New Treatments for Asthma
Paul O’Byrne
(EJ Moran Campbell Professor and Chair, Department of Medicine, McMaster University, Canada.)
Asthma management is focused on achieving total asthma control in two domains. First is current control, where the patient is asymptomatic all of the time, has normal lung function and no limitations in activities. The second in minimizing future risk of severe exacerbations, accelerated decline in lung function and avoiding side effects from medications (1). Current available treatment, particularly with inhaled corticosteroids (ICS) with or without long-acting inhaled β2-agonists (LABA) can achieve good asthma control in many patients. However, most asthma patients do not achieve total control (2).
The commonest reason for this is poor adherence with asthma treatment. There is also a subset of asthmatic patients who, despite treatment with optimal doses of asthma medications, have uncontrolled asthma and are at risk for severe asthma exacerbations. The use of the ICS/LABA combination containing budesonide/formoterol both as a rescue and maintenance treatment greatly reduced exacerbation risk (3).

Some patients will not achieve asthma control, even with maximal doses of currently available therapy, perhaps as many as 10%. These patients are considered to have severe refractory asthma. It has become evident that severe refractory asthma consists of a very heterogeneous population of patients (4). In addition, many diseases can masquerade as severe asthma. An accurate diagnosis and careful phenotyping with relation to atopic status, and the type of airway inflammation present, may provide additional useful information with regards to newer treatment options.

A number of experimental treatments are being developed for severe refractory asthma. An example of the necessity to phenotype patients with severe refractory asthma has been the development of monoclonal antibodies (mAb) directed against interleukin (IL)-5, a cytokine produced by Th2 cells and innate lymphocytes type 2 (ILC2). When studied in patients with a persisting airway eosinophilia, mAbs against IL-5 or its receptor (IL-5Ra) have been shown to reduce asthma exacerbations and improve lung function (5). The use of induced sputum was essential to identify these patients with a persisting airway eosinophilia, despite optimal treatment. Similarly, a mAb directed against IL-13 significantly improved lung function in patients with difficult-to-control asthma, but only in those with an elevated serum periostin (a protein produced by airway epithelial cells after stimulation with IL-13) (6). Also, a mAb directed against the IL-4Ra, which is the common component of the receptor for IL-4 and IL-13, is showing promise in patients with elevated blood eosinophil counts (7).
Thymic stromal lymphopoietin (TSLP) is produced by airway epithelial cells in response to viruses and environmental allergens. It is up-stream to the production of the type-2 cytokines, IL4, IL-5 and IL-13. Treatment with a mAb against TSLP also shows promise in asthma (8).

It is likely that all new treatments for severe refractory asthma will require efforts at phenotyping to target therapy at the populations of patients likely to benefit, as this group of patients have such heterogeneous mechanisms causing their severe disease.

Selected References
**Obesity and Asthma: Lessons from Animal Models**

Stephanie A Shore
(Dept. of Env. Health, Harvard T.H. Chan School of Public Health, USA)

