



Lung Science Conference highlights 2023: Post-viral lung diseases – from basic immunology to clinical phenotypes and therapy

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This article provides an overview of some of the highlights of the Lung Science Conference 2023
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The European Respiratory Society (ERS) Lung Science Conference 2023 was held in Estoril, Portugal, on 9–12 March 2023 in a hybrid format. This conference is organised by the ERS on a yearly basis to focus on the latest basic and translational respiratory science. The topic of this year's Lung Science Conference was “Post-viral lung diseases – from basic immunology to clinical phenotypes and therapy” and included several sessions on the importance of understanding the host response to viral infections, the technological advances made to further study these interactions and how to translate this knowledge to therapy.

The presentations offered a comprehensive understanding of the current research landscape in this area, stressing the need for ongoing investigation and collaboration among scientists and clinicians. It also included a specific session directed at early career delegates, focusing on career development. Early career delegates were involved in several activities, from participating in oral/poster communication sessions as presenters and/or chairs, to mentoring and networking opportunities, as presented in a previous Early Career Forum article [1]. This paper summarises some of the outstanding sessions of the Lung Science Conference 2023, written by early career delegates attending the sessions.

Opening lecture: What can we learn from acute virus infections for chronic disease?

The conference started with the opening lecture by Peter Openshaw (UK) summarising key findings about the long-term effects of infections with respiratory syncytial virus (RSV), influenza virus (IV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Multiple studies have described the associations between early life lower respiratory tract infections (LRTIs), particularly with RSV, and recurrent wheeze and asthma later in life. However, whether severe RSV infection is causal, or rather exposes a common predisposing factor, is still being discussed. Support for a causal relationship comes from a placebo-controlled trial on the effects of palivizumab [2] and from animal models investigating potential underlying mechanisms. Vaccines against RSV, which are expected to be licensed for adults soon, and the recent approval of nirsevimab, a novel long-acting monoclonal antibody for RSV prophylaxis, are expected to improve understanding of the link between RSV and the development of asthma.



Immunity and inflammation have been shown to be determinants of outcomes during the 2009 IV pandemic. In a recent analysis of data from the MOSAIC study, a neutrophil-driven endotype was identified, which was associated with worse outcomes compared to an adaptive or endothelial endotype [3].

The last part of this talk was focused on the importance of sequelae of SARS-CoV-2 infection. Several mechanisms have been proposed to contribute to the diverse symptoms seen in patients with long COVID (or post-COVID syndrome), including immunological dysfunctions [4, 5], virus persistence in the gastrointestinal tract [6], reactivation of herpes viruses [7], and autoantibodies. P. Openshaw highlighted that a better understanding of the main drivers will be crucial to understanding which patients will benefit from which type of therapy.

Keynote lecture: Regulation of pulmonary memory B cell responses to influenza

In this keynote lecture, Andre Ballesteros-Tato (USA) gave insights into the mechanisms behind the development of lung-resident memory B cells (lung BRMs) following IV infection. The generation of lung BRMs in response to IV has been described only recently as an important contributor to immunity against homologous and heterosubtypic infection [8, 9], and the mechanisms controlling the differentiation of lung BRMs have not been fully deciphered yet. A. Ballesteros-Tato presented data highlighting a crucial role for T follicular helper (Tfh) cells and interferon (IFN)- γ signalling in this process. He showed that, in mice lacking Tfh cells, the development of lung BRMs is abrogated, and that intrinsic IFN- γ signalling in B cells is required to establish IV-specific lung BRMs. Tfh cells were shown to be able to transiently express IFN- γ following infection and, using bone marrow chimeras, A. Ballesteros-Tato and his group showed that these IFN- γ^+ Tfh cells are required in the development of protective lung-BRM following IV infection. These findings highlight a novel function of the Tfh cells and show that they significantly contribute to establishing local protection in the lung following viral infection.

Oral presentation session: Host response to virus infections – focusing on the lung stroma

The first session on host response to virus infections was particularly focused on the lung stroma.

First, Thomas Wilkinson (UK) dissected the role of bronchial epithelial and basal cells in respiratory tract infections, highlighting their role in maintaining the integrity of the respiratory epithelium and in the innate immune response to infections. It was described that basal cells have the ability to generate not only immune memory, but also phenotypic memory, which may contribute to long-term disease. A greater understanding of these processes could reveal new therapeutic opportunities.

