Patricia P. Ogger[1], Johnatas Dutra Silva[2], Mahyar Aghapour[3,4], Irma Mahmutovic Persson[5], Christy Tulen[6], Renata Jurkowska[7], Niki D. Ubags[8]

Niki.ubags@chuv.ch

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Early career forum

Early Career Members at the ERS Lung Science Conference 2020: metabolic alterations in lung ageing and disease

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Every year, the European Respiratory Society (ERS) organises the Lung Science Conference (LSC) in Estoril, Portugal, to discuss basic and translational science. The topic of the LSC 2020 was "Metabolic alterations in lung ageing and disease". 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 member to allow ECMs to become acquainted with session chairing. In addition, 40 travel bursaries are made available to abstract authors and all bursary recipients are invited to take part in a mentorship lunch. Moreover, there is a session organised by the Early Career Members Committee (ECMC) dedicated to career development. Here, we describe the scientific highlights of LSC 2020 for those who could not attend.

The ERS presents several awards at the LSC and here we will highlight all winners of the LSC 2020 awards. The five highest ranked abstracts from ECMs are presented during the Young investigator session. Patricia Ogger (UK) was presented with the William MacNee Award for the best presentation in this session. Several abstracts were selected for programmed oral presentations and Renata Jurkowska (UK) was presented with the inaugural Geoffrey Laurent Award for the best oral presentation. Moreover, the organisers presented eight Distinguished Poster awards to Anne-Sophie Lamort (Germany), Julia Frankenberg Garcia (UK), Johnatas Silva (UK), Pauline Esteves (France), Claudio Bussi (UK), Elodie Picard (France), Felix Ritzmann (Germany) and Alen Faiz (Australia) for their excellent contributions during the poster session.

Opening lecture

The introduction and opening lecture was given by Luke O'Neill (Dublin, Ireland). He introduced the term "immunometabolism" [1] and discussed its potential importance in drug efficacy. Prof. O'Neill mentioned that many drugs, although very promising in pre-clinical stages, were not proven to be efficient in clinical trials. This may be because although the immunology and pathology was studied and targeted, the influence of the metabolism was understudied. To move the field forward, these effects and metabolic mechanisms need to be further studied in order to "boost efficacy" of drugs, and ultimately be able to more effectively treat lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). He further discussed the role of cell death, particularly how caspases and inflammasomes can affect homeostasis, being potential targets for improvement of drugs and patient response.

The nucleotide-binding domain leucine-rich-containing family pyrin domain-containing-3 (NLRP3) inflammasome is a sensor for metabolic disturbance and that is why the NLRP3 inhibitor MCC950 (also called diarylsulfonylurea cytokine

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The Lung Science Conference 2020 brought together leading experts in the field to discuss the latest cutting-edge science, as well as various career development opportunities for early career members https://bit.ly/2XZ5YGQ

release inhibitory drug (CRID3)) was considered as a "game changer" [2]. Recent studies have specified the mechanisms of CRID3, indicating that inhibitory effects are exerted *via* the NAIP, CIITA, HET-E and TP1 domain with NTPase activity (NACHT) of NLRP3 [3], and reduce inflammation in murine airway and skin inflammatory disease models [4, 5].

Caspases play a role in inflammatory diseases and caspase-11 has been shown to promote allergic airway inflammation [6]. When performing studies in caspase-11 knockout mice, there is reduced tissue inflammation by histology, decreased total cell counts from bronchoalveolar lavage fluid and, importantly, eosinophil reduction in the knockout animals. Caspase-11 corresponds to caspase-4/5 in humans. Analysis of sputum samples from asthma patients revealed increased caspase-4 levels, as well as elevated levels of NLRP3, caspase-1, caspase-5 and interleukin (IL)-1β [7].

The Warburg effect was first described by Otto Warburg in the context of cancer, observing that cancer cells use glycolysis as their main metabolic pathway, even in the absence of hypoxia. In his talk, Prof. O'Neill highlighted the importance of metabolism for cell function and as a driver of disease, and showed studies linking glucose levels in the lungs to areas of fibrotic foci in patients with idiopathic pulmonary fibrosis (IPF) [8]. Fibrosis is considered to result from dysregulated wound healing and no cure is currently available. New drugs, such as pirfenidone and nintedanib, slow disease progression but a better understanding of the disease is urgently needed. Investigating cell metabolism in the context of pulmonary fibrosis could offer new therapeutic opportunities, as clinical studies [9–11] and pre-clinical fibrosis models [12] indicate a dependence of fibrotic foci on glucose and glycolysis.

