Symposium 1
Severe Asthma

SY-1 (I-1) -1 How close are we to precision medicine for severe/difficult to treat asthma?

Hisako Matsumoto (Department of Respiratory Medicine, Graduate School of Medicine Kyoto University, Japan)

Biologics targeting type-2 inflammation have introduced a new era for the management of patients with severe asthma, who are inadequately controlled with standard asthma treatment. Currently, clinically useful biomarkers to identify type-2 endotype and application of biologics are blood eosinophil counts, exhaled nitric oxide, and serum periostin. However, no single biomarker is ideal and each has its unique characteristics, which should be well understood in precision medicine. For example, blood eosinophil counts and serum periostin levels may behave differently in the overweight/obese population (Sanadome, et al. Allergol Int 2020; Matsumoto. Respir Investig 2020), and exhaled nitric oxide levels behave differently in early-onset obese asthmatics and late-onset obese asthmatics (Holguin, et al. Am J Respir Crit Care Med 2013). In addition, molecular mechanisms behind blood eosinophilia may differ in different phenotypes, as has been demonstrated in a study by George et al. (Allergy 2020) that examined airway epithelial transcriptome in patients with eosinophilic asthma and eosinophilic COPD. Thus, these biomarkers, although useful, should be carefully interpreted in some phenotypes of severe asthma. Another issue to be solved is to improve understanding and management of airway bacterial colonization in severe/difficult to treat asthma. Typical phenotype of this condition would be asthma accompanied with bronchiectasis. Although the directionality of the development is unknown, bronchiectasis is often accompanied with asthma and may worsen its prognosis, where airway neutrophilic inflammation may play an important role. Meanwhile, some asthmatics with bronchiectasis are sensitized to multiple inhaled allergens, as is reported in patients with bronchiectasis alone (Aogain, et al. Am J Respir Crit Care Med 2019), which makes it difficult to speculate its inflammatory profile. For a closer approach to precision medicine in severe/difficult to treat asthma, in this symposium, I would like to focus on two topics, i.e. characteristics of type-2 biomarkers and asthma accompanied with bronchiectasis.

SY-1 (I-1) -2 Phenotypes of severe asthma

Sang Heon Cho (Department of Internal Medicine, Seoul National University College of Medicine, Republic of Korea)

Many investigators reported diverse approaches to reveal the heterogeneity of phenotypes and endotypes of severe asthma. However, phenotypic characteristics are changeable with time and may or may not be associated with underlying disease mechanisms. SARP, together with other international groups, suggested the clinical severe asthma phenotypes which can be applied in clinical settings although relation between phenotypes and underlying pathophysiologic mechanisms is not clearly unfolded. Besides, multiple cluster analyses using different adult asthma cohorts have presented similar results with those described in the SARP cluster analyses. A cohort including 1,031 elderly Korean asthmatics showed 4 phenotypes with different clinical features and progress were identified. These phenotypes were determined by two variables: smoking and maximum FEV1. IgE sensitization to S. aureus exotoxin was closely associated with the severe eosinophilic asthma in the elderly. There also has been a growing interest on quantitative CT measures of severity in asthma. By combining these density measures with the geometric airway measures, asthma phenotypes were radiologically determined with distinct clinical features. Asthma is often characterized by regional variations in ventilation due to small airways disease especially with xenon enhanced CT. We previously demonstrated that ventilation defect score was different between asthmatics and normal controls. With recent expansion of microbiome studies, there have been attempts to classify the phenotypes of severe asthma based on lung microbiota. A recent study from U-BIOPRED group revealed two distinct phenotypes of severe asthma by unsupervised hierarchical clustering of microbial profiles of sputum samples. We also assessed sputum microbiome profiles and found three clusters based on the microbial abundance which showed significant differences in severity. In addition to the variability in clinical features, patients with severe asthma do not respond uniformly to asthma medications. Therefore, further investigation of asthma phenotypes will help physicians understand asthma pathophysiology and enable to optimize medication for the personalized treatment.

SY-1 (I-1) -3 Biology meets biologics: severe asthma treatment in 2020

Sally E Wenzel (Department of Environmental and Occupational Health, Graduate School of Public Health, University of Pittsburgh, USA)

Evidence clearly supports severe asthma heterogeneity. No lines of evidence are as strong as responses to therapy. Severe asthma has been divided into Type-2 Hi vs Lo on the basis of limited biomarkers including blood eosinophils and exhaled NO (FeNO), which are used to guide therapy with T2-directed biologics. Yet, all patients do not respond and some patients may respond better to one type of T2 directed therapy than another. Thus, the Type-2 related (or other) immune pathways which drive elevations in FeNO or blood eosinophils are likely to differ, and those differences may determine the ultimate responses to therapy. New studies suggest that Type-2 inflammation can be divided into those patients who have inhaled corticosteroid (CS) responsive (or mostly responsive) disease, those who require high doses of systemic CSs to respond and those who respond incompletely to even systemic CSs. Those patients with inhaled CS responsive disease are likely to have localized, perhaps larger airway inflammation, with minimal systemic features. These patients typically respond well enough to traditional medications that biologic therapy is not necessary. Their underlying immune process may be primarily driven by localized non-T cell process, including mast cells and macrophages or even localized T-cell processes which are primarily Th2-like. These non-systemic immune processes, may in more severe disease, also involve the distal lung and airway-centric allergic disease. This phenotype is likely to be responsive to systemic delivery of IL-4R antibodies. Patients who require systemic CSs are more likely to have greater peripheral eosinophilia, distal lung inflammation and sinus disease/nasal polyps. Localized autoantibodies may play a role. However, these patients traditionally respond the best to T2-targeted biologics. Finally, the worst Type-2 molecular phenotype is that which co-exists with other adaptive/lymphocytic immune pathways, including Th1 and perhaps Th17. The best therapies for these patients remain unproven, but combinations of T2-targeted therapies with broad immunosuppressives (beyond CSs) may be beneficial. Thus, we are iteratively learning from the use of targeted biologics in relation to molecular phenotypes.
Symposium 2
Prevention of Allergy

SY-2 (P-1) - 1  Environmental exposures and life-course trajectories of allergic diseases
Adnan Custovic (National Heart and Lung Institute, Imperial College London, UK)

Allergic diseases are multifactorial, and are caused by a variety of different mechanisms which result in multiple heterogeneous clinical phenotypes. For example, some children have mild symptoms affecting a single organ/system, but others have more severe symptoms encompassing multiple organs (e.g., skin, upper and lower airways). The mechanisms underpinning this heterogeneity are largely unknown. The clinical presentation of allergic diseases varies widely over the life-course, and the extent to which phenotypic variation signals differences in disease aetiology remains unclear. Allergic diseases are rarely purely genetically or environmentally driven, and usually develop through complex interactions whereby environmental factors modulate the risk in genetically susceptible individuals. The concept that the same environmental exposure may have different effects among individuals with different genetic predispositions has been well established. Such context dependency in terms of interactions with environmental exposure have also been shown for genes with an important and consistent main effect (such as chromosome 17q 21 locus, a major genetic risk locus for childhood-onset asthma, and filaggrin mutations, a major risk for eczema. The impact of environmental exposures changes over the life course. Our recent study has shown that the association between early-life exposure to cat and cat-specific sensitization fundamentally changes as children grow older. For example, in the first three years of life, cat sensitization was much more common amongst cat owners. However, after age 3 years, the increase in sensitization rate was higher among children without a cat, so by adolescence the prevalence of sensitization was numerically higher amongst those who have not had a cat. Therefore, contradictory results reported by different studies may be a consequence of different life-course trajectories of sensitization between exposed and non-exposed individuals. We would argue that in order to understand the relationship between environmental exposures and later clinical outcomes, one should not rely only on cross-sectional analyses, as more useful information can be gained through the analysis of longitudinal trajectories. The life-course perspective is key when ascertaining the impact of environmental exposures on subsequent allergic disease.

SY-2 (P-1) - 2  Allergy prevention by combating skin sensitization
Yukihiro Ohya (Allergy Center, National Center for Child Health and Development, Japan)

Infantile eczema (atopic dermatitis) is the first allergic disease encountered in human life among allergic diseases except non IgE mediated gastrointestinal allergy such as Food Protein Induced Enterocolitis. Early onset eczema has proved to be a strong risk factor for subsequent food allergy. Especially, the early onset persistent type eczema showed higher odds ratio than the early onset transient type did as a risk factor not only for food allergy, but also for asthma and allergic rhinitis emerged thereafter. Based on the dual allergen exposure hypothesis, we have two ways of preventive strategy against the onset of food allergy. One is early introduction of culprit foods when starting weaning foods and the other is to prevent skin sensitization of allergens by manipulation of early onset eczema. We have evidences showed by RCTs regarding to the effectiveness of early introduction of peanut and egg on prevention of each food allergy, however, RCTs to prevent the onset of atopic dermatitis by application of emollient from neonatal period have not yet shown the effectiveness for prevention of skin sensitization nor prevention of food allergy. Only a small pilot RCT by using ceramide containing emollient showed very low prevalence of food sensitization at the first year of age in the intervention group by per protocol analysis. Retrospective cohort of patients with infant onset atopic dermatitis in our center showed that the earlier the aggressive treatment for their eczema started, the less incidence of subsequent food allergy they had. A multicenter RCT named PACI (Prevention of Allergy via Cutaneous Intervention) study to verify the effectiveness of early aggressive intervention of eczema on prevention of food allergy has reached 90% recruitment.

SY-2 (P-1) - 3  Allergy prevention by microbial manipulation: are we ready?
Ting Fan Leung (Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong)

Allergic diseases such as asthma and eczema are prevalent amongst children in Hong Kong. In contrast to these children, similar populations from more rural environment experience a substantially lower incidence of these conditions. Our epidemiological study confirmed much lower allergy prevalence in Chinese children living in rural Conghua when compared to those from Hong Kong. Part of the explanation for this differential finding is the microbial exposure of these children at young age. Such epidemiological findings are consistent with the relationship identified between the gut microbiome in early life and the subsequent development of inflammatory diseases as well as eczema and airway allergies. The benefits of such natural microbial exposures are supported by nutritional strategies that programme the gut microbiota composition using probiotics, prebiotics and synbiotics. However, this preventive approach based on a narrow spectrum of microbes did not yield consistent clinical benefits. Whereas earlier studies linked stool microbiota to significant alterations in the allergy risk in early childhood, contemporary studies making use of enhanced next-generation sequencing technology have also found highly specific influences of microbes on skin, airway and other body sites on the development of allergic diseases. For instance, an Irish birth cohort suggested early-life skin microbiota to be predictive of eczema development in Caucasian infants. My group has completed several studies on the relationship between microbial compositions at different body sites and childhood allergies such as eczema and wheezing illnesses. This presentation will discuss the key findings of these studies and describe future directions in research on these microbe-based interventions.
Symposium 3
Eosinophilic Gastrointestinal Disease (EGID)

SY-3 (M-1) -1
Pathogenesis of Eosinophilic Esophagitis (EoE) - how does the esophagus respond to allergens?

Glenn Faruta (Department of Pediatrics, University of Colorado School of Medicine / Children’s Hospital Colorado, USA)

Clinical experience and basic studies support the fact that EoE is a disease characterized by several different phenotypes. The most well-known is the allergic phenotype defined clinically by the presence of a number of co-morbid atopic diseases and response to dietary elimination of food allergens and molecularly by the presence of dysregulated Th2 associated genes. Alterations in the epithelial barrier function likely contribute to the pathogenesis of EoE by either predisposing to the exposure to food allergens that initiate the mucosal eosinophilia and esophageal dysfunction or by perpetuating the local inflammatory response. Importantly, genome-wide association studies found alterations in epithelial barrier genes such as flaggin and calpain -14 and transcriptomic profiles identified changes in SPINK7 and SLC9A3 associated molecules. Pathological samples clearly demonstrate infiltration in the interstitial space of the interstitial cells as well as reduced desmosomal proteins and impedance monitoring documents changes in barrier function in vivo. Linking all of these components in the elevation of the cytokines, IL-13, a key Th2 molecule that has been shown to not only participate barrier dysfunction in EoE but that also has developed into a key therapeutic target. Critical to the process of inflammatory processes associated with barrier dysfunction and tissue remodeling is the increased metabolic demand in the local site. In this regard, microenvironmental oxygen metabolism and hypoxia may play a role in the pathogenesis of esophageal epithelial barrier dysfunction in EoE.

SY-3 (M-1) -2
Eosinophilic esophagitis what the allergist needs to know

Luc Biedermann (Division of Gastroenterology & Hepatology, University Hospital Zurich, Switzerland)

Almost simultaneously in 1993 and 1994 Steven Attwood and Alex Straumann provided their first description of eosinophilic esophagitis (EoE) both including a handful of patients suffering from an “idiopathic, distinct clinicopathologic syndrome” characterized by esophageal eosinophilia and dysphagia. Further, these first descriptions stated, that the condition appeared to be easily overlooked during upper endoscopy despite the rather typical clinical presentation due the frequently discrete endoscopic findings. EoE is a still is a young disease not having surpassed 30 years since its first description. While numerous scientific and clinical milestones have been achieved in the last years, several open questions and challenges regarding ethiopathogenesis, proper identification and care of these patients as well as treatment options and their positioning remain. Several epidemiological studies have indicated, that the disease is undoubtedly on the rise and this cannot be only attributed to an increase in awareness. Thus, EoE will be increasingly of importance in everyday’s clinical practice, not only for gastroenterologists but specifically also allergists and general practitioners. In several patients, there is a long diagnostic delay, which may be due to frequently subtle clinical symptoms and a lingering increase of solid food dysphagia, which represents the hallmark complaint, on the one hand and a still insufficient awareness of this disease in physicians on the other hand. There is increasing evidence, that prompter appropriate diagnosis and treatment of the condition is not only associated with symptom control and increased quality of life but also a reduced risk of esophageal fibrosis and stricture formation as well as food impaction, the latter representing a medical emergency.

SY-3 (M-1) -3
Eosinophilic gastroenteritis in Japan

Yoshikazu Kinoshita (Steel Memorial Hirohata Hospital, Japan)

Eosinophilic gastroenteritis is a gastrointestinal inflammatory disease with the pathological eosinophil infiltration in stomach and/or intestine. Because of the similarity of clinical characteristics and the frequent overlap with eosinophilic esophagitis, the pathogenesis of eosinophilic gastroenteritis is considered to be similar to that of eosinophilic esophagitis and is believed to be related to the activated delayed Th 2 type immune reaction. Different from eosinophilic esophagitis, however, the prevalence of eosinophilic gastroenteritis does not show the clear peak in the middle-aged persons nor male gender preponderance. In Japan, many patients with eosinophilic gastroenteritis have been reported as case reports or case series. We have collected these reported cases and other newly diagnosed ones by sending questionnaires to the teaching hospitals approved by Japanese Society of Gastroenterology and investigated the clinical characteristics of Japanese patients with eosinophilic gastroenteritis. The mean ages of the cases are 40-50 years old without clear age-related susceptible window. Male to female ratio of the patients is 1 without any gender preponderance. Approximately half of the cases with eosinophilic gastroenteritis have atopic diseases such as bronchial asthma or allergic rhinitis. The most frequently complained symptoms are abdominal pain and diarrhea and cases with gastriic involvement may complain epigastric discomfort. The small intestine is the most frequently involved gastrointestinal tract and cases with small intestinal diseases frequently show the higher peripheral eosinophilia. Although approximately 80% of cases with eosinophilic gastroenteritis show peripheral eosinophilia, other blood tests have limited value for the diagnosis and management of cases with eosinophilic gastroenteritis. Abdominal computed tomography often shows segmental intestinal wall thickening accompanied by localized ascites. Endoscopy has limited value because of the non-specific endoscopic appearance of the involved segments, while endoscopic biopsy is useful for the diagnosis of mucosal type diseases. Majority of the cases are treated with the administration of prednisolone followed by the administration of anti-allergic drugs. The value of topical glucocorticoid administration, elimination diets and molecular target therapies with neutralizing antibodies is under investigation.
Symposium 4

Chronic Rhinosinusitis and Upper Airway

SY-4 (E-1) -1

Chronic Rhinosinusitis (CRS) and the upper airway

Robert Schleimer (Allergy and Immunology, Northwestern University Feinberg School of Medicine, USA)

Chronic rhinosinusitis with nasal polyps (CRSwNP) or without nasal polyps (CRSsNP) is a highly prevalent disease of the upper airways and sinuses that leads to impaired nasal breathing, loss of the sense of smell, congestion, secretions, sleep loss, headache and many other often debilitating signs and symptoms. The Northwestern sinus center has been studying pathogenesis, characterization, heterogeneity, treatments, comorbid illnesses and molecular and cellular mechanisms of disease for many years; this presentation will summarize some of the salient findings.

CRSwNP is generally more severe and less prevalent than CRSsNP and is highly comorbid with asthma, hayfever and bronchiectasis. CRSwNP with asthma and sensitivity to aspirin like drugs (AERD) is a particularly severe form of disease. When intranasal steroids fail to manage severe CRS, surgery has traditionally been the only remaining effective treatment. Recently, type 2 targeting biologics and anti-inflammatory drugs have been used with success. Many studies show that epithelial barrier function is impaired in CRS and have implicated oncostatin M, IL-13, epiregulin, diminished insulin signaling and other mechanisms. Basal epithelial cells appear to be “locked” in an undifferentiated state, tight junctions are not well formed and elements of epithelial mesenchymal transition (EMT) are present. Type 2 inflammation is prominent in the West, and increasingly prominent in Eastern countries such as Japan and China. The major T2 cytokine-producing cells include Th2, ILC2 and mast cells in nasal polyp tissue. These cytokines lead to recruitment and activation of eosinophils, basophils, neutrophils, mast cells and other cells. In AERD patients, single cell RNAseq studies by Stevens et al. have revealed robust activation of the 15-Lipoxygenase pathway via a collaboration of epithelial cells and mast cells. The expansion of nasal tissue to form nasal polyps is characterized by widespread deposition of cross linked fibrin, indicating activation of extravascular coagulation. Studies relating molecular endotype of disease (T1, T2 or T3) to clinical phenotype (asthma comorbidity, smell loss, presence of pur, headache, ocular symptoms etc) reveal that different molecular endotypes are associated with distinct phenotypic features.

SY-4 (E-1) -2

What should a surgeon know about the phenotypes of chronic rhinosinusitis with nasal polyps

Luo Zhang (Department of Otolaryngology Head and Neck Surgery, Capital Medical University, China)

More and more studies about phenotypes and endotypes of chronic rhinosinusitis (CRS) have suggested that the two subtypes, CRS with or without nasal polyps (CRSwNP or CRSsNP) could not meet the medical needs. A huge challenge has already appeared due to the eosinophilic CRSwNP was extremely easy to relapse. In the recent years, the prognosis studies about CRSwNP are rising rapidly with the development of endoscopic sinus surgery. Because with the prognosis of different inflammatory patterns of CRSwNP patients before surgery, we could know the recurrence risk of the patients and give them accurate treatment strategies and provide dedicated postoperative medical treatments if necessary.

Till now, several prognosis methods of CRSwNP have been provided. While some of them are dependent on pathological examination or biopsy, convenience and non-invasive prognosis methods for CRS are needed in clinical practice. Tissue eosinophils are characteristic of inflammation in most but not all patients with CRSwNP and may be useful for defining subgroups and making treatment choices. However, no consistent diagnostic criteria for CRSwNP with eosinophilic inflammation have been established. Sinonasal tissue eosinophils is present in a majority of CRSwNP patients but is currently more common in the West than in the East. Cutoff values of eosinophils as the diagnostic criteria of eosinophilic CRSwNP are subject to change with geographic and ethnic differences over time. It will be important to identify validated eosinophil-related biomarkers in different continents/countries for future research and for the introduction of precision medicine.

SY-4 (E-1) -3

Eosinophilic chronic rhinosinusitis

Shigeharu Fujieda (Division of Otorhinolaryngology - Head & Neck Surgery, Department of Sensory and Locomotor Medicine, Faculty of Medical Science, University of Fukui, Japan)

Eosinophilic chronic rhinosinusitis (ECRS) is a subgroup of chronic rhinosinusitis with nasal polyps (CRSwNP), which is associated with severe eosinophilic infiltration and intractable. Its symptoms include dysosmia, nasal obstruction, and viscus nasal discharge. The pathogenesis of ECRS has not been clear, some microorganism might be involved in stimulating the type 2 inflammation to promote IgE production and eosinophil infiltration through various pathways. We performed RNAseq and proteomics of nasal polyp of ECRS to find the specific cellular and molecular factor contributing to the pathogenesis of nasal polyp. Several factors were found and investigated for the function of them. While, the coagulation system is activated and the fibrinolytic system is suppressed, leading to deposition of fibrinous networks in nasal polyps. A fibrin-degrading agent could be a one of candidate for the new treatment for ECRS. Treatment options of nasal polyps of ECRS are to target the type 2 inflammation, which is characterized by a prominent role of cytokines, such as IL-4, IL-5, IL-13 and IgE. Clinical studies of these biologics, anti-IL-5 antibody (Ab), anti-IL-5 receptor (IL-5R) Ab, anti-IgE Ab and anti-IL-4R chain Ab, have been performed for severe CRSwNP. Anti-IgE Ab (omalizumab) improved nasal obstruction, hyposmia and nasal secretion scores in ECRS patients with aspirin induced asthma. Placebo-controlled double-blind study of anti-IL-5 Ab (mepolizumab) demonstrated to decrease nasal polyps and to improve CT findings in patients with large nasal polyps. Anti-IL-4R chain Ab (dupilumab) improved nasal polyp score, CT score by Lund-Mackay score. QOL scores and the olfactory test score. Promising results of an international phase III trial of dupilumab for CRSwNP with high polyp scores was published. Anti-IL-5R Ab (benralizumab) had been effective for limited patients with ECRS. Precision medicine using biologics will be performed to ECRS patients in the future.
SYMPOSIUM 5
Contact Dermatitis

SY-5 (D-1) -1
The mechanical understanding of allergic contact dermatitis develops the in vitro method to detect sensitising chemicals

Setsuya Aiba (Department of Dermatology, Tohoku University Graduate School of Medicine, Japan)

Spongiosis is a well-known histological hallmark associated with allergic contact dermatitis (ACD). In most cases, however, it is not considered what spongiosis means biologically and physiologically and how it develops. We have reported the following [1]. Cytokine-stimulated keratinocytes produce hyaluronan synthase 3 and down-regulate E-cadherin expression. Accumulated hyaluronan in the intercellular space of the epidermis incorporates free water into its molecular structure, becomes swollen, and widens intercellular space in which cell-to-cell connection becomes loose by decreased E-cadherin expression. These data suggest that ACD is a physiological process to dilute noxious chemicals in the epidermis. The next question is how happen stimulate immune system. We and others have focused on the mechanism by which chemicals stimulate dendritic cells and found that the reaction of happen with high residues in dendritic cells is the initiating event in ACD [2-3,5,6]. This reaction can induce dendritic cell maturation with increased expression of costimulatory molecules and augmented production of several cytokines and chemokines and produce T cell epitopes. Recently, animal experiments have been prohibited for developing cosmetics throughout the world. Therefore, many cosmetic companies are rushing to develop non-animal test methods to predict sensitizing potential of chemicals. In this trend, the molecular understanding of ACD has greatly contributed to the development of in vitro test methods to detect sensitizers. Now, the two in vitro test methods, h-CLAT and IL-8 luc assay, which had been developed based on the basic research from our laboratory [4,6,7], are now approved as OECD test guideline 442E, as test methods that can be used at a regulatory level. References: [1] Ohtani T, et al. J Invest Dermatol, 2009, [2] Aiba S, Kata S, J Immunol, 1991, [3] Aiba S, et al. Eur J Immunol 1997, [4] Ashikaga T, et al. Toxicol in Vitro, 2002, [5] Mizushi M, et al. J Invest Dermatol, 2005, [6] Kagitani S, et al. J Invest Dermatol, 2010, [7] Takahashi T, et al. Toxicol Sci, 2011, [8] Kimura Y, et al. Toxicol in Vitro, 2015

SY-5 (D-1) -2
Clinical variation of hair dye allergy

Jun Young Lee (Department of Dermatology, The Catholic University of Korea, Seoul St Mary’s Hospital, Republic of Korea)

Allergic contact dermatitis (ACD) due to hair dye is a worldwide problem of those who dye their hair and P-Phenylenelediamine (PPD) is known to be the most frequent contact sensitizer of hair dye. Clinical characteristics of hair dye contact allergy (HDCA) are variable including typical allergic contact dermatitis, lichen simplex chronicus, non-specific eczema and dermographism. The purpose of this study is to find out clinical variation of HDCA and its relation with the PPD positivity and with the usage pattern of hair dye. We analyzed 105 patients with hair dye allergy confirmed by patch test from July 2009 to March 2015. The clinical symptoms, signs, associated skin diseases, involved ACD area and hair dye used patterns were obtained by reviewing medical records and interview. Direct contact area was the most frequent involved area. Usage pattern of hair dye, represented with frequency and duration showed positive correlation with extent area of hair dye allergy (p<0.001) however, had no correlation with comorbidity (p=0.30) or the grade of PPD positivity (p=0.39). There is a relationship between extent of hair dye allergy and usage pattern of using hair dye. Many patients had a tendency to dye their hair even after recognizing the HDCA. Therefore, education is essential

SY-5 (D-1) -3
Status of contact dermatitis and patch testing initiatives in Japan

Akiko Yagami (Department of Allergology, Fujita Health University School of Medicine, Japan)

Patch testing is a well-established method of diagnosing contact allergy · a delayed type of hypersensitivity (type IV reaction). Patient with history and clinical picture of contact dermatitis are re-exposed to the suspected allergens under controlled conditions to verify the diagnosis. Applying the “Standard Allergen Series” along with the product brought by the patient when performing the patch test is useful for determining the cause of allergic contact dermatitis (ACD). In 1994, the Japanese Society for Contact Dermatitis (currently Japan Society for Skin Immune Allergies) established the Japanese standard series (JSA), which contains various reagents that cause contact dermatitis. After that, the contents of the constituent reagents of the JSA series were revised to “JSA2008” and “Japanese baseline series (JBS2015”.