Antoine-Emmanuel Saliba (Germany) presented research on the link between alveolar epithelial cell infection and fibrosis, emphasising the crucial role of alveolar epithelial cells in gas exchange and their vulnerability to viral infections [10]. Infection-induced alveolar epithelial cell dysfunction can contribute to fibrotic remodelling of the lung, ultimately leading to impaired lung function. Evidence was provided of specific molecular pathways that could serve as potential therapeutic targets for the prevention and treatment of lung fibrosis.

Next, Ana Lilia Serna Valverde (UK), showcased novel work on *in vitro* modelling of respiratory infections using patient-specific human induced pluripotent stem cells (hiPSC)-derived alveolar epithelial cells [11]. Particularly, the presentation described how these cells provide a valuable platform to study the pathogenesis of idiopathic pulmonary fibrosis (IPF) and investigate the impact of viral infections on the disease progression [12]. A.L. Serna Valverde's findings suggest that laboratory-generated alveolar type 2 cells derived from patient-specific hiPSCs and the genetically corrected counterpart hiPSCs [11, 13] can be used to model infections *in vitro*, providing a new way to explore host-pathogen interactions in IPF-related mutations.

Finally, Maximilian Ackermann (Germany) discussed the response of pulmonary endothelial cells to virus infections, highlighting that each disease has a unique pro-angiogenic profile and describing the differences between classical interstitial lung disease patterns, such as usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). M. Ackermann found that COVID-19 resembles the NSIP pattern more closely than UIP, indicating that prolonged inflammation may be driving this response. His research also showed collagen accumulation and macrophage infiltration in lung tissues up to 9 weeks after the acute phase of the disease.

Oral presentation session: Host-immune response to virus infections of the lung

In this session, Susanne Herold (Germany) focused on the involvement of myeloid cells in respiratory virus infections. This work described the differentiation trajectories of macrophages and their role in tissue

repair after viral lung injury; in particular, the trajectory of depletion and replenishment of tissue-resident alveolar macrophages (TR-AMs) during viral pneumonia [14]. This research explored the functional phenotypes of infiltrating bone marrow-derived macrophages (BMDMs) and their differentiation towards TR-AMs. scRNA-seq data revealed two distinct BMDM phenotypes during the course of pneumonia, one present during the acute inflammatory phase (BMDM-INF) and a consecutively emerging, regenerative population (BMDM-REG). BMDM-REG drive size and numbers of bronchoalveolar lung organoids when co-cultured, inducing alveolarisation and branching morphology. Furthermore, the replenished TR-AMs derived from BMDM-REG retain a regeneration memory at least for 28 days in terms of epithelial proliferation and barrier protection. S. Herold then elaborated on the molecular mechanism of epithelial repair mediated by BMDM-REGs and their TR-AM descendants. Plet1 plays a pivotal role in epithelial repair, as it is a protein expressed highly by BMDM-REG and TR-AM descendants that induces epithelial proliferation and barrier protection [15]. The ongoing research aims to identify the receptor for Plet1 and its involvement in Plet1-mediated signalling. In conclusion, the presentation suggests that BMDMs play a vital role in tissue repair, and Plet1 may serve as a potential therapeutic target for lung injuries.

Next, Anke Faehnrich (Germany) focused on post-COVID syndrome, understood as various long-lasting symptoms after the initial infection [16]. Post-COVID syndrome affects 3–17% of people after infection with SARS-CoV-2 and, therefore, it represents a major health burden. Single-cell RNA sequencing from nasal biopsies was conducted on 10 patients with moderate and 15 with severe post-COVID syndrome, to identify potential biomarkers for risk stratification. Patients affected by severe post-COVID syndrome had decreased populations of ciliated cells (13% less than control) and doubled basal cells in the nasal epithelium compared to controls. Pathway enrichment analysis revealed nuclear factor (NF)- κ B and tumour necrosis factor (TNF) response signatures, particularly identified within immune populations. In severe patients, immune populations showed significantly activated TNF- α and NF- κ B signalling, and downregulation of transforming growth factor (TGF)- β signalling. These findings provide insight into potential biomarkers for risk stratification.

