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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 rheumatism (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 October 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 highlight the work of Chen and colleagues on the development of mathematical model as new tools to predict immunogenicity of biotherapeutic proteins.

In addition, you will find in this issue some news on biopharmaceuticals from the regulatory agencies and a list of forthcoming scientific meetings.

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*



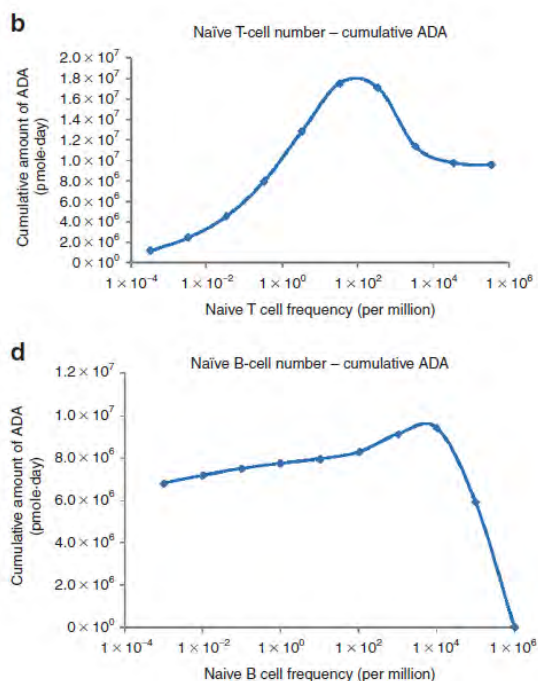
## LITERATURE

### This month's selected articles

In these papers, Chen *et al.* report on further advance\* in the design of mathematical models which could serve as new tools for predicting immunogenicity of therapeutic proteins.

In **part 1**, a multiscale model was established, which recapitulates and accounts for, at the subcellular (antigen presentation), cellular (humoral response kinetics), and whole-body (drug availability) levels, the cascade of biological events underlying the development of unwanted immunogenicity. A total of 88 parameters were included. When inputted with parameters for a hypothetical therapeutic antigen, the model could simulate the human kinetic profiles for DC, T cells, B cells and anti-drug antibody (ADA) production.

Interestingly, when key parameter conditions alleged to impact ADA production were altered, the authors found that the magnitude and timing of ADA production was more affected by the T than the B cell naïve repertoire, as depicted below :

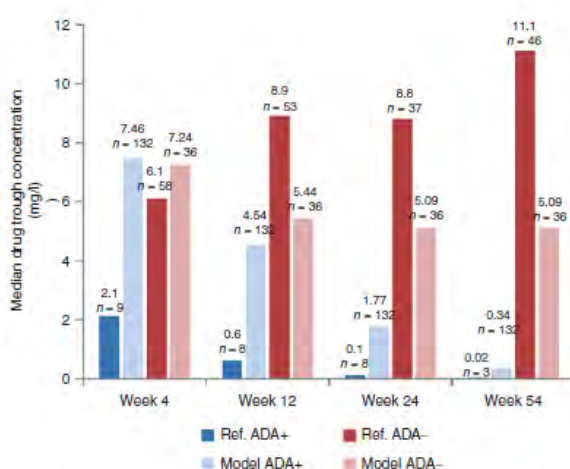


Binding of drug T cell epitopes to MHC class II molecules was also found to greatly impact on ADA magnitude of response. The model also predicted an enhanced secondary humoral response, accompanied with affinity maturation of ADA, consistent with many immunological observations.

In **part 2**, the authors firstly demonstrated a reasonable agreement of the simulated T and B cell responses with *in vivo* data generated in a well established model of immune responses to the OVA antigen in the mouse.

Next, simulation was conducted for one then 1, 000 virtual human subjects under adalimumab treatment. Simulation results confirmed that the number of T cell epitopes had a high impact on ADA development. As ADA levels were found to strongly impact drug availability, the model was further used to replicate a clinical trial with adalimumab and ADA and trough levels simulation data were compared to existing real clinical trial measurements.

