Upcoming Congress in Barcelona
Executive Committee News
Asthma and Sports
Tobacco and Allergy
…and more
Dear EAACI-members,

A very short time remains until we meet in Barcelona, joining a Congress with an exciting scientific programme in a uniquely friendly environment.

Asthma is one of the main topics of this meeting, from pediatrics to geriatrics, from phenotype to therapy, and I must say that there is exciting news too on upper airways, including their impact on asthma co-morbidity. No wonder asthma is one of the focus points of the EAACI – in Barcelona you will be asked to vote for another A to be added to our five letters, symbolising asthma. Read more about this in the message from the EAACI President Roy Gerth van Wijk.

Again, we have gathered the latest information for you on topics such as the asthmatic child and tobacco and asthma. Furthermore we give you a brief and concise update on new developments in the immunology of T-cells, which is so decisive to understand airway pathology. You will also find reports on past meetings as well as announcements of future events, which clearly show the continuous activity and expertise of the European Academy.

Nikos Papadopoulos has taken the lead in the reorganisation of the different communication tools of EAACI and we will try to optimise and enforce communication with our members at the different levels, from scientific journals to online exchange of expertise. This is another interesting event taking place in Barcelona which will affect you as a reader of the EAACI Newsletter.

We’re all looking forward to serving you even better in the future. Don’t miss Barcelona!

Claus Bachert
My wish at the start of my presidency was to create transparency and openness in the operations of EAACI, so I am happy to report the following: To date we have held two meetings of the new Executive Committee, some Board of Officers meetings, and one Scientific Programme Committee meeting. Where do we stand?

The make-up of the new ExCom is well known, but we also approved Pascal Demoly and Stefan Vieths, both representatives of the interest groups, as new adjunct members, in tandem with Christian Virchow, SPC co-ordinator, Ignacio Ansotegui, chair of the Ethics Committee, Jan de Monchy, chair of the Specialty Committee, and Fulvio Braido, chair of the CME Committee. We look forward to meaningful co-operation.

Most importantly, we approved the new budget for 2008. We will spend €325,000 on meetings, schools, and symposia originating from sections and interest groups. We allocated €29,000 towards establishing new task forces (in 2007 we approved €100,000 for the Allergy Exam TF, spread over 2007 and 2008). Other initiatives were allocated €351,000, the most important being the research fellowships (€100,000 shared with GA²LEN, and our communications tools (Newsletter and Website: €130,000 in total). We will use €65,000 to improve the publicity and communications on which our academy depends, and analyse and meet the needs of our community.

In addition, €60,000 was allocated for the 2008 PRACTALL Initiative meeting on Bronchoconstriction, Allergy and Asthma in Sports and Exercise in February in Barcelona. Workshop members are developing a consensus report. In conjunction with the infrastructure budget for the different sections, interest and other groups, the budget for clinical fellowships, GARD, the PAPRICA Programme, and speaker support for national societies, this amount of money represents a spin-off from our congresses. The remainder of the total income is re-invested in congresses, the Executive Office, and EAACI administration. We emphasised the importance of the Exam with a €100,000 investment. It took time to sort out the details, but I am happy to report we will launch an exam that is based solidly on knowledge; one that is open to all EAACI members.

In 2007 we took the decision to co-operate with the World Allergy Organisation again by organising a joint congress in 2013. Several ExCom members visited potential congress venues in 2007, and at the WAO meeting in Bangkok it was decided to hold this congress in Rome. Other proposals are Geneva for 2012 and Copenhagen for 2014. These follow the previous locations of Barcelona, Warsaw, London, and Istanbul, and present balanced coverage of the different regions of Europe.

The previous Newsletter mentioned a planned meeting with the ERS leadership, which took place in January. Both sides expressed a desire to start joint initiatives at this open and friendly get-together. We are exploring the opportunities for co-operation and will probably start with a joint research seminar and web-based educational activities. The EAACI ExCom endorses these activities.

Finally, I would like to draw your attention to our proposal to add an extra “A” to our name. An overwhelming majority of the ExCom (15 for, 1 against, 1 abstention) supported the inclusion of Asthma in the title of our academy. EAACI is home to all those involved in asthma research and care, without neglecting Allergy. The extra “A” is one of the changes we propose; the extension of the ExCom by two representatives from the Interest Groups is another. I believe it is vital that we strengthen the position of the IGs and improve our communications channels. The contribution of Pascal Demoly (Hypersensitivity to Drugs) and Stefan Vieths (Food Allergy), currently adjunct members, is already highly appreciated. In the coming months we will detail the selection and rotation for the Interest Group chairs.

I warmly invite you all to the General Assembly to express your opinion and to vote. This means, in short: Come to Barcelona!

Roy Gerth van Wijk, EAACI President
EAACI News

Presentation of three members of the EAACI Executive Committee

Thilo Jakob rejoices as much in the field of clinical allergology as in basic research into immunology and allergy. The song title “Torn between two lovers” is an accurate description of his predicament, he feels. He recently relocated from Munich to the University of Freiburg to take up the position of Professor of Allergology and Immunodermatology and Head of the Allergy Research Group.

Bridging the gap between basic science and clinical medicine is one of Jakob’s highest priorities. “Everybody aiming to work in translational science needs first to learn the science of translation,” he believes. This requires an open mind and the gift of reducing complex phenomena down to simple concepts. “Sometimes it is more important to be simple than to be correct.” Jakob agrees with this statement, made by a Nobel Laureate at the EAACI-sponsored World Immune Regulation Meeting in 2007.

Jakob’s priority as Chair of the Immunology Section is to ensure that the academy becomes increasingly attractive for young scientists involved in research addressing the basic mechanisms of allergy and clinical immunology. These young researchers are the ones that will push forward the frontiers of science, challenge established concepts, and make sure that the academy stays young at heart and mind, he says.

