

ABSTRACTS

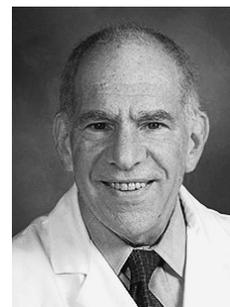
IL1

The “Healthy Smoker” is not Healthy—Smoking-induced Disordering of Lung Biology Starts the Smoker Down the Road to COPD and Lung Cancer

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COPD is a common cause of mortality worldwide. Despite strategies to reduce smoking prevalence and to develop therapies to reduce morbidity and mortality from COPD, the prognosis of COPD remains dismal. To reduce morbidity/mortality from COPD, it will be necessary to develop therapies targeted to reverse/prevent the early biologic abnormalities in the lung associated with smoking and COPD. While inflammation plays an important role in the pathogenesis of the later stages of COPD, the early effects of smoking on the lung are disordered biology of lung cells, including the airway epithelium and pulmonary capillary endothelium. This is not surprising, as each puff of cigarette smoke includes >4000 compounds and 10^{14} oxidants, and lung cells take the brunt of this stress. Based on the concept that effective therapies for COPD will require preventing and/or reversing the smoking-related disordered lung biology that precedes COPD, we have focused on characterizing the disordered biology of the airway epithelium and pulmonary capillary endothelium. In the airway epithelium, there is significant up- and down-regulation of hundreds of genes, processes that occur long before any clinical manifestations of smoking-induced disease. The disordered/dysfunctional airway epithelium is unable to maintain normal mucociliary clearance, allowing for mucus accumulation and pathogen colonization characteristic of COPD. In parallel with disordering of epithelial biology, there is disordering of lung endothelial cell biology, with apoptosis-mediated loss of alveolar capillaries, a process that can be monitored by assessing the levels of pulmonary endothelial apoptotic-derived endothelial microparticles in blood. Finally, based on data that the disordered airway epithelial biology and increased pulmonary capillary apoptosis reverse, at least partially, with smoking cessation, we have developed a novel, gene therapy-based vaccine that, with a single administration, will prevent nicotine from reaching the brain. Focusing on the biology of smoking-induced disordering of lung biology is the future of developing new therapies to treat/prevent COPD.



Dr. Crystal is Professor and Chairman of the Department of Genetic Medicine of the Weill Medical College of Cornell University, where he is also the Bruce Webster Professor of Internal Medicine, Director of the Belfer Gene Therapy Core Facility and Attending Physician at the Weill Cornell-New York Presbyterian Hospital.

After earning a BA degree in physics from Tufts University, an MS degree in physics from the University of Pennsylvania, and an MD degree from the University of Pennsylvania, Dr. Crystal completed his medical post-graduate training at Massachusetts General Hospital in Internal Medicine and in Pulmonary Medicine at the University of California, San Francisco. In 1970, Dr. Crystal joined the National Institutes of Health, where he served as Chief of the Pulmonary Branch of the National Heart, Lung and Blood Institute until moving to Weill-Cornell in 1993.

During the 1970's and 80's, Dr. Crystal focused much of his research on the pathogenesis and therapy of inflammatory diseases of the lung. The work of his laboratory formed the basis of the current understanding of the pathogenesis of lung fibrosis and the hereditary form of emphysema associated with alpha 1-antitrypsin deficiency, a disease for which he developed the FDA-approved therapy now used to treat thousands of patients worldwide.

In the late 1980's, Dr. Crystal shifted his focus to gene therapy, a field in which he is a pioneer. He was the first to use a recombinant virus as a vehicle for *in vivo* gene therapy, and has carried out human trials of gene therapy for cystic fibrosis, cardiac ischemia, cancer and central nervous system disorders. His current research interests are deciphering how human genetic variation modulates gene expression in the context of environmental exposure and exploiting these relationships to recategorize human disease at the biologic level and identify who is at risk for disease.

In recognition of his significant accomplishments as a basic and clinical investigator, Dr. Crystal has received numerous professional honors including an honorary degree from the Johann Wolfgang Goethe University in Germany, an honorary professorship from Sichuan University in China, and an Honorary Fellowship from the Royal Physicians of Ireland. He serves on the editorial boards of numerous biomedical journals. He has published over 800 scientific articles, and his work has been cited over 50,000 times in the scientific literature. He has edited several textbooks, and served on a number of advisory boards to government and industry. Dr. Crystal is responsible for numerous biomedical patents and was the founder of GenVec, a public biotechnology company focused on gene therapy applications.

Outside of his professional activities, Dr. Crystal is an active mountain climber.

IL2

Autophagy in Lung Disease

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Cellular (macro)-autophagy, a regulated pathway for the turnover of cytoplasmic organelles and protein, represents an essential cellular homeostatic mechanism. During autophagy, damaged proteins or organelles are sequestered within double-membrane vesicles, or autophagosomes. Maturing autophagosomes fuse with lysosomes where the contents are degraded. This process regenerates metabolic precursors that are recycled for macromolecular synthesis and energy production. Thus, autophagy provides a mechanism for prolonging survival under cellular stress, including starvation. Accumulating evidence also suggests that autophagy may be linked to programmed cell death. Very little is currently known on the function of autophagy in lung diseases. Our Preliminary Studies suggest that autophagy represents a major cellular and tissue response to lung injury. We have shown that the autophagy protein, microtubule associated protein light chain-3B (LC3B) regulates epithelial cell apoptosis. We have also observed the localization of LC3B to the caveolae (lipid raft) compartment of epithelial cells and its interaction(s) with death inducing signaling complex (DISC), namely Fas. Upon exposure to oxidant stress, the LC3B-Fas complex dissociates, releasing Fas, suggestive of regulatory mechanisms by which autophagy protein LC3B can initiate the extrinsic apoptosis pathway. We will review the mechanism by which autophagy regulates apoptosis. We will also examine the crosstalk between autophagy and inflammation. Recent advances in inflammatory signaling have revealed the existence of a novel signaling complex called the inflammasome which activates caspase-1, leading to the maturation and secretion of downstream pro-inflammatory cytokines such as IL-18 and IL-1b. We recently reported that autophagy deficiency activates inflammasome via mitochondrial dysfunction and reactive oxygen species. We will review the mechanism by which autophagy regulates mitochondrial function and inflammasome activation in lung disease.



Education:

1980	B.S. <i>summa cum laude</i>	Zoology	University of Kentucky, Lexington, KY
1984	M.D.	Medicine	University of Louisville, Louisville, KY
2007	A.M. (Hon.)		Harvard University Cambridge, MA

Postdoctoral Training:

7/1984-6/1985	Intern	Internal Medicine	Duke University Medical Center, Durham, NC
6/1985-6/1987	Resident	Internal Medicine	Duke University Medical Center, Durham, NC
7/1986-6/1987	Asst. Chief Resident	Internal Medicine	Duke University Medical Center, Durham, NC
7/1987-6/1990	Clinical/ Research Fellow	Pulmonary & Critical Care Medicine	Johns Hopkins University, Baltimore, MD

Faculty Academic Appointments:

7/1990-6/1992	Instructor	Medicine	Johns Hopkins University, Baltimore, MD
7/1992-2/1998	Asst. Professor	Medicine	Johns Hopkins University, Baltimore, MD
3/1998-7/2000	Assoc. Professor (with Tenure)	Medicine	Yale University, New Haven, CT
8/2000-9/2007	Professor (with Tenure)	Medicine	University of Pittsburgh, Pittsburgh, PA
10/2007-7/2013	Professor	Medicine	Harvard Medical School, Boston, MA
8/2013-	Professor	Medicine	Weill Cornell Medical College

IL3

Translating Recent Advances on the Molecular Pathogenesis of Lung Cancer into the Clinical Practice

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Lung cancers are tumors with complex biology that we have recently started to understand with the advent of various histological, transcriptomic, genomic and proteomic technologies. However, the histological and molecular pathogenesis of this malignancy, in particular of adenocarcinomas and squamous cell carcinomas, is still largely unknown. Despite, recent encouraging findings from the National Lung Screening Trial (NLST), early detection and prevention of lung cancer is challenging due to the lack of biomarkers for early diagnosis of the disease and to the presence of multiple neoplastic molecular pathways that mediate lung carcinogenesis. Applying high-throughput molecular methodologies currently used in studying established tumors to samples obtained from the field of cancerization airway we are expanding our understanding of the early pathogenesis of this disease. Earlier studies have highlighted a field cancerization phenomenon in which histologically normal-appearing tissue adjacent to neoplastic and preneoplastic lesions display molecular abnormalities some of which are in common with those in the tumors. This presentation will summarize advances in understanding the field cancerization phenomenon and the potential relevance of this knowledge to gain important and novel insights into the molecular pathogenesis of lung cancer, as well as to subsequent development of biomarkers for early detection of lung cancers and personalized chemoprevention.

Research Interests:

- Lung cancer molecular profiling
- Lung cancer early pathogenesis
- Lung cancer next-gen sequencing
- Lung cancer targeted therapy
- Lung cancer resistance to treatment mechanisms

Description of overall research program: One of my major research interests is elucidation of the molecular abnormalities involved in the pathogenesis and progression of lung cancer. My research interests also include identification of new molecular targets, validation of biomarkers for targeted therapy, and identification of molecular markers associated with metastasis development. My lab is furnished with state-of-art molecular biology and pathology equipment and technology, and my research is integrated to the multidisciplinary lung cancer program in MD Anderson Cancer Center. I have established an invaluable tissue and cell bank resource for lung cancer with more than 3,000 frozen and archival lung cancer and airway epithelia specimens, and a database of clinical and molecular information associated with these patient samples. Several lung cancer datasets with comprehensive molecular profiling (RNA, miRNA and DNA) are available for mining and validation studies.

Projects/Techniques:

1. Identification and validation of molecular abnormalities associated to the pathogenesis of lung cancer through comprehensive molecular profiling (miRNA/RNA expression, miRNA/RNA-sequencing, and DNA mutation/copy changes) of the airway (field of cancerization) of patients with lung cancer.
2. Identification and validation of novel molecular changes and potential molecular targets through comprehensive molecular profiling (miRNA/RNA expression, miRNA/RNA-sequencing, and DNA mutation/copy changes) of lung cancer tumors.
3. Identification and validation of novel molecular therapeutic targets through comprehensive molecular profiling (RNA expression, RNA and DNA next generation of sequencing) of tumor tissue specimens treated with AKT and MEK inhibitors (BATTLE clinical trial).
4. Molecular characterization of mechanisms of resistance to platinum-based chemotherapy in patients with lung cancer.

PL

Evidence from Asian-Pacific Respiratory Medicine: Clinical trials and ethnicity for personalized EGFR-TKI in NSCLC and pirfenidone in IPF

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Precise information of the ENCODE study or TCGA project has been emerging from simple whole genome sequence, which ultimately leads to personalized medicine. Such personalization often reveals that person-to-person difference originates from ethnic genetic background. Lung cancer, even a general disease entity, is one such example. Gefitinib, an EGFR-TKI, was approved for NSCLC in Japan in 2002, as the first drug in the world. However, in several months Japanese chest physicians witnessed one of the worst drug adverse events of interstitial lung disease (ILD) in 5% of patients prescribed with high mortality. Questions raised were why gefitinib is effective in nearly 30% of patients with NSCLC, and at the same time causes ILD that is far higher than seen in Caucasians. In 2004, researchers in Boston reported somatic EGFR kinase mutation in tumors of Asian NSCLC, suggesting a possible ethnic difference; which turned out to be a typical driver mutation and a true target of EGFR-TKI. Researchers and chest oncologists in Asia including us immediately started to confirm the information as well as to launch clinical trials. These studies established the evidence that NSCLC patients with EGFR mutation detected should be treated by EGFR-TKI.

Awareness of ethnic difference worked in another clinical trial. IPF is an intractable lung disease, and the prognosis is similar to lung cancer. Understanding of IPF staging comes from clinical experience that acute exacerbation in advanced IPF causes fatal outcome, allegedly specific in Japan. In 2000, Japanese researchers and Shionogi & Co., Ltd. launched a phase II clinical trial of pirfenidone for an orphan drug approval. The difficult part of the design was enrollment criteria and primary endpoint. The staging (severity grade) of patients with IPF has been required since '90s in Japan due to medical cost coverage. Patients with stage II and III were enrolled to obtain significant difference in a year of treatment, and ΔSpO_2 in phase II and ΔVC in phase III were used as primary endpoint. Both phase II and III trials revealed significant suppression of progression in pirfenidone group. It thus became the first drug approved in IPF and currently used also in Europe. Genetics in ethnicity in acute exacerbation is now under investigation using NGS analysis. While current EBMs are believed to be general all over the world, these Asian trials indicate the importance of awareness on ethnic difference in the era of personalized medicine.

SL

Towards the clinical application of iPS cells in the respiratory field

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Induced pluripotent stem (iPS) cells, developed by Shinya Yamanaka in 2006, theoretically have a potential to differentiate into any cells in the body. In this paper, general information about iPS cell application in Kyoto University Hospital is succinctly announced. In addition, the updated research outcome in the respiratory field by our department is commented upon.

In 2011, Kyoto University Hospital developed a division for iPS Cell Application Development in cooperation with the Center for iPS Cell Research and Application (CiRA). This division has two missions. One is disease-specific iPS cell study. The iPS cells obtained from somatic cells of patients are utilized for the analysis of pathogenesis and for the development of new drugs. The other is iPS cell-derived transplantation. The somatic cells of healthy volunteers are supplied to patients. The homogeneous HLA is essential to decrease rejection, and a storage system is now being established. Within a couple of years, Kyoto University intends to initiate iPS cell-derived transplantation to patients with Parkinson's disease and to patients with blood diseases such as thrombocytopenia or pure red cell aplasia.

The lung is one of the most complicated organs in the human body. There is so far no effective drug to repair pathological changes in destructive lung diseases. We, therefore, anticipate that cell therapy or tissue regeneration could be a future therapeutic option. Since alveolar type I cells differentiate from alveolar type II (AT2) cells, one of the key cells for lung regeneration is AT2 cells. We have been developing a strategy to induce AT2 cells from iPS cells by way of endodermal lineage. Our trial-and-error methods have led us to induce AT2 cells, which express surfactant protein-C (SPC), a specific marker of the cells. Through the induction pathway, we discovered a surface marker to sort putative progenitor cells of the lung. In addition, we have developed an SPC-reporter iPS cell line. We are on the way to more efficient induction of AT2 cells using these techniques. Disease specific iPS cells are potential materials for pathogenetic investigation and drug screening and we are planning to use iPS cells from patients with lung diseases. To further realize clinical application of lung cells induced from iPS cells in the future, several important challenges are to be addressed: functional evaluation of the induced cells, massive induction of the cells and construction of transplantable organ structures.

Y11

Knockdown Of Zinc Finger E-Box Binding Homeobox 1 (Zeb1) Reduces Stem Cells Characteristic Of Gefitinib-Resistant-Persisters Of Pc9 Cells

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Background: Acquired resistance to targeted therapy, such as gefitinib, is major problem in EGFR-mutant non-small cell lung cancer (NSCLC). Evidences suggest that cancer stem cells (CSCs) are involved in the resistance of cancer cells to therapy. Zinc finger E-box binding homeobox 1 (ZEB1) is an epithelial-mesenchymal transition inducer that has been linked with stemness maintenance. However, the role of ZEB1 in the maintenance of gefitinib-resistant lung CSC has not been fully understood. **Aim of Study:** To investigate the role of ZEB1 in CSCs phenotype of gefitinib-resistant-persisters (GRPs)-PC9 cells. **Methods:** We exposed PC9 cells to 2 μ M of gefitinib for 9 days to obtained GRPs. Quantitative-PCR was conducted to analyze stem cell factors and sphere formation assay was performed to examine the self-renewal of these PC9-GRPs. We knockdown ZEB1 using short-hairpin RNA to obtained stable ZEB1-low expressing PC9 to see the effect on CSCs features of PC9-GRPs. **Results:** PC9-GRPs expressed high stem cell factors and could form more sphere numbers as compare to parental PC9. Knockdown of ZEB1 reduced stem cell factors expression in PC9-GRPs as well as reduced sphere numbers. **Conclusion:** ZEB1 is required to maintain the CSC features of PC9-GRPs, and knockdown of ZEB1 reduced CSC characteristic. Our results suggest that ZEB1 might be potential target to reverse gefitinib resistance in NSCLC.

Y12

Clinical And Laboratory Profiles And Outcomes Of Critically Ill Chest Disease Patients In A Tertiary Care Chest Hospital

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Background: Critical care in respiratory field has been introduced recently in Bangladesh. Last year total 429 patients were admitted in ICU. This prospective observational study conducted to observe presenting profiles and outcomes of treatment of critically ill chest disease patients. **Methods:** All ICU admitted patients were enrolled consecutively. Baseline demographic and laboratory characteristics including primary diagnosis, present clinical problem, arterial blood gas, electrolytes, sputum microscopic findings were noted. Types of intervention and outcomes of the patients in term of death, referral, discharged were noted. **Results:** Total 429 patients were enrolled. Male: Female was 1.66:1. 294 cases (68.5%) had type-2 respiratory failure, mainly due to COPD (74.8%) followed by bilateral bronchiectasis (17.34%), and severe persistent asthma (7.24%). Type-1 respiratory failure was seen in 105 cases (24.4%); due to acute asthma in 42.6%, ARDS in 24.8%, ILD in 32% cases. Mean PCO₂ was 76 mm of Hg; range 60-158 mm of Hg. BiPAP was given in all patients. 88.75% was compliant and 72.58% had satisfactory improvement. Invasive ventilation was given to rest. No growth was seen in 46.86% patients on sputum or tracheal aspirates culture. Acinetobacter (36.8%) and pseudomonas (52.4%) were main culprit organisms. Acinetobacter was resistant to all antibiotics except colistin (88.5%). Mortality was 32.4%. 12.87% referred to other hospitals and 55.6% discharged. Among intubated patients, ventilation associated pneumonia (VAP) followed by septic shock seen in 64.7% and cardiac arrest due to arrhythmias or myocardial ischemia seen in 32.9% patients as cause of death. **Conclusion:** Type-2 Respiratory failure was the main cause of referral to ICU in this specialized chest hospital. BiPAP was very effective to reduce PCO₂. VAP was predominant cause of death in intubated patients.

YI3

Healthcare Utilization Associated With Misdiagnosis Of COPD In Primary CareMin J. Joo^{1,3}, Ann Bunyan¹, Todd A Lee¹, David H. Au²University of Illinois at Chicago, Chicago, IL, USA¹, VA Puget Sound Health Care System, Seattle, WA, USA², Jesse Brown VA Medical Center, Chicago, IL, USA³

RATIONALE: A diagnosis of chronic obstructive pulmonary disease (COPD) is suggested after history and physical examination and is confirmed by the presence of irreversible airflow obstruction with spirometry. Previous studies have shown problems with both under-diagnosis and over-diagnosis of COPD even in the presence of spirometry. The primary objective of this analysis was to determine if misdiagnosis of COPD was associated with differences in healthcare utilization compared to those accurately diagnosed based on spirometry.

METHODS: A cohort of patients at risk for COPD who met the following criteria was included: ≥ 35 years old; ≥ 2 primary care visits in internal medicine clinic in 2007; had spirometry performed, and at least one respiratory or smoking cessation medication or diagnosis of COPD within the same year. Using lower limit of normal criteria, the following three groups were defined: 1) presence of COPD diagnosis and obstruction on spirometry (true diagnosis-Group 1), 2) COPD diagnosis with normal spirometry (over-diagnosis-Group 2), and 3) obstruction on spirometry without COPD diagnosis (under-diagnosis-Group 3). Medical records were reviewed 18 months past the inclusion date. Data on all-cause and respiratory-related hospitalizations, emergency department (ED) visits, and ancillary tests were extracted. Odds ratios were determined using logistic regression comparing Group 1 to Group 2 and then Group 3. Variables considered statistically significant in unadjusted comparisons were included in multivariate analyses.

RESULTS: Out of 527 patients identified in the cohort, 103 patients were classified as Group 1, 63 patients as Group 2 and 52 patients as Group 3. In adjusted analysis for Groups 1 and 2, patients who were over-diagnosed were more likely to have at least one all-cause hospitalization (AOR 2.04 [95% CI 1.02-4.04]) and/or ED visit (AOR 2.16 [1.05-4.43]) compared to those with an accurate diagnosis. Patients who were over-diagnosed were more likely to have had a chest radiograph (AOR 2.47 [1.10-5.54]), Chest CT (AOR 2.33 [1.18-4.58]), cardiac catheterization (AOR 2.57 [1.23-5.37]), and/or cardiac stress test (AOR 2.28 [1.06-4.91]) compared to those with a true diagnosis. The adjusted analysis between Groups 1 and 3 did not show any statistically significant differences in health care visits or ancillary tests.

CONCLUSION: Discrepancies exist between the results of spirometry testing and the diagnosis of patients with COPD in primary care. Our study shows that over-diagnosis of COPD is associated with more all-cause hospitalizations and ED visits and also more respiratory and cardiac ancillary testing.

FUNDING SOURCE: This study was supported by Award Number K23HL094461 and also supported, in part, by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The views expressed in this abstract are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government, or NHLBI, NIH.

YI4

PET imaging with [¹¹C]PBR28 and [¹⁸F]FDG distinguishes macrophage from neutrophil lung inflammation

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Introduction: Noninvasive methods for quantifying macrophage and neutrophil activation and recruitment in chronic obstructive pulmonary disease (COPD) would be highly useful in assessing the efficacy of anti-inflammatory therapies.

Objective: To test whether positron emission tomography (PET) imaging with [¹¹C]PBR28 and [¹⁸F]fluorodeoxyglucose ([¹⁸F]FDG) could distinguish macrophage-dominant from neutrophilic inflammation in a mouse model of COPD.

Methods: C57BL/6J mice inoculated with PBS or Sendai virus were imaged by microPET (Inveon or Focus 220, Siemens/CTI) with both [¹¹C]PBR28 and [¹⁸F]FDG at Days 3 and 84 post-inoculation (p.i.). Regions of interest placed over the lungs determined the % injected dose per cc (%ID/cc) at 60 min. Lung sections were stained for TSPO ([¹¹C]PBR28 ligand), Ly6G (neutrophil marker) and CD68 (macrophage marker).

Results: Only [¹⁸F]FDG uptake increased significantly during acute illness at p.i. Day 3. Both [¹¹C]PBR28 and [¹⁸F]FDG uptake increased significantly during chronic disease at p.i. Day 84. The [¹¹C]PBR28:[¹⁸F]FDG ratio, calculated for each mouse, was no different between infected (1.9 \pm 0.3) and uninfected mice (2.0 \pm 0.4) at p.i. Day 3. This ratio increased significantly at p.i. Day 84 (3.1 \pm 0.9) in infected mice compared to controls (1.7 \pm 0.5). Lung sections showed macrophages with intense TSPO staining at p.i. Day 84.

Conclusion: PET imaging with [¹¹C]PBR28 and [¹⁸F]FDG quantitatively distinguishes macrophage-dominant from neutrophilic inflammation in a mouse model of COPD. This approach may be useful for monitoring the pulmonary macrophage burden in humans with COPD, thereby guiding emerging targeted anti-inflammatory therapies.

Y15

Study Of Incidence, Outcome And Antibiotic Sensitivity Pattern Of Ventilator Associated Pneumonia In Icu Of Tertiary Care Hospital In Nepal

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Background: Ventilator Associated pneumonia (VAP) is an important intensive care unit (ICU)-acquired infection in mechanically ventilated patients. Early and correct diagnosis of VAP is difficult but is an urgent challenge for an optimal antibiotic treatment. **Aim of study:** To evaluate the incidence, microbiology and antibiotic sensitivity pattern of Ventilator Associated Pneumonia. **Methods:** A prospective, open, epidemiological clinical study was performed in ICU of TUTH, Maharajgunj. 100 patients admitted to ICU and Mechanically Ventilated were evaluated with regard to VAP. Clinical Pulmonary Infection Score (CPIS) was used as tools to diagnose VAP. **Results:** Among 60 long-term ventilated patients, 25 (41.6%) developed VAP. The incidence was 25 VAPs per 100 ventilated patients or 26 VAPs per 1000 ventilator days during the period of study. Days on ventilator and duration in ICU were higher in the VAP group. There was a trend towards increasing mortality in the VAP group (p value .06). The VAP was caused predominantly by Klebsiella pneumonia in 34.5% of cases, followed by Acinetobacter calcoaceticus baumannii in 27.6%, Acinetobacter wolffi and Pseudomonas aeruginosa in 13.8% each and Escheresia coli in 10.3%. The most sensitive antibiotics were Colistin, followed by Polymyxin B and Amikacin with sensitivity rates of 67%, 60% and 58% respectively. **Conclusion:** There exists a high rate of VAP in our ICU. Targeted strategies aimed at reducing VAP should be implemented to improve patient outcome and reduce length of ICU stay and costs.