As shown below, and despite some differences discussed by the authors, the predicted and reality figures still displayed the same high-level trend, which is a reduction of drug exposure in ADA+ patients :



**Figure 5 Comparison of model simulation and clinical trial measurements for adalimumab trough concentrations.** The data are taken from Figure 5 of Karmiris *et al.*<sup>24</sup> and compared with model simulations as described in the Methods section. Published data are limited to 67 patients where adalimumab concentrations had been measured after 4 weeks of therapy, while our simulations attempt to replicate the ADA incidence in the entire trial population (168 patients). ADA, antidrug antibodies.

Further improvement of the model is planned through integration of additional parameters also thought to play a role in the development of unwanted immunogenicity, such as formulation excipient, drug aggregation, comedication, or patient immune status.

\* see 'Article of the month' in ABIRISK Scientific Newsletter October 2013

[A mechanistic, multiscale mathematical model of immunogenicity for therapeutic proteins: part 1-theoretical model.](#)

Chen X, Hickling TP, Vicini P.

CPT Pharmacometrics Syst Pharmacol. 2014 Sep 3;3:e133.

[A mechanistic, multiscale mathematical model of immunogenicity for therapeutic proteins: part 2-model applications.](#)

Chen X, Hickling TP, Vicini P.

CPT Pharmacometrics Syst Pharmacol. 2014 Sep 3;3:e134.



## Immunogenicity

### [Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A.](#)

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Blood. 2014 Sep 24.

### [Influence of Combination Therapy with Immune Modulators on Anti-TNF Trough Levels and Antibodies in Patients with IBD.](#)

van Schaik T, Maljaars JP, Roopram RK, Verwey MH, Ipenburg N, Hardwick JC, Veenendaal RA, van der Meulende Jong AE.  
Inflamm Bowel Dis. 2014 Sep 16.

### [Golimumab trough levels, antidrug antibodies and clinical response in patients with rheumatoid arthritis treated in daily clinical practice.](#)

Kneepkens EL, Plasencia C, Krieckaert CL, Pascual-Salcedo D, van der Kleij D, Nurmohamed MT, López-Casla MT, Wieringa R, Rispen T, Wolbink G.  
Ann Rheum Dis. 2014 Sep 26.

### [Anti-IL21 receptor monoclonal antibody \(ATR-107\): Safety, pharmacokinetics, and pharmacodynamic evaluation in healthy volunteers: a phase I, first-in-human study.](#)

Hua F, Comer GM, Stockert L, Jin B, Nowak J, Pleasic-Williams S, Wunderlich D, Cheng J, Beebe JS.  
J Clin Pharmacol. 2014 Jan;54(1):14-22.

## Methods

### [Rapid establishment of a HEK 293 cell line expressing FVIII-BDD using AAV site-specific integration plasmids.](#)

Liu X, Ping H, Zhang C.  
BMC Res Notes. 2014 Sep 10;7:626.

### [High-Throughput Thermal Stability Analysis of a Monoclonal Antibody by Attenuated Total Reflection FT-IR Spectroscopic Imaging.](#)

Boulet-Audet M, Byrne B, Kazarian SG.  
Anal Chem. 2014 Sep 26.

[Effects of Syringe Material and Silicone Oil Lubrication on the Stability of Pharmaceutical Proteins.](#)

Krayukhina E, Tsumoto K, Uchiyama S, Fukui K.  
J Pharm Sci. 2014 Sep 24.

[Generation and characterization of tabalumab, a human monoclonal antibody that neutralizes both soluble and membrane-bound B-cell activating factor.](#)

Manetta J, Bina H, Ryan P, Fox N, Witcher DR, Kikly K.  
J Inflamm Res. 2014 Aug 20;7:121-31.

**Animal models**

[From classic to spontaneous and humanized models of multiple sclerosis: Impact on understanding pathogenesis and drug development.](#)

Ben-Nun A, Kaushansky N, Kawakami N, Krishnamoorthy G, Berer K, Liblau R, Hohlfeld R, Wekerle H.  
J Autoimmun. 2014 Aug 28.

[Development of ADA Against Recombinant Human Interferon Beta in Immune Tolerant Mice Requires Rapid Recruitment of CD4+ T Cells. Induces Formation of Germinal Centers but Lacks Susceptibility for \(Most\) Adjuvants.](#)

Kijanka G, Sauerborn M, Boon L, Schellekens H, Brinks V.  
J Pharm Sci. 2014 Sep 12.