Torsten Zuberbier first became interested in allergy when he commenced his basic research into basophils and mast cells, followed by clinical research in the fields of urticaria, food allergy, and dermatological allergy. Today, his interests have broadened to cover all areas of allergy, and he is based at the Allergy Centre Charité at the Department of Dermatology and Allergy at Charité-Humboldt University, Berlin. The centre treats a broad range of allergies for both in- and outpatients. The paediatric division of the Allergy Centre Charité, integrated into the Charité’s Department of Paediatrics, is headed by Professor Ulrich Wahn.

Zuberbier heads the European Allergy Research Centre Foundation (ECARF), which works throughout Europe to improve information provided to the public about allergies and to increase awareness. He is also Secretary-General of GA²LEN (Global Allergy and Asthma European Network), which is funded by the EU’s Sixth Framework Programme to bring together more than 80 institutions in the field of allergy across Europe. GA²LEN facilitates research in allergy and asthma, and sets and certifies standards in clinical care. ECARF and GA²LEN closely link their activities with EAACI, their academic counterpart.

Zuberbier aims to align his work for EAACI, as one of the three major forces in European allergy research, even more closely with the organisations of European patients, with the goal of decreasing the burden of allergies for patients and for society.

Brigita Sitkauskiene is an active and enthusiastic member of the group of Lithuanian specialists in allergy and clinical immunology. She leads the Allergy and Clinical Immunology unit at Kaunas Medical University Hospital. Colleagues and patients alike regard her as a skilled and motivated physician. She is also a dedicated scientist, and enjoys brainstorming ideas with her colleagues, especially about the immunological mechanisms of asthma and COPD. Perhaps most importantly, she is the mother of two teenagers, Simonas and Gabija, who always require their mother’s attention but also fully support her with their care and love.

As a new Member-at-Large of EAACI ExCom, Brigita Sitkauskiene strongly supports the role played by EAACI in continuing its tradition of excellence in communications, and the promotion of education and research. She believes that EAACI has a very promising future, and places emphasis on the necessity of collaboration and interaction between all members of the Academy.
The Code of Ethics of the European Academy of Allergology and Clinical Immunology (EAACI)

The EAACI is a supra-national scientific organisation of European national societies and individual members devoted to allergology and clinical immunology.

The purpose of EAACI is to improve the care of patients with allergic and other immune-mediated diseases by:

› promoting basic and clinical research;
› collecting, assessing, and disseminating scientific information;
› functioning as a scientific reference body for other scientific, health, and political organisations;
› encouraging and providing training and continuous education;
› promoting good patient care in this important area of medicine; and
› co-operating with organisations relevant to this field.

EAACI aims to be regarded by the scientific community, social organisations, patients, the public, industry, media, and political decision-makers as an independent scientific society of exceptional competence and integrity that merits the highest respect.

All researchers, physicians and other persons providing medical services and care have an obligation to act in accordance with the principles and rules of bio-ethics, with respect to their patients, their profession, their science, and society. The core principle of ethics is to respect and benefit human beings and their environment in its entirety, and to abstain from any behaviour to the contrary.

Our scientifically-based knowledge of allergies and other immune-mediated diseases is influenced by factors that are genetic, environmental, socio-economic, educational, and subject to our lifestyles, and by the scope and quality of health care and medical services. All clinicians, educators, researchers, and activists must strive to understand and support the optimum conditions for these factors.

Society as a whole, and especially EAACI members, must become active before the manifestation of an illness. This is supported by increasing and implementing the knowledge base about allergology in the field of prevention and prophylaxis. We all share the responsibility of reducing the considerably increasing burden of allergic diseases on the local and global levels.

Scientific diversity and transparency are necessary pre-requisites for the momentum of medical progress. Biomedical research is subject to universally accepted fundamental principles and must guarantee the safety of the patient according to international rules. It also requires commitment from healthy people as well as those suffering from disease to ensure its advancement. Research programmes must be socially lucid and transparent. The goals of research may not be worked out by medicine alone, but in partnership with other social groups, including patients. To reach this goal, we are compelled to educate and inform the global society and local communities.

Prepared by the Ethics Committee of EAACI:

This abbreviated version was finalised in June 2006. The full text of the EAACI Code of Ethics is accessible on the EAACI website www.eaaci.net

EAACI 2008 Barcelona

XXVII Congress of the European Academy of Allergology and Clinical Immunology
Barcelona, Spain, 7–11 June 2008
Clinical Features of Allergy: from Pediatric to Geriatric

The 27th EAACI Congress will be held in Barcelona, 7–11 June 2008, and is expected to attract many delegates. There will be a specific Pediatric Track and all aspects of the clinical care of allergic diseases will be addressed.

All through the EAACI 2008 Congress, together with many simultaneous Symposia and Workshops, Practical Courses will take place, designed to teach the basics of many of the practical skills used in Allergology. On Saturday, 7 June, there is an extensive programme of CME-accredited postgraduate courses.

A programme for Allergy Nurses has been included in the EAACI 2008 Congress. Professionals from different European countries will review practical aspects of nurses’ work. A Round Table will be open to debate the work situation throughout Europe, comparing similarities and differences. An inquiry will be delivered to participants, and a summary of the answers will be presented at the end of the meeting. The European Meeting of Allergy Nursing will take place in Barcelona on Saturday, 7 June.

Read more about the EAACI 2008 Congress programme and register on www.eaaci2008.com
Asthma and Sports: New Developments

Exercise-induced respiratory symptoms in athletes: fact or fiction?

The increased prevalence of asthma as presented by top athletes seems to be a “new” problem. However, the question now arises: does exercise induce bronchoconstriction in asthmatic subjects, or does exercise cause asthma in healthy subjects? These are the facts: exercise at low temperatures increases the risk of the development of asthma symptoms, and there is a greater risk for long-distance runners than there is for speed and power athletes. However, many of those requesting anti-asthma treatment exhibit normal bronchial responsiveness. In addition, there is no distinct correlation between the symptoms and objective asthma features in athletes, leading to a discrepancy in asthma prevalence between experimental and epidemiological studies. The current dilemma concerns the treatment of athletes that experience symptoms but present negative asthma tests. Kjell Larsson’s suggestion for treatment is either a generous or a restrictive attitude towards anti-asthma drugs in general and towards beta-2 agonists in particular.