Y16

Human Rhinovirus Infection Of Asthmatic Airway Epithelial Cells Causes Tight Junction Disassembly Resulting In Increased Permeability.Kevin Looi¹, Alex Larcombe², Graeme Zosky², Paul Rigby³, Darryl A. Knight⁴, Stephen M. Stick^{1,2,5}, Anthony Kicic^{1,2,5}

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Introduction: Human rhinovirus (HRV) has been identified as a major contributor of asthma exacerbations in children and has been suggested to occur by epithelial tight junction (TJ) protein modification and barrier integrity disruption. This study aimed to directly correlate live viral infection with TJ disassembly and whether this leads to barrier compromise.

Methods: Polarised human epithelial colorectal adenocarcinoma cells (Caco-2), modified human airway epithelial cell (NuLi-1) and primary human airway epithelial cells (pAECs) were infected with HRV-1B at various multiplicity of infection (MOI) over 24 hours. HRV receptor and viral replication were assessed via qPCR while cell viability and apoptosis was assessed via proliferation and apoptotic assays. TJ protein expression of occludin, claudin-1 and zonal occludin-1 (ZO-1) was assessed using in-cell western assays. Transepithelial permeability assays were performed to assess effects on barrier integrity.

Results: Elevated basal LDL receptor expression was observed in asthmatic pAECs compared to healthy, but no significant change was seen in both cohorts following HRV-1B infection. Interestingly, viral replication was significantly higher in asthmatic pAECs compared to the healthy. A MOI-dependent effect on cell viability was observed in both healthy and asthmatic pAECs. Despite a significant 400-fold increase in apoptosis, no significant difference was detected in the apoptotic response between healthy and asthmatic pAECs 24h post infection. Although disassembly of tight junctions occurred with increasing MOI in the pAECs, a greater effect occurred within the asthmatic cohorts. A marked increase in transepithelial permeability was concurrent with this disassembly following infection.

Conclusion: Primary airway epithelial cells more susceptible to HRV-1B infection. At lower MOI, this causes a disassembly of TJ proteins, especially exaggerated in the asthmatic pAECs that is concomitant with increased transepithelial permeability. This may facilitate trafficking of small sized aero-allergens into the sub-epithelial space which could lead to the initiation of asthma exacerbation.

Y17

One Year Changes Of Pulmonary Artery Pressure In Interstitial Lung Disease

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Background and Aim of Study: Pulmonary hypertension (PH) may complicate the course of interstitial lung disease (ILD) and potentially impact prognosis. Because interval changes in mean pulmonary artery pressures (mPAP) have not fully been studied until now, we sought to evaluate one-year changes of PAP in ILD.

Methods: We retrospectively reviewed ILD patients who underwent right cardiac catheterization (RCC) both at initial evaluation and at one-year after initial evaluation in Tosei General Hospital from May 2007 to March 2012. Patients treated with pulmonary vasodilators or with pulmonary capillary wedge pressure >14 mmHg were excluded. The prevalence of PH, and the relationships between changes of mPAP and changes of pulmonary functions and exercise capacity were studied. Definition of PH was mPAP >25 mmHg.

Results: Sixty-one patients with diagnosis of chronic fibrotic pneumonia (idiopathic pulmonary fibrosis in 35, others in 26) were studied. The mean age was 65.3±9.5 years, and 67.2% of the subjects were men. The mean forced vital capacity (FVC) % predicted, diffusing capacity of the lung for carbon monoxide (DLco) % predicted were 76.5±22.4%, 45.8±17.4%, respectively. Thirty-two patients (52.5%) underwent surgical lung biopsy. The follow-up mPAP was significantly higher than initial mPAP (20.1 mmHg vs 17.9 mmHg, $p < 0.001$), and more patients complicated PH (4.9% vs 16.4%, $p = 0.075$). Changes of mPAP significantly correlated with changes of FVC, DLco, and 6 MWT distance ($R = 0.266$, $R = 0.277$, $R = 0.321$, respectively).

Conclusion: In one-year prevalence of PH was higher in patients with ILD. Changes of mPAP correlated with changes in pulmonary functions and 6 MWT distance.

Y18

Mechanisms Of Autophagic Regulation Of Myofibroblast Differentiation In Ipf Pathogenesis.

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Division of Respiratory Diseases, Department of Internal Medicine, Jikei University School of Medicine, Japan¹, Division of Chest Diseases, Department of Surgery, Jikei University School of Medicine, Japan²

Background and Aim of Study: Fibroblastic foci (FF), known to be the leading edge of fibrosis development in idiopathic pulmonary fibrosis (IPF), are mainly composed of fibrogenic myofibroblasts. We have recently reported the involvement of insufficient autophagy in myofibroblast differentiation in FF. Autophagy, a process of lysosomal self-degradation, has been implicated in selective removal of damaged mitochondria. Thus, insufficient autophagy may result in accumulation of damaged mitochondria accompanied by increased reactive oxygen species (ROS) production. ROS are involved in various intracellular signaling pathways, including myofibroblast differentiation. Hence, we hypothesized that insufficient autophagy may induce myofibroblast differentiation via regulation of mitochondrial ROS production. **Methods:** To explore the regulatory role of autophagy in mitochondrial ROS production and its involvement in myofibroblast differentiation, in vitro cell culturing models of human lung fibroblasts were used. Autophagy was induced by treatment with Torin1, (an mTOR inhibitor), while transfection of ATG5 siRNA was performed to inhibit autophagy. CM-H2DCFDA and Mitosox Red were used to evaluate total and mitochondrial ROS production and NAC and MitoTEMPO were employed for inhibition of ROS. LY294002, a PI3K inhibitor, and Akt1/2 kinase inhibitor were used to inhibit the PI3K-Akt pathway. **Results:** Inhibition of autophagy increased mitochondrial ROS production and concomitantly induced myofibroblast differentiation in lung fibroblasts, which was clearly inhibited by the treatment with NAC or MitoTEMPO. Autophagy inhibition also activated the PI3K-Akt pathway, and both LY294002 and Akt1/2 kinase inhibitor abrogated myofibroblast differentiation. Furthermore, efficient inhibition of the PI3K-Akt pathway by treatment with MitoTEMPO supports the notion that mitochondrial ROS and subsequent activation of the PI3K-Akt pathway are at least partly responsible for myofibroblast differentiation in the setting of insufficient autophagy. **Conclusion:** These findings suggest that insufficient autophagy-induced mitochondrial ROS production with subsequent PI3K-Akt activation is a potent underlying pathology of myofibroblast differentiation in IPF pathogenesis.

Y19

NOVEL NONINVASIVE TECHNIQUES FOR ASSESSING DYNAMIC PULMONARY VASCULAR FUNCTIONEMT Lau^{1,2}, DL Bailey³, Paul J Torzillo¹, TJ Corte¹, DS Celermajer²Respiratory Medicine, Royal Prince Alfred Hospital, NSW, Australia¹,
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Current techniques for assessing pulmonary arterial hypertension (PAH) are mostly performed under resting conditions. Evaluating the pulmonary circulation under dynamic conditions may provide novel pathophysiological insights and allow early detection of PAH. **Aims:** We used (1) Dobutamine Stress Echocardiography (DSE) to generate multipoint pressure-flow (P-Q) plots; and (2) Quantitative Single Photon Emission Computed Tomography (SPECT) to assess changes in regional lung perfusion related to postural shift. We hypothesized that in subjects with PAH compared to controls, ino-chronotropic stress will produce altered P-Q relationships, and the normal gravity-dependent redistribution of lung perfusion will be lost. **Methods:** (1) Dobutamine infusion (5 mcg/kg/min increments, peak dose 20) was given to generate multipoint P-Q plots. (2) Regional lung perfusion in supine and upright postures were obtained using SPECT. A perfusion redistribution index (PRI) quantified the perfusion shift along the cranial-caudal axis between postures. **Results:** Participants included 16 PAH subjects and 11 healthy controls. Slope of P-Q plots was 5.1 ± 2.7 mmHg/L/min in PAH subjects and 1.1 ± 0.7 mmHg/L/min in controls ($p=0.001$). P-Q slopes correlated inversely with VO_2 peak ($r^2=0.34$, $p=0.038$). (2) Controls displayed the expected upright cranial-caudal gradient in lung perfusion (left lung 0.29 ± 0.21 cm⁻¹; right lung 0.23 ± 0.22 cm⁻¹) which was abolished on supine posture. PRI was markedly reduced in PAH subjects (0.02 ± 0.06 vs. 0.28 ± 0.15 , $p < 0.0001$). **Conclusions:** Dynamic techniques reveal pathophysiologic changes in PAH. These can be measured noninvasively and might have a role early disease detection.

Supported by: Heart Foundation/NHMRC; **Nomination:** Ann Woolcock Young Investigator Award; **Conflict of Interest:** None

CS2-2

Dysfunctional KEAP1-NRF2 System in Non-Small-Cell Lung CancerYoichiro Mitsuishi¹, Keiko Taguchi², Masakazu Ichinose¹,
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Nrf2 is a master transcriptional activator of cytoprotective genes. It activates transcription in response to electrophiles and reactive oxygen species (ROS). Under normal conditions, Nrf2 is constantly ubiquitinated by Keap1 and degraded by the proteasome. Exposure to the stimuli inactivates Keap1 and stabilizes Nrf2. Nrf2 then translocates into the nucleus, binds to the antioxidant response element and activates the transcription of many cytoprotective genes that encode detoxifying enzymes and antioxidant proteins.

Increasing attention has been paid to the role of Nrf2 in cancer cells because the constitutive stabilization of NRF2 has been observed in many human cancers with poor prognosis. Several mechanisms have been reported for the increased activity of NRF2 in cancers. Recent studies have shown that highly activated NRF2 target genes, encoding detoxification and antioxidant enzymes, confer a great advantage for survival against chemotherapy and irradiation. Constitutively stabilized NRF2 also promotes cell proliferation, as NRF2 knockdown inhibits the proliferation of human lung cancer cell lines.

In this speech, we provide an overview of the Keap1-Nrf2 system and discuss its role under physiological and pathological conditions, including cancers. We also introduce the results of our recent study describing Nrf2 function in the metabolism of cancer cells. We found that Nrf2, in addition to conferring resistance against chemotherapy and radiotherapy, accelerates cell proliferation through directly activating the pentose phosphate pathway and simultaneously facilitating purine nucleotide synthesis and glutamine metabolism in the presence of proliferative signals. The sustained activation of proliferative signals enables Nrf2 to induce these metabolic genes, which boosts the reorganization of cellular metabolic activities advantageous for cell proliferation. Nrf2 likely confers a growth advantage to cancer cells through enhancing cytoprotection and anabolism.

CS2-3**Chemotherapy in the combined modality therapy for stage III NSCLC**

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Lung cancer is the leading cause of cancer deaths in most industrial countries. Approximately 80% of all cases of lung cancer are non-small cell lung cancer (NSCLC), and approximately 35% of patients with NSCLC have stage III disease, which represents a heterogeneous population that includes tumors infiltrating into neighboring structures (T4) or chest wall in presence of local lymph node (LN) metastasis (T3N1) and tumors of different size located within the lung parenchyma with metastasis to the mediastinal LN either ipsilateral (N2) or contra lateral (N3). Patients with N2 disease include those who have microscopic LN involvement that is discovered incidentally in the course of surgery as well as those who have bulky LN involvement at presentation.

In patients with occult N2 involvement that identified after a surgical resection, adjuvant platinum-based chemotherapy is currently recommended. Since 2004, the benefit of adjuvant chemotherapy has been shown in several randomized clinical trials. In Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, a stage-specific subgroup analysis showed a survival benefit for patients with completely resected stage III NSCLC receiving cisplatin-based chemotherapy (HR 0.83; 95%CI 0.72-0.94).

A decision on optimal treatments for patients with N2 involvement identified at initial diagnosis should be made by members of a multidisciplinary team, including thoracic surgeons. Surgery alone is not indicated for those patients due to its poor outcomes. In the North American Intergroup 0139 randomized trial, patients with pathologically proven, resectable N2 disease were treated by either concurrent chemoradiotherapy with cisplatin-etoposide followed by surgery or definitive concurrent chemoradiotherapy. Progression-free survival was significantly better in the trimodality arm ($p=0.017$), but no significant difference in overall survival was observed ($p=0.24$), which was explained by the high mortality rate after surgery, especially after pneumonectomy. In an exploratory subgroup analysis, survival was improved in the surgery arm if a lobectomy was done compared with survival in the matched chemoradiation arm. If patients have unresectable, bulky N2 disease, concurrent chemoradiotherapy with a platinum-based regimen is recommended. Taken together, in patients with confirmed N2 disease, both definitive chemoradiotherapy and induction therapy followed by surgery are options. Surgery is preferably considered in patients in whom a complete resection by lobectomy is expected. The management of N2 node positive lung cancer still remains controversial. There is a lack of consensus including the role of consolidation therapy after combined chemoradiation, and the optimal chemotherapy with or without biomarker-based selection.

CS2-4**Maximizing the benefit of chemotherapy for advanced NSCLC**

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Chemotherapy for advanced non-small cell lung cancer (NSCLC) was proved to prolong survival compared to best supportive care in 1995. From the results of ECOG1594 trial in US and FACS trials in Japan, the combinations of platinum with third generation agent were considered to be standard regimen for NSCLC. Bevacizumab, an antibody against vascular endothelial growth factor, has been available in Japan for treatment of non-squamous cell carcinoma since 2009. Around the same time, pemetrexed was approved and used as a clinical practice in Japan. Its efficacies of first line, salvage therapy and maintenance therapy in non-squamous cell carcinoma were established. Thus, we have to make a treatment strategy by histological type (non-squamous versus squamous) rather than a large framework of NSCLC. Furthermore, in recent years, genetic changes responsible for carcinogenicity and tumor progression including EGFR gene mutation and EML4-ALK fusion gene in NSCLC have been discovered. Clinical trials of molecular-targeted agents such EGFR or ALK tyrosine-kinase inhibitors (TKIs) have demonstrated the dramatic effects. Hence, we should take account of both the genetic abnormalities and histological type when we make the therapeutic strategy of NSCLC. The concurrent or sequential combination of available molecular-targeted agents (gefitinib and erlotinib for EGFR mutations or crizotinib for ALK fusion genes) with chemotherapy has been investigated. In order to derive the maximum effect of chemotherapy for NSCLC harboring such driver oncogene, we should plan clinical trial design referring preclinical research. Greater efforts are needed to obtain durable response, to prolong survival, to overcome resistance to TKIs, and ultimately to cure the advanced NSCLC.

CS2-5

Selecting patients for maintenance therapy for advanced non-small-cell lung cancer (NSCLC)Rudolf M. Huber^{1,2}University of Munich, Bavaria, Germany¹, Thoracic Oncology Centre of Munich, Bavaria, Germany²

The standard of care for patients with stage IV non-small-cell lung cancer (NSCLC), which are epidermal growth factor receptor (EGFR) wild-type and have no EML-4-ALK translocation is systemic chemotherapy for four (to six) cycles. The treatment break after first-line therapy is generally only few months (median duration, 2 to 3 months) and carries a risk of rapid clinical deterioration. This situation often rules out second-line treatment. In clinical routine settings one third of the patients is under these circumstances missing a second line treatment. Therefore the idea of a maintenance treatment is discussed for a long time also in non-small-cell lung cancer. With earlier substances this was not possible, as toxicity of the prohibited a longer exposure. With the advent of less toxic substances randomized clinical trials were possible. The substances that were tested are docetaxel, gemcitabine, pemetrexed and erlotinib. Maintenance therapy was defined as the continuation of a treatment after achieving a clinical response or disease stabilization to platinum-based chemotherapy. The intention is to increase the duration of disease control and improve survival. There are two different approaches, continuation maintenance and switch maintenance. With continuation maintenance the non-platinum component of the first-line regimen is continued, whereas switch maintenance requires introducing a drug with proven efficacy in the second-line setting immediately after the end of induction chemotherapy. This allows patients to receive an additional treatment. The most profound data were generated for pemetrexed in the continuation and switch maintenance setting and for erlotinib in the switch maintenance setting. In Europe consequently pemetrexed is licensed as maintenance treatment in the continuation and the switch maintenance setting. Erlotinib is approved for switch maintenance treatment in patients with stable disease after first line chemotherapy. Until now clinical or biological selection criteria for applying maintenance therapy are not generally accepted. In the decision have to be included the wish of the patient, the tolerance or toxicity of first line therapy, the possibility of close follow-up and the probability of early recurrence. A further important issue is the selection of patients who will benefit most from continuation maintenance or switch maintenance. Patients with stable disease after first-line chemotherapy seem to benefit more from switch maintenance, whereas continuation maintenance may be more effective for responders.

CS3-1

Advances in the management of asthma

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Currently, most of the patients with asthma can achieve control of asthma its symptoms and airway inflammation with anti-inflammatory treatment such as inhaled corticosteroid. Despite these advances, patients with severe refractory asthma represent a small subset of the asthmatic population, between 5 to 10% of all patients. This lack of control may be in part due to poor adherence to treatment, psychosocial factors, persistent exposure to allergens, or undertreated co-morbidities such as chronic rhinosinusitis. Since 2009, Omalizumab has been available to use only for patients with severe refractory allergic asthma in Japan. Clinical effectiveness of Omalizumab demonstrated the contribution of IgE to severe refractory asthma. Therefore, we investigated the interaction of IgE with severity of asthma. Similarly to the previous reports, the level of IgE was not correlated with severity of asthma. In contrast, longitudinal change of IgE level was correlated with severity of asthma. This was also confirmed by our prospective study. These results suggest that the increase in IgE may contribute to severity in a number of patients with asthma.

Clinical guidelines for asthma has several goals such as prevention of symptoms and exacerbations; maintenance of normal pulmonary function and activity levels; and minimization of the need for emergency department visits or hospitalizations. The appropriate tools to determine the degree of achievement can depend on the type of goals. Among them, the prevention of exacerbation is one of the most important goals of long-term management in patients with asthma. However, it is sometimes difficult to predict exacerbation risk. ECLIPSE study showed that the most reliable predictor of COPD exacerbation appeared to be a history of exacerbation. We evaluated the components of exacerbation susceptibility in asthmatics. In our study, exacerbations became more frequent as the severity of asthma, the treatment step, and ACT score increased. However, a history of exacerbation was the most reliable predictor of exacerbation in asthmatics, suggesting that the step down strategy might be done considering a history of exacerbation as well as the severity, current asthma condition, ACT score, and pulmonary function.

A number of new strategies are currently under development, including inhaled corticosteroid, molecular targeting therapy, and immunotherapy. It will be of great important to identify furthermore the mechanisms of uncontrolled asthma.

CS3-2

Potential of Heme oxygenase (HO)-1 in COPD

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Chronic obstructive pulmonary disease (COPD) is a progressive disease of complicated combination of chronic airway inflammation/fibrosis, hyperplastic submucosal gland, and emphysema, often coexisted with asthma and pulmonary. On the other hand, a stress inducible protein, Heme oxygenase-1 (HO-1) is known to have protective roles against airway inflammation. In the 4th edition of Guidelines for the Diagnosis and Treatment of COPD published by the Japanese Respiratory Society, HO-1 was mentioned as one of the COPD sensitive genes and it says, "Association of a single nucleotide polymorphism of the gene that inhibits the expression of HO-1, the anti-inflammatory protein, with COPD is reported in Japan as well as in Europe."

In this regard, we think it is very meaningful to measure serum HO-1 levels to study connection between disease status and HO-1 levels; however, there isn't any established method so far. Therefore, we first developed a modified ELISA method for serum HO-1, in which recovery percentage, standard curve, sensitivity, and intra- and inter-assays were validated. With this modified method, we confirmed HO-1 levels of smokers were lower than those of non-smokers ($p=0.005$).

Next, to investigate the possibility of serum HO-1 level as a biomarker of exacerbation of COPD, serum HO-1 of acute exacerbation of interstitial pneumonia (IP) and acute respiratory distress syndrome (ARDS), as severe forms of exacerbation of COPD or CPFE, was studied. As a result, it was suggested that serum HO-1 could be a predictive indicator of disease progression or prognosis. Whether it is the same for exacerbation of COPD or not will be discussed in near future.

To investigate the inhibitory effects of HO-1 in mucin hypersecretion and goblet cell hyperplasia, in vitro study of goblet cell hyperplasia induced by neutrophil elastase (NE) and/or interleukin-13 (IL-13) was designed. We first focused on IL-13 induced hyperplasia. In normal human bronchial epithelial cells grown in air liquid interface, Hemin (HO-1 inducer) suppressed IL-13 induced MUC5AC protein secretion and mRNA expression in a dose dependent manner as well as goblet cell hyperplasia. This suggests that hyperexpression of HO-1 may become one of the treatment strategies for goblet cell hyperplasia, one of the main forms of chronic airway inflammation. Now we are to investigate the effects of HO-1 against goblet cell hyperplasia induced by both NE and IL-13.

We believe that HO-1 has beneficial possibilities not only as a COPD sensitive gene but also as a biomarker and a treatment strategy.

CS4-1

Current understanding on pathogenesis and diagnosis of lymphangioleiomyomatosis

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Lymphangioleiomyomatosis (LAM) is a chronic, slowly progressive neoplastic disease affecting almost exclusively women and seen in both patients with tuberous sclerosis complex (TSC) and those without TSC (hence, called sporadic LAM). LAM is characterized by proliferation and infiltration of abnormal smooth muscle-like cells (LAM cells) in the lungs and along axial lymphatic system and extensive LAM-associated lymphangiogenesis in LAM lesions.

LAM cells are neoplastic cells with combined smooth muscle and melanocytic differentiation and considered to harbor loss-of-function type mutation in either the *TSC1* or *TSC2* gene in TSC-LAM whereas a sporadic LAM is exclusively caused by *TSC2* mutation. LAM cells carrying *TSC2* LOH can be demonstrated in blood, chylous fluid, urine, etc. In chylous fluid, LAM cell cluster, a globular cell aggregate consisting of LAM cells that is covered by a monolayer of lymphatic endothelial cells, are frequently isolated and diagnostic for LAM. Recently, all LAM cells within LAM lesion have TSC mutations by a combination of laser capture microdissection and exome sequencing of *TSC2/TSC1* by next-generation sequencing: TSC mutation was identified in 8/10 LMA patients at allelic frequencies ranging from 4 to 60%, with most seen at a frequency <20%. In addition, the remaining two cases are suggested to be due to other mechanism since LAM cells in two cases were immunopositive for both hamartin and tuberlin, and negative for p-S6K.

It remains unclear what is an origin (a normal counterpart) of LAM cells and where LAM cells originate. Proliferating LAM lesions are very frequently demonstrated in female reproductive systems (uterus, ovary, broad ligament) and intrapelvic lymph nodes of LAM patients or unexpectedly identified in uterus and its regional pelvic lymph nodes that were resected from females with gynecological malignancies. Combining this with the following findings that LAM is a disease of women, axial lymphatic flow can convey LAM cells from pelvic cavity to the lungs, LAM cells may originate somewhere of reproductive system and metastasize to lung via lymphatic stream.

The role of estrogen in LAM pathogenesis has been underestimated since hormonal manipulations have shown marginal clinical benefits if any. However, increasing data suggests that estrogen does have a certain important role in LAM. The analysis of participants in the MIELS trial showed a significantly lowered FEV1 decline in menopausal women than pre-menopausal. The study using AML cells (bearing biallelic *TSC2* inactivation) derived from LAM patients showed a collaborative interaction between estrogen-ERK2 and mTOR/S6K signaling pathways.

CS4-3

Current understanding on pathogenesis and diagnosis of pulmonary alveolar proteinosis

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Pulmonary alveolar proteinosis (PAP) is a rare disorder predominantly affecting the lungs characterized by accumulation of surfactant lipids and proteins in alveoli and terminal bronchioli. Clinically, the diagnosis of PAP was based on the following criteria; histopathological findings of specimens obtained by open lung biopsy or TBLB, or milk-like appearance with typical cytological findings of BALF and typical high-resolution CT findings for PAP such as ground glass opacity, consolidation, interlobular septal thickening. PAP is further classified into three distinct forms, autoimmune, secondary, and hereditary PAP. Since September 1999 to May 2013, we have centrally measured GM-CSF autoantibody in the sera from 619 Japanese cases had been diagnosed as PAP. Of those, 561 cases were positive for the antibody and 58 cases were negative. In the negative patients, 51 cases demonstrated obvious underlying diseases such as hematological disorders, autoimmune diseases, and infectious diseases. Seven cases were negative GM-CSF autoantibody without any obvious underlying diseases. Autoimmune PAP (APAP) is positive GM-CSF autoantibody that disrupts GM-CSF signaling and block the terminal differentiation of alveolar macrophages in the lung (Kitamura T et al., *J. Exp. Med.*, 1999). It has been still unknown why GM-CSF autoantibody excessively produced in the patients. As low concentration of GM-CSF autoantibody is consistently detected in the sera from normal subjects (Uchida K, *Blood*, 2009) and our recent study demonstrate that membrane GM-CSF autoantibody positive memory B cells are present in normal subjects, we consider that GM-CSF autoantibody production is accelerated in the patients at the terminal differentiation of mature B cell or plasma cell level. Secondary PAP (SPAP) is distinguished from APAP by negative GM-CSF autoantibody in the serum, which occurs as a consequence of an underlying diseases presumed to impaired surfactant clearance by abnormal alveolar macrophages. Of forty cases with SPAP reported by us previously (Ishii et al., *ERJ*, 2011), hematological disorders constituted 88% (n=35) of all underlying diseases. The prognosis was very poor with 2 years survival at 46%. Hereditary PAP has been reported to be caused by surfactant abnormalities (SP-B or SP-C gene mutation), surfactant transportation defect (ABCA3 deficiency), or GM-CSF receptor abnormalities (CSF2RA or CSF2RB mutation). In the symposium, I would like to present an overview of the pathogenesis, classification, epidemiology, and clinical aspects of the PAP syndrome, emphasizing ten years progress in Japan.