The Japanese Contact Dermatitis Research Group (JCDRG) collects JBS2015 results from dermatologists and annually reports the positive rate of each allergen. At present, it has been revealed that the positive rates of nickel sulfate, sodium gold thiosulfate, urushiol, paraphenylenediamine (PPD), and cobalt chloride are high in Japan. The positive rate of isothiazolinone has increased in the last few years, and this preservative has attracted attention in cosmetics and daily necessities. Recently in Japan, cosmetics such as soaps containing hydrolyzed wheat protein and whitening agents containing rhododendrol had caused unexpected allergies and skin damage, and these skin disorders had developed into social issues. In 2016, the Skin Safety Case Information Network (SSCI-Net, http://infolscinet.or.jp/index.html) was established in Japan. SSCI-Net is aiming to minimize the cases of skin disorders caused by cosmetics and daily necessities by quickly sharing the cases of skin disorders collected from dermatologists among industry, government, and academia. From April 2018 to March 2019, 456 cases of ACD and 107 cases of non-allergic contact dermatitis were registered with the SSCI-Net.

In this presentation, I show interesting cases whose causes were determined by patch test and describe the current state of contact dermatitis in Japan and the activities of SSCI-Net.
Symposium 6
Roles of ILCs

SY-6 (B-1) -1  The role of group 2 innate lymphoid cells in lung fibrosis

Kazuya Moro (Laboratory for Innate Immune Systems, Graduate School of Medicine, Osaka University School of Medicine; Laboratory for Innate Immune Systems, RIKEN-IMS, Japan)

Idiopathic interstitial pneumonias (IIPs) are a set of diseases characterized by inflammation and fibrosis in lungs. Patients with IIPs mainly suffer from difficulty of breathing, continuous cough, and fatigue. Some types of IIPs show very poor prognosis, and there are no effective drugs against these cases. Many researchers have investigated the pathogenesis of IIPs in order to develop new medication, however a comprehensive mechanism for these diseases has not been clarified yet. One of the main hindrances to increasing current understanding of IIPs is the lack of good mouse models. To date, the bleomycin-induced pulmonary fibrosis model is the most commonly-used model, but there are several fundamental problems. First, in initiation phase of fibrosis cannot be analyzed, because the disease does not spontaneously but is artificially induced by the administration of bleomycin. Secondly, the pathological characteristics of this model are largely different from that of human IIPs. Finally, the progressive phase of fibrosis also cannot be analyzed, since the disease resolves itself naturally several weeks after the administration of bleomycin. Therefore, a better model for IIPs is obviously needed for a better understanding of the pathogenesis of these diseases. Here, by knocking out several genes which are involved in the inhibition of inflammation, we have established a new and better mouse model for IIPs compared to conventional models. In lungs of this mouse model, inflammation and subsequent fibrosis spontaneously occurs without any drug administration. The histological characteristics of this model are similar to that of several types of IIPs. Moreover, the disease progresses with age and is never resolved naturally. Using this new model, we have conducted single cell RNAseq analysis to reveal the whole landscape of pulmonary fibrosis, from initiation to the progressive phase. We clarified which cells are involved in each phase, and identified the fibroblast subtype which seems to be responsive to the deposition of collagen in lungs of these mice. We are expecting that our new findings can offer new insights into research of IIPs.

SY-6 (B-1) -2  Role of group 2 innate lymphoid cells in the development of allergic diseases

Hideaki Morita, Kenji Matsumoto (Department of Allergy and Clinical Immunology, National Research Institute for Child Health and Development, Japan)

Allergic diseases are initially characterized by the presence of high antigen-specific IgE production and antigen-specific Th2 cells. However, many children develop such allergic symptoms as eczema and wheeze before antigen-specific IgE antibodies can be detected in their sera. In addition, recent findings, including the results of genome-wide association studies, demonstrated that allergy-susceptible genes are not associated with IgE production or Th2 cell development. Instead, they are directly associated with barrier function and epithelial cell activation/damage. Thus, genes that encode for filaggrin, IL-33 and TSLP. These evidences suggest that epithelial barrier dysfunction and epithelial cell activation/damage, both of which reportedly activate innate immunity, play crucial roles in the development of allergic diseases. Newly identified innate-type immune cells, group 2 innate lymphoid cells (ILC2s) resembling Th2 cells, express GATA3 and produce type 2 cytokines such as IL-5 and IL-13, and have been implicated in immunity against helminths and allergic diseases. Importantly, activation of ILC2 induces allergic inflammation at the local site of the tissues independent of acquired immunity such as T cells, B cells and IgE antibody. Therefore, ILC2s have critical roles in the development of allergic diseases. Recently we found that innate immunity is dominant compared to acquired immunity during childhood when most of the allergic diseases develop; thus, we focused on the triggers of barrier dysfunction and/or epithelial cell activation/damage during childhood. We will present our recent findings regarding triggers that can activate innate immune responses leading to antigen-specific type 2 responses and allergic inflammation.

SY-6 (B-1) -3  Pathophysiology of severe asthma

Koichi Fukunaga (Pulmonary Division, Department of Medicine, Keio University School of Medicine, Japan)

Possible causes of refractory asthma include the presence of environmental factors and comorbidities or poor adherence to anti-asthmatic medications. However even if these backgrounds are excluded, patients with uncontrolled asthma still exist. Especially patients with steroid-resistant asthma who have the inability to a therapeutic response to steroids is a clinical problem. Genetic factors, abnormalities in glucocorticoid receptor function, decreased H1R/EC2 activity, transcription factor activation, and abnormalities in immune system cells, including lymphocytes, have been considered as possible mechanisms of steroid resistance. Our joint research with Dr. Moro has shown that Group 2 innate lymphoid cells (ILC2), which have received much attention in recent years, may be involved in the pathogenesis of steroid resistance using a mouse model of asthma (Nat Commun. 2013). Liu et al. also showed that ILC2 collected from bronchoalveolar lavage fluid (BAL) of asthmatic patients had steroid resistance (J Allergy Clin Immunol, 2008). Thus, ILC2 may contribute to the pathogenesis of steroid resistance in patients with severe asthma. In the clinical setting, new biologics have been developed and launched, and it is important to consider the incorporation of these novel therapeutic agents and the use of biomarkers in the future treatment of steroid-resistant asthma. In this symposium, I would like to review the pathogenesis of severe asthma, especially steroid resistance asthma and possible therapeutic strategies for the future.
Symposium 7

Adult Food Allergy

Barbara Ballmer-Weber (Clinic of Dermatology and Allergology, Kantonsspital St Gallen, Switzerland)

According to recent studies, the frequency of self-reported food allergy in adults is up to 35%. Furthermore, up to 24% of adult European adults not selected for allergy of any kind are sensitised to foods as recently determined by an in vitro analysis of sera from more than 4000 study participants. Facing the amount of self-perceived food allergies and the high sensitisation rates to foods in adults, one challenge with top priority is to identify the true food allergic patients, which is often only possible by doing food provocation. The diversified dietary habits in adults lead to a high diversity of potentially allergenic foods in this age group and is associated with a higher risk of accidental reactions. Risk factors with impact on the severity of the allergic reaction such as drug intake, exercise or stress particularly need to be considered in the adult food allergic patient.

Occupational food allergy

Yuma Fukutomi (National Hospital Organization Sagamihara National Hospital, Japan)

Allergic diseases in adults are markedly heterogeneous compared to those in children; it is supposedly affected by changes in the lifestyle of an individual over the years. In particular, occupation is an important contributing factor to the presentation of allergic disease in adults. However, the contribution of occupation to food allergy is relatively under-recognized. Generally speaking, food allergy in adults is frequently associated with extra-gut sensitization to foods, or proteins cross-reactive to foods (e.g., pollens). A variety of occupations are associated with repeated transdermal and respiratory exposure to specific allergens. If an occupation-specific allergen is a food allergen or an allergen cross-reactive with food proteins, sensitized individuals can also develop food allergy after ingestion of the relevant food in a non-occupational setting. Since cooks and other food-processing workers frequently handle a large quantity of the same type of food, they are a population at high risk of being sensitized to that food, and developing an occupational food allergy. Latex-fruit syndrome is a well-known example of an occupational food allergy that can develop in healthcare workers. Food-derived protein hydrolysates are frequently used as ingredients in skin and hair care products. Transdermal exposure to these proteins can lead to sensitization to food allergens and development of food allergy in hairdressers and estheticians. The presence of hand eczema is known to be associated with an increased risk of occupational food allergy. In general, identification of the primary route of exposure to a food-related allergen is important for the management of food allergy, because avoidance of the primary route of allergen exposure can contribute to the lowering of serum-specific IgE levels, and attenuation of the clinical symptoms of food allergy. Regarding occupational food allergy in cooks, we frequently encounter patients whose levels of serum-specific IgE antibody to the relevant food allergen decrease after they change their occupation or workplace. Protective equipment, such as gloves, masks, and clothing, and improved workplace ventilation might also contribute to the tertiary prevention of food allergy among food handlers.

Progress in alpha gal allergy

Michael Levin (University of Cape Town, South Africa)

Galactose-alpha-1,3-galactose (alpha-gal) is a carbohydrate epitope found on proteins and lipids in non-primate mammals and present in foods (particularly organ or fat-rich red meat) and medications (e.g., cetuximab, certain vaccines and antivenoms), where it causes delayed onset and immediate onset anaphylaxis respectively. Symptoms are skewed towards urticaria and a high prevalence of isolated abdominal reactions. Diagnosis of alpha gal allergy is primarily through history, showing sensitisation with IgE tests (RAST may be used), and response to dietary avoidance. Wide variety exists in alpha-gal IgE levels, even in subjects with confirmed meat allergy. The value above which there is a 95% probability of having meat allergy is alpha gal IgE of >5kU/L and alpha gal total IgE ratio of 2.12. Age and gender differences seen in various cohorts possibly reflect the prevalence of these exposures that vary according to setting. The reason and mechanisms for delayed onset of food related anaphylaxis and the preponderance of abdominal reactions are not clear but may involve the kinetics of allergen digestion and processing or immunological presentation via a different mechanism from usual immediate type food allergy. Recent studies have shown alpha-gal epitopes in the salivary glands of partially fed and fed A. americanum and I. scapularis, I Ricius, and H longicornis and the mid-guts of ticks belonging to the Ixodes family. However other organisms have not been rigorously examined for the presence of alpha-gal or their ability to induce IgE responses against alpha-gal. In addition to alpha-gal epitopes several species of ticks may contain salivary adjuvants that promote high titre sensitisation and clinical reactivity.
Symposium 8
Mast Cells, Basophils and Eosinophils

SY-8 (B-2) -1 Human mast cell interaction with inflammatory cells in allergic diseases
Yoshimichi Okoyama1,2, Shota Toyoshiba1,3, Chiezi Ra3 (Center for Allergy, Nihon University School of Medicine); Center for Education, Nihon University School of Medicine; Department of Microbiology, Nihon University School of Medicine, Japan

Human mast cells (MCs) are key regulators of IgE-mediated allergic inflammation. Upon stimulation, MCs can rapidly release preformed cytoplasmic granules containing histamine, proteoglycans and proteases. Mast cells can produce leukotrienes, prostaglandins, and cytokines. However, the precise mechanism underlying human MC interaction with inflammatory cells in allergic diseases has remained elusive. Here we report that exosomes derived from human MCs following aggregation of FeεRI enhance IL-5 production from IL-33-stimulated type 2 innate lymphoid cells (ILC2) via silencing protein arginine methyltransferase (PRMT) and that MCs may exaggerate eosinophilic allergic inflammation through ILC2 activation using MC exosomal miRNA. Human cultured MCs were generated by culturing normal and eosinophilic mast cells with stem cell factor for 12 weeks. IgE-sensitized MCs were stimulated with anti-IgE or IL-33 for 4 hours. The supernatants were purified using ExoQuick-TC. Exosomal miRNA expression profiles were investigated using miRNA microarrays. Concentrations of IL-5 and IL-13 in the ILC2 supernatants were measured with ELISAs. Expression of methylated GATA3 was examined using immunoprecipitation and immunoblotting. Expression of PRMT was examined using quantitative PCR and immunoblotting. Exposure of ILC2 to exosomes derived from human MCs following aggregation of FeεRI enhanced IL-5 production from IL-33-stimulated ILC2, but it did not enhance IL-13 production. Exposure of ILC2 to exosomes from IL-33-activated MCs enhanced neither IL-5 nor IL-13 production from IL-33-stimulated ILC2. Anti-IgE-stimulation specifically upregulated seven miRNAs in human MC exosomes compared with IL-33-stimulation. Among them, upregulation of expression for miR223-3p and miR103a-3p was confirmed by quantitative PCR. Exposure of ILC2 to exosomes derived from human MCs following aggregation of FeεRI resulted in upregulation of miR103a-3p expression in IL-33-stimulated ILC2. Exposure of ILC2 to miR103a-3p mimic resulted in enhancement of IL-5 production from IL-33-stimulated ILC2. We confirmed the methylated GATA3 and PRMT expression in ILC2. Addition of exosomes derived from human MCs following aggregation of FeεRI or miR103a-3p mimic in IL-33-stimulated ILC2 downregulated the expression of PRMT mRNA expression in the ILC2. Therefore, miR103a-3p may be a new therapeutic target for treatment of eosinophilic allergic inflammation.

SY-8 (B-2) -2 Basophil activation in oral immunotherapy for peanut allergy
Mindy Tsai1,2, Karii Mukai1, R. Sharom Chinthrajah3,4, Kari C Nadeau1,2, Stephen J Galli3,4 (Department of Pathology, Stanford University School of Medicine); Sean N. Parker Center for Allergy & Asthma Research, Stanford University School of Medicine; Department of Medicine, Stanford University School of Medicine, USA

Basophils are potent effector cells mediating clinical signs and symptoms of food allergy and also some side effects of immunotherapy. Peanut allergy is one of the most common food allergies, with a high risk of anaphylaxis upon accidental exposure. Peanut oral immunotherapy (OIT) can suppress basophil activation and desensitize peanut allergy. However, in many peanut allergic subjects, clinical reactivity returns after cessation of OIT or with low dose peanut maintenance. We evaluated whether basophil activation assessed in whole blood of allergic subjects can predict OIT efficacy and/or monitor treatment progress for peanut allergy. We enrolled 120 adults and children who reacted to < or = 500 mg of peanut protein by oral food challenge in a double-blind, randomized, placebo-controlled, phase 2 peanut OIT study (ClinicalTrials.gov NCT02103270) at the David Geffen School of Medicine at UCLA. Basophils were isolated from peripheral blood mononuclear cells (PBMCs) and stimulated with peanut protein extract for 6 hours. Basophil activation was assessed by measuring intracellular calcium and cytokine production. Basophil activation was defined as the percentage of basophils that produced at least 1000 median fluorescence intensity (MFI) units of IL-4 and/or IL-5. Basophil activation was significantly lower in subjects who achieved sustained unresponsiveness vs. those exhibiting short-term desensitization. Based on basophil responsiveness to ex vivo peanut stimulation at baseline, participants could be classified as low (L) or high (H) responders. We found LRs responded to OIT with better outcomes and, in LRs and HRs, substantial suppression (80-90%) of basophil activation was associated with sustained unresponsiveness after peanut OIT. Assessments of peanut-induced basophil activation may help to predict efficacy and improve treatment protocols for peanut OIT.

SY-8 (B-2) -3 Eosinophil siglecs: biology and therapeutic advances
Bruce S. Bochner (Department of Medicine, Division of Allergy and Immunology, Northwestern University Feinberg School of Medicine, USA)

Sialic acid binding, immunoglobulin-like lectins (Siglecs) are single-pass transmembrane cell surface receptors found primarily on various leukocyte subsets. Most Siglecs, but not all, have conserved cytoplasmic signaling motifs that suggest they primarily function as inhibitory receptors. Among these, Siglec-8, first discovered in 2000, is expressed on eosinophils, mast cells and weakly on basophils. Other Siglecs found on some or all of these same allergic effector cells as well as other cells include CD95, Siglec-6 and Siglec-7. Based on the work of several labs, it is now known that Siglec-8 engagement, either by specific antibodies or via multivalent, specific a 2,3-linked sialylated, sulphated artificial or endogenous glycans, can result in a number of responses in vitro including reduced eosinophil survival and altered integrin function, as well as reduced mast cell secretion responses. Its unique glycan ligand specificity has facilitated the discovery of endogenous tissue ligands for Siglec-8, including several identified so far from human upper and lower airways samples, and has allowed for the development of glycomimetic targeting molecules that permit nanoparticle attachment to Siglec-8 in a selective manner. Following Siglec-8 engagement, it gets internalized, which allows it to also function as an endocytic receptor for the delivery of therapeutic payloads. While Siglec-F is its closest paralog in the mouse, it is not an true ortholog and thus has its own unique pattern of expression, set of sialooid ligands and functions that often differ from Siglec-8. Because Siglec-8 is only expressed on human and primate cells, novel knock-in strains of mice have been developed in which Siglec-8 is expressed on eosinophils, mast cells, or both cell types, enabling further studies of its role in vivo and consequences of its targeting. Finally, a biotechnology company called Allakos, Inc. has created a humanized non-fucosylated IgG1 monoclonal antibody named antolimab (formerly called AK002) that is being tested in clinical trials for the treatment of various diseases involving eosinophils and/or mast cells including eosinophil gastrointestinal diseases, chronic urticaria, severe allergic conjunctivitis, and idiopathic systemic mastocytosis.
Symposium 9
Airway Mycosis in Allergic Airway Disease

SY-9 (I-3) -1
Allergic bronchopulmonary aspergillosis
Ritesh Agarwal (Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, India)

Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disorder caused by immunological reactions mounted against Aspergil- lus fumigatus colonizing the airways of patients with asthma or cystic fibrosis. When allergic respiratory mycosis is caused by fungi other than A. fumigatus, it is characterized as bronchopulmonary aspergillosis. The first case of ABPA was described by Rimoin et al. in 1952. Despite seven decades of research, the disorder remains underrecognized. As many as one-third of the cases are misdiagnosed as pulmonary tuberculosis, espe- cially in developing countries. The disease needs to be identified early and treated appropriately to prevent the development or progression of bronchiectasis. Host susceptibility determines which asthmatic will develop ABPA while host immunologic responses influence the clinical and radiological features and the natural history of this disorder. ABPA is often misdiagnosed for a variety of pulmonary diseases. The ABPA work- ing group formed under the auspices of the International Society for Human and Animal Mycology (ISHAM) has proposed recommendations for simplifying the identification of this enigmatic disorder. Currently, the best investigation in the diagnosis of ABPA is A. fumigatus-specific IgE, and the most specific finding is the presence of hyperattenuating mucoid impaction on CT chest. Certain modifications in the current ISHAM ABPA working group criteria (using A.fumigatus IgE and IgG instead of skin test and precipitins, respectively; and imaging finding of bronchiectasis) will further improve the detection of ABPA. The addition of recombinant A.fumigatus antigens may also simplify the diagnostic algorithm of ABPA. Glucocorticoids are the treatment of choice; antifungal triazoles are alternative therapy. Recurrent exacerbations characterize the natu- ral course of ABPA. Patients with recurrent exacerbations or glucocorticoid-dependent ABPA may be managed with antifungal triazoles, low- dose glucocorticoids, monthly pulses of methylprednisolone, nebulized amphotericin B, oralizumab or anti-Th2 therapies (mepolizumab, dupi- lumab, and others). Finally, early diagnosis and appropriate treatment are associated with good outcomes. To ensure optimal outcomes, all pa- tients of asthma in the specialized clinics, irrespective of the level of control, should be evaluated for allergic respiratory mycoses.

SY-9 (I-3) -2
The presence of basidiomycotenic fungi in the airway- how to take this troublesome pathogen
Katsuhiko Kamei (Chiba University, Japan)

Human bronchi are always exposed to fungi and their cellular components/metabolites. Actually, bronchi are a good reservoir for fungi, which are rich in nutrients, moisture, and oxygen. Because of their ability to produce numerous enzymes, toxins, and other bioactive materials, the con- tinuous presence of fungi in the airways may damage the bronchial epithelium, sensitize human cells, and cause allergic bronchopulmonary myco- sis. Among these fungal species, aspergillus is most well-known, but many other fungi retain the similar ability. In fact, the culture of bronchial specimens sometimes yields a huge variety of filamentous fungi. They could be closely related to human airway diseases, but their significance is yet to be thoroughly studied. Recent progress of molecular biology enabled genetic identification of previously unidentifiable "mycelia sterilia". Now, the fungal perpetrator's identity in the airways is getting apparent, and the significant presence of basidiomycotic fungal filaments (fungi (mushroom) is coming to light.

When our research team led by Dr. Asano analyzed the fungi isolated from the airway (n=108), we found Aspergillus spp. were the most common (35.1%), and, strikingly, basidiomycotenic fungi (61.8%) took a second place. These were followed by Penicillium spp. (17.6%), and dematiaceous (black) fungi (9.4%). Among Aspergillus spp., A. fumigatus (55.3%) and A. niger (22.5%) were the most common. Then we made an analysis of the fungal isolates taken from the lower airway samples collected from various hospitals all over the country. Eighty seven basidiomycotic fungi were identified, and Schizophyllum commune was isolated more frequently than any other species, taking up 51.3%. This was followed by Phanerochaete chrysosporium, Trametes spp., Penicillium spp., Irpex spp., and Bjerkandera spp., but the last five species holds only 26.4%. Now how to remove the basidiomycotic fungi from the airway has emerged as a new issue, and the methodology to determine the effect of antifungal agents remains a problem.

Here in this symposium, we will present some data on the effect of the antifungal agents on the basidiomycotic fungi aiming for the new strat- egy.

SY-9 (I-3) -3
Allergic bronchopulmonary aspergillosis/mycosis in Japan
Koichiro Asano (Division of Pulmonary Medicine, Department of Medicine, Tokai University School of Medicine, Japan)

Allergic bronchopulmonary aspergillosis/mycosis (ABPA/ABPM) is an allergic pulmonary disease caused by a hypersensitivity reaction to As- pergillus or other fungi colonizing the airways. Our epidemiological studies demonstrated that de novo sensitization to Aspergillus spp. is in- creasing during the past 10-20 years both in the general population and in the patients with asthma, especially in those under high-dose inhaled corticosteroid treatment. Such phenomenon is rare for other allergens, suggesting that global warming and indoor environmental changes favor the growth of fungi. Fungi are also unique as allergen as they can colonize in the human body, leading to the development of more refractory conditions such as ABPA/ABPM.

The Japan research program of ABPA/ABPM conducted a nationwide survey to determine the clinical characteristics of ABPA in Japan in 2013. Among 1550 cases analyzed, later-onset disease, developing 50 years of age, accounted for 66% of the cases. A fifth of the patients lacked any under- lying diseases such as asthma or cystic fibrosis, and a third of them exhibited serum total IgE levels lower than the threshold (1,000 IU/mL) in the diagnostic criteria proposed by International Society of Human and Animal Mycology (2013). In addition to Aspergillus species, Schizophy- lium commune was identified in the sputum or bronchial wash in substantial proportion of the cases.