[Role of coagulation-associated processes on FVIII immunogenicity in a mouse model of severe hemophilia A.](#)

Gangadharan B, Delignat S, Ollivier V, Gupta N, Mackman N, Kaveri SV, **Lacroix-Desmazes S.**  
J Thromb Haemost. 2014 Sep 30.

[Preclinical development of AMG 139, a human antibody specifically targeting IL-23.](#)

Köck K, Pan WJ, Gow JM, Horner MJ, Gibbs JP, Colbert A, Goletz TJ, Newhall KJ, Rees WA, Sun Y, Zhang Y, O'Neill JC, Umble-Romero AN, Prokop SP, Krill CD, Som L, Buntich SA, Trimble MW, Tsuji WH, Towne JE.  
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[CXCL13 predicts disease activity in early rheumatoid arthritis and could be an indicator of the therapeutic window of opportunity](#)

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[Disease Activity Improvement in Rheumatoid Arthritis Treated with Tumor Necrosis Factor- \$\alpha\$  Inhibitors Correlates with Increased Soluble Fas Levels.](#)

Romano E, Terenzi R, Manetti M, Peruzzi F, Fiori G, Nacci F, Bellando-Randone S, Matucci-Cerinic M, Guiducci S.  
J Rheumatol . 2014 Sep 1.

[High levels of natural killer cells are associated with response to tocilizumab in patients with severe rheumatoid arthritis.](#)

Daïen CI, Gailhac S, Audo R, Mura T, Hahne M, Combe B, Morel J.  
Rheumatology (Oxford). 2014 Sep 16.

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[Type I interferon blockade in systemic lupus erythematosus: where do we stand?](#)

Lauwerys BR, Ducreux J, Houssiau FA.  
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[Belimumab in systemic lupus erythematosus -- what can be learned from longterm observational studies?](#)

Bengtsson AA.  
J Rheumatol. 2014 Feb;41(2):192-3.

[Normalizing glycosphingolipids restores function in CD4+ T cells from lupus patients.](#)

McDonald G, Deepak S, Miguel L, Hall CJ, Isenberg DA, Magee AI, Butters T, Jury EC.  
J Clin Invest. 2014 Feb 3;124(2):712-24..

## Rheumatoid Arthritis

### [Pharmacokinetics, Pharmacodynamics, and Tolerability of Single Ascending Doses of RCT-18 in Chinese Patients with Rheumatoid Arthritis.](#)

Chen X, Hou Y, Jiang J, Zhao Q, Zhong W, Wang W, Yao X, Li L, Fang J, Zhang F, Hu P.  
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### [Efficacy and safety of tocilizumab in elderly patients with rheumatoid arthritis.](#)

Pers YM, Schaub R, Constant E, Lambert J, Godfrin-Valnet M, Fortunet C, Bourichi W, Prades BP, Wendling D, Gaudin P, Jorgensen C, Maillefert JF, Marotte H.  
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### [Down-titration and discontinuation strategies of tumor necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity.](#)

van Herwaarden N, den Broeder AA, Jacobs W, van der Maas A, Bijlsma JW, van Vollenhoven RF, van den Bemt BH.  
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### [Safety and efficacy of etanercept in children with juvenile idiopathic arthritis below the age of 2 years.](#)

Windschall D, Müller T, Becker I, Horneff G.  
Rheumatol Int. 2014 Sep 11.

### [Judicious use of biologicals in juvenile idiopathic arthritis.](#)

Zhao Y, Wallace C.  
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### [Early lessons from the recent-onset rheumatoid arthritis cohort ESPOIR.](#)

Combe B, Rincheval N.  
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### [The 2013 BSR and BHPR guideline for the use of intravenous tocilizumab in the treatment of adult patients with rheumatoid arthritis.](#)

Malaviya AP, Ledingham J, Bloxham J, Bosworth A, Buch M, Choy E, Cope A, Isaacs J, Marshall D, Wright G, Ostör AJ; BSR Clinical Affairs Committee & Standards, Audit and Guidelines Working Group and the BHPR.  
Rheumatology (Oxford). 2014 Oct;53(10):1914.