Obesity, physical activity, and asthma

The prevalence of asthma and obesity is rising dramatically, and increasing evidence supports the premise that obesity is a risk factor for asthma. Prospective studies indicate that obesity precedes asthma development. In addition, it has been shown that weight loss decreases the severity of asthma.

Increased bodily weight has the potential to affect airway function through a variety of pathways. The first mechanism is through immunity and inflammation: obesity is linked to increased TNF-alfa, IL-6, and leptin levels produced by fat tissue, resulting in enhanced systemic inflammation (reflected by increased CRP). The second link is the mechanical impact of being overweight: obesity results in decreased airway calibre and the inhibition of deep breathing. Thirdly, decreased physical activity as a result of a sedentary lifestyle, general dietary changes, and indoor allergen exposure influence both obesity and asthma. In addition to this, genetic influences are likely to play a role in the development of both asthma and obesity.

Some conclusions can be drawn regarding asthma and physical activity. Decreased physical activity contributes to an increase in asthma prevalence. Most studies indicate that physical training programmes are safe for asthmatic patients and increase their cardiovascular fitness. There is no reason that supports not prescribing a physical training programme for asthmatic patients.

Exercise-induced asthma in children

Exercise is a common trigger of asthma attacks. Exercise-induced asthma (EIA) is defined by respiratory symptoms and signs due to bronchoconstriction related to exercise. The preferred and more accurate term is exercise-induced bronchoconstriction (EIB), defined as a reduction in lung function (usually FEV1) after exercise, e.g., after a standardised exercise test. This term better reflects the underlying pathophysiology and it is also preferred since EIA gives the false impression that asthma is caused by exercise.

An important trigger of exercise-induced asthma appears to be the cold, dry air inhaled into the lungs during strenuous exercise. Exercising in a cold environment decreases exercise capacity as measured by VO2 peak and peak running speed, and increases EIB intensity in subjects suffering from EIB. This has important implications for training procedures in a cold environment for patients and athletes with EIB. However, the influence of similar effects due to a cold environment on exercise capacity in healthy subjects cannot be excluded.

What about the influence of humidity on EIB? Exercise-induced bronchoconstriction
Presented at the EAACI 2007 Congress in Göteborg, Sweden.

**The Asthmatic Child:**

**From Phenotype to Therapy**

*Recurrent wheezing in childhood is a frequent clinical entity, and occurs in up to 30–50% of children in the first three years of their lives.*

It is a heterogeneous entity, similar from a clinical point of view but with a multifactor origin, with several, complex interactions from genetics and environment resulting in different clinical outcomes and responses to treatment, namely to bronchodilators and to preventive therapies, such as inhaled corticosteroids and anti-leukotrienes.

It is indeed a multifactor entity, resulting from the interaction of complex genetic factors and several environmental factors.

Birth cohort prospective studies allowed the identification of three wheezing phenotypes in early age: Transient Wheezing corresponds to a group of children with narrow airways at birth; Non-atopic Wheezing indicates children who wheeze in response to viral infections; and Atopic Wheezing is the term used for children with a strong atopic background.

*Transient early wheezing represents 60% of wheezers in the first three years of life, corresponding to children who usually begin having recurrent wheezing episodes during the first year of their lives and who stop wheezing by the age of three to six years. Their symptoms occur during viral infections (mostly RSV, but also rhinoviruses, para-influenza, and adenoviruses).*

The risk factors for transient early wheezing are passive smoking during the first years of life, day-care attendance or living with older siblings at home, being of male gender, premature birth, and the absence of breast feeding.

*Non-atopic Persistent Wheezing corresponds to about half of persistent wheezers at six years of age.* They have an increased airway lability: lung function is normal at birth; they typically show bronchial hyperresponsiveness (this being a genetic characteristic independent of atopy); and there is no relationship with a family history of asthma, a personal history of allergic conditions, or evidence of allergen sensitisation.

Children with Atopic Persistent Wheezing usually start displaying symptoms during the second or third years of their lives, remaining symptomatic from then on. They have an atopic background, eosinophilia, and high levels of serum total IgE. Positive skin prick tests or specific IgE to common aeroallergens are typical, but can appear later in life (meaning that symptoms can precede the evidence of allergen sensitisation). These children display an allergic inflammation of the airways, so lung function is normal at birth, but from then on it progressively deteriorates and can be reduced as early as at the age of three. They also present increased bronchial hyperresponsiveness and a positive response to bronchodilators and inhaled corticosteroids. Atopic Wheezing is strongly associated with a family history of asthma, and with a personal history of atopic dermatitis and allergic rhinitis.

It is also more likely in infants with food allergy to cow’s milk and eggs.

We learned from the Birth Cohort Studies that the main risk factors for the persistence of wheezing that have been identified are a parental history of asthma (mainly maternal asthma, but even more if both parents have asthma), allergen sensitisation to indoor allergens and egg proteins, and environmental tobacco smoke exposure.

*Other factors have been identified as a decreased risk,* such as day-care attendance in the first six months of life, having older siblings at home, and exposure to farm animals early in life.

One of the most common and yet most challenging problems facing the clinician is the nature and management of the wheezing infant and preschool child.

Further trials are needed to clarify the effect of an early onset of anti-inflammatory treatment in atopic wheezing infants, in order to assess their potential for secondary prevention of airway remodelling and loss of lung function.

*Miguel Borrego*
The relationship between tobacco and allergy is an interesting and challenging research topic with major clinical relevance. In particular, the effect of both active and passive cigarette smoke on asthmatic subjects is an important issue in daily practice.

The effect of both active and passive smoking in atopic subjects is poorly understood. As Guy Joos mentioned in his lecture, epidemiologic data suggests that tobacco smoke is a risk factor for asthma development and contributes to the prevalence and occurrence of exacerbations in asthma, as well as an increase in the severity of asthma. These findings are supported by animal models, where data indicate that acute concurrent exposure to allergen and mainstream cigarette smoke enhances airway inflammation and airway responsiveness in previously sensitised mice. Airway responsiveness to intravenously injected carbachol was increased in smoke- and OVA-exposed mice compared with all other groups. An additive effect of smoke and OVA exposure was seen on total cell numbers, macrophages, and dendritic cells (DCs) in broncho-alveolar lavage fluid and on CD4+ and CD8+ T lymphocytes and DCs in lung tissue. Translation of these results to the clinic support the hypothesis that the development of asthmatic symptoms in young adults with atopy is enhanced by the adoption of active smoking.

