Review of the British Thoracic Society Winter Meeting 2022, 23-25 November 2022

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ABSTRACT

The British Thoracic Society (BTS) Winter Meeting at the QEII Centre in London provided the first opportunity for the respiratory community to meet and disseminate research findings face to face since the start of the COVID-19 pandemic. World-leading researchers from the UK and abroad presented their latest findings across a range of respiratory diseases. This article aims to represent the range of the conference and as such is written from the perspective of a basic scientist, a physiotherapist and two doctors. The authors reviewed showcase sessions plus a selection of symposia based on their personal highlights. Content ranged from exciting new developments in basic science to new and unpublished results from clinical trials, delivered by leading scientists from their fields including former deputy chief medical officer Professor Sir Jonathan Van-Tam and former World Health Organisation (WHO) chief scientist Dr Soumya Swaminathan.

INTRODUCTION

After two years of virtual Winter Meetings, 2,161 scientists, clinicians, nurses and allied health professionals gathered face-to-face in London to discuss the latest findings in respiratory research. Whilst COVID-19 was fresh in the minds of delegates, thoughts turned to what lessons could be learnt from the pandemic to address other challenges in respiratory medicine. This article provides a summary of the highlights of the BTS winter meeting 2022.

BTS CLINICAL LECTURE – PANDEMIC PARABLES

One of the most popular sessions of the Winter Meeting was delivered by Professor Sir Jonathan Van-Tam (Nottingham). Professor Sir Van-Tam navigated the audience on a captivating journey through the COVID-19 pandemic and offered his personal reflections on events and his role during the pandemic response, deservingly receiving a standing ovation from the packed auditorium for his contribution to public policy and communication. Professor Van-Tam highlighted the stellar work of the Scientific Advisory Group for Emergencies (SAGE) in laying out the uncertainty surrounding the data available at the time whilst emphasising that the science could (and would!) change. He also commended the Joint Committee on Vaccination and Immunisation (JCVI), led by "one of our own" Dr Wei Shen Lim, who took a strong, clinical, data-driven approach to vaccination strategy. One such vaccination recommendation was extending the length of the vaccine dose interval between the first and second from the manufacturer recommended 3-4 weeks to 12 weeks, to ensure high levels of vaccine uptake amongst vulnerable individuals to reduce the number of COVID-19 preventable deaths. This was an initially controversial and difficult decision which was eventually justified [1]. The success of therapeutics emerging from the RECOVERY trial, notably dexamethasone [2] was highlighted, with eager anticipation of imminent study data from the novel anti-viral platform, PANORAMIC (REC:21/SC/0393).

BTS GRAND CHALLENGE LECTURE – SCIENCE IN THE TIME OF THE PANDEMIC

Dr Soumya Swaminathan (World Health Organisation, WHO) delivered the Grand Challenge lecture, discussing the lessons learnt from the pandemic on how to rapidly conduct high quality research. During the pandemic, science has seen some important advancements including development and innovations in testing and vaccinating for COVID-19. The Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) and the UK Collaborative on Development Research (UKCDR) have been vital for funding key studies and reducing research waste, demonstrated through collaborative platform trials such as the WHO Solidarity Therapeutic trial [3] and the RECOVERY trial[2]. This has allowed for timely and effective research results and implementation.

Global collaboration is of importance and an area for future development in pandemic planning and will allow for accelerated access to scientific developments. It is acknowledged that much of this research is conducted in high income countries, and as a result implementation (such as vaccine uptake) is lower in low to middle income countries. There have been specific goals developed by WHO in response to the pandemic, including a well-publicised and ambitious target for vaccination development within 100 days. Yet, whilst technology and global collaboration are important tools for successful pandemic research, it can present some barriers. In particular the sharing of false

information- “the infodemic”- and its impact on global trust in science presents a significant ongoing challenge for WHO.