CS4-5

Survey for prevalence and treatment of pulmonary alveolar proteinosis in Asian countries

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Pulmonary alveolar proteinosis (PAP) is a rare disorder in which lipoproteinaceous material accumulates within alveoli. There were few reports on Asian populations with PAP. PAP occurs in three clinically distinct forms: congenital, secondary, and idiopathic (acquired) types.

We compared PAP data between 3 Asian countries (Japanese national survey, 1 center from China, and 10 hospitals from Korea) through literature review and personal communication. Total enrolled patients were 248, 147, and 38, respectively. Prevalence and incidence were 6.2 and 0.49 cases/million in Japan. Male to female ratio was 2.1 (151/72), 2.9 (109/38), and 1.7 (24/14). Mean age was similar showing 51, 43, and 52 years, respectively. Smoker was 57% and 52.4% in Japan and China. Surgical diagnosis was performed more in Korea (42% vs 7.2% and 8.2%). Dust exposure was 26% and 24% in Japan and Korea.

FVC was higher in Japan (88% vs 78% and 77%), DLco was lower in China (60% vs 69% and 68%). LDH and CEA were increased and anti-GM-CSF ab was increased in Japan and China (data unavailable in Korea).

Whole lung lavage was performed in 56.5% and 68% in China and Korea (data unavailable in Japan). Mortality was only 5.3% in Korea (data unavailable in Japan and China).

Last December, Asian PAP meeting were held in APSR 2012, Hong Kong. Doctors from Japan, Korean and China met and discussed the current problems and future directions for Asian PAP research network. We are planning to collect and compare the data on smoking, dust exposure, and treatment modality and survival.

CS5-1

Early-onset COPD in Japan

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In Japan, early-onset COPD is one of the intractable diseases that have resulted from an unidentifiable cause, chronically develop and remain difficult to treat. However, the information and statistics about the prevalence, characteristics and prognosis of this rare disease remain limited. Recently, nationwide epidemiological survey sent to 1,776 medical institutes and hospitals has been conducted by *the Respiratory Failure Research Group in Japan*. This survey has been performed as severe early-onset COPD with following diagnostic criteria: 1) age less than 55 years at diagnosis, 2) persistent airflow limitation defined by the presence of a post-bronchodilator FEV1/FVC<70% and FEV1%predicted<50%, 3) exclusion of other diseases such as asthma, diffuse panbronchiolitis, bronchiectasis, pulmonary tuberculosis, lymphangioleiomyomatosis, and so on. Most of the patients showed low body mass index, and were current or former smokers. In this session, the results of epidemiological investigation will be presented.

* This study was supported by a grant to the Respiratory Failure Research Group from the Ministry of Health, Labour and Welfare, Japan.

CS5-2

Early-onset COPD in Asia

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Patients with early-onset COPD may have different characteristics or etiologies. Alpha1-antitrypsin deficiency has been well known to be a major etiology of the early-onset COPD in Western countries, but not in Asia.

We did a pilot, post-hoc analysis of Asian patients with early-onset COPD to design further studies on the characteristics and etiologies of early-onset COPD. We performed this study using the data of COPD patients recruited from ten Asian regions. Among a total of 1026 COPD subjects, 39 patients (3.8%) met the predefined criteria of early-onset COPD with the age under 55 years and also with GOLD stage of 3 or 4. The 39 COPD patients of early-onset were compared with 388 COPD patients who had age of 55 years or older and also GOLD stage of 3 or 4. The early-onset COPD patients showed more frequent respiratory symptoms of cough, phlegm, and wheeze than the older COPD patient ($p<0.05$ for the three comparisons). However, we did not find any significant difference in the MMRC dyspnea scale, body mass index, the SGRQ score, or the frequency of hospitalization or ER visit in a past year due to lung problem. Nor we found any significant difference in the exposure frequency of cigarette smoking, biomass fuel combustion, or dusty job.

In this study, we found more frequent respiratory symptoms in patients with early-onset COPD but could not find any difference in other characteristics or etiologic exposures. Further studies (e.g. CT and genetic studies) might be needed to elucidate the characteristics and etiology of early-onset COPD in Asia.

CS5-3**Consider occupational causes of severe, fixed airway obstruction**

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It is important to detect occupational causes of severe, fixed airway obstruction because stopping the workplace exposure halts the rapid loss of lung function. Workplace exposures reported to cause severe fixed obstruction include the following: Sulfur mustard gas (chemical weapons), sulfur dioxide gas, butter flavoring (diacetyl fumes), roasting coffee, burning military waste, fiberglass workers (styrene resins), and hydrogen sulfide at an oil refinery. Constrictive bronchiolitis is clinically like COPD. The patients usually report the slow onset of shortness of breath and a non-productive chronic cough. Airway obstruction is common on spirometry testing, usually with no response to albuterol. However, spirometry results range from normal to mild restriction to severe obstruction. The diffusing capacity (DLCO) is normal (ruling out the emphysema phenotype of COPD). The chest x-ray shows hyperinflation, but no blebs or bullae. The lung HRCT may be normal or may show the characteristic mosaic pattern of constrictive bronchiolitis.

Constrictive bronchiolitis is often mistaken for asthma, but is poorly responsive to asthma therapy. In smokers, it is usually misdiagnosed as COPD. However, smoking does not increase the risk of constrictive bronchiolitis. In some flavorings workers, lung disease progresses much faster than does COPD in susceptible smokers. A surveillance program for exposed workers should include high quality spirometry testing done every 3 months with longitudinal analyses done using SPIROLA software which is freely available from the NIOSH website. Indolent constrictive bronchiolitis often remains undiagnosed because no acute presentation points to a cause of lung injury. A high index of suspicion for constrictive bronchiolitis is prudent in evaluating young patients with dyspnea. Report of sentinel cases of constrictive bronchiolitis can motivate public health follow-up of coworkers and others with similar industrial exposures. Only a few workers have an acute presentation with pulmonary edema after an overexposure to noxious gases or vapors. An excellent review of the topic was recently written by Kathleen Kreiss (Occupational causes of constrictive bronchiolitis. *Current Opinion Allergy Clinical Immunol* 2013; 13:167-172).

CS5-4-1**Case Presentation 1: A patient with early onset, non-emphysematous COPD followed up over 10 years.**

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A 52-year-old men presented with cough and sputum from the age of about 35 and was referred to our institute because of dyspnea on exertion (modified MRC scale 1) at the age of 40. The patient had a medical history of chronic sinusitis but no respiratory diseases. He was current smoker (33-pack-year smoking history) and had a history of occupational exposure to sawdust. Pulmonary function testing revealed severe airflow limitation (%FEV₁: 21.8%), hyperinflation (RV/TLC: 60.3%) and hypoxemia (PaO₂: 54.9Torr) with hypercapnia (PaCO₂: 56.2Torr). Significant airway responsiveness to short-acting β_2 agonist was not observed. The chest CT showed airway wall thickening, while emphysematous change was scarcely observed. He was diagnosed with non-emphysematous type of COPD. The treatment was started with the inhalation of LAMA and ICS and the oral administration of theophylline. The next year, long-term oxygen therapy was started because of worsened dyspnea on exertion. Subsequently, the patient showed remarkable weight gain and developed metabolic syndrome. The patient has been followed up over 10 years after the initial diagnosis. The annual decline of FEV₁ was modest (22ml/year) and hypoxemia with hypercapnia did not progress. This case was considered as an early onset non-emphysematous COPD patient with slow progression of the airflow limitation.

CS5-4-2

Case Presentation 2: An asthma-associated early-onset COPD

Two cases of asthma-associated early-onset emphysema with severe airflow limitation

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Case 1: A 33-year old man who had a history of childhood asthma was referred to our hospital in 2003. He had a 12 pack-years, ten-year history of smoking from the age of 20. He had handled with pesticide while he was 19 to 26 years old. He had been receiving inhaled corticosteroids (ICS) since he was 22 years old. He had suffered from a severe asthma attack, requiring ventilator control when he was 23. Total serum immunoglobulin E (IgE), and specific IgE were within normal limits, despite a high percentage of eosinophils (10%) in peripheral blood and in sputum. High Resolution Computed Tomography (HRCT) scans demonstrated bilateral emphysema. Spirometry revealed severe airflow limitation with little reversibility to bronchodilators. Diffusion capacity of the lung for carbon monoxide divided by the alveolar volume (DLco/VA) was reduced to 46.9%. Despite intensive pharmacotherapy with inhaled long-acting beta-agonist (LABA), inhaled long-acting anticholinergics (LAMA), and ICS since then, further progressive deterioration has occurred in airflow limitation and DLco until now. This case illustrates early-onset emphysema evidently associated with asthma, although we are not sure whether this case should be designated as early-onset COPD.

Case 2: A 24-year old woman visited our hospital in 2002. She had a history of hospital admission with bronchitis at the age of one. She had a 4 pack-years, seven-year history of smoking from the age of 17. A lung biopsy had been performed at the age of 22, when she was diagnosed as having pan-lobular emphysema histologically. There was no increase of eosinophils in peripheral blood. The level of total serum IgE was within normal limits, but specific IgE against house dust and mite was positive. Bilateral expiratory wheeze was present on physical examination. HRCT scans demonstrated bilateral, but left lung dominant, emphysema. Pulmonary function tests revealed severe airflow limitation, associated with normal range of DLco/VA. Significant reversibility in FEV₁ was noted in response to salbutamol (180 ml, 29%) and also to oxitropium bromide (120 ml, 21%). Even since then until now, deterioration of emphysema occurred. Although we diagnosed her as having early-onset emphysema (or COPD) in this case, we are not sure whether Swyer-James-MacLeod Syndrome and/or asthma is really denied.

CS5-4-3

Korean female cases of early-onset COPD with emphysema-dominant phenotype

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The leading risk factor for the development of emphysema is smoking. However, about 10% of patients with emphysema have never or have rarely smoked. Emphysema in nonsmoking population has been recognized in a variety of disease processes including: alpha-1 antitrypsin deficiency (AAT), nutritional deficiency, human immunodeficiency virus (HIV) infection, illicit drug use, connective tissue disease, and occupational and environmental exposures.

A 41-year-old woman visited to respiratory clinic for dyspnea aggravation. The dyspnea started about 10 years ago, and it aggravated gradually year by year. Her chest radiograph showed hyperinflation, and lung function showed forced FEV₁ of 2.43L (74% of pred.), FVC 5.13L (131% of pred.) and FEV₁/FVC of 47%. Her computed tomography (CT) showed diffuse homogenous centrilobular emphysema. Her alpha-1 antitrypsin level is 167mg/dL and she showed no evidence of HIV or rheumatologic disease. She is a never smoker. She also denied any specific history of her or familial lung disease. Her occupation is a teacher, and she denied any occupational exposure.

Another 53-year-old woman also visited our clinic for dyspnea. The onset of dyspnea was about 10 years ago and the severity increased gradually. She experienced weight loss of 9kg for 3 years. Her lung function showed FEV₁ 0.69L (28% of pred.), FVC 2.84L (96% of pred.), FEV₁/FVC 24% and RV 153%. Her CT showed diffuse centrilobular emphysema and her alpha-1 antitrypsin level is 168mg/dL. We cannot find other risk factor of COPD such as HIV, rheumatologic disease or smoking. She also has no history of her or familial lung disease. She also denied any occupational exposure to cause emphysema.

Genetic disease such as AAT is extremely rare in Asian countries. However, we can encounter Asian cases sometimes without definite cause including smoking, environmental and acquired disease. With collaboration, we can collect many similar cases and analyze the possible causes.

CS6-2

Definitions of disease: should “possible” and “probable” IPF be enrolled in treatment trials

Kevin K. Brown

National Jewish Health, U.S.A.

Despite significant progress in the clinical evaluation, making a confident diagnosis of IPF remains a challenge in a significant number of patients. Treatment trials prospectively define their target population because when evaluating a clinical response, focusing on a well-defined, homogenous patient population with a predictable natural history provides a high level of confidence in the trial results. However, the universe of patients with fibrotic lung disease is not homogenous. The current scheme for the diagnosis of IPF provides for confident, probable, and possible diagnoses depending upon the features present. When enrolling patients in a prospective treatment trial, how confident must one be in the diagnosis? This lecture will review the relative merits of expanding the population of IPF patients to be enrolled in treatment trials to those with “possible” and “probable” disease.

CS6-4

Essential rules and requirements for rare lung diseases global clinical trial: Sponsor’s standpoint

Thomas Kuerner

Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan

A global clinical trial is a multi-center study in various countries and has the advantage of being able to recruit many patients in a short time. The conclusions of the trial apply to all participating study centers and countries. Therefore, the assumption is that there are no important differences in the situation or the customs of trial administration such as the target patient population, standard care, actual medical treatment, primary endpoints and trial management. In this regard, a global clinical trial on rare lung diseases would face unknown challenges since there might be a difference in consensus on diagnosis and treatment among various countries. The challenge for us as an international company is to conduct clinical trials based on the latest medical findings and guidelines and in consensus with clinical experts and regulatory agencies such as the FDA, EMA and PMDA. Once the inclusion/exclusion criteria and endpoints are determined, we do conduct the trial with the same criteria for all countries. For example, in the global clinical trial on IPF, the first difficulty is to minimize the heterogeneity in diagnosis. HRCT images and, if available, pathological specimens were sent to and assessed by a central reading center. The next difficulty is in recruitment. Facilities that specialize in treating rare lung diseases may not necessarily accept trials all the time or these centers have multiple trials to offer to their patients at the same time. It is necessary for company personnel to sufficiently confirm the trial administrative structure with the study center before the start of the trial. In addition, it is important to determine what safety signals should be monitored based on evolving knowledge of the drug. While working on providing safety information in accordance with each country’s conditions, we establish an external independent data monitoring committee that periodically evaluates the risk-benefit balance and determines whether to continue the trial.

Currently, we are conducting a large-scale global clinical trial in IPF in 26 countries and over 1000 patients. With such a large-scale global clinical trial, we believe we can contribute to the development of medicine for rare lung diseases by assessing the efficacy and safety in appropriate number of patients from different regions in a short period of time.

CS6-5

Use of the severity grade for IPF in Japan? 20 years experience from empirical to RCT practice

Sakae Homma

Toho University Omori Medical Center, Tokyo, Japan

Partial arterial oxygen concentration (PaO₂) at rest and desaturation during a 6-min walk test (6MWT) are prognostic factors in idiopathic pulmonary fibrosis (IPF). Since 1991, the severity of IPF has been classified (stage I-IV) to facilitate decisions regarding subsidization of medical care in Japan. IPF severity is defined as follows: stage I (PaO₂ ≥ 80 torr at rest), stage II (70-79 torr at rest), stage III (60-69 torr at rest), stage IV (<60 torr at rest). Among patients with stage II or III IPF, severity should be increased by one stage if the lowest oxygen saturation on pulse oximetry (SpO₂) is <90% during a 6MWT. Patients with stage III or IV IPF receive Japanese government subsidies for incurable diseases. This staging classification is highly correlated with serial changes in %VC, diffusing capacity of carbon monoxide, incidence of acute exacerbation, and survival in IPF. In a phase II trial of pirfenidone (PFD) treatment for Japanese IPF patients, the entry criteria included a PaO₂ at rest of ≥ 70 torr with a lowest SpO₂ of <90% during a 6MWT (which would include most patients with stage III disease). Furthermore, a phase III trial in Japan showed that IPF patients having a %VC ≥ 70% or a PaO₂ ≥ 70 torr, in addition to an SpO₂ on exertion <90%, at baseline would most likely benefit from PFD, as indicated by changes in VC, %VC, progression-free survival time, and cough and dyspnea symptoms. The participants in that study included many stage III patients. The trials concluded that PFD was more effective in populations of patients with relatively favorable baseline %VC and PaO₂, especially those with desaturation on exertion. Recent post-marketing surveillance of 1370 patients in Japan—67.3% of whom had stage III or IV IPF—showed that PFD was generally well tolerated among those treated for ≥ 6 months (63% of patients). Our recent studies of PFD efficacy showed that it decreased the rate of FVC decline even among patients with advanced IPF (stage III or IV). A Japanese randomized controlled trial of inhaled N-acetylcysteine (NAC) monotherapy showed that this regimen had beneficial effects for patients with early IPF (stage I or II disease with no desaturation on exertion). In sum, these results indicate that NAC monotherapy is suitable for early IPF and that PFD is indicated for advanced disease. Thus, classification of IPF disease severity is very important in identifying potentially clinically responsive patients.

CS7-2

Basic overview to understand influenza H7N9 epidemic

Yoshihiro Kawaoka

Division of Virology, Department of Microbiology and Immunology, Institute of Medical Science, University of Tokyo, Japan

ACADEMIC DEGREES:

D.V.M.	1978	The Ministry of Agriculture and Fishery, Japan
B.S.	1978	Hokkaido University, Japan (Veterinary Medicine)
M.S.	1980	Hokkaido University, Japan (Microbiology)
Ph.D.	1983	Hokkaido University, Japan (Microbiology)

PROFESSIONAL APPOINTMENTS:

1980-83	Research Associate, Department of Veterinary Microbiology, Faculty of Agriculture, Tottori University, Japan
1983-85	Postdoctoral Fellow, Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee
1985-89	Assistant Member, Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee
1989-95	Associate Member, Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee
1991-97	Associate Professor, Department of Pathology, University of Tennessee, Memphis, Tennessee
1996-97	Member, Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee
1997 to date	Professor, Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison
1999 to date	Professor, Department of Microbiology and Immunology, Institute of Medical Science, University of Tokyo, Japan
2004-08	Visiting Professor, Creative Research Initiative, "Sousei", Hokkaido University, Japan
2005 to date	Director, International Research Center for Infectious Diseases, Institute of Medical Science, University of Tokyo
2005 to date	Senior Visiting Scientist, Riken.
2010 to date	Visiting Professor, Kyoto University

PROFESSIONAL COMMITTEES:

1999 to 2006	International Committee on Taxonomy of Viruses, Chair, <i>Orthomyxoviridae</i> Study Group
2002 to date	Influenza Sequence Database, Advisory Board Member
2002 to 2008	International Union of Microbiological Societies, Virology Division, Advisory Council Member
2008 to 2011	International Union of Microbiological Societies, Virology Division, Vice Chair
2011 to date	International Union of Microbiological Societies, Virology Division, Chair

PROFESSIONAL SOCIETY MEMBERSHIPS:

American Society for Microbiology
 American Society for Virology
 American Veterinary Medical Association
 Japanese Society for Virology
 Japanese Society of Veterinary Science

PEER REVIEW COMMITTEES:

1992	Special Review Committee, NIH (Grant reviewer)
07/94-06/98	Virology Study Section Member, NIH (Grant reviewer)
10/01	Virology Study Section Adhoc Member, NIH (Grant reviewer)

JOURNAL EDITORIAL BOARD:

1996 to date	Journal of Virology
1997 to 2002	Virus Research
1999-2001	American Journal of Veterinary Research
2001 to date	Virology
2002 to 2006	Journal of General Virology
2002 to 2005	Editor, Virus Research
2004 to 2005	Journal of Clinical Investigation
2005 to date	Reviews in Medical Virology
2005 to date	Virus Research
2006 to date	PLoS Pathogens
2011 to date	Current Opinion in Virology

AWARDS

1991	Veterinary Science Award
2002	The Hideo Noguchi Memorial Award for Medicine
2006	Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology
2006	Robert Koch Award
2007	The Takeda Prize for Medical Science
2010	Japan Prize of Agricultural Science
2011	The Naito Foundation Merit Award for Advancement of Science
2011	The 8th Takamine Memorial Daiich-Sankyo Prize
2011	Medal of Honor (Purple Ribbon) from the Emperor of Japan

CS7-3

EPIDEMIOLOGICAL SUMMARY OF INFLUENZA H7N9 EPIDEMIC

Vernon J Lee

National University of Singapore, Singapore, Singapore

The first human case of the avian-origin H7N9 was identified in China in end-March 2013. Cases were steadily identified across the country with 132 infections identified across 13 provinces in China by the end of May 2013. Infections have tapered off since and by August 2013, there were a total of 135 cases and 44 deaths (case fatality rate of 33%). The main clinical features were fever and rapidly progressive pneumonia often requiring hospitalization and intensive care treatment. Mild and asymptomatic cases were also identified through contact tracing and community surveillance. In addition, three suspected family clusters of limited human-to-human transmission were reported.

Zoonotic surveillance identified poultry such as quail, chickens and ducks, especially in live bird markets, as possible sources of H7N9, and the virus had low pathogenicity in birds. The virus replicated well in human bronchiole and alveolar epithelial cells, and animal transmission studies in ferrets found that it is possible for virus transmission between subjects.

Among the initial epidemiological studies, older men and urban residents were most likely to be affected. One study found that about three-quarters of cases had recent exposure to animals, including direct contact with chickens or visiting live bird markets. Recent serological surveillance for H7N9 found no positive cases among subjects in the general population, whereas 6% of poultry workers tests were positive. Tests of samples among poultry workers obtained in 2012 did not yield any evidence of H7N9 infection, suggesting that human infections were a recent event.

Compared to H5N1 cases, H7N9 cases were much older on average, and both predominantly affected men and those with previous poultry exposure. However, while rural cases of H5N1 were in regions with low population density and associated with exposure of backyard live poultry or handling of slaughtered poultry, most of the rural cases of H7N9 were in the outskirts of urban areas and were exposed to retail poultry in live markets.

Interventions included the closure of live bird markets in several provinces in April 2013, which was followed by a marked decrease in the number of cases identified in these provinces thereafter. The decline may also have been contributed by increased public awareness and public health education, and the approaching summer months where influenza transmission in temperature regions is at its lowest. Although cases have subsided, continued vigilance is critical to detect any resurgence during the winter months.

CS7-4

Coronavirus infection: Summary of SARS-CoV and watch on MERS-CoV

Shutoku Matsuyama

National Institute of Infectious Diseases, Tokyo, Japan

From March 2012 to October 2013, 138 cases including 60 deaths of Middle East respiratory syndrome (MERS) have been identified in 9 countries (Saudi Arabia, UAE, Qatar, Jordan, France, Germany, Italy, Tunisia, and UK). Recent studies say, while MERS appears to be more deadly in those it infects, it also seems to be less contagious than severe acute respiratory syndrome (SARS) in 2003. All primary cases were connected to the Arabian Peninsula, and nearly half of the cases died due to severe lung inflammation. Nosocomial transmission was implied in 26 percent of the cases. Human-to-human transmission was considered the likely source of infection in hospital. From these cases, the median incubation period was estimated as 5.2 days (95 percent confidence interval 1.9 to 14.7 days). At the same time, some asymptomatic or mildly symptomatic cases have been reported. All MERS-positive cases were diagnosed by using real-time RT-PCR targeting upE and Orf1A genes of MERS-CoV. Specimens were taken from the upper or the lower respiratory tract and blood. Even though over a year has passed since the emergence of the 1st case, many questions on the origin and transmission patterns of the disease remain. The pathogen of MERS belongs to the lineage C of the beta coronaviruses (CoV), which are genetically similar to various coronaviruses detected in bats in Africa and Europe. And two studies suggest dromedary camels in Oman, the Canary Islands and Egypt may have been infected with the virus or a MERS-CoV-like virus in the past. However, human cases have not been detected in these areas. With the Hajj, the Muslim pilgrimage to Mecca in Saudi Arabia, taking place in October 2013 and attracting 1.8 million foreign and 1.4 million domestic visitors, international public health efforts to mitigate and possibly contain this outbreak need to be reinforced. On alert for a possible pandemic, we prepared the PCR system, and shared it to 74 locations of prefectural public health institutes and quarantines in Japan.

