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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.

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WELCOME

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

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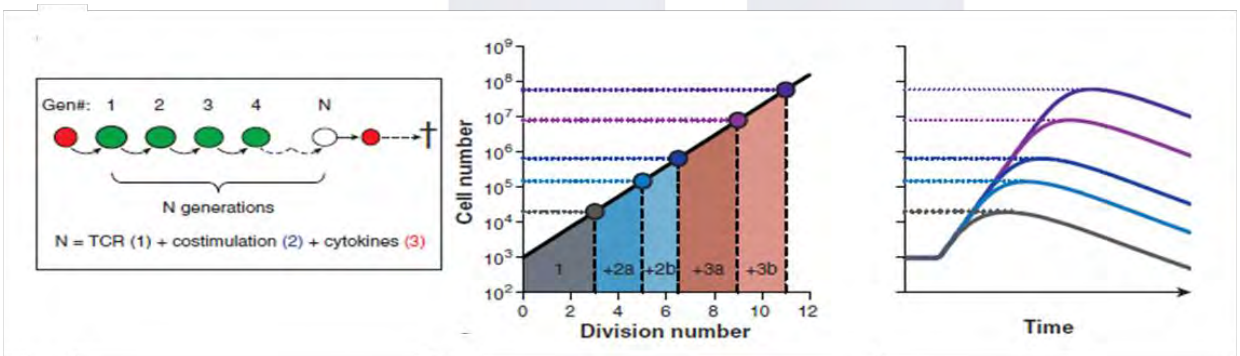
LITERATURE

This month's selected article

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.



Signal 1, 2, and 3 stimuli each individually elicit a small increase in mean population division number. The cumulative effect of these contributions, when summed linearly, would lead to geometric increases in total cell number at the peak response.

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 2 seemed mandatory, but rather multiple small arithmetic effects on DD culminated in large geometric differences in cell population expansion.

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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.

T cell signaling. Antigen affinity, costimulation, and cytokine inputs sum linearly to amplify T cell expansion.
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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

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