Based on the unique clinical characteristics of ABPA/ABPM in Japan, we have developed a new 10-component diagnostic criteria for ABPA/ ABPM in the non-cystic fibrosis patients. The new criteria, being validated in the cases with ABPM that fulfilled the pathological criteria and in those with the physician-diagnosed ABPA/ABPM, show an excellent sensitivity and specificity.
Symposium 10
Pediatric Asthma

SY-10 (P-2) -1 New GINA guidelines

Gary Wong (Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong)

Childhood asthma is one of the common chronic disease affecting a large proportion of children worldwide. Despite the availability of effective treatments for most asthmatic patients, real-life studies have revealed that many asthmatics in different parts of the world are sub-optimally controlled. This may partly be due to a mismatch of treatment and the type of asthma the patients have. Despite the advances in our understanding of the underlying mechanisms of asthma and the improvement of asthma treatments, there are several major areas that still require more research efforts to improve the care and to prevent asthma. There are several major problems with our current approach to treatment. Asthma is a chronic inflammatory disease of the airway. Yet, we recommend as needed PRN bronchodilators as the first line treatment. However, when the severity increases, we recommend that patients should take regular anti-inflammatory treatment and should minimize the use of bronchodilator as much as possible. Many mild asthmatics continue to develop exacerbations and most exacerbations are precipitated by viral infections especially those related to human rhinovirus. Recent clinical trials using the PRN combination of bronchodilators and ICS appears to be a much better option for treating mild asthma. Based on the research studies performed over the past 15 years, GINA has made some major changes and PRN bronchodilator is no longer recommended as the treatment of even the mildest form of asthma. However, recent evidence from the SIENA trial suggested that a significant proportion of mild asthmatics may be related to noncosinophilic disease and these patients may respond better to other treatment. As we accumulate more evidence in children as well as the use of other agents, we will see more updates of GINA recommendations. In order to improve the control of our asthmatics, we may need to rethink how we treat the mild asthma and how to determine the personalized treatments for both mild to severe asthma.

SY-10 (P-2) -2 JPGL 2020

Shigemi Yoshihara (Department of Pediatrics, Dokkyo Medical University, Japan)

At present, the treatment of pediatric bronchial asthma has become more controllable for many asthma patients due to increasing use of inhaled steroid therapy, which has led to a reduction in pediatric asthma death. However, treatment of intractable and severe pediatric asthma, cure and prevention of asthma are not yet enough. Today, I talk about the new content of the Japanese Pediatric Guideline for the Treatment and Management of Asthma 2020 (JPGL 2020). It is important to prevent the development and intractability of childhood bronchial asthma. There is a need to establish the pathophysiology, diagnosis, and treatment of asthma in preschool children. Diagnostic treatment is useful and also effective is the use of ICS/LABA combination therapy in preschool children. However, there is also an urgent need to prevent environmental factors such as mite allergens, viral infections, tobacco smoke, and air pollutants. It also discusses the selection and positioning of biologics such as omalizumab, meftizumab and dupilumab for severe pediatric asthma. Finally, the efficacy of mite sublingual immunotherapy for allergic rhinitis is clear, but its efficacy in pediatric bronchial asthma has not been fully investigated. In the near future, allergen immunotherapy may be positioned as one of the basic treatments for airway allergy in children.

SY-10 (P-2) -3 Do we need new guidelines in pediatric asthma?

Mário Morais-Armeida (Immunology Center, Allergy Center Hospital CUF-Descobertas, Portugal)

Current evidence-based guidelines highlight the importance of treating impairment and risk domains of asthma. For children, providing optimal pharmacotherapy with minimal or no adverse effects is also a main goal to achieve. Several hundred million people have asthma, with all age groups being affected. And we are not achieving asthma control for the majority of our patients and many children are still hospitalized, being childhood asthma a huge global health burden. Global improvement in diagnosis and management has been unsatisfactory. Nowadays there is a special focus on severe asthma treatment, in particular regarding the indication of biological therapies, but about 98% of pediatric patients with asthma can be classified from mild to moderate. Recently, based on real life and randomized controlled trials, a tremendous evolution occurred in the treatment of adolescents and adults with asthma with no tolerance to the single use of short-acting beta2-agonists (SABA). In fact, asthma is an inflammatory chronic disease and must be treated according. But in children, in particular in the preschool age, the situation didn’t change. Mild forms of the disease, that probably represent most of the children with asthma, are still treated mainly with SABA, frequently associated with short courses of oral steroids to control exacerbations. In pediatric asthma guidelines, for Step 1, the current preference goes to rescue SABA validating a symptom-based approach only in children. Evidence-based exist in the alternative indication of regular inhaled steroids (ICS) or montelukast, or even to an intermittent/seasonal approach with controller drugs for step 2 and 3, ultrafine particle ICS, intermittent use of SABA or LABA plus ICS (according with age), tiotropium bromide, and the evaluation of individual variability response to treatment, are several controller options that justify to be more discussed and considered in the guidelines. We must accept the heterogeneous character of the pediatric asthma, where phenotyping is not easy and biomarkers are almost absent. But, beginning in the pre-school children with asthma, we must think always on the best choices.
Symposium 11

Atopic Dermatitis

SY-11 (D-2) -1 Current problems in the management of atopic dermatitis

Norito Katoh (Department of Dermatology, Kyoto Prefectural University of Medicine, Japan)

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by intense pruritus and eczematous lesions. AD most frequently develops in childhood and will persist into adulthood in many cases. AD causes many disease burdens such as poor quality of life. Pruritus and skin pain, repeated flares, mood and sleep disturbances, comorbidities, and economic burdens were frequently experienced in this condition, worsening patients’ quality of life and impairing their productivity and activity. Until the past year, our therapeutic options for the management of AD was primarily topical corticosteroids and calcineurin inhibitors, and systemic immunosuppressants. It is definitely important for physicians to distinguish between non-adenherence and non-response, since non-adherence is one of the most common causes of treatment failure and patients’ adherence to topical treatment is often very poor. According to our study in which 300 adults with moderate-to-severe AD were registered showed that about half of them could achieve remission even after strengthening their AD treatments and/or taking thorough education about AD. These findings suggest that many AD patients, especially those with moderate-to-severe disease, are unlikely to be satisfied with current treatments. The pipeline of more targeted systemic therapies including biologics blocking one specific cytokine is expanding based on recent growing understanding of the mechanism for AD. Their efficacy for signs and symptoms of AD have been shown in many clinical studies and real world practice. It is important to address the long-term risk/benefit ratio of these agents in many patients with AD.

SY-11 (D-2) -2 Biomarkers for severity and endotyping in atopic dermatitis

Edward F Knol (Center Translational Immunology, Department of Immunology and Department of Dermatology/Allergology, University Medical Center Utrecht, The Netherlands)

Atopic dermatitis (AD) is a chronic inflammatory skin disease with both local and systemic underlying immunopathomechanisms. In our studies we have explored the application of serum biomarkers in defining atopic dermatitis endotypes as well as to monitor disease severity. By analysis of 143 different serum biomarkers on a Lumexin platform in 193 moderate-to-severe AD patients we have found distinct AD patient clusters that could represent endotypes with unique biological mechanisms. This finding has been confirmed by a recent selection of 146 severe AD patients. Specific selections of these biomarkers are helpful in defining specific treatment indicative of their use in personalize medicine. Currently, the severity of atopic dermatitis is mostly determined by physician-based scoring systems, which unfortunately are rather subjective. This is especially an issue when monitoring patients during treatment in multicenter studies. In our next approach we have compared serum biomarkers in AD patients during treatment, as well as psoriasis patients and controls, and have examined which biomarkers are related to disease severity. From this analysis we developed a serum biomarker signature consisting of TARC (CCL17), IL-22 and sIL-2R in an algorithm. This algorithm showed a correct prediction of the Eczema Area and Severity Index (EASI) in 90% of the patients (sensitivity 100%, specificity 89%) and is coined predicted-EASI. This pEASI provides a reliable and objective measure for disease severity in AD patients. Application of biomarkers in AD is useful in, next to monitoring of severity, predictive, personalized and preventive medicine.

SY-11 (D-2) -3 What’s new in the treatment and prevention of atopic dermatitis?

Lisa A Beck (Dermatology, Medicine and Pathology, University of Rochester Medical Center, USA)

Atopic dermatitis (AD) is one of the most common inflammatory skin conditions, affecting 15-30% of children and 2-10% of adults. Currently, treatment options for children (≥ 6 yrs of age) and adults with moderate or severe AD are still quite limited but for children <6 years they are clearly inadequate. According to the 2010 Global Burden of Disease survey, among skin conditions, AD is associated with the highest number of disability-adjusted life years (DALY) and years lived with disease (YLD). The cost of managing AD in the United States ranges from approximately 400 million to 4 billion dollars and for individual households, out-of-pocket costs can consume up to 10% of household income. In this talk we will review the current systemic options for AD management, while highlighting a few of the exciting new systemic therapies that are currently being evaluated for their safety and efficacy in AD. But we also recognize that individuals with AD are predisposed to other atopic diseases, a phenomenon known as the “atopic march”. We will highlight a few of the studies that investigate primary prevention strategies for the first two allergic diseases in the “march”, namely, AD and food allergies. These strategies include emollients, breastfeeding, microbial exposures, probiotics, vitamin D and UV light, water hardness, immunotherapy and others. Unfortunately, more well-designed, longitudinal, randomized controlled trials, enrolling at-risk populations, are required before we can make definitive conclusions on what are the best prevention strategies.
Symposium 12
Fruit Allergy

SY-12 (M-2)-1 Basic mechanism on PFAS and the usage of component-resolved diagnostics in fruit allergy
Yasuto Kondo (Department of Pediatrics, Fujita Health University School of Medicine General Allergy Center, Japan)

Component-resolved diagnostics (CRD) is a diagnostic approach that utilizes purified native or recombinant allergens to detect the sIgE antibodies response against the individual allergenic molecules. CRD is considered a more precise and informative option, compared to conventional tests based on allergenic extracts. This approach increases test selectivity, particularly when important allergens are underrepresented or lacking in the extract, and improves test selectivity, especially when the selected IgE repertoire against an allergen yields additional information on potential risks, possible cross-reactivity, or primary sensitization. The major birch pollen allergen, Bet v 1, is the first allergenic PR-10-like protein to be cloned and that is the primary sensitizer in regions with birch pollen exposure. The presence of homologous allergens in Fagaceae (Birch, Alder, Hazel and Hornbeam) and Fagaceae (Beech, Oak and Chestnut) Family. Minute amounts of Bet v 1-homologous proteins found in fruits can induce various, transient, predominantly oropharyngeal symptoms with a quick onset (immediately and often within minutes) after consumption of raw fruits in approximately 2/3 of birch pollen allergic individuals. Thus, the so-called OAS does not represent a defined clinical entity (syndrome), but rather a variable symptom complex. The occurrence of only oropharyngeal symptoms reflects the physicochemical properties of the particular food allergens which, in the case of the Bet v 1-homologues, are instability and excellent aqueous solubility. The Bet v 1-specific IgE response is polyclonal, and epitopes are spread across the entire Bet v 1 surface. Furthermore, the IgE recognition profile of Bet v 1 is reported to be variable and highly patient specific, and that is most likely connected to the list of plant food allergens. In this lecture, I will describe the Basic mechanism on PFAS and the usage of CRD in fruits allergy, with a focus on Bet v 1 homologs. I hope this will provide some hints for future clinical practice.

SY-12 (M-2)-2 Gibberelin-regulated protein allergy
Naoko Inomata (Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Japan)

Gibberelin-regulated proteins (GRP) have, recently, emerged as a new marker allergen related to systemic reactions in fruit allergies. Until GRP was identified as an allergen in 2013, non-specific lipid transfer proteins (LTP) had been known to be a representative of allergens which cause severe reactions in fruit allergies. Interestingly, GRPs have been identified during research to address clinical issues related to peach LTP. Pru p 3. GRPs are members of cysteine-rich antimicrobial peptide families and are ubiquitous proteins that are found in a wide range of plant species. Until now, some GRPs in fruits and pollens have been identified as allergens including peach Pru p 7, Japanese apricot Pru m 7, cherry Pru avs 7, orange Cit a 7, pomegranate Pun g 7, and cucumber pollen GRP. Fruit GRP allergens share some characteristics with LTP allergens: systemic reactions, multiple fruit allergies regardless of plant kingdom classifications and, less frequently, cofactor-dependence. Multiple fruit allergies might be caused by cross-reactivity between GRPs. In addition, GRP allergy induces peculiar clinical symptoms, such as laryngeal tightness and facial swelling, especially eyelid edema. Eyelid edema was proposed to be a clinically predictive factor for Pru p 7 allergy. Sensitization routes in GRP allergies are still controversial. Fruit-derived GRPs have an unusually high content of cysteine, resulting in high stability to heat and resistance to digestive enzymes. Therefore, GRPs are considered "true" food allergens that sensitize hosts via the gastrointestinal tract and induce severe allergic reactions. Cross-reactivity between fruit GRP and cucumber pollen GRP is suspected to be an alternative mechanism of fruit derived-GRP allergies and cucumber pollen GRP may play a role as a sensitizer. While GRPs may cause pollen-food allergy syndrome, it induces more severe reactions than that of PR-10 and profilin. This lecture focuses on our current knowledge of the clinical features and important aspects of GRP sensitization and allergy.

SY-12 (M-2)-3 Immunotherapy in fruit allergy
Ignacio J Ansotegui (Department of Allergy & Immunology, Hospital Quirónsalud Bizkaia, Spain)

Allergen immunotherapy (AIT) is the only disease-modifying treatment strategy for IgE-mediated allergic diseases. AIT is a treatment that involves administering gradually increasing doses of allergen over time to induce immunologic changes. The ultimate goal of allergen immunotherapy is the induction of tolerance, which is the ability to ingest the food without allergic symptoms after discontinuation of the treatment. The possible mechanisms of food immunotherapy includes a shift from a Th2 profile to a Th1 profile, a decrease reactivity of mast cells and basophils, an increase of Treg cells production and food-specific IgG4 antibodies as well as a decrease of food-specific IgE antibodies. There are very few studies published on immunotherapy, including oral (OIT) and sublingual (SLIT), for the treatment of fruit allergy. In the Cochrane review on Immunotherapy (oral and sublingual) for food allergy to fruits by Yepes-Nuez et al. The authors were only able to include two Randomised controlled trials (RCTs) referred to immunotherapy treatment for allergy to peach and apple. Other studies were excluded mainly because there were not RCTs. The two included studies included small numbers of patients and no children, and were judged to be at risk of bias. In some countries, a peach LTP (Pru p 3) extract is commercially available. It is a safe treatment for patients with LTP syndrome, including for those with severe manifestations, such as anaphylaxis. In 2009, Fernandez-Rivas et al. published a double-blind, placebo-controlled, randomized clinical trial assessing the safety and efficacy of SLIT with Pru p 3. This treatment required a build-up phase performed for five days under medical supervision in the hospital followed by six months of three days per week administration of a maintenance dose at home. Recently, Moura et al. proposed an ultra-rush build-up protocol that requires only two days of medical supervision and demonstrates that it is safe and well tolerated. Due to the lack of enough data, immunotherapy treatments for fruit allergy require further RCTs before it would be widely implemented.
Symposium 13

Pollinosis

SY-13 (E-2) -1  Pollinosis - recent epidemiological data
Philip Rouadi (Department of Otolaryngology and Allergy, Lebanese Allergy Immunology-World Allergy Organization, Lebanon)

Pollen is affected by meteorological conditions and so does shifts in phenologies among pollen species. Japanese cedar pollinosis imposes significant health effects in Japan. Furthermore, pollen counts using traditional sampling methods reflect pollen concentration in ambient air and is complemented by molecular acrobiology to determine allergen level in outdoor environment. At the cellular level, pollen-generated allergen aerosol can cause damage to respiratory epithelium in different mechanism: direct trauma to epithelial barrier by pollen proteases, modulation of innate immune response by a TLR mechanism, as well as host sensitization and induction of an inflammatory response. Also, pollution can accentuate allergic airway sensitization and organ hyperresponsiveness in patients with pollinosis through an oxidative stress mechanism. Future research is needed to acquire better knowledge on immunopathologic mechanism involved in pollinosis.

SY-13 (E-2) -2  Climate change effect on pollen allergy and on asthma induced by pollens
Gennaro D’Amato (School of Specialization in Respiratory Diseases, University of Naples Federico II, Italy)

The impact of climate change on the environment, biosphere and biodiversity has become more evident in the recent years. Human activities have increased atmospheric concentrations of carbon dioxide (CO2) and other greenhouse gases. Change in climate and the correlated global warming affects the quantity, intensity and frequency of precipitation type as well as the frequency of extreme events such as heat waves, droughts, thunderstorms, floods and hurricanes. Respiratory health can be particularly affected by climate change, which contributes to the development of allergic respiratory diseases and asthma. Pollen and mold allergens are able to trigger the release of proinflammatory and immunomodulatory mediators that accelerate the onset the IgE-mediated sensitization and of allergy. Allergy to pollen and pollen season at its beginning, in duration and intensity are altered by climate change. Studies showed that plants exhibit enhanced photosynthesis and reproductive effects and produce more pollen as a response to high atmospheric levels of carbon dioxide (CO2). Pollens which proliferation is increased by floods and rainy storms are responsible for severe asthma. Pollen and mold allergy is generally used to evaluate the interrelation between air pollution and allergic respiratory diseases, such as rhinitis and asthma. Thunderstorms during pollen seasons can cause exacerbation of respiratory allergy and asthma in patients with hay fever. A similar phenomenon is observed for molds. Measures to reduce greenhouse gas emissions can have positive health benefits.

SY-13 (E-2) -3  Unique feature of Japanese cedar pollinosis
Daiju Sakurai (Department of Otorhinolaryngology, Head and Neck Surgery, University of Yamanashi, Japan)

Japanese cedar (JC) pollen is the most important allergen to cause allergic rhinitis (AR) in Japan. The prevalence of AR induced by JC has increased rapidly, and was estimated over 40% of Japanese population these days. JC forests produce a large amount of pollen, and JC pollen can travel a long distance over 100 km. Therefore, a large number of patients are observed even in city area. JC pollen dispersal starts in February and lasts April about for 10 weeks, and induces allergic symptoms for a long period. JC pollinosis has been spreading among younger children recently, but a remission is not common until an old age. Once the patients had onset JC pollinosis, therapeutic interventions may be required for a long period. AR induced by JC pollen are treated based on the severity and disease type. Pharmacological treatments such as anti-histamine, anti-leukotriene, and nasal steroids are central to the treatments. As another option, anti-IgE antibody drug, omalizumab has been approved for the patients with severe seasonal allergic rhinitis in 2019. Early treatment from the beginning of pollen dispersal has been recommended to reduce duration of symptoms and suppress the exacerbation in the peak pollen season. Sublingual immunotherapy (SLIT) with the extract of JC pollen has been shown to be a highly effective by the double-blind placebo-controlled study, and is expected to modify the natural history of AR induced by JC pollen. A biomarker predicting the therapeutic efficacy in the early time point of allergen immunotherapy is required to reduce the burden on patients. Allergen-specific memory Th2 cells may play a crucial role in the pathogenesis of AR including JC pollinosis. A decrease of these cells is suggested to be associated with SLIT efficacy, and may be a useful biomarker. In the symposium, I would like to talk about the unique feature of Japanese pollinosis including recent topics.
Symposium 14

Netting ANCA-Associated Vasculitis—Advances in Disease Mechanisms and Targeted Therapies

SY-14 (I-4) -1  Eosinophilic granulomatosis with polyangiitis: disease phenotype and management

Ulrich Specks (Division of Pulmonary & Critical Care Medicine, Mayo Clinic, USA)

Eosinophilic granulomatosis with polyangiitis (EGPA) is one of the three ANCA-associated vasculitis syndromes (AAV). 30-70% of patients with newly diagnosed and untreated EGPA have ANCA reacting with MPO. EGPA is characterized by an allergic background, asthma, peripheral blood and tissue eosinophilia, preceding the development of small vessel vasculitis. Treatment recommendations for EGPA are extrapolated from trials conducted in the other AAV. Patients with life- or organ-threatening disease manifestations such as cardiac, gastrointestinal or renal involvement, or macrovascular complications, have been classified as being “severe” disease, with involvement being the principal risk factor for death. For patients with severe disease manifestations, CYC has been most frequently used for induction of remission in conjunction with glucocorticoids, followed by other glucocorticoid sparing agents such as azathioprine for maintenance of remission. Additional immunosuppression is recommended for patients with non-severe disease if the prednisone dose cannot be effectively reduced to less than 10 mg per day. Recent research indicates that patients can be broadly grouped by clinical phenotype into two groups, even though there is substantial overlap of clinical features between them. The phenotype with prominent vasculitis features seems to present with MPO-ANCA, whereas in ANCA-negative patients clinical features are strongly driven by allergies and eosinophilic inflammation. This separation is supported by results of a genome-wide association study indicating that ANCA -positive patients share an HLA-DQ association with other ANCA-positive vasculitides, whereas ANCA-negative patients may have mucosal barrier dysfunction. These observations may also lead to future differential treatment approaches. Rituximab is emerging as an important alternative to cyclophosphamide in ANCA-positive patients, whereas anti-interleukin-6 therapy targets the eosinophilic inflammation and has been shown to have substantial glucocorticoid sparing effects in EGPA, thus addressing the biggest unmet need in the long-term management of patients with EGPA.

SY-14 (I-4) -2  ANCA associated vasculitis: a personal story of 35 years of research

Jan Willem Cohen Tervaert (Department of Medicine, Division of Rheumatology, University of Alberta, Canada; Department of Medicine-Immunology, Maastricht University, Netherlands)

In 1986/1987, our team demonstrated the presence of antibodies to proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA) in patients with either Granulomatosis with Polyangiitis, Eosinophilic Granulomatosis with Polyangiitis or Microscopic Polyangiitis. Furthermore, we demonstrated that relapses were nearly always preceded by increasing titers of these antibodies and that MPO-ANCA could induce vasculitis in animal models. It is now clear that PR3-ANCA associated vasculitis (PR3-AAV) and MPO-AAV are two distinct diseases. Although difficult to distinguish clinically, they are clearly different based on genetics. The pathophysiology of the initial phases of PR3-AAV and MPO-AAV differs. In PR3-AAV, ciliary motility is severely reduced, facilitating chronic nasal carriage of S. aureus. In addition, chronic infectious rhino sinusitis in PR3-AAV patients results in the release of high-mobility group box 1 (HMGB1), whereas in MPO-AAV patients, chronic sinusitis with nasal polyps results in the release of HMGB1. The release of HMGB1 results in the generation of neutrophil extracellular traps (NETs), a process that is pivotal for breaking tolerance to MPO and/or PR3. In addition, in MPO-AAV, silica exposure and smoking both risk factors for MPO-AAVare well-known causes of NET formation, whereas in PR3-AAV S. aureus causes NET formation. While neutrophils express low levels of PR3 and MPO on their cell surfaces, PR3 and MPO are expressed extensively upon stimulation (‘second hit’), making it possible for ANCA to bind. Both ANCA se-rotypes are able to activate neutrophils via Fab as well as Fcγ engagement, resulting in the release of inflammatory mediators. Importantly, ANCA-stimulated neutrophils induce the generation of NETs, a process that is potentiated by HMGB1. Moreover, ANCA activation of neutrophils and ANCA-induced NET formation results in complement activation via the alternative pathway, representing a pro-inflammatory amplification loop in AAV that is hypothesized to be essential for disease induction and/or progression. Based on above pathophysiological findings, anti-B cell therapy has been studied and now became “standard” therapy for AAV. Furthermore, anti-complement therapy has been more recently demonstrated to be an effective new treatment option.

