HIGHLIGHTS FROM THE EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY (EAACI) CONFERENCE, 2019

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The annual EAACI conference is a highlight for those working in the field of allergy and immunology; it offers a carefully curated programme which affords a unique opportunity to learn about the latest discoveries in this area. The theme of the 2019 conference in Lisbon was '*Mapping the new world of allergy: Towards precision medicine in allergy and asthma'*. The meeting attracts between 7 000 and 8 000 attendees and the real challenge lies in selecting which sessions to attend, given the range of speakers and topics covered. The speakers include healthcare professionals, key scientists and opinion-leaders from around the world and the topics range from allergen structure, aerobiology, disease endotypes, biological treatments to immunotherapy, and to new developments in genomics, proteomics and metabolomics.

The scene is set at the start of the day by a collection of plenary sessions each delivered by the ultimate experts in their field. Smaller symposia sessions and oral abstract presentations, late-breaker abstracts and e-posters then follow on the same or closely related themes. The year-in-review sessions are extreme learning experiences: a rapid immersion in a specific topic with a review of the most landmark publications in the past year that have moulded the research and ideas about the topic and, in the case of clinical subjects, the preventive or therapeutic approaches are presented by the top experts in their fields. In 2019, I attended the year in review of the EAACI journals *Allergy* and *Pediatric Allergy and Immunology*. Interactive sessions are an excellent opportunity to network with similar clinicians from around the world and are conducted around about ten tables with ten participants at each table. The selection of topics summarised shows the eclectic mix of clinical, laboratory and immunological interests that were my focus for EACCI 2019, revealing a bias towards the immunological mechanisms of allergy.

FOOD ALLERGY

In the opening plenary session – '*New concepts in food allergy'* – three speakers addressed new concepts in the understanding of food allergy. Marc Veldhoen (Portugal) discussed '*Immune tolerance: Perspective from the T-cell side'* and outlined that CD8 expressing T cells embedded in the gut have multiple functions and distinct functional subsets including effector memory T cells (TEM), central memory T cells (TCM) and tissue-resident memory (TRM) cells expressing CD69 and CD103.[1] The physiology of intraepithial lymphocytes (IEL), which are ideally positioned at the surface of the intestinal barrier and are metabolically ready for quick action, was described, as was the way in which these cells interact with intestinal epithelial cells (IECs), contributing to immune surveillance and the preservation of intestinal homeostasis and host-microbial relationships.[2] Velhoen also referred to the modulating of immunity towards microbes and how green vegetables affect intestinal homeostasis. Vegetable derived phytochemicals (indole 3-carbinol) present in high levels in cruciferous vegetables such as broccoli and cabbage produce high-affinity ligands for the aryl hydrocarbon receptors (AhR), the presence of which are important to maintain TEM and prevent inappropriate inflammatory responses in the gut.

Harald Renz (Germany) then spoke on '*Exposome and food allergy'*. Whereas genetics sets the stage for food allergy, the drivers are the environmental and lifestyle exposomes outside of the individual. The problems of lifestyle and diet causing an imbalance or dysbiosis in the microbiome, especially in the foetus and new-born, have significant effects on the development of immune tolerance. This relationship is well known and the role of IL4, 5 and 13 in food allergy is well established. In this plenary, the discussion was on histone modification (around which genetic DNA is wrapped) by acetylation or methylation and how this can lead to modified tolerance and food allergy susceptibility. Specifically, the effect of fish oil supplementation and olive oil intake in pregnancy on cord-derived CD4 T cells showed changes in the epigenetics of acetylation of IL13 and the up-regulation of T reg and FOXP3 genes in placental cells respectively. In closing, there was an appeal for larger prospective studies in order to examine more closely the metagenomics and metabolic approaches to harness precision medicine and 'omics' for the benefit of treatment and allergy interventions.

