Review of the British Thoracic Society Winter Meeting 2011, 7—9 December, London, UK

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ABSTRACT

This is the second annual review of the British Thoracic Society Winter Scientific Meeting held from 7—9 December 2011, which was attended by over 2000 delegates. Although a wide spectrum of respiratory research was presented at the meeting, the content of the review focuses specifically on three key themes: cystic fibrosis, pulmonary vascular disease and thoracic oncology. Advances in clinical and translational respiratory research presented within the major symposia and spoken sessions related to these areas are summarised. Additional sessions recognising topics relevant to the forthcoming 2012 London Olympics are also highlighted.

The aim of this article, the second annual review of the British Thoracic Society (BTS) Scientific Meeting, is to highlight exciting and important new developments in key areas of respiratory medicine. As a significant breadth of scientific and clinical research is presented at the BTS meeting, this review will focus on key themes: cystic fibrosis (CF), pulmonary vascular disease and thoracic oncology. In addition, to mark the forthcoming 2012 London Olympics, contrasting sessions were held discussing the physiology of the elite athlete and acquired critical care muscle weakness.

CYSTIC FIBROSIS

This year's BTS meeting highlighted the advances in our understanding of the complexity of CF and how this is now being translated into therapeutic options. Targeting the basic defect in CF and providing personalised medicine, based on the genetic defect of a given patient with CF, now appears a realistic prospect. Professor F Becq (Poitiers, France) gave an overview of therapeutics in development aimed at improving mutant CF transmembrane receptor (CFTR) functions. Exemplified by the commonest class II CFTR mutations, this includes inhibitors of histone deacetylase 7 activity,[1] phosphodiesterase type V inhibitors,[2] glucosidase inhibitors[3] and use of the small molecule VX-809.[4 5] In a parallel session, Dr C Le Camus (Vertex Pharmaceuticals, Cambridge, MA, USA) presented the exciting results from phase III clinical trials of ivacaftor (VX-770), a small molecule directed at the basic defect in patients with a G551D mutation. The CFTR G551D mutation, although rare (approximately 5%) is the most prevalent mutation that results in normal amounts of CFTR at the cell surface with a functional gating defect. Ivacaftor acts as a CFTR potentiator, increasing channel activity at the cell surface. In patients aged 6 years or older, ivacaftor resulted in sustained reductions in respiratory symptoms and sweat chloride concentrations, improvements in pulmonary function and weight gain.[6 7] Future work will examine the drug in the newborn to 5-year age group with the aim of early preventive intervention, its effect in other commoner CFTR mutations (eg, F508del mutation), and in combination with other small molecule CFTR modulators (eg, VX-809).

The advent of high-throughput technologies to examine microbial community composition is furthering our understanding of the CF microbiome, allowing identification of taxa not normally isolated by conventional culture. Professor S Elborn (Belfast, UK) discussed how this polymicrobial environment is more complex than previously thought, including narrowing of bacterial diversity in older patients,[8] the recently recognised contribution of anaerobic organisms, and the modest effect of antibiotic therapy on microbial communities.[9] Cox *et al* presented further work using high-throughput sequencing to reveal a relationship between mucoid *Pseudomonas aeruginosa* and the presence of other pathogens, such as *Achromobacter* species, which may have relevance to patient outcome.[10] In additional spoken sessions, Flight *et al* presented a prospective observational study of viral infections in patients with CF.[11 12] This group demonstrated sputum to be superior to nose and throat swabs for diagnosis of respiratory viruses and that the seasonal influenza vaccination is not 100% effective in the adult CF population.

The issue of broadening antimicrobial strategies in CF, via the use of additional aerosolised agents and antibiotic adjuvants, was addressed by Professor A Smyth (Nottingham, UK). Antibiotic adjuvants represent therapies that act by rendering the organism more susceptible to antibiotics or the immune response, or by reducing its virulence. Although mainly in preclinical research at present, these include the potential use of efflux pump inhibitors, quorum-sensing inhibitors and inhibitors of bacterial adherence.[13]

The inflammatory response in CF is undoubtedly complex,[14] with Professor G McElvaney (Dublin, Ireland) highlighting the importance of innate immune responses and how these are intrinsically altered in CF.[15] He described the key role of neutrophil elastase and how this acts upon the CF epithelium, via the toll-like receptor and epidermal growth factor receptor, to perpetuate a pro-inflammatory response. He suggested that the possibility of using anti-elastase treatment, such as

aerosolised α1-antitripsin,[16] may hold promise in CF. Separately, in a spoken session, Bayes and Evans reported a further novel mechanism for immune dysregulation in CF, with *P aeruginosa* inducing apoptosis of potent antigen-presenting dendritic cells.[17]