Pyruvate kinase M2 has been shown to activate Warburg metabolism in M2 macrophages and is therefore a critical determinant in inflammatory responses [13]. In this opening lecture, Prof. O'Neill emphasised the importance of the Krebs cycle and the products it generates, one of them being itaconate. Besides antibacterial functions, itaconate has recently been shown to limit NLPR3-dependent cytokine release, such as that of IL-1β from peripheral blood mononuclear cells in patients with cryopyrin-associated autoinflammatory syndromes. When lipopolysaccharide and itaconate were administered at the same time, an improved survival rate was observed [14, 15].

The main and important message from Prof. O'Neill was that "metabolism is the driver (of disease) while genes are the passengers". With this statement, he pointed towards the fact that diseases increasing over the past decades have not emerged due to genetic variation, while environmental exposure stimuli, diet and behaviour have drastically changed – and so has metabolism. Metabolism is poised to sense these modifications and thus, in turn, drives changes in gene expression that are causing disease or imbalance of health status. Therefore, understanding the underlying metabolic changes may improve therapeutic targets in the future [16].

Immunometabolism and inflammageing

Craig Wheelock (Stockholm, Sweden) kicked of the first session by discussing the metabolic profiling of severe asthma, and its implications for disease phenotyping and treatment. Metabolomic analysis provides an integrative molecular signature of the genome, transcriptome and proteome, which ultimately can be linked to a disease phenotype. Urinary eicosanoids have been demonstrated to identify molecular phenotypes of asthma and eicosanoids may be important components that aid in our understanding of the biochemical processes that drive asthma severity.

Thereafter, Annika Karger (Bad Nauheim, Germany) discussed how the long coding RNA *ADPGK-AS1* can control antitumour immunity in macrophages *via* metabolic reprogramming. She concluded that enhanced understanding and potential targeting of this long coding RNA could have the potential to serve as a future therapeutic approach in lung cancer treatment.

Next, Rajkumar Savai (Bad Nauheim, Germany) reviewed the impact of metabolic reprogramming of tumour-associated macrophages on lung cancer progression. He discussed the use of a variety of novel high-resolution small animal *in vivo* imaging techniques to gain insight into tumour evolution and progression. Furthermore, he provided an exciting set of data describing the potential to reprogram tumour-associated macrophages towards antitumour responses [17].

The last presenter of the first session, Carol Liang (Los Angeles, CA, USA), showed a reduction in the number and repair capacity of type II alveolar epithelial cells (AECII) in the lung of both ageing and IPF experimental mouse models using single-cell sequencing. Furthermore, she showed that zinc transporter 8 levels are attenuated in the AECII of these models, suggesting deficient zinc metabolism as a shared mechanism in ageing and IPF. Exogenous zinc treatment was able to replenish AECII differentiation in the lungs of IPF patients but not in ageing mice.

Mitochondrial dysfunction in lung ageing and disease

Recent literature suggests a key role for mitochondrial dysfunction in lung ageing, and pathogenesis of lung diseases such as COPD and asthma [18, 19]. Emerging evidence shows that mitochondria are implicated in the regulation of

critical cellular processes of cells of the airways such as inflammation, oxidative stress and cell death pathways, alongside their traditional role as the powerhouse of the cell [19, 20]. That is why the focus of this second session was on mitochondrial dysfunction in lung ageing and disease.

Matt Whiteman (Exeter, UK) opened this session by describing that mitochondrion-targeted hydrogen sulfide (H_2S) suppresses and reverses cigarette smoke-induced inflammasome activity and lung injury in experimental COPD, and showed results of an *in vivo* animal smoke exposure study. This research built further on previous findings suggesting a central role for H_2S in the development of COPD and one of the key processes involved in COPD pathogenesis, *i.e.* inflammation, which appointed H_2S as a potential therapeutic target [21, 22].