BTS SCIENTIFIC LECTURE – TARGETING THE TRANSFORMING GROWTH FACTOR BETA IN PULMONARY ARTERIAL HYPERTENSION

Professor Marc Humbert (Paris) treated us to a masterclass in understanding pulmonary arterial hypertension (PAH) from basic mechanisms which have been translated to successful therapies. He led the new 2022 European Respiratory Society guidelines on managing pulmonary hypertension (PH) which has seen the haemodynamic definition of PH revised to a mean pulmonary arterial pressure (mPAP) >20mmHg at rest [4]. The commonest genetic cause of PAH is due to mutations in bone morphogenetic protein receptor type 2 (*BMPR2*) - a member of the transforming growth factor β (TGF-β) superfamily – and leads to defects in endothelial integrity[5]. Current treatments for PH target prostacyclin, endothelin-1 and nitric oxide pathways [6], but the poor 5-year survival rate (50-60%) emphasises the need for new approaches. To this end a novel fusion protein Sotatercept has been developed to target the BMPR-II-Smad1/5/8 pathway by binding to activins and growth differentiation factors in order to restore the balance between growth-promoting and growth inhibiting signalling pathways in pulmonary vascular smooth muscle and endothelial cells [7]. Treatment resulted in reduced pulmonary vascular resistance and suggests positive efficacy in the phase III STELLAR trial [8], highlighting a potentially new therapeutic option for this devastating condition.

JOINT BTS/BALR/A+LUK EARLY CAREER INVESTIGATOR AWARDS

Six outstanding early career researchers showcased their exciting research in the prize symposium as they competed for the BTS/British Association for Lung Research (BALR) and Asthma + Lung UK (A+LUK) early career investigator awards. A+LUK award winner Dr Beatriz Guillen-Guio (Nottingham) kicked off the session describing the first genetic overlap study between idiopathic pulmonary fibrosis (IPF) and acute respiratory distress syndrome (ARDS). She utilised large meta-genome-wide association studies (GWAS) of IPF risk (4,125 cases, 20,464 controls)[9] and post-sepsis ARDS (716 cases, 4,399 controls)[10], as well as individual-level data from the ARDS GWAS (321 cases, 3,249 controls). Polygenic risk scores (PRS) were calculated and found that IPF GWAS variants predicted ARDS risk (OR 1.24;95%CI 1.10, 1.39).

BALR award winner Dr Merete Long (Dundee) explored altered neutrophil proteomes in COVID-19 patients. Peripheral blood neutrophils were isolated from 84 COVID-19 patients, 91 non-COVID-19 respiratory infection patients and 42 healthy volunteers. Delayed recovery at day 29 was associated with reduced abundance of migratory receptors (e.g. C3AR1, LTB4R), and reduction in inhibition machinery (e.g. SHIP-1), highlighting the potential for targeted neutrophil treatment in long COVID.

BTS award winner Dr Suzanne Miller (Nottingham) presented data on the role of cathepsin K (CTSK) in the rare multisystem disease lymphangioleiomyomatosis (LAM). Lung damage is considered to be mediated by aberrant protease activation and CTSK is the most strongly expressed protease in LAM compared to control lungs [11], demonstrating it as a potential therapeutic target. In a murine model of LAM, CTSK inhibition with Odanacatib reduced CTSK activity in bronchoalveolar lavage (BAL) and lung tissue, whilst also reducing size of lung nodules and cellular proliferation. This highlights its potential as a future therapy for LAM.

BTS highly commended researcher Dr Kiran Reddy (Belfast) discussed hyperinflammatory and hypoinflammatory subphenotypes of ARDS[12]. Latent class analysis (LCA) on 437 extracorporeal membrane oxygenation (ECMO) patients, identified a two-class best fit model. Class 2 with 26% of patients had higher mortality than class 1 (49% vs. 31%, p = 0.001) and were characterised by higher cytokine concentrations, increased metabolic acidosis and non-pulmonary organ failure, consistent with the ARDS hyperinflammatory subphenotype, helpful in developing precision medicines.