Cigarette smoke is a modulator of both airway inflammation and airway responsiveness, but is also capable of facilitating primary allergen sensitisation. Again, animal data support the finding that mainstream cigarette smoke temporary disrupts the normal lung homeostatic tolerance to innocuous inhaled allergens, thereby inducing primary allergic sensitisation. This is characterised not only by the development of persistent IgE, but also by the emergence of an eosinophil-rich pulmonary inflammatory reaction. These features of atopy normally do not occur either in mice or in humans when exposed to inhaled harmless allergens, as the normal immune response is tolerance. When creating models of allergen-induced airway inflammation, the normal tolerance has to be overcome, mostly by applying an adjuvant such as aluminium hydroxide, limiting the clinical relevance of this approach. Cigarette smoke can act as an effective adjuvant in facilitating primary allergic sensitisation to inert antigens such as ovalbumin. The murine models may help to unravel the relationship between cigarette smoke and asthma.

The aggravating effect of cigarette smoke in asthmatics was depicted by Mario Cazzola, comparing the smoking asthmatic to the COPD patient. Despite both being inflammatory conditions, asthma differs from COPD as more CD4+ T cells and less smoking is linked to asthma, whereas CD8+ T cells and heavy smoking is seen in COPD. Numerous data support the vision that morbidity and mortality from asthma increase in individuals that smoke cigarettes. Cigarette smoking and asthma combine to accelerate the decline in lung function to a greater degree than either factor alone. [Thomson N, Chaudhuri R, Livingston E. Active cigarette smoking and asthma. Clin Exp Allergy 2003; 33:1471-5.]

Compared with non-smoking asthma patients, smoking asthma patients have disease features similar to those found in early stages of COPD. For asthmatic smokers, there is a continuum between asthma and COPD. As one moves towards COPD and emphysema, there is a progressive increase in alveolar destruction, parenchymal injury, and remodelling.

Despite these facts, active cigarette smoking is common in adult asthmatic patients although the consequences – and in particular the therapeutical consequences – are far from negligible. Asthmatic smokers need a specialised approach, as data shows that active cigarette smoking impairs the efficacy of short-term inhaled corticosteroid treatment in mild asthma. Given these facts, alternative or additional treatment to inhaled corticosteroids may be required for asthmatics that continue to smoke, reinforcing the need for smoking cessation in asthma, even in patients with mild disease. When treating smoking asthmatics, the clinician must realise that these patients could benefit from an increased dose of inhaled corticosteroids. In addition, for some asthma control outcomes, recent data shows that the lung
function response to montelukast was better in patients with asthma that smoke than in non-smoking asthmatics.

Inhaled corticosteroids are not only beneficial in asthma in the short term, but their long-term use in moderate to severe adult asthma is associated with a smaller decline in FEV1 in men in a dose-dependent approach. Cigarette smoke, however, annuls this protective effect as it is shown that for men with more than five years of smoking at least one pack a day, the long-term beneficial effects of inhaled corticosteroids on FEV1 decline were absent. For that reason, Neil Thomson again stressed the fact that significant efforts should be made to motivate people with asthma to refrain from smoking, particularly since it obstructs the long-term beneficial effects of the best treatment currently available. Smoke cessation in smokers with asthma resulted in improved lung function as early as one week after ceasing smoking, with a further improvement up to six weeks later. A reduction of sputum neutrophil percentage was noticed after six weeks of smoking cessation, although no change in common inflammatory mediator levels was observed.

In this session, Antonio Nieto also discussed passive smoking, and particularly childhood passive smoking. Cigarette smoking has many adverse reproductive and early childhood effects, including increased risk of infertility, preterm delivery, stillbirth, low birth weight, and sudden infant death syndrome (SIDS).

Other adverse effects of both pre- and postnatal parental smoking on children’s respiratory health are known. Asthma is most strongly associated with maternal smoking during pregnancy, but post-natal exposure shows independent associations with a range of other respiratory symptoms. The importance of pre-natal smoke exposure appears from data indicating a greater influence of exposure to maternal smoking (pre-natal and post-natal) than post-natal paternal smoking on the development of respiratory symptoms in young children. These findings stress that all tobacco smoke exposure has serious consequences on children’s respiratory health and should be reduced without delay.

To summarise this interesting and stimulating session, both animal and human data point towards the aggravating effect of cigarette smoke on asthma. These data should encourage both researchers and clinicians to expand the attention received by this particular topic, as the short- and long-term consequences are significant.

More information: www.cdc.gov/tobacco

Wouter Huvenne
Drug hypersensitivity reactions represent one of the most difficult challenges in allergy practice.

Andreas Bircher from Switzerland outlined a clinical diagnostic approach for patients with suspected drug hypersensitivity based on the morphology of clinical manifestations and the chronology of the reaction. A precise description of skin lesions is important in establishing the mechanism responsible for the reaction, and helps to rule out other dermatological diseases. Thorough recognition of chronological patterns also ensures better definitions of the putative pathophysiological mechanism of the reaction. The time lag between the start of pharmacotherapy and the onset of clinical manifestations is the induction interval, while the period between the previous dose and the onset of symptoms in a sensitised individual is a reaction interval, which varies according to the underlying pathophysiology. However, a schematic distinction between immediate and non-immediate reactions at one hour is of limited value in assigning the pathogenic mechanism to the reactions, since the onset of drug hypersensitivity reactions due to various mechanisms may overlap.

It is also important to identify co-factors affecting the course of the drug hypersensitivity reaction such as viral infection, treatment with corticosteroids, antihistamines, immunosuppressive agents, concurrent food intake, activity of underlying disease, enzyme activity, drug metabolism, and interactions. The selection of appropriate diagnostic tools in drug hypersensitivity should be guided by a pathogenic hypothesis based on the morphology and chronology of the reaction. For example, skin prick tests can be helpful in identifying a culprit drug in immediate reactions, while patch tests, intradermal tests, and LTT should be considered for suspected delayed drug hypersensitivity.