PULMONARY VASCULAR DISEASE

Within the remit of pulmonary vascular disease falls pulmonary thromboembolic disease and a packed auditorium heard four informative discussions from leading experts in this field. Professor P Corris (Newcastle, UK) provided a detailed introduction to pulmonary thromboembolism (PTE) and discussed the advantages and disadvantages of the use of scoring systems for PTE.[18] The role of advanced treatments for PTE such as thrombolysis, catheter disruption (including newer ultrasound accelerated disruption) and surgical embolectomy, were addressed by Professor A Torbicki (Warsaw, Poland).[19] He reminded us that although thrombolysis can reduce the pulmonary vascular resistance by as much as 70% within the first hour, this should only be used in specific clinical circumstances such as hypotension. Reminding us that historical studies still have clinical relevance, Professor Torbicki showed us that Dr Barritt had got it right in 1964 when his study showed heparin was still one of the most important drugs in the management of PTE and should be administered as a matter of priority.[20]

The symposium also addressed the haematological implications for patients with PTE. Dr R MacLean (Sheffield, UK) gave an elegant account of thrombophilia testing in PTE and suggested that a relatively small number of patients warrant thrombophilia testing as other factors, such as the mode of presentation, are better predictors of recurrence. In addition, testing is not useful in the acute situation and can be misleading as certain anticoagulant proteins are altered naturally during an acute PTE episode. Dr T Baglin (Cambridge, UK) further discussed duration of warfarinisation following PTE and the implications of using novel anticoagulants in clinical practice. He highlighted that there was no difference in the rate of PTE recurrence following 3 months versus 6 months of anticoagulation and that the choice of anticoagulation duration should be either 3 months or lifelong. Indeed in patients who have suffered an unprovoked PTE, their recurrence rate is 7.4% per year and if they have a low bleeding risk they should be considered for lifelong anticoagulation.[21] The newer anticoagulants, such as rivaroxaban and dabigatran, have many advantages over existing therapy, including a predictable therapeutic response, not requiring routine monitoring and having minimal food or drug interactions.

Although many patients with pulmonary arterial hypertension (PAH) now respond to new disease targeted therapies, for example, sildenafil or bosentan, patients who have pulmonary hypertension (PH) associated with chronic lung disease or left heart disease do not appear to respond to these therapies. Promising new treatments are in development yet all speakers agreed that currently there is no role for the treatment of this group of patients with disease targeted therapies outside of specialist PH units or in clinical trials. Professor A Ghofrani (Giessen, Germany) delivered an informative talk on PH and chronic obstructive pulmonary disease.[22] Recent work has raised the possibility that the earliest changes seen in emphysema are not in the airways but in the pulmonary vasculature with upregulation of inducible nitric oxide synthase, raising the intriguing possibility of chronic obstructive pulmonary disease having a predominant vascular pathobiology in its early stages. This theme was continued by Dr J Wort (London, UK) who discussed PH and interstitial lung disease showing evidence of early vascular remodelling in the disease.[23] Despite some initial hopes, many of the disease targeted therapies have not improved the primary endpoints in the majority of interstitial lung disease trials and there remains a desperate need for new treatments in this field.[24]

There is a general recognition that the number of patients with PH and left heart disease is increasing, which is important given that these patients have a poorer prognosis. Professor J L Vachiery (Brussels, Belgium) emphasised that optimal management includes oxygen, diuretics and left ventricular targeted therapies. He also suggested that diastolic dysfunction and heart failure with preserved ejection fraction will contribute to the increase in PH-associated left heart disease.[25] Dr L Howard (London, UK) gave an interesting lecture on the future role of specialist PH centres once the specific drugs used to treat PH become generic. After outlining the complexity of the organisation of the current PH referral units in the UK, he made a strong case for these to exist in the generic era. Not only do specialist centres offer accurate diagnosis, they also provide an escalation service of therapy and perhaps more importantly a vital support network of experienced multidisciplinary staff who can advise the patient with this uncommon disease.

