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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 December 2013 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 and analysis of the *in silico* epitope prediction methods currently available and of particular interest to those involved in the design of less immunogenic protein drugs.

In addition as usual, you will find in this issue some news from the biopharmaceuticals regulatory 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

Immunogenicity of biopharmaceuticals mainly translates to the development of anti-drug antibodies (ADA) during immunotherapy. As ADA production is linked to T helper cell responses, identification and deletion of specific regions of the drug protein that are targeted by T helper cells represent a promising approach to limiting built-in biopharmaceuticals immunogenicity.

In this review, Paul *et al.* firstly present and summarize the various *in silico* prediction methods currently available for identification of such T cell epitopes.

These methods, based on the identification of peptide sequences that are expected to bind to HLA class II molecules, form the basis of the Immune Epitope Database and Analysis Resource (IEDB) on line free tool.

In effect, straightforward prediction of HLA class II binding can be obtained using the *default* IEDB method, or 'consensus' method, which is composed of three of the most successful individual prediction methods listed in the table below :

Methods	Prediction based on	Reference
Consensus	Combination of NN-align, SMM-align and CombLib	Wang et al., 2010 [38]
NetMHCIIpan	Artificial neural network	Nielsen et al., 2010 [31]
NN align	Artificial neural network	Nielsen and Lund, 2009 [35]
SMM-align	Stabilization matrix alignment	Nielsen et al., 2007 [11]
Combinatorial library	Position scanning combinatorial libraries	Wang et al., 2008 [33] Wang et al., 2010 [38]
Sturniolo	Scoring matrix based	Sturniolo et al., 1999 [39]
ARB	Average relative binding	Bui et al., 2005 [30]

The authors then discuss the advantages and limitations of the IEDB tool for immunogenicity prediction and reduction in the context of two publications focusing on epitope identification within proteins of interest : i) the biopharmaceutical erythropoietin (Oseroff *et al.*, 2010), and ii) the Timothy grass pollen major allergen family Phl p (Tangri *et al.*, 2005).

In both studies, binding of synthetic peptides derived from protein sequence was evaluated *in vitro* and combined to *in vitro* T cell activation experiments to determine immunodominant peptides or regions.

The work conducted by Tangri and colleagues revealed a role for HLA class II binding promiscuity in EPO immunogenicity. In fact, EPO variants carrying fewer promiscuous peptides were less immunogenic than their native counterpart. Hence, peptide promiscuity could be used to rank the relative immunogenicity of protein

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variants. Promiscuity as a feature of immunogenicity has since been exploited to identify immunodominant epitopes in the Phl p family (Oseroff *et al.)* and many other allergen targets.

As tools such as IEDB permit the prediction of promiscuous regions, the authors conclude that *in silico* HLA class II binding prediction may be useful in helping decision making process in the development of new biopharmaceuticals with potentially reduced immunogenicity.

Evaluating the Immunogenicity of Protein Drugs by Applying In Vitro MHC Binding Data and the Immune Epitope Database and Analysis Resource.

Paul S, Kolla RV, Sidney J, Weiskopf D, Fleri W, Kim Y, Peters B, Sette A.

Clin Dev Immunol. 2013

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Immunogenicity

Identification and Elimination of Target-Related Matrix Interference in a Neutralizing Anti-Drug Antibody Assay.

Schwickart M, Mehrzai F, Pearson J, Shaghasi N, Chavez C, Schneider A, Wu S, Roskos L, Liang M.

J Immunol Methods. 2013 Nov 25.

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Schwabe N, Lawson V.

Drug Discov Today. 2013 May;18(9-10):417-9.

T-cell dependent immunogenicity of protein therapeutics: Preclinical assessment and mitigation.

Jawa V, Cousens LP, Awwad M, Wakshull E, Kropshofer H, De Groot AS.

Clin Immunol. 2013 Sep 25;149(3PB):534-555.

Methods

Development of scoring functions for antibody sequence assessment and optimization.

Seeliger D.

PLoS One. 2013 Oct 21;8(10):e76909.

High degree of correlation between whole blood and PBMC expression levels of miR-155 and miR-146a in healthy controls and rheumatoid arthritis patients.

Mookherjee N, El-Gabalawy HS.

J Immunol Methods. 2013 Oct 11

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Animal models

Murine Models of Inflammatory Bowel Disease (IBD): Challenges of Modeling Human Disease.

Devoss J, Diehl L.

Toxicol Pathol. 2013 Nov 13.

