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## Highlights of the ERS Lung Science Conference 2022

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This article presents the highlights of the ERS Lung Science Conference 2022, including a session organised by the Early Career Member Committee (ECMC) dedicated to career development <https://bit.ly/3tarCXc>

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Every year, the European Respiratory Society (ERS) organises the Lung Science Conference (LSC), in Estoril, to discuss basic and translational science. The topic of the 20th LSC was “Mucosal immunology of the lung: balancing protective immunity and chronic inflammation”. This was the first time that the LSC was organised as a hybrid congress with both in person and online attendance. In addition to an outstanding scientific programme, the LSC provides excellent opportunities for career development and inclusion of early career members (ECMs). All scientific and poster sessions are chaired by an ECM who is paired with a senior faculty to allow ECMs to become acquainted with session chairing, and there is a session organised by the Early Career Member Committee (ECMC) dedicated to career development. Moreover, travel bursaries are made available to abstract authors, and all bursary recipients and first-time attendees are invited to take part in a mentorship lunch. In this article, we provide the names of the ECM awardees and describe the scientific highlights of the LSC 2022 for those who could not attend.

### ECM awardees

The ERS presents several awards at the LSC and here we highlight all LSC 2022 awardees. The five highest ranked abstracts from ECMs were presented during the young investigator session. Elza Evren (Sweden) received the *William MacNee award* for the best presentation in this session. Several abstracts were selected for oral presentations, and Theodore Kapellos (Germany) was presented with the inaugural *Geoffrey Laurent Award* for the best oral presentation. In addition, the organisers presented eight distinguished poster awards to: Guilherme Dragunas (the Netherlands), Cornelia Blume (UK), Valeria Viteri-Alvarez (Germany), Florent Foisset (France), Isabelle Dupin (France), Sudip Das (Switzerland), Merete Long (UK) and Aicha Jeridi (Germany) for their excellent contributions during the poster session.

### Opening lecture

Anne O’Garra (Francis Crick Institute, UK) kicked off the conference on Thursday evening with an opening lecture on the role of cytokines in orchestrating immune responses in tuberculosis (TB). Her work has involved the identification of diagnostic biomarkers for active TB infection, focusing on blood biomarkers as a more accessible biofluid than bronchoalveolar lavage or sputum samples, which can be hazardous to obtain during active TB. Transcriptomic analysis of blood revealed a type 1 interferon (IFN)-inducible gene signature in TB. These signatures have the potential to be used in diagnostics to determine disease status. One diagnostic challenge is to be able to differentiate active TB from the



common cytokine signature seen during other viral infections, such as influenza, but transcriptomics revealed other unique gene signatures active in TB compared with other viral infections [1]. To date, there has been no test to determine which of the 5–10% of individuals with latent TB will progress to active TB. However, a recent study from Prof. O’Garra’s group followed household contacts of active TB patients to identify changes in gene expression in incipient *versus* latent TB, which increased during subclinical and clinical TB, were detectable prior to clinical diagnosis, and responded to treatment [2].

### **Lung cell atlas in health and disease**

The opening session of the LSC 2022 revolved around the applications of molecular atlases of the human lung in health and disease. Laure Emmanuel Zaragosi (IPMC, France) started the session with her talk on the variations in cell composition along the healthy human airway tree. Using single-cell RNA sequencing, she found a more prevalent population of secretory cells in tracheobronchial than in nasal biopsies and she showed that the expression of *ACE2*, a major entry factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which correlates with infectivity, is expressed at higher levels in the upper respiratory tract. Such single-cell atlases are usually built from several donors and different datasets and can be integrated together into a consensus map to remove batch effects and facilitate cell type annotation. In this regard, Malte Lücken from the Helmholtz Center in Munich (Germany) launched the human lung cell atlas (HLCA), a reference map based on 14 published healthy human lung datasets [3], which can be used for further exploration, overlay of new genomics data for rapid analysis and the discovery of rare cells and gene modules. Dr Lücken nicely demonstrated that the HLCA can also be applied to respiratory disease samples and used to evaluate the deviation from the healthy status with computational approaches. Next, Elo Madisson (Sanger Institute, UK) presented her fascinating work on a spatial multi-omics atlas of the healthy adult lung that combined single-cell with single-nuclei sequencing in five airway locations, spatial transcriptomics and VDJ sequencing [4]. Dr Madisson increased the number of known cell types/states in the lung stroma to 79 (from 58) and described new fibroblast populations (peribronchial, perichondrial, nerve-associated and immune-recruiting) that associate with lung disease. Moreover, she enhanced the transcriptomic resolution of the lung vasculature by the addition of novel immune-recruiting pericytes. Kerstin Meyer (Sanger Institute, UK) closed the session with an exciting talk about the local and systemic responses of children and adults to SARS-CoV-2 [5]. Dr Meyer discovered that airway and innate immune cells from healthy children display a pre-activated IFN response which contains the infection at a very early stage and prevents it from becoming systemic. In contrast, she observed an expansion in the peripheral cytotoxic and memory immune population in adults who present with an increased systemic IFN response. Together, all the speakers made a strong case for how molecular lung atlases may be used for novel discoveries about lung cell composition and functionalities in both health and respiratory diseases.