SY-14 (I-4) -3  Updates on the pathogenesis of ANCA-associated vasculitis

Akihiro Ishizu (Department of Medical Laboratory Science, Faculty of Health Sciences, Hokkaido University, Japan)

ANCA-associated vasculitis (AAV) is a vasculitis that affects systemic small vessels especially in the kidneys and lungs, accompanied by the presence of ANCA in the serum. Similar to other autoimmune diseases, AAV develops in patients with a predisposing genetic background who have been exposed to causative environmental factors. Several genes such as HLA have been listed as susceptible or resistant genes, and it has been shown that environmental factors, including infectious agents and drugs, are involved in the development of this disease. The pathogenic mecha-nisms includes 1) priming of neutrophils, 2) ANCA binding to the primed neutrophils and an excessive activation of neutrophils with neutrophil extracellular trap (NET) release, 3) vascular endothelial cell injury due to the NETs, and 4) disordered NET regulation and ANCA production. Recent studies have suggested the contribution of pro-inflammatory cytokines and the complements to the priming of neutrophils. Although NETs are essential elements in the innate immunity, decrease in serum activity of DNase I (physiological NET degradation enzyme), disorder of the semaphorin 4D and plexin B2 system (physiological NET regulation system) and acquired resistance to DNase I have been demonstrated in AAV patients. Therefore, a vicious cycle of NET formation and ANCA production is considered to be involved in the pathogenesis of AAV. In addition to this role of NETs in AAV, some other important discoveries have been made in the last few years. Incorporating these new insights into our understanding of the pathogenesis of AAV is needed to fully understand and ultimately overcome this disease.
Symposium 15
Barrier (Lung, Skin, GI)

SY-15 (B-3) -1 Epithelial barrier in bronchial epithelium

Cezmi A Akdik (Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Christine Kühne-Center for Allergy Research and Education (C-CARE), Switzerland)

A defective epithelial barrier of the affected tissues has been demonstrated in asthma, atopic dermatitis, allergic rhinitis, chronic rhinosinusitis, eosinophilic esophagitis, and inflammatory bowel disease. There are multiple proposed roles of tissues in immune regulation and chronicity in asthma, such as continuous low level tissue inflammation takes place during remissions, which increases during exacerbations. Prevention of basal epithelial cell death from apoptosis full epithelial recovery occurs, when submucosal inflammation is suppressed. Apoptotic cell death of highly activated superficial epithelial cells is the mechanism of cromoglycans and epithelial shedding. Drainage of inflammation to mucosal lumens by opening of tight junctions/drainage of inflammation by lymphatic vessels suppression of submucosal inflammation by various regulatory cell subsets. Treg cells, Breg cells regulatory T, regulatory T17, cells etc. continuous angiogenesis and remodeling of tissue cells basement membrane (Laminin reticulins) barrier takes place in asthma to make a physical barrier between disease-inducing factors (allergens, environment, etc.) of the immune system. It is often in mucosal surfaces and may play an essential role in mucosal immune response. Group ( innate lymphoid cells (ILC3) may play a role in asthma development independent of the adaptive immune system. Bronchial epithelial keratization has been shown to be involved in asthma, however the role of ILC3 in the regulation of bronchial epithelial tight junctions (TJs) and barrier function was not known. Therefore, we determined the role of ILC3 in bronchial epithelial TJs barrier. Co-cultures of human ILC3a and air-liquid interface (ALI) cultures of primary bronchial epithelial cells were used to determine the measurement of transmural epithelial resistance (TEER), paracellular flux, TJ mRNA and protein expression and cytokines. To analyze the in vivo relevance of barrier disruption by ILC3a, the effect of ILC3a on TJs was examined using a murine model of IL-33-induced airway inflammation in wt, Rag2-/-, Rag2-/- and RORc-/- deficient Staggerer (fly x y) mice, which is specifically deficient for ILC3a. ILC3a significantly reduced the TEER and increased FITC-dextran permeability in ALI, after 30 hours, suggesting the induction of epithelial keratization. Consistently, ILC3a disrupted TJs proteins as well as decreased the expression of the molecule Claudin-4, Claudin-6 and Occludin. Neutralization of IL-33, but not IL4 restored the impaired epithelial barrier function by ILC3a, suggesting that ILC3a induced human bronchial epithelial TJs barrier disruption through IL-33. The intracellular administration of recombinant IL-33 to wild-type and Rag2-/- mice triggered TJs disruption in an ILC3a and IL-33-dependent manner as demonstrated by the analysis of cellular infiltration, broncho-alveolar lavage cell counts, lung mRNA and cytokine mRNA expression, whereas Rag2-/- and Rag2-/- mice, which lack IL4-/- did not respond to the response. These data demonstrate for the first time that ILC3a target bronchial epithelial TJs barrier as a novel mechanism in asthma pathogenesis. This damage to epithelial barrier can be induced by histone deacetylase inhibitors in vitro and in vivo. To conclude, the balance between inflammation inducing factors, epithelial barrier, barrier repair factors, wash away factors and suppression factors plays a decisive role in the resistance, exacerbation and chronicity of asthmatic inflammation, the same mechanisms seems to play roles in many different types of inflammations.

SY-15 (B-3) -2 Homeostatic mechanisms of skin barrier and their disruption in skin inflammation

Masaya Mamiaga (Department of Dermatology, Keio University School of Medicine; Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences, Japan)

Enhanced cutaneous senescence by skin barrier dysfunction has been extensively investigated as an initial important step for the onset of allergic disorders. Staphylococcus aureus-dominated dysbiosis in the skin plays an important pathogenic role for development of atopic dermatitis (AD). To understand how the dysbiosis is induced on the surface of stratum corneum (SC), we have been characterizing the normal nature of SC as niche for skin microbiota. SC consists of stacked dead keratinocytes which are generated from terminally-differentiated keratinocytes in stratum granulosum (SG). Visualization of SC by time-of-flight secondary-ion-mass-spectrometry (TOF-SIMS) demonstrated that SC has at least three layers of distinct functional properties; upper sponge-like layer which allows passive influx and efflux of ions, middle hydration layer, and lower barrier layer which is abrogated by filaggrin deficiency. To visualize in vivo pH in SC and dissect a role of pH in SC homeostasis, transgenic mice with a ratiometric pH biosensor with pH sensitive fluorescent protein, Venus/H156G, and pH insensitive protein, mCherry, were generated. Confocal microscopic analysis of living pH imaging demonstrated that SC has at least three distinct layers which are weak-acidic, acidic, and neutral from top to bottom, rather than gradual pH changes across the layers. Furthermore, the upper-neutral layers showed mosaic patterns of uneven pH distribution by differentiated units with en face view. These findings indicated the dynamic and complex nature of SC in terms of pH regulation. Stratum granulosum (SG) has three layers (SG1, SG2, SG3). Tight junction (TJ) is formed between SG2 cells, leaving SG1 cells out of the living body. In vivo intravital imaging of skin barrier (TJ) demonstrated that the basic shape of SG cells is a flattened Kelvin’s tetrakidekahedron, and uncovered a sophisticated mechanism that exploits the naturally-occurring polyyhedral shape of the cells to prevent TJ barrier breakdown during cell turnover. Uncovering the physiological mechanisms of SC homeostasis will lead us to develop a novel body surface technique to conquer the dyshbio- sis of the skin.

SY-15 (B-3) -3 The mucosal barrier in GI learned for the clinician from basic science

Luc Biedermann (Division of Gastroenterology & Hepatology, University Hospital Zurich, Switzerland)

In the gastrointestinal tract the mucosal barrier has emerged as a highly regulated and developed construct to form a delicate balance between enabling resorption of an enormous amount of nutrients as well as liquids on the one hand and prevention of entry of harmful luminal contents including pathogenic microorganisms on the other hand. There is a complex amount of highly specialized function according to the anatomical side in the considerably long one-way tubular route lined up by epithelial cells from the mouth to anus. Over roughly six meters several distinctive anatomical, immunological and microbiological characteristics according to the defined segments can be observed. And the mucosal barrier in the gastrointestinal tract is indeed a spot where a lot of functions occur. In view of the evident responsive function for liquids and nutritional constituents, it is often forgotten, that an impressive amounts of secretory (and subsequent resorptive) activity in the range of about nine liters per day occurs, specifically in the proximal parts of the small bowel. Right within this highly dynamic environment there is the largest collection of innate and adaptive immune cells within the different layers of the barrier as well as a number of microbes outlining the number of human cells by a factor of about 10. In the last years we gained several insights from basic science on the complex interaction of luminal anti-gen, the intestinal microbiota, intestinal immune cells and microanatomy and physiology of the intestinal mucosal barrier including the modifying role of genetic factors. This has contributed to an increased understanding of the complex functioning of the G.I. mucosal barrier in health and disease. In this talk the translation of these finding into the way patient with several gastrointestinal diseases are addressed already at present and potentially in the future shall be highlighted from a clinical perspective with a focus on inflammatory bowel disease, eosinophilic esophagitis and irritable bowel syndrome.
Symposium 16
Allergic Diseases and Immunodeficiency

SY-16 (P-3) -1  Overview of inborn errors of immunity: from a point of view of allergists

Yusei Ohshima (Department of Pediatrics, Faculty of Medical Sciences, University of Fukui, Japan)

Inborn errors of immunity (IEI) are a varied group of heritable disorders characterized by defects in components of the innate and/or adaptive arms of the immune system. More than 350 IEI have been recognized by the International Union of Immunological Societies. Patients with IEI have an increased susceptibility to infectious diseases and non-infectious complications including allergies, malignancies and autoimmune diseases, the latter being the first manifestation of IEI in several cases. Patients with IEI experience recurrent respiratory tract infections, leading to bronchiectasis and continuing decline in lung function. As expected, due to the obstructive nature of bronchiectasis, decline in FEV1 and recurrent respiratory symptoms might lead misdiagnosis of asthma. Asthma and allergic airway diseases were documented in about 30% of patients with common variable immunodeficiency (CVID). IEI are often associated with other conditions that, based on their morphology, distribution and symptomatology, may suggest a specific underlying diagnosis. Some IEI, such as DOCK8 immunodeficiency syndrome, Wiskott-Aldrich syndrome, and immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome X-linked recessive FOXP3, present with eczematous dermatitis meeting criteria for atopic dermatitis. When asthma or atopic dermatitis does not respond to standard treatment, immunodeficiency conditions need to be excluded. Autoimmunity and autoinflammation can be presenting symptoms instead of infections and/or complicating features of IEI. Evaluation for IEI in patients who have early-onset, multiple, familial and/or atypical autoimmunity can enhance diagnosis. Genetic testing is a component of evaluation of patients with IEI. Inherent advantages and limitations of diagnostic modalities must be considered during assessment of results. Distinct clinical phenotypes may be caused by Gain-of-Function or Loss-of-Function mutations in the same gene. Various degrees of activity of mutant proteins may also cause phenotypic variability. Thus, functional validation of potential disease-causing genetic candidates is critical.

SY-16 (P-3) -2  Early diagnosis in primary immunodeficiencies: red flags and alert signs

José Antonio Ortega-Martell (Department of Immunology, Autonomous University of Hidalgo, Mexico)

Our immune system is a network of cells and molecules very well organized in two branches, the unspecific innate immune system and the specific adaptive immune system. These cells and molecules work together to defend and protect the rest of the body from potential pathogenic intruders. A primary immunodeficiency disease (PIDD) occurs when part of the immune system is absent or not working properly, and is caused by genetic defects which are hereditary. More than 300 single-gene inborn errors of immunity underlying 5 phenotypes have been described: infection, allergy, malignancy, autoimmunity and autoinflammation. When a baby is born with a genetic defect affecting the immune system, the time is critical to implement opportunistic diagnosis and treatment in order to avoid opportunistic infections, inflammation, complications and sequelae. Signs that may indicate a primary immunodeficiency disease are: a) recurrent, unusual or difficult to treat infections, especially pneumonia, ear infections or sinusitis; b) poor growth or loss of weight; c) multiple courses of antibiotics or IV antibiotics necessary to clear infections; d) recurrent deep abscesses of the organs or skin; e) swollen lymph glands or an enlarged spleen; f) a family history of primary immunodeficiencies; g) or an autoimmune (unexpected by age) disease. Educational programs to increase PIDD awareness and diagnosis can be effective with more nationwide and worldwide campaigns for physician education, networking, public relations and opportune referral for appropriate treatment in a PIDD specialized center. Around 60% of PIDDs can be easily suspected with a simple and inexpensive set of blood tests, hopefully, as the technical ability to identify gene defects improves, more and more genetic cases of PIDD will be identified and novel therapies that target the specific cause of the disease will rapidly become available.

SY-16 (P-3) -3  Common variable immunodeficiency (CVID)

Kohsuke Imai (Department of Pediatrics, Tokyo Medical and Dental University (TMDU), Japan)

Primary antibody deficiency (PAD) is the most common type of primary immunodeficiency (PIDD). It is classified to 4 types: severe combined immunodeficiency (SCID), B cell deficiency (BCD), hyper-IgM syndrome (HIGM) due to the defect of Ig class switch recombination (CSR), and common variable immunodeficiency (CVID). CVID is the most common form of the PIDD with the presence of T cells and B cells, but the phenotype and the causative genes are highly variable. Pediatric CVID should be tested for the presence of T cell defect by TREC and KREC. We found the correlation of TREC and KREC levels with clinical life-threatening complication. Adult classical CVID is characterized by terminal B cell developmental defect due to memory B cell deficiency and/or plasmacyte deficiency. More and more causative genes are discovered recently with the use of next generation sequencing. Recently, we found novel causative gene for CVID, "APRIL." APRIL deficiency is characterized by the plasmacyte defect which tells us the contribution of APRIL to life-long maintenance of plasmacyte and immunoglobulin production in human. To study and to learn CVID is useful for the understanding of antibody production in human.
Anaphylaxis occurs worldwide and the estimated lifetime prevalence is 0.3 - 5.1%, depending on geographical areas, but also the definition and study methodology used. Although the mortality of anaphylaxis remains low within the last years, an increasing time trend for hospitalizations due to anaphylaxis has been reported. A recent study identified 629,906 anaphylaxis cases and the incidence increased from 153 in 2004 to 218 in 2016 (per 100,000). In this population based sample from the United States 26% were pediatric patients below 18 years old, 53% of cases below 60 years and 21% 60+ years. The strongest increase of anaphylaxis occurred among the pediatric population due to food allergy and in elderly patients due to drug hypersensitivity. However, venom was for example with 38% the most frequent trigger factor of anaphylaxis in the US 2016. These data are consistent with observations from other countries. However, especially the frequency of venom-induced anaphylaxis depends on the geographical region. Besides population based studies epidemiological data is necessary to acquire more detailed information on circumstances and treatment modalities of anaphylactic patients. Such data is provided by the anaphylaxis-registry, which obtains via an online questionnaire from allergy specialists information on anaphylactic patients. Currently more than 10 countries throughout Europe and Brazil are participating. These data from >10,000 registered patients support the important role of cofactors for the severity of anaphylaxis and the underuse of epinephrine (the treatment of choice for anaphylaxis) in all countries investigated. These findings, together with the epidemiological data, showing an increase of anaphylaxis worldwide makes it necessary to improve the awareness, diagnostics and treatment of this potentially life-threatening disease worldwide.

Venom immunotherapy is the standard of care for people with severe reactions and has been proven to reduce risk of future anaphylactic events. There is a moral imperative to ensure production, supply and worldwide availability of locally relevant, registered, standardized commercial venom extracts for diagnosis and treatment. Insects causing severe immediate allergic reactions vary by region worldwide. The most common culprits include honeybees (Apis mellifera), social wasps including yellow jackets (Vespula and Dolichovespula), paper wasps (Polistes) and hornets (Vespa), stinging ants (Solenopsis, Myrmecia, Pachycondyla, and Pogonomyrmex), andbumblebees (Bombus). Insects with importance in specific areas of the world include the Australian tick (Ixodes holocyclus), the kissing bug (Triatoma spp), horsfieldies (Tabanus spp) and mosquitoes (Aedes, Culex, Anopheles). Reliable access to high quality venom immunotherapy to locally relevant allergens is not available throughout the world. Many current commercially available therapeutic vaccines have deficiencies, are not suitable for, or are unavailable in vast areas of the globe. New products are required to replace products that are unstandardized or inadequate, particularly whole-body extract products. New products are required for insects in which no current treatment options exist. Venom immunotherapy should be promoted throughout the world and the provision thereof be supported by health authorities, regulatory authorities and all sectors of the health care service.

Anaphylaxis is a killing hypersensitivity reaction, considered as a public health problem by the allergy community. However, the epidemiological data can vary widely and it has been proved to be underreported in population based studies, having huge consequences in the visibility of this condition. A known reason for the undernotification of the allergic and hypersensitivity conditions, including anaphylaxis, was the misclassification in the World Health Organization’s (WHO) International Classification of Diseases (ICD). If conditions are not well recorded in official statistics, it can prevent investments on health care of patients suffering for these disorders. One example is the availability of adrenaline auto-injectors limited to 35% of world countries. In order to have a better classification of these conditions in the ICD-11, the ALLERGY in ICD-11 initiative has been launched, led by Luciana Kate Tanno and Pascal Demoly. The evidence-based academic and technical process have been documented by peer-review publications and has been so far supported and acknowledged by the international regional allergy academies*, the WHO Classifications, Terminology and Standards governance and the WHO group of experts. The main achievements of the initiative were: The construction of the pioneer "Allergic and hypersensitivity conditions" section in the ICD-11 Changes in mortality coding rules by the possibility of adding allergic or hypersensitivity conditions as underline cause of deaths in the death certificates.Better representation of the allergy specialty in other WHO international classifications-Designation of the Montpellier WHO Collaborating Centre on Classification Scientific Support, the only one representing the allergy specialty-Nomination in the Medical and Scientific Advisory Committee to support the WHO All the efforts will contribute to improve the counting measures of anaphylaxis and, therefore, implicate in quality care of anaphylactic patients.
Symposium 18
Treatment Adherence

SY-18 (M-4) -1 Adherence to topical treatment

Steven Feldman (Department of Dermatology, Wake Forest School of Medicine, USA)

Topical treatment is the foundation of treatment for patients with mild-to-moderate atopic dermatitis. When patients with atopic dermatitis don’t improve when prescribed topical steroids, it may be because they didn’t use the topical corticosteroid. This session will present objective adherence data collected using electronic monitors in the caps of the medication containers. Patterns of non-adherence will be described. Reasons for poor adherence will be discussed. Finally, many different approaches for improving patients’ adherence to treatment will be presented.

SY-18 (M-4) -2 Adherence to inhaled corticosteroids in children and adolescents

Takao Fujisawa (Allergy Center, Mie National Hospital, Japan)

Poor adherence leads to poor control of asthma and eventually to poor outcome. Adherence is often hidden or unrecognized not only for physicians but for patients themselves. Objective evaluation of adherence can help identify poor adherence and provide a clue to intervene it. We aimed to develop a novel questionnaire for the identification of poor adherence.

Study psychologists performed semi-structured interview to children and adolescents with asthma who were treated with inhaled corticosteroids, asking thoughts, feeling, attitude and habit in relation with adherence. Concepts possibly link to adherence was selected from the interview records to form candidate-item questionnaire. Actual use of prescribed inhaled corticosteroids was obtained by using a “confidential” written questionnaire asking them to answer “honestly” about frequency of “forgetting to take medicine”. Children with asthma in 9 to 15 years of age were recruited in the study. Answers to questionnaire in the first group of 445 children were used for development dataset and those in the second group of 273 children for validation. Logistic regression analysis was performed with adherence based on actual frequency of ICS use as objective variable and answers to the candidate items as explanatory variables. The analysis identified a logistic model comprising 6 items to predict adherence. The model showed good fit with AIC=449 and P=0.81 in Hosmer-Lemeshow test. We designated the set of questions as “Pediatric Asthma Adherence Questionnaire”; PAAQ. Propensity score was then calculated in the model and designated as PAAQ score. PAAQ well discriminated adherence with AUC at 0.8135 and 0.7588, with sensitivity of 68.4% and 64.5%, specificity of 82.4% and 73.9% at cut-off PAAQ score of 0.65 in development and validation datasets, respectively. PAAQ scores for the physicians’ ratings of adherence and patient-reported adherence differed significantly in the hypothetic direction. PAAQ is a valid patient-completed questionnaire of adherence to inhaled corticosteroids in children and adolescents with asthma in whom true adherence may be “hidden” or “under-recognized”.

SY-18 (M-4) -3 Adherence to allergen specific immunotherapy

Ralph Mössges (Department of Clinical Research International, University at Cologne, Germany)

Allergies are steadily gaining in importance in the Western world. For over one hundred years, immunology has been the only causal treatment. Specific immunotherapy (SIT) aims at the cure of allergy or at least freedom from allergy symptoms. In association with this, adherence poses a complex problem. Both treatment applications commonly used—sublingual and subcutaneous immunotherapy—show poor persistence on the part of the patients. In most cases, SIT is not carried out to the end of the recommended duration and instead is discontinued prematurely. Corresponding figures from 3 year studies in the literature range from 41-93% for uncompleted SLIT and from 40-77% for uncompleted SCIT. Patient adherence is subject to influencing factors of various dimensions that are interdependent in complex relationships. The physician-patient relationship is just as decisive a factor for treatment success as the patient’s understanding of allergy, treatment, and the importance of adherence.
Symposium 19  
New Insights in Allergen Immunotherapy: Adult

SY-19 (I-5) -1  
New insights in allergen immunotherapy: adult

Giovanni Passalacqua (Allergy and Respiratory Diseases, University of Genoa, Italy)

SY-19 (I-5) -2  
Allergen immunotherapy: an American perspective

Bryan Martin (Departments of Internal Medicine, The Ohio State University, USA)

The practice of allergen specific immunotherapy (SIT) has been utilized in the United States for decades, since the first description of this procedure by Noon over a century ago. The United States has three US Food and Drug Administration (FDA) approved routes of specific immunotherapy; Subcutaneous injection (SCIT), Sublingual (SLIT) and Oral (OIT). The primary focus has been on Subcutaneous injection of allergens, with sublingual immunotherapy obtaining FDA approval in 2014, and Oral Immunotherapy receiving approval for peanut immunotherapy in 2020. This talk will focus on immunotherapy as provided in the United States. That begins with the selection of the right patient for immunotherapy, to include what conditions respond well to immunotherapy, and what patient is best suited for immunotherapy, to include age and comorbid conditions.

Appropriate antigen choice is also important. Licensing of individual allergic extracts falls under the FDA. The first non-standardized subcutaneous allergenic extracts were licensed in the 1920s when regulations that were not as stringent as they are today. There is now a focus on standardizing American subcutaneous immunotherapy extracts. All Hymenoptera extracts are standardized, as are house dust mite, grass pollen, cat and ragweed, but there is inconsistency in the nomenclature of standardization of extracts.

Americans commonly use multiple antigens in a single immunotherapy treatment vial. Therefore, consideration must not only be given to the individual antigens, but the effect the antigens have on one another when mixed in a single vial. Both the potential for cross reactivity and the potential for degradation of antigen strength due to the presence of proteases in other antigens must be considered.

The final immunotherapeutic injections are typically formulated in the Allergist’s office for the provision of allergen immunotherapy to an individual patient. While immunotherapy is highly effective, allergists recognize the need for additional research focused on the development of safer and more effective immunotherapy.

SY-19 (I-5) -3  
Allergen immunotherapy in Japan

Makoto Nagata (Department of Respiratory Medicine/Allergy Center, Saitama Medical University, Japan)

Allergen immunotherapy (AIT) is a curative treatment for allergic diseases caused by environmental allergens including house-dust-mite and tree/grass pollens. Subcutaneous immunotherapy (SCIT) in Japan was first approved to treat allergic asthma caused by house-dust-mite (HDM) allergy in 1963. Traditionally, house-dust (HD) including certain amounts of HDM-allergen has used in Japan, however, following the standardization and a clinical trial, a standardized purified HDM-allergen became available in the last decade in Japan. Japanese cedar (Cryptomeria japonica) pollinosis (JCP) is a seasonal common disease in Japanese islands during spring time especially from February to April. The prevalence of JCP is much higher than those with other pollinosis in Japan. JCP induces symptoms including rhinitis, conjunctivitis, and exacerbation of asthma, and hence has been a significant social issue in Japan. Standardized Japanese cedar allergen extract is available and SCIT using the extract successfully reduced symptoms such as rhinitis, and developed long-term tolerance in JCP patients. However, the major drawbacks for usage of SCIT potentially possesses serious side effects such a local pain and anaphylaxis. In Japan, sublingual immunotherapy (SLIT) using the standardized JCP-pollen allergen extract became available in the last decade, indicating “Renaissance” of a curative treatment for allergic patients in Japan. SLIT appears to be associated with a lower incidence of systemic reaction. To date, SLIT has received much attention as an advanced clinical application in AIT for both JCP and HDM-allergy. We found that seasonal exacerbations of asthma during JC-pollen season can be blocked by SLIT using JCP-pollen allergen. Recently, efficacy of HD-poll tablets in adult asthma was also confirmed in Japanese population of allergic asthmatics. In this presentation, current status and future directions of SCIT and SLIT for asthma and JCP in Japan will be discussed.
Symposium 20

Non-IgE Food Allergy

Non-IgE-mediated gastrointestinal food allergy in Japan

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**Background:** Non-IgE-mediated gastrointestinal food allergy (non-IgE-GFA) is a group of allergic diseases with non-IgE-dependent mechanisms, which present vomiting, bloody stools, and poor weight gain. Unlike with IgE-mediated allergy, the central mechanism of pathogenesis is unknown. There are no diagnostic tests to identify causative foods other than oral food challenge tests (OFC). **Classification:** Cluster assignment was used to classify patients (Nomura et al., JACI 2016). It is divided according to whether the patient has had bloody stools. Cluster 1: vomiting (+), bloody stools (+). Cluster 2: vomiting (+), bloody stools (+). Cluster 3: vomiting (+), bloody stools (+). Cluster 4: vomiting (+), bloody stools (+). Research progress in recent years: Many studies have been conducted to solve the problems of this disease. A nation-wide survey was conducted in Japan in 2016. The annual incidence rate was 0.02%. Cluster 1 (16% of the total patients): Half of them developed up to 7 days after birth. Cord blood eosinophils were increased, suggesting the intruterine onset of the disease. Cluster 2 (30%) is identical to food-protein-induced enterocolitis syndrome. Criteria for OFC, centered on vomiting starting within 4 hours after food ingestion, were defined in international guidelines (Nowak et al. 2017). Immunological studies showed activation of innate immunity after OFC. Cluster 3 (18%): food-protein-induced enteropathy and infantile eosinophilic gastroenteritis (IEGE) are included. Thirty percent is classified as IEGE and showed elevation of specific serum cytokines (Shouda et al. JACI 2016) Cluster 4 (38%). It is considered to include food-protein-induced proctocolitis with only bloody stool and more severe iEGE. Unlike in Western countries, peripheral blood and gastrointestinal eosinophilia are prominent in all clusters. It may be appropriate to call these patients with IEGE. Food eosinophil-derived neurotoxin will be an important biomarker. Future plans: it may be necessary to divide groups scientifically using precision medicine. If the central mechanism of immunity can be elucidated, diagnostic methods for causative foods will be developed.

