Welcome to Barcelona in June 2008
Revised EP3OS Guidelines
Innate Immunity Link with Hygiene
Novel and Controversial Issues in Asthma
and more...
Dear EAACI-members,

Let me first of all wish you a Healthy and Happy New Year, in which you will have many opportunities to increase your knowledge as well as satisfaction from your profession!

The European Academy of Allergology and Clinical Immunology and the EAACI Newsletter will certainly accompany you through the year, when you look for scientific top news and practice-oriented guidelines, or when you join an international congress or allergy school. In less than six months we all meet in Barcelona for the yearly EAACI Congress. Ignacio Ansotegui and his team have prepared an extensive and stimulating programme, covering all aspects of the clinical care of allergic diseases from pediatrics to geriatrics. Apart from science, Barcelona will surprise us by its arts and lifestyle. For more information, please read pages 6 and 7 of this issue.

As always in the EAACI Newsletter we present a number of top articles – still easy to read – this time on innate immunity, urticaria, immunotherapy, recombinant allergens and controversies in asthma. The article by Maciej Chalubinski on pages 15–16, “Cellular Therapy for Asthma: Science Fiction or Science Fact?”, is a must, whether you are a pneumologist or not. As an ENT-surgeon, and immunologist, I would also like to draw your attention to the upper airways, where great progress has been achieved in putting together the European guidelines for rhinosinusitis and nasal polyps. It is pleasing to see how much “upper airway” and “lower airway” specialists can learn from each other!

That the EAACI is an active society is shown by the reports on last year’s meetings and events. In this issue the EAACI President, Roy Gerth van Wijk, focusses on new ideas about congresses, educational programmes and transatlantic initiatives. Finally, why not experience EAACI live by visiting the website. Here you will find expert opinions, position papers, step-by-step case reports and a lot of useful information, but also webcasts of keynote lectures.

Be prepared for Barcelona and mark the dates in your busy schedules. And enjoy reading the Newsletter!

Claus Bachert
From Göteborg to Barcelona

We are in the habit of referring to congresses when we speak about EAACI. Thus, 2007 was the year of Göteborg, and 2008 will be the year of Barcelona. Although our congresses are the main events held by EAACI, we should not forget that the annual meetings are part of a much wider programme to promote research, knowledge exchange, training, and education. Our Academy makes an effort to support Allergy Schools, meetings, and educational programmes. These meetings included the 2nd International Symposium on Molecular Allergology (ISMA) in Rome in April, and the joint EAACI-ERS symposium organised by the EAACI pediatrics section and the ERS pediatric chapter in Portugal in October.

EAACI endorses an important series of Allergy Schools. In 2007 we supported the 5th EAACI-GA²LEN Davos Meeting, which as always was a very successful event, focussing on immunology. The Oxford Allergy School and the Allergy School in Cluj Napoca, Romania, covered general aspects of clinical allergy, whereas the Bischenberg-Bischoffsheim Allergy School was devoted to the use of recombinant allergens in diagnosis and treatment. Other interesting schools were held in Helsinki and Crete. The Allergy School in Cork on food allergy had to be postponed, and will be held in Denmark instead. EAACI also supported the Paprica Programme in 2007. This educational programme for general practitioners was held in the Netherlands in April and in Lithuania in November.

Going beyond our borders is not simply a matter of geography. When organisations work together, they are prepared to look beyond their own boundaries. Currently, EAACI is exploring new ways of co-operating with other organisations such as WAO and ERS. In autumn 2007, both EAACI and WAO signed an agreement to hold a joint EAACI-WAO congress in 2013 in Europe. In November 2008, EAACI will meet WAO and Interasma during the World Asthma Congress to be held in Monte Carlo.

Another established form of co-operation is the PRACTALL Initiative, one of the most important liaisons with the AAAAI. In August 2007, the American Academy organised a workshop in Aspen on indoor allergens and chronic allergic diseases. It will be the turn of EAACI in 2008. We intend to hold a PRACTALL meeting on allergy, asthma, and sports in Barcelona, as was scheduled in February 2007 to keep pace with the Olympics in 2008. The amount of scientific information collected already by both organisations is substantial. The goal is to update our information and to spread the message that neither allergy nor asthma should constitute any kind of barrier for allergic patients or athletes. I look forward to working with Tom Casale, the president of AAAAI, and his team.

The EAACI congresses are our milestones and our Congress presidents, our Vice President for Congresses and the SPC co-ordinator go to considerable effort to ensure their success. However, we do not forget all that has been achieved in the periods between congresses.

I take the opportunity now to thank all the active members of EAACI. You make such a difference.

Roy Gerth van Wijk, EAACI President
EAACI Website News

EAACI.net is increasingly becoming an indispensable resource for researchers, physicians, and scholars.

Visit www.eaaci.net now and make use of the various E-learning centre features, such as:

- Expert Opinions. Get the latest one, by Isil Barlan (Marmara University, Istanbul, Turkey) on “SUBLINGUAL IMMUNOTHERAPY: What is the Role in mucosal tolerance induction?”.
- Position Papers. Read the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (EPOS) and discover all you need to know about these increasing health problems.
- Web Casts. You no longer need to worry about missing out on the keynote lectures of the 5th EAACI-GA2LEN DAVOS meeting. Now you can make full use of this interactive resource by eaaci.net and listen to presentations given by world top immunologists, view their slides and take the assessment test. In addition you will be rewarded by obtaining CME educational credits!
- Case-Reports Series from leading European allergy centres: Read the latest case-report on “Asthma of recent onset in a 43 years-old lady” step by step and take the test to assess your knowledge.

www.eaaci.net also features:

- EAACI events. Get informed about all EAACI activities, such as congresses, section meetings, allergy schools, workshops etc. The Functional Genomics and Proteomics Interest Group of EAACI invites all members interested in applying FGP to their research, to a workshop that will take place in Aspenäs, Sweden, May 8-11, 2008. You can also find out about other allergy-related events around the world and make notes in your calendar!
- News. Editorials on “hot” allergy issues, press releases, profiles (interviews) from active scientists within EAACI as well as new books and publications – all of this can be found in News section.