There were two strong sessions presenting the interactions between basic and clinical research in PH in the UK. In the first presentations Toshner *et al* discussed the characterisation of the late outgrowth endothelial progenitor cell and proposed it as a better candidate for the elusive circulating endothelial progenitor cell.[26] Church *et al* demonstrated the importance of p38 mitogen-activated protein kinase signalling to the development of PH.[27] Novel applications of MRI in the diagnosis and prognosis of patients with PH was highlighted by Swift *et al*.[28] Results from the UK and Ireland PH registry were presented by Ling, showing interesting data suggesting that older patients presenting in the current era with PH may have a different disease phenotype compared with the classical young female preponderance that was seen historically.[29] The second session explored in detail the role of bone morphogenetic protein receptor type 2 (BMPR2) signalling in PH. Heterozygous mutations in the BMPR2 gene in mice do not result in PH. However, Long *et al* presented data of a knock-in mouse model, using a known human disease-causing mutation, which after 6 months developed mild PH.[30] When this model was crossed with a mutation in Smad-1, which is downstream of BMPR2, the resulting offspring developed more severe PH. Taken together this underpins the relevance of the BMPR2 signalling axis to PH. Soon *et al* explored the role of BMPR2 and the expression of cytokines in the development of PH.[31] Both human and murine smooth muscle cells which harbour a BMPR2 mutation have at baseline increased mRNA levels of interleukin (IL)-6 and IL-8 and further increase these cytokines in response to lipopolysaccharide compared with wild type cells. This increase in IL-6 and IL-8 was also seen in an in vivo BMPR2 heterozygous mutant mouse model following exposure to lipopolysaccharide, suggesting that BMPR2 mutations may lead to dysregulation of cytokine expression in PH.

Venous abnormalities in PAH are well recognised but the mechanisms leading to it are not clearly understood. Cannon *et al* used a transgenic zebrafish model to show that inhibition of the BMPR2 pathway by various means results in abnormal venous development but not arterial angiogenesis.[32] This may suggest an important role for BMPR2 in vasculogenesis. Previous work has shown that BMPR2 protein trafficking is regulated

through a lysosomal pathway. The anti-malarial drug chloroquine can inhibit lysosomal function and Dunmore *et al* have shown that in vitro this agent can increase cell surface expression of BMPR2.[33] Indeed, administration of chloroquine in a monocrotaline rat model of PAH showed evidence of both preventing and inhibiting the progression of PAH.

THORACIC ONCOLOGY

This year's joint BTS and British Thoracic Oncology Group symposium addressed the issue of early diagnosis of lung cancer. Dr M Peake (Leicester, UK) presented international data demonstrating that the UK lung cancer 5-year survival rates remain lower than many other countries, with wide differences among regions.[34] He highlighted that late diagnosis is a major element in the UK's poor outcomes, with 40% of patients presenting as an emergency and having the poorest prognosis. The National Awareness and Early Diagnosis Initiative have established local initiatives to improve this situation, including social marketing campaigns, healthcare professional awareness and chest x-ray (CXR) self-referral systems, with long-term results awaited.[35] In addition, Dr T Rogers (Doncaster, UK) presented an innovative local initiative focusing on the symptom of cough to prompt individuals to seek a CXR via primary care.[36] Significant increases were seen in CXR and secondary care referrals, with a non-significant increase in new lung cancer diagnoses.

Early detection of asymptomatic patients remains an attractive prospect[37] but lung cancer screening studies have shown limited benefit to date. Professor A Lynch (Denver, Colorado, USA) presented the exciting results of the National Lung Screening Trial in which high-risk individuals were randomised to undergo three annual screenings with either low-dose CT or CXR.[38] The trial was halted early due to a relative reduction in mortality from lung cancer of 20.0% (95% CI 6.8 to 26.7; p=0.004) with low-dose CT screening, with increased detection of early stage disease. Further work will examine cost effectiveness and potential over diagnosis (ie, the detection of cancers that never would have become symptomatic) due to CT screening.

The issue of resection rates in the treatment of lung cancer was discussed in a dedicated symposium. Dr K Naunheim (St Louis, Missouri, USA) identified a number of potential reasons that the USA has a higher resection rate compared with the UK. Possibilities included a lower number of thoracic surgeons in the UK, a degree of therapeutic nihilism, especially in patients aged over 75, and a higher proportion of patients presenting with advanced non-surgical disease. However, he did acknowledge that there was an economic incentive in the USA to operate on more patients. This was followed by Professor H Moller (London, UK) who demonstrated that there was a significant improvement in survival in patients who were operated on in an area with higher surgical resection rates, which may be due to better selection of patients rather than expertise.[39] Mr R Page (Liverpool, UK) discussed the findings from an audit of the Society of Cardiothoracic Surgeons. The resection rates seem to be increasing across the UK with in-hospital mortality decreasing[40] and a reduction in the number of patients who are inappropriately taken to theatre. Finally, Mr D Waller (Leicester, UK) emphasised the importance of the multidisciplinary team meeting in deciding which patients require surgical intervention and that there was a responsibility to ensure that patients who could get surgery were discussed with a thoracic surgeon. He highlighted the fact that higher resection rates result from multidisciplinary team meetings where surgeons are actually physically present and also in hospitals where there are at least two dedicated thoracic surgeons working.