AS1-1

Newer Diagnostic methods

Yee-Chun Chen

National Institute of Infectious Diseases and Vaccinology, National Health Research Institutes; Department of Medicine, National Taiwan University Hospital and College of Medicine, Taiwan

A brief review of newer diagnostic methods for invasive fungal infections focused on invasive mould disease in immunocompromised patients is presented. Conventional microbiological and histopathological methods are important and fundamental for clinical practice and research such as developing new diagnostic methods. However, these conventional methods are limited by low yield rate and feasibility of invasive procedure. New diagnostic methods have been developed in order to facilitate early diagnosis and intervention. In recent years there have been significant advances with the commercial availability of tests for detection of galactomannan (GM) and b-(1,3)-D-glucan (BDG). GM is a component of the cell wall of *Aspergillus* spp. However, *Penicillium* spp and *Paecilomyces* spp. may have GM in their cell wall. In non-neutropenic patients with invasive aspergillosis (IA), the sensitivity of serum GM detection is no greater than 50%. Recent studies have analysed the use of GM quantification in BAL in patients with haematological diseases. The Third European Conference on Infections in Leukaemia (ECIL3) consensus report recommends that when this test is used the results should be evaluated in conjunction with high-resolution CT in adult neutropenic patients undergoing intensive chemotherapy for leukaemia or in those who have received an allogeneic transplant of haematopoietic stem cells. Serum determinations must be performed every 3 or 4 days. BDG is a cell wall component present in many fungal species. The BDG test is considered to be a panfungal diagnostic method except for *Cryptococcus* spp., other basidiomycetes and zygomycetes. BDG quantification has been used for the diagnosis of aspergillosis and other mycoses, such as candidiasis, in critically ill patients and in cases of Pneumocystis pneumonia. As with the GM test, series of serum determinations two or three times a week are recommended while the risk of infection continues. In addition, fungal nucleic acid detection in clinical samples has always been considered to be an alternative method that has great potential. However, the high theoretical sensitivity of the PCR-based techniques has not been confirmed to date in clinical practice. It has not been included as a diagnostic criterion of infection in the latest consensus of EORTC/MSG and ECIL3. Moreover, its availability is limited. With respect to nucleic acid detection techniques for diagnosis of invasive mold infection other than IA, there are much more limited data to support their use. Work has been performed with PCR techniques with other mould species such as Zygomycetes, *Scedosporium* spp., *Fusarium* spp. and endemic fungi. Each newer method has limitation. The current trend is to recommend a combination of several diagnostic techniques to rule out fungal infection in patients at risk.

AS1-3

Guideline of pneumonia and treatment responses

Ki-Suck Jung

Hallym University Sacred Heart Hospital, Gyunggi, Rep of Korea

Pneumonia continues to be the main cause of death due to infection in the world, and it produces a high consumption of healthcare resources. The decision about the antibiotic treatment, the evaluation of the severity, and its overall management play a key role in the prognosis of pneumonia. The guidelines established by the scientific committee improve the care of patients with pneumonia. Local adaptation of guidelines is the important factor for the successful treatment, as the pattern of microbial agents and their resistance varies from country to county and even in the same country from hospital to hospital. Therefore, Korea, Japan, and China have developed the treatment guidelines for community-acquired pneumonia (CAP) since 2000 and published in the journal of their respiratory society as their first language. In addition, there were retrospective studies on the etiology of CAP in Korea, Japan, Malaysia, Thailand, and Taiwan, which are different from those of Western countries. In contrast, the guidelines for hospital acquired pneumonia (HAP) were published only in the United States and Europe. In Asia, Japan published the guideline for the management of HAP in 2008 as well as for the health care associated pneumonia in 2011.

The impact of guidelines on the treatment response can be evaluated by analyzing prognostic factors including mortality, stability, length of stay and costs. To evaluate this effect, cohort studies have been performed using before-after, observational, and cost-effectiveness in the difference settings such as outpatient, hospitalized, and intensive care units (ICU). Majority of previous studies show that the implementation of ATS/IDSA guideline for CAP is accompanied by lower inpatient hospital mortality rate and length of stay. However, there is not much evidence about the influence of guidelines on the outcome of the patients with HAP. Previous two studies validating the 2005 ATS/IDSA guidelines showed that adherence to the empirical treatment in the guideline did not influence major outcome variables such as hospital mortality. Additionally, the guideline had a low positive predictive value concerning infection or colonization with MDR bacteria at ICU patients.

AS1-4

Diagnosis and Management of Pneumonia in Lung Cancer

Masaki Fujita

Fukuoka University Hospital, Fukuoka, Japan

The incidence of lung cancer is increasing explosively. At the present time, every year more than 70,000 people die of lung cancer every year in Japan, and more than 1.3 million in world. One out of every eight Japanese will die of lung cancer in future. This is a similar rate to that of pulmonary tuberculosis in 1940s. On the other hand, every year 120,000 people die of pneumonia. Final cause of death in lung cancer patients are frequently pneumonia. Pneumonia is a big issue in lung cancer patients.

Lung cancer and pneumonia are connected in several ways. Pneumonia can develop as a complication of cancer. Pneumonia may also be a first symptom of some types of cancer. To understand how we care pneumonia in lung cancer patients, it is important to know what type of problem exists in pneumonia and lung cancer. (1) Diagnosis approach and pneumonia. Bronchofiberscopy caused the infection such as pneumonia. Sometimes, the image of lung cancer mimics that of pneumonia. (2) Lung cancer per se and pneumonia. Frequently, lung cancer located in the central bronchus causes post-obstruction of pneumonia. Also, immune dysfunction in lung cancer could be observed. (3) Treatment for lung cancer and pneumonia. Anti-cancer chemotherapy compromised the immune system and caused pneumonia. Although it is not infectious origin, radiation induces pneumonia and anti-cancer chemotherapeutic agents cause drug-induced pneumonia. In addition, pneumonia leads to the delay of anti-cancer chemotherapy.

For the care of pneumonia in lung cancer patients, it is essential to understand the exact conditions and to treat promptly. Several clinical case reports and summarize data from my institute will be presented.

AS2-1

Heterogeneity of COPD from Asian perspective

Sang-Do Lee

Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Clinicians have been long aware that neither the traditional distinctions of "emphysema" versus "chronic bronchitis" nor the traditional clinical phenotypes of "blue bloater" and "pink puffer" are sufficient to categorize patients that suffer from chronic obstructive pulmonary disease (COPD). With an increased understanding of pathophysiologic variation, COPD now clearly represents a spectrum of overlapping diseases with important extrapulmonary consequences.

To understand the heterogeneity of COPD in Asian countries we organized Asian Network for Obstructive Lung Diseases (ANOLD) in 2008. Through this network we found that characteristics of COPD patients in Asian countries vary and the history of exposure to biomass fuels or dusty jobs was related to frequency of symptoms, severe airflow limitation, and poor quality of life. We also evaluated whether there are subgroups of COPD patients with distinct phenotypes. We evaluated a total of 1022 COPD patients recruited from ten Asian cities which were classified into four regions of China/Taiwan, India/Sri Lanka, Philippines/Thailand/Malaysia/Vietnam, and Korea/Japan. To find principle variables for the phenotype of COPD patients, we performed factor analysis using the variables of age, body mass index, modified Medical Research Council dyspnea scale, Charlson comorbidity index, cigarette smoking amount, the St. George Respiratory Questionnaire (SGRQ) score, FEV₁, FVC, and the ratio of FEV₁/FVC. To find subgroups of COPD with distinct phenotypes, we performed hierarchical cluster analysis of Wald's method with the principle variables found by factor analysis. We found subgroups of COPD patients with distinct phenotypes. The fractions of the COPD subgroups among four Asian regions were different and might suggest that there are substantial differences in the severity and a potential subtype in Asian regions.

AS2-2

Role of CT in COPD phenotyping

Shigeo Muro

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Chronic obstructive pulmonary disease (COPD) is characterized by the presence of airflow limitation caused by loss of lung elasticity and/or airway narrowing. The pathological hallmark of loss of lung elasticity is emphysema, and airway wall remodeling contributes to the airway narrowing. Emphysema, a main constituent of lung pathology in COPD, is characterized pathologically by abnormal and permanent enlargement of distal airspaces and destruction of alveolar walls. This can be assessed by measuring low attenuation areas (LAA) in CT images.

The severity of emphysematous change (LAA%; the ratio of LAA to whole lung area) has been shown to associate with airflow limitations and impaired diffusing capacities, which are important determinants of COPD mortality. Moreover, the increase in LAA % associate with loss of bone mineral density and lowered Body mass index which are considered as part of systemic manifestation in COPD. Interestingly, a low BMI is associated with the presence of emphysema, but not with airway wall thickening in COPD patients, suggesting that there may be different systemic manifestations of these emphysema-dominant or non-emphysematous COPD phenotypes. It is also shown that patients with the phenotype in which emphysema predominates have lower BMI and poorer health-related QOL, however, the severity of emphysema varies widely even in patients with the same stage of COPD, and chronic bronchitis symptoms are equally distributed irrespective of emphysema severity. Thus, LAA in CT image seems to reflect the specific features in COPD pathophysiology.

The emphysema-dominant is also associated with a rapid decline in FEV₁ and the severity of emphysema increases the risk for a rapid decline. In addition to whole-lung emphysema severity, regional distributions of emphysema can be quantified by CT, and it is reported that more homogeneous distribution of emphysema in terms of the cranial-caudal distribution contributed to an accelerated decline in FEV₁ independently of baseline pulmonary function, whole-lung emphysema severity, and smoking status.

Airway remodeling/narrowing is also estimated by CT indices such as luminal area of airways and percentage wall area (WA%). These CT indices are shown to associate with airflow limitation and bronchitic symptoms, however, the role of these in COPD are less investigated compared to CT-emphysema because of the difficulties in methodology.

AS2-3**How COPD affects the heart: the CVD Phenotype of COPD**

Don D. Sin

PHC Respiratory Medicine, St. Paul's Hospital, University of British Columbia, Canada

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung condition that affects more than 200 million adults worldwide. Most patients have mild to moderate disease and as such have only modest symptoms of cough and breathlessness. However, many will go on to experience ischemic heart disease and stroke and die from cardiovascular complications rather than from their lung disease. Indeed, nearly 50% of all hospitalizations and 25% of all deaths in patients with mild to moderate COPD are cardiovascular system related. Reciprocally 1 out of 3 patients with angiography-proven atherosclerosis has COPD. Experimental and epidemiological data over the past 20 years provide compelling evidence that chronic lung inflammation (related to COPD or exposure to irritants such as tobacco smoke or air pollution) contributes to atherosclerotic plaque progression and acute inflammatory stimulus such as acute respiratory tract infections or acute exacerbations of COPD induce plaque rupture, leading to cardiovascular events. In this short review, an overview of the epidemiological and experimental data linking COPD with cardiovascular disease will be provided with an emphasis on the clinical implications of this linkage for clinicians who evaluate and manage patients with COPD, cardiovascular diseases or both, especially that related to the use of beta-blockers.

AS2-4**Assessment of comorbidities in COPD**

Akihito Yokoyama

Kochi University, Kochi, Japan

Half of patients with COPD have 3 or more comorbidities (multimorbidity) and such comorbidities are important prognostic factors in COPD. Therefore, recognition and management of comorbidities are important. Commonly, these are cardiovascular disease (CVD), osteoporosis, diabetes mellitus (DM), and lung cancer. CVD is a major comorbidity; probably the most frequent and most important disease coexisting with COPD.

We previously measured subclinical atherosclerosis (carotid artery intima-media thickness: IMT) using complete medical check-up data in healthy persons 45 to 60 years of age. We found that more increased IMT was observed in smokers with airway obstruction, than non-smokers and smokers without airway obstruction. Based on these results, we concluded that persons with airway impairment due to smoking are simultaneously prone to atherosclerosis, and that this type of subclinical atherosclerosis is likely to occur in the early stages of COPD.

On the other hand, a study of DM using the same complete medical check-up data revealed that there was no association between DM and airway obstruction in this age group, unlike the case of subclinical atherosclerotic lesions. In cross sectional analysis, decreased vital capacity (%FVC) but not FEV1/FVC (FEV1%) was associated with the frequency of DM and prediabetes. As DM per se had been reported to cause reduced pulmonary function, the causal relationship could not be clarified by a cross-sectional study. Therefore, we performed a longitudinal study to investigate the incidence of newly-diagnosed prediabetes during a mean period of 28 months in a population with normal glucose tolerance at baseline. As a result, we showed the incidence of pre-diabetes, especially impaired glucose tolerance (caused by insulin resistance in muscles), had a significant inverse correlation with %FVC but not FEV1% at baseline. These results may indicate that DM may occur in a later phase of COPD with decreased %FVC, and also DM may occur in COPD patients with less lung volume which may have developmental origin.

In this symposium, I would like to show our above-mentioned data and our hypothesis on the relationship between COPD and comorbidities.

AS3-2**Early recognition and diagnosis of pulmonary hypertension**

Sean Gaine

Mater Misericordiae University Hospital, Dublin, Ireland

Despite progress in the management of patients with pulmonary arterial hypertension (PAH) the long-term prognosis remains poor. Evidence suggests that World Health Organization functional class I or II patients have significantly better long-term survival rates than patients in higher functional classes, and therefore provides a rationale for earlier diagnosis and treatment of PAH. However, early diagnosis remains challenging and there is a consistent delay between symptom onset and diagnosis. Screening programmes, where applicable, play an important role in PAH detection. Current guidelines favour echocardiographic screening of asymptomatic patients predisposed to the development of PAH (e.g. systemic sclerosis). However, echocardiography has limitations in clinical practice and it may be that a combination of screening tools will improve the sensitivity and selectivity of current screening programmes. The recent DETECT study has cast important new light on this important area. Timely diagnosis and therapeutic intervention is essential if we are to impact on the long-term prognosis in PAH.

Humbert M, Yaici A, de Groote P, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. *Arthritis Rheum* 2011; 63: 3522-3530.

Galiè N, Hoeper MM, Humbert M, et al Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219-1263.

Hachulla E, Gressin V, Guillevin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005; 52: 3792-3800.

Galiè N, Rubin LJ, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 2093-2100.

Coghlan JG, Denton CP, Grünig E, et al Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis*. 2013 May 18. [Epub ahead of print]

AS3-3**Vardenafil in pulmonary arterial hypertension and Chinese experience**

Zhi-Cheng Jing

Thrombosis and Vascular Medicine Center, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China

Despite the targeted drugs for pulmonary arterial hypertension (PAH) were available in worldwide, only bosentan and iloprost were found in Chinese market as well as a great economic burden in 2006, which prompts us to explore more new drugs to overcome difficulties in China. The enzyme phosphodiesterase-5 (PDE5) is known to be abundant in lung tissue, where it hydrolyses cyclic guanosine monophosphate (cGMP), a second messenger of nitric oxide (NO), causing constriction of blood vessel walls. PDE-5 inhibitors exert their effect on pulmonary hypertension by increasing levels of cGMP and up-regulating NO-cGMP signaling. Vardenafil, a new PDE5 inhibitor, has demonstrated greater potency than that of sildenafil in the inhibition of PDE5 in pharmacodynamics. In 2008, a multicentre, open-label study of 1-year duration was undertaken in patients with PAH to determine the long-term safety and efficacy of vardenafil (5 mg once daily for the first 4 weeks, then 5 mg twice daily). To our excitement, this study demonstrated that long-term vardenafil treatment is well tolerance and has sustained beneficial effect on PAH, as measured by patients' exercise capacity, WHO functional class and the pulmonary vascular hemodynamic parameters. (Zhi-Cheng JING, et al. *HEART*. 2009; 95: 1531-1536.). Whereafter, we organized a randomized, double-blind, placebo-controlled study, patients with PAH were randomly assigned to 5 mg vardenafil once daily for the first 4 weeks increasing to the target dosage of 5 mg twice daily. This EVALUATION STUDY further confirmed vardenafil was effective and safe in patients with PAH at a dose of 5 mg twice daily in Chinese patients in *BLUE Journal* (Zhi-Cheng JING, et al. *Am J Respir Crit Care Med*. 2011; 183: 1723-1729.). Notedly, the survival and prognosis have also improved in vardenafil monotherapy in China. In additional, a recent published study in our center also provides a novel insight into the mechanism of vardenafil monotherapy, exhibiting that vardenafil is associated not only with increased NO levels and nitric oxide synthase expression but also with reduced oxidative stress (You-Fei FAN, et al. *Cardiovasc Res*. 2013; 99: 395-403.). Vardenfil has a positive effect on hemodynamics, pulmonary artery remodeling, right ventricular hypertrophy, and cardiovascular function, suggesting a potential new role for the drug in the treatment of PAH.

AS3-4**Pathogenesis and treatment of pulmonary hypertension associated with combined pulmonary fibrosis and emphysema**

Masayuki Hanaoka

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Combined pulmonary fibrosis and emphysema (CPFE) is frequently complicated with pulmonary hypertension (PH) that importantly impacts upon the poor prognosis in CPFE. The frequency and severity of PH are relatively higher in patients with CPFE than those with simply single idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD). The level of pulmonary hypertension did not show any correlations with either pulmonary functional tests or radiological lung scores in IPF or COPD. Therefore, the presence of PH could not be precisely predicted by pulmonary functions or radiological findings in these diseases including CPFE. The loss of pulmonary vascular bed is suggested to play a crucial role in the pathogenesis of PH in CPFE; however, the precise mechanism remains unknown. Recently, the vascular remodeling is thought to be an additional important mechanism of PH in CPFE. We performed the genome-wide microarray analysis to investigate the mechanism of CPFE in genetic level by comparing the microarray sequences between fibrotic and emphysematous lesions in the lungs of CPFE patients. The results showed that the genes involving with vascular growth, development and biology (processes that contribute to the destruction and repair of vessels) were significantly overexpressed in emphysematous lesions, suggesting a relationship of the PH with the existence of emphysema in CPFE. Currently, the long-term oxygen therapy is believed to be one of the effective treatments for PH in CPFE. Using vasodilators for pulmonary arterial hypertension is not established as a treatment of PH in CPFE; rather such drugs may even be deleterious in patients to impair oxygenation by worsening ventilation/perfusion mismatch in the lung of CPFE. In this symposium, the current knowledge and understanding in the pathogenesis and treatment of PH associated with CPFE will be reviewed concisely.

AS3-5**Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension**

Hiromi Matsubara

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Recent progress in medicinal treatment for pulmonary hypertension has improved the prognosis of pulmonary arterial hypertension. However, patients with CTEPH have been left behind this progress. There have been no effective therapeutic options, especially for the patients diagnosed as unsuitable for pulmonary endarterectomy. Balloon catheter would easily reach to surgically inaccessible lesions and therefore, we hypothesized that balloon pulmonary angioplasty (BPA) would be an effective treatment for inoperable patients with CTEPH. We treated 190 patients with CTEPH who diagnosed as unsuitable for pulmonary endarterectomy (WHO functional class II - IV despite medical treatment, mean age 62.4 ± 12.0 years old) with BPA. Mean pulmonary artery pressure (PAP) significantly decreased after BPA (from 43.0 ± 11.8 to 23.2 ± 6.3 mmHg ($P < 0.001$)). Forty patients developed severe reperfusion pulmonary injury after BPA and 5 of them died during hospitalization. Additional 3 patients died during follow up period and 3- year survival rate was 94%. Ninety-eight out of 190 patients have been followed up for more than 6 months after BPA (1.3 ± 1.0 years). Decrease of mean PAP was maintained (23.0 ± 6.3 mmHg) at follow up. Thus, BPA would be an effective therapeutic option in these patients who have otherwise no proven treatment.

AS4-1

Recent Advances in OSA pathophysiology and treatment

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The pathophysiology of Obstructive Sleep Apnea (OSA) involves a complex interaction of structural and functional factors that result in upper airway collapse during sleep. Moreover, there is considerable variation in contributing factors between individuals. An abnormal anatomical substrate is a key factor in the development of OSA. Craniofacial abnormalities, enlargement of upper airway soft tissue structures, central obesity, and an excess of regional adipose tissue are known anatomic risk factors for OSA. Although obesity is generally considered the major attributing risk factor for OSA, craniofacial morphology is increasingly recognised as an important interacting factor in OSA pathogenesis. It is well established from studies using imaging techniques that craniofacial abnormalities are common in patients with OSA. Mandibular retrusion, maxillary deficiency, inferior displacement of the hyoid bone and cranial base abnormalities are amongst the most commonly reported findings. Sleep-related changes in upper airway dilator muscle activity are also important, and inter-individual variability in the degree of neuromuscular compensation has been noted. The basis for this variability may relate to neuropathy of upper airway muscles, impaired muscle function or defects in mechanical coupling. Ventilatory control instability and impaired arousal responses appear to play a role in perpetuating respiratory events. More recently, additional factors such as airway surface tension and rostral fluid shifts in the recumbent position have been implicated to play a role in the pathophysiology of OSA.

CPAP remains the treatment of choice for OSA, acting as a pneumatic splint that overcomes the pathophysiological factors, regardless of their relative contributions. However, issues with suboptimal compliance have driven the quest for alternative treatments. Such alternatives include oral appliance therapy, nasal valves producing expiratory positive airway pressure, oral exercises, and novel surgical approaches (including hypoglossal nerve stimulation). Advances in our understanding of OSA pathophysiology, coupled with therapeutic innovations point to the need for a more personalised approach to the diagnosis and management of OSA. Such an approach requires more comprehensive characterisation of specific contributing factors at the individual patient level ("phenotyping"), forming the basis of a tailored approach to management. Innovative and cost-effective phenotyping techniques that can be easily implemented in clinical care are needed to realise the vision of personalised medicine for our field.

AS4-2

Obstructive Sleep Apnea and Metabolic Dysfunction: translating animal data to humans

Vsevolod Polotsky

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Obstructive sleep apnea (OSA) causes sleep fragmentation and chronic intermittent hypoxia (IH). OSA is a common disease with the prevalence of 24% in men and 9% in women, but the prevalence exceeds 50% in obese individuals. IH of OSA has been associated with insulin resistance, glucose intolerance, impaired insulin secretion and the development of type 2 diabetes as well as with atherogenic dyslipidemia and non-alcoholic fatty liver disease. We have developed a mouse model of IH mimicking oxyhemoglobin desaturations in patients with OSA and have shown that, in mice, IH causes: 1) insulin resistance and impaired insulin secretion; 2) inhibits clearance of triglyceride rich lipoproteins inactivating adipose tissue lipoprotein lipase (LPL) leading to dyslipidemia and atherosclerosis; 3) converts hepatic steatosis to steatohepatitis and liver fibrosis. Experimental evidence suggests that there are two pathogenic pathways leading to metabolic complications of OSA, systemic and tissue specific. Systemic mechanisms are related to stimulation of the carotid bodies with subsequent activation of the sympathetic nervous system and adrenal medulla. Carotid body denervation (1) attenuates IH-induced insulin resistance and glucose intolerance decreasing hepatic glucose output; (2) activates insulin signaling in liver and skeletal muscle; (3) activates adipose tissue lipolysis, which may lead to fatty liver with activation of triglyceride biosynthesis. Adrenal medullectomy prevents IH-induced inhibition of insulin secretion at baseline and in response to glucose. Tissue specific mechanisms are related to activation of hypoxia-induced factor alpha (HIF-1a) by tissue hypoxia and oxidative stress. In adipose tissue, IH up-regulates HIF-1a, which increases levels of a key LPL inhibitor, angiopoietin like protein 4 (Angptl4). Angptl4 neutralizing Ab prevents IH-induced dyslipidemia and atherosclerosis. In the liver, IH-induced HIF-1a upregulation increases levels of a collagen cross-linking enzyme lysyl oxidase, which may accelerate the progression of fatty liver to liver fibrosis.

Clinical evidence indicates that human OSA is associated with activation of OSA and the carotid body, but the role of carotid body in IH-induced insulin resistance and type 2 diabetes is unknown. Emergent evidence suggests that both adipose Angptl4 and liver LOX are increased in patients with severe hypoxemia of OSA, but the role of these pathways in dyslipidemia and steatohepatitis is also unknown. In conclusion, animal models of IH allow us to identify potential therapeutic targets in metabolic dysfunction of OSA.

AS4-3**Cardiovascular consequences of Obstructive Sleep Apnoea**

Patrick Lévy

Joseph Fourier University, Grenoble, France

Obstructive Sleep Apnoea (OSA) is a well-known public-health problem owing to its high prevalence and the numerous consequences of the disorder, including excessive daytime somnolence, cognitive impairment, as well as cardiovascular and metabolic morbidity. Thus there is an excess in cardiovascular mortality that has been repeatedly evidenced in longitudinal cohorts, both in general and clinical populations. Despite many confounding factors, including age, sex and obesity, there is accumulating evidence regarding strong associations between OSA, cardiovascular diseases i.e. hypertension, coronary artery disease (CAD), cerebrovascular disease, heart rate and conduction disorders—and excess mortality. It seems however that this is mainly true before 70 years old. In older patients, the cardiovascular risk does not seem to be increased compared to non-OSA at least for hypertension and CAD. OSA causes myocardial as well as arterial damage. Untreated OSA might, therefore, promote the progression of cardiac disease, resulting in heart failure and increased mortality in patients with heart failure. The mechanisms include sympathetic activation, oxidative stress and systemic inflammation. There are also major metabolic factors including visceral fat contribution to vascular remodelling. Whether treating OSA reverses chronic cardiovascular consequences remain uncertain. On-going randomised controlled trials may provide this answer in the future.