There is a worldwide epidemic of obesity. The World Health Organization estimates that approximately 2 billion people are either obese or overweight. Obesity is a risk factor for type 2 diabetes, hypertension, and atherosclerosis. Recently, obesity has also emerged as an important risk factor for asthma. Obesity increases both the prevalence and the incidence of asthma and obesity is extremely common in severe asthma. Importantly, weight loss reduces asthma symptoms, improves lung function, and reduces airway hyperresponsiveness (AHR). Asthma is more difficult to control in obese individuals, and corticosteroids are less effective in obese than lean asthmatics. Understanding the mechanistic basis for obese asthma may lead to novel therapeutic strategies for this difficult to treat population. Animal models provide a means to identify the mechanistic underpinnings of obese asthma. We have established that obese mice, regardless of whether their obesity is genetic or diet-induced, have innate AHR. Ozone, an air pollutant, is a common asthma trigger, and obese mice exhibit exaggerated responses to acute ozone exposure including greater airway inflammation, greater changes in pulmonary mechanics, and more pronounced airway hyperresponsiveness (AHR). Ozone causes greater increases in bronchoalveolar lavage (BAL) IL-33 and IL-17A in obese than in lean mice. Importantly, antibodies neutralizing either IL-17A or ST-2 (the receptor for IL-33) attenuate ozone-induced AHR in obese but not lean mice. The target of IL-33 in obese mice is likely innate lymphoid cells type 2 (ILC2) that express type 2 cytokines: ozone increases IL-13 and IL-5. ILC2 in the lungs of obese but not lean mice, and ozone also causes greater increases in BAL IL-5 and IL-13 in obese than lean mice. Furthermore, anti-IL-13 attenuates aspects of the response to ozone in obese but not lean mice. IL-17A+ ILC3 were increased following ozone exposure in obese but not lean mice and appeared to be the source of the IL-17A that augmented ozone responses in the obese mice. These results indicate that pulmonary responses to ozone are not just greater, but qualitatively different in obese versus lean mice. In particular, in obese mice, ozone induces activation of ILC2 and ILC3 which exacerbate airway hyperresponsiveness.
The LEAP (Learning Early About Peanut allergies) study was a randomised controlled trial to test the hypothesis that early introduction of peanuts into the diet of high risk infants would prevent the development of peanut allergy. Six hundred and forty infants with severe eczema and/or egg allergy were randomised to early introduction of peanuts or complete avoidance continuing during the first 5 years of life. Peanut allergy or tolerance was determined at 5 years of age in nearly all children using oral peanut challenges, and in a minority using diagnostic criteria based on Skin Prick Testing and Specific IgE. An Intention to Treat analysis (even with a worse case imputation scenario) revealed a more than 80% reduction in the rate of peanut allergy at 5 years of age in the peanut-consuming group. Early introduction of peanut was effective in preventing peanut allergy irrespective of whether children were sensitised to peanut or not at the onset of the study and irrespective of ethnic background.

The LEAP-On study was designed to see whether ongoing peanut consumption was necessary for the protective effect of early consumption to remain. Children in the LEAP cohort after completion of the LEAP study at 5 years of age were asked in both the original consumption and avoidance groups to completely avoid peanuts for a 12 month period. At 6 years of age after a year of avoidance, the children had peanut allergy status determined again. The findings were that original consumption of peanut despite a year of peanut avoidance continued to have a protective effect against developing peanut allergy.

Immunological changes observed in the LEAP study included a very early rise in IgG and IgG4 antibodies to peanut in the consumption group: a high IgG4/E ratio appeared to be protective against peanut allergy.

Specific IgE to peanut was not statistically different in the 2 groups during the course of the study, but during the 12 months of peanut cessation in LEAP-On, between age 5 and 6 years specific IgE to peanut significantly dropped in the original peanut consumption group. Specific IgE to Ara h2 declined after 2½ years of age in the LEAP study and continued to decline during LEAP-On in the consuming group. This suggests that both early induction of IgG4 and late inhibition of peanut specific IgE synthesis are both important mechanisms that contribute to tolerance.
**IL4**  
**Chronic Urticaria Management Diagnosis and instruments to determine/monitor disease activity**  
Torsten Zuberbier  
(Department of Dermatology and Allergy, Charité Universitätsmedizin Berlin, Germany)

According to the international guidelines, chronic urticaria is defined by the sudden appearance of wheals, angioedema or both, lasting for a period overall of at least six weeks. Chronic urticaria encompasses both, chronic spontaneous urticaria, where wheals appear without any external stimulus and the chronic inducible urticaria subtypes: a) physical urticaria like cold urticaria, as well as b) other types of urticaria like cholinergic urticaria or contact urticaria.

Severe chronic urticaria is highly debilitating, influencing both, quality of life (QoL) as well as performance at work.

The management of chronic urticaria in general is based on the principles of ideally identifying and avoiding the trigger of the disease, e.g. in chronic spontaneous urticaria an infectious agent like helicobacter pylori—which can be treated but this is not always possible. In diagnosis, the first steps are to make certain which subtype of chronic urticaria prevails. It must be noted that more than one subtype can occur in one single patient of different severity and different responsiveness to treatment.