The last session in this plenary, intriguingly titled '*Can food allergy be cured?',* was delivered by Kari Christine Nadeau (United States). This discussion reiterated that eight common foods (egg, milk, fish, peanut, wheat, soya, tree nuts and shellfish) cause most food allergies and that IgE sensitisation may sometimes be misinterpreted as food allergy. Food allergy therapies and desensitisation are now being developed, but to

be effective they need to be tailored to each individual patient. A 'cure' means different things to different patients and can be interpreted to mean that the patient can eat the food every day – or must they still live in fear of a future exposure? And, also, can multi-food cures or desensitisations be done all at the same time? Cure of food allergy was defined as desensitisation or regular exposure to a particular food to allow safety thresholds and sustained tolerance. The problem with achieving this cure is that there is no 'biomarker' to measure cure and nothing on which to ensure that the desensitisation response will be maintained in the long term, as demonstrated in various randomised double-blind controlled trials such as the POISED phase 2 study. This study showed that peanut oral immunotherapy (OIT) could desensitise individuals with peanut allergy to 4 000 mg peanut protein but that discontinuation, or even reduction to 300 mg daily, could increase the likelihood of regaining clinical reactivity to peanut.[3] Novel therapeutics were also presented based on the knowledge that IL33 (pro-inflammatory alarmin) mediates atopic disease and in a study in adults with anti-IL33 treatment, 67 % of adults could pass challenge after one dose of the drug.[4] This presentation concluded with the need to identify key mechanisms of desensitisation and sustained unresponsiveness to an offending food.

At the presidential PRACTALL symposium, three other speakers expanded further on the discussions initiated at the opening plenary on food allergy. PRACTALL (practical allergy) is an initiative between American and European allergy associations with the aim of harmonising approaches for best clinical practices and science in allergy and immunology. Wayne Shreffler (United States) discussed an '*Endotype-driven approach for immune modulation in food allergy*'. Endotypes are subtypes of a condition defined by a distinct functional or patho-biological mechanism, as illustrated for asthma endotypes identified by multivariate analysis and encompassing multiple phenotypes. Parameters usually considered for this classification include disease severity, biomarkers, genetics, histopathology, epidemiology and treatment response. In asthma the familiar endotype is Th2 dominant but further refinements can tease out contributors to the disease syndrome, for example exercise-induced asthma. In IgE-mediated food allergy the endotypes include food-protein-induced enterocolitis syndrome (FPIES), food-protein-induced enteropathy (also sometimes referred to as cow's milk-sensitive enteropathy (FPE)), eosinophilic oesophagitis (EOE) and food-protein-induced allergic proctocolitis (FPIAP, formerly known as allergic or eosinophilic proctocolitis, or 'protein intolerance'). The point was clearly made that there may be some commonality in the disease pathways, but there is heterogeneity within each of these disease entities and at this time there are few distinct biomarkers except IgE concentrations to distinguish between them clinically. Future directions are to include antibody repertoire, CD4 effector phenotypic diversity and barrier function, alarmins and T-cell diversity to outline food allergy endotypes.[5]

In the presentation by George Du Toit – '*Prevention of food allergy – a realistic target?*' – it was noted that there was sufficient and robust evidence that both peanut and egg allergy can be reduced, but the factors that are preventing the cure of food allergies are unknown. Various hypotheses have been put forward as contributors to this inability to offer long-lasting cures for food allergies, including dual-allergen exposure, cutaneous exposure as shown in various experiments done by Gideon Lack's group. Eczema and concurrent *Staphylococcus aureus* colonisation (which occurs in 18 % of children with eczema) have been suggested as the reason that those particular children do not eventually 'outgrow' egg allergy. A follow-up analysis of the participants in the LEAP study has identified a strong association between the development of peanut allergy and the MALT 1 gene (mucosa associated lymphoid tissue lymphoma translocation).[6] Whole genome sequencing was conducted on these study participants to identify genetic factors associated with peanut allergy. This found the highest association in patients with a single nucleotide variant (SNV) of the MALT 1 gene: 58.6% of carriers of this gene became peanut allergic compared to 12.7% of non-carriers of the gene, suggesting that MALT 1 is an independent factor for peanut allergy and this implicates the pathway controlled by this gene in the progression to peanut allergy if peanut is avoided.