AS4-5**New insight in the management of patients with obstructive sleep apnea**

Kazuo Chin

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Recent data have shown that obstructive sleep apnea (OSA); especially severe OSA is a significant risk factor for cardiovascular diseases (CVDs) and increase in mortality. The other factors such as sleep duration, obesity, metabolic syndrome (Mets) and its related factors (hypertension, diabetes mellitus, lipidemia and visceral fat accumulation) have also significant effects on CVDs and mortality. However, two reports but one have shown that obstructive sleep apnea is associated with an increased risk of CVDs only in men. In addition, it has been reported that patients who are prescribed CPAP therapy can get more improvement in their Mets related parameters, the longer they use CPAP machine. From these data, it is important for us 1) to investigate the relationships among OSA, sleep duration and Mets related parameters, 2) to find a parameter that distinguish patients with severe OSA from the public subjects, because they would be easy to become CVDs without the treatment, 3) to make the patients use the CPAP machine for the enough time, and 4) to investigate whether there is a sex difference in the associations between OSA and Mets related several risk factors. From these points, we have investigated the OSA related issues. We found that 1) Subject with severe OSA had significantly short sleep duration ($P < 0.05$) in bed. Sleep duration in Mets subjects was also significantly shorter than in those without ($P < 0.05$). 2) Lipocalin-type prostaglandin D synthase (L-PGDS), which is responsible for the biosynthesis of prostaglandin D₂, has been reported to have a close connection with cardiovascular disease and sleep regulation. Urine L-PGDS might be a useful marker to identify patients with severe OSA that should be promptly treated, 3) Of three modes of PAP delivery [auto-adjusting positive airway pressure (APAP) and two different flex positive airway pressure (PAP) devices (A-Flex, C-Flex)], adherence was greatest with APAP with C-Flex, and 4) Only in men, OSA was independently associated with the visceral fat accumulation. The lesser associations between OSA and visceral fat in women might account for OSA's lower impact on CVD or mortality in women.

AS5-1**When and how to treat IPF: a US perspective**

Kevin K. Brown

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There is considerable uncertainty about the role of active medical treatment in the management of IPF in the US. Medications that had long been considered to be standard therapy have recently been shown more likely to be harmful than beneficial. A drug approved for use in other countries has been rejected by US regulatory authorities for failing to show convincing clinical benefit. The impact of treating comorbidities known to occur in IPF is uncertain. The increasingly frequent identification of patients with minimal fibrosis combined with a heterogeneous clinical course provides considerable prognostic uncertainty. This lecture will review the history and current practice of treatment of IPF in the United States.

AS5-3**The past and current treatment patterns of IPF in Korea.**

Soo-Taek Uh

Soon Chun Hyang University, Seoul Hospital, Korea

The new guideline published on 2011 changed treatment pattern of IPF in Korea. The treatment patterns before 2011 were obtained by nationwide survey of IPF. The patients with IPF diagnosed from 2003 to 2007 by 2002 diagnostic criteria were collected from 54 hospitals. Total number of IPF patients was 1,685 and their mean age was 69. The number of patients diagnosed by clinical criteria without lung biopsy was 1,027 (61%). Of 1,685 patients, 1,544 patients were available for analysis of treatment pattern. Treatment patterns were as follows: no treatment in 633 (40.9%), only steroid in 363 (23.5%), only N-acetylcysteine (NAC) in 69 (4.4%), steroid + azathioprine in 187 (12.1%), steroid + NAC in 38(2.5%), steroid + azathioprine + NAC in 31 (2.0%). The current treatment status was evaluated by questionnaire from pulmonologists working in university hospitals. 42 physicians from 36 hospitals answered and the response rate was 79%. About 80% of patients are diagnosed by HRCT finding without lung biopsy. Their mean experience duration of IPF treatment was 11.4 years. More than 95% of physicians have understood and trusted 2011 new guideline of IPF and 80% of physicians applied this guideline to real clinical fields. The prescribed patterns are as follows: steroid by 29 (69%), NAC by 40 (95%), anticoagulants by 9 (21%), pirfenidone by 22 physicians (52%). Most physicians among prescribing pirfenidone have used in less than 10% of IPF patients. Clinical trials have performed by 13 (31%) physicians. The physicians more than 11.4 years of experience in treatment of IPF believe some drugs can modulate the natural course of IPF in 10 of 16, but the physicians less than 11.4 years of experience believe that in 8 of 26 ($p=0.044$ by Pearson chi square).

AS5-4**When and how should we treat IPF?**

Arata Azuma

Nippon Medical School, Japan

Idiopathic pulmonary fibrosis (IPF) is one of the most devastating pulmonary diseases with a very poor prognosis. IPF has primarily a progressive clinical course with irreversible fibrosis. Several comorbidities may occur during the progression of the disease. IPF has been treated with anti-inflammatory agents including corticosteroids and immunosuppressants based on evidence from small-scale clinical trials and on the potential involvement of the inflammatory response in the pathogenesis of the disease. However, the therapeutic benefit of anti-inflammatory agents is currently disputed because no objective clinical improvement has been observed. Anti-fibrotic agents that can block the decline of vital capacity/forced vital capacity have been recently developed. Treatment with the anti-fibrotic agent, pirfenidone, the first approved drug, is indicated when the FVC is 50 to 80% of predicted value (mild to moderate impairment) in European Countries. The start of treatment is recommended when the decline of %FVC was more than 5% in the last 6 months prior therapy or when the symptoms become worse in patients with mild and moderate impairment of %FVC. Adverse reactions should be taken into consideration to assess the risk and benefit balance. In future studies, the impact of pirfenidone treatment on survival, quality of life, and reduction of the risk of comorbidities including acute exacerbation, pulmonary hypertension and carcinogenesis should be evaluated. When should treatment with pirfenidone be stopped? In general, 10% or more decline of %FVC against pirfenidone therapy is an indication of treatment change. However, prognostic factors should be assessed to predict clinical outcome in the future.

Novel therapeutic compounds are currently under development; Nintedanib, a kinase inhibitor of three profibrotic molecules, is one of the candidate compounds. Over 1,000 patients with IPF were enrolled in a phase III trial with nintedanib all over the world; observation of the last patient for one year was completed on September, 2013. The results of this clinical trial will be reported in the upcoming 2014 ATS International Conference.

AS5-5**Current strategy of IPF treatment in China**

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1. The prevalence of ILD and IPF in China

There are not any English publications about Chinese ILD prevalence so far, and we haven't the epidemiologic survey about the ILD prevalence among the whole population in mainland of China. However, there is an analysis of inpatients with ILD in 14 hospitals located in different cities hospitalizing from 1990 to 2003, which was performed by Chinese Thoracic Society (CTS). This result was published in Chinese at 6th Respiratory Diseases Congress (Abstract. P15-16, 2004; Shenyang, China). The main points are as follows. Among the 2764 ILD cases, idiopathic pulmonary fibrosis (IPF) accounts for 25.2%, collagen vascular diseases-interstitial pneumonia (CVD-IP) 15.2%, sarcoidosis 5.1%, extrinsic allergic alveolitis (EAA) 3.6%, non-classified ILD 50.9%. The proportion of ILD inpatients to all inpatients in respiratory department increased from 1.98% in 1990-1993 to 4.66% in 2000-2003, which reflected the increasing ILD morbidity indirectly.

2. The prognosis of IPF in China

Although there are no data about frequency of acute exacerbation in IPF (AEIPF) in China, more than 100 cases of AEIPF had been reported since first case report in 2006 (Yu N, et al. Chinese Journal of Practical Internal Medicine. 2006;26:986-988). In order to determine whether clinical situation affects the survival in IPF, our hospital had followed more than 200 patients with IPF. The frequency of acute exacerbation was about 10% in first year after diagnosis. In our hospital, another study followed 43 IPF patients, the result showed that the median survival time was 28.5 months after diagnosis, maybe it was shorter than that of USA and Europe. The reason of the shorter survival time in China probably is that many patients were not in early IPF stage while diagnosed (Peng SC, Li ZH, Kang J, et al. Chin J Tuberc Respir Dis. 2008; 31:260-263).

3. Treatment of IPF in China

Chinese Thoracic Society made Chinese guideline for diagnosis and treatment for IPF in 2002 (Chin J Tuberc Respir Dis. 2002;25:387-389), which was mainly complied with ATS/ERS statement. In terms of medicine treatment for IPF in China, NAC is routinely given to IPF patients. Steroid and/or immunosuppressant therapy are only recommended to patients with possible UIP HRCT pattern (without surgical lung biopsy) within 3-6 months as a "diagnostic therapy". Steroid is recommended to patient with AEIPF. Pirfenidone will be available in the clinical setting in China by the end of this year.

AS6-1

Novel treatment for virus induced asthma exacerbations.

Sebastian L Johnston

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Asthma exacerbations are a major unmet medical need. Current therapies fail to prevent the majority of exacerbations, and new preventive/treatment approaches are needed.

Respiratory virus infections are the dominant cause of asthma exacerbations with human rhinoviruses the commonest precipitant. Experimental studies and models of rhinovirus induced asthma exacerbations have identified impaired innate and Th1-mediated antiviral immune responses as important in asthma exacerbation pathogenesis. The mechanisms behind this impaired immunity are poorly understood.

Asthma is believed a Th2 mediated disease in the stable state, but Th1 mediated inflammation is induced following viral infections. It is not known whether respiratory virus infection in asthma leads to additional amplification of Th2 inflammation *in vivo*, but studies reporting powerful synergistic interactions between allergen exposure and virus infection in increasing risk of asthma exacerbations, suggest that Th2 cytokines may be important.

IL-25 and IL-33 are epithelial-derived mediators identified as inducers of type-2 inflammation. The role of IL-25 and IL-33 in asthma exacerbations is unknown.

A series of studies investigating these mechanisms in models of asthma exacerbations will be discussed.

Therapeutic implications of these findings in asthma exacerbations will then be discussed.

AS6-2

Pathogenesis of asthma and its implications for treatment-what's new?

Hae-Sim Park

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Asthma is a chronic inflammatory airway disease derived by Th2 derived immune responses composing of eosinophils, mast cells, epithelial cells and other structural cells, whether patients have allergic or non-allergic background. Recent studies suggested that non-Th2 like immune responses are involved with eosinophil activation via increased expression of TSLP and IL-33. Clinically, asthma is a heterogeneous condition presenting many different phenotypes. Most patients with mild to moderate asthma can be well controlled by anti-inflammatory medications, whereas severe asthma exhibits frequent asthma exacerbations(AEs) with progressive loss of lung function although they had used maintenance medications. Ongoing clustering studies are further linking molecular pathways with clinical characteristics.

For the management of asthma, a stepwise maintenance medication has been recommended by GINA guideline to achieve optimal asthma control with reduction of AE. Inhaled corticosteroid (ICS) and leukotriene receptor antagonist (LTRA) are major anti-inflammatory agents to control symptoms. ICS with long acting beta2 agonist (LABA) in a combination inhaler is widely used as a controller medication to improve lung function with reduction of AEs. New combination inhalers using different devices are developed to target small airway dysfunction. LTRA is useful as an additional maintenance medication on ICS/LABA treatment and useful for upper and lower airway symptoms for most aspirin exacerbated respiratory disease patients. As a non-pharmacologic treatment, allergen immunotherapy, subcutaneous or sublingual routes is widely applied in allergic asthma patients to achieve symptom control and disease remission.

Recent trials have demonstrated several potential biologics targeting specific phenotypes of asthma. The recombinant humanized monoclonal anti-IgE antibody, Omalizumab improves asthma control and reduces AEs in patients with severe allergic asthma. Anti IL-5 antibodies, Mepolizumab and Reslizumab have been shown to improve lung function and asthma control with the reduction of AE in severe asthma (especially eosinophilic asthma). A monoclonal antibody to IL13, Lebrikizumab showed clinical benefits in a phase II study for the treatment of moderate-to-severe uncontrolled asthma, especially in patients with high periostin level. In addition, a human monoclonal antibody to the α -subunit of the IL-4 receptor, Dupilumab has shown efficacy in aspects of improved lung function with reduced levels of Th2-associated inflammatory markers. Further studies are required to confirm efficacy in a 'real-life' setting and examine the long-term clinical consequences. The variability among the individual therapeutic responses of patients highlights the requirement to characterize different asthma subtypes so that phenotype-targeted treatments can be implemented.

AS6-3**Individualized treatment for asthma - are we there yet?**Ken Ohta^{1,2}National Hospital Organization Tokyo National Hospital, Tokyo, Japan¹,
Teikyo University School of Medicine, Tokyo, Japan²

Asthma has been recognized as a syndrome, but not a disease, based on its variations in phenotypes and endotypes. The phenotypes in asthmatics have been classified by focusing on clinical manifestations, laboratory data, and ultimately results of molecular, cellular and genetic analyses (endotypes). By validation of clinical parameters in patients with asthma, the study conducted by SARP (Severe Asthma Research Program) in US disclosed that five clusters could determine phenotypes of asthma from mild to severe. To what extent the results of cluster analyses reflect on asthma treatment is not known yet. At present, inhaled corticosteroids (ICS) are the first choice as a controller and the clusters will be helpful to predict the natural course of each asthma patient treated with ICS and bronchodilators, but we will not avoid using ICS and replace other drug(s) because of the patient's corresponding cluster. In practice, individualized treatment has been implemented by considering patients' age, gender, adherence, comorbidities, social life, level of education, economic state and so forth instead of their phenotypes or clusters so far. In other words, we have not obtained enough number of various molecular-targeting drugs, which make it possible for us to choose according to patients' phenotypes and/or endotypes. We are sure that there are significant number of patients whose asthma cannot be controlled even with most potent medication including the high dose ICS. These intractable asthma phenotypes are the target for endotype-based individualized treatment. So far omalizumab is the only drug on market targeting at the C epsilon 3 domain of the immunoglobulin E (IgE) molecule, and other molecules such as IL-5, IL-13, IL-4 and TSLP are or might be candidates to be modified by new agents. We do not know how close we are to make it real, but we should keep going to establish and implement the individualized treatment further more.

AS6-4**Towards a new taxonomy for asthma**

Richard Beasley

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The call for the development of a new taxonomy for the disorders of airflow obstruction has emanated from the recognition that asthma and chronic obstructive pulmonary disease (COPD) are not single diseases, but rather syndromes made up of a complex of multiple separate disorders. A better understanding of the distinct disorders of airways disease has the potential to inform on underlying mechanisms, risk factors, natural history, monitoring, and most importantly, treatment.

The concept of differential treatment responses in different phenotypes of asthma is already established, with eosinophilic asthma preferentially responding to inhaled corticosteroid therapy and monoclonal antibody to IL-5, with asthma associated with high Th2 status and high serum periostin levels to monoclonal antibody to IL-13, and severe refractory non-eosinophilic asthma to macrolide antibiotics. Similarly in COPD, patients with predominant upper lobe emphysema have better outcomes from lung volume reduction surgery, sputum eosinophilia predicts responders to short courses of oral corticosteroids, and the presence of chronic bronchitis may predict preferential response to PDE4 inhibitor treatment.

Preliminary evidence suggests that there may be five distinct phenotypes of airways disease defined by cluster analysis. These include an overlap group characterised by smokers with features of atopic asthma, chronic bronchitis and emphysema. This group has the most severe disease and morbidity, yet there is a limited evidence base for its management, as patients in this group would not have met the inclusion criteria for the major randomised controlled trials (RCTs) of either asthma or COPD. Indeed, most patients with asthma or COPD on treatment in the community are taking medication on the basis of RCTs for which they would not have been eligible.

The priority is to further define the distinct phenotypes that make up the syndromes of asthma and COPD, in particular whether the phenotypes vary in their response to different pharmacological treatments. This knowledge could lead to treatments specifically targeted for defined phenotypic groups, rather than for asthma and COPD in general, which represents the current management approach.

AS7-1

BAP1 gene mutation and mesothelioma pathogenesis

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Malignant mesothelioma (MM) is a lethal cancer whose pathogenesis results from complex interactions between host genetics and environmental carcinogens, such as asbestos and erionite fibers. Recently, we identified *BAP1* (BRCA associated protein 1) as a novel MM tumor suppressor gene located at 3p21, a region frequently deleted in MM, which encodes for a deubiquitinase enzyme known to target histones and other proteins. Despite its name, BAP1 appears to exert its anti-tumor activities mainly in a BRCA-independent manner, through association in diverse multi-protein complexes. So far, BAP1 is known to be an important regulator of cell epigenome, gene transcription, gluconeogenesis, and possibly DNA repair.

We discovered that germline *BAP1* mutations cause a novel cancer syndrome characterized by a significant excess of both pleural and peritoneal MM, uveal and cutaneous melanoma, renal cell carcinoma and possibly other tumors. Carriers of this syndrome develop benign melanocytic tumors that we called "melanocytic *BAP1*-mutated atypical intradermal tumors" or MBAITs. We also found that 22% of sporadic MMs harbored somatic *BAP1* mutations. Several other studies supported a relevant role of BAP1 in MM; in fact BAP1 absence (due to genetic, genomic, epigenomic or post-translational causes) was reported in about 60% of pleural MM. No studies so far have thoroughly investigated BAP1 expression in MMs arising from other sites.

BAP1 expression is not associated to asbestos exposure, suggesting that its role in MM pathogenesis may be independent from the known asbestos-related pathways. Other clinicopathological associations are at this moment too weak to be conclusive, possibly due to limited tumor sample sizes, methodological differences in the studies (e.g. mutation analysis with PCR vs. MLPA) or finally ethnical differences of the analyzed populations (i.e. BAP1 mutations have been reported to be more prevalent in epithelioid MM in a Japanese population, but not in Caucasians). It appears, but remains unproven, that patients with germline *BAP1* mutations have less aggressive MMs compared to sporadic MMs, in which *BAP1* mutations do not appear to influence prognosis. The impact of this work obviously extends to other cancers with BAP1 mutations.

Testa JR et al., Nat. Genet. 2011; Carbone M. et al., JTM 2012; Carbone M. et al., Nat Rev Cancer 2013

AS7-2

Trends in Smoking and Cancer Development

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It is well known that tobacco smoking is the most dangerous and preventable intoxication that man has constructed and is accepted worldwide.

In this world of strict regulation and demands on quality assurance of food and medication it is an appalling that we allow the continuation of this "medicinal" product with all its secret ingredients.

Despite a growing force against smoking in the developed world, most cigarette consumption occurs in the developing countries where legal regulation is even weaker than in Europe and the US. Half of all smokers will die from their addiction and the estimates of morbidity are higher.

For the following years we will have to spend a large portion of our national budget on the medical costs related with smoking habits.

Many kinds of cancer develop in relation to smoking (table 1) with cancer of the Head & Neck and Lung as leading causes. Only strict regulation by authorities and the banning of smoking advertisements for young people could turn this around.

The trends of lung cancer incidence in Europe show that in general there is a decrease of 3-4% in males but an increase of 4-9% in women. For Japan these figures are a decrease of $\pm 2\%$ in males and 0% in females.

Table 1. AFp: attributable factor to smoking; CI: confidence interval.

Tumor site
AFp (%)*
C.I. (%)
Larynx
84
72-92
Lung
82
79-84
Lower urinary tract
50
44-56
Oropharynx
49
36-69
Esophagus
35
23-50
Oral cavity
33
23-48
Liver
25
5-42
Stomach
21
11-33

AS7-3**Asbestos-related diseases in Korea-background and incidence (based on the data of Asbestos Health Damage Relief System)**Soon-Hee Jung¹, Hyoung Ryoul Kim², Jeung Sook Kim³Yonsei University Wonju College of Medicine, Wonju, Gangwon-Do, Korea¹, the Catholic University of Korea, Seoul, Korea², Dongguk University Ilsan Hospital, Seoul, Korea³

Background: The Republic of Korea is approximately 99,720 square kilometers and the population is 50 million (2012 estimates). Today Korea is an industrial nation standing on the leading edge of global markets in the area of semiconductor, automobile, shipbuilding, steel making and IT industries. However, we do not have the national data for prevalence of asbestos related diseases (ARDs) such as malignant mesothelioma, asbestosis, and lung cancer. Current scattered asbestos regulations had resulted in the enforcement of the act on asbestos damage relief system on the 1st Jan, 2011. **Method:** The data of 622 patients or special bereaved families compensated by asbestos damage relief law during the last two and half years were analysed. **Results:** Among 622 cases, there were 165 cases (26.5%) of malignant mesothelioma, 417 cases (67.1%) of asbestosis, and 40 cases (6.4%) of lung cancer. The average age of patients were 69 year old and the gender were 429 men (68%) and 193 women (31%). The patients had a history of environmental (436 cases, 70.1%) and occupational exposures (402 cases, 64.6%). The location (or main residence) for environmental exposure was asbestos mine (362 cases, 58.2%), asbestos related factory (56 cases, 9%), train station (near asbestos mine), and other possible environmental exposure source. The major occupation of patients were asbestos miner (190 cases, 47.3%), construction (67 cases, 16.7%), asbestos industry (51 cases, 12.7%), asbestos textile, ship building & repair, automobile repair, and gasket. On the point of radiologic grade of asbestosis by chest CT, there were 8 cases of suspicious lesion, 394 cases (63.3%) of early change, and 51 cases (8.2%) of progressive lesion. Also 405 patients (65.1%) had a plaque. The pulmonary function were normal (195 cases, 31.3%), moderate (187 cases, 30.1%), severe (29 cases, 4.7%), and poor quality (9 cases, 1.4%). **Conclusion:** The peak time of asbestos usage in Korea was 1995, so the incidence of is expected to increase continuously by 2030s. Although the law about asbestos victim's relief act had already started in Korea, we need more information and further multivariate analysis for the duration of environmental or occupational exposure with the multidagnosis about the second manage of data such as lung cancer with asbestosis, trying to approach systematically to prevent the occurrence of ARDs.

AS7-4**Airborne particulate matter and respiratory diseases in Japan**

Masayuki Shima

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Air pollution is recognized as a major health problem in many countries. In Japan, the increasing automobile traffic has caused considerable increases in levels of particulate matter and nitrogen dioxide, and their potential effect on the health of residents who live near trunk roads is a matter of concern. To evaluate the effects of traffic-related air pollution on respiratory diseases, we have conducted a school-based prospective cohort study in the three metropolitan areas in Japan. To evaluate the exposure to automobile exhaust, the individual exposure levels of elemental carbon (EC) were estimated by simulation model for each child. Of the 10,069 children who had no asthmatic symptoms at the beginning of the study, 309 children had an onset of asthma during the follow-up period from 2005 to 2009. The incidence of asthma significantly associated with the estimated levels of personal exposure to EC, after adjustment for various factors.

In addition, the health effects of airborne fine particulate matter (PM_{2.5}) have become a major concern. A panel study was conducted to evaluate the acute effects of exposure to PM_{2.5} on daily peak expiratory flow (PEF) and wheezing among asthmatic children. The PM_{2.5} concentrations were monitored at a monitoring station proximal to the hospital. Moreover, PM_{2.5} concentrations inside and outside the hospital were also measured. The changes in PEF in the morning and evening were significantly associated with increases in the average concentration of indoor PM_{2.5} 24 h prior to measurement. The change in PEF was also significantly associated with outdoor PM_{2.5} concentrations, but the changes were smaller than those observed for indoor PM_{2.5}. The prevalence of wheezing in the morning and evening were significantly associated with indoor PM_{2.5}. The odds ratios for wheezing relative to the lowest quartile of indoor PM_{2.5} concentrations of 15.4µg/m³ or higher were significantly associated with increased wheezing in the morning. Wheezing in the evening was associated with indoor PM_{2.5} concentrations ≥11.0µg/m³ and stationary-site PM_{2.5} concentrations ≥18.2µg/m³. In this way, exposure to considerably low concentrations of PM_{2.5} was associated with PEF and wheezing among asthmatic children.

In conclusion, traffic-related air pollution may be of importance in the onset of asthma among children, and the short-term exposure to PM_{2.5} was shown to affect respiratory morbidity among asthmatic children. The estimation of the levels of personal exposure to automobile exhaust is desirable to evaluate the effects of air pollution.

AS7-5

Advances of diagnosis and treatment for mesothelioma

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Malignant pleural mesothelioma (MPM) has become a serious issue because of its poor prognosis and its growing incidence. Since the European guidelines on MPM management from the ERS/ESTS Taskforce in 2010, some innovative potential diagnostic tools and therapeutic strategies have been proposed.

To obtain an earlier and reliable *diagnosis* of MPM is a crucial issue. Thoracoscopy with multiple biopsies, studied by immunohistochemistry, is the "gold standard" for this diagnosis. The performances of other procedures, pleural cytology or guided pleural biopsies, are still lower than thoracoscopy, but are getting better with increasing experience of the clinicians. New soluble biomarkers, such as fibulin-3, were suggested as diagnostic tools in MPM.

The *staging* of MPM is a difficult issue in the absence of a uniform, robust and validated staging system. However a new staging system will be proposed soon by experts from a joined IASLC-IMIG project, and represents a crucial step to improve cancer treatment.

MPM exhibits a high resistance to validated first line (platinum-pemetrexed) chemotherapy. Patients demonstrating prolonged symptomatic and objective response with first line chemotherapy may be treated again with the same regimen (pemetrexed) in the event of recurrence. Alternatively, inclusion of the patients in first and second-line clinical trials is highly encouraged. Radiotherapy indications are limited and controversial in MPM, even using intensity-modulated radiotherapy (IMRT). Only few patients are candidate for radical surgery that should be performed only in clinical trials, in specialized centres, as a part of multimodal treatment. Moreover, extrapleural pneumonectomy (EPP) recently lost many supports after the results of several negative trials on the feasibility and the value of EPP, in particular the highly discussed MARS trial. In contrast, it has been suggested that extended pleurectomy/decortication (eP/D) could be of interest if associated with chemotherapy ±intrapleural treatments such as photodynamic therapy (PDT). Promising therapeutic strategies including targeted (pro-apoptotic, anti-angiogenic...) drugs, gene or cell therapies under investigation will be detailed during this talk.