### **Tissue resident *versus* recruited immunity**

Scott Budinger (Northwestern University, USA) kicked off the session by introducing alveolar macrophages (AMs), sentinels of healthy lung function. In mice, AMs differentiate from fetal monocytes right after birth and are capable of self-renewal [6–8]. By contrast, bone marrow-derived monocytes are recruited to the lungs during injury and give rise to monocyte-derived AMs [9–11]. By analysing bronchoalveolar lavage fluid from SARS-CoV-2 patients, Prof. Budinger and his team have established a model of SARS-CoV-2 pneumonia in which infected tissue-resident AMs attract T-cells that in turn induce monocyte infiltration to the alveoli [12]. The inflammatory signalling between T-cells and AMs is mediated through calcium release-activated calcium (CRAC) channels. In order to suppress this self-sustaining signalling circuit between macrophages and T-cells, the team conducted promising clinical trials using the CRAC-channel inhibitor Auxora, in collaboration with CalciMedica. The next talk by Franziska Hartung (Helmholtz Zentrum München, Germany) focused on allergic airway inflammation. Exposure to house dust mite (HDM) increases tumour necrosis factor (TNF) release by macrophages and triggers allergen-induced inflammation. Moreover, TNF signalling induces central trained type-2 immunity of macrophage progenitors, which leads to chronic airway inflammation characterised by strong interleukin (IL)-6, CCL17 and leukotriene production [13]. In the third talk of this session, René Lutter (Amsterdam UMC, the Netherlands) gave an overview on innate and adaptive responses to rhinovirus. He explained that antiviral responses to rhinovirus are heterogenous (both in asthma patients and healthy individuals) and depend on IFN signalling [14]. Interestingly, asthma patients show faster antiviral responses in nasal and bronchial epithelial cells, despite having an attenuated IFN response. A possible explanation for this observation resides in metabolic differences between bronchial epithelial cells in asthma patients and those in healthy individuals [15]. Next, Nicoletta Bruno (Imperial College London, UK) discussed the effects of granulocyte colony-stimulating factor (G-CSF) on the pathophysiology of rhinovirus-induced exacerbation of allergic asthma. G-CSF stands out as a potential target to neutralise, as it induces both neutrophilic and type 2 inflammation. An important concern when targeting G-CSF is that patients can be more susceptible

to infection; however, there is still a residual level of granulopoiesis happening independently of G-CSF and previous studies have shown that an anti-G-CSF receptor antibody is well tolerated [16]. Finally, Mustapha Si-Tahar (Université de Tours, France) concluded the session by presenting his work on an innovative metabolic therapy. He proposed to use the metabolite succinate to treat influenza infection as succinate disrupts the influenza virus cycle by causing the retention of specific viral proteins in the cell nucleus [17].

### **Neonatal immune development**

Before the conference dinner, Petter Brodin (Karolinska Institute, Sweden and Imperial College London, UK) presented his group's research on the development of the neonatal immune system. Prof. Brodin introduced the immune system as a sensory system for environmental factors, that determines which pathogens to tolerate and which to reject. He briefly described his team's mass cytometry methodology, which by reducing technical variation can reliably profile immune cells from small-volume whole blood samples, with useful applications in paediatric immunology research [18]. Prof. Brodin then presented results from the IMPRINT study, which mapped changes in immune development in early life [19]. Faecal samples collected in the first months of life showed that gut microbial composition was heterogenous at birth but converged over time. At 3 months, children with low levels of bifidobacteria showed a heightened inflammatory profile. A reduced ability of the gut microbiome to utilise human milk oligosaccharides was associated with systemic inflammation, promoting T-helper cell (Th)2 and Th17-type immune responses in favour of Th1 immunity. Infants receiving *Bifidobacterium infantis* supplementation had improved immune outcomes, and faecal water from supplemented infants upregulated galectin-1 in T-cells *in vitro*, promoting tolerogenic immune status. Thus, probiotic intervention in this key window of immune system development has potential to mitigate, from a lung science perspective, paediatric asthma and allergy risk.

