Interview with the new EAACI President
Reports from EAACI 2009 in Warsaw and more...
New approaches, new break-throughs

Jan Lötvall has been elected as the new president of the EAACI. He shares with us some of his ideas for the development of the Academy, his plans for its new directions, and the challenges that it faces.

He also speaks about the future of Allergy as a specialty. Lötvall says that one of his top priorities is to improve communication between the members of the Academy and the International Allergy Community, and he outlines some of the new tools that will be used to achieve this goal. The aim is to increase access to members of the Academy in virtual time as well as real time.

The Newsletter continues to inform you about the most exciting topics in our field, such as the role played by innate immunity in allergic diseases and the current understanding of T regulatory cells and their clinical implications. Yet another hot topic is the work on genes and global strategies, describing allergy as a multi-organ disease and delineating new approaches that can finally hold out the hope of a cure for our patients.

I would like to take this opportunity to thank our co-editors for the excellent work they do in translating immunology for specialist practice. I would also like to motivate all our readers to make an extra effort to follow these ground-breaking developments and master the new science, as this will translate into daily practice in the very near future. Acquiring this knowledge and using it in daily practice for diagnostic and therapeutic approaches will be decisive for our specialty. This extra effort will distinguish the allergist from other specialties.

After all, it is truly remarkable to see this field of knowledge and application expanding and finally leading to new therapeutic approaches – approaches that hold out the promise of great benefits for our patients!

Claus Bachert
Editor of the EAACI Newsletter
Chrysanthi Skevaki: The theme of this year’s EAACI Congress was “Allergy without Frontiers.” How do you apply that motto on a European and international level?

Jan Lötvall: The pace of political developments in Europe in the last 20 years has been extraordinary, ranging from peace and friendship to open borders. The EAACI defines its mandate as reaching out to all Europe and beyond, and is investing in enhanced communication in the field of allergy. The annual EAACI congress is the ideal platform for disseminating science and knowledge, as well as education and training. Just as importantly, it is the place that unites people from different specialties and disciplines in the common interests of allergy, asthma, and immunology: a place where they can establish and strengthen their professional and personal networks.

Chrysanthi Skevaki: What was your impression of this year’s Congress?

Jan Lötvall: Basing the Congress in Warsaw at the old Palace of Culture was very fruitful. The Palace was not intended as a modern congress venue, but the meeting rooms there served their purpose ideally, and it is always pleasant to locate the Congress in the middle of a city and not in the suburbs. The meeting was of the very highest quality scientifically, and I am very grateful to the VP of Congresses, Cezmi Akdis, as well as our Scientific Programme Committee Chairman Christian Virchow, for their hard work in compiling the excellent programme. Equally, our PCO Congrex and their manager Susanne Rothschild also did a wonderful job with the logistics.

Chrysanthi Skevaki: Which themes do you consider future EAACI Congresses might cover?

Jan Lötvall: Well, local organisers usually propose the Congress theme, and I am looking forward to hearing their suggestions for next year.

Chrysanthi Skevaki: What challenges do you face as the new President of the Academy? And how do you plan to meet these challenges?

Jan Lötvall: The EAACI is increasing in size and strength every year. The enormous growth in recent years has meant an increased workload for the leadership. We have now established our new EAACI Headquarters in Zurich, lead by Executive Director Silvia Schaller, who has put together a bright and energetic team to take on most administrative responsibilities. This is in line with our aims to make the EAACI more professional, which is a crucial step for our organisation at this time.

Another key aim is to involve members and increase their democratic rights in the organisation. We are using several tools to reach this goal, one being increasing the number of democratic elections.

The speed of communications in today’s society is remarkable, and increases from day to day. The EAACI plans to invest in efficient communications tools, so that we can help our members and the allergy community to find information in the most efficient and fastest way possible.

Chrysanthi Skevaki: What are your plans for developing the EAACI during your Presidency?

Jan Lötvall: The EAACI scientific meetings are strong, but may actually increase in number. Our yearly EAACI Congress is the jewel in our crown, but smaller topic-focused meetings may provide additional value to our membership and specialists in different areas of allergy. One such example is the Pediatric Allergy and Asthma Meeting (PAAM) in Venice in November 2009, but additional specialist meetings will be developed and organised in 2010.
In the area of education, the EAACI arranges at least four EAACI/CAAI LEN Allergy schools every year. The next step should be to develop more online educational tools. The EAACI Allergy Knowledge Test is another interesting development, and will most likely gain greater importance in the future.

Our highest priority for the EAACI in the next few years must be to develop communications, including both online communications and other media such as news coverage. We have recruited a professional communications expert, Panthea Sayah, and she is currently developing a communications strategy for the next few years. We look forward to coming back to you with more information about this shortly.

Science and research
Chrysanthi Skevaki: How do you see the future of allergy as a disease and as a discipline in five to ten years?
Jan Lötvall: Allergology as a clinical specialty has different origins in different European countries, and it seems quite difficult to harmonise this specialty. However, it is important to try, and the EAACI is collaborating with UEMS in this regard.

Allergies still continue to increase, and the volume of allergy-associated healthcare is not going to decrease in the near future. Many different specialists treat allergy patients, and we shall have to spread our knowledge about allergy and associated diseases even further. However, medication is becoming more efficient and the understanding of allergy phenotypes is increasing. As a result, the science in this area in the next ten years is going to be crucial to find cures for different allergic diseases. This must be our long-term aim.

Chrysanthi Skevaki: How has the global financial crisis affected allergy research and motivation?
Jan Lötvall: The allergy field does not seem to be suffering any downturn. We enjoy a great deal of interest from different kinds of sponsors, who seem committed to investments in this area. It is clearly important that governments are aware of the huge burden and the unmet needs in the allergy field, and therefore maintain investment in this important disease area.

Chrysanthi Skevaki: Allergy as a disease keeps rising steadily: Do you think people are well informed about allergic disorders?
Jan Lötvall: Public knowledge about allergy is clearly improving. But I also believe that self-management plans for patients need to be improved and largely expanded.

EAACI Communications Tools
Chrysanthi Skevaki: What is your opinion of the EAACI Newsletter?
Jan Lötvall: Spreading information about what is going on in the EAACI is important, and the EAACI Newsletter is one way of doing this. People still appreciate printed information, but I think other communication tools will have to complement the Newsletter in the future. We are in the process of evaluating which tools serve their purpose best to benefit the EAACI membership.