Regarding symptomatic treatment, an algorithm has been developed. Most important in this area are modern non-sedating second-generation antihistamines which should be increased in dosage in second line if required up to fourfold. Third line treatment encompasses Ciclosporin A, and Omalizumab—which is now licensed for urticaria in many areas worldwide—among other alternative options in special patients. In inducible urticaria, counseling the patient on avoidance measures is important, e.g. explaining that in pressure urticaria cushioning in shoes may be helpful.
IL5  The Expanding Role of Eosinophils in Health and Disease
James J Lee
(Department of Biochemistry and Molecular Biology, Mayo Clinic Arizona, USA)

The role(s) of eosinophils in health and disease is often summarized as a pervasive consensus opinion: Eosinophils are rare white blood cells whose activities are primarily destructive in character and are only relevant in parasitic infections and asthma. However, the wealth of available studies investigating the role(s) of eosinophils in both health and disease now demonstrate that the activities of these granulocytes are far more expansive than previously appreciated. Instead of being simply destructive end-stage effector cells, we have suggested that tissue-infiltrating eosinophils are important regulators of Local Immunity and/or Remodeling/Repair in both health and disease—The LIAR hypothesis (Lee, JJ, et al., 2010) Clinical and Experimental Allergy 40, 563-575). The LIAR hypothesis proposes that eosinophil-mediated events center on activities associated with tissue/organ homeostasis and have functions in disease processes that are diverse and contributory at multiple levels. In this paradigm, eosinophils are neither singularly destructive nor penultimate regulatory cell types. Instead, they mediate activities whose effects are wide in scope and while the LIAR hypothesis suggests that many of the more significant eosinophil activities are not cytoidal in character, it does not preclude that eosinophils are linked to tissue pathology. This more expansive view of eosinophils and their potential effector functions has led to the realization that these cells pervasively contribute to a wide range of diseases extending beyond helminth infections and allergic diseases such as asthma. Indeed, eosinophil activities not only appear to modulate local tissue/organ immune and remodeling/repair responses but also host defense mechanisms against pathogens (e.g., viral infections). We hypothesize that the roles of eosinophils in these ever-increasingly diverse settings highlight the true complexity and importance of this granulocyte. The translational consequence of this hypothesis is significant. Clinical interventions targeting ALL eosinophils may have unpredictable and even long-term deleterious effects. That is, the multiple eosinophil activities occurring in various disease settings may be specific and unique to a given tissue/organ microenvironment with some activities contributing to pathology while others are linked with homeostatic functions, rendering the removal of all eosinophils too severe of a therapeutic approach that may also have unintended consequences.
**IL6**

*Novel actions of macrolides and macrolide therapy for pulmonary inflammation*

Bruce K Rubin  
(Department of Pediatrics, Virginia Commonwealth University,  
Children’s Hospital of Richmond at VCU, USA)

The non-antimicrobial properties of macrolides were suspected as far back as the 1960s however, their dramatic clinical effectiveness in treating diffuse panbronchiolitis has served to extend their use to a number of chronic inflammatory diseases. Macrolide antibiotics administered in sub-antimicrobial doses improve pulmonary function and decrease exacerbation frequency for persons with bronchiectasis or cystic fibrosis. Data also suggest a beneficial effect of macrolide antibiotics in the treatment of steroid dependent asthma, non-CF bronchiectasis, and COPD.

The effects of macrolides in patients with chronic inflammatory airway disease appear to be independent of antimicrobial properties. Immunomodulation, which differs from immunosuppression or anti-inflammation, is a resetting of the immune response by modifying or regulating one or more function of the immune system. We use the term immunomodulation to describe the down regulation of a hyperimmunity or hyperinflammation without impairing the normal immune or inflammatory response to defend against infection. Macrolides accumulate within cells, suggesting that they may associate with receptors or carriers responsible for the regulation of immune cell activities.

Macrolides have a sustained suppression of abnormal cytokine secretion from normal human bronchial epithelial cells through inhibition and activation of extracellular signal-regulated kinases (ERK). Consistent with this, macrolide antibiotics reduce mucin production as well as neutrophil migration by interfering with ERK signal transduction.
招請講演 7