… and please do not forget information about:

- EAACI Membership. Become an EAACI member and enjoy all the on-line benefits such as access to the journals “Allergy”, “Paediatric Allergy and Immunology” and the EAACI Newsletters.
- Junior members of the EAACI have their own subsite, in which they are presented with information motivating communication, career advancement and active involvement within the Academy.
- Job Centre: A resource centre that is constantly updated with open positions and new professional challenges for young allergists and scientists.

As you can see, there are many reasons to visit www.eaaci.net and we plan on making them more.

The EAACI Website Team

Presentations of two members of the EAACI Executive Committee

Nikos Papadopoulos spends most of his free time thinking about virus-induced asthma and food allergy. However, reading Terry Pratchett’s novels about the Discworld has taught him that it is more than possible to lead several lives in a parallel multiverse.

As a result, one life involves running a research center in Athens (not as easy as it might sound), a second life entails the care of young allergic patients, and yet another concerns the editing of the EAACI website. Other time continuums are devoted to keeping some time for his family. This has yet to be confirmed by his wife.

This inherent optimist regards achievements in these parallel universes as propitious (one frequent quotation being “… he is the author of numerous publications …”). His relaxed quantum approach to his own perception of reality provides increasing opportunities for more achievements.

In the capacity of Vice President for Communications and Membership, his vision is to develop a communications strategy that will take into account the requirements of members, highlighting the various opportunities EAACI has to offer, co-ordinating available tools, and introducing professional campaigns to increase allergy awareness in Europe. He strongly believes in the ability of EAACI to continue promoting education, research, and awareness in allergy, thus making an enormous difference in the lives of allergic patients.

Glenis Scadding is an Allergist and Rhinologist working at the only postgraduate ENT hospital in the UK. She has a busy clinical practice – but has recently semi – retired from this in order to devote more time to teaching, writing and research ( chronic rhinosinusitis, aspirin hypersensitivity, nitric oxide ) as well as her roles of Membership Secretary to the British Society of Allergy and Clinical Immunology and Chair of the ENT Section of EAACI.

Her mission is to increase the membership of both, thus improving the care of patients by better understanding of allergy in primary care and otorhinolaryngology.
In June 2007, the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) group, chaired by Wytske Fokkens and co-chaired by Valerie Lund and Joaquim Mullol have announced updates to their 2005 guidelines on the management of acute and chronic rhinosinusitis and nasal polyposis. These new guidelines, presented by Wytske Fokkens and Joaquim Mullol in a Hot Topics session at the annual EAACI Congress in Goeteborg, offer the most comprehensive evidence-based recommendations on the diagnosis and treatment of rhinosinusitis and nasal polyposis for primary care physicians and non-ENT specialists, as well as for ENT specialists. 

Developed by a broad international group of both primary care physicians and specialists to update the knowledge of acute and chronic rhinosinusitis and nasal polyposis, the 2007 EP3OS guidelines include a review of diagnostic methods and treatments, propose a step-wise approach to the management of the disease, explore new findings on how rhinosinusitis develops and consider how progress can be made with continued research in this area. The complete guidelines are published in the Supplement 20 of the journal Rhinology and an Executive Summary will be soon published in Allergy.

Among the updated information in the guidelines is a new definition of rhinosinusitis aimed at helping physicians better identify and diagnose the disease. EP3OS defines rhinosinusitis as the inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal congestion or nasal discharge, but also including other symptoms such as facial pain or pressure, reduction or loss of smell, and either endoscopic signs of nasal polyps or mucus and pus discharged primarily from the middle meatus, or CT scan showing mucosal changes within the sinuses.

Rhinosinusitis symptoms are diagnosed as mild, moderate or severe, depending on symptom severity; and acute or chronic, depending on symptom duration. Individuals with symptoms present less than 12 weeks, with complete symptom resolution, are classified as having acute rhinosinusitis (ARS). Patients with symptoms present more than 12 weeks, without complete resolution of symptoms and subject to symptom exacerbations, are classified as having chronic rhinosinusitis (CRS).

Another important component of the new guidelines are the updated treatment schemes for primary care physicians and non-ENT specialists that reflects the significant amount of clinical research done in this area in recent years. EP3OS supports a new step-wise management approach and recommends that primary care physicians and non-ENT specialists prescribe topical corticosteroids and oral antibiotics, for example, as first-line therapy for adults with moderate to severe ARS. For adults with CRS with or without nasal polypos, EP3OS recommends that primary care physicians and non-ENT specialists prescribe topical steroids and oral douching as first-line therapy. The guidelines also provide recommendations on when primary care physicians and non-ENT specialists should refer their patients to an ENT specialist.

Updates for ENT specialists are also included in the new guidelines. For ENT specialists, diagnosis of ARS is recommended beyond presence of symptoms for ARS. EP3OS recommends a nasal examination (swelling, redness, pus), oral examination (posterior discharge), and nose and throat examination including nasal endoscopy. Diagnosis of CRS includes nasal endoscopy to determine whether there are visible nasal polyps, as well as a review of the primary care physician’s diagnosis and treatment and an allergy questionnaire. Appropriate medical treatment is as effective as surgery for the majority of CRS patients, so sinus surgery should be reserved for patients who do not satisfactorily respond to recommended medical treatment. In CRS without polyps additional long-term antibiotics may be of benefit whereas when polypos are present the use of topical (sprays or drops) and oral corticosteroids are stratified according to nasal polypos severity.

The new EP3OS report also includes an expanded section on the treatment of acute and chronic rhinosinusitis in children, stratifies the severity of disease based on a visual analogue score, and provides new information on the pathogenesis of rhinosinusitis and the relationship between the upper and lower respiratory tracts.

Wytske Fokkens, Valerie Lund, Joaquim Mullol on behalf of the European Position Paper on Rhinosinusitis and Nasal Polyps group

References:

Web: www.rhinologyjournal.com
Dear Friends and Colleagues,

Welcome to the XXVII Congress of the European Academy of Allergology and Clinical Immunology in Barcelona, 7–11 June 2008. We have prepared an extensive and stimulating programme covering all aspects of the clinical care of allergic diseases, from Pediatrics to Geriatrics.

On the first day there is an extensive programme consisting of CME-accredited postgraduate courses – as well as the European Meeting of Allergy Nursing.