The final talk in this symposium on '*Efficacy, safety and monitoring of current treatment modalities*' was given by Nonhlanhla Lunjani. People with food allergies are not given clear direction about how to manage their food allergy: they are left weighing up either avoidance or exposure at low or incremental doses to induce tolerance or fearing accidental exposure. There is a significant evidence base that oral immunotherapy (OIT) for food allergies is effective and frequently accomplishes desensitisation for the individual; however, the ultimate goal of sustained unresponsiveness may not be attained. There may also be serious adverse events on exposure to increasing doses of the food in question, including chronic abdominal pain or unanticipated reactions under certain circumstances if the individual undergoes a physiological change (exercise, menses, viral infection). Different modes of delivery of OIT (oral/sublingual/subcutaneous) also may have an impact on the final outcome, as does the preparation of the food products used. Standardisation is difficult to achieve.

DRUG ALLERGY

The afternoon symposium on managing patients with drug sensitivities was divided into three talks on non-beta lactam antibiotics, antiepileptics and chemotherapeutics. Approximately 40% of outpatients are on non-beta-lactam (NBL) antibiotics, which include macrolides, sulphonamides and quinolones. The prevalence of NBL allergy is approximately 17%. Macrolides are relatively safe and sensitivity to them usually presents as urticaria. Hypersensitivity to sulphonamides is T cell-mediated via a direct T cell-receptor mechanism and not IgE-mediated. Sulphonamide hypersensitivity reactions are frequently severe and may present with toxic epidermal necrolysis (TEN) epidermolysis. Sulphonamides frequently demonstrate cross-reactivity, the exception being dapsone, which may be tolerated even in allergic patients. The diagnosis of sulphonamide drug reactions may be measured using EliSPOT interferon gamma-release techniques. Vancomycin reactions are usually delayed, although immediate reactions have been documented and

recently associated with the HLA A 32 01 locus. Quinolones have a very high prevalence of sensitivity reactions (about 50%) and may be diagnosed on basophil activation tests.

Antiepileptics are among the top five drugs that cause drug reactions, especially the aromatic-derived compounds. The most common presenting symptom is a macular papular rash and urticaria and, in rare cases, scaring. Most studies have been done in adults, however, there is minimal data in paediatric patients, even though up to 31% of children may have an epileptic drug reaction. Carbamazepine and valproate reactions are rare and reducing doses are generally successful in reducing reactions. Information is important for children, especially those children treated with multiple other drugs plus antiepileptics, because these patients often present with severe reactions, especially if there is a concurrent viral infection. Skin tests and patch tests are recommended for children reacting to epileptic drugs, although the optimal concentrations for children for these tests have not been defined. No drug-provocation tests exist for antiepileptics as there are multiple patient-specific factors that may influence the outcome of the provocation test, including age (faster metabolising enzymes), drug doses, viral infections, *Mycoplasma pneumonia* infection and concomitant neurological or immunological diseases. Genetic factors such as HLA B15:02 and A31:01 have been implicated in adult populations of Asian or European origin predisposing to carbamazepine reactions. It remains unresolved when, after a sensitivity reaction to an anti-epileptic drug if a new drug can be introduced, and, if so, what alternative therapies are available. Fifty-two per cent of patients with a carbamazepine-induced rash will react to phenytoin, so it is usually recommended to avoid all aromatic antiepileptic compounds because of their cross-reactivity. Desensitisation can be done after evaluating the risks, and experts can achieve 95% success with these protocols.

IMMUNITY AND ALLERGY

The third plenary on the second day was '*Fuelling the immunity: From immunometabolism to novel therapeutic strategies'*. The objectives of the plenary were to highlight recent studies regarding changes in intracellular metabolic pathways in immune cells, which influence immune cell function, and to translate current knowledge into clinical application for the immunotherapy of immune-mediated diseases.