### [Certolizumab pegol \(CDP870\) for rheumatoid arthritis in adults.](#)

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[Biologic-free remission of established rheumatoid arthritis after discontinuation of abatacept: a prospective, multicentre, observational study in Japan.](#)

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[The use of biologic therapies in the treatment of rheumatoid arthritis.](#)

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[Memory B cell subsets and plasmablasts are lower in early than in long-standing Rheumatoid Arthritis.](#)

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[Assessing the likelihood of new-onset inflammatory bowel disease following tumor necrosis factor-alpha inhibitor therapy for rheumatoid arthritis and juvenile rheumatoid arthritis.](#)

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## Inflammatory Bowel Diseases

[Vedolizumab: An  \$\alpha 4\beta 7\$  Integrin Inhibitor for Inflammatory Bowel Diseases.](#)

Smith MA, Mohammad RA.

Ann Pharmacother. 2014 Sep 3.

[Vedolizumab for induction and maintenance of remission in ulcerative colitis.](#)

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Cochrane Database Syst Rev. 2014 Aug 8;8:CD007571.

[Longitudinal study of circulating protein biomarkers in inflammatory bowel disease.](#)

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[Adalimumab in Crohn's disease patients: pharmacokinetics in the first 6 months of treatment.](#)

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Aliment Pharmacol Ther. 2014 Sep 28.

[Management of inflammatory bowel disease in poor responders to infliximab.](#)

Guerra I, Bermejo F.  
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[Editorial: drug monitoring targets for optimising adalimumab in Crohn's disease.](#)

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[Role for Therapeutic Drug Monitoring During Induction Therapy with TNF Antagonists in IBD: Evolution in the Definition and Management of Primary Nonresponse.](#)

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[Health outcomes and cost-effectiveness of certolizumab pegol in the treatment of Crohn's disease.](#)

Augustine JM, Lee JK, Armstrong EP.  
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[Development of Drugs to Target Interactions Between Leukocytes and Endothelial Cells and Treatment Algorithms for Inflammatory Bowel Diseases.](#)

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## Multiple Sclerosis

[Current perspectives on interferon Beta-1b for the treatment of multiple sclerosis.](#)

Marziniak M, Meuth S.  
Adv Ther. 2014 Sep;31(9):915-31.

[Review of the novelties presented at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis \(ECTRIMS\) \(I\).](#)

Fernandez O, Alvarez-Cermeno JC, Arnal-Garcia C, Arroyo-Gonzalez R, Brieva L, Calles-Hernandez MC, Casanova-Estruch B, **Comabella M**, Garcia-Merino JA, Izquierdo G, Meca-Lallana JE, Mendibe-Bilbao MM, Munoz-Garcia D, Olascoaga J, Oliva-Nacarino P, Oreja-Guevara C, Prieto JM, Ramio-Torrenta L, Romero-Pinel L, Saiz A, Rodriguez-Antiguedad A, Grupo Post-Ectrims GP.  
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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.

www.imi.europa.eu



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Acta Neurol Scand. 2014 Sep 10.

### Hemophilia

[A large-scale computational study of inhibitor risk in non-severe haemophilia A.](#)

Shepherd AJ, Skelton S, Sansom CE, Gomez K, Moss DS, Hart DP.

Br J Haematol. 2014 Sep 22.

### Basic immunology

[The alarmin IL-33 promotes regulatory T-cell function in the intestine.](#)

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Science. 2014 Sep 26;345(6204):1623-7.

Opinions/Commentaries/Across diseases reviews

[Editorial: biologics in autoimmune diseases.](#)

Shi G, Liu Y.

Curr Pharm Biotechnol. 2014;15(6):509.

[Current therapeutic agents and treatment paradigms for the management of rheumatoid arthritis.](#)

Gibofsky A.

Am J Manag Care. 2014 May;20(7 Suppl):s136-44.

[Are sample sizes of randomized clinical trials in rheumatoid arthritis too large?](#)

Celik S, Yazici Y, Yazici H.

Eur J Clin Invest. 2014 Sep 10.