Chrysanthi Skevaki: What is your opinion of the EAACI website, eaaci.net?
Jan Lötvall: eaaci.net is the face of the EAACI, and is one of the most important tools to communicate with members and the allergy community in general. The current format has served the EAACI very well over the last six years, but I am also excited to see that a new EAACI face, or website, is being launched in the autumn.

Chrysanthi Skevaki: a) From an educational perspective (e-learning applications)...
Jan Lötvall: The current EAACI website holds a vast amount of information, and perhaps we can develop this part of the site to provide more CME courses and other types of educational material and develop more webcasts.

Chrysanthi Skevaki: b) From an informational perspective (news, press releases on “hot” issues in allergy and clinical immunology, etc.)
Jan Lötvall: One of my top priorities is for the EAACI to provide its members and the international allergy community with the fastest, most reliable information linked to the latest publications, preferably on a daily basis. This will require substantial investment, and we are now working to see how this could be achieved.

Chrysanthi Skevaki: The EAACI has joined Facebook, following the social networking trend. Can you suggest other ways of social interaction for EAACI members and the scientific community?
Jan Lötvall: Facebook, Twitter, and other social media are providing new tools for communication, and I think every approach should be assessed and used to our benefit. The Facebook EAACI group has grown from two members to 80 in just over a week, and I am confident we shall have many more members. However, we must assess how efficiently these groups communicate and if the media is used appropriately.

Chrysanthi Skevaki: Good luck with your busy schedule and thank you for your time!
Jan Lötvall: Thank you very much. I am certainly looking forward to dedicating my next two years to the Academy.
**Dear EAACI members,**

Time has come to say good-bye and to close the Executive Office in Stockholm. It has been a privilege and a great pleasure for us to serve the Academy and its members for more than a decade.

It has been fantastic to have taken part in the development of the Academy, to see it grow in terms of structure, activities and membership over the years.

We are happy to hand over the baton in regard to the administration of such a dynamic Society and are confident that the Academy will continue to grow strong now with the assistance of the new Headquarters in Zürich.

We certainly will miss our large family, now 5,500 active members in EAACI, which we have become quite close to over the years. We have enjoyed corresponding with you and seeing you from time to time at various meetings around the world. We will certainly have fond memories when we think back on our time with EAACI.

Perhaps some of our paths will cross again somewhere some time.

With our very best wishes,

Catharina Öström, Executive Manager
Deirdre Öwerström, Executive Assistant
Janna Schaffhauser, Membership Co-ordinator

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**The 10th Allergopharma Award, 2010**

The Award was first established in 2000 on the initiative of Allergopharma Joachim Ganzer KG and in collaboration with the European Academy of Allergy and Clinical Immunology. It is intended that the Award should recognize scientific achievement on the part of younger members of the EAACI in the field of allergy and encourage their engagement in further research. Applications for the Award are therefore restricted to members or affiliates of the EAACI, under the age of 40 years, who have conducted their research in a European centre.

An application for consideration for the award shall take the form of a full research paper published in an international peer reviewed journal in 2007/2009, together with a covering letter and curriculum vitae including a list of publications. The applications will be considered by an ad hoc Commission nominated by the EAACI Executive Committee and Allergopharma. The tenth Award will be presented during the European Academy of Allergy and Clinical Immunology Congress, London 2010.

Applications should be submitted before 31 December 2009 electronically to both the EAACI Headquarters (silvia.schaller@eaaci.net) and Allergopharma (oliver.cromwell@allergopharma.de). The research paper, curriculum vitae and a covering letter should be included as three separate attachments. If this is not possible, then postal applications can be sent to EAACI Headquarters, Genferstrasse 21, CH-8002 Zurich, Switzerland (Tel.: +41 44 205 55 33).

Allergopharma Joachim Ganzer KG is committed to furthering excellence in allergy diagnosis and specific immunotherapy through investment in scientific research.
EAACI Website Corner

www.eaaci.net is the leading resource for researchers, physicians, and scholars working in all fields associated with allergy and clinical immunology. Visit www.eaaci.net now to access top educational features from annual EAACI events and more. This year’s digital education experience commenced with the XXVIII EAACI Congress in Warsaw and continues with the summer Allergy Schools.

More specifically:

Webcasts from Warsaw 09 are presented by allergy and immunology specialists in an easy-to-follow, flash-based format

Case Report Series are presented by Junior Members and Affiliates of the Academy

Slide Kit Series, that is PowerPoint presentations from the EAACI Allergy Schools that offer an additional rewarding experience

EAACI official Journals and Journals supported by the EAACI

Also ...

Do not forget: The brand-new EAACI Handouts microsite (www.eaacihandouts.net), launched in Warsaw 09, makes cutting-edge science even more accessible for you. Go to the “Table of Contents” section to search by congress day, or the “Author Index” section to browse by the presenter’s family name. For more, visit the website!

Did you know ... in August 2009, 40.83% of visits to the site originated from new visitors in Europe and beyond?

There are many reasons to visit www.eaaci.net right now, and we plan to offer even more. Stay tuned!

On behalf of the EAACI Web Management Team,
Chrysanthis Skevaki, Co-ordinating Editor

Success in Warsaw!

More than 6000 participants and 43 exhibitors from 94 countries attended the XXVIII EAACI Congress in Warsaw, Poland, 6-10 June 2009. The total number of sessions was 226, including 41 symposia, 16 workshops and 21 Meet the Expert and 7 plenary sessions. The total number of submitted abstracts was 1570. During the Congress, the EAACI 2009 Congress Handouts “microsite” – www.eaacihandouts.net – was officially launched.

The venue for the Congress was the centrally located Palace of Culture and Science in Warsaw. More than 85 national and international journalists were present.

We can look back at another successful EAACI event. See you in London next year!

New Allergy Research and Education Center established in Davos

The Kühne-Foundation, Schindellegi/Switzerland, has launched a new project: the Christine Kühne – Center for Allergy Research and Education (CK-CARE).

CK-CARE is formed by the following professors and centres:

- Prof. Dr. med. Heidrun Behrendt, ZAUM, Munich
- Prof. Dr. med. Cezmi Akdis, Swiss Institute of Allergy and Asthma Research (SIAF), Davos
- PD Dr. med. Roger Lauener, Hochgebirgsklinik, Davos; Zurich University Children’s Hospital
- Prof. Dr. med. Dr. phil. Johannes Ring, Technical University, Munich

CK-CARE will conduct fundamental, clinical, translational and epidemiological research and turn results into clinical practice and information for patients and the public. The ability to coordinate studies involving patients from different environments and leading different lifestyle is fundamental, if we want to understand the mechanisms of allergic diseases, their evolution through life and finally how to treat them more effectively.