BALR highly commended researcher Mr David Butler (Belfast) highlighted a novel organoid model of the distal lung comprising of epithelial, endothelial and mesenchymal stromal cells (MSCs). Cells were co-cultured in Matrigel for 21 days and reached 1000µm in size with the development of budding bulbous structures that were composed of alveolar epithelial cells (ATI-like and ATII-like), whilst transmission electron microscopy confirmed luminal surfactant secretion.

A+LUK highly commended researcher Dr Sanjay Ramakrishnan (Oxford) presented a randomized controlled trial of point of care (POC) blood eosinophil guided oral prednisolone use for COPD exacerbations[13]. In primary care, 203 exacerbations were randomised to POC eosinophil guided (≥2% or <2%) or standard of care (prednisolone 30mg) for 14 days. Treatment failure occurred in 28 and 34 patients in the eosinophil-biomarker guided and standard care arms respectively (RR 0.82 95%CI 0.54–1.23, p=0.34). There was no difference in adverse events, highlighting that avoiding steroids in low eosinophil COPD exacerbations may be safe, especially with access to POC testing.

HIGHLIGHTS FROM THORAX

This session showcased three outstanding recent publications in Thorax. Dr Tess Kramer (Amsterdam) presented the results of her single arm trial investigating the feasibility of needle-based confocal laser endomicroscopy (nCLE) in the diagnosis of peripheral lung tumours [14]. In comparison to radial endobronchial ultrasound which may miss up to 65% of lesions [15], this technique allows real-time microscopic visualisation and may be a useful tool in improving “hit rates” for peripheral tumour biopsies.

The session moved from cutting edge technology to low-tech pragmatic research. Dr Christopher Green (Birmingham) described the results of his study using “a glorified hoover and a bunch of swabs”; nasopharyngeal samples and swabs from nearby surfaces were taken from 30 hospitalised patients with COVID-19 receiving either supplemental oxygen, high flow nasal oxygen or continuous pressure ventilation as part of the RECOVERY-RS study [16]. Overall, RT-qPCR positivity rates were low and none of the surface samples produced detectable virus on culture, challenging our assumptions about risk from aerosol generating procedures.

Fanny Rancière (Paris) focused on the short-term effects of combined pollen and air pollution (“polluen”) on lung function in French school children using the PARIS (Pollution and Asthma Risk: an Infant Study) cohort [17]. In 1063 children, there was an association between exposure to grass pollen or pollution and lower FEV_1 and FVC six days later. With increasing pollen counts expected in future years as a consequence of climate change, could this be the latest challenge to children’s respiratory health?

PLENARY SCIENTIFIC

Professor Mona Bafadhel (Oxford) opened the Plenary Scientific Symposium outlining stark figures on the impact of COPD exacerbations, which remain common and associated with major morbidity and mortality. Despite their importance only 1.6% of patients understand the term 'exacerbation' [18]. A UK respiratory nurse perspective on terminology highlighted a lack of consensus on the definition of exacerbation [19]. Professor Bafadhel proposed renaming 'exacerbation' to ultimately lead to better definition of clinical endotypes [20]. Although routinely prescribed for COPD exacerbations, corticosteroid efficacy remains contentious, but using blood eosinophil count as a biomarker is associated with more appropriate use of corticosteroid treatment [21,22].

Professor Louise Wain (Leicester) discussed how Genetic Risk Scores (GRS) generated from multi-ancestry GWAS predicted genetic susceptibility for COPD, identifying a 4.73-fold increased relative risk for COPD. Furthermore, incorporating clinical information found an absolute risk of COPD of 82.4% for smokers in the highest-risk score decile [23]. The pleiotropic nature of genetic associations was exemplified by IPF and COVID-19 overlapping signals, with MUC5B identified as a IPF risk allele, but protective for COVID-19 [24].