The first presentation on '*Innate immune cells and immunometabolism for novel therapeutic interventions'* by Adam Byrne (United Kingdom) discussed the change in understanding of macrophage biology and phenotypes. Previously, macrophages were thought to be derived from monocytes, but now the model is that macrophages seed to organs (airway and liver) during gestation and after the first breath of the infant become resident homeostatic cells that regulate *in situ*. Airway macrophages are part of the innate immune response and function to produce surfactant and which, after exposure to viruses, take on an inflammatory phenotype. It is unclear at this stage if cells get replaced or if resident quiescent cells change. What is understood, though, is that the different macrophage types have different metabolisms: the M1 type of metabolism uses sugars for glycolysis and produces lactate; M2 metabolisms use fatty acids for energy and metabolites produced via these pathways seem to have an inhibitory effect on the macrophage changes. Itaconate is specific to macrophages and demonstrates unique metabolic reprogramming, it inhibits succinate dehydrogenase and is an endogenous regulator of inflammation.[7] Using an idiopathic pulmonary fibrosis (IPF) model, macrophages in IPF lungs have decreased expression of immunoresponsive gene 1 (Irg1). Wild-type mice exposed to bleomycin resolve induced fibrosis but Irg1-deficient mice could not make changes to their remodelled airways. Irg1-gene expression also influences T cell phenotypes. Exogenous itaconate limits fibroblast proliferation and activation in a dose-dependent way, so it is anti-fibrotic.

Domingo Barber (Spain) then discussed *'Metabolic reprogramming in T cells as a target of immunotherapy'*. He highlighted that, although there have been a number of allergy immunotherapy clinical trials in the last few years, most use symptom data to measure outcomes. But monitoring is required at the immunological level in order to understand the responses and to determine whether and how long responses to immunotherapy will persist. In the first year after desensitisation there are increased T cell responses and a shift in immunoglobulin production from IgE to IgG4; within two years there is acquisition of T reg T cell phenotypes. This gradation of responses was seen in the GAP study, a five-year sublingual immunotherapy asthma prevention trial in children with grass pollen allergy.[8] Severe profilin food allergy was used as a model to understand the effects of sublingual immunotherapy (SLIT) on the oral mucosa. The oral mucosa is an immunocompetent epithelial site and disruption of this mucosa with loss of tolerance to profilins may result in food allergy. Metabolomics and transcriptomics of grass pollen allergy have been used to identify biomarkers of severity, in particular sphingolipid metabolism in which sphingosine phosphate shows increased inflammation.

Milena Sokolowska (Switzerland) spoke on '*Translating novel concepts in metabolomics into allergy interventions'*. Allergen-specific T cells in allergy immunotherapy targets T regs and effector cells, and molecular signatures of Th2 responses in patients allergic to Bet V1 and Phip 5 can be characterised. In winter, the Th2 cytokines expressed were different at the transcriptome level and comprehensive bioinformatics analysis showed a changed metabolism in allergen-specific cells with increased cholesterol biosynthesis and aberrant fatty-acid signalling responsible for functional defects of T regs. AIT-induced regulatory phenotypes showed increases in sphingolipid biosynthesis and decreased prostaglandin D2 (PG D2) metabolism.

In the 'hot topic' session immediately after this plenary, '*Advances in immunologic aspects of allergic diseases',* the role of epithelial cells and tissue damage in promoting IgE responses was discussed – and, more specifically, the role of respiratory progenitor cells in allergy and the plasticity of innate lymphoid cells in inflammation. The speakers were Jessica Strid (United

Kingdom), Jose Ordova-Montanes (United States) and Suzanne Bal (The Netherlands).

In the opening talk, Jessica Strid presented on '*Epithelial damage and tissue γδ cells promote a unique and targeted IgE response'*. The purpose of IgE as a rapid humoral response important in host defence was postulated, and backed up with experimental evidence to show that tumours accumulate IgE. In animal models, IgE protected against induced carcinogenesis through its high-affinity receptor FCR1. A higher expression of FCR1 correlated with tumour surveillance. IgE induction also occurs in response to cellular DNA damage, which sends stress signals to naïve T cells by an NKG2D mechanism. Lymphoid stress surveillance can monitor epithelial dysregulation via molecular interactions between the epithelium and lymphoid cells. IgE also regulates epidermal hyperplasia and skin inflammation both enhance local IgE production and drives the recruitment of IgE-effector cells into the skin and basophils, in which the FCR1 mechanism is used to induce keratinocytes.