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated food allergy that manifests with projectile, repetitive emesis (1-4 hours following food ingestion) that can be controlled by diarrhea (6-10 hours later) and may be accompanied by lethargy, hypotonia, hypothermia, hypotension, and metabolic derangements. PPIES usually starts in infancy although onset in older children and adults, especially to mollusks and crustaceans is being increasingly recognized. PPIES is not rare, with the range of the cumulative incidence of FPIES in infants estimated to be 0.015-0.07% worldwide. In the recent population-based study in the US, PPIES prevalence in the children was 0.51% and 0.22% in adults. PPIES triggers vary, depending on the country of origin and local dietary patterns. In the US, the most common food triggers are cow’s milk, soy, rice, and oat. In Spain and Italy, fish are a very common solid food trigger. Since the implementation of the early peanut introduction guidelines, there are increasing reports of FPIES in infants induced by peanut. The majority of infants react to a single food, although recent reports emphasize a larger number of solid foods triggers. While the prognosis is generally favorable, FPIES has a negative impact on the caregiver’s quality of life and is associated with increased financial costs to the families. FPIES diagnosis is challenging and might be missed due to later (1-4 hours) onset of symptoms following food ingestion, lack of typical allergic skin and respiratory symptoms, and food triggers that are perceived to be hypoallergenic such as infant cereal grains. Diagnosis is based on the recognition of symptoms because there are no biomarkers of FPIES. The pathophysiology remains obscure although activation of the innate immune compartment has been detected. Management relies of avoidance of food triggers, treatment of accidental exposures and periodic re-evaluations with supervised oral food challenges to monitor for resolution. There are no strategies to accelerate development of tolerance in FPIES.

Non-IgE-mediated food allergies

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Non-IgE-mediated food allergies include a spectrum of clinical conditions partially or totally determined by immune mechanisms triggered by specific foods. In these situations, the specific IgE to foods are not important and the cell compartment of the immune system is responsible for food allergy. This include not only the alterations of the T lymphocytes, but also alterations in mastocytes, eosinophils, in the natural immunity, in some cytokines, in the intestinal microbiome. In general, non-IgE-mediated food allergies present as delayed reactions and can be chronic in nature like Eosinophilic Esophagitis (EoE), Eosinophilic Gastrointestinal Diseases (EGID), Food Protein-Induced Proctocolitis (FPIAP), or some forms of Atopic Dermatitis (AD). The only acute non-IgE-mediated food allergy is Food Protein-Induced Enterocolitis (FPIES). Although the mechanisms that determine them are sometimes similar, they are not identical in different situations and a broad spectrum of symptoms can be attributed to forms of non-IgE-mediated food allergy. After a brief description of the different forms, we will face the challenge of the appropriate etiological diagnosis. Since it is not possible for them to base the diagnosis on a formal oral food challenges as for IgE-mediated allergies, the diagnosis is usually based on elimination and reintroduction diets. This technique is delicate to apply, not easy to interpret, and may expose patients to the risk of overdosage of non-IgE-mediated food allergies. Among the main risks, that of the long-term elimination of essential foods such as milk from the diet of children with the diagnostic suspicion of non-IgE-mediated food allergy is frequently incurred. We will therefore devote our time to circumscribe the criteria of suspicion and diagnosis, in order to help our patients to walk on a balanced path between the excess of elimination and the lack of a diagnosis.
Symposium 21

Chronic Cough

SY-21 (I-6) - 1 Pathophysiology and treatment of cough in asthma

Akio Niimi (Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University, Japan)

Cough is the commonest complaint for which patients seek medical attention, and chronic cough lasting for >8 weeks is especially an important problem. Asthma or cough variant asthma, upper-airway cough syndrome, and gastroesophageal reflux disease have been the top three causes of chronic cough world-wide. In asthma, cough is the most troublesome and refractory symptom, associated with poor disease control. Pathogenesis of asthmatic cough has mainly been attributed to airway inflammation and bronchoconstriction, being responsive to the mainstay treatment ICS/LABA. However, recent evidence indicates that cough reflex hypersensitivity or ‘neuronal dysfunction’ is a feature of asthma, even in mild stable disease. Cough reflex hypersensitivity is commonly tested by cough reflex test to inhaled capsaicin, and is likely resistant to ICS/LABA (Niimi PA. Pharmacol Ther 2019). Such refractory asthmatic cough might manifest more predominantly in the day-time rather than night-time (Kanemitsu: J Invest Allergol Clin Immunol 2019). Treatment options of refractory asthmatic cough or cough reflex hypersensitivity include LTRA’s (Takeamura: Respiration 2012), tiotropium (Fukumitsu: JACIP 2018), and bronchial thermoplasty despite very preliminary (Kanemitsu: Ann Intern Med 2018). Recently we prospectively enrolled 157 nonsmoking asthmatics (I22 with severe asthma), to determine the impact of capsaicin cough reflex sensitivity (C-CS); C-CS (minimal capsaicin concentration to induce at least five coughs [CS]) spirometry, blood eosinophils/neutrophils, FeNO and comorbidities were assessed. Associations of these indices with four clinical features of severe asthma suggested by the ERS/ATS guidelines (poor control [Asthma Control Test<20, n=58], frequent exacerbations [≥2/year, n=28], admissions [≥1/year, n=17], and airflow limitation [%FEV1<80, n=30]) were analyzed. Heightened C-CS was associated with poor asthma control, frequent exacerbations and admissions, particularly in non-atopic patients. C-CS was unrelated to airflow limitation. With multivariate analysis, heightened C-CS (CS≥224 μg) was a significant risk for poor asthma control, and frequent exacerbations. Regarding comorbidities, ex-smoking, diabetes mellitus, and chronic rhinosinusitis were associated with features of severe asthma (Kanemitsu: AJRCCM 2020). Heightened C-CS is a risk factor for severe asthma, and airway neuronal dysfunction may be an important therapeutic target in severe asthma.

SY-21 (I-6) - 2 Chronic cough in children

Anne Chang (Department of Respiratory Medicine, Queensland Children’s Hospital; Centre for Children’s Health Research, Queensland University of Technology; Menzies School of Health Research, Charles Darwin University, Australia)

Cough is the most common presenting symptom to medical practitioners in many countries. Worldwide, the desire to reduce the impact of the symptom of cough is reflected in the billions of dollars spent on over the counter cough medications. When is cough a ‘nuisance’? When is cough a serious symptom? Does chronic cough matter? To parents, the symptom of cough in their child is always important and evidence of its effect on parents will be presented. Missing a serious aetiology may lead to increased later morbidity. Thus, each child that presents with a chronic cough requires thorough clinical evaluation. In the management of paediatric cough, operational definitions are clinically useful. These definitions are not exclusive (i.e. can overlap) and distinct from adult definitions. Based on current data, paediatric cough definitions have been formulated on three main categories, built on different constructs: 1. Duration facute, protracted acute and chronic) 2. Cough quality and characteristics (dry vs wet/ productive, classical recognizable cough sounds, protracted bronchial) and 3. Clinical characteristics based on the likelihood of an underlying disease or process (expected cough, specific cough, non-specific cough). In almost all situations, a chest radiograph and spirometry (if age appropriate) should be performed as a minimum. Further investigation is likely required when the child’s clinical characteristics is consistent with specific cough. The depth of these investigations is highly dependent on the clinical characteristics present. If medications are tried, the concept of ‘time to response’ is important in the management of cough in children to minimize possible associated morbidity of the therapies. ‘Time to response’ is defined as the expected timeframe to which the cough should significantly reduce if the medication is beneficial. In most situations ‘time to response’ is generally 2 weeks. The evidence (as well as the lack of evidence), for and against, the above will be presented, along with the recommendations from the updated USA chronic cough guidelines.

SY-21 (I-6) - 3 Management of chronic refractory cough

Kian Fan Chung (National Heart & Lung Institute, Imperial College London & Royal Brompton Hospital, UK)

Chronic refractory cough (CRC) is a cough that persists despite undergoing guideline-based management protocol. Anatomic-diagnostic protocols were the first breakthrough leading to improvement of outcomes in CRC but are not always successful. CRC is commonly seen in specialist cough clinics and has a significant impact on quality of life and healthcare utilization. The cough hypersensitivity syndrome (CHS) has been proposed as a cause of CRC, providing an understanding of the dry irritated cough localized around the laryngeal region, associated with other symptoms including globus, dyspnea, and dysphonia. CRC has common features with other conditions such as the laryngeal hypersensitivity syndrome and chronic pain syndrome, which has helped to bring light to the pathophysiology of the condition. Mechanisms underlying CRC include central sensitization and peripheral sensitization, likely caused by neuropathic inflammation with altered regulation of neural circuits involved in the processing of increased central nervous system integration of sensory inputs and reductions in the descending control mechanisms. The diagnosis of CRC is made when the main diseases that cause chronic cough have been excluded or treated and the cough remains refractory to medical treatment either directed at any potential causes or at suppressing the cough itself. Treatments include speech pathology interventions using techniques adapted from the treatment of hyperfunctional voice disorders, as well as the use of centrally-acting neuromodulators such as gabapentin and pregabalin, and amitriptyline. Opiate can be considered. Novel anti-sweases, such as P2X3 (an ATP receptor) antagonists, may become available within a few years. Physiopathological mechanisms underlying chronic refractory cough are likely to be heterogeneous across different clinical context and molecular etiopathology may remain the key to making further advances in clinical practice.1-4

**Symposium 22**

**Food Allergy Diagnosis**

**SY-22 (P-5) -1  Molecular features of food antigen: from mechanisms to diagnosis and therapy**

Rudolf Valenta (Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Austria)

**SY-22 (P-5) -2  Application of allergen component**

Komei Ito (Aichi Children’s Health and Medical Center, Japan)

Diagnosis of food allergy should be based on the appearance of allergic symptoms and detection of specific IgE antibodies to the offending food. Generally, specific IgE tests to the crude allergen extract show good sensitivity in the diagnosis of food allergies, but the specificity is limited. On the other hand, allergen component-specific IgE tests offer favorable diagnostic specificity. Recent development of allergen components took place in the diagnosis of peanut and tree nuts allergies. Specific IgE tests to Ara h 2 (peanut) offers 99% positive predictive value (PPV) when the level is 40 kU/L. Specific IgE tests to Jug r 1 (walnut) and Ana o 3 (cashew nut) also offers almost 100% PPV at the level of 0.35 kU/L. Combination of crude- and component-specific IgE tests helps the diagnostic accuracy without performing an oral food challenge testing in most of the patients with suspicious peanut and tree nut allergies. Detection of α-5 gliadin-specific IgE helps the diagnosis of immediate-type wheat allergy in children, and wheat-dependent exercise-induced anaphylaxis (WDEIA) in adult patients. However, caution has to be taken that this test shows negative result in WDEIA in children and WDEIA caused by the hydrolyzed wheat product. Detection of Gly m 4 (soy bean) - specific IgE suggests the occurrence of pollen-food allergy syndrome (PFAS) caused by the Bet v 1 homologue in soymilk even in the negative finding of soybean-specific IgE. Most of the patients with fruit allergy are categorized into PFAS-type caused by the Bet v 1 homologue or profilins. However, patients suffered from anaphylaxis or exercise-induced anaphylaxis to peach, plum or apple are often sensitized to the glibberelin-regulated protein (GRF) in the offending fruits. Development of clinical test to GRF-specific IgE may help the differential diagnosis of fruit allergy into PFAS-type and anaphylaxis-type.

**SY-22 (P-5) -3  Stepwise oral food challenge**

Noriyuki Yanagida (Department of Pediatrics, National Hospital Organization Sagamihara National Hospital, Japan)

The oral food challenge (OFC) is a specific and vital tool used in clinical practice to identify the level of tolerance a person exhibits toward certain foods while diagnosing food allergies. OFCs are becoming more important because of the increasing demand of early food introduction, and low-dose OFCs with the goal of daily ingestion of a small amount of protein could accelerate oral tolerance development. The stepwise oral food challenge, starting with a low dose and progressing to medium and full doses, was reported as an effective approach to enable children with allergies to determine the maximal quantity of the allergen that they can safely consume. Low dose OFC can stratify prolonged food allergic patients and patients expected good prognosis. The aim of this presentation is to evaluate efficacy and safety of clinical approach of stepwise OFC starting from low dose OFC.
Symposium 23

Microbiome and Allergy

SY-23 (B-4) -1 Exposure to environmental microbes - from the hygiene hypothesis to a mechanistic understanding

Harald Renz (Institute of Laboratory Medicine and Pathobiology, Molecular Diagnostics, Philipps University Marburg; University Hospital Giessen and Marburg GmbH, Germany)

The hygiene hypothesis is currently the leading concept to explain the dramatic increase in chronic inflammatory disease including autoimmunities and allergies. Conversely, several gram-positive and gram-negative bacteria have been isolated from rural environmental communities which provide protection of allergic asthma. Overwhelming evidence indicates a strong impact of environmental microbes on the programming and the development of (early) immune responses. Based on clinical and epidemiological data, a certain exposure of environmental microbes - particularly of bacteria - seems to be an important pre-requisite in order to program immune responses towards the tolerance default program. This program on the level of the adaptive immune responses is necessary and required in order to prevent unwanted (chronic) inflammatory diseases which may develop early in life (such as allergies and asthma) or which may occur even later in life, such as many autoimmune diseases at the gut, the brain, or other organs. The Grand challenge is to define the appropriate microbial environment on the cellular and molecular level in order to delineate the underlying mechanism of microbe-host interaction. An important concept in this context. This is the microbial diversity. Conversely, reduced diversity is closely linked to several clinical phenotypes, particularly in early life such as allergies and asthma. Even more compelling, reduced diversity precedes the clinical onset of the disease, suggesting a cause-effect relationship. This concept implies the loss of (ancient) evolutionary core-evolved microbial strains and is the result of changes in lifestyle condition, particularly under westernized and industrialized environmental conditions. Therefore, microbial exposure seems to be a surrogate marker for biodiversity, as observed in the above mentioned living conditions. The great challenge in this research field is to delineate the molecular pathomechanism of gene-environment interactions and the impact of microbial communities on this complex and intimate relationship. Only through better understanding of these mechanisms, we will be able to define novel and attractive strategies for the prevention of chronic inflammatory diseases. Therefore, it is urgently needed to move this research field towards translational activities. The next few years will provide a compelling amount of novel data, which will hopefully improve the understanding of mechanisms of this important communication between the host and the microbial communities.

SY-23 (B-4) -2 Lung and gut microbiota in asthma - bacteria, viruses, fungi and archaea

Milena Sokolowska (Swiss Institute of Allergy and Asthma Research, University of Zurich, Switzerland)

Asthma is a common chronic respiratory disease with heterogeneous immunological, molecular and clinical features. Asthma management strategies are heading to the more and more personalized medicine approaches, including lung and gut microbiome analysis. Lung and gut microbiota are inseparable parts of the development and maintenance of healthy immune responses. Microbial dysbiosis at any point of life is followed by subsequent dysregulation of immunological processes affecting the onset of the asthma, its clinical presentation and responses to treatment. Bacteria and viruses are the most extensively studied microorganisms relating to asthma, but other microbes, including fungi and archaea are important players in its pathogenesis. Their constant interactions with each other and with the host cells shape airway inflammation and the phenotype of the disease.

SY-23 (B-4) -3 Intestinal bacteria promote intestinal barrier integrity and modulate retinoic acid metabolism to prevent allergic responses to food

Cathryn Rose Nagler1,2, Andrea M Kenter1 (Department of Pathology, The University of Chicago, USA; Biological Sciences Division and Pritzker School of Molecular Engineering, The University of Chicago, USA)

We previously reported that intestinal bacteria of the Clostridia class modulate epithelial barrier function through induction of IL-22 and hypothesized that this was crucial for their allergy protective effect (Proc. Natl. Acad. Sci. 2014;111:13145-13150). We now confirm that hypothesis and further describe the mechanisms underlying this protection. Clostridia colonization of weaning germ free mice induced colonic IL-22 production and expression of the antimicrobial peptides Reg3b and Reg3g within three days. At the same time, the numbers of CD11b+CD103+ and CD11b−CD103− dendritic cells (DC) in the colon lamina propria were reduced, while the number of macrophages remained unaltered. Seven days post colonization, the numbers of those same DC subsets were increased in the colon draining mesenteric lymph node (cMLN) and we detected an increased ability to produce retinoic acid (RA) in CD11c+ cells in the cMLN. We also observed increased expression of Reg3b, Reg3g and the retinol dehydrogenase Rdh57 in the ileum and the RA-responsive gene Iex in colon epithelial cells. At 14 days, Clostridia colonization increased percentages of RORγt+Foxp3+ regulatory T cells (Tregs), which are known to efficiently suppress type 2 immune responses. Finally, the TLRS ligand flagellin replicates Clostridia-induced production of IL-22 and intestinal barrier protection but not modulation of RA metabolism. With the rapid induction of IL-22, which supports intestinal barrier integrity, and the slower modulation of retinoic acid metabolism and Treg induction we describe two mechanisms by which Clostridia promote tolerance to food antigens. Detailed knowledge of these mechanisms will enable us to develop new strategies to combat the dramatic rise of food allergies.
Symposium 24
Aspirin-Exacerbated Respiratory Disease (AERD)

SY-24 (I-7) -1  Role of inflammatory cells and lipid mediators in AERD pathogenesis
Sven-Erik Dahlen (Centre for Allergy Research, Karolinska Institutet, Sweden)

SY-24 (I-7) -2  Pathophysiology of phenotype/endotype of AERD
Hae-Sim Park (Department of Allergy & Clinical Immunology, Ajou University Medical Center, Republic of Korea)

AERD is characterized by more severe clinical outcomes in aspects of lower FEV1/frequent asthma exacerbation (AE)/type 2 inflammation in upper and lower airway mucosa compared to non-AERD. Overproduction of cysteinyl leukotrienes followed by eosinophil activation is a major pathogenic mechanism, however, recent clustering studies demonstrated different clinical outcomes according to each subtype. We reported 4 distinct subtypes of AERD based on the presence of chronic rhinosinusitis/nasal polyps, atopy and urticaria. In addition, our 10 years’ longitudinal study with maintaining anti-asthmatic medications (including ICS and leukotriene modifier) shows that subtype 1/2 (having chronic rhinosinusitis/nasal polyps and higher blood/sputum eosinophilia) show poor clinical outcomes in aspects of progressive lung function decline and frequent AE compared to subtype 3/4. AERD patients with frequent AE had higher blood eosinophilia and platelet counts as well as higher medication requirements (including systemic steroid use). We propose that AERD patients have various phenotypes/endotypes, and individualized treatment with identifying subtypes is essential to achieve better clinical outcomes.

SY-24 (I-7) -3  Aspirin-exacerbated respiratory disease: clinical manifestations and therapeutic advances
Masami Taniguchi (Center for Immunology and Allergology, Shonan Kamakura General Hospital, Japan)

The characteristics in aspirin-exacerbated respiratory disease (AERD) is severe adult-onset asthma, eosinophilic rhinosinusitis with nasal polyposis, and cysteinyl leukotriene (CysLT) overproduction. The most important characteristics of clinical feature in AERD is eosinophilic rhinosinusitis with nasal polyposis that may lead to hyposmia. More than half of adult patients with moderate-severe asthma who have nasal polyposis complicated with AERD. Nasal symptoms (particularly hyposmia) generally develop several years before the onset of AERD. Currently, the symptoms of asthma in AERD patients are often stabilized by inhaled corticosteroid therapy; however, symptoms other than those in the lower respiratory tract become noticeable. In recent years, eosinophilic otitis media, skin rash, eosinophilic enteritis, and variant angina-like chest pain have been observed in more than half, 30%, 30% and 105% of patients with AERD, respectively. Peripheral blood eosinophilia is more prominent in patients with moderate-severe AERD than in those with aspirin-tolerant asthma (ATA). The cause of AERD have remained unclear, however the decrease in the production of PGD2 caused by the reduction in COX-2 activity is considered to main pathological mechanism of AERD. The mast cell activation and the interaction between platelets and granulocytes lead to the CysLT overproduction and severe eosinophilic inflammation. The activation of mast cells is important key pathogenesis in not only stable AERD but exacerbated AERD by aspirin and NSAIDs. In recent years, anti-IgE therapy, omalizumab may be an effective option for AERD via suppression of mast cell activation and CysLT overproduction (Hayashi et al. JACI 2016). We reported very recently that omalizumab treatment inhibited urinary leukotriene E4 overproduction and upper/lower respiratory tract symptoms during oral aspirin challenge, resulting in aspirin tolerance in 62% in sixteen patients with AERD (AJRCCM 2020). Laidlaw et al. reported that dupilumab (anti-IL-4/13) improves sinus symptoms especially in patients with AERD (JACIP 2019). In near future, anti-platelet drug, CRTH2 antagonist, and anti-TSLP antibody may be useful candidate of therapeutic options in patients with AERD.
Symposium 25
Severe Cutaneous Allergic Reaction (SCAR)

SY-25 (D-3) -1 Pathogenesis of SCAR: necroptosis in Stevens-Johnson syndrome/toxic epidermal necrolysis

Richiro Abe (Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Japan)

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening mucocutaneous reactions characterized by extensive detachment of the skin. We previously showed that keratinocyte death in SJS/TEN can be triggered by the interaction of annexin A1 and formyl peptide receptor (FPR) 1 to induce necroptosis, a programmed form of necrosis. Recently we revealed a variety pattern of necroptosis-related molecules, such as RIP3 and MLKL, expression in non-severe adverse drug reaction, suggesting an adjustment mechanism of cell death in keratinocytes. In addition we show anti-SJS/TEN drug development targeting FPR1.

SY-25 (D-3) -2 From immune mechanism to treatment on SCAR

Wen-Hung Chung (Department of Dermatology and Drug Hypersensitivity Clinical and Research Center, Chang Gung Memorial Hospital, Taiwan)

The clinical presentations of drug eruptions vary from mild maculopapular exanthema, fixed drug eruption (bullous or non-bullous) to Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN). Our previous findings of drug-specific genetic markers related to drug eruptions (e.g. HLA-B*1502) for carbamazepine-induced SJS/TEN, HLA-B*5801 for allopurinol-induced SJS/TEN, and HLA for phenytoin-induced SJS/TEN (DRESS) are important steps for the implementation of personalized medicine by performing genetic tests before prescribing risk medications. It has been known that the HLA associations in drug allergy is more than just a genetic marker and has a functional role as well. This reaction can be mediated by CD8+cytotoxic T lymphocytes (CTLs) in an HLA-restricted immune reactions. CTLs-associated cytokines/cytotoxic proteins, such as IL-15 and granulysin are important immune molecules responsible for cytotoxic mechanism and are correlated with the disease severity in patients with SJS/TEN. The role of the drug-specific T cells and their T-cell receptors (TCR) has also been clarified. A public αβ TCR is identified from the CTLs of patients with SJS/TEN, with its expression showing drug/phenotype-specificity. The public αβ TCR has binding affinity for specific and its structural analogs, thereby mediating the immune response and demonstrating an essential role of TCR in the immune synapse mediating SJS/TEN. Currently, there is still no standardized guideline for the treatment of SJS/TEN. TNF-α is a proinflammatory cytokine and also a mediator, triggering keratinocyte death. Our recent study of randomized controlled clinical trial of biologic anti-TNF-α for patients with SJS/TEN a beneficial effect for patients with SJS/TEN, including lower mortality and shorter time for skin healing. More specific therapeutics targeting immune mechanism of SJS/TEN as well as DRESS are urgent to improve the high mortality and related complications of SCAR in the near future.