The use of drug skin testing in the evaluation of patients with drug allergy was reviewed by Maria Teresa Audicana Berasategui from Spain. According to ENDA recommendations, skin tests should be performed with commercial forms of drugs at optimal non-irritating concentrations and with appropriate controls (histamine and saline) [Allergy, 2002]. The established optimal drug concentrations should be used in order to avoid non-specific false-positive results due to irritation. The observations of systemic reactions during drug skin testing justify caution during these diagnostic procedures. In addition, serial skin re-testing with drugs may augment skin test response (a booster effect). Skin tests can be used to confirm drug hypersensitivity reaction and the identification of the eliciting drug, and also to assess a drug’s potential for cross-reactivity.

Several in vitro tests can be used to establish the different mechanisms of drug hypersensitivity reactions. The RAST test is helpful in detecting drug-specific IgE antibodies in the serum of patients with immediate drug allergies. The basophil activation test is an ex-vivo test based on the detection of flow cytometry activation markers expressed on the patient’s basophils upon stimulation with a suspected drug. This assay is available for a few drugs including β-lactams,
Drug Allergy

Point of View

muscle relaxants, NMBA, and others. The lymphocyte transformation test can be used in the diagnosis of delayed drug allergies, but involves a labour-intensive and cumbersome technique and its diagnostic value in drug hypersensitivity reactions needs further evaluation. Overall, diagnostic work-up in drug allergies can involve a detailed clinical history and various diagnostic tools including skin testing, the detection of specific IgE, drug challenges, and ex vivo tests.

Prof. Antonio Romano, Italy, highlighted potential pitfalls in the diagnosis of drug allergies. A thorough history is the cornerstone in the diagnosis of drug allergy. However, this history is often imprecise and lacks important information, so that an offending drug can not be identified in many cases. [Kroigaard, 2007] There is a possibility of hapten, metabolite [Popescu, 1996], excipients, and additives [Lee, 2003] being the cause of a reaction but not a drug itself, which further complicates the identification of a culprit allergen. Other pitfalls arise from the limitations of skin testing in drug allergies.

In vivo tests should be selected according to the suspected mechanism of the reaction. A choice of inappropriate diagnostic tests unrelated to the mechanism of the reaction can be misleading in the drug allergy diagnostic work-up. Drug metabolism, antigen presentation, and the involvement of haptns contribute to further limitations of skin testing in drug allergies. In addition, co-factors such as food intake, drug interactions, stress, and exertion situations may play a role in the development of the drug reaction and should be recognised. The absence of co-factors during skin testing may also explain false-negative results. Drug testing in a patient's state of natural desensitisation or a refractory period after the reaction may also result in false-positive test results. The erroneous attribution of responsibility to the tested drug can serve as another explanation for negative skin test results. In vitro tests are available for a limited number of drugs and appear to be less sensitive than skin testing. LTT is time consuming and is known for false-positive test results. In addition, the patient's treatment may affect skin test results. The diagnosis of drug allergy is always challenging, and it is particularly important to recognise and, if possible, to avoid the diagnostic pitfalls in a drug allergy work-up.

Josefina Rodrigues from Portugal addressed the most challenging questions of drug tolerance induction. The graded challenge or incremental test dosing is a method of involving the cautious administration of drugs to patients with a low likelihood of allergic reaction to the drug, in order to prove its safety and to provide reassurance to the patient. By contrast, rapid drug desensitisation modifies the immune response to a drug in an allergic patient, leading to the induction of temporary unresponsiveness to the drug. It is used to provide the patient with essential medication and to protect the patient against a severe reaction.

Drug desensitisation can be considered for patients with a convincing history of immediate IgE-mediated reaction to a drug, when an alternative non-crossreacting drug can not be used, when the benefit exceeds the risk of desensitisation, and when the patient's survival depends on the drug in question. Drug desensitisation has been successfully achieved using different protocols and routes of administration including oral, intravenous, and intramuscular. Natural desensitisation may sometimes develop in penicillin allergy, as penicillin-specific IgE antibodies have been reported to wane over time in some cases.

The mechanism of drug desensitisation is poorly understood. Possible explanations are the consumption of drug-specific IgE antibodies, the hapten inhibition of crosslinking of mast cell-bound drug-specific IgE antibodies, mediator depletion from mast cells and basophils, and antigen-dependent mast cell desensitisation. Remarkably, antigen-dependent mast cell desensitisation appears to be a responsible mechanism for acute oral desensitisation to penicillin V in murine models [Woo HY, et al. Allergy, 2006].

Elena Borzova

Presented at the EAACI 2007 Congress in Göteborg, Sweden.
The immune response mediated by memory T lymphocytes is classically associated with protective immunity to pathogens. In contrast to naïve responses, memory responses can be elicited by lower antigen concentrations and reduced costimulatory requirements, enabling rapid effector function. Memory T cells are generated from activated/effector T cells following an initial antigen (Ag) encounter, and are distinguished by their ability to survive long-term and to mediate rapid effector responses upon antigenic recall. The CD28/B7 costimulatory pathway is generally considered dispensable for memory T cell responses, largely based on in vitro studies demonstrating memory T cell activation in the absence of CD28 engagement by B7 ligands. It was demonstrated that inhibition of CD28/B7 profoundly alters the recall function of memory CD4 T cells generated by priming with Ag or during infection with the influenza virus. The CD28/B7 costimulatory pathway can be modulated by a well-characterised fusion of CTLA4 to the Fc portion of human IgG1 (CTLA4Ig). A biased inhibition of IL-2 production by CTLA4Ig from TCR-transgenic or polyclonal influenza specific memory CD4 T cells was found in vitro. Although CTLA4Ig does not inhibit early activation events by Ag-stimulated memory CD4 T cells, as shown in two Ag systems, there are striking defects in proliferative expansion in vivo coincident with a biased loss of the CD62Llow TEM subset in the responding population. Specific recall functions of memory CD4 T cells, such as up-regulation of activation marker expression, are independent of CD28 costimulation: optimal IL-2 production and proliferative expansion of memory CD4 T cells require CD28 costimulation. This susceptibility of memory CD4 T cells to CTLA4Ig-mediated inhibition of CD28 costimulation has important clinical implications. Interestingly, the CD28 costimulatory pathway, which was thought to be uniquely required by naïve T cells, also plays a key role in memory T cell recall, rendering secondary responses susceptible to CD28-mediated inhibition.

