PreDicta News

Post infectious immune-reprogramming and its association with persistence and chronicity of respiratory allergic diseases

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Editorial: Sebastian L. Johnston

Increased susceptibility to respiratory virus and bacterial infections in asthma - an update.

Predicta is focused on trying to increase our understanding of interactions between infection and allergic diseases, so what do we know now and what do we need to learn?

We have known for some time that people with asthma have increased susceptibility to virus infections. In studies of naturally occurring infections[1], and rhinovirus challenge studies[2], people with asthma have increased susceptibility to rhinovirus infection, with more severe and more prolonged lower respiratory symptoms[1,2], reductions in lung function[1,2] and increased airway inflammation[2].

We previously reported that this increased susceptibility may be a result of deficient antiviral innate immune responses in the asthmatic lung, with deficient virus induction of interferon –β and –λ both being observed in asthma[3,4]. This work has been accompanied by other work indicating deficient type I immune responses, with deficient virus-induction of interferon-γ[2,5], IL-12[5], and IL-15[6] also being reported. An obvious question that arises is why are people with asthma deficient in all these anti-viral immune responses? We do not know, but understanding interactions between anti-viral immunity and allergic responses is likely to be pivotal to unraveling these complex relationships. Early Predicta work has elegantly shown that type III interferon-λ potently suppresses allergic airway inflammation[7], we now need to know whether this occurs also with type I interferons, and also whether allergic airway inflammation is able to suppress anti-viral immune responses. We hope Predicta may give some answers as a result of ongoing work in this area soon!

Bacterial infections are also becoming of increasing interest in both stable and exacerbating asthma: Traditionally it has been thought that the lower airway was sterile and that bacteria do not play an important role in asthma. However recent evidence suggests this is not correct. Standard bacteria[8] as well as both *Chlamydophila pneumoniae*[9] and *Mycoplasma pneumoniae*[10] are all increased in respiratory tract samples in stable asthma. This is supported by recent microbiome data which demonstrated pathogenic Proteobacteria, particularly Haemophilus spp., were much more frequently identified in bronchi of adult asthmatics ($p<10^{-7}$) and asthmatic children ($p<10^{-13}$) than in controls[11].

A growing body of data indicates that bacterial infections interact with virus infections to increase risk or severity of asthma exacerbations. Children with evidence of *Chlamydophila pneumoniae* infections had much more frequent virus induced asthma exacerbations than those without[12] and 40% of adults with virus induced asthma exacerbations had evidence of reactivation of *Chlamydophila pneumoniae* infection and those with evidence of reactivation had 4 fold greater neutrophilic and eosinophilic airway inflammation than those without[13]. Bacterial infections were recently detected just as frequently as virus infections in acute wheezing episodes in young children[14] and antibacterial therapy has been shown to be a clinically effective therapy for asthma attacks in adults, resulting in improvements in both symptoms and lung function that were almost twice as great as those observed with placebo, as well as a time to a 50% reduction in symptoms that was 3 days faster[15].

An approximately three fold increase in invasive pneumococcal disease in asthma has been reported in three separate studies in the USA[16,17], and Finland[18]. The Finnish study was particularly important as this study found risk was increased to 12 fold in severe asthma and asthma was a more important risk factor in terms of population attributable risk than diseases of the spleen (such patients receive pneumococcal vaccines and life-long penicillin).

Impaired host defense against bacterial infections also appears to be present in asthma. The mechanisms of host defense against bacterial disease are complex and not fully understood, however interferon-γ production is known to be central and mouse studies indicate host defense against *Chlamydophila pneumoniae*[19] and *Streptococcus pneumoniae*[20] is mediated by type I interferons as well as type II. There is intriguing data that type III interferon induction following stimulation of lung macrophages with a bacterial stimulus (LPS) is deficient in asthma[4], and LPS-induction in macrophages of IL-12[2,21] and IL-18[22], which are important for induction of IFN-γ and Th1 immune responses and for host defense against bacterial infections, are also all deficient in asthma. Predicta will therefore also need to focus on host defense against bacteria in asthma and to investigate why such responses also appear deficient in asthma.

As a final thought, interferon deficiency has also recently been reported in both COPD[23] and cystic fibrosis[24] – if these findings are confirmed in further studies, and if they extend to other aspects of anti-viral and anti-bacterial immunity as increasingly appears to be the case in asthma, then perhaps we will be lucky enough to find a common mechanism that might explain deficiencies of all these responses in all these diseases. That would be quiet a breakthrough for Predicta….. Time to get to work!