SY-25 (D-3) -3 Diagnostic test and biomarkers in SCAR

Elizabeth J Phillips (Medicine, Pharmacology, Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, USA)

Severe cutaneous adverse drug reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are diseases that lead to significant short- and long-term sequelae and contricted future drug treatment options. The maintain of treatment is early diagnosis and discontinuation of all implicated drugs. Drug causality is often complicated by the presence of multiple implicated drugs at the time of presentation. Our understanding of SCAR has been fueled by the discovery that SJS/TEN and DRESS are MHC class I restricted diseases which has fueled prevention and screening efforts as well as early diagnosis for some drugs and understanding of immunopathogenesis. Biological markers such as granulysin may be useful adjuncts to clinical appearance for early recognition of SJS/TEN. In vitro and ex vivo assays such as ELLISpot and lymphocyte transformation test have been limited by lower sensitivity as have in vivo testing strategies such as patch testing. Single cell analyses of samples from the site of tissue damage are informative to identify a dominant TCR, transcriptome and proteome signatures of the antigen driven CD8+ T cells and other cells of interest. These multidimensional approaches will be the key to understanding both the immunopathogenesis, why the minority of patients with a risk HLA allele develop SCAR as well as novel diagnostic approaches to SCAR in the future.
Dendritic cells (DCs) comprise heterogeneous subsets, functionally classified into conventional DCs (cDCs) and plasmacytoid DCs (pDCs), and cDCs were further divided into type I cDC (cDC1) lineage for CD8α⁺ and CD103⁺ cDCs, and cDC2 lineage for CD11b⁺ and CD172a⁺ cDCs on the basis of their distinct developmental pathway and function. DCs are considered to be essential antigen (Ag) presenting cells (APCs) that play crucial roles in activation and fine-tuning of innate and adaptive immunity under inflammatory conditions, as well as induction of immune tolerance to maintain immune homeostasis under steady-state conditions. Sublingual immunotherapy (SLIT) is established in IgE-dependent respiratory allergens, such as allergic rhinitis and rhinoconjunctivitis, in clinical setting to grass or tree pollens, as well as house dust mites as an effective and safety profile with rare incidence of anaphylaxis, conventional alternative allergen-specific immunotherapy (AIT) to subcutaneous immunotherapy (SCIT). However, the efficacy of SLIT for other allergic disorders and how it controls allergic pathogenesis remain unclear. Here, we show the pre-requisite role of cDCs in submandibular lymph nodes (ManLN) in the effectiveness of SLIT for the treatment of murine allergic disorders. While SLIT suppresses the development of allergic asthma and food allergy as well as systemic anaphylaxis, accompanied by impaired Ag-specific CD4⁺ effector T (T-ɛ) responses and antibody productions, the deficiency of cDCs or CD4⁺Foxp3⁺ regulatory T (T-reg) cells abrogates the protective effect of SLIT against allergic disorders. Furthermore, sublingual antigenic application induces Ag-specific CD4⁺Foxp3⁺ T-reg cells in draining ManLNs, but not other lymphoid tissues, whereas their generation is impaired in the absence of cDCs. In ManLNs, migratory 1-A/-E⁺CD11c⁺CD11b⁺ cDCs are superior to migratory 1-A/-E⁺CD11c⁺CD103⁺ cDCs and resident 1-A/-E⁺CD11c⁺ CD11b⁺ cDCs for the generation of Ag-specific CD4⁺Foxp3⁺ T-reg cells, and that is reflected by their dominance in the tolerogenic features to favor this program. Thus, ManLNs are privileged sites in triggering mucosal tolerance mediating protective effect of SLIT on allergic disorders that requires a tolerogenesis of migratory CD11b⁺ cDCs.

**SY-26 (B-5) -2** Regulatory T cells in allergic disorders
Talal Chatila (Division of Immunology, Boston Children’s Hospital; Department of Pediatrics, Harvard Medical School, USA)

Whereas allergic diseases are commonly appreciated as arising from exaggerated type 2 immune effector mechanisms, attention has recently shifted to the role of aberrant immune regulation in disease pathogenesis, especially as relates to altered function of regulatory T cells (Treg cells). Tolerogenic circuits centered around different subsets of tissue Treg cells, such as ROR γ T. Treg cells in the gut, play a key role in sustaining immune tolerance to allergens at the different mucosal interfaces. However, in the context of pro-allergic inflammatory signals such as those triggered by dysbiosis, epithelial cell injury and/or exposure to particulate pollutant matter, Treg cells may shift toward pathogenic phenotypes that promote and perpetuate disease. Key molecular pathways involved in tissue-specific pathogenic Treg cell subversion are beginning to be identified, including Th2 cell-like reprogramming relevant to food allergy and IL-6-mediated reprogramming relevant to asthma. Therapeutic interventions to aim at stabilizing tissue Treg cells and prevent their pathogenic reprogramming may include immunomodulatory bacteria and their metabolites, and these directed at destabilizing cytokines receptor pathways including IL-4 and IL-6 receptors. These advances highlight opportunities for novel therapeutic strategies that aim to re-establish immune tolerance in chronic allergic diseases.

**SY-26 (B-5) -3** Novel B cell subsets and immune regulation
Mübeccel Akdis (Swiss Institute of Allergy and Asthma Research (SIAF), Switzerland)

The function of B cells has long been thought to be limited to the generation of immunoglobulin-producing plasma cells. However, B cells can exert a more diverse range of immune-effector and regulatory functions. Distinct functional B cell subsets have been identified based on their cytokine production profiles. Immunosuppressive B regulatory (Treg) cells and other potential B cell subsets such as B effector (Bε) 1 and Bε2 cells, as well as IL-17-producing B cells have been reported. Angiogenesis is an essential physiological process that occurs during embryogenesis, normal tissue development and repair after injury. Through a controlled series of events, angiogenesis allows new vessels to grow from pre-existing vessels in order to meet the physiological needs of tissues. Angiogenesis also plays a role in tumor growth and is involved in tissue remodeling in chronic inflammatory conditions such as asthma and eosinophilic esophagitis (EoE). In this study we used transcriptomics analysis of immortalized B cell clones to identify an IgG4+B cell subset with a unique function. These B cells are characterized by simultaneous expression of pro-angiogenic cytokines including VEGF, Cyr61, ADAM, FGF2, PDGF and MDK. Consequently, supernatants from these clones efficiently promote endothelial cell tube formation. We identified CD49b and CD73 as surface markers identifying pro-angiogenic B cells. Circulating CD49b⁺CD73⁺ B cells showed significantly increased frequency in melanoma and eosinophilic esophagitis patients, two diseases that are associated with angiogenesis. In addition, tissue-infiltrating IgG4⁺CD49b⁺CD73⁺B cells expressing pro-angiogenic cytokines were detected in EoE and melanoma patients. Our results demonstrate a novel pro-angiogenic B cell subset characterized by expression of CD49b, CD73 and pro-angiogenic cytokines.
Symposium 27
Allergen Immunotherapy for Allergic Rhinitis

SY-27 (E-3) -1 Novel mechanisms of immune tolerance for allergen immunotherapy
Mohamed Shamji (Imperial College London National Heart and Lung Institute; Asthma UK Centre in Allergic Mechanisms of Asthma, UK)

Allergen immunotherapy is effective in patients with IgE-dependent allergic rhinitis and asthma. When immunotherapy is given continuously for three years, there is a persistent clinical benefit for several years after its discontinuation. This disease-modifying effect is both antigen-specific and antigen-driven. Clinical improvement is accompanied by decreases in numbers of effector cells in target organs, including mast cells, basophils, eosinophils, and type 2 innate lymphoid cells. Immunotherapy results in the production of blocking IgG1/IgG4 antibodies that can inhibit IgE-dependent activation mediated through both high-affinity IgE receptors (FceRI) on mast cells and basophils and low-affinity IgE receptors (FcεRII) on B cells. Suppression of Th2 immunity can occur as a consequence of either deletion or anergy of antigen-specific T cells; induction of anti-inflammatory T cells and the B-cell compartment. Recent data highlight a clinical remission against allergen exposure. In Japanese cedar/cypress pollinosis (JCCP), the most prevalent allergic rhinitis in Japan, both subcutaneous (SCIT) and sublingual (SLIT) immunotherapy is currently available without age limitation. However, SLIT has become popular due to a fewer risk of systemic reactions and a painless in addition to its efficacy. Patients showing polysensitization is getting popular worldwide. In Japan, a high proportion of AR patients were sensitized to both house dust mite (HDM) and Japanese cedar/cypress pollen. Because it remains unclear whether co-administration of two allergen extracts, so called “dual SLIT” is safe and effective, we conducted a clinical trial to examine the safety of dual SLIT with HDM and JCP tablets in 2018 (n=109). Our result shows that no new safety concerns were identified moving from mono to dual SLIT tablet regimens involving JCP and HDM SLIT tablets. The safety profiles were similar regardless of which SLIT tablet was administered first. Efficacy of AIT with Japanese cedar pollen extract is lessened during the period of Japanese cedar pollen dispersal when the dispersal is high. This is because of unique allergen component in Japanese cypress pollen, identified as Cha o 3. Cha o 3 is a glycoprotein with approximately 63 kDa molecular weight. It shows biological activity of cellulase. Japanese cedar pollen contains such a component showing 85% homology to Cha o 3, denominated as Cry j 4. Interestingly, content of Cry j 4 in Japanese cedar pollen extract is quite few as compared with that of Cha o 3 in Japanese cypress pollen extract. These results suggest that AIT with Japanese cedar pollen extracts cannot induce enough immune tolerance to Cha o 3, and show decreased efficacy when Japanese cypress pollen dispersal is high. In the session, role of salvia in the efficacy of SLIT with Japanese cedar pollen for JCCP is discussed.

SY-27 (E-3) -2 Allergen immunotherapy for Japanese cedar/cypress pollinosis
Mitsuhiko Okano (Department of Otorhinolaryngology, International University of Health and Welfare Narita Hospital, Japan)

Allergen-specific immunotherapy (AIT) is indicated for patients with allergic rhinitis (AR) resistant to standard pharmacotherapy including anti-histamines and intranasal corticosteroids or those who want a clinical remission against allergen exposure. In Japanese cedar/cypress pollinosis (JCCP), the most prevalent allergic rhinitis in Japan, both subcutaneous (SCIT) and sublingual (SLIT) immunotherapy is currently available without age limitation. However, SLIT has become popular due to a fewer risk of systemic reactions and a painless in addition to its efficacy. Patients showing polysensitization is getting popular worldwide. In Japan, a high proportion of AR patients were sensitized to both house dust mite and Japanese cedar/cypress pollen. Because it remains unclear whether co-administration of two allergen extracts, so called “dual SLIT” is safe and effective, we conducted a clinical trial to examine the safety of dual SLIT with HDM and JCP tablets in 2018 (n=109). Our result shows that no new safety concerns were identified moving from mono to dual SLIT tablet regimens involving JCP and HDM SLIT tablets. The safety profiles were similar regardless of which SLIT tablet was administered first. Efficacy of AIT with Japanese cedar pollen extract is lessened during the period of Japanese cedar pollen dispersal when the dispersal is high. This is because of unique allergen component in Japanese cypress pollen, identified as Cha o 3. Cha o 3 is a glycoprotein with approximately 63 kDa molecular weight. It shows biological activity of cellulase. Japanese cedar pollen contains such a component showing 85% homology to Cha o 3, denominated as Cry j 4. Interestingly, content of Cry j 4 in Japanese cedar pollen extract is quite few as compared with that of Cha o 3 in Japanese cypress pollen extract. These results suggest that AIT with Japanese cedar pollen extracts cannot induce enough immune tolerance to Cha o 3, and show decreased efficacy when Japanese cypress pollen dispersal is high. In the session, role of salvia in the efficacy of SLIT with Japanese cedar pollen for JCCP is discussed.

SY-27 (E-3) -3 The EUFOREA model to improve care in allergic rhinitis
Peter Hellings (Department of Otorhinolaryngology, KU Leuven, Belgium)

European experts in respiratory and allergy fields join forces in EUFOREA (European Forum for Research and Education in Allergy and Airways diseases; www.euforea.eu) with the aim to arrest the epidemics of chronic respiratory diseases including respiratory allergy. The epidemics of respiratory allergies, affecting up to 1/3 of the total population, can be arrested in part by 1) implementation of preventive strategies in real life, 2) education of patients and physicians on optimal care pathways, and 3) political and patient advocacy for better understanding and support of allergy sufferers. High-quality digital education and personalised guidance of both patients and physicians in care is the EUFOREA model to improve outcomes in the 21st century. AIT specific actions of EUFOREA before and during COVID-19 will be presented in the context of an open invitation to partner and join forces. The coordinated action of all stakeholders in the allergy field, i.e. patients, pharmacists, primary care physicians, and a variety of specialists, is key to success of the mission of EUFOREA.
Ocular allergy treatment remain a major concern for allergists. A systematic review of relevant publications was recently published by the Interest group on Ocular allergy (IOGA) of EAACI. Furthermore main questions was re-evaluated through a Delphi questionnaire to reach consensus on treatments. Recently we add some inputs related to COVID-19 infected patients. Non pharmacological means should be systematically advised for benign form as well as for severe forms of OA: wearing glasses, lid hygiene, cold compresses and eye washing, repeated use of tear substitutes to stabilize tear film. Topical antihistamines, mast cell stabilizers, or double - action drugs are the first choice of treatment. All of them are effective in reducing signs and symptoms of the early phase inflammatory reaction yielded by IgE mediated hypersensitivity. Rhinitis is commonly associated with IgE mediated ocular allergy. In such cases local or systemic treatments can be used for the time and severity of ocular signs. Indications for second line treatments include systemic antihistamines and leukotrienes inhibitors. Local non-steroidal anti-inflammatory drugs are not of common use in most countries in Europe. Third line treatment consist in topical steroids. Steroid eye drops play a pivotal role in the therapeutic pattern of ocular allergy, for many reasons. Pulse protocols are recommended to control breakthroughs of allergic keratoconjunctivitis when symptoms become too intense, or to disrupt an emerging complication. Managing of long term topical steroids need control of the ophthalmologist. Safety and optimal dosing regime are still a major concern. Fourth line treatment is reserved to specialists for selected cases of severe vernal and atopic keratoconjunctivitis. Topical calcineurin A inhibitors are used in steroid dependent/resistant cases of severe allergic keratoconjunctivitis, tacrolimus ointment 0.03% or 0.1% is mostly reserved to selected cases of AKC. Some biologics were assayed. Allergen - specific immunotherapy may be considered in cases of failure of first - line treatments or to modify the natural course of OA disease. The wide spectrum of drugs available to control ocular allergy highlight the importance of close collaboration between specialists to cope with Ocular allergy.

Treatment of severe allergic conjunctivitis in Japan, focus on immunosuppressive eye drops

Drug treatment is the preferred treatment for allergic conjunctival diseases in Japan. The first option in antiallergic eye drops, which are the basic treatment for allergic conjunctivitis, followed by the differential use of steroid eye drops as necessary according to the severity. For severe allergic conjunctivitis such as Vernal keratoconjunctivitis (VCK) and Atopic keratoconjunctivitis (AKC), additional use of immunosuppressive eye drops. At present, 2 kinds of immunosuppressive eye drops (cyclosporin and tacrolimus) have been approved as treatment drugs for VCK and AKC. Immunosuppressive eye drops are expected to have equivalent or better effects than steroid eye drops. We evaluated the effectiveness and safety of cyclosporine 0.1% aqueous ophthalmic solution in 594 patients with VCK and AKC for 6 months. All scores for symptoms and signs significantly decreased from Month 1 through Month 6 of treatment in both VCK and AKC. In both VCK and AKC, approximately 30% of steroid users were able to discontinue topical steroids. Next, we examined the efficacy of tacrolimus ophthalmic suspension 0.1% in treating severe allergic conjunctivitis. This was a multicenter, randomized, double-masked, placebo-controlled clinical trial. 64 patients with severe allergic conjunctivitis in whom topical antiallergic agents and corticosteroids had been ineffective were randomized to tacrolimus or placebo treatment for 4 weeks. Mean change from baseline in total score for objective signs was significantly greater in the tacrolimus than in the placebo group. Another prospective observational study included 1436 patients with refractory allergic conjunctivitis whose condition had responded poorly to conventional antiallergic drugs and/or topical steroids and/or topical cyclosporine. Total signs and symptoms score significantly decreased after 1 month of treatment. Giant papillae and corneal lesions were also reduced by tacrolimus eye drops use. The drug proved effective in patients whose condition did not respond well to topical cyclosporine therapy. Therefore, in Japan, the treatment of immunosuppressive eye drops is recommended to the first choice for VCK and AKC, especially for children. Because steroid eye drops frequency elevate the intraocular pressure in children.
Symposium 29
Risk Factors for Pediatric Allergies

SY-29 (P-6) -1 Particulate matter as a risk factor in children with atopic dermatitis

Kangmo Ahn (Department of Pediatrics, Samsung Medical Center, Republic of Korea)

Atopic dermatitis (AD) is a chronic inflammatory skin disease most frequently found in children. Clinically, AD symptoms such as pruritus, erythema, xerosis and sometimes exudate repeatedly waxed and waned because they are triggered by a variety of environmental factors including air pollution. Particulate matter (PM), one of the major air pollutants, is a growing concern particularly in developing countries with rapid industrialization and urbanization. PM exposure is associated with the severity or exacerbation of AD. In 91,642 US children aged 017 years, moderate-severe eczema was associated with higher mean annual PM2.5. In a panel study to follow AD children for 18 months, outdoor PM10 concentration was associated with AD symptoms with lag effect. A time series data analysis in an industrial urban area showed that adjusted odds ratio (OR) for AD symptoms was 1.39 for a 10 g/m3 increase of PM2.5 concentration. The significant harmful effect of PM2.5 on AD symptoms was influenced by a dry, moderate weather type according to spatial synoptic classification (SSC). Those studies suggest that short-term exposure to PM is associated with skin symptoms in AD. Recently, our in vitro study using a human 3-dimensional organotypic skin model showed that direct exposure of human keratinocytes to PM2.5 inhibited the expression of skin barrier structural components at RNA and protein levels in the AhR-dependent pathway. PM2.5 also increased the expression of pro-inflammatory cytokines such as thymic stromal lymphopoietin (TSLP) which can further downregulate filagrin (FLG) expression. More importantly, we showed that PM2.5 and Th2 cytokines synergistically inhibit FLG expression at RNA and protein levels. Clinically our results imply that AD skin with Th2-skewed immune responses is more susceptible to PM exposure. In conclusion, PM exposure impairs the skin barrier structurally and functionally, and subsequently aggravates AD symptoms. Environmental control to minimize the exposure to PM is of importance for the proper management of AD in children.

SY-29 (P-6) -2 Risk factors for pediatric allergies, food allergy

Philippe Eigenmann (Department of Woman, Child and Adolescent, University Hospital of Geneva, Switzerland)

IgE-mediated food allergy is a disease present in approximately 5% of young children. It has been well recognized for decades that a personal or familial atopic predisposition is a risk factor for developing a food allergy. The usual first manifestation of this atopic predisposition is atopic dermatitis, explaining why children with atopic dermatitis have a higher risk of developing food allergies. These prevalence has been defined to be approximately one third of children with moderate to severe atopic dermatitis having an associated food allergy. It has also been well defined that children presenting with egg allergy in infancy, have a higher risk of developing later peanut allergy. Defining a risk also implies prevention, whenever effective. Primary prevention of food allergy has been studied by various dietary interventions during pregnancy, breastfeeding, or early infancy; nevertheless with low of no efficiency. The most efficient prevention for food allergy is probably early introduction of small amounts of eggs as shown in recent studies. With regard to secondary prevention of peanut allergy when the child has already allergies, early introduction of peanut has been shown to be effective for prevention.

SY-29 (P-6) -3 Risk factors for allergic asthma in children

Jio-Yao Wang (Center for Allergy and Clinical Immunology Research (ACIR) Department of Pediatrics, College of Medicine, National Cheng Kung University, Taiwan)

Asthma is the leading cause of chronic (long-term) illness in children. There are many risk factors for developing childhood asthma. These include, allergies, family history of asthma, allergies and atopy (a genetic, or inherited, likelihood to develop allergies and asthma), frequent respiratory infections, low birth weight, exposure to tobacco smoke before and/or after birth, living near traffic freeways, and being male. In fact, genetic susceptibility, environmental change, and the immunological development are the three major intertwined factors for the allergic disorders to occur in young infants. In children who are under five years of age, the most common cause of asthma exacerbation is upper respiratory viral infections such as rhinovirus (RV) and respiratory syncytial virus (RSV). Epithelial damages, disruptions and inflammations are the main pathogenesis for the initiation of type 2 inflammatory response in the bronchial airways. How the microbiota that colonized in the mucosal epithelial and interact with host innate immunity that lead to type 2 immune inflammation is the recent hot topics to understand the role of lung microbiome in allergic asthma of children. In this talk, I will present our studies in the risk factors of childhood allergic asthma in Taiwan, and try to formalize a prevention strategy for the development of allergic asthma, which has been rising as most common chronic disorder for children in Asia Pacific regions.
Symposium 30
Severe Urticaria

SY-30 (D-4) - 1  Pathogenesis of urticaria refractory to antihistamines
Michihiko Hide (Department of Dermatology, Hiroshima University, Japan)

Urticaria developing wheal-and-flare reactions for more than 6 weeks is classified as chronic urticaria (CU), and approximately half of them may be refractory to antihistamines. The refractoriness to antihistamines may be due to either a large amount of histamine release beyond the capacity of administered antihistamine or crucial involvement of other mediators in the process of wheal formation. In fact, a substantial population of patients with CU refractory to a standard dose of antihistamine may be controlled by higher doses of antihistamines. Moreover, mast cells release histamine together with a variety of other mediators, cytokines and proteases, which also induce wheal-and-flare reactions of the skin. Histological observation of mast cell degranulation in skin lesions, and the effect of newly developing mast cell-targeted medications, such as Bruton-kinase inhibitors and antibodies, are first line in treatment. Furthermore, various geographic distributions and kinetics of wheals are unique to CU and not commonly developed in other subtypes of CU or anaphylaxis. To explain the involvement of all these players and kinetics of eruptions observed in urticaria, we proposed a formula based on a reaction-diffusion model assuming the presence of self-activating and inhibitory functions of histamine (mediator) release from mast cells. Of note, only a few percent release of histamine from mast cells triggered consequential reactions of mast cells and reproduced wheal formation in silico resembling urticaria in patients. Further studies based on this model is expected to reveal effective targets for new treatments of urticaria.

SY-30 (D-4) - 2  Diagnostic tests and biomarkers in severe urticaria
Sarbjit S Saini (Johns Hopkins University, USA)

A biomarker is a characteristic that is measured and evaluated as an indicator of a normal biological process, disease process or pharmacologic response to a therapy. In CU, such biomarkers are used to distinguish CU from other diseases, evaluate disease severity, or predict response to treatment. Diagnostic tests are used to establish the diagnosis and could also serve as a biomarker. Some biomarkers for CU disease and severity are summarized below and will be discussed. A unique feature of CU is basophilia and this feature is correlated to disease severity. Basophil IgE receptor histamine release profiles are also unique and segregate into two groups. One group shows histamine release similar to normal subjects (>10% release of total cellular histamine content) and is termed CU-responder. The other subset is called CU non-responders and has suppressed histamine release responses (<10% of total histamine content). These functional subsets are stable in active disease and revert towards normal in disease remission. A third subset are those with extreme basophilia. In natural disease remission, basophilia improves. Basophil functional phenotypes are linked to outcomes, with longer disease observed in CU responder phenotype, but more severe symptoms in non-responders. There are emerging observations for baseline biomarkers to predict therapeutic response. Basophilia and eosinopenia have been linked to antihistamine-resistant CU. Lower baseline total serum IgE has been proposed as a negative predictor for omalizumab response. In studies of omalizumab treatment of CU, an increase in basophil blood levels reflected clinical symptom improvement. Other potential predictors include thyroid antibodies and immune measures such as CRP.

SY-30 (D-4) - 3  Current and future management of chronic urticaria
Mario Sánchez-Borges (Allergy and Clinical Immunology, Centro Médico Docente La Trinidad, Venezuela)

According to the International Guidelines for the definition, classification, diagnosis and management of urticaria, the treatment of chronic spontaneous urticaria (CU) is based on a first line consisting in non-sedating anti-H1 antihistamines at recommended doses. If no improvement is observed, the guidelines recommendation is to increase antihistamine dose up to 4 times. However, according to some experts about 50% of CU patients are not controlled with antihistamines administered in conventional or increased doses. In patients unresponsive to antihistamines add on therapy with monoclonal anti-IgE antibodies (Omalizumab) is indicated, and alternatively Cyclosporine could be administered to patients who do not respond to anti-IgE or in cases where this medication is not available, although this immunosuppressor has a less favorable profile of adverse effects than Omalizumab, needing especial attention to the possibility of renal toxicity. Currently, Omalizumab is the only biologic drug approved by regulatory agencies as add-on therapy for the treatment of adult and adolescent patients (aged >12 years) with CU who remain symptomatic despite optimized H1-antihistamine therapy. Additionally, there are a number of other biologicals that have been proposed for the treatment of severe CU. Some of them are under investigation, and others have been tried off-label in small series of patients. They include other monoclonal anti-IgE antibodies such as Ligilizumab and Quilizumab, Intravenous immunoglobulin (IV Ig), tumor necrosis factor alpha (TNF-) inhibitors, anti-CD20 (Rituximab), IL-1 inhibitors, Syk inhibitors, PDGR2 antagonists, Btk inhibitors, and anti-Siglec-8. Potential and future therapies for refractory chronic urticaria will be discussed in this Symposium.
Symposium 31
Precision Medicine

SY-31 (M-6) -1  Allergen immunotherapy-AIT
Giorgio Walter Canonica (Internal Medicine, Humanitas University & Research Hospital, Italy)

The introduction of personalized medicine (PM) has been a milestone in the history of medical therapy, because it has revolutionized the previous approach of treating the disease with that of treating the patient. AIT has been reported to be a real example of precision medicine, when we published this concept in 2015 (Canonica et al WAOJ 2015). From precision medicine we should move to personalized medicine, where the patient is the real target of the best treatment possible. This new approach has already improved the precision of allergy diagnosis and is likely to significantly increase, through the higher performance achieved with the personalized treatment, the effectiveness of allergen immunotherapy by enhancing its already known and unique characteristics of treatment that acts on the causes. The step by step approach, will be described and discussed.