Finally *monitoring* of patients still relies mostly on clinical examination and chest CT-scan data, using modified RECIST criteria. Based on recent but limited literature, PET-scan and soluble tumor markers such as blood mesothelin (SMRP) seem promising in this goal but are not validated in routine yet.

In conclusion, because of still limited data available on the best combination treatment for MPM in 2013, it must be emphasized that inclusion of MPM patients in first and second-line clinical trials is highly encouraged.

AS8-1

New clinical test for evaluation of cardiovascular risks in OSAS and in COPD using a conventional hematology analyzer

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[Background] OSAS and COPD are known to be associated with increased risk of arterial thrombosis, such as stroke and coronary heart disease. Enhanced platelet function is suggested as a potential cause for cardiovascular events. Although early detection of platelet hyperaggregability is important, a routine clinical test has not been established yet. We have previously reported a simple method for detection of platelet hyperaggregability in patients with cerebral infarction by using a conventional hematology analyzer (CELL-DYN SAPPHERE[®], Abbott Diagnostics, USA). We applied this method to patients with OSAS and those with COPD to detect hyperaggregability. [Methods] In Experiment 1, 44 patients (39 males and 5 females, 49±11(SD) years) with OSAS, and 50 healthy subjects (30 males and 20 females, 48±5 years) were enrolled. Blood samples were drawn into a plastic tube containing sodium citrate and another plastic tube containing K₂-EDTA. Both tubes were placed in the hematology analyzer. The analyzer was run under standard procedures without any special modification. If platelet clumps exist, they appear on the scatter plot as a population of events extending diagonally through a region between mononuclear and polymorphonuclear cells. Platelet clumps were deemed to be positive when they were detected in citrated but not in K₂-EDTA blood. Measurements were carried out before and after CPAP. In Experiment 2, 26 stable COPD patients (stage2-4) and 26 healthy controls were enrolled. The methods were essentially the same as described above. [Results] In Experiment 1, none of the samples obtained from the healthy subjects exhibited platelet clumps, while those obtained from 21 of the 44 patients (48%) showed platelet clumps. One month after CPAP, the apnea-hypopnea index (AHI) decreased significantly from 43±25 to 6±9. Platelet clumps subsided in 12 of the 21 patients. However, in the remaining 9 patients, hyperaggregability was still detected. These patients were considered to need anti-platelet drugs in addition to CPAP. In Experiment 2, platelet clumps were positive in 4 of 26 (15.4%) in COPD patients, but only 1 of 26 (3.8%) in healthy controls. The results indicate that patients with stage 2-4 COPD have a significant risk of thrombosis. [Conclusion] The results indicate that platelet clumps can be easily detected by this method. Since the measurement is simple, does not require complex data analysis and can be performed in the outpatient department, the present method would be useful and effective for early detection of cardiovascular risks in OSAS and in COPD.

AS8-2

Pediatric Pulmonary Function

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Lung function testing provides an objective assessment of respiratory status, changes in health over time and the response to interventions or exacerbants. Furthermore, it can provide insight into the pathophysiology of the disease process itself.

Recent evidence supports the notion that chronic respiratory diseases have their origin early in life and that lung function and clinical status later in life may be determined by early events. Our ability to detect lung function early in life and to monitor changes over time are essential if we are to improve health outcomes in the future. Over the past decade our ability to perform such testing, and the knowledge gained from this, has considerably advanced our understanding of conditions such as asthma, cystic fibrosis, chronic lung disease of infancy and even chronic obstructive pulmonary disease in later life.

New modifications of old tests, such as multiple breath washout, appear to have significant advantages over more routinely used tests, such as spirometry. However, to appreciate the potential of all tests a sound knowledge of their performance, validation and physiological relevance are essential.

This talk will discuss recent developments in paediatric lung function testing and the latest insights gained from their use in clinical practice and research studies in relation to disease pathophysiology and lung development.

AS8-4

Deep Inspiration: Its role in causing Airway Hyperresponsiveness in Asthma

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Deep inspiration (DI) has a profound effect on lung function. Not only does deep inspiration alter the pressure volume relationship of the lung by recruiting surfactant molecules to the air-liquid interface but DIs also stretches the airway smooth muscle and increases airway caliber. In this talk I will focus on this effect of DI. There is increasing evidence that an abnormal response to DIs contributes to the airway hyperresponsiveness which is characteristic of asthma. After administration of a bronchoconstricting stimulus DI substantially reduces airway resistance in non-asthmatic subjects but has a much reduced effect in asthmatics. This is termed the bronchodilating effect of DI. Perhaps more importantly DIs taken before administration of a bronchoconstricting agent attenuate the subsequent airway narrowing as measured by FEV1 but not by measures of airway caliber that do not involve a DI (eg airway resistance and partial flow volume curve measurements). This is termed the bronchoprotective effect of DI. Data from our laboratory suggests that the control of airway smooth muscle stiffness, and thus its response to DIs, is regulated independently the smooth muscle's contractile capacity. These results point to airway smooth muscle stiffness as a potential new therapeutic target in asthma.

AS8-5

Structure and function changes in children and adults with cystic fibrosis

Harm Tiddens

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Cystic fibrosis (CF) lung disease starts early in life and is characterized by chronic lung inflammation and infection which persists throughout life. Both inflammation and infection lead to early irreversible structural lung damage. The most important pathology changes are bronchiectasis and bronchiolitis obliterans like changes of the small airways. The course of disease and spectrum of the structural changes varies widely between patients due to genotypic and environmental differences. The primary aim of CF therapy is to prevent any structural damage and to conserve lung function. Adequate monitoring of CF lung disease starting early in life is paramount to tailor treatment to a patient's need and to prevent irreversible damage from occurring. Functional tests are relatively insensitive to detect localized abnormalities. In addition functional tests do not reveal the nature of the structural abnormalities. Imaging techniques are needed to visualize the structural changes related to CF lung disease. Chest Computed tomography (CT) is currently the most sensitive imaging modality to detect and monitor structural lung abnormalities. In young children chest CT show extensive trapped air and airway wall thickening in most children. At the age of 5 years more than half of these children show bronchiectasis. In end stage lung disease patients show a highly variable mix of bronchiolitis obliterans like changes and bronchiectasis. This disease spectrum is important to personalize treatment. To use chest CT to monitor CF lung disease image analysis systems have been developed and validated to quantify the most important components of CF lung disease.

AS9-1

Challenges to Investigate Lung Carcinogenesis at the University of Texas M.D. Anderson Cancer Center Thoracic Molecular Pathology Lab.

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We have established a large collection of surgically resected (stages I-IIIa) frozen and archival formalin-fixed and paraffin-embedded (FFPE) tissue from lung cancer, with a subset of ~1,000 cases having annotated clinical information, including a detailed smoking history and follow-up. Using these resources, we have aimed to develop an integrated pathological and molecular classification of non-small cell lung cancers (NSCLCs) to better prognosticate survival of patients and identify novel biomarkers to predict response to therapies. To accomplish these aims, our lab played an important role in National Cancer Institute (NCI)-Specialized Programs of Research Excellence (SPORE) program and several US Department of Defense (DoD) grants. We have developed the following resources: a) Comprehensive collection system of NSCL tumor tissue specimens in operation rooms, institutional tissue bank and clinical suites (e.g., bronchoscopy and interventional radiology suites) to collect high quality tissue and cell research specimens in collaboration with clinical groups; b) A large collection of DNA, RNA and protein samples obtained from frozen NSCLCs with annotated pathological and clinical information to be used for profiling analyses; c) Prospectively collected airway specimens and corresponding NSCLC tumors as part of our field of cancerization (FC) project to identify new molecular markers associated to lung cancer pathogenesis and to develop novel chemopreventive strategies; and, d) several FFPE NSCLCs in tissue microarrays (TMAs) for validation of novel molecular markers in tumor tissues specimens, including proteins using immunohistochemistry (IHC), genes by mRNA expression in situ hybridization (ISH) and DNA by fluorescent in situ hybridization (FISH). From our NSCLCs TMA set, we have identified multiple markers and several pathways' activation that associate with patients' clinical and pathological characteristics, including recurrence-free and overall survivals, and tumors' genomic properties. This integration of achievements has been important for the discovery and validation of novel markers for lung cancer diagnosis and treatment using personalized approaches.

AS9-2

Targeted therapy for lung cancer: Clinical trials for lung cancer in EuropeRudolf M. Huber^{1,2}University of Munich, Bavaria, Germany¹, Thoracic Oncology Centre of Munich, Bavaria, Germany²

Lung cancer in Europe has a varying incidence and mortality in the different countries. In some countries lung cancer rates are among the highest throughout the world. Most lung cancers in Europe are smoking related. Therefore, there is still a rather high rate of squamous cell lung cancers and smoking associated adenocarcinomas in some parts of Europe. The incidence of activating EGFR mutations is consequently much lower than in Asia. Also the frequency of EML4-ALK translocations is low.

Regarding targeting therapies and the corresponding molecular testing, we have now established quality assurance programs from the pathologists in some European countries, e.g. in Germany and France. In France there is also a national program for centralized and science driven testing of various driver mutations. Apart from EORTC the European Thoracic Oncology Platform (ETOP), a union of various European Thoracic Oncology Centres and research institutes, is also organizing a European wide approach for molecular testing. Regarding treatment of activating EGFR mutations there is one specific European randomized trial (EURTAC), which has proven the efficacy of erlotinib also in Caucasian patients. Afatinib was also tested partly in randomized trials in the European population. This is also true for crizotinib in the patients with EML-4-ALK translocation.

Due to the overall low frequency of activating EGFR mutations and EML-4-ALK translocations clinical trials regarding molecular testing and treatment of these alterations are much more demanding in Europe than in Asia.

AS9-4

Molecular mechanisms of resistance to EGFR-TKI in lung cancer

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Dramatic response has been achieved by EGFR inhibitors in lung cancer expressing EGFR activating mutations. However, cancer cells show either intrinsic or acquire resistance to EGFR tyrosine kinase inhibitors (EGFR-TKI), gefitinib and erlotinib, and cause disease progression. Known major mechanisms for acquired resistance to EGFR-TKI include T790M gatekeeper mutation in the EGFR gene and activation of bypass survival signal via receptors other than EGFR. The latter mechanism can involve Met gene amplification and ligand-triggered receptor activation as well. For example, HGF, the ligand of a tyrosine kinase receptor Met, activates Met and the downstream PI3K/Akt pathway and triggers resistance to EGFR inhibitors in *EGFR* mutant cancer cells.

A common *BIM* deletion polymorphism, occurs specifically in East Asian individuals was reported to be a novel mechanism of intrinsic resistance to EGFR-TKIs in *EGFR* mutant lung cancer. We demonstrated that the histone deacetylase (HDAC) inhibitor vorinostat can epigenetically restore BIM function and death sensitivity of EGFR-TKI, in cases of *EGFR* mutant lung cancer where resistance to EGFR-TKI is associated with a *BIM* polymorphism. We are now conducting a clinical trial with vorinostat and EGFR-TKI to circumvent *BIM* polymorphism associated EGFR-TKI resistance.

Our findings proposed new therapeutic strategies providing the rationale for conducting clinical trials on molecular targeted drugs to overcome resistance in lung cancer.

AS10-1**Update on COPD biomarkers**

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Chronic obstructive pulmonary disease (COPD) is a multisystem set of lung and systemic conditions. Many factors have been identified which contribute to susceptibility to COPD, disease progression and acute exacerbations. These factors include cigarette smoke, environmental and occupational pollutants, respiratory infections and multi-morbidities. The diversity of phenotypes and disease journeys make personalisation of management difficult for patients and their clinicians, in this complex chronic disease. A wide range of clinical, inflammatory, genomic and epigenomic biomarkers for COPD could be used to individualise treatment, in order to improve chronic disease management and prevention in patients with COPD. This presentation will highlight and critically analyse: 1) biomarkers for COPD susceptibility and disease progression; 2) biomarkers during acute exacerbations; 3) biomarkers to predict the frequency of exacerbations; and 4) biomarkers for common comorbidities such as lung cancer, pulmonary hypertension, coronary artery disease and frailty related to ageing. The most promising COPD biomarkers, particularly those that have been demonstrated in larger studies, require replication to test their applicability in the clinical setting. Together, clinical, genomic and molecular biomarkers have considerable potential to personalise therapy for patients with COPD.

AS10-2**The Initiation of Allergic Asthma; Bacterial Products Revisited**

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Allergic asthma is a complex disease characterized by eosinophilic pulmonary inflammation, mucus production and reversible airway obstruction. Exposure to indoor allergens is a risk factor for asthma, but this disease is also associated with high household levels of total and particularly Gram-negative bacteria. The ability of bacterial products to act as adjuvants suggests they might promote asthma by priming allergic sensitization to inhaled allergens. In support of this idea, house dust extracts (HDEs) can activate antigen-presenting dendritic cells (DCs) *in vitro* and promote allergic sensitization to inhaled innocuous proteins *in vivo*. It is unknown which microbial products provide most of the adjuvant activity in HDEs.

A screen for adjuvant activity of microbial products revealed that the bacterial protein flagellin (FLA) stimulated strong allergic airway responses to an innocuous inhaled protein, ovalbumin (OVA). When instilled into the airways of mice, purified FLA or FLA-containing extracts of house dust promoted allergic sensitization to co-instilled OVA. Subsequent challenge of these mice with aerosolized OVA triggered multiple asthma-like responses, including eosinophilic airway inflammation and airway hyperresponsiveness. These responses were dependent on toll-like receptor (TLR) 5, which senses bacterial FLA, but independent of TLR4, which senses lipopolysaccharide (LPS). Repeated instillations of house dust extracts alone elicited similar asthma-like responses in a TLR5-dependent manner. Moreover, human asthmatics had higher levels of anti-FLA antibodies than did non-asthmatic individuals. Together, these findings suggest that household FLA promotes asthma by TLR5-dependent priming of allergic responses to indoor allergens.

AS10-3**Infections and COPD exacerbations *Focus on respiratory viruses***

Alberto Papi

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Acute exacerbations are the major cause of morbidity in COPD. Infections of the tracheobronchial tree are the major trigger of COPD exacerbations. Bacterial infections play a primary role in exacerbating COPD patients. However, the precise pathophysiology of bacterial infection is still debated as COPD patients are chronically colonized by pathogen species. Recently, a number of epidemiological and clinical studies have suggested a major role for respiratory viral infections during COPD exacerbations, rhinovirus being the most frequently identified virus. Whether COPD patients are more susceptible to virus infection compared with normal subjects is not fully elucidated. A recent study documented that patients with frequent COPD exacerbations have more frequent episodes of naturally occurring viral colds when compared with patients with infrequent exacerbations. These results suggest that COPD subjects with frequent exacerbations represent a subgroup particularly susceptible to viral infections. Recent evidence documented impaired innate (Interferons) and (possibly) acquired immune responses to viral infection in COPD patients, with increased susceptibility to viral infections. In addition, using a mouse model of cigarette smoke exposure, it has been demonstrated that cigarette smoke increases susceptibility to viral infections, possibly via alteration and/or inhibition of immune responses. Therefore, cigarette smoke exposure, which is the most important risk factor for the development of COPD, might cause impaired immune response to viral infections in COPD patients. Another mechanism that might lead to increased susceptibility to viral infections is the upregulation of ICAM-1, the receptor for the major group of human rhinoviruses. Solid evidence shows that patients with COPD are chronically colonized with airway bacteria, and the bacterial load is related to airway inflammation and disease progression. It has been postulated that bacterial colonisation contributes to increased susceptibility to viral infection in COPD patients, for example, by increasing ICAM-1 expression in bronchial epithelial cells, either directly or through induced inflammation. Further studies are required to investigate the interaction between chronic bacterial colonisation and respiratory viral infection and, in particular, whether chronic bacterial colonisation can increase susceptibility to viral infection or *vice versa*.

The development of the first human model of virus induced COPD exacerbation, has recently clarified several aspects of virus associated COPD exacerbations. In controlled conditions, experimental respiratory virus infection, can reproduce many of the features typical of COPD exacerbations. In particular, human experimental models have identified specific immunological deficiencies in COPD subjects that can contribute in turning harmless rhinovirus infections into severe exacerbation episodes, especially in frequent exacerbators.

This model has been demonstrated to be feasible and safe, will facilitate identification of novel pharmacological targets that will provide opportunities to develop new treatments for exacerbations of COPD.

AS11-1**Overview: Challenges in 21st century TB Clinical Research**

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A review of the medline shows that PubMed lists 980 TB articles from 2000-present for Clinical Trials and Tuberculosis. The US NIH website ClinicalTrials.gov lists approximately 980 past, ongoing and proposed studies under tuberculosis. At no time since the golden period 1943-1963 (when the 5 frontline TB drugs were discovered) has there been so much recent activity in the discovery of new tools than in the last decade. But the advent of new diagnostics, drugs and potential vaccines has also illustrated the challenges facing TB studies. Ginsberg and Spigelman of the Global TB Alliance in 2007 spelled out the challenges in TB studies particularly the need to identify pre-clinical approaches for optimized drug combinations as well as novel clinical and regulatory approaches to phase 2 and 3 trials. They also likewise pointed to the need to develop capacity for more GCP clinical trial sites in high burden TB countries. In 2011, the Critical Path to TB Drug Regimens Initiative identified 91 potential sites for TB drug trials across the world. O'Brien and Pai have raised the issue of lack of methodological rigor in TB diagnostics and suggests the QADAS checklist for assessing studies. Given these challenges, the author also will present his own personal insights based on his own experience on the above mentioned issues and as an overview to the next series of speakers.

AS11-2

Development of Delamanid for the Treatment of Multidrug-Resistant Tuberculosis

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Delamanid (OPC-67683), a nitro-dihydro-imidazooxazole derivative, is a new anti-tuberculosis medication that inhibits mycolic acid synthesis and has shown potent *in vitro* and *in vivo* activity against drug-resistant strains of *Mycobacterium tuberculosis*. The compound was discovered by Otsuka in 2002 and entered human testing in 2004. After rigorous phase 1 testing and early phase 2 evaluation in drug-susceptible TB, the evaluation of delamanid in the treatment of multi-drug-resistant tuberculosis (MDR-TB) began in 2008 with the launch of the largest randomized controlled trial (RCT) yet performed among MDR-TB patients. Results from the RCT demonstrated that delamanid substantially increases the proportion of patients achieving 2-month sputum culture conversion, a key milestone in MDR-TB treatment, and data from longer-term trials support the longer-term benefit for MDR-TB patients from treatment with delamanid. Enrollment in a 30-month global confirmatory trial is nearly complete.

AS11-4

International standards for TB care: implications of new tools

Philip Hopewell

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The first edition of the *International Standards for Tuberculosis Care (ISTC)* was developed in 2006 and the second edition in 2009. We are currently revising the second edition and plan to launch the new edition on World TB Day March 24, 2014. The main purpose of the ISTC continues to be describing a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, are suspected of having, or are at increased risk of developing tuberculosis. The standards are intended to facilitate the effective engagement of all care providers in delivering high quality services for tuberculosis. Engagement of all providers is a critical component of global tuberculosis control and the *ISTC* will serve as a means of facilitating implementation of a new global strategy, especially among private providers. The updated *ISTC* presents the framework necessary for effective tuberculosis care and control and, when fully implemented, provides the elements essential for delivery of high quality tuberculosis care and prevention.

The major changes in the 3rd edition are related to the recommendations for use of rapid molecular diagnostic tests, especially Xpert MTB/RIF®. The revised Standard 3 states, "All patients (including children) who are presumed to have pulmonary tuberculosis and are capable of producing sputum should have at least two sputum specimens submitted for AFB smear microscopy or a single sputum sample for Xpert MTB/RIF® testing a quality-assured laboratory. In patients at risk for drug resistance, who have HIV risks, or who are seriously ill, Xpert MTB/RIF® assay should be performed as the initial diagnostic test. Blood-based serologic tests and interferon gamma release assays should not be used for diagnosis of active tuberculosis."

Standard 4 now is as follows: *For all patients (including children) presumed to have extrapulmonary tuberculosis, appropriate specimens from the suspected sites of involvement should be obtained for bacteriological (AFB microscopy, culture, Xpert MTB/RIF®), and histological examination. Xpert MTB/RIF® should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing CSF from patients presumed to have TB meningitis, given the urgency for a rapid diagnosis.*

The scientific basis for these and other changes will be presented.

AS12-1**Effects of Lung Inflammation on Cardiovascular Health**

Don D. Sin

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Acute and chronic lung inflammation is an under-recognized risk factor for cardiovascular disease. Yet, there are compelling epidemiological data to indicate that airway exposures to cigarette smoke, air pollution particles, and viral and bacterial pathogens are strongly related to acute ischemic events. Over the past 10 years, there have been important human and animal studies that have provided experimental evidence to support a causal link. In this session, an overview of the mechanisms linking lung inflammation with cardiovascular disease will be provided with the emphasis on how this knowledge will translate to new biomarkers and new therapies for patients with lung and heart disease.

AS12-3**Impact of air pollution on lung health**

Hajime Takizawa

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Air pollution is a global burden that threatens human lungs and other organ systems. Epidemiological studies have suggested a causative relationship between air pollution and the increased mortality and morbidity due to respiratory disorders. These pollutants include ozone, nitrogen dioxide and, particulate matters of a wide range of diameters, which were produced by traffic-related and industrial activities. There is also an accumulating evidence that strongly supports a relationship between air pollution and the exacerbation of asthma and other respiratory diseases. Recent cohort studies have further suggested that air pollutants play a role in the development of asthma and allergies. Among a variety of pollutants, particulate components, particularly PM_{2.5}, are especially suggested to be harmful to our lung health. Basic researches *in vitro* and *in vivo* have elucidated that diesel exhaust particles (DEPs), the major component of PM_{2.5} in urban districts, induce and exaggerate allergic airway inflammation. Studies of molecular mechanisms have focused on the role of reactive oxygen species (ROS) generated directly and indirectly by exposure to DEPs. The ROS play an important role in pro-inflammatory reaction in airways. We have demonstrated in mouse systems that Nuclear erythroid 2 P45-related factor 2 (Nrf2) is a key transcription factor that regulates host antioxidant defense that contributes to regulate airway inflammation induced by DEPs. Oral antioxidants such as N-acetyl cysteine (NAC) ameliorated DEPs-induced oxidants stress and resultant inflammatory changes in animal models.

We studied the airway inflammatory/fibrogenic responses from patients with asthma. Participants were asked to present exhaled breath condensates (EBC) by R-tubes during spontaneous breathing for 5 minutes, which were processed to measure several inflammatory/fibrogenic markers. Among these molecules, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (FGF), IL-1 receptor antagonist, IL-8 and epidermal growth factor (EGF) were increased in severe asthmatic group as compared to mild asthmatics. There was a significant correlation between the PM₁₀ concentration 1 month before the sampling of EBC and EBC biomarkers. EBC pH showed a significant relationship with the distance from main traffic roads. A multiple regression analysis among moderate and severe asthma patients showed that PM₁₀ concentrations significantly contributed to EBC biomarkers. These results suggested that mass screening using simple methods such as EBC and appropriate biomarkers might facilitate the progress in the prophylaxis against hazardous health effects of DE exposures in subjects with high susceptibility to DEPs.

AS12-4

Protozoal Parasites and Lung Diseases

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The important protozoal parasites that cause pulmonary diseases are *Entamoeba histolytica*, *Leishmania donovani*, malarial parasites, *Babesia* spp and *Toxoplasma gondii*. The main symptoms in pleuropulmonary amebiasis are fever, cough, hemoptysis, right upper quadrant abdominal pain, and chest pain. Some patients may present with respiratory distress and shock. Lung abscess, hepatobronchial fistula, and bronchopleural fistula with pyopneumothorax have also been reported. Expectoration of anchovy sauce-like pus indicates amebiasis. Treatment is with metronidazole in a dosage of 750 mg orally 3 times a day for 7 to 10 days or with tinidazole in a dosage of 800 mg orally 3 times a day for 5 days. Visceral leishmaniasis is characterized by irregular fever, weight loss, enlargement of liver and spleen, and anaemia. Pneumonitis, septal fibrosis, pleural effusion, and mediastinal adenopathy are reported in patients coinfecting with HIV. Treatment of leishmaniasis includes amphotericin B (liposome formulations) and pentavalent antimonials. The main symptoms of malaria are fever, headache, and vomiting. Falciparum malaria is the most deadly type. The pulmonary manifestations in falciparum malaria range from cough to acute respiratory distress syndrome (ARDS). Acute lung injury and ARDS have also been reported to occur in infections with *P. vivax* and *P. ovale*. Chloroquine sensitive malaria can be treated with chloroquine. Artemisinin-based combination therapies are the best antimalarial drugs. Severe malaria can be treated with quinine dihydrochloride, quinidine gluconate, and injectable artemisinin derivatives. Patients presenting with ARDS require invasive mechanical ventilation. The symptoms in babesiosis are fever, drenching sweats, cough and tiredness, loss of appetite, myalgia, and headache. ARDS is an important pulmonary manifestation. Chest radiological features include bilateral infiltrates with an alveolar pattern and thickening of the septa. Treatment of babesiosis is with a combination of clindamycin (600 mg every 6 hours) and quinine (650 mg every 8 hours) for 7 to 10 days. The symptoms of toxoplasmosis are flu-like syndrome, enlarged lymph nodes, or myalgia. Toxoplasma pneumonia can manifest as interstitial pneumonia/ diffuse alveolar damage or necrotizing pneumonia. Toxoplasmosis can be treated with a combination of pyrimethamine (25-100 mg per day orally) and sulfadiazine (1-1.5 g 4 times a day orally) for 3 to 4 weeks. Many protozoal parasites such as *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, *Trichomonas* spp., *Lophomonas blattarum*, *Cryptosporidium parvum*, *Cyclospora cayatanensis*, *Encephalitozoon* spp., *Enterocytozoon bieneusi* and *Balantidium coli* that are known to be nonpathogenic to humans are reported to cause pulmonary diseases, especially in immunocompromised individuals.