Allergy research requires the interdisciplinary cooperation of various medical disciplines (e.g. dermatology, internal medicine, pneumology, pediatrics, otorhinolaryngology, occupational medicine, etc.) as well as natural sciences, engineering science and life sciences (including immunology, climatology, aerobiology, epidemiology, nutrition science, etc.) and psychology and psychosomatics. The allergy research network of the CK-CARE groups will enable this interdisciplinary cooperation and networking at highest level.

Research made by CK-CARE aims to discover novel targets for drug discovery, develop preventive allergy vaccines, investigate gene environment interaction and perform innovative research for diagnosis and better treatment of allergies. Through improved education and training of students, residents as well as in the postgraduate phase, a long-term effect and sustainability will be achieved.

Cezmi Akdis
in Warsaw!
The EAACI Fellowship Award

- Supports research and training of EAACI Junior members and Affiliates (JMAs) by offering the possibility to make short (3 months) or long-term (1 year) fellowships in a foreign European country.
- Increases the mobility of young researchers within Europe. Movement between EAACI members outside of Europe can also be considered.
- Spreads the implementation of new techniques between European laboratories.
- Highlights the work of EAACI JMAs through increased publications and a special Fellowship Symposia at the EAACI annual Congresses.

EAACI is very proud to announce

The Winners of the EAACI Fellowship Awards 2009

LONG TERM FELLOWSHIP:

- Alexandra Nikonova
- Maciej Chabibinski
- Marija Macesic
- Jelena Radosavljevic
- Kestutis Cerniauskas
- Themis Alissafi
- Maria Jose Goikoetxea
- Teresa Garrig Baraut
- Teresa Garrig Baraut
- Francesco Gaeta

SHORT TERM FELLOWSHIP:

- Natalija Polovic
- Marija Macesic
- Peter Kopac
- Adebolajo Adeyemo
- Vito Sabato
- Maciej Chalubinski
- Natalija Polovic
- Teresa Garrig Baraut
- Francesco Gaeta
- Teresa Garrig Baraut
- Vito Sabato
- Peter Kopac

MEDIUM TERM FELLOWSHIP:

- Natalija Polovic
- Maciej Chalubinski
- Teresa Garrig Baraut
- Francesco Gaeta
Allergic diseases such as allergic rhinitis or allergic asthma are characterised by the presence of allergen specific T cells and allergen specific IgE antibodies. It has long been understood how a relevant allergen can activate mast cells or basophils via the specific IgE present on their surfaces. Similarly, the process of specific T cell activation by a relevant allergen is well understood. However, the question of why exposition to an individual allergen leads to production of specific T cell clones and specific IgE synthesis in an individual person remains unanswered.

**Dendritic cells (DCs) are necessary for the development of antigen specific T cell clones from naïve T cells and the subsequent production of specific immunoglobulins by B cells.** DCs have a unique ability to translate external danger signals into a language understood by cells responsible for adaptive immunity such as T cells and B cells. They are considered essential in the initiation and maintenance of the adaptive immune response, including the Th2 type immune response and IgE synthesis. However, the presentation of antigenic peptides by DCs may result in clonal expansion of different T cell types such as Th1, Th2, Th17, and T reg cells. Several exogenous and endogenous factors skew the adaptive immune response towards individual Th type cells. DCs sample airway lumen using long processes that are located between bronchial epithelial cells. In order to facilitate the uptake of foreign particles, DCs utilise a broad range of receptors that recognise molecular patterns, or pathogen associated molecular patterns (PAMPs), present on micro-organisms but not in human tissue. Those receptors are called pattern recognition receptors (PRRs). After recognition and binding by PRRs, foreign particles are ingested and undergo degradation in the endosomes.

Some peptides, usually containing 10-30 residues, are trapped in the binding groove of MHC class II molecules. Binding to MHC class II molecules protects peptides from further digestion and allows them to be transported to the cell surface and presented to T cells. Not every peptide, however, can bind to every MHC class II molecule. Only peptides with a structure that suits the pocket of the MHC class II binding site can be bound. The genes encoding MHC class II molecules are among the most polymorphic genes in the human genome, and the most polymorphic region of those genes encode amino acids located in and adjacent to the peptide-binding groove. This means that the affinity of the binding groove of MHC class II differs significantly in different persons leading to the selection of different peptides for presentation.

There are several practical implications of such a huge variability of the selection process. Firstly, since individual humans are characterised by a unique MHC class II repertoire including the structure of the binding groove, different antigenic peptides will be predominantly trapped by MHC class II molecules derived from one person but not from others. This in turn predisposes the development of immune response directed to some but not to other epitopes. This may explain why the digestion of mite fecal particles by DCs leads to the synthesis of IgE specific to some but not other allergens of Dermatophagoides pteronyssinus or Dermatophagoides farinae. Secondly, the initiation of the immune response directed to epitopes located in the regions of high homology with other antigens (or allergens) may predispose the development of T cells and immunoglobulins, which crossreact with other antigens or allergens. Clinically, this may explain why some patients allergic to house dust mites do not tolerate shellfish, or why patients allergic to latex develop symptoms after eating a kiwi or a banana. Thirdly, when the immune response is mounted against epitopes that share homology with human proteins, an autoimmune disease may develop.

However, the signal provided by MHC class II molecules to T cell receptors is insufficient to trigger a T cell response. Additional signals are necessary to induce optimal T cell activation. Those signals can be provided by co-stimulatory molecules, cytokines secreted by DCs and by other cells as well as by the extrinsic and intrinsic adjuvant factors present in the microenvironment. Those additional signals may exert stimulatory, inhibitory, or modulatory effects. For instance, different cytokines such as interleukin (IL) 12 and IL4 exert opposite effects on the differentiation of naïve T cells. In the presence of IL12, naïve cells differentiate into Th1 cells secreting interferon gamma (IFNγ), while IL4 inhibits differentiation into Th1 cells but promotes differentiation into Th2 cells secreting IL4, IL5, and IL13. DCs are potent sources of IL12. When DCs ingest bacteria they are strongly stimulated via toll-like receptors (TLR), including TLR4 which responds to endotoxin, TLR9 which responds to CpG motifs, and TLR5 which responds to flagellin. That complex activation of DCs via several TLRs leads to the secretion of IL12, a cytokine that strongly favours the differentiation of naïve T cells into Th1 type cells.