The next talk focussed on the development of asthma, in which the role of mitochondrial (dys) function is increasingly gaining attention. As airway remodelling, *i.e.* airway smooth muscle hypertrophy and hyperplasia, is a crucial hallmark involved in the pathogenesis of asthma [23], Thomas Trian (Bordeaux, France) discussed mitochondria located in airway smooth muscle as a driver of airway hyperresponsiveness in asthma. Elevated mitochondrial mass, increased abundance of key regulators of mitochondrial biogenesis, elevated carnitine palmitoyltransferase 2 protein levels and upregulation of oxidative phosphorylation were shown in *in vitro* studies investigating airway smooth muscle cells of asthma patients.

Thereafter, an ECM, Thomas Meul (Munich, Germany), demonstrated that mitochondrial metabolism is a regulator of cellular proteostasis in a short oral presentation. In mitochondrial DNA-mutated mice, accumulation of NADH, and decreased levels of protein synthesis and degradation were observed. Resupplying those mice with aspartate, an important regulator of the malate–aspartate shuttle involved in translocation of electrons over the mitochondrial inner membrane, reactivated the metabolic system (*i.e.* shift from oxidative phosphorylation to glycolysis) and rescued proteostasis.

In the second part of the session, Suzanne Cloonan (Dublin, Ireland) discussed the role of mitochondrial iron in the susceptibility to, and pathogenesis and progression of COPD. Besides impairment of the immunometabolism of alveolar macrophages of smokers and COPD patients [24], and the involvement of ferroptosis in COPD development, she discussed the central role of iron-associated mitochondrial dysfunction in the pathogeneses of COPD. This was illustrated by a study in which her group showed that preventing cigarette smoke-induced mitochondrial dysfunction in the structural cells of the airways of mice (*e.g.* iron regulatory protein 2-deficient mice, mice treated with a mitochondrial iron chelator or mice fed a low-iron diet) protected against the development of emphysema and bronchitis [25]. This presentation further highlighted the causal role that mitochondria, particularly mitochondrial iron, play in the development of COPD.

Next, Christy Tulen (Maastricht, the Netherlands) focussed on the effect of cigarette smoke exposure on the molecular regulation of mitochondrial metabolism in human bronchial and AECs. She showed that key regulators of mitochondrial metabolism, mitochondrial biogenesis and mitophagy were disrupted at the gene and protein levels in various human smoke exposure models, *i.e.* (un)differentiated primary bronchial epithelial cells exposed to cigarette smoke extract (submerged) or cigarette smoke (air–liquid interface), and peripheral lung tissue of (non-)COPD patients.

Cellular senescence, an indicator of lung ageing, is also seen as a driving mechanism involved in the pathogenesis of chronic lung diseases and considered as a potential therapeutic target [26]. Accordingly, Peter Barnes (London, UK) provided an overview of his work on senotherapies to target cellular senescence in chronic lung diseases by discussing potential therapy strategies and drugs targeting the phosphoinositide 3-kinase/mechanistic target of rapamycin (mTOR) signalling pathway (*e.g.* metformin and rapamycin), the senescence-associated secretory phenotype (SASP) response, activation of sirtuins (*i.e.* sirtuin 1 and 6), microRNAs, oxidative stress (*e.g.* antioxidants), mitochondrial function and senolytics [27].

The final presentation of the session was provided by Elena Lopez Rodriguez (Berlin, Germany) on air space distension preceding spontaneous fibrotic remodelling and impaired cholesterol metabolism in the absence of surfactant protein C.

Cellular senescence

Reinhold Medina (Belfast, UK) opened this session with an excellent overview of the role of endothelial cell senescence in the development of chronic diseases. He demonstrated that senescent cells cannot be defined by a single marker but rather, exhibit multiple hallmarks including growth arrest, senescence-associated β-galactosidase, DNA damage, mitochondrial dysfunction and SASP. Interestingly, a diabetic microenvironment triggers premature senescence in endothelial cells, which is associated with their decreased functionality driven by diminished mitochondrial respiration and altered mitochondrial ultrastructure. Hence, senolytic drugs specifically targeting senescent cells could be an attractive therapeutic approach for diabetes and other chronic diseases. However, their mechanism requires further study, because of potential toxicity and off-target effects. Furthermore, senolytics will likely need to be used in combination with regenerative medicine approaches to trigger the repair of the functional blood vessels.