AS13-1

Biomarkers for Diagnosis, Prognosis and Clinical Trial Design in ARDS

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Although plasma biomarkers are commonly used in the diagnosis and treatment of clinical problems such as acute coronary syndromes and heart failure, biomarkers for clinical management of ARDS are still under investigation. A variety of plasma biomarkers have been tested for their diagnostic and prognostic accuracy in patients with ARDS including biomarkers of endothelial activation and injury such as von Willebrand factor antigen and angiotensin-2 (Ang-2), biomarkers of lung epithelial injury such as surfactant protein D (SP-D), club cell protein 16 (CC-16), and receptor for advanced glycation endproducts (RAGE), biomarkers of inflammation such as interleukins 6 and 8 (IL-6, IL-8), biomarkers of alterations in coagulation and fibrinolysis such as protein C and plasminogen activator-inhibitor-1 and biomarkers of fibroblast activation such as procollagen peptide-3. In patients with sepsis, plasma levels of lung epithelial biomarkers outperformed other biomarkers for distinguishing patients with ARDS from those without ARDS. Similarly, in patients with established ARDS, a lung epithelial marker (SP-D) combined with IL-8 and age had strong prognostic performance. Interestingly, in patients with sepsis and ARDS, patients with direct causes of ARDS (pneumonia, aspiration) had higher levels of circulating lung epithelial (SP-D) markers whereas patients with indirect causes of ARDS (non-pulmonary sepsis) had higher levels of circulating endothelial injury markers (Ang-2). These findings suggest that the pathophysiology of direct and indirect lung injury may differ in regard to the primary site of lung injury. Biomarkers such as SP-D and Ang-2 may be useful in selecting patients with more epithelial or more endothelial injury, respectively, for potential new therapies that target these cell types.

AS13-2

High-resolution computed tomography in ARDS: What has it taught us?

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The clinical significance and limitation of high-resolution CT (HRCT) findings in ARDS were reviewed. Diffuse alveolar damage (DAD) is the pathological features of ARDS and is classified into three pathological phases (exudative, proliferative, and fibrotic). The HRCT findings correlate well with pathological phases of DAD, although it cannot detect early exudative phase. Traction bronchiolectasis or bronchiectasis within areas of increased attenuation on HRCT is a sign of progression from the exudative to the proliferative and fibrotic of DAD. Cystic changes associated with traction bronchiectasis are the sign of the fibrotic phase. Extensive HRCT abnormalities indicative of fibroproliferative changes were independently predictive of poor prognosis in patients with clinically early ARDS. Such findings were also associated with ventilator dependency and its associated complications (ventilator associated pneumonia, ventilator-associated lung injury, barotraumas) in patients with ARDS. Pulmonary fibroproliferation assessed by HRCT in patients with early ARDS predicts increased mortality with an increased susceptibility to multiple organ failure, including ventilator dependency and its associated outcomes.

AS13-3

Berlin definition of Acute Respiratory Distress Syndrome

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A valid operative definition of acute respiratory distress syndrome (ARDS) is essential to identify 'best-evidence' treatments; and to assist with prognostication, resource allocation and with the inclusion of patients with homogeneous characteristics into clinical trials.

The Berlin definition provides a conceptual model and definition criteria for ARDS and its severity spectrum. It combines a conceptual methodological model (feasibility, reliability and validity) with its empirical evaluation of large patient cohorts. The 'conceptual model' defines ARDS as a type of *acute* diffuse lung injury with a known predisposing *risk factor*; leading to a defined *clinical syndrome* within seven days of a known clinical insult, and it is associated to a group of *physiological derangements* and specific *pathological findings*. The identification of specific predisposing risk factors is a crucial step, and enables the exclusion of cardiogenic pulmonary oedema.

The Berlin definition unequivocally clarifies the nomenclature of the syndrome. The term 'acute lung injury' is replaced with mutually exclusive sub-categories of ARDS based on the degree of hypoxaemia: 1) 'mild ARDS' ($\text{PaO}_2/\text{FiO}_2$ 201-300 mmHg); 2) 'moderate ARDS' ($\text{PaO}_2/\text{FiO}_2$ 200-101 mmHg); 3) 'severe ARDS' ($\text{PaO}_2/\text{FiO}_2 \leq 100$ mmHg). The latter category has the highest accuracy to identify a homogeneous clinical and pathological subgroup with the highest mortality. In addition, the oxygenation criterion requires a minimum level of 5 cmH₂O PEEP. A PEEP >10 cmH₂O and $\text{FiO}_2 > 0.7$ were proposed as additional criteria to identify severe ARDS, but they did not increase predictive validity. The chest imaging criterion mandates bilateral opacities on frontal chest-X Ray (or CT) - not fully explained by effusions, lobar collapse or nodules. Although additional physiological parameters (e.g., static respiratory system compliance, corrected minute ventilation) did not improve overall predictive validity in 'severe ARDS' a compliance of <20 mL/cmH₂O or a corrected minute ventilation >13 L/min identified patients with the highest mortality.

It is very likely that future research will identify different accurate diagnostic and/or prognostic criteria for ARDS and this may lead to future revision of a definition for ARDS that better serves the clinical management and directs patient enrolment into research trials. In the meantime, the Berlin definition improves on the predictive validity for mortality of the AECC definition and clarifies both the conceptual model of ARDS and the definition criteria of the syndrome and of its spectrum of severity.

AS13-4

How to Manage Acute Respiratory Distress Syndrome?

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In a national study, the incidence of ARDS almost doubled but hospital mortality decreased during the 23 years of observation¹. Currently, in spite of the remarkable advancements in the understanding of its pathogenesis, the only effective therapeutic measure to decrease mortality is low tidal volume mechanical ventilation and prone ventilation² for severe ARDS cases. In extreme, life threatening cases, ECMO seems to serve as a bridge to recovery and enables protective lung ventilation. In adults with moderate-to-severe ARDS, early application of HFOV compared with an employment of a ventilation strategy of low tidal volume and high positive end-expiratory pressure, does not reduce, and may increase, in-hospital mortality³. In a recent randomized trial, the use of NMBA in ARDS patients showed a beneficial outcome. In addition, short-term infusion of cisatracurium besylate reduced hospital mortality and barotrauma, and did not appear to increase ICU-acquired weakness for critically ill adults with ARDS⁴. In hemodynamically unstable patients, dynamic monitoring of lung fluid balance needs to be implemented to guide the administration of fluids in ARDS patients⁵. Despite a putative beneficial role in the resolution of alveolar edema seen in preliminary studies, recent evidence has indicated significant detrimental effects associated with beta-2 agonist use in ARDS patients⁶. In summary, most ARDS patients die of multi-organ failure rather than irreversible respiratory failure, indicating that ARDS is closely associated with other organs by neurological, biochemical, metabolic, and inflammatory reactions. Moreover, the lungs may play an important role in the development of non-pulmonary organ failure in ARDS. So, early recognition of ARDS modified risk factors and the avoidance of aggravating factors during the patient's hospital stay (e.g., nonprotective mechanical ventilation, multiple blood product transfusions, positive fluid balance, ventilator-associated pneumonia, and gastric aspiration) can help decrease its incidence. In addition, efficient antifibrotic strategies are still lacking for patients with late stage ARDS. Therefore, new therapies that address the underlying pathophysiology are needed to reduce the mortality of patients with ARDS.

References

1. Sigurdsson MI, Sigvaldason K, Gunnarsson TS, Moller A, Sigurdsson GH. Acute respiratory distress syndrome: nationwide changes in incidence, treatment and mortality over 23 years. *Acta Anaesthesiol Scand* 2013;57:37-45.
2. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159-68.
3. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;368:795-805.
4. Alhazzani W, Alshahrani M, Jaeschke R, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. *Crit Care* 2013;17:R43.
5. Huh JW, Koh Y. Ventilation parameters used to guide cardiopulmonary function during mechanical ventilation. *Curr Opin Crit Care* 2013;19:215-20.
6. Gao Smith F, Perkins GD, Gates S, et al. Effect of intravenous β -2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet* 2012;379:229-35.

AS14-1

Cellular and molecular mechanisms of epithelial mesenchymal transition in airway epithelial cells under airway inflammation

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Mechanisms involved in lung fibrosis have been suggested to associate with continuous injury to epithelium and following abnormal wound healing process. Sustained injuries to the epithelium caused by various stimuli activate the epithelial cells, which produce several cytokines, chemokines, and growth factors. Those mediators promote chronic airway inflammation, which induce excessive repair process and provide fibrotic change in airway and lung. The cells related with fibrosis have been reported to consist of residual fibroblasts, bone marrow-derived progenitors of fibroblasts, and mesenchymal cells that underwent epithelial-mesenchymal transition (EMT) from epithelial cells. Transforming growth factor (TGF) β is one of the key mediators in the pathogenesis of fibrosis, since TGF- β regulates production of extracellular matrix proteins, proliferation, and differentiation of fibrosis and myofibroblasts. Also, TGF- β is a potent inducer of EMT and would play important roles on the fibrosis through EMT process. Since chronic inflammation induces abundant TGF- β and associates with the formation of fibrosis, inflammatory mediators would affect EMT process. Several inflammatory cytokines under chronic inflammation, such as tumor necrosis factor (TNF) α , interleukin-1 β , and TNF superfamily 14 (LIGHT), enhance TGF- β -induced EMT. The mechanisms of EMT in airway epithelial cells under chronic airway inflammation would be summarized.

AS14-2**New advances in lung stem cell and cancer stem cell fields**

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Stem cells are generally thought of as cells that are capable of unlimited self-renewal and can develop into more differentiated cell types. Stem cells have been shown to contribute to the repair and regeneration of injured lungs. These stem cells are resident in specific protected niches in the lung. Airway structure is complex due to the presence of several compartments and the diversity of their cellular phenotypes. There is evidence for the existence of multipotent stem/progenitor cells in all compartments.

Cancer stem cells have been identified as the initial cell type in the formation of carcinomas. They form all the cell types of a tumor by dividing asymmetrically to form daughter cells as well as more differentiated transient amplifying cells, resulting in the heterogeneity seen in tumors. The remarkable ability of lung cancer to recur despite definitive local and/or systemic therapy suggests the presence of cancer stem cells.

In my talk, we will review the current knowledge of the well characterized lung stem cell as well as the recently described not-yet well characterized ones. We will also discuss the recent effort to obtain differentiated airway epithelium from embryonic stem cells or iPS cells. Current research on human lung disease modelling using iPS cells will also be discussed. Finally, we will debate the candidate Stem/Cancer Stem Cells in the lungs and how they can be identified.

AS14-3**Molecular Mechanisms Underlying ALI/ARDS**

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ALI/ARDS is a clinical syndrome of non-cardiogenic pulmonary edema caused primarily by increased permeability to proteins across the endothelial and epithelial barriers of the lung. Increased-permeability pulmonary edema is primarily caused by injury to the lung endothelium and epithelium. Neutrophil-dependent lung injury has been well established as a major pathway in the pathogenesis of ALI/ARDS. Neutrophils degranulate and release several toxic mediators, including ROS, proteases, proinflammatory cytokines, and procoagulant molecules. The lifespan of mature neutrophils is between 6-12 h in peripheral blood. This short half-life limits neutrophil-induced tissue damage. In ALI/ARDS, delayed apoptosis provides activated PMNs with a longer lifespan, which in turn allows them to cause persistent tissue damage. Migration of neutrophils from circulation to lung is required to initiate alveolar inflammation. After becoming activated within the general circulation, some neutrophils lodge within the pulmonary microcirculation and then firmly adhere to endothelium via $\beta 2$ integrin. We demonstrated that neutrophils are activated through I κ B/NF- κ B pathway during adhesion to endothelial cells. Once reaching the alveoli, neutrophils are further activated by various cytokine released from alveolar macrophages.

Loss of epithelial cells is noted in ALI/ARDS, and the extent of this epithelial injury correlates with the clinical outcome. In addition to the injury caused by proteases and oxidants released from neutrophils, apoptotic cell death is recently thought to represent an important mechanism contributing to epithelial cell injury. Activation of the death receptor Fas, with subsequent activation of caspases, appears to be a potential mechanism mediating epithelial cell death.

In addition to direct cellular damage, inflammatory cytokines, including TNF- α , IL-1 β , and IL-6, are capable of alveolar coagulopathy. A large body of evidence has demonstrated that coagulopathy is an important event in ALI/ARDS. Enhanced intrapulmonary fibrin deposition results from increased activation of coagulation and inhibition of fibrinolysis, which correlates with severity of inflammation. Proteases in coagulation cascade interact with protease-activated receptors (PARs) to enhance inflammation. PAR-1, -3, and -4 are thrombin receptors, whereas PAR-2 can be activated by the TF-factor VIIa complex and factor Xa. Thrombin exerts proinflammatory effects through its regulation of cytokine transcription and release and is responsible for the increased production of IL-6, IL-8, and monocyte chemoattractant protein-1. We demonstrated that neutrophil elastase released in alveolus binds to PAR-2 in epithelial cells to enhance inflammation through IL-8 production. Thus, the complex crosstalk between inflammation and coagulopathy in ALI/ARDS is important in its pathogenesis.

AS14-4**Novel roles of T cells in airway remodeling**

James G. Martin

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Airway remodeling in asthma involves a variety of tissues but perhaps the change with the most significance for airway function is the increase in airway smooth muscle (ASM) mass. ASM mediates airway narrowing and an increase in mass may account for exaggerated airway narrowing and airway hyperresponsiveness. Most of the observed increase is associated with an equivalent increase in cell nuclei, indicating that proliferation of smooth muscle is likely to have accounted for the excess tissue mass. Hypertrophy is reported in some subjects with asthma but is less frequently encountered. ASM increases in proportion to asthma severity. Animal models have implicated a variety of biochemical mediators in smooth muscle hyperplasia, and in particular cysteinyl leukotrienes. However the epidermal growth factor receptor (EGFR) is also involved in the mechanism of remodeling and may be transactivated downstream of the EGFR. ASM in the airways of asthmatic subjects is infiltrated by T cells suggesting a possible role for these cells in muscle growth. In vitro experiments demonstrate that T cells in contact with muscle cells trigger muscle proliferation when T cells are activated. This proliferation is also EGFR-dependent. Activated T cells synthesize ligands for the EGFR, in particular heparin binding-EGF (HB-EGF). IL-17-expressing CD4+ T cells are most strongly associated with HB-EGF expression. Gamma-delta T cell receptor bearing cells are also frequently associated with HB-EGF expression. These studies suggest a novel trophic role for T cells, which may contribute to smooth muscle growth and airway hyperresponsiveness in asthma.

AS15-1**Relevance of innate immunity in childhood asthma**

James G. Martin

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Innate immunity has multiple roles in the induction, maintenance and triggering of asthma. Much of the focus in research has been on allergy as a trigger for asthma. However respiratory viral infections, in particular rhinovirus, are the most frequent cause of visits to emergency rooms for acute asthma in children and adults. Other viruses such as respiratory syncytial virus and metapneumovirus are also common infecting agents. The respiratory epithelium appears to be the principal target of these viruses. Children are more likely than adults to be infected with more than one virus concurrently. Once the epithelium is infected with these viruses pro-inflammatory molecules are synthesized and inflammatory cells are recruited to the site. Prolonged lower respiratory tract symptoms are a feature of the asthmatic and are attributed to deficient epithelial responses to infection with failure to produce antiviral proteins such as the type I and III interferons. These deficient responses are associated with prolonged viral replication in airway epithelial cells and are postulated to account for the lower respiratory tract symptoms in asthmatic subjects. Eosinophils impair interferon production by epithelial cells in culture, providing a possible mechanism by which innate immunity may be influenced by eosinophilic inflammation. Innate immune effector cells may also trigger asthma. Evidence is derived largely from animal models that establish the plausibility of such mechanisms. Innate lymphoid cells are emerging as possible mediators of non-allergic asthma phenotypes. Airway insults may lead to activation of natural killer T cells that are now recognized to react to glycolipid in the context of an invariant T cell receptor, CD1d. These cells may produce interleukin (IL)-5 and IL-13, typical cytokines associated with allergic inflammation and responsible for airway eosinophilia and airway hyperresponsiveness, respectively. Other naive T cells called nuocytes that may respond to epithelial-derived cytokines such as IL-33 that may then drive the expression of IL-13. Again models have shown that airway hyperresponsiveness may be driven through cells by this pathway. Other innate T cells such as those bearing the gamma delta T cell receptor may also drive asthma in models. Dendritic cells which bridge innate and adaptive immune mechanisms are also important mediators of airway inflammation and modulation of their function through Toll-like receptors and other pattern recognition receptors may influence the response to allergens. As our knowledge of innate immune mechanisms increases the varied clinical presentations of asthma become less perplexing.

AS15-2

Ontogeny of innate immunity in the lung-an overview

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Early childhood is characterised by relative immaturity of the immune system and heightened susceptibility to infections and allergic sensitisation. The nature of these developmental deficiencies, and the way in which they change in response to age, genetic and environmental exposures is only partially understood.

This presentation will discuss current knowledge of innate and adaptive immune function, T-cell polarisation, immune regulation, tolerance and host defence in childhood. Examples will be presented of the ways in which immune function is altered in diseases such as asthma, protracted bacterial bronchitis and chronic suppurative lung disease.

Better understanding of the processes governing immune system development in children is a key to better understanding many of the diseases that affect lung health during childhood.

AS15-3

Innate immunity in children with protracted bacterial bronchitis

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Protracted bacterial bronchitis (PBB) is a pediatric condition clinically defined as (a) the presence of isolated chronic (>4 weeks) wet cough, (b) resolution of cough with antibiotic treatment and (c) absence of pointers suggestive of an alternative specific cause of cough. This condition has only been adequately characterized (by broncho-alveolar lavage and clinically) recently. PBB has been officially recognized by the cough guidelines of Australia, the Britain and the USA.

Children with PBB are typically young (median age 3 years). Some parents may also report a 'wheeze' which is actually a rattle (reflective of airway secretions) and not a true wheeze.¹ In PBB the child's cough resolves only after a prolonged course (at least 10-14 days) of appropriate antibiotics.² Common respiratory pathogens found are *H. Influenza*, *S. Pneumoniae* and *M. catarrhalis*. Their chest x-rays may be reported as 'normal' but usually show peribronchiolar changes. In some children, co-existent trachea-bronchomalacia is present.

We have examined several aspects of innate immunity in children with PBB. The bronchoalveolar lavage (BAL) of children with PBB have marked airway neutrophilia and increased IL-8 and active matrix metalloproteinase-9.³ Airway TLR-2 and TLR-4 mRNA expression, as well as human β -defensin-2 and mannose-binding lectin levels are also elevated in children with PBB when compared to controls.^{3,4} In contrast, airway surfactant protein-A are not elevated and the ability of BAL cells to respond to stimuli are unlikely to be deficient. PBB is also characterised by increased IL-1 β pathway activation. IL-1 β correlated with BAL neutrophilia, and the duration and severity of cough symptoms.

References

1. Chang AB, Redding GJ, Everard ML. State of the Art - Chronic wet cough: protracted bronchitis, chronic suppurative lung disease and bronchiectasis. *Pediatr Pulmonol* (2008) 43:519-31.
2. Marchant JM, Masters IB, Champion A, Petsky HL, Chang AB. Randomised controlled trial of amoxicillin-clavulanate in children with chronic wet cough. *Thorax* (2012) 67:689-93.
3. Marchant JM, Gibson PG, Grissell TV, Timmins NL, Masters IB, Chang AB. Prospective assessment of protracted bacterial bronchitis: airway inflammation and innate immune activation. *Pediatr Pulmonol* (2008) 43:1092-99.
4. Chang AB, Yerkovich ST, Gibson PG et al. Pulmonary innate immunity in children with protracted bacterial bronchitis. *J Pediatr* (2012) 161:621-25.

AS15-4

Innate immunity responses to common respiratory pathogens in the upper airways

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Chronic rhinosinusitis and acute otitis media (AOM) is one of the most common infectious diseases in children, and the peak incidence of this disease occurs in early childhood and is associated with hearing loss, delayed speech development, permanent middle ear damage, and mucosal changes. Non-typeable *Haemophilus influenzae* (NTHi) is considered one of major pathogens in upper airway.

The innate immune system is important for the elimination of bacteria from the respiratory tract. In recent years, Toll-like receptors (TLRs) have been emerged as the key regulators of innate immune responses to infection in mammals. To date, 13 different members of the TLR family have been identified in mammals. In our department, we are investigating the innate immunity responses to common respiratory pathogens such as NTHi in the upper airways, especially in relation to TLR4. We developed an AOM murine model induced by NTHi inoculation into the middle ear of C3H/HeJ mice which come into existence spontaneously and have nonfunctional TLR4, and normal wild-type C3H/HeN mice, and we showed the importance of protective immunity via TLR4 in the early phase of inflammation of the middle ear. To investigate the effect of TLR4 to acquired immune responses, we investigated the kinetics of humoral and related cellular responses when C3H/HeJ mice and C3H/HeN mice are immunized intranasally with outer membrane proteins (OMP) from NTHi, we showed that TLR4 enhanced mucosal and systemic antibody secretion, the migration of antibody producing lymphocytes to the mucosa during the course of intranasal immunization. Additionally, we also explored the potential of a clinical new strategy, which induces the innate immune response via TLR4, and investigate the mechanisms of protective innate immunity induced by TLR4. We evaluated the effectiveness of monophosphoryl lipid A (MPL), such as TLR4 agonist, for clearance of bacteria from the nasopharynx and the kinetics of cellular responses when MPL was administered intranasally to mice before challenge with NTHi and *M. catarrhalis*. In this study, we showed innate immune stimulation with MPL prior to bacterial challenge may be effective for eliciting clearance of both NTHi and *M. catarrhalis* from the nasopharynx.

Based on our results, the immune responses via TLR4 to common respiratory pathogens in the upper airways plays an important role for acquired immune responses as well as innate immune responses.

AS16-1

Thin bronchoscopy for peripheral pulmonary nodules

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Bronchoscopy has been widely used for the diagnosis of peripheral lung lesions, however, the diagnostic yield of conventional bronchoscopy for peripheral lung lesions, for small lesions in particular, has not been satisfactory. Recent modification of this procedure using some new devices, such as ultrathin bronchoscopes, endobronchial ultrasound or navigation systems dramatically increased the diagnostic yield of bronchoscopy, and seems to be reasonable as a first diagnostic test in terms of accuracy and safety. The idea of using thinner bronchoscopes for the evaluation of peripheral lung lesions is not novel. In fact, bronchoscope manufacturers have continued efforts for developing thinner bronchoscopes with a larger working channel and higher visibility since flexible bronchoscopes were invented. The advantage of ultrathin bronchoscopes for evaluating peripheral lung lesions is the good bronchial selectivity and smooth maneuverability in the small airway. So, ultrathin bronchoscopy is particularly useful when it is combined with image guidance devices such as navigational bronchoscopy, CT guidance or endobronchial ultrasound. The combination of ultrathin bronchoscopy and navigational bronchoscopy seems reasonable for making the best of mutual abilities, as ultrathin bronchoscopes can follow the bronchial route provided by navigational devices. Unfortunately, the now available thin/ultrathin bronchoscopes have a limited-sized working channel less than 1.2 mm, through which the ultrasound probe cannot pass. However, some studies have reported on the usefulness of combination of a prototype thin bronchoscope with 1.7-mm channel and a 1.4-mm thin ultrasound probe for evaluating peripheral lung lesions. In the near future, ultrathin bronchoscopes with a working channel large enough for an ultrasound probe to be passed through, will be developed. Multimodal bronchoscopy using an ultrathin bronchoscope, endobronchial ultrasound and navigation device will be available in clinical practice, and it may lead to enhanced diagnostic yield.

AS16-2

SPN: EMB or TTNA, which is your choice?

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Lung cancer is still the most common cause of cancer deaths in males and females. The death rate in females continues to increase. The prevalence of smoking is less, but this will not have any desirable impact on death rates for many years. From the 60's to the 90's peripheral non-small cell lung cancer (Adenocarcinoma sub-group) are at increased incidence rate due to the use of filter in smoking and a lung delivery of smaller cigarettes particles. In the era of screening for early diagnosis of lung cancer using low radiation chest CT the physician is face with the dilemma of what approach to choose to make the diagnosis of small peripheral nodules (SPN).

