG4 and 1 of undetermined subclass. All clones exhibited different V(D)J recombination and the CDR1 and CDR2 regions showed a Replacement/Suppression mutation ratio characteristic of antigen-driven maturation. Eleven out of the sixteen clones were expressed as recombinant IgG1 monoclonal antibodies to explore binding affinity to adalimumab and neutralizing capacity. Ten out of eleven clones exhibited high affinity, all proved neutralizing and more interestingly, all could compete with each other for binding to adalimumab, thus confirming that they recognize overlapping regions of adalimumab TNFα binding site. Single amino acid mutations experiments revealed that several B cell epitopes within this region were recognized by the clones. Moreover, differences in propensity to form dimeric and multimeric immune complexes with adalimumab were also observed.

Based on this findings, the authors suggest that adalimumab immunogenicity might be reduced through the introduction of point mutations within the CDRs regions but further studies will be needed to estimate the risk of impairing TNFα specificity and/or generating new immunogenic amino acid sequences.

Functional Analysis of the Anti-Adalimumab Response using Patient-Derived Monoclonal Antibodies.
Immunogenicity

**Statistical evaluation of several methods for cut point determination of immunogenicity screening assay.**
Shen M, Dong X, Tsong Y.

**A method to quantitate the neutralizing capacity of anti-therapeutic protein antibodies in serum and their correlation to clinical impact.**
Kaliyaperumal A, Pennucci J, Nagatani J, Juan G, Swanson S, Gupta S.

**The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease.**

**Non-normal Random Effects Models for Immunogenicity Assay Cut Point Determination.**
Zhang J, Yu B, Zhang L, Roskos L, Richman L, Yang H.

**The antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region.**
van Schie KA, Hart MH, de Groot ER, Kruithof S, Aarden LA, Wolbink GJ, Rispens T.

**Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000-2011.**

**Therapeutic drug monitoring in inflammatory bowel disease.**
Kopylov U, Ben-Horin S, Seidman E.
Methods

Computational modelling and inhibitor risk: predicting the future?
Hart DP.

Systematic verification of bioanalytical similarity between a biosimilar and a reference biotherapeutic: committee recommendations for the development and validation of a single ligand-binding assay to support pharmacokinetic assessments.

Animal models

Generation of improved humanized mouse models for human infectious diseases.
Brehm MA, Wiles MV, Greiner DL, Shultz LD.

Critical assessment of human antibody generation in humanized mouse models.
Villaudy J, Schotte R, Legrand N, Spits H.

Detection of T cell responses to a ubiquitous cellular protein in autoimmune disease.

Biomarkers

A multi-biomarker disease activity score tracks clinical response consistently in patients with rheumatoid arthritis treated with different anti-tumor necrosis factor therapies: A retrospective observational study.
Proinflammatory cytokines in monitoring the course of disease and effectiveness of treatment with etanercept (ETN) of children with oligo- and polyarticular juvenile idiopathic arthritis (JIA).

FOXP3+ regulatory T-cell counts correlate with histological response in Crohn's colitis treated with infliximab.

Targeting IL-6 signalling in early rheumatoid arthritis is followed by Th1 and Th17 suppression and Th2 expansion.

Identification of interferon-inducible genes as diagnostic biomarker for systemic lupus erythematosus.

Soluble CD163, a specific macrophage activation marker, is decreased by anti-TNF-α antibody treatment in active inflammatory bowel disease.

Prior response to infliximab and early serum drug concentrations predict effects of adalimumab in ulcerative colitis.

Systemic Lupus Erythematosus

Update on belimumab for the management of systemic lupus erythematosus.

Pathogenesis and prevention of rheumatic disease: focus on preclinical RA and SLE.
Human leukocyte antigens and systemic lupus erythematosus: a protective role for the HLA-DR6 alleles DRB1*13:02 and *14:03.

**Rheumatoid Arthritis**

Canakinumab for the treatment of systemic juvenile idiopathic arthritis.
Grom AA.

Activation of Syk in peripheral blood B cells in patients with rheumatoid arthritis: A potential target for abatacept therapy.
Iwata S, Nakayamada S, Fukuyo S, Kubo S, Yunoue N, Wang SP, Yoshikawa M, Saito K, Tanaka Y.

Tocilizumab in rheumatoid arthritis: A case study of safety evaluations of a large postmarketing data set from multiple data sources.