SY-31 (M-6) -2  Atopic dermatitis
Kenji Kabashima (Department of Dermatology, Kyoto University Hospital, Japan)

Atopic dermatitis (AD) is the most common inflammatory skin disease in the industrialized world, and has multiple etiologies. Over the past decade, data from both experimental models and patients have highlighted the primary pathogenic role of skin barrier deficiency in AD. Increased access of environmental agents into the skin results in chronic inflammation and contributes to the systemic “atopic (allergic) march”. In addition, persistent skin inflammation further attenuates skin barrier function, resulting in a positive feedback loop between the skin epithelium and the immune system that drives pathology. Understanding the mechanisms of skin barrier maintenance is essential for improving management of AD and limiting downstream atopic manifestations. In this session, we review the latest developments in our understanding of the pathomechanism of atopic dermatitis, with a particular focus on skin barrier, type 2 immunity, and pruritus. These integrated knowledges will lead to the advancement of precision medicine in atopic dermatitis.

SY-31 (M-6) -3  Genetic susceptibility to asthma in the era of precision medicine
Kathleen Barnes (Colorado Center for Personalized Medicine, Department of Medicine, University of Colorado, USA)

Asthma is a common, complex disease where both genetic factors and environmental exposures control susceptibility and disease progression. With the publication of initial efforts in sequencing the human genome the opportunity to genotype markers directly in genes of interest was greatly expanded. Relying upon one of the simplest of these polymorphisms, single nucleotide polymorphisms (SNPs), this advancement allowed researchers to expand genetic studies beyond linkage toward the genetic association study design, and ultimately, genome-wide association studies (GWAS). To date, there are over 247 significant associations from multiple GWAS’s for asthma and its related traits across the genome. Polygenic risk scoring, or PRS, is a relatively new technique in which a number is derived from variation in multiple genetic loci and their associated weights (typically from multiple GWAS studies of a specific trait) to predict risk of disease. PRS has been enabled by the availability of large research and institutional biobank-based GWAS data. A challenge with both of these approaches is that the vast majority of publicly available GWAS data are derived from populations of European ancestry, and the portability of PRS to other ancestry groups is unclear. Another tool in precision medicine being used with success in disentangling the genetic basis of asthma is harnessing the rich data captured in the electronic health record (EHR) and combining it with genomic data. With this, researchers are leveraging phenome-wide association studies, or PheWAS, to test for association for a single variant across many different traits, or subphenotypes of a specific trait, in an unbiased manner. Success in leveraging precision medicine tools in understanding the genetics of asthma is dependent upon the emergence of ancestrally diverse and sufficiently large institutional biobanks. A growing federation of biobanks, including the Colorado Center for Personalized Medicine’s biobank, is enabling novel discoveries in asthma, including genetic testing to reveal predisposition to disease, accurate disease diagnosis enabling individualized treatment strategies, and improved outcomes through targeted treatments and reduced side effects (i.e., pharmacogenetics).
**Symposium 32**

**Learning from Birth Cohort Studies**

**SY-32 (P-7)-1 Early-life origins of COPD**

Adnan Custovic (National Heart and Lung Institute, Imperial College London, UK)

Longitudinal studies suggest that lung function tracks from school-age to adulthood. FEV1 in early adulthood, at its physiological plateau, is as important in the genesis of chronic obstructive pulmonary disease (COPD) as rapid decline of lung function in later years. Furthermore, low FEV1 in the third decade of life is associated with early mortality from all causes. Data-driven analyses identified a group of individuals with persistently low lung function which may be partly established at birth, comprising nearly 1 in 10 people in the population. We have provided evidence that within a population, there are four groups of individuals with distinct trajectories of FEV1 from pre-school age to adolescence, which extend to adulthood. Persistently low trajectory comprised approximately 1 in 20 people and was characterised by low lung function in the third decade of life, at the time of the maximal attained physiological plateau beyond which lung function starts to decline with aging. Compared to other trajectories, FEV1 in this group was up to 25% lower, and FEV1/FVC ratio was up to 10% lower. Analysis of lung function trajectories in the Tasmanian Longitudinal Health Study described similar trajectories. Individuals in persistently low trajectory were at higher risk of COPD, with or without additional adverse exposures (such as active smoking) in adulthood. Together, these studies elucidate the developmental patterns of lung function through life-course and provide evidence that different factors affect growth from those affecting the decline of lung function. The persistently low lung function trajectory is determined by early-life events which include maternal smoking, recurrent episodes of wheeze with severe exacerbations in the first three years of life, and multiple early allergic sensitization. Among these individuals, COPD has predominantly early-life origins. We urgently need to reduce tobacco smoke exposure in early childhood, and develop strategies to minimising the risk of early childhood exacerbations of wheezing and of early-life allergic sensitization, to reduce the risk of low lung function trajectory and future COPD development.

**SY-32 (P-7)-2 JECS and T-child study-cohort studies in Japan**

Kiwako Yamamoto-Hanada, Yukiko Ohya (Allergy Center, Medical Research Center for Japan Environment and Children’s Study (JECS), National Center for Child Health and Development, Japan)

1. Japan Environment and Children’s Study (JECS) is a nationwide, multicenter, birth cohort study conducted by the Ministry of Environment of Japan. A general population of 103,099 pregnant women was enrolled in the JECS at 15 regional centers across Japan from April 2011 to March 2014. The prevalences of asthma, allergic rhinitis (hay fever), atopic dermatitis, and food allergy among 99,013 mothers was 10.9, 36.0, 15.7 and 4.8% respectively. IgE sensitization was found in 73.9% of mothers (Yamamoto-Hanada, W AO Journal, 2017). Maternal mental health depression and QoL) was associated with maternal allergic diseases (Yamamoto-Hanada, JACI in Practice, 2018). Maternal allergy was associated with SGA births (Saito Abe, Allergy, 2018). We found three clusters of children exhibiting different cytokine/chemokine patterns (Yamamoto-Hanada, Cytokine, 2019).

2. The Tokyo Children’s Health, Illness and Development Study (T-CHILD Study) is a birth cohort study of the general population conducted at the National Center for Child Health and Development (NCCHD) in Tokyo. Participants will be followed-up until they reach adulthood. In total, 1701 pregnant women were recruited between 2003 and 2005, and 1550 newborns were included in the cohort. Five phenotypes of wheeze and four types of atopic dermatitis were identified (Yang, PAI, 2018; Yamamoto-Hanada, AL, 2019). The prevalence of allergic rhinitis increased considerably from 8% of age to 9 years of age (10.9%-31.2%). Prevalence of IgE sensitization to all allergens at 9 years of age was 74.8%. That to Der f 1 (mites) and was. Cry j 1 (Japanese cedar) was 94.3% and 77.8% respectively (Yamamoto-Hanada, W AO Journal, 2020). FLG loss-of-function mutations were significantly associated with infantile onset AD (Koseki, Journal of Human Genetics, 2019). Oral contraceptives before pregnancy, Beta-2 receptor agonist exposure in the uterus, antibiotics during first two years of life were associated with offspring allergic features (Yamamoto-Hanada, Al 2016; Ogawa, PAI, 2017: Yamamoto-Hanada, ANAI, 2017).

**SY-32 (P-7)-3 Early life gut microbiome in allergic diseases**

Soo Jong Hong (Department of Pediatrics, Childhood Asthma and Atopy Center, Humidifier Disinfectant Health Center, Asan Medical Center, University of Ulsan College of Medicine, Republic of Korea)

The ‘microflora hypothesis’ proposes that the hygienic western life style limits general microbial exposure and alters the colonization of the human gut, which shapes immune development and promotes the development of allergic diseases. Infancy is a critical period for the colonization of the gut microbiome. Perturbation of the infant gut microbiome can shape the development of the immune system and link to the risk of allergic diseases. However, the underlying mechanism, the cause-effect relationship, and particularly the identification of helpful individual microbes and microbial compounds remain to be investigated. We investigated the composition and functional differences of gut microbiome according to feeding type in COCOA birth cohort by using pyrosequencing and whole-metagenome sequencing.

We found that the composition of gut microbiome differed according to feeding type. Furthermore, the reduction of microbiome genes for oxidative phosphorylation, PI3K-Akt signaling, estrogen signaling, NOD-like receptor signaling, and antigen processing and presentation induced by reduced colonization of mucin-degrading bacteria was associated with stunted immune-development in the AD infants. These findings suggest that the colonization of mucin-degrading bacteria and their contribution to innate immune development in gut plays a crucial role in infants with AD. In addition, this mucin degrading bacteria suppressed allergic inflammation via SCFAs in AD mouse model. The roles of gut microbiota on the natural course of AD are not yet fully understood. We investigated whether the gut microbiota at 6 months of age could affect the natural course of AD in early childhood. We found that low levels of Streptococcus and high amounts of Akkermansia were evident in transient AD cases and low Clostridium, Akkermansia and high Streptococcus were found in children with persistent AD. These findings suggest that compositions and functions of the early gut microbiome are related to not only AD development but also natural courses.
Symposium 33
Problem to be Solved in Adult Asthma
SY-33 (I-8) -1  Problem to be solved in adult asthma: onset and risk factor
Anahi Yáñez (Department of Research, Allergy and Respiratory Disease Research Center, Argentina)

Asthma is a major global health problem and poses a significant health and socioeconomic burden worldwide. The prevalence of asthma differs geographically and varies ranging from 4% to 12% in elderly. Asthma in the elderly is associated with higher morbidity and mortality than asthma in younger subjects. The age at onset is a key determinant of different phenotypes in the elderly adults with asthma. Elderly subjects with Late Onset Asthma (LOA) have different clinical and physiological characteristics compared to those with Early Onset Asthma (EOA). Considerable mechanistic heterogeneity exists in such a complex population with multiple and diverse phenotypes. The phenotype of LOA is largely divided into two types according to the presence or absence of eosinophilic inflammation, T-helper (Th1) and non-Th2-associated LOA. Especially in Th2LOA related to rhinosinusitis, as pulmonary function at onset is poor and asthma exacerbations occur frequently, it is important to detect this phenotype in the early phase. Age-related declines in immune function, known as immunosenescence, also play a key role in the development of LOA. The coexistence of immunosenescence and viral infection promotes persistent inflammation. Today, advances in understanding different phenotypes in LOA, have shown that appropriate individual management of the disease is required in asthma in older adults.

SY-33 (I-8) -2  Asthma and COPD Overlap (ACO)
Takeshi Kaneko (Department of Pulmonology, Yokohama City University Graduate School of Medicine, Japan)

The Japanese Respiratory Society published guidelines for the management of asthma and chronic obstructive pulmonary disease (COPD) overlap (ACO), which provided definitions, diagnostic criteria, and treatment strategies. ACO is defined as "a disease that exhibits chronic airflow obstruction and has the characteristics of both asthma and COPD." ACO is characterized by a higher disease severity, higher susceptibility to exacerbations, and markedly reduced QOL and respiratory function than either asthma or COPD alone. According to the diagnostic criteria of ACO in the above-mentioned guidelines, the characteristic features of asthma include items such as the fractional exhaled nitric oxide (FeNO) test and assessment of reversibility of airway obstruction. However, these tests may be difficult for non-specialists to perform.

The basis of pharmacotherapy of ACO is a combination of anti-inflammatory therapy with inhaled corticosteroid (ICS) for asthma and bronchodilator therapy with a long-acting muscarinic antagonist (LAMA) and a long-acting beta2-agonist (LABA) for COPD. Recently, a triple combination (LAMA/LABA/ICS) inhaler was launched for COPD, and ACO is a good indication for its use. However, it contains a medium dose of ICS, which may be insufficient if the patient's asthma is severe.

In this symposium, I would like to discuss the problems of ACO diagnosis and treatment with reference to the guidelines that have been widely used in Japan.

SY-33 (I-8) -3  Elderly asthma in the era of aged population
Yoon-Seek Chang (Department of Internal Medicine, Seoul National University Bundang Hospital; Department of Internal Medicine, Inha National University College of Medicine; Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul National University, Republic of Korea)

Population aging is a global issue. Asthma is a chronic respiratory allergic disease that can occur in any age. The prevalence of asthma has two peaks in childhood and in the elderly. The prevalence of elderly asthma is increasing in the era of aged population (6.8~12.7% in Korea). The socioeconomic burden of asthma is especially high in the elderly. Asthma affects the quality of life and could be even life-threatening. Elderly asthma has different features from childhood asthma. Risk factors of asthma could be atopy, airway hyperresponsiveness, smoking, obesity, and others. Recent studies showed that the sensitization rate to inhalant allergens could be maintained until the age of early 70s, which differs from the old studies. However, atopy, sensitization to inhalant allergens, showed a different feature in the elderly. Interestingly atopy may not be the risk factor for elderly asthma. Recent studies showed that the sensitization to Staphylococcal enterotoxin and other proteins such as serine protease like protein D could be risk factors for elderly asthma. Disturbance of regulatory T cell subpopulations may be involved in the pathogenesis of elderly asthma. Recent microbiome studies showed different features in the young adult and elderly asthma. Rhinitis is a common comorbidity in the elderly asthma. Epidemiologic studies showed different sensitization pattern of inhalant allergens, and prevalence of rhinitis according to urbanization in the elderly. Asthma is an important cause of chronic cough, which is also true in the elderly together with upper airway cough syndrome and gastroesophageal reflux disease.
Symposium 34
Food Allergy Treatment

SY-34 (P-8) -1
Oral immunotherapy for food allergy

Sakura Sato, Motohiro Ebisawa (Department of Allergy, Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Japan)

Various treatments have been studied for IgE-mediated food allergy. Oral immunotherapy (OIT) has been a significant increase in published studies in the past decade. There have been reported OIT for peanut, cow’s milk, and hen’s egg. OIT can increase the threshold of reactivity to food allergens in the majority of food-allergic patients. However, the safety of OIT is a major concern. Adverse reactions commonly occur and eosinophilic GI diseases are sometimes observed during OIT. A recent meta-analysis of peanut OIT showed OIT was associated with an increased risk of adverse reactions and anaphylaxis compared to food avoidance. Some studies indicated recurrence of reactions to food allergens was observed after withdrawing OIT. In our study, 41% of the cohort of patients who had experienced allergic reaction to a causative food. Therefore, most patients need to continue to ingest food allergen to keep desensitization status. To improve the safety of OIT, recent studies have aimed at the efficacy endpoint for OIT to reduce the risk of adverse events on accidental ingestion. OIT with lower doses is associated with high compliance and lower risk of adverse reactions during OIT. OIT with adjuvants (Omalizumab, Dupilumab, probiotics, Food Allergy Herbal Formula-2) is now evaluating whether to enhance the efficacy and safety of OIT. A phase 3 trial of peanut OIT using a standardized product was found to increase the dose of allergen that could be safely ingested without symptoms. In early 2020, the Food and Drug Administration approved the product of the first treatments for peanut allergy, Palforzia, and accompanying protocol. Although OIT has still many obstacles to improve safety and long-term efficacy, it seems a desirable treatment option for food-allergic patients. However, we are still not sure that OIT can be a routine practice for food allergy in the future.

SY-34 (P-8) -2
Epicutaneous immunotherapy for the treatment of food allergy

Hugh A Sampson (Department of Pediatrics, Icahn School of Medicine at Mount Sinai, USA)

Epicutaneous immunotherapy (EPIT) introduces a minute (g) quantity of peanut protein through the skin, where it is taken up primarily by epidermal Langerhans cells and to a lesser extent by dermal dendritic cells via dendrites extended into hair follicles. These antigen-presenting cells (APCs) then transport the allergen to regional lymph nodes via the lymphatic system, thus largely eliminating systemic allergen circulation responsible for generalized adverse allergic reactions but consequently bypassing the rapid effector cell (mast cell/basophil) desensitization, i.e., “initiation phase,” seen with other forms of immunotherapy, e.g. subcutaneous and oral immunotherapy. In the regional lymph nodes, these APCs activate unique long-lived T regulatory cells (Tregs) that express multiple homing receptors, enabling migration to all major organs associated with the allergic response (skin, lung and gut). Here, Tregs directly suppress mast cell activation via the secretion of TGF-. In addition, allergen-loaded APCs activate T effector cells (Teffs) that promote B-cells to secrete protective IgG antibodies. Preclinical studies indicate that EPIT generates immunological memory through epigenetic remodeling of long-lived, stable Tregs and Teffs, resulting in sustained suppression of mast cell activation, allergy-associated Th2 cytokines and allergen-specific IgE, and enhancement of protective IgG. In the absence of the rapid “initiation phase”, the protective effect of EPIT takes more time to evolve, relying on the induction of Tregs and generation of allergen-specific IgG. Nevertheless, Phase II and III clinical trials in peanut-allergic children have demonstrated increased eliciting dose thresholds following peanut-EPIT, increased peanut-sIgG4, decreased peanut-sIgE, and increased sustained unresponsiveness and epigenetic changes compared to children treated with placebo. EPIT is a novel form of immunotherapy that safely activates a unique tolerogenic mechanism, which should lessen the risk of allergic reactions in peanut allergic patients following accidental ingestion of peanut protein.

SY-34 (P-8) -3
New treatments in food allergies

Alessandro Fiocchi (Department of Allergy, Pediatric Hospital Bambino Gesù IRCCS, Italy)

Foods responsible of food allergy cannot always be avoided, and oral Immunotherapy (OIT) cannot always be implemented. Especially in cases of multiple food allergy, the help of drug therapies is proving to be useful in order to achieve a reduction in the risk of anaphylaxis in children and affected patients. Among these new therapies, biological drugs stand out. We have so far some potential allergen-specific therapies, and some potential non-allergen specific treatments. Among the main candidate strategies, which will be discussed in this presentation, we will include: Allergen-specific approaches -Epicutaneous immunotherapy-Sublingual immunotherapy-Subcutaneous immunotherapy with inactivated allergens -Recombinant protein vaccine (EMP-123)-Synthetic peptide vaccine (PVX-108)-DNA- LAMP vaccine (ASP0929)-High-affinity mAb specific for food allergens, e.g. Ara h 2. b. Non-allergen specific approaches -Food Allergy Herbal Formula-2 (FAHF-2), a Chinese 9-herb preparation effective for preventing anaphylaxis in mice-T3H-promoting immune adjuvants such as TL1 agonists (B288, Cpg oligodeoxynucleotides) chitosan (a fungal cell wall component), and OMP-16 (a membrane protein from Brucella abortus)-Probiotics. Since we have specific monoclonal antibodies available for a variety of targets implied in the pathogenesis and development of foods the allergic disease, the idea of using them as a complement in oral immunotherapy practices or as a food allergy treatment in itself has been making its way into the scientific community. Among them, -Anti IgE (Omalizumab) alongside OIT-Omalizumab instead of OIT-Etokumab, directed against IL-33, a mediator necessary for sensitization to food allergens and allergic responses -Dupilumab, an anti-L4/anti-IL-13 receptor alpha antibody already approved for the treatment of asthma and atopic dermatitis, alongside OIT.-Dupilumab alone -Anti-IL-5 antibodies mepolizumab and reslizumab, specifically in EoE.
Symposium 35

Eosinophilic Inflammation in Airways

Bruce S Bochner (Department of Medicine, Division of Allergy and Immunology, Northwestern University Feinberg School of Medicine, USA)

Sialic acid-binding, immunoglobulin-like lectins (Siglecs) are single-pass transmembrane cell surface receptors found primarily on various leukocyte subsets. Most Siglecs, but not all, have conserved cytoplasmic signaling motifs that suggest they primarily function as inhibitory receptors. Among these, Siglec-8, first discovered in 2000, is expressed on human eosinophils, mast cells and weakly on basophils. Based on the work of several labs, it is now known that Siglec-8 engagement, either with specific antibodies or via multivalent, specific a 2,3-linked sialylated, sulphated artificial or endogenous glycan ligands, can result in a number of responses in vitro including reduced eosinophil survival. Examples of specific Siglec-8 glycan ligands identified by glycan array assays include 6-sulphated sialyl Lewis X and 6-sulphated sialyl LacNac. Its unique glycan ligand specificity has facilitated the discovery of endogenous virus ligands for Siglec-8, including several viruses that so far have been unappreciated lower airway samples using Siglec-8 affinity purification and mass spectrometry. Examples of such endogenous ligands isolated and identified from human airways include glycans displayed as sialylated keratan sulphate on aggregran (from human trachea) and DMBT1 (from human nasal mucosa), both of which primarily localize to airway glands. In mice, ligands for the closest counterpart of Siglec-8, namely Siglec-F, are also a 2,3-linked sialylated glycans but are not the same sulphated molecules as found in humans. Indeed, mice deficient of ST3GalI do not make lung ligands for Siglec-F, and develop exaggerated type 2 lung inflammation, while mice deficient in ST3GalIII make normal amounts of Siglec-F lung ligands and do not develop exaggerated type 2 lung inflammation. Now that Siglec-8 knock-in mice are available, targeting of human Siglec-8 on mouse eosinophils with or without Siglec-8 can be studied in vivo in a preclinical model, and will help to determine whether Siglec-8 can substitute for Siglec-F during type 2 inflammatory responses.

Eosinophils, viruses and childhood asthma

James E Gern (Departments of Pediatrics and Medicine, University of Wisconsin-Madison, USA)

Viral infections are common triggers for exacerbations of asthma in both children and adults. This relationship is especially strong in individuals with respiratory allergies and eosinophilic inflammation of the airways. Furthermore, recent evidence from interventional studies with inhibitors of IgE, IL-5 and the IL-4/IL-13 receptor provide causal evidence that eosinophils and type-2 inflammation promote exacerbations of asthma, including those due to viral infection. These findings are supported by experimental evidence that respiratory viruses can promote eosinophilic inflammation, and that eosinophilic inflammation can inhibit epithelial cell barrier function and antiviral responses. During viral infections, both eosinophils and neutrophils are recruited into the airway by a combination of chemokines and increased expression of adhesion molecules. In turn, virus-induced inflammation can enhance eosinophil degranulation and superoxide production that can cause epithelial cell cytotoxicity and increase susceptibility to viral infection. Another interaction between viruses and eosinophils is the related to catherin-related protein-3 (CDHR3). This protein serves as the receptor for RV-C, and infections with this virus are closely linked to wheezing illnesses during childhood. A polymorphism in CDHR3 is associated with increased RV-C binding and increased susceptibility to RV-C illnesses. While not much is known about the cellular functions of CDHR3, a recent study found that this protein can bind eosinophils. Notably, the genetic variant associated with increased RV-C binding and illnesses is also associated with increased eosinophil binding and an increased risk for childhood asthma. Other eosinophil functions that could also inhibit antiviral responses include secretion of TGF-β and inhibition of the TLR7 pathway, which is crucial for antiviral responses. Collectively, these findings provide insights into mechanisms of interactions between respiratory viruses and eosinophils that can promote airway obstruction, and indicate that control of eosinophilic inflammation is a key component in the prevention of virus-induced asthma exacerbations.

Eosinophil EToxins-mediated extracellular traps and diseases

Shigeharu Ueki (Department of General Internal Medicine and Clinical Laboratory Medicine, Akita University Graduate School of Medicine, Japan)

A novel form of rapid neutrophil cell death, namely NETosis, was recognized in 2007. In contrast to other known cell death types, including apoptosis and necrosis, NETosis is characterized by the striking final morphology: release of web-like chromatin structures (neutrophil extracellular traps; NETs) through breakdown of nuclear and plasma membranes. Since other immune cells can undergo similar type of cell death, ETosis is also used to describe them. Nowadays, ETosis/extracellular traps (ETTs) have been shown to be present in various infectious diseases and pathological conditions.