In the absence of the stimulation of TLRs, or when TLRs are stimulated suboptimally, antigen presentation occurs in the absence of IL2, that favours differentiation into Th2 cells.
However, in healthy persons, the ingestion of allergens, which do not carry motifs stimulating TLRs, does not result in the development of specific Th2 type immune response and specific IgE synthesis, but leads to the development of T reg cells with a subsequent tolerance of the allergen. One of the reasons for the differentiation of naïve T cells into T reg cells upon exposure to aeroallergens is that no TLR stimulation produces only a very weak up regulation of co-stimulatory molecules. Another reason is that the differentiation into Treg cells is favoured in the absence of IL12 and IL4. Therefore, not only the absence of IL12 but also the presence of IL4 early in the process of T cell differentiation is crucial for the development of Th2 cells.

**In the Airways of House Dust Mite Allergic Asthmatic Patients**

Basophils seem to be the main source of IL4 during the process of sensitisation to dust allergens. The influx of basophils to the airways is mediated by chemo-attractant mediators released by epithelial cells exposed to house dust mite allergens. Recent studies demonstrated, in experimental asthma models, that bronchial epithelial cells expressing TLR4 play a very important role in the initiation and maintenance of allergic reaction. They are necessary and sufficient to attract DCs to the airways and their subsequent activation in the lungs, which results in the priming of effector T helper response to dust mite allergens. In the airways, the activation of TLR4 on structural cells leads to the production of several biologically active mediators, including thymic stromal lymphopoietin (TSLP) and granulocyte macrophage colony stimulating factor (GM-CSF), which attract and activate immune cells, including DCs.

To summarise, although signals delivered by MHC-TCR interaction accompanied by co-stimulatory molecule and cytokine signalling are sufficient to induce T cell response, they do not fully explain the development of allergic sensitisation. Interestingly, the mode of activation of bronchial epithelial cells depends on some properties of individual antigens/allergens.

**Allergens Themselves Possess Several Features Which Affect Immune Response**

And which can be important for the development of allergic diseases. Only a minority of proteins present in our environment is proved to be allergens. Several studies tried to find characteristic physico-chemical features that would distinguish allergens among other proteins frequently encountered in the human environment. The physico-chemical analysis of the major allergens has shown that most are small (<70kD), negatively charged proteins with low hydrophobicity and high stability, with a structure that is modified posttranslationally by glycosylation and the presence of disulphide bonds. These posttranslational modifications increase the stability and bioavailability of allergens. However, none of those parameters alone or in combination results in a prediction that a given protein would induce IgE dependent immediate hypersensitivity.

**Allergens Lack Typical PAMPs and Therefore do not seem to be the Primary Target for PRRs**

present on DCs. Analysis of the individual major allergens provided some insight into our understanding of how allergens can induce immune response. The most studied of all the allergens are the major allergens of the Dermatophagoides species such as Der p1, Der f1, Der p2, and Der f2. Many dust mite allergens have protease activity including cystein protease (Der p1 and Der f1) and serine protease (Der p3, Der p6, Der p9) activities. The activities have been extensively studied as co-factors facilitating the sensitisation and development of allergic diseases. Cystein protease activity of Der p1 is essential for its ability to induce Th2 type immune response. Enzymatically inactive Der p1 has a much lower ability to induce the immune response. However, neither Der p1 nor other cystein proteases such as papain can directly activate DCs. Bronchial epithelial cells can be directly activated by Der p1, and the activation only partially depends on its enzymatic activity. Most interestingly, basophils can also be directly activated by Der p1 and by other cystein proteases such as papain. The activation of basophils by cystein proteases such as papain is not dependent on IgE but depends on its protease activity and leads to the secretion of IL4. This non-IgE dependent, direct induction of basophil IL4 secretion by Der p1 may be a crucial source of “early” IL4 in the induction of Th2 immune response to dust mites. Moreover, recent studies provided evidence that basophils can also function as antigen presenting cells and not only as accessory cells. This seems to be particularly important in enzymatically active allergens such as dust mite allergens.

**Another Major Allergen of D. pteronyssinus, Der p2, Interacts with TLR4 Enhancing Cell Activation upon Endotoxin Exposure**

Der p2 has no enzymatic activity and thus cannot be directly activated by Der p1. However, Der p2 can replace the function of MD-2, and at least in experimental settings, triggering TLR4 on bronchial epithelial cells by house dust mite allergen was necessary and sufficient to activate mucosal DCs and the induction of allergic inflammation. TLR4 dependent activation of epithelial cells led to the secretion of many biologically active mediators such as chemokines CCL2 and CCL20 and cytokines such as GM-CSF, TSLP, IL25, and IL33, which resulted in the subsequent influx of inflammatory cells to the airway mucosa, their activation and propagation of allergic airway inflammation.

**Finally, Pollen Allergens Carry “Pollen Associated Lipid Mediators” that have Strong Biologic Activities Affecting the Immune Response**

Those include phytoprostanes which express immunomodulatory function acting through the PPAR receptor, and oxylipins, which mainly function as chemotactic molecules.

In all, innate immunity plays an important role in the induction of allergic inflammation. Both characteristic features of allergens and the components of the innate defence system in the human body are crucial for providing instructions to T and B cells and for prompting them to develop a specific immune response and allergic inflammation.

Krzysztof Kowal
Medical University of Białystok, Poland
EAACI 2009
PEDIATRIC ALLERGY & ASTHMA MEETING

Venice - Italy
12-13-14
November 2009

www.eaacipediatrics-venice2009.org

MAIN TOPICS

• Allergy as a skin barrier disease
• Role of early allergy in childhood asthma development
• Anaphylaxis in children and infants
• Inflammation as a systemic problem
• Early allergy vs lung function development
• Anti-inflammatory treatment of airways: current and future
• Role of LABA and Leukotriene-receptor antagonist in childhood asthma
• Asthma diagnosis: still a challenge?
• Clinical phenotypes in childhood asthma

• Nose and lung interactions: importance of nose when treating asthma
• Imaging the airway
• Insights in oral tolerance
• Food allergy: towards clinical practice guidelines
• Cow’s milk allergy prevention and treatment
• Atopic eczema in children: novel approaches
• Immunotherapy in children: should we use SCIT or SUT? High vs low doses?
• Novel forms of immunotherapy
• Drug allergy in children

AND MORE...