Immunometabolism is a rapidly advancing field and increasing evidence implicates a key role for metabolic reprogramming in airway macrophage function [25]. Dr Adam Byrne (London) presented data showing decreased levels of the metabolite itaconate in BAL of IPF patients, and airway macrophage downregulation of *ACOD1* gene expression [23] the gene for the enzyme aconitate decarboxylase 1, which catalyses the production of itaconate from cis-aconitate. Furthermore, higher levels of fibrosis and poorer outcomes were reported in $Acod^{-/-}$ mice, whereas mice with normal itaconate levels demonstrated better resolution. Dr Byrne also showed how house dust mite challenge initiated a metabolic switch from oxidative phosphorylation to glycolysis, inducing a more 'energetic', glycolytic macrophage phenotype.

Although preclinical evidence indicates a role for the IL-6 pathway in PAH[26,27], there was no significant treatment effect of tocilizumab in the TRANSFORM-UK phase 2 open-label study [28]. Despite the negative outcome, Dr Mark Toshner (Cambridge) remarked how this emphasised the need for multicentre collaborations, leading to the conception of UniPHy, the first national investigator-led clinical trials network. However, as only 1 in 5 PAH patients have enrolled in clinical trials, Dr Toshner considered the importance of patient involvement in the design of his new study, StratosPHere.

JOINT BPRS/BTS SYMPOSIUM – BACK TO THE FUTURE: WHERE NOW FOR DIGITAL HEALTHCARE?

Professor Heather Elphick (Sheffield) presented the results of the 2019 UK Long Term Ventilation (LTV) survey involving 25 centres caring for 2383 children demonstrating a 2.5-fold increase over 10 years. Over 95% of the cohort used LTV at home with a move toward more non-invasive ventilation and fewer children using 24-hour ventilation. These results highlight the need for better telemonitoring and a national children's LTV register.

Dr Andrew Fogarty (Nottingham) described racial bias in pulse oximetry readings and its potential impact in clinical decision making during the COVID-19 pandemic. The results were disturbing; hypoxia may be missed in 11.7% of individuals with black skin in comparison to 3.6% of those with white skin [29] with individuals from Black or Asian heritage demonstrating lower PaO2 and higher

respiratory rate at the point of transfer to critical care than those with white skin during the COVID-19 pandemic [30], potentially suggesting a delay in delivery of lifesaving treatment.

Dr David Drummond (Paris) highlighted the opportunities and pitfalls of telemonitoring in respiratory disease. He presented the results of a systematic review showing limited evidence overall for telemonitoring to improve lung function, healthcare utilisation or quality of life [31] although some interventions such as smart inhalers with synchronous monitoring have showed a benefit to quality of life [32]. The future perhaps involves "super-telemonitoring" with passive continuous collection of data from multiple sources and automated decision making to reduce the burden on healthcare providers.

COPD: PIECING TOGETHER THE JIGSAW

This symposium combined the latest findings from cell science, imaging and clinical trials in Chronic Obstructive Pulmonary Disease (COPD) to understand how these findings can provide direct patient benefit. Professor Louise Donnelly (London) argued that COPD is a disease of accelerated aging caused by increased oxidative stress and increased inflammation with a key role for senescent cells. Key to this pathway appears to be miR-34a which causes a decrease in sirtuins and therefore reduced DNA repair and release of pro-inflammatory mediators [33], therefore blocking miR-34a provides a potential therapeutic target in COPD.

Professor Eric Hoffman (Iowa) discussed stratification using imaging in COPD including the role of mucus plug scoring [34] and dual-energy CT (DECT) perfused blood volume (PBV). PBV can be used as a surrogate of lung perfusion [35] with PBV heterogeneity increased in emphysema susceptible smokers, a phenotype that is potentially reversible through sildenafil mediated vasoconstriction [36]. Further phenotyping might be possible through the use of upright CT, moving radiology assessment closer to the physiology laboratory [37].