Genes are expressed in particular patterns that define cell states of activation, and cell types can now be measured using new technology (*Seq-well*). In the second presentation, Jose Ordovas-Montanes presented on 'Allergic Inflammatory Memory in Human Respiratory Epithelial Progenitor cells'. Allergic inflammatory memory also exists in human respiratory epithelial progenitor cells as part of the adaptive immune response. The discussion was how to define adaptive immunity versus inflammatory memory and how to assess if these responses are maladaptive. Immune cells have evolved specific sensory modalities and response modules. Using a cytokine network various disease phenotypes are interpreted by cells and tissues. Seq-well technology 'bar-codes' RNA and may distinguish groups of genes associated with disease states. Chronic rhinosinusitis is a barrier dysfunction disease caused by Th2 activation via IL4 and 13. The histology of polyp tissue confirms this and shows both eosinophilic infiltration and mast cells and changes in core transcriptional signatures. This concept is confirmed across species and tissue stem cells appear to remember immune events via epigenetic mechanisms.

In the last 'Hot Topic" talk '*Innate lymphoid cells in allergy and immune tolerance'* Suzanne Bal discussed how ILCs are T helper cell counterparts that function by being rapidly activated after infection or inflammation to try to contain the problem before it is escalated to the T helper cells. They are non-specific and antigen independent. In chronic rhinosinusitis both circulating and resident innate type 2 cells (ILC2) are found; however, nasal polyp cells are more responsive to cytokines which, at a protein level, is because of CD45RO predominance with down regulation of CD69. Activated ILC2 cells as seen in inflammation are characterised by high-expression CD45RO. In patients on SLIT therapy for pollen allergy, ICL2 clones have a higher potency to produce IL10; they therefore model the immune response with therapy. Microbiota have also been shown to modulate IL1 β, which is necessary for the induction and maintenance of T reg cells.

VACCINE ALLERGY

An interactive session on '*Managing a child with possible vaccine allergy'* provided insights into vaccine allergy, which is clouded by many myths. The two speakers, Susana Lau (Germany) and Odilija Rudzeviciene (Lithuania), contextualised the issue that food allergy and allergy to vaccine is a very rare occurrence. However, there is a misperception because of the timing of vaccines and the appearance of early-onset eczema overlapping. Epidemiological data show that egg-allergic children may safely receive MMR and influenza vaccination. The prevalence of reactions to vaccines is 1 : 50 000 mild/skin reactions and anaphylaxis 0.1/100 000. So in every 5/100 000 vaccine doses there is the potential for a sensitivity reaction. Local reactions can be mild with non-specific inflammation, pain, redness or swelling and they are type-IV hypersensitivity reactions usually to thimerosal and formaldehyde. Large local reactions may occur 24–72 hours after vaccination and usually resolve within two weeks.

Gelatine is the commonest reason for vaccine reactions in adults, but other substances in the vaccine – including antibiotics, alum, phenoxyethanol and remnants of proteins from hen's egg fibroblasts – have been implicated in MMR, rabies and yellow-fever vaccines. Egg-protein concentrations are very low in these vaccines: around 0.09 µg/mL of ovalbumin is found in influenza vaccines, which is below the threshold for eliciting a clinical anaphylactic response. Nevertheless, the recommendation is that MMR vaccines and influenza vaccines are done under observation in a health facility setting for egg-allergic children. Yellow fever vaccination, on the other hand, has high levels of egg protein and can induce anaphylaxis.

Investigating a child with possible vaccine allergy and how to vaccinate children at risk were discussed, giving important practical clinical information based on consensus guidelines[9] that can be applied. It was suggested that in the case of any child with a possible history of egg sensitisation or reaction to a vaccine, the following should be assessed:

- Is the reaction immediate or delayed?
- Is it IgE- or not IgE-mediated?
- Are the symptoms local/systemic or common/rare?
- What is the severity of the symptoms?
- Document possible ingredients of the vaccine (egg/latex/gelatine) to which the reaction occurred.
- Measure specific IgE to vaccine antigens (diphtheria and tetanus toxoid antibody responses are present in 50% after 1st vaccine and > 90% have a response to a booster dose).
- Pre-immunisation allergy tests do not reliably predict or exclude future reactions, so they are not recommended.
- Do mast cell tryptase levels as marker of anaphylaxis within two hours after reaction and at 48 hours after.
- Do IgG levels to immunising agent to assess whether protective levels have been attained and if a booster is needed.