SCIENTIFIC SECRETARIAT
EAACI Section on Pediatrics Board
Antonella Muraro M.D., Ph.D., Susanne Halken M.D., Ph.D.
Contact:
Antonella Muraro M.D., Ph.D.,
Pediatric Allergy Unit, Food Allergy Centre, Veneto Region, Department of Pediatrics, Padua General University Hospital
Via Giustiniani 8 - 35128 - Padova Italy
email: eaacipediatrics2009@pediatria.unipd.it

ORGANIZING SECRETARIAT
key congress & communication
Via Makalié, 75 - 35138 Padova - ITALY
Ph. +39 049 8729511 - Fax +39 049 8729512
E-mail: eaacipediatricsvenice2009@keycongress.com
Exposure to allergens is one of several factors determining sensitisation and allergic symptoms. Exposure to aeroallergens from pollen is assessed by counting allergenic pollen in ambient air. However, proof is lacking that pollen count is representative for allergen exposure. We therefore monitored simultaneously birch, grass, and olive pollen counts and their corresponding major pollen allergens Bet v 1, Phl p 5, and Ole e 1 across Europe.

Already in Europe – in Munich, Germany – we found that the same amount of pollen from different years, different trees, and even different days released up to 10-fold different amounts of Bet v 1. Thus, exposure to allergen is poorly monitored by only monitoring pollen count. Monitoring the allergen itself in ambient air might be an improvement in allergen exposure assessment.

The objective of the HIALINE project is to evaluate if these effects found in Munich are also measurable over a larger geographic area like Europe, and at the same time implement an outdoor allergen early warning network, in addition to the pollen forecasts. The climatic factors that influence allergen exposure will be extracted and used to calculate the effect of climate change on local airborne allergen exposure. Current users of national pollen information services (atopic patients, physicians, and health authorities) will benefit.

The major allergens from the top three airborne allergens in Europe (grass, birch, and olive) are sampled with a cascade impactor, extracted and analysed by allergen specific ELISAs. Pollen counts are measured by standard pollen traps. Weather data are correlated. The allergen forecast will be calculated by incorporating our measurements and climatic factors in the SILAM pollen forecast programme.

Expected outcomes are the implementation of a network of European outdoor allergen measurements to improve predictions of allergic symptoms. In addition, the climatic factors that govern allergen exposure in outdoor air will be established. These can be used to calculate the effect of climate change on the health effects of airborne allergens.

For more information, please see: www.hialine.com

Jeroen Buters, Project Co-ordinator
Lorenzo Cecchi, Project Dissemination Leader

Acknowledgement: The research leading to these results was funded by the Executive Agency for Health and Consumers under grant agreement No 2008 11 07.
Monitoring Asthmatic Patients to Single Out Those at High Risk

Bronchial asthma is a chronic disease. Its prevalence has steadily increased in industrialised societies. This heterogeneous disease is clinically characterised by variable airway obstruction leading to the impairment of lung function and symptoms such as dyspnea and wheezing. The majority of asthmatic patients achieves normalized airflow spontaneously or after appropriate therapy. However, persistent, irreversible airway obstruction develops with a subgroup of patients despite intensive bronchodilator and anti-inflammatory therapy. In clinical practice, more severe asthma, accelerated loss of lung function, and increased mortality rates characterise this group. Nevertheless, some severe asthmatic patients can achieve normalized lung function.

The association between accelerated loss of lung function and deaths related to increased asthma is particularly important from the epidemiological and clinical points of view. The ability to single out patients that risk developing progressive, irreversible damage to their lungs at an early stage in the disease and treating them with intensive, novel therapeutic strategies may help to attenuate the progression of the disease. Unfortunately, relatively little is known about the pathophysiology of progressive, irreversible airway obstruction in asthmatics. Smoking is the most important factor associated with increased risk of persistent airflow limitation for healthy people, although only a minority of smokers develops lung impairment. Asthmatic patients with no history of smoking can develop progressive, irreversible obstruction, indicating that asthma itself leads to progressive lung function decline. Epidemiological studies indicate that in nonsmoking asthmatic patients, several factors are associated with an increased risk of accelerated lung function impairment. These include atopy, increased airway hyperresponsiveness, increased reversibility upon inhalation of beta agonist, and the advent of asthma after 18 years of age. Moreover, low baseline lung function, long asthma duration, and high diurnal variability of lung function are associated with accelerated lung function decline. Recently, it has been demonstrated that frequent asthma exacerbations are also strongly associated with excess lung function decline in asthmatics. This progressive lung function decline has been linked to airway wall remodelling and eosinophilic inflammation.

Several indices of airway inflammation and airway remodelling have been compared in severe asthmatic patients with and without persistent airway obstruction. Analysis of bronchial biopsies revealed that only the smooth muscle area was significantly different in patients with persistent asthma, in comparison with those with intermittent airway obstruction. The smooth muscle area was significantly greater in the former group, and inversely correlated with FEV1. No other airway remodelling markers, such as submucosal fibrosis, reticular basement membrane thickness, or epithelial detachment, was significantly different in patients with persistent airway obstruction. The comparison of concentrations of several cytokines, growth factors, chemokines, matrix metalloproteinase-9 and its inhibitor TIMP-1 in induced sputum revealed no difference between the subgroups studied. Moreover, sputum concentration of markers of eosinophil and neutrophil activation did not differ significantly between the subgroups. Similarly, neither was the concentration of exhaled nitric oxide in exhaled air different. Finally, the application of high resolution computed tomography (HRCT), with careful assessment of airway wall thickness and the cross-section of airway lumen, did not distinguish patients with progressive airway obstruction from those with intermittent airway obstruction.

It is crucial to establish a method that evaluates asthmatic patients and singles out those at risk of developing a severe form of the disease or irreversible airway obstruction. Several non-invasive methods, such as assessing exhaled nitric oxide concentration, determining several physical and chemical features of exhaled breath condensate or induced sputum, and lung function tests including bronchial challenges and image techniques, have been used to evaluate asthmatic patients for several years. Unfortunately, no non-invasive single marker has been found that could be applied repeatedly to classify high-risk asthmatic patients with high sensitivity and specificity. Moreover, no known indicator or marker can single out, with absolute specificity and sensitivity, patients at risk of developing persistent airway obstruction later in their lives. Further studies are vital to standardise current methods and extend the diversity of tools used to classify high-risk asthmatics, so they can receive appropriate therapeutic strategies aimed at diminishing the risk of developing severe disabilities due to asthma.