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Message from the coordinator

Nikos Papadopoulos
National and Kapodistrian University of Athens

After almost a year and a half of creative planning, setting up and initiating all the PreDicta projects, it is now about time to formally report to our funder, the European Commission. Although the process of official reporting can be tedious, it can also be a very positive experience. First, it increases tidiness, as every activity is presented and outputs clearly demonstrated. Then, if there are any loose ends, it gives the consortium the opportunity to put time in evaluating and solving them. Finally, it helps communication, as all the members get detailed information in a formal format.

In any case, it feels nice to see things from their optimistic perspective…! And we have all reasons to feel thus, as the core science in PreDicta is healthy and boiling! May I remind you however, that in our world it is important to advertise and promote one's activities, trying to get added value out of them. So, in addition to the reports of experiments, patient evaluation and mouse model setups, please also remember and report all the instances you have mentioned PreDicta in your presentations, the public or any other dissemination activity. I feel it is now time to intensify dissemination activities: many of our plans appear to be producing results. I hope that in our next meeting in Davos (March 17), in addition to a warm interaction, we will listen to ground-breaking findings!

See you soon!

Christina Tsakiropoulos is born on January 1st 2012!

Dahlia and Christina are doing very well!

What's new in PreDicta's Workpackages?

In WP1:
Longitudinal cohort

Centers participating in W.P.1 have already recruited their first 60 pediatric patients with a great success! All teams have made a significant progress but especially the Finnish group as well as the Polish one have brought some outstanding results!
Controls are still difficult to get, but all centers are working hard on this.
In more detail, the exact numbers of the recruited children are as follows:

W.P.1 team	cases	controls
NKUA, Athens, Greece	6 (3 in the waiting list)	0
Medical University of Lodz (LODZ), Poland	16	0
University of Ghent, Belgium	2	0
University of Erlangen, Germany	7	0
Turku University Hospital, Finland	29	1 (3pending)

Moreover, the follow up procedure has been initiated. With the use of telephone questionnaires in the recruited patients, the first episodes of asthma exacerbations have been identified:

W.P.1 team	No of patients in follow up	No of asthma exacerbations
NKUA, Athens, Greece	1	1
Medical University of Lodz (LODZ), Poland	8	1
University of Ghent, Belgium	-	-
University of Erlangen, Germany	3	1
Turku University Hospital, Finland	14	4 (all caused by RV)

All W.P.1 colleagues are anticipating the launch of the electronic diary system as well as the use of home spirometer devices which are currently under process.

Regarding the laboratory part, all collected samples have been stored and are ready to be shipped out to the collaborative research laboratories for further analysis. Moreover, results from bacterial cultures are already available from Lodz and Athens.
Congratulations to all the members of the PreDicta W.P.1 for their hard work and commitment!

WP4: Virus-Bacteria interactions

N. Zhang, T. Dutré, C. Bachert: There was a lot of progress in the virus model: The ex-vivo model of interactions of Herpes Simplex Virus (HSV) Type 1 and Staphylococcus aureus (SA) infection in human nasal mucosa has been set up! The innate and adaptive immune responses to viral and bacterial infection were studied in control and nasal polyp mucosa. In order to confirm some of the novel finding, we have tested 7 nasal polyp and 6 control nasal mucosa with HSV and SA interactions, the supernatants are ready to be send out to Professor Sebastian Johnston's lab for further measurements.

An ex-vivo model of interactions of Rhinovirus (RV) 1beta or RV16 and S. aureus infection in human nasal mucosa has been set up. RVs have been provided by Prof Papodopoulos lab. IL-6 as an inflammatory marker after RV infection was evaluated in supernatants; Il-6 was clearly increased after RV of/or SA infection.
Evaluation of RV16 and SA mucosal spread by confocal microscopy was performed.
Immunofluorescence image series of stained cryosections were acquired with a Leica TCS SP2 confocal microscope (Leica Microsystems GmbH). After infection with RV16 for 48h and S. aureus for 24h, the whole epithelium was infected with RV16, and SA was able to pass the basement membrane

What's new in PreDicta's Workpackages?

and invade the mucosa. Further study on this model is going on.

Also the clinical part of the study is progressing well. The different participating centers have obtained approval from their ethics committees. The patients will be followed for 2 years and will be monitored when they have 1 common cold or airway infection. We hope to see trends in which way these infections affect the course of pathologies like nasal polyps, allergic rhinitis and how it affects a control population. The first patients were already recruited in 2011, the other ones will follow in 2012. We look forward to the results!