Philippe Gevaert

Reference:
Dendritic cells and immunity: TSLP a master switch of allergic inflammation

The interleukin 7 (IL-7)-like cytokine produced by epithelial cells, thymic stromal lymphopoietin (TSLP), could significantly activate human myeloid dendritic cells (mDCs) to induce an inflammatory Th2 response characterised by high tumour necrosis factor-alpha (TNFα) and low IL-10 production, distinct from the regulatory Th2 responses characterised by low TNFα and high IL-10 production1.

TSLP was found highly expressed by the keratinocytes of skin lesions of atopic dermatitis and associated with DC activation in situ. Soumelis V showed that human TSLP can potently activate CD11c+ DCs and induce the production of the Th2-attracting chemokines TARC (thymus and activation-regulated chemokine; also known as CCL17) and MDC (macrophage-derived chemokine; CCL22)2. TSLP-activated DCs primed naïve Th cells to produce the pro-allergic cytokines IL-4, IL-5, IL-13, and TNFα, while down-regulating IL-10 and interferon-gamma (IFNγ).

In atopic dermatitis, TSLP was highly expressed by epithelial cells (especially keratinocytes). TSLP expression was associated with Langerhans cell migration and activation in situ. Ito T reported that TSLP-induced human DCs express OX40 ligand (OX40L) but not IL-12. TSLP-induced OX40L on DCs was required for triggering naïve CD4+ T cells to produce IL-4, IL-5, and IL-13. In addition, Soumelis and Ito revealed the following three novel functional properties of OX40L: (a) OX40L selectively promotes TNFα, but inhibits IL-10 production in developing Th2 cells; (b) OX40L does not retain the ability to polarise Th2 cells in the presence of IL-12; and (c) OX40L exacerbates IL-12-induced Th1 cell inflammation by promoting TNFα, while inhibiting IL-10. Therefore, OX40L on TSLP-activated DCs triggers Th2 cell polarisation in the absence of IL-12, and OX40L can switch IL-10-producing regulatory Th cell responses to TNFα-producing inflammatory Th cell responses.

The initial finding that epithelial cell-derived TSLP triggers DC-mediated inflammatory Th2 responses through OX40L in humans, combined with the exciting in vivo studies, suggests that TSLP represents a master switch of allergic inflammation at the epithelial cell-DC interface. TSLP and OX40L should, therefore, be considered as key targets for immunologic intervention in the treatment of allergic diseases3.

Presented at the EAACI 2007 Congress in Göteborg, Sweden.

Reference:
New Aspects on Regulatory Cells in Allergy

DCs – regulators between immunity and tolerance

The main function of dendritic cells (DCs) is to process antigen material and present it on the surface to other cells in the immune system, thus functioning as antigen-presenting cells. DCs are highly specialised professional antigen-presenting cells present in tissues that are in contact with the external environment, mainly through the skin (where they are often called Langerhans cells) and the mucosa of the nose, lungs, stomach, and intestines. Once activated, DCs migrate to secondary lymphoid organs, which is crucial for the initiation and maintenance of T cell-mediated immune responses. DCs undergo a maturation process, induced by inflammatory cytokines, bacterial, or viral products, which leads to their migration to lymph nodes, where they efficiently attract and activate T cells. Thus DCs, because of their potent antigen presentation function, are critical in the initiation and type of emergent immune response. It is increasingly evident that the failure of the ability of DCs to maintain tolerance can lead to autoimmune and/or inflammatory diseases.

Lactobacilli are probiotic bacteria that are frequently tested in the management of allergic diseases and gastroenteritis. Recently, it has been shown that probiotics have immunoregulatory probiotics and promote mucosal tolerance. On the basis of pathogenic or tissue-specific priming, DCs acquire different T cell-instructive signals and drive the differentiation of naive TH cells into either TH1, TH2, or regulatory effector T cells. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating DC function through DC-specific intercellular adhesion molecule 3-grabbing non-integrin (Smits et al, JACI 2005).

NK cells and their role in allergy

Natural killer (NK) cells are bone marrow-derived lymphocytes which constitute a major component of the innate immune system. Distinct from T and B cells, NK cells are controlled by a limited repertoire of germ line-encoded receptors that do not undergo somatic recombination. Thus, NK cells are a branch of the innate immune system. NK cells play a major role in the rejection of tumours and...
virally infected cells. They kill unwanted cells by releasing small cytoplasmic granules of perforin and granzyme that cause the target cell to die by apoptosis.

There is substantial correlative evidence suggesting that NK cells play an important role in combating several inflammatory diseases including asthma, atopy, and auto-immune conditions.

The establishment of a Drosoophila insect cell system to study NK cell responses upon recognition of specific target cell ligands showed that cytotoxicity by resting NK cells is controlled tightly by separate or co-operative signals from different receptors for granule polarisation and degranulation.

Resting NK cells can have strong cytotoxic activity, given the right signals, even in the absence of exogenous cytokines (Bryceson et al, JEM 2002).

Several reports have suggested a critical role for NK cells in affecting dendritic cell (DC) maturation and function upon direct contact between these cells. The yeast Malassezia can act as an allergen in atopic eczema/dermatitis syndrome, and induce the maturation of DCs. These findings indicate that NK cells and DCs can interact in the skin and that Malassezia affects the interaction between both types of cells. NK cells may play a role in regulating DCs in atopic eczema/dermatitis syndrome (Buentke et al, J Invest Dermatol 2002).