Professor Chris Brightling (Leicester) described how we can use knowledge of cell biology and phenotypes to provide stratified patient care. The "Comprehensive Respiratory Assessment" (CRA) [38] provides a model to deliver interventions such as lung volume reduction or corticosteroids to patients based on measured biomarkers. Targeted care based on the presence of eosinophilia has led to a change in the GOLD strategy document [39], an example of research leading to a direct benefit to patient care. Looking to the future, the distinct airway microbiome [40] may allow an opportunity for a more targeted approach to macrolide therapy, and there is continued hope for the role of biologics in COPD including anti-ST2 [41].

RESPIRATORY PHYSIOLOGY IN 2022 – INNOVATIONS AND EVOLUTION

Physiology proved to be a popular topic at the Winter Meeting and three excellent speakers presented to a busy Churchill auditorium on Friday morning. Professor Brendan Cooper (Birmingham) discussed the new Global Lung Initiative (GLI) Global 2022 single equation for spirometry reference values. These new race neutral reference values attempt to address long standing challenges of the impact of socioeconomic status, environment and structural racism on lung function interpretation but emphasised that spirometric values should be viewed in the context of the individual patient.

Professor William Man (London) tackled the complexity of using artificial intelligence (AI) in respiratory physiology. AI has the potential to improve quality control, pattern recognition and decision making and may provide a helpful tool for those conducting spirometry in primary care. AI can assess and report spirometry results at 900 times the speed of pulmonologists with greater diagnostic accuracy[42]. Even when compared to experience clinicians, AI had a 12.5% better correct diagnostic rate.

Dr James Hull (London) discussed the role of remote monitoring in respiratory physiology. Wearable technology is increasingly part of our day-to-day life and respiratory physiology is beginning to adapt to this change. However, uptake is variable, adherence weans over time, and home spirometry is unreliable as an outcome measure in randomised controlled trials [43]. However, these issues may improve with virtual supervision of spirometry [44].

IMPROVING UPTAKE OF PULMONARY REHABILITATION: A PATIENT CENTRED APPROACH

Pulmonary Rehabilitation (PR) is a highly cost effective intervention; however is under-utilised. PR is designed for those with respiratory conditions and a Medical Research Council Breathlessness Scale of 2 or more however Dr Jane Watson (London) highlighted that, despite improving from around two thirds in 2015, only 88% of programmes accept the full range of MRC 2-5 [45]. Barriers and enablers to uptake of PR include knowledge and awareness of staff and patients of PR, regular contact with PR centres and perceived or assumed social limitations to engagement [46]. However, the literature surrounding interventions that increase uptake is scarce [47,48]. Future interventions that aim to change behaviour and attitudes of service providers and patients regarding PR may be of benefit.

The development of flexible approaches to PR was discussed by Dr Linzy Houchen-Wolloff (Leicester). Digital interventions have shown some promise at increasing completion rates [49] however improvements in important outcomes such as walking capacity are less convincing. Two systematic reviews have demonstrated broadly equivalent results in unsupervised exercise training and home based PR for those with COPD [50,51]. However all interventions should consider the key components of PR [52].

Professor Keir Lewis (Swansea) presented the results of the VIPAR study delivering PR at a central hub and streams to satellite hubs in the community [53]. The programme demonstrated improvements in exercise capacity, hospitalisations and exacerbations and may be a valuable consideration for geographically sparce areas.

JOINT BTS/BALR SYMPOSIUM PART 1 – SEVEN AGES OF THE LUNG: IN THE BEGNINNING…

Dr Purushothama Rao Tata (Duke University, USA) opened the BTS/BALR symposium by eloquently demonstrating how combining spatial transcriptomics with scRNA Sequencing could delineate region-specific molecular signatures of previously uncharted distal lung regions. Seven previously uncharacterised cell types were identified, including the terminal and respiratory bronchioles (TRB)-specific alveolar type-0 (AT0) cell [54]. Validation of *in silico* trajectory predictions using a non-human primate model of lung injury, human organoids and lung tissue demonstrated dynamic cellular regulation during lung development and repair. Computational methodologies identified signalling pathways which control cell transition states [55], which are crucial to understand for developing relevant model systems to explore lung regeneration strategies.