In the second presentation, Joaquim Gea (Barcelona, Spain) summarised the newest research

on the senescence of muscles during ageing and in COPD. Respiratory senescence is caused by an interplay of different factors, including genetic background, early-life exposures, diet, drugs, physical activity and comorbidities, which influence muscle structure and function [28, 29]. Muscle strength and mass physiologically decline with age at a rate that is dependent on physical activity and overall health [30]. In COPD, general loss of muscle mass is frequent, including limb, intercostal and diaphragm muscle mass. Both respiratory and limb muscles of COPD patients show oxidative stress, signs of damage and metabolic changes. Pulmonary hyperinflation and increased airway resistance, which are hallmarks of COPD, lead to additional strain and functional impairment of respiratory muscles. In turn, limb muscle dysfunction in COPD, which is characterized by a decrease in muscle strength and endurance, accompanied by lower metabolic efficiency and increased cellular senescence, directly impact the exercise capacity of the patients [31].

In the third talk, Christina Brandenberger (Hannover, Germany) presented her exciting results on the contribution of ageing to impaired alveolar repair upon injury. She investigated the functional changes in AECII, the main epithelial stem cell population of the alveoli, in an acute lung injury (ALI) model in young (3 months) and old (18 months) mice. Interestingly, she found increased senescence and DNA damage markers, accompanied by lower proliferation potential, exclusively in old AECII cells after induction of injury. Similarly, lower expression of surfactant genes and impaired surfactant function were specifically observed in old AECII compared to young AECII after injury. These important findings provide a molecular explanation for the worsened pathology and limited survival in the elderly patients suffering from ALI, and further emphasise the urgency of studying lung repair processes in old mice for better translation of lung mouse models to human pathologies.

Next, Renata Jurkowska (Cardiff, UK) presented a novel and versatile workflow based on tissue cryopreservation, which allows long-term storage of lung tissue for subsequent profiling using next-generation sequencing (NGS) [32]. She demonstrated that cryopreservation does not compromise cell viability and thereby enables isolation of multiple functional cell types (*e.g.* fibroblasts, bronchial epithelial basal cells and AECs) from healthy and diseased human lung. Importantly, using RNA sequencing (RNA-seq) and Illumina EPIC Array (methylation profiling), she found that genome-wide gene expression and DNA methylation signatures of isolated fibroblasts are maintained upon cryopreservation. Finally, high viability of cryopreserved lung tissue also enabled generation of excellent quality single-cell RNA-seq data from human epithelial cells, emphasising the suitability of the developed workflow for 'omics profiling of lung cells. Development of simple tissue preservation methods compatible with biobank infrastructure will empower prospective collections of viable human lung samples that could be used for cell-type resolved NGS-based profiling and disease modelling, boosting future basic and translational research.

The session was closed by Herbert Schiller (Munich, Germany), who presented data from three recent projects. Using state-of-the-art single-cell transcriptomic and proteomic profiling of young and old mice, he provided exciting insights into cellular networks during ageing [33]. He showed that ageing leads to increased transcriptional noise, altered frequency of epithelial cells in the airways and extracellular matrix remodelling. Another project, examining the kinetics of mouse lung regeneration, led to the discovery of an alveolar progenitor cell state specifically induced during injury [34]. These progenitor cells, characterised by the expression of keratin 8 (Krt8), arise from AECII cells or bronchial epithelial club cells, and differentiate into AECI cells during repair. Finally, Dr Schiller presented an ongoing project aiming to characterise mesenchymal populations of the mouse and human lung, and to investigate their role during lung repair in the bleomycin mouse model. Single-cell profiling of enriched mesenchymal cells identified several distinct cell types, including mesothelial cells, smooth muscle cells and distinctive fibroblast-like populations. Interestingly, the fibroblast subtypes all had distinct locations in the lung, indicative of specialised functions. The cellular origin of the injury-induced myofibroblasts in the human lung is currently unknown; therefore, these data will provide invaluable insights into the role of distinct fibroblasts subsets during alveolar injury and repair.