Murine models suggest the critical role played by NK cells, but not that of NKT cells, in the development of allergen-induced airway inflammation, and suggest also that this effect of NK cells is employed during immunisation. If translatable to humans, these data suggest that NK cells may be critically important in deciding whether or not allergic eosinophilic airway disease develops. These observations are also compatible with a pathogenic role for the increased NK cell activity observed in human asthma (Korsgren M et al, J Exp Med 1999).

**Regulatory T cells**

To function properly, the immune system must keep life going in harmony with the internal and external environment, must realise and neutralise danger (infections), must tolerate “self” and “non-infectious non-self”, and must maintain tissue integrity. The immune system is a highly interactive network, which makes its decisions on the basis of input from all organs and tissues, infections, normal flora bacteria, and many or even any environmental agents.

Recent developments in T cell subsets and regulation of the balance between these T cells include the two subsets of Th cells: Th1 cell types, important in inflammatory delayed hypersensitivity producing IFN-γ, TNF-α, and TNF-β; and Th2 cells characterised by IL-3, 4, 5, 9, and 13 secretion. The discovery of new subsets such as T regulatory cells and IL-17-producing Th17 cells gave new insights into understanding T cell biology.

Regulatory T cells are a specialised subset of T cells that actively suppresses activation of the immune system and thereby maintains immune system homeostasis and tolerance to self-antigens. Recent studies indicate that regulatory T cells play an important role in controlling Th2-biased immune responses.

Another subset of T cells producing interleukin 17 (Th17 cells) has been identified as highly pro-inflammatory and inducing severe auto-immunity. Emerging data regarding Th17 cells suggest that this T cell subset upholds an important function in immunity and disease. The role of TH17 cells in allergy is still largely unclear, but experimental models suggest that TH17 cells may be important in regulating neutrophilic inflammation in acute airway inflammation.

Nicholas Van Bruaene

Presented at the EAACI 2007 Congress in Göteborg, Sweden.
For the last eight years the EAACI Immunology Section has organised a winter school for young doctoral and postdoctoral scientists active in the field of basic allergology and immunology research. The 6th EAACI-GA²LEN Immunology Winter School took place from January 31st to February 3rd 2008, with the generous support from GA²LEN. Keeping the previously successful combination of science and winter sports, the meeting took place in an alpine setting in Austria, namely Pichl close to Schladming.
As previously, the major goal of the 6th EAACI-GA2LEN Immunology Winter School was to educate junior researchers by providing an environment allowing close interaction with renowned allergy and immunology experts. This year the meeting focused on basic immunological research in skin allergy and immunotherapy; topics representing important issues in basic and clinical sciences.

80 scientists from 17 different countries attended the meeting. After an introductory lecture, main symposia were held on innate immunity in the skin, innate immunity, adaptive immunity, allergen-specific immunotherapy and immune regulation, and the allergic immune response. Each symposium was opened by a keynote lecture given by scientists with high international reputation followed by 5 presentations of junior scientists, selected for the quality of their abstracts. The keynote speakers this year included: Georg Stingl, Vienna, Austria; Jens-Michael Schröder, Kiel, Germany; Stephen J. Galli, CA, USA; Mark Larché, Canada; Thomas Platts-Mills, VA, USA and Gennaro De Libero, Basel, Switzerland. All speakers gave brilliant overviews combined with latest insights into topics such as “modern and postmodern” dermatological research, antimicrobial peptides, the role of mast cells as immune regulators, basic mechanisms of allergen-specific immunotherapy, immune responses to carbohydrate epitopes and T cell recognition of lipids.

In addition to these scientific aspects, all keynote speakers gave excellent examples of how to present scientific data in a comprehensive and fascinating way, and how to combine science and entertainment in a highly intellectual manner. For example, Steve Galli summarized his data in a poem, Gennaro de Libero demonstrated that T cells are archangels and Mark Larché used the famous verse from Gammer Gurton’s Garland to convince us that “Roses are red, violets are blue, I love immunotherapy and so should you!” Thus, a relaxed and stimulating atmosphere developed resulted in fruitful discussions between young scientists, keynote speakers and members of the faculty.

After each main symposium young researchers took the chance to have intense discussions with the keynote speakers. This active interaction between the juniors and the “experienced stagers” was continued during tasty dinners and poster sessions until late in the evenings. After the morning sessions (starting at 8 o’clock sharp) everybody took the chance to recover and reload their batteries, either by skiing or by relaxing in the wellness area.

Thanks to the support of GA2LEN and the EAACI as well as each participant of the 6th EAACI-GA2LEN Immunology Winter School, again several major goals of the EAACI Immunology Section were achieved: The communication between areas of basic immunology and various allergy disciplines was improved, young scientists and physicians were trained in basic immunology and the latest data regarding progress in immunological research were disseminated. And finally, an engaging scientific environment in which allergy and dermatology related immunological concepts was achieved. The evaluation of the meeting by the attendants resulted in 9,4 out of 10 points.

The success of the meeting has convinced the EAACI Executive Committee to continue supporting the Immunology Winter Schools. So mark your calendars: The 7th EAACI-GA2LEN Immunology Winter School will be held in Davos, February 5–8th, 2009. We encourage young scientists to apply for the meeting! Details regarding the abstract submission will be communicated via the EAACI web page this autumn.

Thilo Jakob
Chairman of the EAACI Immunology Section

Barbara Bohle
Secretary of the EAACI Immunology Section
3rd International Symposium on Molecular Allergology (ISMA), held in Salzburg, Austria, April 18–20, 2008

...and other activities

EAACI support paves the way for young congress on molecular allergology

After the meetings in Rome in 2006 and 2007, the IG Allergy Diagnosis once again received generous support from the EAACI for a 3rd meeting in Salzburg: The ISMA 2008. The scientific committee generated a unique programme and involved EAACI Sections and Interest Groups, emphasising the “cross-sectional” nature of the topic. Fatima Ferreira and her team from the Christian Doppler Laboratory for Allergy Diagnosis and Therapy took the lead and provided excellent local organisation within the Department of Molecular Biology at the University of Salzburg.