IL7 —再生医療に向けた篩器創生—

清水達也
（東京女子医科大学先端生命医科学研究所）

再生医療はiPS 細胞に代表される幹細胞研究と工学的技術を駆使して細胞から組織を作製するティッシュエンジニアリング研究をその２輪としてめざましい発展をとげている。ティッシュエンジニアリングに関して世界的には体の中で分解する高分子を細胞の足場として組織を作る方法が広く用いられており、皮膚、軟骨などの再生組織が臨床応用されている。これらの手法に対し我々はシート状の細胞を基層あるいは複層化して組織を作製し移植するという独自の概念「細胞シート工学」（Cell-sheet-based tissue engineering）を提唱し、研究開発をすすめてきた。細胞シートは細胞だけからなり、異物を含まないという利点がある。これにより細胞シートを疾患部に直接移植したり、その酸化化により細胞密度が高い立体組織の構築が可能となっている。既に角膜・食道・心臓・歯周・軟骨・中耳疾患に対する細胞シート再生治療が開始されている。さらに、次世代の再生医療を目指し、細胞シートの酸化化により心臓や肝組織などの立体組織の構築が可能となっている。立体組織構築における大きな課題としては酸素・栄養の供給不足、老廃物の蓄積に起因するスケールアップの限界があげられる。この課題を克服するためには立体組織に生体と同様の毛細血管網を導入する必要がある。これまでに 1．血管内皮細胞との共培養シートの利用、2．複層化細胞シートを血管網の新生を持たせて継返し移植する手法、3．バイオアクターを用いた組織灌流により灌流可能な毛細血管網を含有した立体心筋組織の作製に成功している。さらに心臓再生に向けてポンプ機能を有するような管状あるいは囊状の立体心筋組織を構築する研究を開始している。ヒトiPS 細胞から分化誘導した心筋細胞を用いて作製したヒト心筋シートの管化により、内圧測定が可能な管状の立体心筋組織の作製が可能となっている。今後血管網付与技術との融合によりスケールアップを図り、より高機能な管状立体心筋組織の構築を実現し、重症心不全患者の救済につなげたい。
IL8 PATHOGENESIS OF NASAL POLYPsis

紀太博仁
（Department of Medicine and Immunology, Mayo Clinic, USA）

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a complex and heterogeneous inflammatory condition of the upper airways and sinus cavities, affecting a large proportion of the population worldwide and associated with significant morbidity. CRSwNP is typically recognized as a type 2 inflammatory condition in the United States and Europe, including production of IL-5, IL-13 and eosinophilic inflammation. In contrast, nasal polyps from Asian patients may have an enhanced type 1 immune response with increased levels of IFN-γ while those with eosinophilic inflammation appear to be increasing in Asian countries. The innate immunity of the airway epithelium likely plays one of the key roles in the disease. In particular, defects in the innate immune function of the airway epithelial cells, including diminished expression of antimicrobial molecules and loss of barrier integrity, combined with colonization by fungi and bacteria likely play a critical role. In addition, epithelial cells produce potent cytokines, such as TSLP, IL-33 and IL-25, that promote functions of Th2 cells, mast cells and group 2 innate lymphoid cells (ILC2s), resulting in increased production of type 2 cytokines. Lipid mediators, such as prostaglandin D2, that are produced by mast cells and other inflammation cells also play important roles by promoting recruitment and activation of inflammatory cells. Thus, CRSwNP is likely mediated by an inter-twined immunological network of airway epithelial cells and immune cells. Recent clinical trials of patients with CRSwNP and/or asthma show the beneficial effects of monoclonal antibodies that target IL-5, IL-4Ra, IgE and TSLP, suggesting importance of these cytokines in the pathogenesis of CRSwNP. Better understanding of the key molecules and processes involved in the pathogenesis of nasal polyps will help to develop novel treatment approaches for the patients.
IL9
Role of CD8⁺ T Lymphocytes in Steroid–Refactory Asthma
Erwin W Gelfand
(Division of Cell Biology, Department of Pediatrics, National Jewish Health, USA)
Steroid–refractory (SR) asthma can be defined as the limited response to inhaled corticosteroids (ICS) but little is understood regarding the underlying mechanisms or pathways (endotypes) responsible. A number of asthma studies have focused on one well-defined asthma endotype driven by CD4⁺ T cells and Th2 cytokine production. Beyond the indisputable contribution of CD4⁺ T cells, especially in steroid–sensitive asthma, our focus has been on defining a novel endotype involving CD8⁺ T cells and their unique properties which contribute to SR asthma. We have shown an important role for a subset of effector CD8⁺ T cells as major contributors to IL–13 production in the lung. Increased numbers of these effector CD8⁺ T cells have been demonstrated in SR asthmatics and correlated with lower lung function and basement membrane thickening. Unlike CD4⁺ T cells, both human and mouse CD8⁺ T cells are insensitive to corticosteroids and fail to undergo apoptosis in the presence of corticosteroids. An essential feature of this subset of effector CD8⁺ T cells was their capacity to undergo conversion from IFNγ-producing Tc1 cells to IL–13–producing Tc2 cells in the presence of IL–4. This conversion process has been defined at distinct stages of differentiation, initially characterized by epigenetic and transcriptional reprogramming resulting in pathogenic effector cell function. Our approach focused on epigenetic mechanisms which resulted in the targeting of chromatin–modifying enzymes to specific genomic loci which controlled critical cellular functions involved in asthma pathobiology. We demonstrated that an atopic (IL–4) environment can poise CD8⁺ T cells for pathogenic effector function via epigenetic histone protein methylation modifications that facilitated open chromatin at pro–asthmatic, Tc2–associated genes and closed chromatin at Tc1–associated genes. We have now tested and validated novel therapeutic strategies for epigenetic–based treatments for SR asthma. Targeting steroid–insensitive CD8⁺ T cells represents a novel therapeutic strategy in the treatment of SR asthma.