The ageing lung under stress

This session contained two presentations exploring different aspects of proteostasis during ageing and age-related chronic lung disease. Topics discussed included proteasome and immunoproteasome activity, the effects of reactive oxygen species (ROS) and other metabolites on protein degradation as well as protein oxidation and endoplasmic reticulum (ER) stress. Silke Meiners (Munich, Germany) started this session by linking proteostasis to immune activation in the ageing lung. Protein degradation in the proteasome is an integral part of proteostasis and essential for cell function. Proteostasis is tightly linked to immune cell function, as proteasomes in immune cells (immunoproteasomes) degrade proteins for display *via* the major histocompatibility complex (MHC). In the lung, the immunoproteasome is expressed particularly in alveolar macrophages and enables the lung to mount adaptive immune responses upon intracellular infections [35]. During ageing, the activity of the immunoproteasome is increased, which might account for increased autoimmunity during ageing, although this link needs to be further investigated. Furthermore,

the immunoproteasome is increased in immune cells during ageing-associated IPF and in the bleomycin mouse model of pulmonary fibrosis [36]. Recently, Prof. Meiners has shown that ROS can affect proteostasis, while the proteasome complex becomes unstable in lung epithelial cells and mouse lungs after smoke exposure, indicating proteasome dysfunction underlying not only IPF but also COPD [37]. Ongoing projects in the Meiners laboratory include investigations into the role of mitochondrial dysfunction in cellular proteostasis and linking proteasome activity to cellular metabolism. While treatment with aspartate- or pyruvate-induced proteasome activity in fibroblasts, it was reduced by treatment with metformin. These findings open exciting new opportunities for understanding and manipulating proteostasis during ageing and ageing-associated chronic lung diseases such as IPF and COPD.

The second speaker of this session was Martina Korfei (Giessen, Germany), who presented on protein oxidation as a driver and potential target of pulmonary fibrosis. Proteins are folded and trafficked by the ER, which is dependent on a redox balance. Oxidative stress can cause protein oxidation, disrupt protein folding in the ER and result in increased ER stress. In this talk, Dr Korfei showed that protein levels of ER stress mediators are increased in lung homogenates and AECII in the lungs of IPF patients, and severe ER stress underlies AEC apoptosis and development of pulmonary fibrosis [38]. Furthermore, her research has identified specific transcription factor binding sites for induction of the proapoptotic ER stress-related transcription factor C/EBP homologous protein (CHOP). These transcription factors, activator protein 1 and c-Ets-1, are upregulated in AECII from IPF patients, while overexpression of CHOP *in vitro* resulted in AECII apoptosis, lung fibroblast proliferation and increased production of collagen I [39]. This indicates CHOP activation as a key process of the ER stress response and a potential driver of pulmonary fibrosis pathogenesis. Finally, using a mouse model overexpressing CHOP with a Tet-ON system in AECII specifically, she showed that CHOP overexpression *in vivo* in AECII resulted in apoptosis and development of pulmonary fibrosis after infection with a gammaherpesvirus. In summary, this session highlighted the importance of functional proteostasis in ageing and age-related chronic lung disease, and provided exciting new insights into the link between proteostasis, immune function and cell metabolism.

Therapeutics targeting metabolic alterations in disease

The last session of the LSC focussed on potential therapies to address metabolic alterations applied to lung inflammation and chronic diseases, such as acute respiratory distress syndrome (ARDS), COPD and IPF.

Anna Krasnodembskaya (Belfast, UK) reported exciting data regarding mesenchymal stromal cell (MSC)-mediated mitochondrial transfer as a potential therapeutic strategy to protect mitochondria from injury or enhance biogenesis in cells affected by the inflammatory environment. Through cell–cell contact or by the release of extracellular vesicles, MSCs demonstrated the ability to carry and transfer mitochondria [40], resulting in metabolic reprogramming of primary human macrophages towards an anti-inflammatory phenotype [41, 42]. Transfer in mitochondria also resulted in the restoration of mitochondrial function in primary human distal lung epithelial and endothelial cells, and alleviated mitochondrial dysfunction in the impairment of the alveolar–capillary barrier in ARDS.