All through the Congress, together with many simultaneous Symposia and Workshops, there will be Practical Courses designed to teach the basics of many of the practical skills used in Allergology.

The Free Communications, Poster Discussions and Poster Sessions will get increased attention in Barcelona. The poster area is spacious, providing ample opportunity to interact with young scientists and other colleagues. The well attended JMA Poster Session will take place on Sunday evening and a new Case Report Session has been scheduled on Tuesday evening. A large number of awards are waiting for JMA members participating in these sessions.

The EAACI 2008 programme is completed with Meet the Expert sessions, Hot Topics and Pros & Cons sessions as well as with a new Business Meetings format including keynote lectures. The plan is to provide plenty of activities for everyone during EAACI congresses, and introducing the new activities mentioned above is in line with this ambition.

The social aspects are also very important for the EAACI Congress, and we offer various opportunities for you to meet colleagues and friends. The Opening Ceremony and Welcome Evening, including buffet and party, on Saturday evening 7th June is the key social event. It is included in the registration fee.

We are confident that you will enjoy memorable days discovering more about allergy and immunology, as well as the spirit of Barcelona!

On behalf of the Local Organising Committee.

Ignacio J. Ansotegui
Congress President EAACI 2008
Welcome to Barcelona!

If you are planning to discover Barcelona, there is plenty to see. The number of museums is more than 50, and among the most well-known are the Museu Nacional d’Art de Catalunya (MNAC), the Museu d’Art Contemporani de Barcelona (MACBA) and CaixaForum. Listed below are some of the sites you should not miss when visiting Barcelona.

Barcelona’s location on the shores of the Mediterranean Sea means that it enjoys a warm, welcoming climate and pleasant temperatures all year round. The average temperature in June is 21 degrees Celsius.

Source: www.barcelonaturisme.com

La Rambla

La Rambla is a lively street where a lot happens, starting at the Pl. Catalunya and continuing down towards the harbour. You will find anything here, from shops, cafés and markets to theatres and art galleries.

Mirador de Colom (Columbus Monument)

The Columbus Monument is located at the end of La Rambla, close to the harbour. This major landmark was built in 1888 in memory of the discovery of America.

Park Güell

Park Güell is the largest work in terms of size which Gaudí realised in Barcelona. It is a beautiful garden with architectural elements situated on the hill of el Carmel in the Gràcia district.

Sagrada Família

The Sagrada Família temple is the most famous building in Barcelona and is a symbol of the city. It was originally designed by Antoni Gaudí (1852–1926) and construction began in 1882.
Urticaria is considered to be one of the most challenging problems in clinical allergy practice. In reviewing the pathophysiology of urticaria, Professor Marcus Maurer from Charite University, Berlin, pointed out that many triggers may result in one pathophysiological pattern involving skin mast cell degranulation. Maurer explained that autoreactivity, infections, and intolerance were regarded as the main causes of chronic urticaria, but that some cases remained idiopathic. Some patients have chronic urticaria with mast cells that can be activated by anti-FceRI antibodies, but rarely by anti-IgE antibodies or by circulating mast cell secretagogues. The professor underlined the difference between autoreactive chronic urticaria associated with positive autologous serum skin tests and auto-immune chronic urticaria diagnosed by cell activation assays. Autoreactive and auto-immune chronic urticaria cases may feature overlapping attributes but they are not identical. Patients with autoreactive chronic urticaria have longer disease duration and require higher antihistamine doses to control their disease. Maurer also reported the beneficial effect of autologous whole blood injections for patients with autoreactive chronic urticaria.

Dr Clive Grattan from the U.K. focussed on recent advances in our knowledge and understanding of auto-immune chronic urticaria that can be diagnosed by direct and indirect evidence for functional antibodies in up to 50% of patients with ordinary presentation. No routine assays confirm the diagnosis as yet. Although the autologous serum skin test is widely used as a screening test for functional factors in the blood of patients with continuous urticaria, it should not be regarded as a specific test for functional auto-antibodies. The current gold standard test is the basophil histamine release assay, but this is only available at a few specialist centres. Immuno-assays for IgG with specificity for the high affinity IgE receptor (FceRI) and IgE detect non-functional as well as functional auto-antibodies and are therefore of limited value. Recent studies using flow cytometry indicate that the expression of CD63 on the circulating basophils of urticaria patients and on healthy donor basophils after incubation with chronic urticaria sera may be a potential surrogate marker of in vivo histamine releasing auto-antibodies and may therefore be useful in clinical practice.

Professor Antonio Romano from Italy pointed out that urticaria can be caused by exercise, drugs, and foods, from one source or in various combinations, and appears to be one of the most frequent manifestations of anaphylaxis occurring in more than 80% of cases.

In evaluating urticarial reactions to drugs, it is important to distinguish between immediate (i.e., occurring within one hour since the last drug administration) and non-immediate (i.e., occurring more than one hour after the last drug administration) reactions. Most immediate reactions to betalactam antibiotics are due to an IgE-mediated mechanism which can be revealed by positive skin tests, serum specific IgE assays, and/or basophil activation tests. A cell-mediated pathogenic mechanism is rarely diagnosed in patients with delayed urticarial eruptions associated with betalactams. Most urticarial reactions to NSAIDs are non-allergic hypersensitivity reactions caused by the inhibition of the constitutive isoform of cyclooxygenase (COX)-1, as was proved by biochemical observation in ASA-induced urticaria. However, an IgE-mediated allergy to NSAIDs has been reported in some immediate urticarial reactions.

The role of food in the aetiology of acute urticaria is generally over-estimated: in a study by Zuberbier et al. (T Zuberbier, J Invest Dermatol Symp Proc 2001), 63% of patients with acute urticaria suspected a food substance as an eliciting factor, but an IgE-mediated pathogenic mechanism was confirmed in less than 1% of patients. Addi-
tionaly, NSAIDs may aggravate hypersensitive reactions to foods.

Neither exercise nor foods can elicit urticarial or anaphylactic reactions. Food-dependent exercise-induced anaphylaxis (FDEIAn) can be triggered by exercise following the ingestion of any food (non-specific FDEIAn) or a specific foodstuff (specific FDEIAn), to which the patient has become sensitised. It is crucial to assess these patients by using both in vivo and in vitro tests for food hypersensitivity.