Eosinophil EToxins (EEToxis) mediates eosinophil cytalysis that is well-recognized in tissues in association with diverse eosinophil-associated diseases. Eosinophil extracellular traps (EETs), containing antibacterial proteins such as histones and intact granules, are considered to play a role in innate immunity by trapping various microorganisms with their sticky nature. EETs are well-conserved with nucleosomes that contribute to the highly viscous sequestration observed in allergic diseases, such as allergic bronchopulmonary aspergillosis and eosinophilic chronic rhinosinusitis. In addition, EEToxis mediates the formation of Charcot-Leyden crystals, known as a classical hallmark of eosinophilic inflammation. The pathogenesis of eosinophilic diseases could be reconsidered from a new aspect of cell fate. Excess EEToxis/EETs might be potential therapeutic targets.
**Symposium 36**

**Mechanism of Itch**

**SY-36 (D-5) -1**  
Pathogenesis of pruritus

Kenji Kabashima (Department of Dermatology, Kyoto University Hospital, Japan)

Itch is induced by a variety of pruritogens (antigens, molecular mediators such as histamine and other substances inducing pruritus, that is, itch) and mediated by cutaneous pruripruritile primary sensory nerves. In animal models of atopic dermatitis skin, sprouting, density and thickness of epidermal neurons is increased, a finding that could explain the characteristic skin pruritus produced by innocuous mechanical stimulation. Such hyperinnervation is probably caused by an imbalance between nerve elongation factors (such as nerve growth factor and IL-31) and nerve repulsion factors (such as semaphorin 3A). The best studied pruritogen is histamine, which typically is released from mast cells and basophils in the context of a type 1 hypersensitivity reaction; histamine activates a subset of sensory neurons that express histamine H1 receptor (HHR) and H4R and transient receptor potential melastatin 8 channel subfamily A member 1 (TRPM8). In addition to histamine, the increased expression of type 2 cytokines such as IL-4, IL-13 and IL-31 and signalling via histamine-independent molecular pathways could be more important than histamine for the induction of itch.

**SY-36 (D-5) -2**  
Management of atopic dermatitis in special situations

Andreas Wollenberg (Department of Dermatology, Ludwig-Maximilian University, Germany)

Atopic dermatitis (AD) is a common, highly pruritic, chronic inflammatory skin disease with a high burden of disease and a high socioeconomic impact. Regional and national guidelines have been produced by many scientific societies, which give advice on recommended treatment. Culture, climate, tradition, healthcare systems and economic restrictions are among the factors influencing guideline content. There are, however, some special situations such as paediatric age, pregnancy, infectious complications, comorbidity or an ongoing COVID-19 pandemic, which may influence the recommended management procedures for AD. This presentation will summarize clinical aspects of AD management in special situations.

In childhood age, most systemic drugs needed - and actually used in clinical reality - are not licensed. Oral corticosteroids are widely used in practice, but not generally recommended as a systemic treatment option for AD in children. Cyclosporine will induce rapid and robust responses in children, and short-term treatment with this drug is usually well tolerated. Azathioprine, mycophenolate mofetil, and methotrexate are all reasonable safe and effective alternatives for long-term maintenance therapy in recalcitrant cases. Dupilumab is safe, effective but expensive, and licensed for adolescents in Europe. A license for 6 years and above is expected soon. Additional biological substances will become available for paediatric AD patients soon.

Pregnant women should be treated with liberal use of emollients, topical corticosteroids and UV-light or combinations of the above as needed. Topical calcineurin inhibitors are also safe, but not licensed during pregnancy, and should also be combined with emollients. Systemic treatment should be initiated following a shared decision making process. A stable systemic treatment should not be changed in non-SARS-CoV2-infected patients just because of the COVID-19 pandemic running. For the initiation of systemic treatment, Th2 blocking biologics are preferred over Cyclosporine for theoretical reasons during the COVID-19 pandemic. AD patients receiving systemic treatment and affected by COVID-19 should be treated in a tertiary center.

**SY-36 (D-5) -3**  
Mechanisms of pruritus

Martin Steinhoff (Department of Dermatology, Translational Research Institute, Dermatology Institute, Hamad Medical Corporation; Qatar University, School of Medicine, Qatar; Weill-Cornell Medicine, USA)

Beside pain, pruritus (itch) is one of the most frequent symptoms among dermatological and systemic diseases. This debilitating symptom is initiated at different anatomical levels and thus needs different therapeutic strategies. Cellular cross-talk between the immune and nervous system elicit evolutionary responses such as itch (pruritus) or pain to protect the host from ‘danger signals’. Recent molecular itch research along with genetically modified models and translational human studies have markedly improved our understanding of histamine-dependent and - independent itch. In the skin, novel studies revealed an armada of molecules capable of inducing pruritus by activating high-affinity receptors for cytokines, chemokines, proteases, peptides, neurotrophins and amines; for example, Heterodimeric cytokine receptors (e.g. IL-4, IL-13, TSLP) ion channels (e.g. TRP; K+; Ca2+) or G protein-coupled receptors (e.g. histamine, PARs, prostanooids) activate signaling cascades in primary afferent sensory neurons controlling transduction of signaling as well as excytosis of itch mediators to the dorsal horn of spinal cord under control of SNARE proteins, for example. In the spinal cord, several new mediators and circuits have been identified that regulate communication between projection and interneurons as well as astrocytes and microglia, thereby controlling central pathways of pruritus. Various new clinical trials and translational studies on the effects of central mediator-receptor interactions like neurokinins, for example, have emerged from this basic research accomplishments that will change our treatment options for chronic and neuropathic itch. Accordingly, pruritus is transmitted to the brain via ascending trails that activate various poorly defined brain regions involving motor and affective responses including scratch response and emotional responses to the pruritic trigger. Future molecular itch research in the central nervous system using modern technologies will significantly improve our therapeutic repertoire to combat chronic itch. Finally, more innovative translational human studies combined with analytic genetic and molecular approaches including omics technologies and single cell studies depicting selective cellular machineries and pathways as well as neuro-immune networks will open new avenues for treating this frequent debilitating symptom with novel systemic and topical modalities significantly impacting patient’s quality of life.
Symposium 37
Drugs Hypersensitivity and Desensitization

SY-37 (M-7) -1  Pathogenesis of severe drug reactions

Mario Sánchez-Borges (Allergy and Clinical Immunology, Centro Médico Docente La Trinidad, Venezuela)

Among severe allergic reactions induced by drugs anaphylaxis, vasculitis, Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN). Drug reaction with eosinophilia and systemic symptoms (DRESS), serum sickness, and Acute generalized exanthematous pustulosis (AGEP) are the most common. Other frequent but less severe conditions include exanthems, Fixed drug eruptions, drug-induced systemic lupus erythematosus, phototoxic and photoallergic reactions, multiorgan erythema. The most frequent drugs inducing allergic reactions are antimicrobials (beta lactam antibiotics, sulphonamides), anti-epileptic drugs and non steroidal anti-inflammatory drugs (NSAIDs). The pathogenesis of allergic drug reactions may involve the 4 classic types of immunological mechanisms described by Gell and Coombs, that were more recently modified by Pichler (Ann Intern Med. 2003;139:653-313) as follows: Type 1: immunoglobulin E. Mast cells. Systemic anaphylaxis induced by beta lactam antibiotics. Type 2: Immunoglobulin G/ complement. FcR+phagocytes. NK cells. Hemolytic anemia (beta lactams, rifampin, sulphonamides). Type 3: Immune complexes. FcR+cells. Vasculitis, serum sickness (beta lactams, sulphonamides, minocycline, NSAIDs, diuretics). Type 4a: T cells. IFN-gamma, TNF-alpha. Macrophages. Contact dermatitis. Type 4b: TH1 cells. IL-4/IL-13. IL-5. Eosinophils. DRESS (antinepileptics, allopurinol, sulphonamides, minocycline, dapsonex, sul-fasalazine, abacavir, nevirapine, hydroxychloroquine, vancomycin, celecoxib, efalizumab). Type 4c: CD8+cells. NK cells. NKT cells. T cells SJS/TEN, (allopurinol), bullous exanthema, fixed drug eruptions (tetracyclines, NSAIDS, carbamazepine, TMP/SMZ, gemfibrozil, imidazoles), hepatitis (flu- cloxacilline) Type 4d: T cells. CXCR8, GM-CSF. Neutrophils. AGEP (hydroxychloroquine). Three models of immune activation have been described in allergic reactions to drugs (Kahn D et al. J Allergy Clin Immunol Pract 2013; 7: 2105-14): 1. Hapten/prohaptent model. 2. F-I model. 3. Altered peptide repertoire model.

SY-37 (M-7) -2  Beta-lactam allergy: provocation or predictive model

Pascal Demoly (Department of Pulmonology, Division of Allergy, Université Hospital of Montpellier, France)

Beta-lactams (BL) are major providers of drug hypersensitivity reactions (DHRs). Most suspicions are ruled out by a thorough drug allergy work up. Both under-diagnosis (due to under-reporting) and over-diagnosis (due to an over-use of the term “allergy”) are common. A definitive diagnosis of such reactions is required in order to institute adequate treatment options and proper preventive measures. Misclassification based solely on the DHR history without further testing may affect treatment options, result in adverse consequences and lead to the use of more expensive or less effective antibiotics. Several guidelines and/or consensus documents on BL induced DHRs are available to support the medical decision process. Drug provocation tests are commonly performed in case of negative skin tests. The use of standardized systematic approaches for the diagnosis and management of BL DHRs carries the potential to improve outcomes, and should thus be disseminated and implemented. They are based on published materials. Modern mathematics has allowed a better understanding of the usefulness of the different diagnostic steps. As an example, a recent data-driven approach (based on a survival analysis) using 20-year experience of one centre prospectively exploring patients with suspicions of DHR to BL has identified eliciting thresholds and suggested the following steps for DPT to BL: 5%-10%-30%-50% of daily therapeutic dose (with additional lower steps of 0.01%, 0.1% and 1% for index reactions of anaphylaxis). Its negative predictive value has been shown to be high (94%) in a multicentre study using one-day DPT and including both children and adults.

SY-37 (M-7) -3  Drug hypersensitivity and desensitization: update

Emilio Alvarez-Cuesta (Division of Allergy, La Luz University Hospital, Spain)

Desensitization to Drugs is a cost-effective technique that enables hypersensitive patients to receive their first-choice treatments. This procedure allows desensitization to multiple types of drugs: antineoplastic, biological agents, antibiotics, among others. There is an increase in the diagnosis of neoplastic and inflammatory diseases, and this implies that a larger number of patients are exposed to the use of antineoplastic and biological agents for longer periods of time, and Drug Hypersensitivity Reactions (DHR) have been reported with increasing frequencies. In the Allergy Division of the Ramón y Cajal University Hospital (Madrid, Spain), we performed a 7-year prospective, observational, longitudinal study with reactive patients referred to the Desensitization Program in our division. Patients were selected after following our systematic and validated diagnostic approach; clinical history, skin test, risk assessment, specific IgE and Drug Provocation Test (DPT), before a Rapid Drug Desensitization (RDD). In the first three years of the study, a total of 186 patients were assessed. A total of 104 (56%) patients underwent DPT. Sixty-four percent of all DPTs were negative, excluding hypersensitivity, and avoiding unnecessary desensitizations in no hypersensitive patients. Drug provocation test was also vital to evaluate other diagnostic tools, as oxaliplatin-specific IgE and oxaliplatin skin test, with 74-oxaliplatin-reactive patients in our study. In our 7-year study, 1027 intravenous RDDs were performed using our protocol (399 platin, 395 taxanes, 178 biologicals, 55 other drugs), and 1026 were successfully accomplished in the 186 patients (635 referred patients) who met inclusion criteria for RDD. Most breakthrough reactions were mild. A total of 341 DPTs were performed, and 229 were negative (67%), excluding hypersensitivity in 44% (229 of 519) of referred patients. Drug challenge confirms whether or not a patient is hypersensitive to drugs and is essential in validating diagnostic tests. Desensitization is crucial in selected patients.
Symposium 38
New Insights in Allergen Immunotherapy: Pediatric

SY-38 (P-9) -1 New insights in allergen immunotherapy: pediatric
Sandra Nora González Díaz (Regional Center of Allergy and Clinical Immunology, University Hospital Dr José Eleuterio González, Mexico)

Allergen-specific immunotherapy (AIT) is currently indicated as the only clinically effective treatment due to its disease-modifying effect for IgE-mediated allergic diseases. Novel options include allergoids, which maintain desired immunogenicity, with a reduced allergenicity. AIT is allergen-specific, its efficacy and effectiveness depends on identification of the triggering allergens, a “precision medicine”, and implies an accurate clinical history and acknowledging environmental exposure, confirmed by diagnostic tests. AIT should be considered in pediatric patients with rhinoconjunctivitis and/or asthma with an IgE-associated respiratory allergy, caused by clinically relevant allergens. Clinical studies have shown the efficacy and safe administration of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) in preschool children. In children<4 years old, a careful risk/benefit evaluation should be considered individually for each patient. Treatment should last minimum 3 years. Asthma symptoms should be well-controlled, the parameters of lung function should be measured in order to assess the level of asthma control. A significant reduction of symptoms has been found in patients treated with dust mite and pollen AIT with overall reduction of symptoms (SMD ~ 0.59, 95% CI ~ 0.33 to ~ 0.38). Medication scores and bronchial hyper-reactivity are significantly reduced as well. Oral immunotherapy (OIT) and SLIT confer protection against accidental allergic reactions and contribute to improve nutritional status and quality of life of the affected patients. It is not clearly defined if when desensitization has been achieved, a permanent tolerance persists, independent of the regular ingestion of the responsible food such as cow’s milk, egg and peanut. It is still controversial whether AIT may benefit patients with atopic dermatitis (AD). Considering the clinical effectiveness of AIT in IgE-associated allergic diseases, trials have shown the efficacy of AIT for patients with extrinsic AD. If a clinical improvement along with significant reduction in the use of medications is not observed after 1 year of therapy, the indication for AIT must be reevaluated. Therefore it is necessary to reassess the selection of the allergens and eventually the diagnosis of respiratory allergy.

SY-38 (P-9) -2 Specific immunotherapy in Asian children
Hugo Van Bever (Department of Paediatrics, National University of Singapore, Singapore)

Specific allergen immunotherapy (IT) is considered the only curative treatment of allergic diseases and has now been used for more than a century. While in the past, IT was mainly an injection-treatment (i.e. subcutaneous immunotherapy SCIT); during recent decades a switch has taken place towards more child-friendly types of IT, including sublingual immunotherapy (SLIT) and oral immunotherapy (OIT), the latter mainly to treat food allergies. Knowledge on IT (its efficacy and its pathophysiology) has improved substantially, due to the publication of a large number of high-quality studies. In Asia, popularity of IT is mounting, despite the fact that IT is still not available in all Asian countries, leading to the existence of wide differences in knowledge and usage policy of IT. These differences are mainly associated to socio-economic development of individual countries (i.e. availability of IT). In countries, such as Japan, S-Korea, China, Thailand, Hong Kong, Singapore and others many types of IT, such as SLIT and OIT, are now commonly used as a routine treatment for inhalant (SLIT) or food (OIT) allergy. The talk will give an overview of available data on IT in different Asian countries (although data from all Asian countries are not available), pointing also to unmet needs, such as the lack of clinical studies in Asian children. The talk will also give suggestions on essential future studies and ways to improve the quality of IT treatment.

SY-38 (P-9) -3 Allergen immunotherapy in Japan: current status and future perspective
Mizuho Nagao (Institute for Clinical Research, National Hospital Organization Me National Hospital, Japan)

Major allergens in pediatric allergic rhinitis in Japan are house dust mite (HDM) and Japanese cedar pollen (JCP) and are the main targets of allergen immunotherapy (AIT). In pediatric asthma, majority of patients are sensitized to HDM. Currently, approved AITs in Japan are JCP subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for JCP-induced seasonal allergic rhinitis. HDM SCIT for HDM-induced perennial allergic rhinitis and asthma and HDM SLIT for HDM-induced allergic rhinitis. HDM SLIT for asthma, however, is yet to be approved. Accumulating evidence shows that HDM AIT improves symptoms of allergic rhinitis and asthma in adults and children. However, evidence in children and adolescents are not sufficient. We investigated lung function trajectories in children and adolescents with HDM-induced allergic rhinitis and asthma who were treated with HDM SLIT and SCIT. We found that about half of the patients exhibited improvement of FEV1 and half of them showed no improvement. The patients with improved FEV1 had higher HDM-IgE levels and lower eosinophil count before the treatment than those without improvement, suggesting that high potency of HDM sensitization and low (or controlled) eosinophilic inflammation are factors to predict AIT responsiveness. Control of eosinophilic inflammation with inhaled corticosteroids may be crucial to gain best possible outcome with AIT. Prevalence of JCP-induced allergic rhinitis is as high as almost 50% in children and adolescents in Japan and onset age is getting lower. Previous concept of “allergy march” was that allergic rhinitis, especially JCP-induced allergic rhinitis, was the last manifestation of the “march”. However, a recent report showed that prevalence in preschool age was doubled, even tripled. Considering possible “molecular spreading”, a hypothesis that allergen sensitization is “spreading” from single molecule to multiple allergen molecules during early life leading to more severe disease, early intervention with AIT in young children may be important to prevent the “accelerated allergy march”. Recent advance in this field will be reviewed.
Symposium 39
New ARIA

SY-39 (E-4) -1 Implementation of ARIA guidelines by ARIA score and mobile technology

Jean Bousquet (Pulmonary Medicine at Montpellier University, France)

Digital anamorphosis is used to define a distorted image of health and care that may be viewed correctly using digital tools and strategies. MASK digital anamorphosis represents the process used by MASK to develop the digital transformation of health and care in rhinitis. It strengthens the ARIA change management strategy in the prevention and management of airway disease. The MASK strategy is based on validated digital tools. Using the MASK digital tool and the CARAT online enhanced clinical framework, solutions for practical steps of digital enhancement of care are proposed.

SY-39 (E-4) -2 Treatment of AR based on new EUFOREA algorithm

Peter Hellings (Department of Otorhinolaryngology, KU Leuven, Belgium)

All physicians dealing with patients suffering from allergic rhinitis realise the shortcomings of current guidelines and published care pathways, leading to lack of usefulness in real practice. Therefore, a consortium of EUFOREA experts undertook action to develop and find a true consensus on a treatment algorithm that would reflect existing evidence-based guidelines for treatment on the one hand, and the reality of patients seen by pharmacists, primary care, and specialists. The patient advisory board of EUFOREA was actively involved in the development of the algorithm, that was largely based on the British guidelines for allergic rhinitis treatment.

The EUFOREA treatment algorithm for allergic rhinitis is presented in a pocket guide, which is made available online (www.euforea.eu) and disseminated to all stakeholders in allergy care via classic and digital dissemination.

The mission of EUFOREA is to provide care providers in the allergy and respiratory field with optimal guidance for better care of affected patients.

SY-39 (E-4) -3 ARIA care pathways for allergic rhinitis in Japan

Yoshitaka Okamoto (Otorhinolaryngology, Chiba Rousai Hospital; Chiba University, Japan)

37 allergy researchers from different countries made public the consensual report ‘Allergic rhinitis and its impact on asthma’ (ARIA) in 2001. ARIA was thought to be an international guideline concerning diagnosis, influence on asthma, and management of allergic rhinitis. This evidence based report came to be used widely in the world as a guide for treatment. In 2010, ARIA-GRADE guideline was published. The Grade (grading of recommendations assessment, development and evaluation) methodology considers all types of study designs and evidence about values and preferences, acceptability and feasibility or directness of findings. The levels of evidence were strictly evaluated in the ARIA-GRADE guideline. On the other hand, there has been an increasing trend to use real-world evidence to inform clinical practice. From the data obtained by mobile health tools, such as apps, it has been shown that patients did not follow guidelines and often self-medicate. Patients treat themselves as they need to, depending on the control of the disease, and increase their treatment when they are unwell, however co-administration does not improve the control. Both types of evidence were expected to be merged. New-generation guidelines for the pharmacological treatment of AR were developed using existing GRADE-based guidelines for AR, tested using real-world evidence provided by mobile technology. These recommendations were used to refine the treatment algorithm for proposed AR. Although the management of AR is influenced by different situations among countries, such as prevalence and characteristics of AR, as well as medical insurance systems, this new-generation guideline could offer useful managements of AR in Japan, such as the classification of severities using visual analogue scale system, the simplified treatment algorithm. We have also recently developed the Japanese version of mobile (MASK-air) and have been studying the real-world evidence in Japanese patients. We believe the real-world information from mobile technology would add valuable intelligence to the AR management in Japan.
**Symposium 40**

**Mastocytosis**

**SY-40 (B-6) -1**  
**Novel immunopharmacological interventions in mastocytosis**

Francesca Levi-Schaffer (Pharmacology & Experimental Therapeutics Unit, The Hebrew University of Jerusalem, Israel)

Mastocytosis is an heterogeneous disease in which mutated mast cells (MCs) are clonally proliferating and releasing mediators causing the main symptomatology. Treatments aim at blocking effects of MC mediators, reducing MC activation and tumor burden. Drugs against the tyrosine kinase activity of KIT have improved the quality of life and prognosis of mastocytosis patients. Nevertheless, no available drug is a solution for the disease, especially for advanced systemic mastocytosis that is still untreatable. In my lecture I will review the most recent immunopharmacological drugs for mastocytosis such as AK002 (anti-Siglec-8 antibodies (Abs)), brentuximab-vodotin (anti-CD30 Abs), omalizumab (anti-IgE Abs), and concentrate on anti-Siglec-7 Abs that have been studied in our laboratory providing pre-clinical promising results. Blocking Abs against inhibitory receptors (IRs) expressed by NK and T cells, also known as "checkpoint IRs", have revealed both anti-inflammatory and anti-cancer treatment. However IRs, such as Siglec-7, are expressed not only on normal immune cells (we described its expression and function on MCs, eosinophils and basophils) but also on neoplastic cells. We have shown that the Siglec-7 is indeed expressed by primary neoplastic MCs from systemic mastocytosis patients and by MC leukemia cell lines. We therefore investigated whether activation of Siglec-7 on mastocytosis cells through anti-Siglec-7 monoclonal Abs can lead to growth inhibition. We found that anti-Siglec-7 activating Abs caused phosphorylation of Src homology region 2 domain-containing phosphatase-1 (SHP-1), reduced phosphorylation of KIT and induced growth inhibition in MC lines. In SCID-beige mice injected with either the human line HMC-1.1 and HMC-1.2 or with Siglec-7 transduced B cell lymphoma, anti-Siglec-7 Abs reduced tumor growth by a mechanism involving Siglec-7 cytoplasmic domains in ‘preventive’ and ‘treatment’ settings. These data demonstrate that activation of Siglec-7 on MC lines can inhibit directly their growth in vitro and in vivo. Therefore Siglec-7 could represent a suitable candidate to be activated by anti-Siglec-7 Abs or to deliver toxin, chemotherapeutic agents or other drugs into Siglec-7 positive MCs for treatment of tumors such as mastocytosis or other cancers.

**SY-40 (B-6) -2**  
**Mastocytosis: clinical spectrum of disease**

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**Background:** This presentation is part of the Symposium on Mastocytosis and complements the previous presentation on pathophysiology on mastocytosis and the subsequent talk on its association with anaphylaxis. **Aim:** The focus of this talk is the clinical spectrum of disease in mastocytosis. It will cover not only primary mast cell (MC) disorders associated with clonal MC proliferation, but also diseases associated with inherent increases in MC activity, particularly hereditary alpha-tryptasemia. **Learning objectives:** By the end of this session participants should understand the clinical spectrum of disease in mastocytosis, in particular differences in the presentation and prognosis of mastocytosis in children who usually present with cutaneous mastocytosis and adults who are more likely to present with systemic disease affecting other organ systems. Treatment options for mastocytosisediseases associated with excessive MC activity, particularly hereditary alpha-tryptasemia: diagnosis, spectrum of disease and clinical implications of diseases where MCs may contribute to the pathogenicity and severity, including vascular diseases of infants (BOP, BPD, SIDS), vascular diseases in adults and neoangiogenesis of tumours. **Additional reading:** (1) Castells M & Butterfield J. Mast cell activation syndrome and mastocytosis: Initial treatment options and long-term management. JACI Pract. 2019. (2) Wilcock A et al. Mast cell disorders: Form infancy to maturity. Allergy, 2018. (3) Lyons JJ et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet, 2016.

**SY-40 (B-6) -3**  
**Association to anaphylaxis**

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Dermatological Allergology, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt - Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany. Mastocytosis is characterized by a clonal expansion of mast cells (MCs) in one or more organs ranging from indolent disease to aggressive forms with potential fatal outcome. Patients with indolent systemic mastocytosis (ISM) usually have a good prognosis but may suffer from signs and symptoms of the disease and can be even at risk of experiencing life-threatening anaphylactic episodes. Anaphylaxis has been reported to affect up to 30-50% of ISM patients and the increased MC burden puts them at risk to experience severe reactions. Interestingly, an existing population of patients suffering from severe anaphylaxis do not present with obvious signs and symptoms of mastocytosis (despite anaphylaxis) by which these patients lack skin involvement and elevated basal tryptase levels. However, since the majority of ISM patients carrying the KitD816V mutation, its detection by high-sensitive qPCR in the peripheral blood became an important marker to identify underlying mastocytosis in anaphylaxis patients. Several studies have shown that about 7% of patients presenting with severe anaphylactic reactions without any obvious clinical evidence for mastocytosis are tested positive for the KitD816V-mutation in peripheral blood. The detection of mastocytosis in anaphylaxis patients is an important issue since it affects the risk stratification as life-long immunotherapy is considered.