In WP6: Resolution of inflammation

LC-MS/MS based methodologies have been developed for the determination of a panel of specialized pro-resolving lipid mediators (SPMs) in biological samples. Methods have been validated in biological material obtained by experimental animals (i.e. murine serum and lung tissue). Application of these methodologies in a murine model of allergic airway inflammation offered proof-of-concept for the preferential production of two specific SPMs in the inflamed lung which undergoes resolution.

Recently, our methodologies were successfully transferred to different cell culture media and human sera. These new advances enabled a series of preliminary experiments on cell cultures that demonstrated the importance of two omega-3 polyunsaturated fatty acids DHA and EPA for the generation of SPMs, at least in the context of a cell culture set-up.

Active Participants:
Evangelos Andreakos [1], PI
Constantin Tamvakopoulos [2], PI, Katerina Pyrillou [1,2], PhD Student, Aikaterini Chairakaki [1], PhD Student

[1] Immunogenetics Laboratory, Centre of Immunology & Transplantation
[2] Division of Pharmacology – Pharmacotechnology, Centre of Basic Research
Institution: Biomedical Research Foundation, Academy of Athens - Greece

In WP7: Diagnostics

Partner 3: during the last months, we identified, expressed and purified different structural and non-structural proteins derived from closely and distantly related RV strains to be used for the establishment of serological diagnostic tests. Furthermore, we published our first results from the investigation of mechanisms of memory immune responses during RV infections in FASEB J (FASEB J, Nov 2011; 10.1096/fj.11-193557), which will also be commented by JACI soon. We reported that the major RV immune response was directed against an N-terminal non-neutralizing peptide in VP1, which, paradoxically, is located inside the viral capsid. We suggested that the misdirection of antibody responses may serve as a possible explanation for the lack of protection against recurrent RV infections. We believe that these findings may pave the road for the further development of diagnostic tests for rhinovirus infections and of rhinovirus vaccines which may help to prevent airway diseases such as asthma and COPD. Last, but not least, we are happy to announce that the PhD thesis of Katarzyna Niespodziana has awarded a prize "Award of Excellence 2011" of the Austrian Federal Minister for Science and Research (see Photo). We would like to thank all who contributed to the work.

Partner 9 has analyzed respiratory viruses from 11 patients who participated in the study at University Central Hospital Turku.

Three patients have been negative, 5 have had rhinovirus and one enterovirus infection. Two patients have hade a dual infection by rhino- and enterovirus.

"Award of Excellence 2011". Left: Dr. Katarzyna Niespodziana; Right: Dr. Karlheinz Töchterle (Austrian Federal Minister for Science and Research)

State of the Art beyond PreDicta

IL-6 orchestrates the effects of Rhinovirus in the airways

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IL-6 is a pleiotropic cytokine produced by hematopoetic cells (e.g. dendritic cells, B cells and macrophages) as well as structural cells (e.g. epithelial cells and fibroblasts) and T lymphocytes. It is secreted in response to diverse external stimuli such as IL-1β and TNFα [1-3].

IL-6 binds to the IL-6R alpha chain and then induces gp130 dimerization resulting in the intracellular activation of Janus kinase and signal transducers and activators of transcription (STAT) pathways[1,2,4,5].

IL-6 has recognized to be an important factor that influences the effector functions of several CD4+ T cell subsets. In fact, IL-6 is able to promote Th2 cell differentiation during early CD4+ T cell priming while it inhibits the differentiation of Th1 cells. In the presence of TGFβ it enhances the development of Th17 cells. Moreover IL-6 along with IL-21 induces the T follicular helper cells (Tfh) which also produce IL-6. By contrast, IL-6 suppresses CD4+CD25+ regulatory T cells[1,5-10]. We recently demonstrated that treatment with Galiellalactone, a fungal secondary metabolite, selectively inhibited IL-6/STAT3 signalling in CD4+ T cells resulting in amelioration ofasthmatic symptoms associated with induction of T regulatory cells[11]. Taken together these findings suggest that IL-6 plays an important role in the onset and/or progression of inflammatory, autoimmune and malignant diseases.

Respiratory viral infections are characterized by mucus hypersecretion, airway epithelial cell damage and Th2 cytokine hyper-production[12]. It has been shown that these infections have profound effects on many aspects of bronchial asthma. Especially rhinovirus (RV) infection increased the risk of allergy and asthma in children[13,14].

In a recent study it was established that the group of children at highest risk of developing clinically significant bronchiolitis and childhood asthma, are infants at 121 days of age during the winter virus peak (between December and February) compared to younger or older children at this time point[15,16,17]. The danger of developing asthma during infancy after bronchiolitis is also linked to other indicators of allergy, e.g. food allergy, allergic rhinitis or atopic dermatitis[16,18,19].