Professor Martina Kozel, from the Netherlands, gave some guidance on urticaria management and reviewed the evidence for different treatment agents in urticaria. She addressed the controversy surrounding the clinical use of antihistamines at doses higher than those licenced for the treatment of chronic urticaria. The use of higher doses of antihistamines in chronic urticaria is a common clinical practice and a fourfold increase in antihistamine doses has been recommended in the EAACI guidelines on urticaria management. Existing evidence in the literature is limited. A paper by U. Raap et al [2004] demonstrated that two-thirds of urticaria patients used higher doses of antihistamines to control their disease, while a recent paper by R. Asero [2006] showed that an increase in doses of antihistamines was of no benefit to most patients with severe auto-immune chronic urticaria.

Kozel reviewed the existing protocols for ciclosporin, intravenous immunoglobulins, etc., and accumulating evidence for alternative off-licence treatment for urticaria including anti-leukotrienes, sulfasalazine, dapsone, methotrexate, stanzol, and micophenolate. She also focussed on new therapeutic approaches such as biologicals, reviewing the first case reports on the beneficial effects of anti-IgE antibodies for cold-induced urticaria and anti-TNF antibodies for delayed pressure urticaria.

Elena Borzova

Acknowledgements: Prof. Maurer, Dr Grattan, and Prof. Antonio Romano for submitting slides and the main points in their talks for this report from the EAACI 2007 Congress in Göteborg, Sweden.
There is increasing concern about the lack of environmental microbial influence on immune system development, as this seems to be a possible reason for the growing incidence of allergic diseases in many areas. Many share the opinion that the over-hygienic, urban lifestyle of the industrialised world has a detrimental effect on the development of immune systems. The avoidance of infections, the widespread use of antibiotics, and extensive vaccination may all contribute to the improper functioning of innate and acquired immune mechanisms, sensitisation to allergens, and the development of allergic inflammation.

It comes as little surprise to many researchers that people who live in farming environments are much less sensitised than people who live in urban areas. Although exposure to allergens is much higher in rural farming areas than in cities, agricultural communities experience a strong simultaneous influence of microbes and their structural elements on the human organism. According to Roger Lauener, a significant amount of evidence exists to support this thesis. Mice growing up in a germ-free environment exhibit a lower CD4+ cell count, while the repopulation of gut flora with B. fragilis leads to the normalisation of the immune system.

There appear to be some answers to questions on whether or not it is possible to establish a few of the microbial compounds which could be the most important for the immune system. Such a role may be played by polysaccharides affecting Toll-like Receptors (TLR), among others, leading to the development of Th1 responses. The ALEX study shows that children in farming communities have higher TLR2 and CD14 gene expression than children who live far from agriculture. The PARSIFAL study confirms these results. This study also provided evidence that children living near farms have a higher gene expression of TLR4, CXCR3 (Th1 cell marker), but not CCR3 (Th2 cell marker). It is also interesting that the higher the expression of TLR2 and TLR4 is, the less sterile germ line IgE transcripts synthesis occurs. In addition, high SOCS (Suppressor of Cytokine Signalling) gene expression lying in a signal transduction pathway from TLR is accompanied by higher endotoxin exposure.

It has been established beyond doubt that the diversity of some genes underlies varying immune responses to microbial factors when farming and non-farming communities are compared. Erica von Mutius pointed out that protection against allergic development may depend on the presence of particular genes and their polymorphisms. For instance, only children with TT genotype at NOD1/-21596 are protected from allergy in a farming environment. In addition, children with AA and AG genotypes in CD14/-1720 who consumed farm milk in their first year had lower frequency of pollen-specific IgE ≥ 3.5kU/L in relation to children with GG in this position. However, there were no differences for children not drinking farm milk regardless of CD14/-1720 polymorphism.

Therefore, not only infections, but also exposure to viable and non-viable micro-organisms in the environment might confer protection against allergies. Specific gene/environment interactions support the evidence of the role of microbial exposure in the aetiology of asthma and allergies.

Environmental microbial factors also may affect the specific immune response through the elements of innate immunity. Antoon Oosterhout said that macrophages, which have not received much research attention recently, may be a bridge between the structural elements of germs and specific immune cells. Alveolar macrophages exert tonic suppression on the maturation of dendritic cells (DCs) and inhibit their antigen-presentation capacity as well as...
Hygiene

T-cell activation and proliferation. Furthermore, as based on studies with rats, they may suppress secondary IgE responses and T-cell infiltration, without affecting primary responses. It has also been shown that an adoptive transfer of alveolar macrophages from allergy-resistant rats abrogates the bronchial hyperresponsiveness of BN rats.

Since evidence suggests that the immunosuppressive effects of macrophages can be exploited to provide long-term inhibition of asthma manifestations in animal models, a precise explanation of the significance of macrophages in allergic inflammation may contribute to the development of new therapies for allergic diseases. This is supported by results showing that the stimulation of allergen-loaded macrophages by TLR9-ligand helps the IL-10-dependent suppression of asthma manifestations. Similarly, reprogramming macrophages with mycolic acid promotes a tolerogenic response in experimental asthma, and specific intra-airway IgG administration leads to inhibiting allergic macrophage-dependant inflammation. Moreover, a therapeutic potential is possible for macrophage-based immunotherapy in allergic asthma, since macrophages may induce cellular immunity by activating Th1 responses and suppressing Th2 cells.

Local conditions must always be taken into account whenever the pathogenesis of allergic inflammation is analysed. According to Angela Haczku, the innate immune molecule surfactant protein-D (SP-D) plays an important regulatory role in allergic airway response, since it inhibits maturation, promotes the retrograde migration of DCs, and directly suppresses T-cell activation. In vitro studies established that SP-D inhibited TNF-α, CD86, MHC II, and CD11b on CD11c+ cell expression. Furthermore, a lack of SP-D in SP-D-deficient mice resulted in constitutive Th2-lymphocyte activation in airway tissue, enhanced susceptibility to allergic sensitisation, and abnormal macrophage and DC morphology and function.