Then, Harry Karmouty-Quintana (USA) presented a relevant study on non-resolvable COVID-19 (NR-COVID-19), a condition in which COVID-19 patients with lung injury progress rapidly to the point where lung transplantation is necessary [17]. This study aimed to identify the cellular mechanisms that lead to lung fibrosis in NR-COVID-19. Lung explants from 23 NR-COVID-19 patients, 11 IPF patients and 13 controls were analysed to investigate molecular markers and histological changes. The results showed increased fibrotic markers in NR-COVID-19, including COL1A2, COL3A1 and periostin, compared to IPF, which had increased COL2A1 expression. The study also found increased TGF signalling in NR-COVID-19 and IPF. Periostin, a marker of activated fibroblasts, was highly upregulated in NR-COVID-19, and bronchiolisation and expression of transitional cell markers were observed. The study also found increased levels of Six1, which is linked to IPF, in NR-COVID-19; its deletion inhibits lung fibrosis induced by bleomycin in mice. Six1 is also elevated in SARS-CoV-2 infection and in Krt8-positive cells.

The second part of the session started with Katie Daly (Australia) explaining how infection of recombinant histone deacetylase 6 (rHDAC6) knockouts with influenza A virus resulted in absent or severely blunted IFN response [18]. This protective IFN response was found to be stimulated by HDAC6 through deacetylation of DDX1. To explore the therapeutic potential of HDAC6, mice were treated with rHDAC6 before infection with H1N1 strain and subsequently tested for lung function analysis. Treatment with rHDAC6 led to a decrease in viral titre, improved lung function and protection against infection-induced weight loss.

Hermelijn Smits (the Netherlands) then provided an overview on adaptive immunity against respiratory viruses, discussing the Beat-COVID study, which explored mucosal immunity in COVID-19 patients. An influx of granulocytes and monocytes was observed using mass cytometry, which was followed by multi-omics factor analysis to visualise relationships between immune factors and clinical features. Latent factor 3 was found to be negatively associated with oxygen saturation. SARS-CoV-2-specific CD8⁺ and CD4⁺ T cells from blood and CD8 T cells from nasal mucosa during convalescence were sequenced and showed that individuals developed SARS-CoV-2-specific T cells in their nose compartments, which may have a protective effect.

Next, Nadia Suray Tan (Canada) presented a study on post-acute COVID-19 sequelae patients (PACS) with rheumatological symptoms [19]. Flow cytometry analysis of peripheral blood mononuclear cells from 108 patients with PACS, including 19 with autoimmune disease (PACS-AID), were conducted. Double-negative B cells were found to be positively correlated with PACS symptoms, and double-negative

B cells were found to be elevated in PACS-AID. The autoimmune phenomena may be attributed to a skewed ratio of B effector and B regulatory cells observed in PACS patients.

Hamida Hammad (Belgium) presented work on dendritic cell subsets in respiratory virus infection. Infection of mice with pneumonia virus of mice (PVM) and single-cell RNA sequencing of different dendritic cell populations revealed that cDC2s are present and they exhibit strong type-1 IFN signalling signature [20]. Sorting of the dendritic subsets from lymph nodes following PVM immune serum transfer showed that inflammatory cDC2s exposed to serum derived from convalescent mice were able to produce the highest amount of IFN- γ in T cells, indicating that they use antibodies to further boost the antiviral response.

Finally, Milena Espindola (USA) identified epigenetic reader BRD4 as a biomarker through *in silico* and immunohistochemical analysis of lethal COVID-19 [21]. Treatment with BRD4 inhibitor BRD4-Protac led to the reduction of fibroblast and airway epithelial cells outgrowth. Furthermore, inhibition of BRD4 in PASC-fibrosis bronchospheres limited the formation, size and the quantity of the bronchospheres and reduced interleukin (IL)-6 levels, compared to dimethylsulfoxide or standard-of-care drugs.