Recent studies showed that in human primary airway fibroblasts RV infection induces the production of IL-6[14]. Another study described significantly elevated serum levels of IL-6 in patients with RV-induced acute exacerbation of asthma compared to controls[20].

Thus the level of IL-6 increases with the severity of symptoms of asthma associated to the RV infection[16,21].

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PreDicta' series of portraits: Spotlight on PreDicta researchers

Frank Stolz

Partner 11—Biomay, Austria

Senior Scientist at Biomay AG

What is your scientific background?

- Study of Molecular Genetics, Master thesis , Institute of Genetics, University of Vienna
- Ph.D. thesis at the Children Cancer Research Institute (CCRI), Vienna
- Postdoctoral fellowship at the department of Clinical Chemistry and Immunology, Ghent University Hospital, Ghent, Belgium
- Group Leader at the VIB 10, Institute of Biotechnology , Leuven, Belgium
- Senior Scientist at F-Star, Modular Antibodies Forschungs- und Entwicklungsges.m.b.H.; Vienna
- Senior Scientist at S-target, Modular Allergy Vaccines Forschungs und Entwicklungsges.m.b.H., Vienna
- Senior Scientist at Biomay AG in terms of preclinical and clinical Product Development of novel innovative allergy vaccines.

For you, what was the most valuable scientific discovery in 2011?

structure of the human Histamine H1 receptor protein, which has been described in Nature by Shimamura et al., was a breakthrough in allergy research, because it will open the way for the development of antihistamines, specific drugs effective against various allergies without causing adverse side-effects. It will be a great starting point for exploring in detail how histamine triggers allergic reactions and how drugs act to prevent this reaction.

For you, what was the best scientific article published in 2011?

Scientific American 306, 54 - 59 (2012) Published online: 28 December 2011

The Patient Scientist from Katherine Harmon is not an article, which describes one of the breakthroughs in 2011, but provides us an insight into the life of Ralph M. Steinman, his discovery and his fight against pancreatic cancer. Ralph M Steinman died just 3 days before winning the Nobel Prize.

One book you would recommend?

Wish I'd Made You Angry Earlier. Essays on Science, Scientists and Humanity. M. Perutz. Oxford University Press (1999): A book that explores all the aspects of science.

Which career were you planning while being a child?

At the age of a child I always saw myself as a medical doctor, who cures and supports patients. My interest in Molecular Biology and fundamental research was awaken by the book the Double Helix: A Personal Account of the Discovery of the Structure of DNA, from James D. Watson, which stimulated and convinced me to change my plans in order to study Molecular Genetics at the University of Vienna.

Have you participated in other EU projects?

- EC-funded Marie Curie Research Training Network, called CanTrain, in which we were studying nutrient receptors as potential targets for antifungals and this both in C. albicans as well as in C. dubliniensis;
- Life quality program: Ligand-Activation of GPCRs;
- MeDALL, FP7, Mechanisms of the Development of ALLergy;
- FAST, FP7, The FAST project aims at the development of safe and effective treatment of food allergies.

What is your opinion about the PreDicta network?

To my opinion PreDicta network is an excellent opportunity to gather leading experts in clinical allergy and asthma research. As a consequence every research group within the network will profit from the knowledge of each participant and from the possibility to use the latest technologies of molecular biology, virology and cytology. This advantages will hopefully lead to the elucidation of the mechanisms of allergy-associated diseases.

PreDicta' series of portraits: Spotlight on PreDicta researchers

Alar Aab

Partner 4—SIAF, Davos

Researcher at the Swiss Institute of Allergy and Asthma Research

Which experiment are you dreaming to perform?

I dream to perform the experiments, which are working nicely, without funny technical problems and which results fulfill or exceed my pears and mine expectations.

Without joking – there is a method called bimolecular fluorescence complementation. I would like to use the method to make Rhinoviruses shining in the moment when they are assembled in the cell.

For you, what was the most valuable scientific discovery in 2011?

Hand-Washing Key to Stopping Spread of Disease

News release from the Society for Women's Health Research.

This discovery is simple, but saves huge amount of money

For you, what was the best scientific article published in 2011?

Novel highly sensitive IL-10-beta-lactamase reporter mouse reveals cells of the innate immune system as a substantial source of IL-10 in vivo. Bouabe H, Liu Y, Moser M, Bösl MR, Heesemann J. J Immunol. 2011 Sep 15;187 (6):3165-76.

One book you would recommend?

Understanding Power: The Indispensable Chomsky. Mitchell, Peter and John Schoeffel

Or something from Gabriel García Márquez –"Hundred years of solitude" ?