Interactions between external environment factors and innate as well as specific immunity seem to be rather complicated. The final outcome of this interactive network is highly unpredictable, given the highly polymorphic variants of the hundreds of genes for cytokines and receptors. Yet scientists continue to intensively investigate the influence of microbes and their structural elements on non-specific immune mechanisms, in the hope that this will lead them, finally, to finding out the secret of allergy.

Presented at the EAACI 2007 Congress in Göteborg, Sweden.

Maciej Chalubinski – mchalubinski@poczta.onet.pl
Allergen-SIT, which is based on the administration of disease-eliciting allergens or derivatives, is the only treatment that results in a life-long tolerance of prior disease-causing allergens due to the restoration of normal immunity toward allergens. The treatment has been shown to be particularly beneficial in the treatment of allergic rhinitis, mild and moderate asthma, and insect venom hypersensitivity. Entire aqueous extracts of natural allergen source materials such as pollens, mites, moulds, and animal epithelia are the basis for the therapeutic preparations that are currently used in clinical practice. The extracts are standardised in terms of total allergic activity, or potency, and possibly the concentration of one individual major allergen, while product consistency is assessed in terms of protein and allergen profiles determined by techniques including electrophoresis and immunoblotting. An extract may contain numerous proteins, of which only some are allergens. The composition is determined to a large extent by the quality of the raw material and the method of extraction and purification. Although raw materials are provided by certified suppliers and produced under controlled conditions, differences in quality can occur.

In addition, many extracts derived from natural materials contain endotoxin. The use of recombinant DNA technology appears to provide a realistic means of achieving improvements in obtaining more precisely defined preparations. This technology also provides the possibility of creating allergen derivatives with reduced IgE reactivity.
Recombinant Allergens

These are hypoallergenic molecules that have a reduced risk of inducing undesirable allergic reactions during the course of immunotherapy but which retain their therapeutic activity. Numerous allergens have now been cloned for research purposes, but as yet only some have been developed to the stage at which they can be used in clinical studies.

Recombinant DNA technology provides the possibility of creating therapeutic vaccines containing only relevant allergenic proteins. These preparations hold great potential in regard to pharmaceutical quality, standardisation, dosage formulation, etc., but their clinical efficacy has yet to be investigated.

Recently, two double-blind placebo-controlled clinical trials with recombinant allergen vaccines were held with grass pollen allergic patients (1) and birch pollen allergic patients (2) suffering from rhino-conjunctivitis with or without asthma.

A vaccine containing a cocktail of five allergens (Phl p 1, 2, 5a, 5b and 6) in approximately equivalent ratios was used with grass-pollen allergic subjects. The combined symptom-medication-score adopted as a primary end-point showed a 39% improvement in the active treatment group relative to the placebo group (p=0.041). The Rhinitis Quality of Life Questionnaire (RQLQ) registered an overall significant benefit (p=0.024) from active treatment, providing further evidence of clinical efficacy. Significant effects were seen in five of the seven domains tested: activities (p=0.040), non-hay-fever symptoms (p=0.032), practical problems (p=0.040), nasal symptoms (p=0.016), and eye symptoms (p=0.007). Adverse events were observed with 10.4% of injections of active preparation and 5.9% of the placebo preparation, mainly as mild local reactions. Only seven of the 731 active treatment injections (0.8%) were associated with systemic reactions including rhinitis and urticaria.

The second study using hypoallergenic Bet v1 folding variant (FV) derivative, presented by Narkus and colleagues at the EAACI Congress in Gothenburg, had 228 subjects, making it the most significant multicentre study using recombinant vaccine. The study also included a baseline year. The study showed that SMS improved by 42% as compared to placebo (p=0.0137). The study also showed a good safety profile with no serious adverse events related to study medication.

In both studies, active treatment induced highly significant increases in both IgG1 and IgG4 specific antibody concentrations. Specific IgE showed a downward trend with values significantly less than baseline in the active treatment groups. Thus, recombinant DNA technology has delivered the prospect of a new generation of preparations for allergen specific immunotherapy. The first clinical studies with recombinant allergens have yielded very encouraging results, suggesting that there is a very good chance of similar preparations becoming available for use in the routine management of allergic disease.

References:

Marek Jutel, Oliver Cromwell
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Asthma

One of the best attended symposia at the EAACI 2007 meeting in Gothenburg was the one dealing with aspects of asthma pathogenesis and treatment, which have both generated great controversy recently.

Ignacio Ansotegui, Spain, chaired the session with Leif Bjermer, Sweden. It opened with an address by Claes-Goran Lofdal, Sweden, on the benefits of long-acting beta2 agonists (LABAs) in asthma treatment. The professor commenced his talk with a historical account of the first patient ever to have been treated with formoterol, in 1985, and continued by commenting on the pharmacokinetics of LABAs such as formoterol and salmeterol. He also stressed that these medications should always accompany treatment with inhaled corticosteroids, and presented results from the FACET study as well as data regarding the exacerbation rates of patients under LABA treatment. Professor Lofdal analysed the efficacy of these drugs based on total asthma control and the quality of life achieved, as well as associated mortality rates in countries such as Sweden. He concluded that LABAs have beneficial bronchodilating and anti-inflammatory effects, and are associated with a reduction in asthma exacerbations and improvement of quality of life.

Christian Virchow, Germany, gave a talk on insights into the background to the contrary belief that LABAs are bad for asthmatics. He referred to the range of adverse effects presented by the Fenoterol Study and expressed widely acknowledged concerns that the use of LABAs may mask underlying airway inflammation, and result in negative effects regarding asthma control. The professor commented on the outcomes of the CASTLE and the SMART studies, which have influenced and changed GINA guidelines. He summarised his speech by saying that LABAs may be used to alleviate airflow obstruction but may be harmful when used as part of standard preventive therapy.

Professor Sebastian Johnston, U.K., followed this up with a topic attracting considerable attention lately, i.e., the role of atypical bacteria in asthma exacerbations and the effect of antibiotic treatment. The professor stated that the vast majority of exacerbations in both children and adults belong to the post-infectious phenotype, while asthmatic patients exhibit an impaired interferon production in response to both viruses and bacteria. Several antibiotic treatment trials were analysed, including roxithromycin, azithromycin, clarithromycin, and telithromycin as the administered agent and all demonstrated beneficial results in terms of lung function and symptom improvement. Macrolides have, therefore, been considered as steroid sparing agents while some demonstrate antiviral activity as well, through the induction of interferon production. He related the results of atypical bacterial infection with phenotypes such as new onset asthma in adults, as well as severe and neutrophilic asthma.