Modeling pharmacokinetics/pharmacodynamics of abatacept and disease progression in collagen-induced arthritic rats: a population approach.

Lon HK, Liu D, Dubois DC, Almon RR, Jusko WJ.

J Pharmacokinet Pharmacodyn.

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Rituximab-induced IL-15 reduction associated with clinical improvement in rheumatoid arthritis.

Díaz-Torné C, de Juana Ortiz MA, Geli C, Cantó E, Laiz A, Corominas H, Casademont J, de Llobet JM, Juárez C, Díaz-López C, Vidal S.

Immunology. 2013 Nov 12.

Natalizumab treatment alters the expression of T-cell trafficking marker LFA-1 α-chain (CD11a) in MS patients.

Jilek S, Mathias A, Canales M, Lysandropoulos A, Pantaleo G, Schluep M, Du Pasquier RA.

Mult Scler. 2013 Nov 20.

Systemic Lupus Erythematosus

Biologics in SLE: Towards new approaches.

van Vollenhoven RF, Parodis I, Levitsky A.

Best Pract Res Clin Rheumatol. 2013 Jun;27(3):341-9.

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Epratuzumab for patients with moderate to severe flaring SLE: health-related quality of life outcomes and corticosteroid use in the randomized controlled ALLEVIATE trials and extension study SL0006.

Strand V, Petri M, Kalunian K, Gordon C, Wallace DJ, Hobbs K, Kelley L, Kilgallen B, Wegener WA, Goldenberg DM.

Rheumatology. 2013 Nov 22.

Rheumatoid Arthritis

Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study.

Tanaka Y, Hirata S, Kubo S, Fukuyo S, Hanami K, Sawamukai N, Nakano K, Nakayamada S, Yamaoka K, Sawamura F, Saito K.

Ann Rheum Dis. 2013 Nov 28.

A phase Ib multiple ascending dose study evaluating safety, pharmacokinetics, and early clinical response of brodalumab, a human anti-IL-17R antibody, in methotrexate-resistant rheumatoid arthritis.

Martin DA, Churchill M, Flores-Suarez L, Cardiel MH, Wallace D, Martin R, Phillips K, Kaine JL, Dong H, Salinger D, Stevens E, Russell CB, Chung JB.

Arthritis Res Ther. 2013 Oct 25;15(5):R164.

Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab.

Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, Askling J; for the ARTIS Study Group.

Ann Rheum Dis. 2013 Nov 27.

Tocilizumab in rheumatoid arthritis: A meta-analysis of efficacy and selected clinical conundrums.

Navarro G, Taroumian S, Barroso N, Duan L, Furst D.

Semin Arthritis Rheum. 2013 Nov 18.

Biological therapies in rheumatic diseases.

Conti F, Ceccarelli F, Massaro L, Cipriano E, Di Franco M, Alessandri C, Spinelli FR, Scrivo R.

Clin Ter. 2013 Sep-Oct;164(5):e413-28.

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Emerging cell and cytokine targets in rheumatoid arthritis.

Burmester GR, Feist E, Dörner T.

Nat Rev Rheumatol. 2013 Nov 12

Comparative evaluation of the effects of treatment with tocilizumab and TNF-α inhibitors on serum hepcidin, anemia response and disease activity in rheumatoid arthritis patients.

Song SN, Iwahashi M, Tomosugi N, Uno K, Yamana J, Yamana S, Isobe T, Ito H, Kawabata H, Yoshizaki K.

Arthritis Res Ther. 2013 Oct 2;15(5):R141.

Remission in rheumatoid arthritis patients treated with etanercept monotherapy: clinical practice and clinical trial experience.

Cannon GW, Wang BC, Park GS, Koenig A, Collier DH, Keystone EC.

Clin Exp Rheumatol. 2013 Nov 14.

Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects.

Krieckaert CL, Nair SC, Nurmohamed MT, van Dongen CJ, Lems WF, Lafeber FP, Bijlsma JW, Koffijberg H, Wolbink G, Welsing PM.

Ann Rheum Dis. 2013 Nov 21.

Inflammatory Bowel Disease

Treatment of ulcerative colitis.

Blonski W, Buchner AM, Lichtenstein GR.

Curr Opin Gastroenterol. 2013 Nov 26.

Targeting TNF-alpha for the treatment of inflammatory bowel disease.

Billiet T, Rutgeerts P, Ferrante M, Van Assche G, Vermeire S.

Expert Opin Biol Ther. 2013 Nov 11.

Letter: effectiveness of split-dose certolizumab pegol for Crohn's disease.