[IL-1 blockade in autoinflammatory syndromes.](#)

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## REGULATION

### EMA

[Opinion/decision on a Paediatric Investigation Plan \(PIP\): Simponi, golimumab. Therapeutic area: Immunology-Rheumatology-Transplantation](#)

Updated  
September 2014

[Human medicines European public assessment report \(EPAR\): Betaferon, interferon beta-1b](#)

Revision: 25, Authorised  
September 2014

[Human medicines European public assessment report \(EPAR\): RoActemra, tocilizumab](#)

Revision: 14, Authorised  
September 2014

[Human medicines European public assessment report \(EPAR\): Remsima, infliximab](#)

Revision: 4, Authorised  
September 2014

[Human medicines European public assessment report \(EPAR\): Remicade, infliximab](#)

Revision: 42, Authorised  
September 2014

[Human medicines European public assessment report \(EPAR\): Avonex, interferon beta-1a](#)

Revision: 21, Authorised  
September 2014

[Human medicines European public assessment report \(EPAR\): Rebif, interferon beta-1a](#)

Revision: 29, Authorised  
September 2014

[Human medicines European public assessment report \(EPAR\): Enbrel, etanercept](#)

Revision: 40, Authorised

## CONFERENCES & MEETINGS

### 2014

#### November

AAPS Annual Meeting	2-6, San Diego, USA	<a href="http://www.aaps.org/annualmeeting/">http://www.aaps.org/annualmeeting/</a>
Annual meeting of the French Society for Immunology	4-6, Paris, France	<a href="http://www.alphavisa.com/sfi-afc/2014/en/">http://www.alphavisa.com/sfi-afc/2014/en/</a>
International Congress of Neuroimmunology	9-13, Mainz, Germany	<a href="http://www.isnicongress.org/">http://www.isnicongress.org/</a>
ACR/ARHP	14-19, Boston, USA	<a href="http://acrannualmeeting.org/">http://acrannualmeeting.org/</a>
Immunogenicity and Bioassays Summit 2014	17-19, Bethesda, USA	<a href="http://www.immunogenicitysummit.com/">http://www.immunogenicitysummit.com/</a>

#### December

British Society for Immunology Annual Congress	1-4, Brighton, UK	<a href="http://www.bsicongress.com/">http://www.bsicongress.com/</a>
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### 2015

#### January

Immunogenicity and Immunotoxicity Conference	29-30, San Diego, CA, USA	<a href="https://www.gtcbio.com">https://www.gtcbio.com</a>
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#### February

Open Scientific EIP Symposium	23-25, Lisbon, Portugal	<a href="http://www.e-i-p.eu/">http://www.e-i-p.eu/</a>
AAA1	20-24 March, Houston, USA	<a href="http://annualmeeting.aaaai.org/">http://annualmeeting.aaaai.org/</a>

#### March

Biotherapeutics Analytical Summit	9-13, Baltimore, USA	<a href="http://www.biotherapeuticsanalyticalsummit.com">http://www.biotherapeuticsanalyticalsummit.com</a>
World Immune Regulation Meeting	18-21, Davos, Switzerland	<a href="http://wirm.ch/index.html">http://wirm.ch/index.html</a>

#### May

PEGS summit	4-8, Boston, USA	<a href="http://www.pegsummit.com/">http://www.pegsummit.com/</a>
Immunology 2015™	8-12, New Orleans	<a href="http://www.immunology2015.org/">http://www.immunology2015.org/</a>
FOCIS 2015	24-27, San Diego, USA	<a href="http://www.focisnet.org/">http://www.focisnet.org/</a>

#### June

EAACI	6-10, Barcelona, Spain	<a href="http://www.eaaci2015.com/">http://www.eaaci2015.com/</a>
AAPS National Biotechnology Conference	8-10, San Francisco, USA	<a href="http://www.aaps.org/nationalbiotech/">www.aaps.org/nationalbiotech/</a>
EULAR 2015	10-13, Rome, Italy	<a href="http://www.congress.eular.org/">http://www.congress.eular.org/</a>

#### July

Neuroimmunology and Therapeutics	20-22, San Francisco, USA	<a href="http://neuroimmunology.omicsgroup.com/">http://neuroimmunology.omicsgroup.com/</a>
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#### September

ECI + ABIRISK symposium and SC meeting	5-9, Vienna, Austria	<a href="http://www.eci-vienna2015.org/">http://www.eci-vienna2015.org/</a>
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