Which career were you planning while being a child?

I wanted to be a professional swimmer. So far I am very professionally swimming through the life. I must admit that sometimes there is occasionally not enough oxygen available, but friends can help you in this situation to get your breath back again.

Where do you see yourself in 10 years from now?

Being a happy grandfather and teaching my grandchildren to swim, to ride a bike, skiing etc.

Have you participated in other EU projects?

I have been involved in European project for implementation of LOINC standard into the health-care system in Estonia. This standard is meant to standardize health care data transfer between European and non-European countries overcoming linguistic and cultural barriers. We finished the Estonian part in 2011

What is your opinion about the PreDicta network?

It is friendly and enjoyable.

There is rising incidence of asthma and rhinitis in Europe with a substantially high socioeconomic burden. We urgently need for novel preventive, diagnostic and therapeutic approaches. Strong recent evidence associating rhinovirus infections with the origins, triggering and persistence of asthma is the strong epidemiological background of our studies. We now need to understand the pathophysiological mechanisms linking infections to inflammation persistence in asthma and rhinitis. Predicta will serve as the best platform to understand this.

More information on the European project Alar Aab has been involved in:

http://loinc.org/international

http://www.e-tervis.ee/e-labor-loinc.html

Clinical trials started in 2011

An Exploratory Phase IIa Study to Investigate the Biological Activity of Oral FX125L in Adult Patients with Chronic Inflammatory Disease. Sponsor: Funxional Therapeutics Ltd, Country: UK. Start date: 29/11/2011 More information here.

A randomized, double-blind, placebo controlled, incomplete block, 3 way cross over study in subjects with allergic rhinitis to assess the effect of intranasal repeat doses of SB-705498 when administered alone or in conjunction with intranasal fluticasone propionate on the symptoms of rhinitis in the Vienna allergen challenge chamber. Sponsor: GlaxoSmithKline Research and Development Ltd, Country: Austria. Start date: 19/04/2011. More information here.

Active-Controlled Trial of the Safety and Tolerability of MP29-02 in Subjects with Chronic Allergic or Nonallergic Rhinitis. Sponsor: MedPointe Pharmaceuticals, start date: 30/03/2011. More information here.

A multi-centre, randomized, double-blind, placebo-controlled, dose range finding study to identify the optimal (i.e. safe and effective) dose of PURETHAL® Mites SCIT in patients with house dust mites-induced persistent allergic rhinitis/rhinoconjunctivitis. Sponsor: HAL Allergy B.V, Countries: DE (Ongoing) NL (Ongoing) ES (Ongoing), Start date: 23/08/2011. More information here.

Related European projects

- http://www.airprom.eu/ : AirPROM (Airway Disease Predicting Outcomes through Patient Specific Computational Modelling) brings together existing clinical consortia (EvA FP7, U-BIOPRED IMI and BTS Severe Asthma), with expertise in physiology, radiology, image analysis, bioengineering, data harmonization, security and ethics, computational modeling and systems biology.
- http://medall-fp7.eu/ : MeDALL- Mechanisms of the Development of ALLergy
- http://www.chicosproject.eu/: CHICOS: Developing a Child Cohort Research Strategy for Europe
- www.p3agi.eu : to develop a research network of expertise in imaging, genomics and bioinformatics to be utilized in monitoring therapies and disease progression in severe allergic asthma
- FAST: TOWARDS SAFE AND EFFECTIVE IMMUNOTHERAPY OF PERSISTENT LIFE-THREATENING FOOD

Publications from the network

- Misdirected antibody responses against an N-terminal epitope on human rhinovirus VP1 as explanation for recurrent RV infections. *Katarzyna Niespodziana, Kamila Napora, Clarissa Cabauatan, Margarete Focke-Tejkl, Walter Keller, Verena Niederberger, Maria Tsolia, Ioannis Christodoulou, Nikolaos G. Papadopoulos and Rudolf Valenta.* **The FASEB Journal Published online November 25, 2011**

Next events

PreDicta 3rd consortium meeting

PreDicta will hold its third consortium meeting in Davos, Switzerland, on March 17 2012. Partners will present the work performed during the first reporting period of the project. About 15 participants are expected.

EAACI Focused Meeting: DHM 2012 12 - 14 April 2012 Munich, Germany

http://www.wca-2012.com/ : XXI World Asthma Congress 2012 – Québec, Canada, 18 – 21 August 2012

EAACI Focused Meeting: ISMA 2012 5 - 7 October 2012 Rome, Italy

http://www.dc2012.kr/ : 12th International Symposium on Dendritic cells – Daegu, Korea., 7 – 11 October 2012