Professor Tom Plats-Mills, U.S., was the last speaker at the session and gave a talk on the relation between obesity and asthma, which was first observed in studies reporting such an association in the 1980s. Thereafter, data regarding the relevance of obesity and body mass index (BMI) to the prevalence of asthma and type II diabetes in children, as well as the percentile distribution of BMI for children with or without asthma, were presented. Both the pattern and the intensity of physical activity appear to play an important role in the development of asthma, with moderate activity now thought to represent the best way of boosting energy consumption. Furthermore, additional factors such as vitamin D intake and sunlight exposure contribute to obesity and indirectly to an increase of the risk for recurrent wheezing. The professor concluded that changes towards a more sedentary, indoor lifestyle in the second half of the 20th century, together with critical alterations in water, food, and urban life conditions, have all led to a higher prevalence of both asthma and obesity.

The enthusiastic audience asked many questions after each presentation, creating a responsive environment for the interactive and successful session.

Presented at the EAACI 2007 Congress in Göteborg, Sweden.
Cellular Therapy for Asthma: Science Fiction or Science Fact?

The treatment of allergic diseases such as bronchial asthma is currently based on glucocorticosteroids, which strongly reduce the whole activity of the immune system. However, allergic inflammation is a complex process involving mechanisms on every level of immunity, many of which have yet to be fully understood. Recent findings presented by scientists during one of the main symposia at the EAACI Congress in Vienna (2006), dedicated to cellular therapy for asthma, gave some hope that cellular modulating methods in the treatment of allergic diseases may become more “science fact” than science fiction. Quoting the results based on studies on both animal models of allergy and human material in vitro and in vivo, scientists presented interesting findings on the immune mechanisms of allergic inflammation and summed up possible novel approaches to allergy treatment in the future.

According to Dr Douglas Robinson, U.K., some instability regarding regulatory T cells may partly play a very important role in asthma and allergy development. A significant portion of many populations, especially in Westernised countries, presents positive in skin prick tests for common allergens. However, not all the people in this group develop allergic disease. Quite possibly, those that develop allergic sensitisation have problems with regulating the immune responses on a cellular level in regulatory CD4(+) CD25(+) T cells. Apart from surface markers, T regs, first described as having the ability to prevent auto-immune disturbances, are characterised by the expression of transcription factor fox p3. Another feature of those cells is IL-10 and TGF-beta synthesis, playing the role of regulatory functions. There also exist subtypes of T reg cells such as Th3 and Tr1. Robinson and his team focussed especially on the significance of CD4(+) CD25(+) cells in the regulation of immune responses during allergic inflammation. Potential therapeutic approaches could involve isolating CD4(+) CD25(+) cells from the peripheral blood of non-atopic individuals and stimulating them in vitro with allergen extracts.
Cont’d. Cellular Therapy for Asthma: Science Fiction or Science Fact?

Presented at the EAACI 2006 Congress in Vienna, Austria.

some functional differences and investigated their influence on immune responses. Regulatory T cells such as CD4(+) CD25(+), Tr1 cells, and cells secreting IL-10 and TGF-beta may strongly affect the proliferation of immune cells, as well as their activation and the production of cytokine. Regulatory T cells were shown to have a modulatory effect on the activity of antigen-presenting cells (APCs), including dendritic cells (DCs), Th1- and Th2-mediated response, and cell differentiation and maturation. The results of the analysis of naïve T cells co-cultured with DCs and both antigen-specific T reg cells and Tr1 cells showed that the mechanism of suppression depends on the existence of different subsets of T regulatory cells and may also depend on the stage of their maturation and activation. These cells, then, would appear to control the allergic response.

Dr Bart Lambrecht, the Netherlands, described the significance of resident dendritic cells (DCs) – initiating adoptive pulmonary immunity – in the development of allergic inflammation in bronchi after exposition to allergen. Interestingly, this process may depend on the contribution of DC subsets absorbing the allergen, draining regional lymph nodes, and presenting it to other cells. Computer images of pulmonary tissue show that DCs, which comprise two main big families called plasmacytoid and myeloid DCs, form a kind of network. Myeloid DCs share some characteristics with monocytes, while the view of plasmacytoid DCs resembles matured plasma cells. They are found in humans, and in rats as well as in mice. So if DCs play an important role in allergic inflammation, there occurs the possibility that they may become a therapeutic target in the future treatment of asthma.

Lambrecht raised the question of whether the depletion of DCs in the lungs after inducing inflammation could cure the disease. To investigate this potential, mice, following sensitisation, were re-challenged with antigen and exposed to diphtheria toxin. Interestingly, normal mice with DCs developed eosinophilia, while in DC knock-out transgenic animals eosinophils did not appear. Furthermore, T cells polarised towards Th2 profile in vitro and transplanted into naive mice followed by antigen exposition resulted in strong Th2 cytokines synthesis reduction only in DC knock-out mice, but not with DC positive mice. This indicates that T cells may need DCs to develop inflammation in vivo. Another interesting point was that the allergen challenge of sensitised mice caused an increase in ATP protein in lavage fluid, a DC receptor modulating their migration in lymph nodes and eosinophilia. These findings suggest that DCs should be taken under consideration as a potential target in any future allergy treatment.

The features of DCs give the possibility of therapeutic significance not only in allergic diseases, but also in cancer treatment. Dr Karolina Palucka, U.S., gave a speech about the anti-tumour behavior of DCs. It has been proved that immature DCs are responsible for peripheral tolerance, including the induction of regulatory T cells. In contrast, mature DCs strongly induce immunity. In vitro and in vivo studies show that DCs may be activated by different factors such as microbial products, the products of tissue damage, tumour antigens, and other cells in innate and adaptive immunity. Palucka’s results in clinical studies observing vaccination with DCs loaded with tumour antigens in vitro to patients with melanoma show that DCs can strongly induce immune response in blood. Furthermore, the DC vaccine administered to metastatic melanoma patients resulted in the regression of the metastases and was associated with strong clinical improvement.