Combined inhibition of TNFα and IL-17 as therapeutic opportunity for treatment in rheumatoid arthritis: Development and characterization of a novel bispecific antibody.
Arthritis Rheumatol. 2014 Oct 9

Experience with subcutaneous abatacept for rheumatoid arthritis: an update for clinicians.
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Efficacy and safety of rituximab in elderly patients with rheumatoid arthritis enrolled in a French Society of Rheumatology registry.

Sugihara T, Ishizaki T, Hosoya T, Iga S, Yokoyama W, Hirano F, Miyasaka N, Harigai M.
Growing Up With Juvenile Idiopathic Arthritis.
McKeever A, Kelly MM.

Divergent Gene Activation in Peripheral Blood and Tissues of Patients with Rheumatoid Arthritis, Psoriatic Arthritis and Psoriasis following Infliximab Therapy.

Analysis of associations between polymorphisms within genes coding for tumour necrosis factor (TNF)-alpha and TNF receptors and responsiveness to TNF-alpha blockers in patients with rheumatoid arthritis.

Tumor necrosis factor inhibitors: clinical utility in autoimmune diseases.
Willrich MA, Murray DL, Snyder MR.
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Inflammatory Bowel Diseases

Biological therapy for ulcerative colitis.
Arora Z, Shen B.

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Therapeutic peptides in inflammatory bowel disease.
Herrlinger KR, Stange EF, Fellermann K.

Tumor necrosis factor-alpha antagonists twenty years later: what do cochrane reviews tell us?

The role of integrin antagonists in the treatment of inflammatory bowel disease.
Beniwal-Patel P, Saha S.

Multiple Sclerosis

Extended interval dosing of natalizumab: a two-center, 7-year experience.
Bomprezzi R, Pawate S.

Intrathecal Rituximab Therapy in Multiple Sclerosis: Review of Evidence Supporting the Need for Future Trials.
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Immunomodulatory activity of interferon-beta.
Kasper LH, Reder AT.
Intrathecal anti-CD20 efficiently depletes meningeal B cells in CNS autoimmunity.

Therapeutic uses of anti-α4-integrin (anti-VLA-4) antibodies in multiple sclerosis.
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Interleukin-1β promotes long-term potentiation in patients with multiple sclerosis.

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Circulating Levels of Interleukin-35 in Patients with Multiple Sclerosis: Evaluation of the Influences of FOXP3 Gene Polymorphism and Treatment Program.

CD19 mRNA quantification improves rituximab treatment-to-target approach: A proof of concept study.
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Review of the novelties presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (III).
Limmroth V.

Multiple sclerosis: Pegylated IFN-β1a could lessen patients' injection burden.
Chase A.

Hemophilia

Long-term treatment course of a patient with mild haemophilia A who developed a high titre factor VIII inhibitor.
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Pharmacokinetics of plasma-derived vs. recombinant FVIII concentrates: a comparative study.
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Atypical MHC class II-expressing antigen-presenting cells: can anything replace a dendritic cell?
Kambayashi T, Laufer TM.

Dendritic cells control fibroblastic reticular network tension and lymph node expansion.

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Huizinga TW.

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Kalkan A, Roback K, Hallert E, Carlsson P.

Combination cytokine blockade: The way forward in therapy for rheumatoid arthritis?
Taylor PC, Williams RO.

Biologics in rheumatoid arthritis: where are we going?
Fechtenbaum M, Nam JL, Emery P.
Are we on our way to change our mode of thinking and treating inflammatory bowel disease patients?
Magro F, Eliakim R.

Biological therapies in rheumatic diseases.
Conti F, Ceccarelli F, Massaro L, Cipriano E, Di Franco M, Alessandri C, Spinelli FR, Scrivo R.

The role of public-private partnerships in addressing the biomedical innovation challenge.
Said M, Zerhouni E.
REGULATION

EMA

**Scientific guideline: Guideline on similar biological medicinal products**
Adopted
October 2014

**Human medicines European public assessment report (EPAR): Humira, adalimumab**
Revision: 36, Authorised
October 2014

**Human medicines European public assessment report (EPAR): Extavia, interferon beta-1b**
Revision: 14, Authorised
October 2014

**Human medicines European public assessment report (EPAR): Kogenate Bayer, octocog alfa**
Revision: 26, Authorised
October 2014

**Scientific guideline: Draft concept paper on the revision of the guideline on the development of new medicinal products for the treatment of ulcerative colitis, draft: consultation open**
Consultation start date 01/10/2014
Consultation end date 31/12/2014