Oral presentation session: Technological advances to study acute and chronic virus infections of the lung

Philip Hansbro (Australia) discussed experimental models of coronavirus infection as a scaffold for the application of omics technologies in researching viral infections and respiratory disease. Single-cell sequencing (scRNA-seq Rhapsody) was used to identify changes in immune cell populations and gene expression in time course and dose-response investigations in their novel mouse model of coronavirus infection [22]. Sex-specific differences in expression of viral entry factors and antiviral response genes were determined to underly the increased susceptibility to infection displayed by males in clinical data [23, 24]. The role of specific cell types, such as macrophages, was also assessed *via* scRNA-seq wherein cell marker expression was used to map the development of macrophages over “pseudotime”, demonstrating that interstitial macrophages increased during infection and the level of infection can induce different immune cell changes. P. Hansbro highlighted the ease at which these techniques [22] could be adapted to different experimental models and diseases by describing the research performed by their group on human primary cell cultures from patients with COPD [25]. P. Hansbro concluded that the proper utilisation of these technologies can greatly improve our understanding of the mechanisms of pathogenesis of respiratory disease and infection and drive the development of more effective therapies.

Next, Anna Semenova (Germany) discussed longitudinal proteomic profiling of patient samples to identify molecular signatures of pneumonia induced by bacterial or SARS-CoV-2 infection [26]. Bacterial pneumonia was associated with increased neutrophilic signatures and innate immune cell proteins in bronchoalveolar lavage fluid (BALF), while COVID-19 samples showed elevated complement cascade activation, immunoglobulins, and fibrotic markers that persist over the course of infection, both in serum and BALF [22]. Stefanie Wamat-Herresthal (Germany) discussed the potential of swarm learning for decentralised and confidential clinical machine learning. S. Wamat-Herresthal first described the importance of large, high-quality, diverse and representative datasets for appropriate training of predictive clinical algorithms. The confidential and decentralised nature of the medical industry prevents the generation of a centralised data source for these purposes, meaning training is currently being done in isolation. Swarm learning overcomes the need for a central repository by uniting edge computing with blockchain-based peer-to-peer networking and coordination while maintaining confidentiality [27], allowing the integration of private medical data from any data owner worldwide without data sharing or violating privacy laws. The feasibility of using swarm learning to develop disease classifiers using distributed data was demonstrated in cases of leukaemia, tuberculosis, lung pathologies and COVID-19, in which swarm learning consistently outperformed models trained with data from a single site [27].

Finally, Isabelle Dupin (France) discussed the generation of an experimental model of tubular organoids that recapitulates morphological and functional characteristics of distal airways. The model utilised microfluidics to encapsulate bronchial epithelial cells and smooth muscle cells within an alginate scaffold. Temporal characterisation of the model showed it retained structure and viability for over 10 days, and cellular differentiation tight-junction formation and localisation of D cells were reflective of the biological airway. The lumen of this model is also capable of being perfused to establish an air liquid interface and is also permissible to infections [28].

Young investigator session – the William MacNee award

Pauline Bardin (Canada) presented her work on developing a gene therapy to treat *SFTPC* mutation-induced pulmonary fibrosis [29]. Inherited disorders of surfactant metabolism account for >10%

of all childhood interstitial lung diseases and are associated with the development of pulmonary fibrosis in adults [30]. The most common *SFTPC* mutation is a substitution of isoleucine to threonine at codon 73 (I73T) [31]. P. Bardin showed that while the *SFTPC*^{I73T} knock-in mice did not undergo fibrosis, they presented type II alveolar epithelial cell hyperplasia and focal airspace enlargement when compared to wildtype mice, suggesting they suffer from spontaneous emphysema. Adeno-associated virus vector-based gene therapy carrying the wildtype form of *SFTPC* reversed the spontaneous emphysema and when combined with a miR-strategy (which silences only the mutant form of *SFTPC*) it restores the alveolar space structure back to wildtype.

Joseph Bell (UK) presented data on the transcriptomic profile within distinct regions of the fibrotic niche [32]. The fibrotic niche is characterised by an interplay of mesenchymal, epithelial and immune cells, and extracellular matrix components. Of particular interest are the fibroblastic foci, *e.g.* the area of active fibrogenesis [33]. J. Bell compared three *in vitro* human fibroblast models (two-dimensional fibroblast culture on plastic, scar-in-a-jar and three-dimensional spheroid model) to assess their similarity in terms of transcriptomic to fibroblastic foci obtained from laser capture microdissection of lung tissue from pulmonary fibrosis patients. The data clearly showed that the three-dimensional spheroid model had the greatest similarity to the transcriptome of the fibroblastic foci and, therefore, represents an accurate culture model to study the human fibrotic niche.