ALLERGIC RHINITIS

In the symposium '*Allergic rhinitis impacts more than the airways',* the speakers described the role of inflammation on

olfaction and the impact of allergic rhinitis (AR) on middle ear infusions and finally how nasal treatment may affect the ocular system. The speakers were Joaquim Mullol (Spain), Peter Valentin Tomazic (Austria) and Banu Bozkurt (Turkey).

The sense of smell works through 355 neural receptors and there has been an evolutionary decrease in the sense of smell in humans with loss of some of these receptors. However, receptors may be 'trained' to distinguish the intensity and character of smells, as seen in experiments with winemakers. Epidemiological studies using the OLFACAT-RL self-administered two alternative forced choice test procedure showed that 1 in 5 people have hyposmia and 0.3% have anosmia with a total loss of smell, which has a significant impact on quality of life.[10] Anosmia may occur post viral infection and is correlated with asthma severity. The sense of smell is better in young people, women, people with a higher education and, surprisingly, smokers. This is because nicotine increases the neuronal life of the receptors associated with smell. AR is associated with a loss of the sense of smell, which appears to be related to the eosinophilic infiltration of mucosa. Steroids, mepolizumab and omalizumab can improve the sense of smell in AR.

Also discussed was otitis media and the effusion occurring with no signs or symptoms of acute infection. Predisposing factors to this include adenoid hypertrophy, atopy and upper respiratory tract infection (URTI). Effusions occur because of a blockage of the Eustachian tube post infections (viral or bacterial), with reflux or polyps that may be infiltrated with eosinophils.

The ocular impact of AR was also included in this session. AR is common, with 25% of the world's population being affected. And 30% of those patients have ocular symptoms, which are frequently reported as the most troublesome symptom for patients. Ocular symptoms related to AR occur because neuropeptides from irritated nerves are released and use the histamine pathway to amplify the allergic response through the afferent and efferent naso-ocular reflex. This results in ocular symptoms similar to those in the nose, with an allergic cascade including hyperaemia, itching and tearing. Oral antihistamines will abort symptoms in the nose and eyes and occasionally topical steroids need to be added to dampen this inflammatory process.

TOLERANCE AND SYSTEMS BIOLOGY

In the plenary '*Allergy today – targeting barriers and tolerance',* the session focused on how muco-cutaneous barriers are key components of the immune response. These surfaces are where pathogens first encounter a barrier and are also where tolerance to many substances takes place.

Cezemi Akdis (Switzerland) discussed '*Barrier dysfunction – the Achilles' heel of allergy*' and outlined that cosmetics and detergents disrupt the normal microbiome of the endothelial barriers, resulting in disease. Detergents have a surfactant added to them which disrupts the epithelial layers and has toxic effects on cells in 1 : 10 000 dilutions. Normal laundry detergents remain on clothes in concentrations of 1 : 2 500 and an additive to dishwashing liquid, *lemonin*, has been implicated as a possible reason for the rising prevalence of eosinophilic oesophagitis, because this substance does not rinse off cutlery and crockery easily. Specifically, these substances threaten the integrity of tight junctions (TJ) between cells, which are disrupted in asthma, chronic sinusitis, nasal polyps, atopic dermatitis and bronchitis.