### **The mucosal immunity in the lung and infections**

Laurent Gillet (Université Liege, Belgium) started the session discussing the role of infection with gammaherpesviruses in protection against asthma development. Early-life Epstein-Barr virus (EBV) infection protects against IgE sensitisation [20], which in Western countries occurs later in life, whereas the prevalence of type 2 diseases, such as asthma, are increasing. Prof. Gillet used a murine intranasal infection model with Murid Herpesvirus 4 (MuHV-4) to study the effect of gammaherpesviruses on HDM-induced asthma. Compared with mock-infected mice, MuHV-4 lowered HDM-induced pulmonary inflammation and eosinophils and Th2 cytokines in bronchoalveolar lavage [21]. This protection was driven mainly by AMs, as transfer of MuHV-4 infected AMs protected against HDM-induced eosinophilia. RNA sequencing revealed that MuHV-4 infected AMs displayed a M1/Mreg phenotype, with better antigen presenting capacity and major histocompatibility complex-II expression, compared with mock-infected AMs. Furthermore, genes related to monocytic origin were increased in AMs. Using chimeric mice, they showed that, upon MuHV-4 infection, the percentage of AMs increases until day 5, after which they are replaced by Ly6C<sup>high</sup> monocyte-derived macrophages, which under homeostatic conditions does not occur [6, 7]. These monocyte-derived AMs lowered costimulatory molecule expression on dendritic cells [22], which impaired their capacity to activate Th2 cells upon an HDM challenge. These findings show that these trained macrophages support the hygiene hypothesis [23]. Next, Martijn Nawijn (Groningen, the Netherlands) showed single-cell RNA sequencing data demonstrating various cell types and a varying cell composition along the tracheobronchial tree [24]. Based on the transcriptional state, it was shown that in asthma there is an increase in mucous ciliated cells. Using pseudotime analysis, the authors showed a stable state of the epithelial cells in health, whereas in asthma a higher proportion of the epithelial cells displayed intermediate cell states along the trajectory towards a dedicated cell phenotype. Furthermore, type 2 cytokines *IL4/IL13* and Notch signalling was increased in asthma, which likely mediates goblet cell metaplasia. Finally, using SmartSeq2 profiling, pathogenic CD4 T-cells were identified in the asthma airway wall. Due to the growing number of available datasets of single-cell RNA sequencing, Prof. Nawijn proposed the application of the common coordinate framework to identify the anatomical location in the lung, which is based on the branching generation.

### **Cytokine targeted therapies/personalised medicine in the context of (chronic) respiratory diseases**

The session was opened by Guy Brusselle (Ghent University, Belgium), who discussed the role of cytokine targeting therapies in asthma and COPD. Prof. Brusselle began by describing type 2-high asthma or type 2-low phenotypes of asthma [25]. This characterisation has led to the successful identification of treatable traits and subsequent therapies, including anti-type 2 cytokine antibodies and anti-alarmin antibodies. Prof. Brusselle highlighted that treatment success can be affected by factors such as age of asthma onset and blood eosinophil count, and these factors in combination with biomarkers should be used