To sum up: during the main session scientists discussed in detail cellular immune mechanisms, focusing on regulatory T cells and dendritic cells, which both seem to play a very important role in total immunity. Unfortunately, any instability determining non-proper functioning appears to be a crucial feature of allergic inflammation as well as tumour development. However, due to the results of quoted studies, we may claim that the more we know about cellular mechanisms of immunity, the closer we are to finding the exact cure for allergy and cancer.

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EAACI Standards for Practical Allergen-specific Immunotherapy

The quality of healthcare and the optimal use of resources represent nowadays a primary interest in the medical community. In the case of specific immunotherapy, the clinical practice is often non-evidence based, it is rather the result of an experience-based approach, which is much influenced by the local culture. In order to improve the practice of SIT, which is unanimously recognized as an effective treatment, the EAACI prepared a comprehensive document (1), published as a supplement of Allergy, with the aim of providing practical recommendations that are based on scientific information as far as possible.

In this document, some important aspects (e.g. dosing adjustments, administration, safety procedures) are based on evidence (when existing), combined with the authors’ long-term experience, in order to make the treatment as rational as possible. A special attention is paid to the safety issue, with the identification of risk factors, precaution rules, and an updated classification of the adverse events is also established. Of note, in the EAACI standards, detailed practical recommendations are provided on how to organize the administration of injection immunotherapy. These include competencies, staff education, facilities and recording of the outcome of and of the adverse events. Concerning sublingual immunotherapy, which is self managed by the patient at home, a special remark is put on the appropriate prescription and the adequate patients’ education/information, in addition to the necessity of a strict follow-up.

The document is the final result of a collective effort that lasted several years and it will be updated in the near future. It represents therefore an attempt to establish a European gold standard to ensure optimum quality for SIT treatment, which will be harmonized into the local guidelines. Moreover it is intended as the starting point of a continuous educational process that will directly involve all staff dealing with allergen-specific immunotherapy.

G. Passalacqua and E. Valovirta

The World Allergy Organization (WAO) Recommendations for Immunotherapy Trials

During the last 20 years there has been a blossoming of specific immunotherapy (SIT) and, in addition to the extensive studies on the traditional subcutaneous and sublingual sublingual routes, new intriguing approaches have been proposed (1). Among these approaches, adjuvants (bacterial or DNA), peptides and recombinant allergens seem to be the most promising. On the other hand, it is acknowledged that many past SIT studies have methodological flaws such as the small number of participants, high frequency of withdrawals and conclusions based on unmatched groups with respect to disease severity. Moreover, trials are often planned using study designs that may not confirm the clinical value of SIT as an effective treatment. To achieve more robust evidence and to minimize the risk of misusing limited financial resources for trials, a panel of experts of the World Allergy Organization recently prepared guidelines for the methodology of future immunotherapy studies (2). In the document, it is recommended that appropriate study plans and statistical analysis are utilized, with a particular care in evaluating the sample size, the patients’ selection and the randomization procedure. In particular, it is underlined that prior calculation of sample size is mandatory, as it is unethical to treat with placebo more or less patients than are needed to achieve the study outcome.

SIT trials often assess symptom and medication scores independently, whereas the treatment reduces both, and they are strictly interdependent. For practical reasons it can be assumed an equivalent importance of symptoms and medication scores, so that each of these account for half of the clinical burden of the disease. Therefore in the WAO document it is recommended that a combined symptom+medication score be utilized as the primary outcome measure. Another important recommendation is that, based on the current literature, the minimal clinically relevant efficacy should be at least 20% higher than placebo. In addition to the clinical evaluation and the various additional outcomes (either functional or immunological), the assessment of the Quality of Life is regarded as a mandatory evaluation parameter in SIT clinical trials.

The WAO recommendations have been approved and endorsed by the main Regional Societies (AAAAI, ACAAI, APAACI, EAACI, SLAAL), and therefore would represent the ideal basis for a future standardization of immunotherapy trials.

G. Passalacqua and E. Valovirta

References:
The course focussed on the needs of allergy trainees to build up competence and knowledge about defined molecules involved in respiratory allergic diseases and food allergies. It covered the molecular and structural aspects of allergens, the determination of specific IgEs (both advantages and disadvantages), recombinant allergens and their use for improving diagnosis, applications in immunotherapy, and epidemiological studies.

The programme included:
– lectures by experts in the field,
– interactive workshops with presentations of clinical cases prepared in a pedagogical way by – clinicians orchestrated by C. Metz-Favre (France),
– laboratory work organised by I. Swoboda (Austria), and
– round-table discussions.

The scientific core course was given in a vast auditorium at Bischenberg, and commenced on the 21st September, at 17:30 hours. EAACI President Gert Van Wijk introduced the three courses comprising the summer school. The topics covered: the historical overview of the development of purified and recombinant allergens by G. Pauli, France; the many procedures leading to the identification and cloning of a new allergen by A. Casset, Austria; and the presentation of an allergome (fraxinus as a model) by P. Poncet, France.

On the 22nd September, the programme commenced with courses on IgE measurements and the advantages of defined allergens (these included a critical review of the detection methods for IgEs by L. Guilloux, France; the predictive, positive, and negative values of specific IgE determination by J. Kleine-Tebbe, Germany; the opportunities and advantages of defined allergens in specific IgE testing by J. Lidholm, Sweden; and the development of an allergen microarray by U. Schulmeister, Austria). M. Villalba, Spain, presented epidemiological studies performed with pure and recombinant allergens. In the afternoon, C. Radauer, Austria, presented the molecular and structural classification of allergens, with a prediction of protein allergenicity.

The participants chose interactive sessions with clinical cases or laboratory work (determination of specific IgEs by ELISA or CAP-FeIA) later in the morning and in the afternoon.

In the evening, the group visited Mont Ste Odile, then had dinner at a wine cellar in Barr. The wine-tasting session was enjoyable, as were the excellent local cuisine and the folk dancing in traditional costumes from Alsace.

On the 23rd September, the morning session focussed on cross-reacting allergenic molecules. Four lectures were given by experts. The topics comprised: recombinant mite allergens by S. Vrtala, Austria; animal-derived allergic molecules by C. Hilger, Luxembourg; recombinant parvalbumin, the major fish allergen, by I. Swoboda, Austria; and recombinant weed allergens by N. Wopfner, Austria. Another session of interactive workshops and laboratory work was organised before lunch.