Claudins are a multi-gene protein family (with approximately 27 members) that are polymerised into TJs[11] and claudin-7 has been shown to be non-functional in patients with atopic dermatitis (AD). Immune responses elicited by allergic reactions and parasitic worm infestations are characterised by the induction of Th2 responses which secrete various interleukins IL4, 5 and 13. IL13 is the main interleukin involved in a Th2 expulsion response.[12]

'*Targeting the molecules and mediators – "magic bullets" for allergy treatment'* was the topic presented by Ioana Agache (Romania). In this talk, a biomarker and endotypes approach to allergic diseases using 'big data' analysis and surveillance information before allergic diseases start was discussed. Currently, we depend on visible properties of allergic conditions to describe and classify them but these are not necessarily related to the mechanisms of disease. To target treatment effectively, a precision medicine approach is needed and disease endotypes must be linked to the phenotype of an allergic condition.[13] Targeted treatment in asthma is limited because there are no good biomarkers to indicate which intervention has worked. Similarly, in AD there are three phenotypes with mixtures of the disease mechanisms of inflammation (ie Th2/Th17). Dupilumab reverses AD-associated epithelial abnormalities and affects the Th17- and Th1-related pathways, emphasising the need to target the therapeutic options for the individual.[14]

The talk by Tari Haahela dealt with '*Biodiversity, hypothesis and immune tolerance'.* In this excellent presentation, the reasons for the allergy and asthma epidemics were dissected. The loss of biodiversity with global warming and the influence of airborne chemicals was discussed. Various studies have found that individuals living in smaller farming communities have greater environmental and microbiota biodiversity and a lower prevalence of allergy-related conditions. This review included studies from various parts of the world, including Russia, Finland and the United States, that used different methodologies but demonstrated the same findings. Other studies have shown that even urban-dwelling dogs suffer from the same decrease in biodiversity of their microbiome, resulting in dysbiosis and disease. Studies show that enriching microbiota can prevent asthma and that enriching urban environments with trees can have a positive impact on microbiome diversity. The conclusion of the talk is that the epidemics of allergic diseases are the result of a loss of microbial protection, but ultimately the changes that have occurred to innate immunity may not be permanent and may be trained back to a more balanced environment.

In the symposium '*Understanding the complexity of atopic diseases through a systems biology approach',* both the common and disease-specific pathways and the complementary role of genetic and epigenetic factors in the pathogenesis of atopic

disease were discussed. The impact of genome-wide association studies (GWAS) was also outlined. The speakers were Gerard Koppelman (The Netherlands), Paul Lavender (United Kingdom) and Michael Portelli (United Kingdom). The first talk of this session was on the '*Link between asthma, hay fever and eczema'* as a shared disease with shared co-morbidities due to IgE sensitisation. The atopic march is a controversial idea of a temporal progression of atopic disease, starting with eczema and progressing to asthma and then rhinitis associated with IgE sensitisation. The trajectories taken by individual patients along this pathway differ. Systems biology uses mathematical models to understand the interactions between each atopic disease as well as what controls the trajectory. Atopy is a multifactorial disease, with thousands of genes interacting to cause disease. Single nucleotide polymorphisms (SNPs) are single variations that may be associated with allergic diseases – for example, filagrin deficiency increases the risk for the asthma trajectory. GWAS studies test millions of SNPs but need very large populations to make significant associations. In a GWAS study to determine the march from eczema to asthma the filagrin locus was identified as significant, but two other loci were also found to be related to the asthma phenotype. The role of epigenetics, which can potentially be heritable, also needs to be examined – in particular, the role of methylation, which has been strongly associated with allergic diseases.

Paul Lavender presented on '*Environment, epigenome and asthma',* which examined the hypothesis that the epigenome is not stable and is constantly being influenced by the environment. How genes are packed around histones controls how much translation occurs and there is little post-translational modification thereafter. New technology called *ChipSeq* allows histones to be modified using GWAS that look for chromatin architecture in cells. Methylation enables Th2 cytokines, and these gene modifications have been identified for asthmatics compared to normal controls, in particular with *periostin* expression. Asthmatics have less methylation, which is permissive for the expression of periostin.

In the last talk, '*Lessons learnt from 100 years of GWAS',* Michael Portelli discussed the multiplex nature of allergy and the interplay of genetics and immunology that results in disease. Genetics may assist with the heritable components of asthma but also with the pathogenic and novel therapeutic interventions. Using a hypothesis-free GWAS chip-based system allows for standardised and reliable genetic data. Because of the very large populations needed to afford the necessary granularity to determine specific disease loci for all subtypes of disease, chip technology has been added to GWAS studies for better phenotyping of disease.

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