Then, Nuria Mendoza Barco (Spain) shifted the focus of the audience from pulmonary fibrosis to post-COVID syndrome [34]. Most individuals recover after COVID-19, but some develop post-COVID syndrome characterised by persistent symptoms or chronic pulmonary sequelae, defined by abnormal lung function/structure [35]. N. Mendoza-Barco's work showed that, 1 year after the acute COVID-19 episode, individuals experiencing long-COVID or *sequelae* presented a higher virus-specific T cell response when compared to individuals who recovered fully, suggesting persistent stimulation by residual viral reservoirs.

Next, Lucia Rodriguez Rodriguez (Belgium) presented work on long-lasting alterations in lung anti-tumour immunity by viral infections [36]. Viral infection has an immunomodulatory role which could impair anti-tumour surveillance [37]. L. Rodriguez-Rodriguez employed a mouse model of Lewis lung carcinoma and infected it with two respiratory viruses (MuHV-4 and PMV, homologous to the human Epstein-Barr and RSV viruses, respectively) in order to assess the specific role of viral imprinting in tumour development in the lung. The research elegantly showed that pre-infection with these two viruses affects oppositely the development of lung tumour, with MuHV-4 having an anti-tumour response while PMV shows a pro-tumorigenic effect. This suggests that anti-tumour immunity in the lung could be shaped by a specific history of infection.

Lastly, Daniel C. Wendisch (Germany) presented published data on macrophage signature following SARS-CoV-2 infection and its role in triggering fibrosis in the lung [10]. Macrophages are stabilisers of lung homeostasis and pathological states [38, 39]. D.C. Wendisch's team has shown an accumulation of CD163-expressing monocyte-derived macrophages that acquired a profibrotic transcriptional phenotype during COVID-19 infection. These macrophages present a very similar transcriptomic profile to those of macrophages identified in single cell RNA sequencing data from IPF patients available from the literature. Proteomic studies confirmed the activation of a profibrotic signature in monocytes infected with SARS-CoV-2 but not influenza A virus.

Early career delegate session: Successfully funding your future research

The early career delegates' session is a key feature of the ERS Lung Science Conference and allows early career members to come together, socialise and learn about topics that are specifically designed for their career stage. This session was introduced by Sara Cuevas Ocaña (UK), who is the current early career assembly 3 representative and chair of the Early Career Member Committee (ECMC) [40]. S. Cuevas Ocaña described the role of the early career member representatives within ERS and explained how to get involved with the society [41].

After this brief informative introduction, four excellent speakers gave short talks around the general topic of "Successfully funding your future research" [42]. The first talk was given by Sejal Saglani (UK), ERS Fellowships and Awards Director, who gave an overview of the funding opportunities available for early career members funded by ERS [43]. This short talk was given in the spirit of transparency to explain how the ERS fellowships application and review process works, how applications are scored, and some very useful tips for writing a successful proposal. The second talk was given by Jessica Denning (UK), who is a representative of the patient-led European Lung Foundation [44]. J. Denning gave an exceptional perspective on how important it is to involve patients from the very beginning of our research and how to

write dissemination materials (including abstracts for conferences and grant applications) that are comprehensible to a non-expert audience. She touched upon issues of sensitive words and phrases when interacting with patients and she gave very practical tips and guidance on how to approach this important issue. The third speaker was Niki Ubags (Switzerland), the previous chair of the ECMC [41], who provided some tips on how to prepare for an interview to defend a research proposal. She mentioned the importance of reading guidelines and being sure about the specific tasks/format/platform related to that interview. She highlighted the key factors contributing to the success of a research proposal, *e.g.* the science (and its wider impact on/for patients), the applicant and the institution. The last speaker was Daiana Stolz (Switzerland), whose presentation was focused on equity, diversity and inclusion in workplaces and their importance in achieving employee satisfaction and research team success and fulfilment.