In the area of chronic lung disease, Annemie Schols (Maastricht, the Netherlands) talked about how nutritional modulation could correct metabolic alterations in COPD. She demonstrated how metabolic and mechanical inefficiency may contribute to elevated energy expenditure during physical activity, and highlighted weight loss in COPD as a consequence of an imbalance between increased energy requirements and dietary intake. This leads to loss of muscle fibres and alteration of molecular markers for pathways of a mitochondrial breakdown in skeletal muscle of COPD patients, which are related to disease severity and loss of mitochondrial quantity [43, 44]. Challenges were presented and placed within the context of the future of utilising therapeutic targets that will address mitochondrial homeostasis in skeletal muscle of COPD, potentially leading towards new targets for maintaining or enhancing mitochondrial health.

The final presentation was provided by Rachel Chambers (London, UK), who presented mTOR signalling as a critical signal node during fibrogenesis in IPF [45, 46]. She highlighted that mTOR inhibition stimulated fibroblasts to restore their ability to support alveolar epithelial regeneration and proposed that targeting this axis may hold broad promise for the development of novel antifibrotic strategies, which can potentially lead to increased survival rates and improved quality of life for IPF patients. Alterations in metabolism have emerged as an additional hallmark of several lung conditions. While targeting metabolic pathways is a novel area with pre-clinical data suggesting efficacy, care must be taken to minimise adverse effects when targeting these pathways. Ideally, future (pre-)clinical studies will help to elucidate the role of cell metabolism in lung diseases and progression, and may lead to the discovery of novel therapies.

In conclusion, the overall message that permeated through the introductory lecture, as well as throughout all presentations and discussion sessions, was that metabolism and ageing are

factors we need to take into account even more when designing experiments, and setting up studies and protocols. The fact that the incidence of various diseases mainly occurs in older patients should also be represented in experimental studies by making use of aged rodents. Moreover, nutrition plays an important part in these studies, and we need to consider this in our experimental setup. The use of starvation medium or supplements can have inhibitory or stimulating effects on cytokine release from cells in *in vitro* studies. Although it is important to see all these process in light of the complexity of the human body, it is important to also zoom in on certain mechanisms every now and then.

Early career delegates session: strategically and successfully funding your future

The topic of the LSC 2020 ECMC session was "Strategically and successfully funding your future", and included four talks covering grant and seminar proposal writing, and different fellowship opportunities within the ERS and the European Union (EU), with the aim of helping young researchers to boost their careers. The session was opened by the current ECMC representative for Assembly 3, Niki Ubags (Lausanne, Switzerland). She provided an introduction into the ECMC, and their vision and mission [47]. Moreover, she provided insight into opportunities for ECMs to become more active and involved in ERS activities.

Reinoud Gosens (Groningen, the Netherlands) provided an overview on how to write a convincing research grant. He stressed the importance of reading the guideline of the grant that you are applying for carefully and make sure to adhere to this guideline. It was advised to first write the abstract for your grant, as this provides you with a backbone for your application, and forces you to have a structured line of thought throughout the grant and a clear problem definition. In addition, if you are not sure about an idea, pitch it to your colleagues and get their input. His last advice was, "even if you do not agree with the reviewer comments and may be disappointed with the outcome, not to be defensive to the reviewers".

Dr Ubags also provided an overview of how to obtain a grant to organise an ERS research seminar. Like Dr Gosens, she mentioned that reading the guidelines and timely submission of the application is very important. Furthermore, it is necessary to have clear objectives, cover an unmet need, and clearly specify your target audience and the envisioned output from the seminar. This output should not be limited to a publication, you can also consider post-event activities such as a session at the International Congress. She further mentioned that it can be useful to ask the assembly heads and secretaries for input on your proposal, as they often have very valuable advice.

Next, Louise Donnelly (London, UK) talked about getting your first personal research grant within the ERS fellowship programme. She provided an overview of the different fellowship programmes that the ERS has on offer and specified the goals of these different programmes [48]. Moreover, she explained the application and interview process, and provided valuable do's and don'ts for your applications. One of these is that you must choose your keywords wisely, as this determines to which reviewers your application will be allocated. Furthermore, she stressed that it is important to make sure that your proposed work is feasible for the requested fellowship time. In addition, it is important to highlight how the fellowship will advance your career and your potential involvement in the ERS. Lastly, Dr Donnelly mentioned that it is important to not give up if you are not successful the first time. Read the feedback carefully, integrate this in a resubmission and re-apply.