Table 1. Possible application of several diagnostic methods for evaluating airway inflammation and remodelling in asthmatic patients.

<table>
<thead>
<tr>
<th>Method</th>
<th>Inflammation</th>
<th>Remodelling</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry + reversibility + methacholine challenge</td>
<td>poor</td>
<td>good, indirect</td>
<td>poor, good, indirect</td>
</tr>
<tr>
<td>Exhaled NO concentration</td>
<td>good</td>
<td>poor (use Only eosinophilic inflammation)</td>
<td></td>
</tr>
<tr>
<td>Exhaled breath condensate analysis</td>
<td>good, poor</td>
<td>Research lab needed</td>
<td></td>
</tr>
<tr>
<td>Induced sputum analysis</td>
<td>good, poor</td>
<td>Research lab needed</td>
<td></td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
<td>vary, good</td>
<td>vary, very good</td>
<td>Invasive, research lab needed</td>
</tr>
<tr>
<td>High resolution computed tomography (HRCT)</td>
<td>poor, good</td>
<td>High X-ray exposure</td>
<td></td>
</tr>
</tbody>
</table>

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Krzysztof Koseal
Medical University of Bialystok, Poland
Current Understanding of the Immunology of T Regulatory Cells and Their Clinical Implications

Immune regulation

The immune system is subject to complex regulatory controls. T cells may up regulate (helper function) or down regulate (suppressor function) the immune response. T cells can function as both effector cells in cell-mediated responses and as helper cells (Th) in both humoral and cell-mediated responses. Th1 and Th2 subsets secrete cytokines that can suppress one another to a certain extent. A family of CD4+ T-cells that was recently shown to suppress the responses of other T cells is called T regulatory cells (T regs). These studies suggest that diverse populations of T reg cells play an important role in regulating immune responses and maintaining functional tolerance [1]. It is likely that T reg cells play a role in regulating self-tolerance but may have a harmful effect on tumour immunity [2].

Regulatory responses appear to be compromised in allergic individuals and may be reconstituted to some extent with specific allergen immunotherapy. Generally, most immune responses show a combination of both features of Th1 and Th2 pathways and a prolonged immunisation process may lead to one pathway becoming the most dominant. In experimental models, T reg cells can suppress Th2 responses to allergens, airway eosinophilia, mucous hypersecretion, and airway hyperresponsiveness. Cytokines, including transforming growth factor beta (TGF-β) and interleukin (IL) 10 produced by Th3/Trl (T reg 1) cells, are of interest because they can mediate immunosuppressive effects and may be involved in the induction of mucosally induced tolerance [1].

Identification of T reg cells

The existence of a dedicated regulatory population of T cells was the subject of significant controversy among immunologists for many years. Recent advances in medical science have decisively established their existence. Several subsets of T reg cells have been reported, each with a distinct surface phenotype, cytokine profile, and mechanism of action for suppressing immune responses. Initially, high CD25 (IL2 receptor α chain) expression was used to identify the majority of human T reg cells. The T cell population bearing the CD4+CD25+ phenotype houses both activated T helper cells and T reg cells [3]. This is interesting because it was proven that patients with persistent herpes virus infections usually have a significant decrease of the marker of early positive activation CD3+CD25+ [4]. It was found that the herpes simplex virus (HSV) conferred protection against atopy amongst western populations that resulted in less prevalence of atopy compared to non-infected individuals [5]. A common immune suppression strategy used by such pathogens involves the increased production of the regulatory cytokines such as IL10 and/or transforming growth factor beta (TGFβ) by innate immune cells or by way of the generation of T reg cells [6]. These cytokines, by down regulating the function of antigen-presenting cells and effector T cells, are crucial for the development of tolerance against allergens [5].

Numerous molecules have been recognised that make it possible to differentiate these two populations both phenotypically and functionally. A considerable number of other surface markers has also been shown on T reg cells but their expression is not as great or as consistent as CD25 [7].

Recent discoveries have identified the intracellular protein FOXP3 as a key molecule involved in driving the activity of T regs, and it is currently being used as a marker to enumerate these natural T reg cells (CD4+CD25-high Fox p3+) that constitute 5–10% of the peripheral T cell pool in humans and mice (Picture 1). These do not proliferate in response to either polyclonal anti-CD3 stimulation or antigenic stimulation and, furthermore, can inhibit the proliferative responses of CD4+CD25 negative T cells [3].

The majority of peripheral natural T reg cells develops in the thymus, but CD4+CD25-high Fox p3+ cells have also been induced in the peripheral lymphatic organs, in an antigen specific, TGFβ dependent manner through low-dose antigen (peptide) exposure [9].

All T cells begin as CD4-CD8-TCR- cells when at the DN (double-negative) stage, where an individual cell will combine its T cell receptor genes to form a functional molecule which they in turn test against cells in the thymic cortex for a minimal level of interaction with the host’s MHC. If they receive these signals, they proliferate and express both CD4 and CD8, becoming double-positive cells. Thymic differentiation of these cells occurs through positive selection events facilitated by medullary epithelial cells (particularly within Hassall corpuscles) and thymic stromal lymphopoietin (TSLP) activated medullary dendritic cells (DCs) [10]. It appears that during the DP (double-positive) stage they are selected by their interaction with the cells within the

TSLP activated medullary dendritic cells (DCs) [10]. It appears that during the DP (double-positive) stage
thyroid. This begins the transcription of Foxp3 and the become T reg cells, although may not begin to express Foxp3 until the single-positive stage, at which point they are functional T regs.

Discovery
Suppressor T cells were first identified by Gershon and Kondo [11, 12] during studies designed to understand the process of “high-zone” tolerance. Injection of supra-optimal doses of an antigen including sheep red blood cells (SRBCs) resulted in specific tolerance or non-responsiveness to subsequent challenge with that antigen.

Research in this area rapidly shifted from studies of the function of intact T cells to studies of their soluble products [13]. By the late 1970s, soluble factors from T suppressor cells were described by several groups, and cloned T cell hybridomas that produced such factors were generated. T-cell suppression was regarded as being mediated by numerous soluble antigen specific and non-specific factors that comprised a functionally unique network [14].