to guide treatment regimens [26]. Although treatment of eosinophilic asthma has been highly successful, unfortunately these treatments have been less effective in eosinophilic COPD, most likely due to a less in-depth understanding of the biological mechanisms driving inflammation in this disease [27, 28]. Chris Brightling (University of Leicester, UK) focused on treatments and targets for asthma beyond type-2 inflammation. He started by outlining the heterogeneity of asthma, including allergic and non-allergic eosinophilic subtypes but also mixed granulocytic and Th1/Th17 dominated subtypes, which have a less defined treatment pathway [29]. Anti-TSLP (thymic stromal lymphopoietin) therapy with tezepilumab showed efficacy across asthma subtypes including in patients with low blood eosinophil counts [30]. Anti-alarmin strategies therefore present a potential strategy for a broad group of asthma patients. Encouraging results from a phase 2 trial of the anti-ST2 antibody astegolimab were also presented, showing promising trends towards reduced exacerbations including in type 2 low patients [31]. However, caution was emphasised in targeting this subgroup, as a study targeting IL-23 with risankizumab showed an increase in exacerbations [32]. Developing treatments for the non-eosinophilic subtype will require careful phenotyping and the development of new biomarkers. James Chalmers (University of Dundee, UK) closed the session by discussing the lung microbiome in chronic lung disease, focussing on COPD and bronchiectasis. Cross-sectional studies show that severe airways diseases are frequently associated with a loss of diversity and an increase in pathogenic Proteobacteria, but Prof. Chalmers emphasised the importance of moving beyond descriptions of the microbiome towards understanding its relationship with the host response and changes with treatment [33]. In this respect, he presented studies showing relationships between proteobacteria dysbiosis and neutrophil extracellular trap formation, and also a subset of patients with both COPD and bronchiectasis with Firmicutes dominance and eosinophilic inflammation [34–38]. Studies show that inhaled corticosteroids and antibiotics can modify the microbiome and Prof. Chalmers highlighted the importance of incorporating microbiome sequencing into interventional studies in the future.

#### **Early-career delegates session: tools for career development**

The ERS ECMC chair, Niki Ubags (University Hospital Lausanne, Switzerland), introduced this year's ECM session with the theme of career development across teaching, collaboration, transferrable skills and editing. For development opportunities within ERS, Dr Ubags encouraged ECMs to register with an ERS Assembly, complete the myERS platform competency list and contact the ECM representatives. Agnes Boots (Maastricht University, the Netherlands) then presented on effective teaching in science, in its varied forms, and where to begin. Dr Boots advised that success always requires teachers or mentors to strive to appropriately tailor content to the audience and promote engagement, utilising interactive methods wherever possible, from quizzes to addressing concerns, and crucially, active listening. On successful collaboration between industry and academia, Alexander MacKay (Basel, Switzerland), currently in industry, and Rachel Chambers (University College London, UK), a current academic, provided their perspectives. Referencing the development of the Oxford–AstraZeneca SARS-CoV-2 vaccine, key elements of good collaborations were described as mutual scientific interests and contribution of ideas and resources, implementing robust and deliverable research plans, and equally weighted partnerships. In addition, consideration was encouraged for payment in-kind. This may include technology, expertise, data storage and analysis, which could provide greater impact and mutual benefit than monetary contributions. The advice from both speakers was to start conversations with industry early, as projects often have long timelines, and to take opportunities to connect with industry across the translational research pipeline, from industrial placements to entrepreneurial training and networking events.

Talking about developing transferrable skills as a scientist, Verity Elston (University of Lausanne, Switzerland) explained the Horizon 2020 DocEnhance project [39], and reported 83% of university researchers teach, mentor or supervise, and almost 25% are involved in administration, staff management, budget management or international partnerships. Dr Elston emphasised career management must be directed towards developing skills ECMs will need to progress, like those above, and its critical importance demands dedicated time. Additional selected resources included the ERS website, podcasts (Papa Phd Podcast, <https://papaphd.com/>; Hello PhD, <https://helloworld.com/>) and books (*The Squiggly Career* by Helen Tupper and Sarah Ellis; *The Compass and the Radar: The Art of Building a Rewarding Career While Remaining True to Yourself* by Paolo Gallo).

Finishing the session, Timothy Powell (Oxford, UK), editor at *Nature Communications*, talked about careers and involvement in scientific editing. Dr Powell's advice for ECMs to gain experience valued by journals included asking advisors or other academics for opportunities to review manuscripts, writing papers, editorials and magazine articles, and participating in Early Career reviewer and editor mentoring programmes available from *Nature Communications* and other journals.

### Final remarks

This paper provides an overview of the LSC highlights, including a session organised by the ECMC dedicated to career development. For those who could not attend the conference or want to re-watch the sessions, learning resources are available: 1) recordings of the sessions are available to ERS members on the e-learning website (<https://www.ers-education.org/events/conferences/?idP=255013>); and 2) abstracts from the LSC 2022 are available as online supplement in *ERJ Open Research* ([https://openres.ersjournals.com/content/8/suppl\\_8](https://openres.ersjournals.com/content/8/suppl_8)).

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