A variety of lung cancer research was presented in the spoken sessions. The diagnostic capability of endobronchial sampling techniques was discussed. Rintoul *et al* showed that an initial approach to staging mediastinal disease in non-small cell lung cancer (NSCLC) using combined endoscopic and endobronchial ultrasound (EBUS) was cost effective and had better quality of life scores compared with surgical staging alone.[41] Navani *et al* then showed similar findings using EBUS to investigate isolated mediastinal lymphadenopathy, with this method being cost effective, safe and highly sensitive.[42] However, EBUS did have a low negative predictive value and it was emphasised that if the result is negative the patient should still have a mediatinoscopy. A future technique to establish malignant versus reactive nodal disease with transbronchial needle aspiration (TBNA) sampling could be to use gene expression profiling. Lee *et al* demonstrated that RNA extraction from cytological specimens was possible and microarray technology could demonstrate different gene expression profiles for malignant and reactive nodes.[43]

The standard of care in advanced NSCLC is platinum-based chemotherapy but the optimal dose of cisplatin and comparison with carboplatin is uncertain. The results of the British Thoracic Oncology Group trial (BTOG2) were presented, with this large phase III randomised trial comparing treatment with gemcitabine combined with cisplatin 50 mg/m^2, cisplatin 80 mg/m^2 or carboplatin area under the curve (AUC) 6 (with dose based on the Wright equation).[44–47] The authors concluded that, in advanced NSCLC, the dose of cisplatin is important with cisplatin 50 mg/m^2 giving the poorest outcome for overall survival and response rate. In addition, in combination with gemcitabine, carboplatin was equivalent to cisplatin in terms of survival.

Mesothelioma remains an aggressive and incurable tumour and there is a need to develop novel therapeutic strategies, including possible immunotherapy. Steer *et al* demonstrated that, in a murine model, suppressive CD4 cells were preventing an effective anti-tumour CD8 T-cell response, thus raising the possibility that removal of these suppressive CD4 cells is required to enable curative mesothelioma treatment.[48] In addition, Sage *et al* utilised mesenchymal stem cells, which migrate to and incorporate into tumours, to produce tumour necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL); this resulted in the induction of apoptosis in several human mesothelioma cell lines.[49]

THE BTS/BLF/BALR EARLY CAREER INVESTIGATORS AWARD

The annual Early Career Investigators symposium, jointly hosted by the BTS, the British Lung Foundation (BLF) and the British Association for Lung Research (BALR), recognises the new generation of UK respiratory researchers who do not yet have a permanent position at consultant level or lecturer level for non-clinical scientists, and as ever was a stimulating and lively session. There was an eclectic mix of tremendous work covering a diverse range of respiratory research.

Singh *et al* were awarded the BTS prize for their interesting work demonstrating the importance of matrix metalloproteinases (MMPs) in tissue destruction seen with tuberculosis (TB).[50] There were higher levels of MMPs expressed in bronchial biopsies and bronchoalveolar lavages from patients with TB, with IL-17 implicated in driving this. Using molecular

and pharmacological techniques, mammalian target of rapamycin (mTOR) was identified as important in upregulating these MMPs and rapamycin, which inhibits TOR, was proposed as an adjunct in limiting tissue destruction in TB infection.

Chalmers *et al* received the BLF prize for demonstrating the importance of recently described Ficolin molecules, which act as opsonisation proteins, with in vitro studies showing key activity in promoting complement and neutrophil directed killing of bacteria such as *Pseudomonas*.[51] Increased incidence of bronchiectasis was observed in patients with lower serum levels of ficolin-2 and single nucleotide polymorphisms in the ficolin-2 gene. In addition, patients who were ficolin-2 deficient had increased bacterial colonisation (especially *Pseudomonas*) and higher rates of infective exacerbations.

Roach *et al* were awarded the BALR prize for their work looking at myofibroblasts in idiopathic pulmonary fibrosis (IPF).[52] They have shown that human lung myofibroblasts express the KCa3.1 channel and that there is a functional difference in this channel in cells derived from patients with IPF compared with healthy donors. Furthermore inhibition of this channel leads to a reduction in growth factor driven wound healing by these myofibroblasts, raising the possibility that blocking these channels could attenuate abnormal myofibroblast function in patients with IPF.