The afternoon session was taken up with the presentation of the application of molecular knowledge in clinical practice. R. Asero, Italy, spoke about the clinical significance of plant food derived crossreacting allergenic molecules; R. Van Ree, the Netherlands, covered the topics profilin and CCD; while M. M. Fernandez-Rivas, Spain, lectured on the modification of allergenicity after proteolytic enzymes and heat treatment. Later, F. de Blay, France, spoke about the application of recombinant allergens for the detection of allergens; M. Raulf-Heimsoth, Germany, covered the topic of the diagnosis of occupational asthma; and G. Peltre, France, focussed on the subject of non-hydrosoluble allergens.

In the evening, the entire group took the opportunity to explore Strasbourg by walking in the historic heart of the city with two English-speaking guides. Many participants expressed a wish to make a return visit.

The presentations in the session on the 24th September, until 12.30 hours, focussed on the therapeutic applications of recombinant allergens. M. Van Hage, Sweden, talked about the experimental designs of hypoallergenic molecules; G. Pauli, France, spoke about the clinical results obtained with recombinant pollen allergens immunotherapy; and, in his contribution as an expert from the Regulatory French Office (AFSSAPS), J. Dayan-Kenigsberg examined the place of recombinant allergens in the future. S. Vieth, Germany, headed a round-table discussion with clinicians who had already included recombinant allergens in their practice, and this closed the session.

A total 92 medical doctors and researchers in allergology attended the Allergy School, representing 23 different nationalities. All appreciated the practical courses that were offered at this school and the fruitful discussions about the new allergological field of molecular allergens.

The Allergy School took place in a beautiful, somewhat isolated location at the foot of the Vosges mountain range in mild, sunny autumn weather after a summer full of rain. This contributed to making the working days very pleasant. The participants also appreciated their accommodation being integral to the school’s location. These favourable conditions made possible many information exchanges between the participants and expert speakers, and we thank the many experts who stayed with the participants for two or even three days.

Gabrielle Pauli
GA²LEN/EAACI Allergy School
St. Catherine’s College
Oxford, UK
20–23 August 2007

A very successful general allergy school was held in Oxford from 20-23 August. Just over 100 delegates and faculty gathered at St Catherine’s College Oxford to discuss the full range of clinical allergy topics.

Starting with epidemiology and the demographic challenges that face us, the programme moved through the key parts of allergy theory and practice with a special focus on practical management of patients with allergic disease. We tried a number of new formats for the sessions including small group tutorials and case presentations by the delegates to a small panel of experts who had to answer questions and advise without prior knowledge of the cases!

The Oxford college setting ensured a high degree of interaction between the delegates and faculty, especially with the long refectory tables at which we ate all our meals. A visit to Blenheim Palace and a rounders match complemented the scientific programme, while some delegates found time to look round a few of the Oxford colleges.

As the local organisers, the British Society for Allergy and Clinical Immunology is delighted to acknowledge the support from EAACI and GA²LEN both in financial terms and also in helping us to organise everything. Once again we were able to offer travel grants for many younger participants from different parts of Europe, with priority given to those who had not attended another allergy school in the past 12 months. A few highlights are shown in the accompanying images, but for further photographs, please see the EAACI website.

Anthony Frew

PAPRICA Symposia
in Kaunas and Vilnius, Lithuania
21st and 22nd November 2007

Two PAPRICA Symposia have recently taken place in Lithuania, addressing primary care physicians. They were held in Kaunas and Vilnius, co-organised by the Lithuanian Society of Allergology and Clinical Immunology, EAACI and GA2LEN. Lithuanian allergists are closely linked to the community of European allergists and in 2005, Lithuania together with EAACI was host to the first Baltic Allergy Congress.

State-of-the-art lectures were held on five topics: “How and when to diagnose allergy in childhood”, “Respiratory allergy”, “Atopic dermatitis”, “Food allergy”, and “Immunotherapy”. The speakers were Peter Schmid-Grendelmeier, Christian Virchow, Erkka Valovirta, Jonathan Hourihane and Philippe Eigenmann. The topics were highly appreciated by the participants who had a large number of questions regarding practical aspects of patient care.

Close to 200 participants attended the two Symposia, coming from various regions of Lithuania and also from the neighbouring country Latvia.

Allergy and clinical immunology has a long history in Lithuania. However, just like elsewhere in Europe, the speciality has to struggle to promote the specificity of allergic diseases in the various age groups. The general opinion is that PAPRICA will help further promotion of allergy care in Lithuania.

Similar to previous PAPRICA sessions, these Symposia were a unique opportunity to directly address doctors in their pratical work, as well as to establish new and long lasting friendships.

Philippe Eigenmann, Geneva, Regina Emusyte, Vilnius, and Brigita Sikauskiene, Kaunas, co-organisers of the Symposia
Committed to integration and sustainability

Networks of Excellence have been designed by the EC to strengthen Europe’s excellence in a particular research area, tackle the fragmentation of European research and spread excellence within and beyond the confines of the Network.

Integrating research is a high priority in Europe as bringing together multiple forces to focus on the same research interest’s, following standardised protocols and effective coordination will maximise the benefits from research funding and create bridges between European centres of excellence.

Within GA²LEN, it means enhancing collaboration and integrating knowledge, activities and perspectives between its consortium partners, research centres, between medical and scientific disciplines and also collaboration outside the scientific community with primary care professionals, patients, lay public and industrial partners.

The genius of the Network of Excellence research structure is twofold. On the one hand, it allows “networking” to stimulate cross-fertilisation of ideas, knowledge and data while helping to avoid duplication of efforts. On the other, “sharing of excellence” is promoted via partnerships with scientific practitioners, consumer groups, and industry throughout Europe.

The goal is to create via GA²LEN a durable and integrated platform with harmonised tools and joint activities for ensuring the future competitiveness of European research in allergy and asthma.

Examples of GA²LEN shared tools
- Pan-European skin prick tests
- Questionnaires: AQUA/AQUE - QOL - indoor environment
- Epidemiology surveys
- Birth cohorts database
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