Function
The physiological role of CD4+ regulatory cells expressing the IL2 receptor α-chain (CD25) [15] is to protect the host against the development of auto-immunity by regulating immune responses against antigens expressed by normal tissues through suppressing the activation and function of other T cells [16]. Since tumor antigens are largely self antigens, T regs may also prevent the tumour-bearing host from mounting an effective antitumour immune response. Previous studies have shown that elevated numbers of CD4+CD25+ T regs may be found in advanced cancer patients and that a high frequency of T reg cells is associated with reduced survival [17]. CD4+CD25+ T reg cells play an important role in controlling tumour growth. In addition, anti-CD25 therapy is now recognised as enhancing the therapeutic efficacy of GM-CSF secreting B16 tumour cells and prolonging the survival of animals with tumours. Collectively, the research data suggest that the efficacy of cancer vaccination could be enhanced by treatment with agents that lead to the preferential depletion of CD4+CD25+ T regs, such as compounds that target cells expressing the IL2 receptor CD25 subunit [18].

We now recognise that the suppression of T reg cells in cancer patients has a positive effect on their condition. DAB389IL2 (also known as denileukin diftitox and ontak) is capable of selectively eliminating CD25 expressing T regs from the PBMCs of cancer patients, resulting in the enhanced stimulation of proliferative and cytotoxic T cell responses without inducing toxicity on other cellular subsets with intermediate or low expression of CD25. Consequently, DAB389IL2 has been shown to significantly reduce the number of T regs present in the peripheral blood of metastatic renal cell carcinoma (RCC) patients and abrogated T reg mediated immunosuppressive activity in vivo (picture 2) [19].

Auto-immune diseases are rare because of the existence of a mechanism of peripheral tolerance that ultimately controls autoreactivity. Multiple mechanisms of peripheral tolerance exist including deletion, anergy, and suppressive cytokines.

In allergic responses, CD4+CD25+ T cells have the capacity to suppress Th2 responses to allergens and IL10 producing T reg cells. In allergic asthma, these cells are capable of selectively eliminating allergen-specific Th2 responses. CD4+CD25+ regulatory T cells are an essential chain in various pathological conditions including rhinitis, atopic dermatitis, and asthmatic bronchitis. This also implies that many fungi including Candida albicans may cause various pathological conditions starting from persistent vaginal and oral candidiasis to severe systemic conditions in immunocompromised patients. It is important to mention that some fungi (including Candida) have common antigens with skin, gastric mucosa, esophageal mucosa, pulmonary mucosa, vaginal mucosa, and the kidneys and may in case of chronic infection result in auto-immune pathologies. [21].

Future perspectives
Regulatory T cells are an indispensable cellular constituent of the normal immune system with a crucial role in establishing and maintaining immunologic self-tolerance and immune homeostasis. Ongoing studies show that they are an essential chain in various pathological conditions including tumours, allergies, fungi related and auto-immune diseases and will increasingly contribute to our understanding of these processes in the near future. It is anticipated that new discoveries will disclose a potential clinical benefit of T regulatory cells for the treatment of immunological diseases and the control of physiological and pathological immune responses.

Dr. Michael Rudenko MD, PhD
Official Representative of EAACI
ENT Section JMAWG
mrudenko@interasma.org

Prof. Jozef Dumanar
Head of Research Mycological Institute FMHH, NJ, U.S.
medicalsmycologist@gmail.com

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Genes code the proteins that play essential roles in the pathogenesis of allergic diseases. The components of IL4/IL13 signalling pathway such as cytokines, receptors, and intracellular signalling molecules (STAT6) regulate the level and type of immune response. IL4 and IL13 signal through STAT6 and increase production of IgE by plasma cells. Genetic variants in these genes, leading to deviations in expression of the proteins or functions of the proteins, affect the total IgE level, related to the risk of allergic diseases (Diagram 1).

Studying genetics has had a huge impact in establishing the importance of locally acting factors in allergic illnesses. Not all atopic individuals have allergic disease and not all affected individuals have the same pattern of disease. This implies variation in the target organs due to tissue specific factors.

End-organ cells (e.g. lung fibroblasts, smooth muscle, epithelium) respond differently to environmental stimuli than those from healthy volunteers. Allergic disease and end-organ phenotypes (lung function, bronchial hyperresponsiveness or BHR) show heritability distinct from atopy. The genetic factors predisposing to atopy are different to the genetic factors predisposing to particular allergic diseases. End-organ specific genetic factors, acting locally and predisposing to allergic disease (atopic dermatitis, asthma), are not atopy genes, such as locally acting factors in atopic dermatitis (Diagram 2).


Allergy


(a) A schematic of the profilaggrin molecule (predicted from the ten-repeat allele FLgN) showing positions of known loss-of-function FLG mutations, all of which are either nonsense or out-of-frame deletion mutations. Variants shown in red are those known to be prevalent in at least some populations; those shown in black appear to very rare or family specific. The domain structure of the profilaggrin protein is as follows (from N terminus, left): green 1/4 S100 domain; light green 1/4 B domain; blue hexagons 1/4 partial filaggrin repeats; red hexagons 1/4 filaggrin repeats; black 1/4 unique C terminus.

(b) Immunohistochemical staining of skin biopsy material for filaggrin (monoclonal antibody 15C10) shows abundant keratoxyalin granules in normal epidermis, but in the skin of an RS01X/R2447X compound heterozygote, there is appreciable but greatly reduced staining. Original magnification = 400x.

(c) Immunoblot analysis shows that a greatly reduced amount of a truncated profilaggrin molecule (arrow) is expressed in the RS01X/R2447X compound heterozygote compared with a normal control. Processed filaggrin was not detected, implying that the mutant proprotein cannot be processed normally. The R501X homozygote, lacking the 15C10 epitope, shows neither profilaggrin nor filaggrin staining. Keratin 14 staining of a duplicate blot was performed as a loading control.

Genes also control timing. What point of life is important for the development of the disease? Some genes are linked to the onset of the disease in early or late childhood, while others come into play in adulthood (e.g. ADAM33 and early decrease in lung function, ORMDL3/GSDL and early onset of asthma).

Environmental exposure is often highly correlated (e.g. diet, smoking, socio-economic status), so confounding can make it difficult to identify what is important. Genetic variants are unlikely to be confounded by an environment. Functional genetic variants in biological pathways that modulate response to environmental exposure help to prove causality. For example, in studies on the protection offered by farming environments against the development of allergic diseases in children growing up in proximity to dairy farming through lipopolysaccharide (LPS) exposure (endotoxins), genetics can help disentangle relevant factors from confounders (Bruce S. et al. J Med Genet. 2009 Mar; 46(3):159-6) (Diagram 3).