Kane SV, Neis B, Becker BD, Bruining D, Faubion WA, Kisiel J, Loftus EV Jr, Pardi D, Raffals L, Schroeder K, Tremaine WJ.

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Antibodies to Infliximab and Risk of Infusion Reactions in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis.

O'Meara S, Nanda KS, Moss AC.

Inflamm Bowel Dis. 2013 Nov 25.

Multiple Sclerosis

Human autoimmunity after lymphocyte depletion is caused by homeostatic T-cell proliferation.

Jones JL, Thompson SA, Loh P, Davies JL, Tuohy OC, Curry AJ, Azzopardi L, Hill-Cawthorne G, Fahey MT, Compston A, Coles AJ.

Proc Natl Acad Sci U S A. 2013 Nov 26.

ExtaviJect® 30G device for subcutaneous self-injection of interferon beta-1b for multiple sclerosis: a prospective European study.

Boeru G, Milanov I, De Robertis F, Kozubski W, Lang M, Rojas-Farreras S, Tomlinson M.

Med Devices (Auckl). 2013 Nov 15;6:175-184.

Long-term impact of interferon beta-1b in patients with CIS: 8-year follow-up of BENEFIT.

Edan G, Kappos L, Montalbán X, Polman CH, Freedman MS, Hartung HP, Miller D, Barkhof F, Herrmann J, Lanius V, Stemper B, Pohl C, Sandbrink R, Pleimes D; for the BENEFIT Study Group.

J Neurol Neurosurg Psychiatry. 2013 Nov 11.

Treatment options for patients with multiple sclerosis who have a suboptimal response to interferon-β therapy.

Freedman MS.

Eur J Neurol. 2013 Nov 15.

Also, see the special focus on MS in the December issue of *Expert Review of Neurotherapeutics* (Vol. 13, No. 12s, December 2013)

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Hemophilia

Limited Promiscuity of HLA-DRB1 Presented Peptides Derived of Blood Coagulation Factor VIII.

van Haren SD, Wroblewska A, Herczenik E, Kaijen PH, Ruminska A, Ten Brinke A, Meijer AB, Voorberg J.

PLoS One. 2013 Nov 14;8(11):e80239.

Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A.

Mahlangu J, Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I, Hanabusa H, Gupta N, Kulkarni R, Fogarty P, Perry D, Shapiro A, Pasi KJ, Apte S, Nestorov I, Jiang H, Li S, Neelakantan S, Cristiano LM, Goyal J, Sommer JM, Dumont JA, Dodd N, Nugent K, Vigliani G, Luk A, Brennan A, Pierce GF.

Blood. 2013 Nov 13.

Treatment of ulcerative colitis.

Blonski W, Buchner AM, Lichtenstein GR.

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Targeting TNF-alpha for the treatment of inflammatory bowel disease.

Billiet T, Rutgeerts P, Ferrante M, Van Assche G, Vermeire S.

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Basic immunology

Self-antigen-Driven Activation Induces Instability of Regulatory T Cells during an Inflammatory Autoimmune Response.
Bailey-Bucktrout SL, Martinez-Llordella M, Zhou X, Anthony B, Rosenthal W, Luche H, Fehling HJ, Bluestone JA.
Immunity. 2013 Nov 14;39(5):949-62.

Opinions/Commentaries/ Across-diseases reviews

Do Tregitopes have the potential to impact the current treatment landscape of autoimmune diseases?
Groot AS.
Expert Rev Clin Immunol. 2013 Dec;9(12):1155-7

Antibodies to watch in 2014.
Reichert JM.
MAbs. 2013 Nov 25;6(1).

Treating inflammation by blocking interleukin-1 in humans.
Dinarello CA, van der Meer JW.
Semin Immunol. 2013 Nov 22.

Autoantibody repertoires, natural biomarkers, and system controllers.
Cohen IR.
Trends Immunol. 2013 Jun 12

Raw data from clinical trials: within reach?
Peter Doshi, Steven N. Goodman, John P.A. Ioannidis

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REGULATION

EMA

Opinion/decision on a Paediatric Investigation Plan (PIP): Benlysta, belimumab

Therapeutic area: Immunology-Rheumatology-Transplantation (updated)

November 2013

Workshop on biosimilars, European Medicines Agency, London, UK, From: 31-Oct-2013, To: 31-Oct-2013

Presentations & list of participants

November 2013

Human medicines European public assessment report (EPAR): Enbrel, etanercept

Revision: 38, Authorised

November 2013

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol

Revision: 9, Authorised

November 2013

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