Related References
Asthma–COPD Overlap Syndrome (ACOS)

Daniel Dusser
(Hôpital Cochin, Université René Descartes, Paris Sorbonne Cité, France)

The concept of overlaps between asthma and COPD is not new: in the early 1960’s it was the foundation of the Dutch hypothesis, which considered asthma and COPD as two facets of a more global condition, namely “non-specific lung disease”. More recently the term ACOS has been proposed for patients presenting several features some of them being recognized as characteristic of asthma and others as characteristic of COPD. Although such description was present in the literature for some years, the concept was made official in 2014 by a common document of the GOLD and GINA committees.

The clinical relevance of ACOS is obvious in routine practice where patients in whom making a firm differential diagnosis between asthma and COPD is difficult do exist. In such patients, having roughly the same number of arguments in favor of asthma and in favor of COPD is the cornerstone of a diagnosis of ACOS. One condition is always required, namely permanent airflow obstruction.

Among patients with chronic obstructive airways disease, the proportion of ACOS has been highly variable, from about 10% to as high as 50%, depending on the studied population, the definition of ACOS used and, most importantly, the quality of the differential diagnosis workup. This illustrates the heterogeneity of ACOS. Although all studies do not provide homogeneous results, patients with ACOS appear to have more exacerbations and poorer quality of life than those with only asthma or COPD.

The main therapeutic consequence of a diagnosis of ACOS is that it indicates the need for inhaled corticosteroids, which are not always indicated in “pure” COPD. One difficulty when dealing with these patients is the lack of specific treatment trials.

To conclude it must be outlined that, for now, the differential diagnosis workup should be as complete as required to get a diagnosis of asthma or COPD. ACOS should be a diagnosis of exclusion. In the future, all chronic inflammatory obstructive airways diseases may fall in the same basket containing patients with various “treachable traits” guiding treatment, but we are not fully there yet.

Key references
Chronic rhinosinusitis (CRS) in children is defined as symptoms of nasal congestion with anterior/posterior nasal drainage and cough for 12 or more weeks with objective evidence of sinus involvement provided by nasal endoscopy or computed tomography scan. This problem adversely affects the quality of life of children more than many other pediatric chronic diseases such as asthma and juvenile rheumatoid arthritis. There are limited studies about tissue inflammation in pediatric CRS. These show more lymphocytic and neutrophilic predominance and absence of epithelial disruption in the tissues of children with CRS when compared to those of adults. The bacteriology involves common childhood acute upper airways disease pathogens (S. pneumoniae, H. influenza, and M. catarrhalis) as well as S. aureus and Streptococcal species. In contrast to adult sinus disease, the adenoids have been shown to play an important role in children, primarily based on their contribution as a bacterial reservoir as well as harboring biofilm. The diagnosis of CRS in children is made by the constellation of clinical symptoms obtained by careful history taking, and supported by objective findings of sinonasal inflammation obtained by nasal endoscopy and computed tomography scans. Careful investigation and awareness of commonly associated co-morbidities is important in management. These include allergic rhinitis, asthma, primary ciliary dysmotility, cystic fibrosis, immune deficiency, and gastroesophageal reflux disease. Medical therapy consists of antibiotics to treat signs of infection, nasal saline irrigation, and intranasal and systemic steroids. In the children where medical therapy fails, surgical options include adenoidectomy (with or without a sinus wash and balloon dilation) and endoscopic sinus surgery and these have success rates that vary between 50–90%.