Dr Renata Jurkowska (Cardiff) introduced a fascinating, useful protocol of lung tissue cryopreservation [56] which can better enable access to viable samples, improve reproducibility of study workflows, widen demographic inclusion, and increase collaborative opportunities. Importantly, cryopreservation did not compromise tissue viability, cellular integrity or modify the transcriptional and epigenetic profiles of cells. Subsequent whole-genome bisulfite sequencing found genome-wide methylation alterations in lung fibroblasts of ex-smokers associated with COPD disease stage [57]. This level of molecular resolution may reveal early disease trajectories and identify potential biomarkers for disease onset and progression.

ADAM33 was identified 20 years ago as an asthma susceptibility gene associated with airway hyperresponsiveness (AHR)[58] and has since found to be associated with airway remodelling, asthma development and severity [59,60]. Dr Hans Michael Haitchi (Southampton) demonstrated that soluble ADAM33 not only plays a role in remodelling, but increased susceptibility to allergen sensitivity and development of allergic airway inflammation (AAI) [61]. His recent work suggests that interactions between maternal AAI during pregnancy and ADAM33 can shape early life trajectories. Reversibility of airway remodelling in DTg *Ccsp/ADAM33* transgenic mice offered a ray of hope [61], implicating ADAM33 as a potential therapeutic target.

JOINT BTS/BALR SYMPOSIUM PART 2 – SEVEN AGES OF THE LUNG: WEAR, TEAR AND REPAIR?

The COPD lungs display several of the hallmarks of ageing [62], however the hallmark of epigenetic alterations in COPD is not as well studied. By performing an epigenome-wide association study (EWAS) on whole blood from the LifeLines cohort [63], Dr de Maaike Vries (Groningen) identified 15 CpG-sites associated with smoking pack years, 10 of which were associated with lung function. Importantly, 5 CpG-sites were validated in lung tissue, indicating tissue-specific epigenetic changes [64]. Dr de Vries showed that methylation levels of certain CpG-sites for ex-smokers were closer to that of never smokers than current smokers, suggesting potential reversibility upon smoking cessation.

Epidemiological and mechanistic studies have shown the impact of air pollution on the host [65–67], but the impact on airway bacteria remains an underappreciated concept. Professor Julie Morrissey (Leicester) demonstrated that bacteria (*Streptococcus pneumoniae* and *Staphylococcus aureus*) more readily disseminated from the nasopharynx into the murine lung when co-exposed with black carbon (BC) [68,69]. Furthermore, co-exposure increased *S.aureus* adhesion and invasion of human epithelial cells *in vitro*, which increased further when *S.aureu*s was pre-grown in the presence of BC. This direct impact of BC on *S.aureus* behaviour was shown by global transcriptomic alterations in bacterial stress responses, metabolic pathways and the expression of virulence factors such as proteases, toxins and immune evasion factors [69].

Dr Marko Nikolić (London) closed the joint BTS/BALR symposium outlining how the early stages of lung development offer insights into repairing the diseased lung. Lung development is often studied using murine models, however differences exist between human and mice embryonic lungs [70]. Identification of human-specific progenitor cells and suitable environmental conditions allowed for generation of self-renewing human embryonic lung organoids. Dr Nikolić showed recent data emphasising the importance of cell-cell interactions during development [71], giving examples of

mesenchymal-epithelial cell interactions directing airway zonation and fetal lung-derived immune cells influencing epithelial cell differentiation.

CONCLUDING REMARKS

The BTS winter meeting 2022 featured 27 symposia, 366 abstracts including 136 oral presentations and 230 poster presentations. This review presents selected highlights, and it is not possible to discuss all the novel data presented. After 2 years without face-to-face meetings due to the COVID-19 pandemic, BTS winter meeting has firmly re-established itself as part of the respiratory calendar.

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