After their first introduction in 2022 [45], the short talks were followed again in 2023 [1] by round tables where early career delegates could ask questions to the experts, move around the tables and interact with each other. The round tables were led by the presenters of the short talks, with an additional round table on the subject of ERS fellowships, which was facilitated by Rory Morty (Germany), who was the ERS Fellowships and Awards Director prior to S. Saglani. The informal setup enabled everyone who had a question or curiosity about one of these topics to ask to the presenters. While the topics were assigned according to the content of the talks, conversation moved freely, and it promoted interaction between senior and junior members and experts.

Oral presentation session: Translation to therapy

Bart Haagmans (the Netherlands) discussed the development of novel treatment strategies to fight coronavirus infections and emphasised the need for preparedness and adaptability in research for the development of effective clinical interventions. Early in the pandemic, treatment with monoclonal antibodies for SARS-COV-1 S1 subunit showed great therapeutic promise, but as novel variants emerged with significant antigenic divergence this approach became effectively redundant [46]. Early investigations in cell lines identified that therapies such as chloroquine [47] could inhibit the virus; however, this could not be replicated clinically [48]. The development of more appropriate models, such as airway organoids [49] modified *via* CRISPR-Cas9, facilitated more accurate identification of therapeutic targets, such as serine proteases [50], which are showing great promise in early studies. A biobank of these modified organoids has now been developed [51] to increase pandemic preparedness and facilitate prompt mechanistic investigations in other viral infections.

Michael Holtzman (USA) discussed the need for treatments that achieve disease modification in respiratory disease, where mucus production is a key feature that is closely related to morbidity and mortality [52, 53]. M. Holtzman developed a model of post-viral lung disease which identified basal epithelial stem cells (basal-ESCs) as drivers of IL-13 mediated mucus production and hyperplasia *via* release of CXCL17 to attract and activate macrophages in the remodelling phase of infection [54]. Escalation of basal-ESC activation and expansion mediated by MAPK13 is linked to mucus production [54]. M. Holtzman developed the first selective MAPK13 inhibitor, NuP-4a, designed to prevent stem cell activation and reprogramming that occurs following viral infection and inhibit mucus production. In pre-clinical proof-of-concept investigations, NuP-4a was shown to block the activation of the target molecule (MAPK13) and target cell (basal-ESC) growth and mucus production in human cell culture. It also corrects basal-ESC reprogramming and disease (airway inflammation and mucus production) in animal models, provides therapeutic benefit that continues after treatment cessation, and correlates with clinical biomarkers of basal-ESC reprogramming and airway disease. This is the first drug designed to potentially correct basal-ESC reprogramming and that achieves disease modification in post-viral lung disease.

Daiana Stolz (Switzerland) discussed the challenges of treating virus infections in patients with chronic lung disease, and highlighted the difficulty of accurately diagnosing respiratory infections due to their similar clinical presentation. Community-acquired respiratory viruses typically follow seasonal patterns, but pandemic-related changes have resulted in out-of-season viral outbreaks [55], further complicating diagnosis. RT-PCR is the primary diagnostic tool for viral infections; however, conventional microbiology and upper respiratory tract PCR can only identify 38% of community-acquired pneumonia cases [56]. To obtain more accurate results, lower respiratory tract samples are necessary, and bronchoscopy and bronchoalveolar lavage investigations can be utilised to aid and advise patient management. D. Stolz provided an overview of the six primary respiratory viral infections that are clinically significant, emphasising that most of them still lack effective vaccines or antiviral therapies, and highlighting the urgent need for more translational research in this field.

Take-home messages

- Sessions on host–response and host immune–response to virus infections provided valuable insights into the complex interplay between lung cells, viruses and the immune system.
- By examining the roles and responses of lung cells during viral infections, researchers can identify novel therapeutic targets and develop more effective interventions for respiratory diseases.
- This knowledge will prove indispensable to enhance the diagnosis, treatment and management of respiratory infections, and their associated complications.
- Interdisciplinary research is fundamental to unravel the complexities of lung response to viral infections, ultimately benefiting patients worldwide.

Final remarks

This article provided an overview of some of the most remarkable sessions of the Lung Science Conference 2023. The abstracts submitted to the conference are available as supplement 10 of *ERJ Open Research* in March 2023 (https://openres.ersjournals.com/content/9/suppl_10). We hope to see you in the next edition!

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