Treatment of patients is another example of environmental exposure, as the polymorphism of genes can influence the different effects of treatment. Genetic factors can define a more responsive group of patients for a specific type of treatment.

Allergic disease genetics is complex but reflects the complexity of the phenotype.

When we define disease based on common clinical symptoms, we must bear in mind that each patient is different despite sharing some features. Genetics modulates the level and the type of immune response and the response to the environment, as well as defining locally acting factors e.g. barrier function. Conversely, genetics predicts disease poorly if we regard it as one single entity and base the diagnosis on common symptoms alone.

The next challenge is to use genetics to cluster individuals with common symptoms to improve predictions of outcomes and treatment response. Genetics will help us understand predisposition with early detection and allow us to personalise therapy, by dividing patient populations into different subgroups based on genetic factors, and achieve a better response to specific treatments.

Atopic dermatitis is the most common disease in young children. Unfortunately, at this time we cannot predict which patients will have the disease for their entire lives. In the largest cross-sectional study of a cohort of 2,270 children with a diagnosis of atopic dermatitis confirmed by physicians, nearly 66% had symptoms of asthma or allergic rhinitis and 38% had both associated with their atopic dermatitis. Nearly 80% reported some additional allergic illness (asthma, allergic rhinitis, seasonal allergy, food allergy, animal allergy, or drug allergy) by the third year of life (Kapoor R, et al. J Am Acad Dermatol 2008;58:68).

Patients with atopic dermatitis have abnormal skin barrier function and become sensitised.
Young children are easily sensitised by contact with allergens such as food proteins as well as house dust mite particles through damaged skin. In addition, these patients are heavily colonised by staphylococci which secrete various toxins.

Atopic dermatitis is strongly associated with filaggrin gene mutations, some of which have a unique phenotype that predisposes these individuals to early onset of severe persistent atopic dermatitis and asthma associated with other allergies. Th2 cytokines (IL4 and IL13) down regulate filaggrin gene expression as well as the gene expression of other structural proteins of the skin (loricrin and involucrin). This suggests a role for anti-inflammatory immunomodulatory therapy in this disease (Diagram 4).

The standard approach to the treatment of atopic dermatitis, according to U.S. guidelines, includes topical corticosteroids applied to areas of eczema. Intermediate- and high-potency corticosteroids should be used for the treatment of clinical exacerbation and applied to affected areas of skin over short periods of time. Patients should be instructed to apply topical corticosteroids to skin lesions and to use emollients on uninvolved skin (Summary statement 16, 17, Ann Allergy Clin Immunol 2004;93:S1).

The British National Formulary states: “In order to minimise the side-effects of a topical corticosteroid, it is important to apply it thinly to affected areas only, no more frequently than twice daily, and to use the least potent formulation that is fully effective.” (52. Section 13.4. British Medical Association and Royal Pharmaceutical Society of Great Britain. London: BMJ Publishing Group/ RPS Publishing, 2006)

The European Academy of Allergy and Clinical Immunology and The American Academy of Allergy, Asthma and Immunology in the PRACTALL Consensus Report note: “The side effects of uncontrolled topical steroid use, particularly on delicate skin areas, are well documented, and therefore topical steroid preparations should be applied no more than twice daily as short-term therapy for acute eczematous lesions.” (Allergy 2006;61:969 & J Allergy Clin Immunol 2006;118:152-69)

Early intervention strategy


Diagram 5. PRACTALL Consensus Report. J Allergy Clin Immunol 2006;118

Proactive therapy is an attempt to control residual disease with minimal use of anti-inflammatory drugs and to avoid the application of an active drug to non-involved skin. The choice of a proactive therapy regimen is favoured by immunological data, clinical efficacy data, quality of life data, and phar-
Perspectives of specific treatment of atopic dermatitis

Allergen avoidance is already part of the recommendations. Data confirms the efficacy of specific immunotherapy in adults with established atopic dermatitis (Werfel T, Drugs Today (Barc). 2008 Dec;44 Suppl B:47-9), and a study from Italy suggests that sublingual immunotherapy may benefit children with definite sensitisation and mild to moderate atopic dermatitis (Pajno GB, Lombardo F, Canonica GW, Passalacqua G, et al. J Allergy Clin Immunol. 2007 Jul;120(1):164-70. Epub 2007 Jun 1.). However, not enough data yet supports the routine recommendation of this approach.

Thinking much more globally, the World Health Organization (WHO) is attempting to reduce the risk of chronic respiratory diseases and allergies through GARD. Each inhabitant of this planet is exposed to risk factors of chronic respiratory diseases: 2 billion people inhale products of biomass fuel combustion, 1 billion smoke tobacco, 300 million have occupational exposure, and everyone has contact with allergens. By 2030 the prevalence of chronic respiratory diseases will increase: chronic obstructive pulmonary disease (COPD) will be the fourth cause of death, there will be more than 8 million tobacco-related deaths (Plos Med 2006), biomass fuel combustion will result in more than 10 million deaths (Ezzatti, Science 2005), and more than 50% of the global population will be allergic.

WHO defines severe asthma as “Uncontrolled asthma that can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children).”

Severe asthma comprises three groups that present different public health messages and challenges: untreated severe asthma; difficult-to-treat severe asthma; and treatment-resistant severe asthma (asthma for which control is not achieved despite the highest level of recommended treatment and asthma for which control can be maintained only with the highest level of recommended treatment).

In high-income countries, patients can receive adequate diagnosis and treatment, but they are insufficiently diagnosed and treated. A disease-specific approach is required. The goals of GARD are to improve the diagnosis, treatment, and education of patients.

In middle- and low-income countries, few or very few patients receive adequate diagnosis or treatment. The first goals of GARD are to reduce under-diagnosis. The second goals of GARD are to provide accessible, affordable, and acceptable treatment for all patients. In the most of these countries, this will require a comprehensive approach integrating all major non-communicable diseases. In addition, health promotion and prevention are essential in all countries.

The management of allergic pathologies as multi-organ diseases should be initiated as a global tactic, starting from genes, the environment, and patients and reaching further from patients to governments. We must aim to reduce the burden of these diseases by implementing global strategies and making this planet a world where all people can breathe freely.

Dr. Michael Rudenko MD, PhD
Official Representative of EAACI ENT Section
Junior Member Working Group
Email: mrudenko@interasma.org

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