Farahi *et al* presented the first study to look at eosinophil kinetics in vivo in healthy volunteers.[53] The anatomical distribution and circulating time was examined using eosinophils isolated by immunomagnetic beads, then radio-labelled with indium and re-injected. This study showed an initial accumulation of eosinophils in the lung which cleared after 45 min and the authors proposed this as a non-invasive technique allowing the efficacy of drugs targeting eosinophils to be assessed. Davies *et al* presented data in a small study using a nasally delivered plasmid vector containing the *CFTR* gene in patients with CF.[54] There was a drop in the forced expiratory volume in 1 s following initial administration but this resolved quickly and the study showed that there was an eventual expression of the gene and improvement in nasal potential difference, a surrogate marker of CFTR function. Finally Hameed *et al* presented a very interesting study demonstrating the potential importance of TRAIL in PAH.[55] Using anti-TRAIL antibodies and a genetic knockout model of PH, this group showed that PH could be prevented and, perhaps clinically more relevant, also reversed by targeting TRAIL.

THE EXTREMES OF PHYSIOLOGY—THE VERY FIT AND THE VERY ILL

In recognition of the forthcoming London 2012 Olympics, a novel symposium was held on the Physiology of the Elite Athlete. Sport represents an excellent forum in which to study physiology, with elite athletes representing the extremes of the gene pool and training to the limits of performance. Professor R Maughan (Loughborough, UK) discussed the numerous factors at play in the physiology of the elite athlete. He highlighted that muscle fibre composition (ie, fast-twitch vs slow-twitch fibres) is genetically determined and thus an individual will have a predetermined preference to a given type of sport. He further gave a clear description of the biochemical and physiological factors limiting exercise capacity (eg, oxygen carrying capacity, buffering capacity, etc) and how athletes can manipulate these by training and by other illicit measures (eg, use of androgenic steroids, self-transfusions, etc). In contrast, the study of exercise capacity and performance in the normal ageing population was discussed by Professor S Harridge (London, UK). Performance appears to decline linearly until the eighth decade, followed by a more rapid decline, in non-athletes. However, he demonstrated that physiological systems remain responsive to training even in much older people.[56]

Elite athletes performing endurance sports have a high prevalence of airway hyper-responsiveness and exercise-induced asthma, with estimates of asthma effecting between 2.7% and 22.8% of summer sports athletes. Professor L Boulet (Quebec, Canada) described how athletes present with a specific asthma phenotype characterised by a poor correlation of symptoms with pulmonary function, high baseline lung volumes, non-eosinophilic airways inflammation, a reduced response to treatment, and partial reversibility of airways dysfunction with training cessation.[57–59] Such airways disease may be induced by exposure to inhaled agents (eg, allergens, chlorine derivatives and pollutants) and mechanical stress itself.[60] He emphasised that further research is needed on the long-term consequences of high-level training on airway function and how airway damage can be prevented.

To complement discussion of the physiology of muscle in the elite athlete, a further symposium addressed the pathophysiology of muscle weakness seen in the critical care patient. Dr T Sharshar (Paris, France) discussed critical care acquired weakness and highlighted that the best treatment is prevention. Avoidance of sedatives and steroids, tight glycaemic control and early mobilisation appear the best preventive measures. Professor M Singer (London, UK) gave an eloquent exposition on the potential role of mitochondrial dysfunction in the development of multi-organ failure (MOF). He demonstrated that the mitochondrial transcriptome switching off in MOF and survival seemed to be associated with patients' ability to switch the transcriptome on again. This was followed by Professor M Rennie (Nottingham, UK) who showed that muscles develop anabolic resistance in MOF and seem to be unable to use amino acids and increase basal turnover of protein. Furthermore a pro-inflammatory response in the muscle with increases in IL-6 and TNF-α is observed within the first few days of a patient being admitted to an intensive care unit. The final talk from Dr L Price (London, UK) reminded us that research advances must be translated into patient care. Dr Price developed Guillian-Barré syndrome while attending the BTS meeting 3 years ago and reflected on her prolonged period in intensive care where she lost considerable muscle strength and required months of rehabilitation.

CONCLUSION

The forthcoming 2012 Olympics will showcase the world's finest athletes, just as the BTS Scientific Meeting continues to do the same for the world's finest science in respiratory medicine. It sets out to allow the dissemination and discussion of novel and cutting edge respiratory research and it is clear the 2011 meeting achieved these goals, confirming it as an important forum in the research calendar.

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