Lastly, Nadia El Mjyad (Brussels, Belgium) from the EU/European Research Council (ERC) talked about funding possibilities within the EU/ERC programme. She mentioned that for ERC starting grants, the excellence of the researcher and the research proposal are the main criteria. The host institute is not taken into account. It is important to familiarise yourself with the process and all required documents early on. Moreover, when selecting a panel to which to submit an application, it can be helpful to have a look at what kind of projects have been funded before in that panel, to make sure that you chose the right panel for your application. She also mentioned that early career researchers are eligible for the ERC Synergy grant mechanism.

In conclusion, the 2020 LSC provided an overview of excellent science on metabolic alterations in lung disease and career development opportunities for ERS ECMs. We look forward to seeing you all during the LSC next year.

Key messages from scientific sessions at LSC 2020

- Environmental and lifestyle changes affect the metabolism, and these modifications can drive changes in gene expression, which are thought to cause disease or lead to an imbalance in health status.
- Mitochondrial dysfunction has been implicated in lung ageing and the pathogenesis of lung diseases, which indicates the potential therapeutic value of mitochondria-targeted therapies and senotherapies for lung ageing and disease.
- Mitochondrial dysfunction can affect several key functions in different lung structural cells during the pathogenesis of lung diseases and mitochondrion-derived treatments have the potential to mitigate progress of these conditions.
- Proteostasis, the process of protein degradation that, in immune cells, results in protein display

via the MHC, is important in ageing and age-related chronic lung disease.
- ROS and oxidative stress, such as that induced through smoke exposure, affect proteostasis, protein folding and trafficking in the ER, thereby contributing to IPF and COPD. Regulation of proteostasis by metabolites (pyruvate and aspartate) and the drug metformin offers a better understanding of the process and new therapeutic options.
- While targeting metabolic pathways is a novel area, with pre-clinical data suggesting efficacy, care must be taken to minimise adverse effects when targeting these pathways. Moreover, the interplay between metabolic targets and current therapies could be an important therapeutic strategy to consider as more metabolism-targeting agents reach clinical trials in the future.
- Ideally, future (pre-)clinical studies will help to elucidate the role of cell metabolism in lung diseases and progression, and may lead to the discovery of novel metabolic therapies, stratifying groups likely to benefit from specific intervention.

Take-home messages from the early career delegates session

- Key steps in writing a convincing research grant are: 1) accurately read the guidelines; 2) start by writing a structured abstract; 3) pitch your research plan to colleagues; and 4) carefully consider reviewers' comments to improve future or revised applications.
- Resilience is key. Do not give up if you are not successful the first time around. Carefully review the comments and use them to improve your application.
- Do not be discouraged to apply for funding from the ERC. If you have an outstanding project suggestion and the skills to carry out the proposed project, there are good chances to get far in the process.

Affiliations

Patricia P. Ogger[1], Johnatas Dutra Silva[2], Mahyar Aghapour[3,4], Irma Mahmutovic Persson[5], Christy Tulen[6], Renata Jurkowska[7], Niki D. Ubags[8]

[1]National Heart and Lung Institute, Imperial College London, London, UK. [2]Wellcome–Wolfson Centre for Experimental Medicine, School of Medicine, Dentistry, and Biomedical Sciences, Queen's University Belfast, Belfast, UK. [3]Infection Immunology Group, Institute of Medical Microbiology, Infection Control and Prevention, Health Campus Immunology, Infectiology and Inflammation, Otto-von-Guericke University, Magdeburg, Germany. [4]Immune Regulation Group, Helmholtz Center for Infection Research, Braunschweig, Germany. [5]Institution of Medical Radiation Physics, Dept of Translational Medicine, Lund University, Malmö, Sweden. [6]School of Nutrition and Translational Research in Metabolism (NUTRIM), Dept of Pharmacology and Toxicology, Maastricht University Medical Center+, Maastricht, The Netherlands. [7]School of Biosciences, Cardiff University, Cardiff, UK. [8]Faculty of Biology and Medicine, University of Lausanne, Service de Pneumologie, CHUV, Epalinges, Switzerland.

Conflict of interest

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