Parallel to the scientific meeting, the local organising committee organised a Symposium for high school biology-teachers with the topic molecular allergology and general immunology. Some invited ISMA speakers also gave special presentations to biology teachers.

Molecular allergology 2008: Hot topics and intensive discussion

In total, 242 scientific participants from 38 countries from all over the world and 38 biology teachers from Austria joined the 3rd ISMA 2008 in Salzburg. The Allergome School opened the meeting activities, teaching participants how to use the Allergome platform and how to get the best from the last software implementations (www.allergome.org). 27 invited experts, including EAACI President Prof. Roy Gerth van Wijk, gave presentations and moderated the sessions. Each of them started with a keynote lecture on topics of general interest, followed by three talks on molecular allergology, and one oral presentation selected from 69 submitted abstracts for poster presentation, being discussed during 2 separate 2.5 hour poster sessions on structural biology and bioinformatics, allergen identification and characterization, epitope characterization, allergic sensitization and allergy diagnosis and therapy (www.isma2008.eu/programme.htm). Six young researchers received awards for their excellent work.

EAACI ISMA 2008: True success holds promise for future activities

Basic researchers and clinicians discussed the topics in sequential sessions: Structural biology of allergens, special allergen sources like potential occupational hazards, and animal models in allergic diseases proceeded clinical sessions on allergy diagnosis, demonstrating the shift from extracts to molecules in daily practice, decision making and immunomonitoring of allergen-specific immunotherapy, and the “all-time favourite”, food allergy. Due to the excellent hosts in Salzburg, and the audience’s enthusiasm, the 3rd ISMA became a true success: Participants followed the entire meeting with great interest, discussing science, interacting with colleagues and peers and meeting new friends.

After an open discussion with EAACI representatives and conducting an instant poll, future EAACI-supported ISMA meetings might follow every two years. This will bundle the interest of potential participants and give enough time to establish new results. The 4th ISMA edition under the EAACI umbrella is foreseen for 2010.

Great interest of members from abroad and envisioned support from other institutions, however, might lead to unique transitions of the ISMA concept between its regular schedule to other continents outside Europe.

Ambitious tasks and new members

Since the EAACI 2007 Congress in Göteborg, Sweden, new ideas and activities have fuelled the work of the Interest Group on Allergy Diagnosis (IGAD). Thanks to a solid number of experts from research laboratories, allergy clinics and industry, future plans were fruitfully pushed forward during the IGAD business meeting in 2007. The interest group covers a broadened scope: Laboratory diagnostics, including serological in vitro assays for IgE detection, functional ex vivo tests involving basophils or other cellular components, are handled by the IGAD as well as all aspects of in vivo diagnosis, i.e. skin tests, challenge tests.

Improved standards for flow cytometric basophil activation tests (BAT)

Flow cytometry based cellular assays utilizing basophils are explored by various European
Join the 7th Symposium on Experimental Rhinology and Immunology of the Nose (SERIN) in November

The 7th Symposium on Experimental Rhinology and Immunology of the Nose (SERIN) will take place in Dubrovnik, Croatia, on 13–15th November 2008. The organisers, the ENT Section of EAACI, aim to attract ENT researchers and all interested in the immune response in the nose and its adjacent areas.

The symposium, held every thirty months outside the congress season, i.e. in February and November, follows the previous successful 6th SERIN symposium in Barcelona in February 2006, also organised by the ENT Section. Its location moves to the eastern Mediterranean region, to the beautiful medieval city of Dubrovnik on the coast of the Adriatic Sea.

As at previous SERIN meetings in Barcelona, Dusseldorf, Ghent, London, and Rotterdam, this symposium will host experts and young researchers and their contributions from basic and clinical research in rhinology, allergology, and respiratory medicine. The main attraction of SERIN is its active interaction between experts, researchers, and those who intend to upgrade the scientific level of their research in the field of ENT and respiratory medicine.

The SERIN meeting is traditionally a plenary meeting. Topics currently in the news are integrated into discussions at the main symposia, held by invited international experts. This year the subjects include: upper-lower airway interaction, non-allergic rhinitis/brain-nose interaction, and novel treatments in rhinosinus disease. Other key topics are covered by introductory lectures by invited speakers, and followed by open discussion. Added contributions are presented at poster sessions and short presentations. The main topics of the meeting cover basic and clinical research on allergic and non-allergic rhinitis, rhinosinusitis, nasal polyps, upper-lower airways interaction (infection, allergy, hyperreactivity), neurogenic inflammation, brain-nose axis, olfaction, neural regulation, novel approach to treatment of rhinosinus disease, genomics, and proteomics. Recent revisions of EAACI position papers (EPOS 2007 and ARIA 2008) will also be presented. The international experts indicating their attendance at time of writing include: Claus Bachert, James Baraniuk, Andrew Bush, Adnan Custovic, Wytske Fokkens, Roy Gerth van Wijk, Peter Howarth, Joaquim Mullol, Carlos Nunes, Giovanni Passalacqua, Herbert Riechelmann, Glenis Scadding, Pontus Sjöner, Elina Toskala, Cornelis van Drunen, and Martin Wagenmann.

Updated information on the meeting can be found online at (www.hdorl.net/serin2008).

Livije Kalogjera
President of the Local Organising Committee
GA²LEN is a Network of Excellence that brings together leading European research teams in the field of allergy and asthma. GA²LEN fosters a holistic, multidisciplinary approach to allergic diseases, including its genetic basis, clinical treatment, environment aspects and social causes throughout age groups.

Since its creation in 2004, GA²LEN has worked to establish an internationally competitive network of European centres that will strengthen European research and accelerate its translation to health professionals and patients. The objective is to set-up a generic research platform, with centres across Europe, for harmonised research on allergy and asthma.

- From birth to allergy
  Karin Lødrup Carlsen, Norway
- Mechanisms linking sensitisation to symptoms
  Wytske Fokkens, The Netherlands
- Which sensitised individuals become allergic?
  Philippe Bousquet, France
- Interaction between allergens and viruses
  Nikos Papadopoulos, Greece

Visit the GA²LEN stand in Barcelona

www.ga2len.net