The alternative for the pulmonologist to choose for the diagnosis of small peripheral nodules or opacities are to perform the biopsy by bronchoscopy or transthoracic needle aspiration/biopsy (TTNA) CT guided. Real-time Electromagnetic navigation bronchoscopy enables guidance for transbronchial biopsies for SPNs. (Schwarz Y. Clin Chest Med. 2010 Mar;31(1):65-73). EMN has a diagnostic yield of 71% and a pneumothorax rate of 1.5%. CT guided biopsy approach have a higher yield but also risk for complications as (pneumothorax) especially in the presence of emphysema, which is high in smokers. The pooled sensitivity of TTNA for the diagnosis of lung cancer is 90%, but pneumothorax rate is higher than 30%. Adequate tissue acquisition for histologic and molecular characterization of NSCLCs is paramount. The condition of the patient's lung and pulmonary function are the guide for choosing the appropriate diagnostic minimal invasive approach.

WS1

Lessons learned from 10 years' collaborations in Japan—evolution and perspectives from professional society viewpoint

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Academic professional organizations such as the Japanese Respiratory Society (JRS) are charged with identifying and providing the needs of patients with respiratory disease in maintaining better QOL and survival. JRS has launched the Japan Federation of Patient Organizations for Respiratory Diseases (J-PORD) in 2004 to work in close collaboration with patients with respiratory disease to meet their unmet needs. Before the development of these activities, JRS became officially chartered organization to open for the public in 2002. Major collaborative actions and achievements with J-PORD can be summarized as following, (1) collaborated on the national survey of physicians and patients with respiratory disease. The Japanese white paper for home respiratory care was published in 2005 and 2010 to clarify the demands regarding the needs of patients and actions health care professionals should take, (2) implemented pulmonary rehabilitation (PR) and self-management education and JRS published practical guidelines for health providers in collaboration with other societies. PR and six-minute walk test were reimbursed by the Health, Labor and Welfare Ministry from 2006 and 2012, respectively, (3) established Japan Lung Day to increase public awareness of respiratory disease and patients with respiratory disease, and also to put force antismoking campaigns, (4) launched the Federation of Diet Members to promote strategy for respiratory related disease: COPD caucus, (5) keep conducting the clinical studies to improve welfare especially for disability category and long-term care insurance of patients with respiratory disease, and (6) keep making actions to create a system of safe, anxiety-free, and disaster-relief home respiratory care. This presentation will address a summary of these actions and achievements with J-PORD in the past 10 years and perspective for the next 10 years.

WS2

Lessons learned from 10 years' collaborations in Japan: Evolution and perspectives from patient organization viewpoint

Kazuko Tohyama

President of NPO J-Breath, JPORD Adviser, Japan

Japan Federation of Patient Organizations for Respiratory Diseases (JPORD) started in 2004, from a call for roundtable meeting of patient organizations by the Japanese Respiratory Society (JRS). Until then, there was no cooperation among the respiratory disease patient organizations. Our JPORD has been focusing on adult chronic respiratory disease, mainly on patient on LTOT and COPD. Our first task with JRS was to do survey on patients with chronic respiratory disease, especially on LTOT patients or patients on home mechanical ventilation, which revealed unmet needs of 2,716 patients. It became a chapter of White Paper. The launch of Federation of Diet Members Promoting Strategy for Respiratory Related Disease is another remarking achievement for JPORD and JRS collaboration. Through this Diet Member Federation, we submitted petition for better subsidies for patients on LTOT with 50,000 signatures and petition for tobacco tax rise directly to the Minister of Health and Labor.

As working as JPORD, we are now able to send public messages effectively. For example, there was a long term black out in wide area in the Great Eastern Japan Earthquake in March 2011, LTOT patients suffered from lack of oxygen tanks in black out area and planned black out area. We sent out message via web sites and mass-media what patients should do in such circumstances. After the quake, we made brochures out of this experience and it is on our web-site now. There were many advantages of patient organization and scientific professionals working together for the common aim of better lung health and treatment.

Our perspective for next 10 years is that provincial patient group and scientific professionals should work more closely. The awareness of lung health is still not enough in Japan. The collaboration will give us more opportunity to receive effective integrated care such as pulmonary rehabilitation and self-management programs in our resident area in the near future.

WS3-2

Contribution of Indonesian Pulmonologists to the Indonesian Asthma Foundation Activities

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The Indonesian Asthma Foundation is Non-Government Organization founded by community leaders and some pulmonologists who care for patients with asthma on February 26, 1986 in Jakarta. The aim of this foundation is to support asthma patients cope with the disease so they can live normally. The foundation periodically conducts symposia for the layman to raise awareness about asthma and to educate asthma patients. The lectures are given by pulmonologists. In 1987 this foundation built an asthma building. Funds to construct the building were obtained by carrying out fundraising by holding a golf tournament, and charity night. On January 20-30, 1994 the foundation held a workshop to create an exercise for patients with asthma. The workshop participants were pulmonologists from different part of the country, the sports physicians, medical rehabilitation physicians, and physiotherapist. The workshop resulted in a gymnastic movements named Indonesian Asthma Gymnastic that scientifically beneficial for asthma patients to improve respiratory muscle and increase physical fitness. In 2003 this Gymnastic was revised, the period of exercise become one hour, fifteen minutes longer than the previous one. Some researches have been conducted by Pulmonology resident doctors to evaluate the efficacy of asthma gymnastic on lung function, symptoms, asthma drug consumption, and quality of life of asthma patients.

Indonesian Asthma Foundation has 17 branches all over the country. Its branch has several asthma clubs that conduct the Indonesian Asthma Gymnastic regularly. There is a pulmonologist at every club asthma as a supervisor who oversees the activity of gymnastics. He also gives a lecture on asthma every month to increase patients' knowledge on their disease. In Jakarta there are 24 asthma clubs with the number of members of more than 1,000 asthma patients. When there are natural disasters such as floods and volcanic eruptions, the foundation and pulmonologists jointly organized medical aid to help the victims of the disaster. To commemorate the World Asthma Day, in every branch, every year the foundation cooperate with pulmonologists perform mass gymnastics followed by more than 1,000 participants. In addition to carrying out gymnastics sometimes they held fun bike, free spirometry measurement, and conducting Asthma Control Test examination for asthma club members. Prior to World Asthma Day, they also conducted a radio or television talk show to raise public awareness on asthma; moreover parallel symposia for general physicians and public were also conducted.

WS3-7**Sharing common aim for better respiratory care-
Professional Societies' and Patient Organizations**

Ki-Suck Jung

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Historically, COPD patients have not engaged in organized patient advocacy activities because of low awareness of this disease. But there is an increasing global realization that COPD patients need to work together to advocate for improved COPD care and prevention. As a result, the International COPD Coalition (ICC), a global COPD patient organization, was founded in 1999. The mission of ICC is to develop a coalition of COPD Patient Organizations worldwide for health promotion among COPD patients and COPD education. In 2009, the ICC announced 'The COPD Patient's Global Bill of Right'. It consists of 7 rights that are divided between responsibilities of caregivers and responsibilities of society itself. Most of these rights are a shared responsibility. Therefore, it is important to share the common aims for respiratory care between professional society and patient organization. In many countries, patient organizations have worked with scientific and clinical communities to improve awareness, public policy and advancing research for COPD.

In this lecture, we will review the global effort to promote the cooperation between the medical professionals and patient organizations and share the experiences in Korea.

WS4**A GLOBAL UPDATE ON COPD AWARENESS AND ACTION AMONG PATIENTS AND THE PUBLIC**

Lawrence D Grouse

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An omnibus study of COPD awareness in 2001 found that global public awareness of COPD was very low. It ranged from 4% in Brazil to about 10% in Germany. Today, a global survey of ICC national leaders showed an average COPD awareness of 20-30%; however, developing countries had a much lower average COPD awareness (0-10%). 60% of country leaders believe that COPD awareness is increasing. Norwegian colleagues increased COPD awareness from 27% to 78% through a national COPD awareness initiative from 2002 to 2005 involving national television PSAs and government educational activities. A global survey of COPD patient organizations showed that education, information, awareness campaigns, public policy, lobbying, and research were the major activities that these groups conducted; however, fewer than 50% of organizations had sufficient funding to organize such activities and in developing countries less than 25% could. From 20%-50% of both developed and developing countries have respiratory patient organizations, but very few COPD patient organizations exist in developing countries compared to developed countries. In another study of which educators provide respiratory patient education, respiratory specialists provide the most; primary care physicians provide much less; 80% of COPD patient organizations provide patient education in developed countries but less than 20% provide education in developing countries. 63% of global deaths result from non-communicable diseases. 80% of global deaths occur in low and middle income countries and 90% of global deaths from COPD occur in developing countries. The critical need for COPD patient organizations in developing countries could be alleviated by a concept to improve respiratory patient education and COPD prevention developed by the WHO's GARD program: Patient Micro-Organizations built locally and from the ground up. To deal with these problems, ICC believes that there needs to be a partnership between 4 key medical groups to benefit COPD patients: COPD patient organizations, health care professionals, suppliers, and governments and their health ministries. ICC's COPD patient's bill of rights, which has been translated into multiple languages and used worldwide, includes the right to receive early and accurate diagnosis, the right for education about COPD, the right for support and understanding, the right to receive beneficial treatment, the right to society's involvement and investment in their welfare, their right to advocate for improved COPD care and COPD prevention, and the right to safe air and environment.

GINA1

New recommendations: asthma management for adults

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The Global Initiative for Asthma (GINA) report provides a global strategy for asthma management that can be adapted to national and local needs. A major revision of the report, to be published in 2014, comes at a time of transition in our understanding of chronic airway disease, an expanding evidence base in respiratory research, increasing interest in individualised health care, and growing attention to utility and feasibility for end-users of the report across the spectrum of clinical practice, research, industry and government.

Asthma is a heterogeneous disease, with a range of underlying pathophysiological mechanisms producing common clinical features of variable symptoms and variable airflow limitation. The GINA 2014 report focusses on achieving good symptom control and minimising future risk, in partnership with the patient. At a population level, the 'preferred' controller medication option for each treatment step is based on group mean data for efficacy and effectiveness, together with safety, availability and cost. However, for individual patients, the choice of controller medication also takes into account patient characteristics (phenotype) that may predict their treatment response, the patient's own preferences, and practical issues such as their ability to use the medication and their likely adherence.

The GINA 2014 report provides new recommendations about initial controller treatment, an updated stepwise treatment algorithm based on symptom control and risk factors, and options for stepping down treatment once good control is achieved. For patients with poor asthma control, there is an emphasis on confirming that symptoms are due to asthma and on identifying and addressing common issues such as poor adherence and poor inhaler technique, before any step-up is considered. There is a continued focus on asthma self-management education, including self-monitoring, a written asthma action plan, and regular medical review, and an increased emphasis on health literacy.

Non-pharmacological strategies are provided to assist in improving symptom control and reducing future risk; these include smoking cessation, weight loss for obese patients, physical activity, and avoidance strategies for triggers such as allergens and pollutants. Patients should be evaluated for comorbidities such as gastro-oesophageal reflux, obstructive sleep apnoea and anxiety or depression, as these may contribute to respiratory symptoms and impaired quality of life, and sometimes to poor asthma control. The GINA report also features a new chapter that will be co-published with GOLD, about the asthma-COPD overlap syndrome.

GINA2

Asthma Management for Young Children

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The GINA management aims in young children are the same as the aims in older children and adults: Achievement control of the manifestations of the disease and reduction of future risks. Almost 80% of pediatric asthmatic patients start having symptoms during the first 5 years of life and typically wheezing is associated with upper respiratory tract infections. However, many young children *without* asthma may also wheeze with viral infections and deciding when the presence of wheezing with infections is a clinical presentation of childhood asthma is difficult. Decisions on who should be treated have to be based on symptom patterns and symptom severity combined with a careful clinical assessment of family history and physical findings or a therapeutic trial of treatment with short-acting bronchodilators and inhaled corticosteroids for 8 - 12 weeks.

The pharmacologic intervention strategy should be developed in partnership with the family/caregiver. Inhaled corticosteroids (ICS) and leucotriene modifiers have been shown to have clinical effects in children 5 years and younger (Evidence A). However, maintenance treatment with inhaled corticosteroids (ICS) is the most effective way to control symptoms and prevent asthma exacerbations in these age groups (Evidence A). A pressurized metered-dose inhaler (MDI) with a valved spacer (with or without a face mask, depending on the child's age) is the preferred delivery system. If the treatment is ineffective and the adherence and inhalation technique good the diagnosis should be re-evaluated and differential diagnoses considered.

The role of intermittent treatment with ICS or leucotriene modifiers during worsening of symptoms needs more studies in young children. Oral steroids should be restricted to the treatment of acute, very severe exacerbation.

Continued need for asthma treatment, inhalation technique, adherence and growth should be regularly assessed (around every 6 months) in children under age 5 and all families/caregivers should be provided with a written Home Action Plan.

GINA3**GINA Management Strategy: Prevention and Management of Acute Asthma.**

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All patients with asthma have the potential to experience an asthma exacerbation. All of these attacks even among mild asthma patients may be associated with a risk of death. Maintenance controller treatment of asthma especially with regular use of inhaled corticosteroids (ICS) is the most effective way to prevent asthma exacerbations (Evidence A). All patients require education and the provision of a written action plan (Evidence A). Depending upon the usual maintenance treatment taken a patient will have different responses to take with a worsening in their asthma. On ICS a quadrupling of the maintenance dose will usually be effective (Evidence B). Subjects on a formoterol containing combination inhaler with an ICS can increase their maintenance dose to prevent progression (Evidence A) while patients with a salmeterol containing maintenance treatment may use increasing doses of a beta-agonists and the addition of a course of oral corticosteroids (Consensus). If despite these measures a patient progresses to a more severe exacerbation they should be triaged and if necessary admitted to ICU. Measurement of lung function and arterial blood gases should be used to monitor the severity of the acute asthma attack as indicated. Treatment should include bronchodilatation with regular short acting beta agonists and ipratropium bromide (Evidence A). All patients should receive controlled oxygen therapy as needed to maintain oxygen saturation greater than 92% (Evidence A). Most patients will require a short course of oral corticosteroids (OCS) (Evidence A). There is some evidence for the use of high dose ICS in acute asthma but issues of cost and the likelihood of a response to OCS precludes its routine use (Evidence B). If not already on a controller maintenance therapy a patient recovering from an acute exacerbation should have this initiated (Evidence A). Patients with more severe attacks should receive magnesium sulphate 2 grams intravenously (Evidence B). There is no role for the routine use of antibiotics, rehydration and sedatives (Level A). With effective inhaled bronchodilator therapy there is no role for the routine use of intravenous beta agonists or theophylline. Leukotriene receptor antagonist therapy has not been extensively studied in acute asthma and its role is not well defined. Patients who achieve an FEV1 of 60% or greater of their best or predicted can be safely be discharged. All patients should be followed up and where appropriate adjustments be made to their maintenance treatment.

LS1-1**Improving lung function through dual bronchodilation in COPD**Jørgen Vestbo^{1,2}Institute of Inflammation and Repair, University of Manchester, Manchester, UK¹, Department of Respiratory Diseases, University of Southern Denmark, Odense, Denmark²

Long-acting bronchodilators are the cornerstone of treatment for chronic obstructive pulmonary disease (COPD) due to their beneficial effects on lung function, dyspnea, health-related quality of life, hyperinflation and exercise capacity, as well as their potential to reduce exacerbations.¹ However, many patients remain symptomatic despite treatment with either a long-acting β_2 -agonist (LABA) or a long-acting antimuscarinic agent (LAMA).²

LABAs and LAMAs provide bronchodilation via complementary modes and sites of action.³ Combining different classes of bronchodilators may, therefore, provide benefits beyond that which is achievable with either drug alone. Indeed, various clinical studies have demonstrated that the free combination of a LABA plus LAMA provides superior improvement in lung function,⁴ symptoms⁵⁻⁷ and exacerbations⁸ versus treatment with either a LABA or LAMA alone.

QVA149 is a once-daily, fixed-dose combination of indacaterol and glycopyrronium, two previously approved 24-hour bronchodilators. Indacaterol is a fast-acting, once-daily LABA, and glycopyrronium is a selective, fast-acting, once-daily LAMA. QVA149 is now approved in Japan and the EU for the treatment of patients with COPD, following the extensive IGNITE Phase III clinical program, which was conducted in more than 5,700 patients.

This presentation will provide an overview of the clinical evidence supporting the rationale for dual bronchodilation and explore some of the data that emerged from the QVA149 IGNITE program. Specifically, the effects of QVA 149 on improvements in lung function versus the monocomponents indacaterol and glycopyrronium, as well as versus current standards of care, will be described. Safety data from the IGNITE program will also be presented. Together, these data support the use of fixed-dose combinations as a treatment option for patients with COPD.

References

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). Updated 2013. Available from: <http://www.goldcopd.org/> (last accessed 19 September 2013).
2. Dransfield et al. *Prim Care Respir J* 2011;20:46-53.
3. Cazzola, Molimard. *Pulm Pharmacol Ther* 2010;23:257-67.
4. Mahler et al. *Thorax* 2012;67:781-8.
5. Tashkin et al. *COPD* 2009;6:17-25.
6. Tashkin et al. *Respir Med* 2008;102:479-87.
7. van Noord et al. *Respir Med* 2010;104:995-1004.
8. Vogelmeier et al. *Respir Med* 2008;102:1511-20.

GMCC_168051. NP4_JP1310142392.

LS1-2

Measuring the impact of dual bronchodilation on COPD patient outcomes

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Chronic obstructive pulmonary disease (COPD) has a major impact on patients' lives: COPD exacerbations affect patients' ability to work and continue with normal life,¹ and significantly accelerate the rate of lung function decline.² Symptoms of COPD also affect activities such as ability to exercise and socialize, and can cause depression, anxiety and loss of independence.^{3,5} Thus, it is essential that new COPD therapies demonstrate improvements in patient-reported outcomes, in addition to lung function.

Bronchodilators are central to the management of COPD symptoms management,⁶ but many patients remain symptomatic despite treatment with a long-acting β_2 -agonist (LABA) or a long-acting antimuscarinic agent (LAMA).⁷ LABAs and LAMAs have complementary mechanisms of action,⁸ suggesting dual bronchodilation may produce benefits beyond those achievable with mono-bronchodilator therapy.

QVA149, the once-daily, fixed-dose combination of indacaterol (once-daily LABA) and glycopyrronium (once-daily LAMA), is now approved in Japan and the EU following an extensive Phase III clinical development program (IGNITE). In addition to improving lung function,⁹ QVA149 significantly reduced moderate-to-severe exacerbations, compared with glycopyrronium ($p=0.038$), and reduced all exacerbations, compared with both glycopyrronium and open-label tiotropium ($p=0.003$).¹⁰ Rescue-medication use was significantly reduced with QVA149 versus glycopyrronium and tiotropium (both $p\leq 0.001$).¹⁰ QVA149 significantly improved dyspnea, as measured by an increase in transition dyspnea index focal score ($p\leq 0.05$), compared with tiotropium.¹¹ Furthermore, QVA149 resulted in a significant improvement in health status (St George's Respiratory Questionnaire total score), compared with tiotropium and glycopyrronium.^{9,10}

This presentation will provide an overview of some of the QVA149 IGNITE program data, including the effects of QVA149 on COPD symptoms, exacerbations and health status versus its mono-components, and current standards of care. After reviewing this evidence, the presentation will explore the potential role of dual bronchodilation within the GOLD 2013 treatment strategy guidelines⁶ by considering which patients may benefit from dual bronchodilation and those who may gain from additional incremental benefit provided by dual bronchodilation versus current therapies.

References

1. Miravittles *Respir Med* 2007.
2. Halpin *Eur Respir J* 2012; Abstract 194.
3. Rennard *Eur Respir J* 2002.
4. Barnett *J Clin Nurs* 2005.
5. Cleland *Fam Pract* 2007.
6. GOLD guidelines. Updated 2013.
7. Dransfield *Prim Care Respir J* 2011.
8. Cazzola *Pulm Pharmacol Ther* 2010.
9. Bateman *Eur Respir J* 2013; in press.
10. Wedzicha *Lancet Respir Med* 2013 (New Drug Application Dossier).
11. Mahler *Am J Respir Crit Care Med* 2013; Abstract A6070.

GMCC_168051. NP4_JP1310142392.

LS2

Current asthma control and future risk of exacerbations-what can we do to manage our patients effectively?

Claus Vogelmeier

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Profile

Claus Vogelmeier is Professor of Medicine and Head of the Department for Pulmonary Medicine at the Philipps-University of Marburg, Germany. After qualifying in medicine from the University of Munich, Dr. Vogelmeier started his professional career at the Hospital of the University of Munich.

He is board certified in Internal Medicine, in Pulmonary Medicine, in Cardiology and in Allergology. Dr. Vogelmeier spent two years as a Postdoctoral Fellow at the Pulmonary Branch of the National Heart, Lung and Blood Institute, Institutes of Health in Bethesda, MD, USA. He was nominated Professor of Medicine at the Philipps-University of Marburg in 2001.

Claus Vogelmeier is an active member of several respiratory societies including the American Thoracic Society and the European Respiratory Society. From 2002 to 2008 he was Section Editor of the *European Respiratory Journal*. From 2009 till 2011 he was president of the German Respiratory Society. Also in 2009 he became Chairman of the German Asthma and COPD Network. Since 2010 he is a member of the Science and the Writing Committee of GOLD.

He has a long-standing scientific and clinical interest in obstructive lung diseases with topics ranging from pathogenetic aspects to novel diagnostic methods and clinical studies.

LS3

Are we making progress? chemotherapy for advanced non-small cell lung cancer

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Efficacy of cytotoxic chemotherapy appears to be modest. However, "conventional" chemotherapy has achieved what EGFR-TKI or ALK inhibitors have not. Just let me remind you, for example, that post-operative adjuvant chemotherapy has significantly increased the "cure" rate, whereas it is not yet clear whether target-based drugs could "cure" a single patient. We must not underestimate the power of chemotherapy, nor should we run to medical nihilism, such as that everything is equal as long as it is platinum-based. What we need to do: properly interpret the results of clinical trials, and optimize our patient care.

LS4

Current & Future Treatment Strategy in EGFR gene mutation positive NSCLC.

In the past 10 years, the treatment strategy of non-small-cell lung cancer has dramatically changed. The discovery of EGFR gene mutations, the routine testing of lung cancers for these EGFR mutations, and initial treatment with EGFR-tyrosine kinase inhibitors have all contributed to this progress. Several Phase III trial have now been conducted and all of them demonstrate superiority of EGFR-tyrosine kinase inhibitor over platinum-based therapy. But even with EGFR-TKI, most patients progress in 10 to 12 months. New issues are how we can prolong the treatment duration by treating after RECIST progression and how we can effectively treat the patients after EGFR-TKI failure. In this seminar, these future directions will be discussed based on the activity in CTONG group and Dana-Farber Cancer Institute.

Chair

Prof. Kazuhisa Takahashi

Professor and Chairman, Division of Respiratory Medicine, Juntendo University Faculty of Medicine & Graduate School of Medicine

Speakers

Bruce E. Johnson, M.D.

Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, USA

Yi-Long Wu, M.D.

Professor of Guangdong Lung Cancer Institute/Guangdong General Hospital. Guangzhou, PR China

LS5-1

Fluticasone and formoterol: a powerful partnership

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Fluticasone propionate is a highly effective corticosteroid that is widely used in the treatment of asthma which suppresses airway inflammation mainly through repression of activated inflammatory genes. Corticosteroids are very effective in suppressing the transcription factor GATA3, which regulates the expression of T helper 2 cytokines, such as interleukins-4, -5 and -13 (Th2 cytokines). Formoterol is a rapidly acting long-acting β_2 -agonist (LABA), which provides additional benefit in asthma control when added to an inhaled corticosteroid. LABA have complementary effects to inhaled corticosteroids in the treatment of asthmatic inflammation, which explains how LABA can improve lung function and symptoms beyond the maximal effects of a corticosteroid. There are important interactions between corticosteroids and LABA. Firstly, corticosteroids increase the expression and coupling of β_2 -adrenoceptors and this may enhance the effects of β_2 -agonists on airway smooth muscle and other cells and also prevent down-regulation and uncoupling of β_2 -receptors, which may occur with prolonged administration of β_2 -agonists, particularly LABA. Secondly, LABA enhance the effects of corticosteroids by increasing the translocation of glucocorticoid receptors (GR) from the cytoplasm to the nucleus, which may be impaired in asthma because of phosphorylation of GR as a result of inflammatory mediator activation of MAP kinases. Formoterol activates phosphatases which dephosphorylate GR resulting in increased nuclear translocation and thus enhanced effects of corticosteroids. Thus corticosteroids and LABA enhance each other's effects. Furthermore, administration of both drugs together from the same inhaler may be advantageous as the distribution of inhaled drugs in asthma is patchy and variable so that only simultaneous administration can ensure that the two drugs are delivered simultaneously to cells to allow these molecular interactions to occur. Thus a combination of fluticasone and formoterol is very efficacious in the treatment of asthma.

LS5-2

flutiform[®]: Discovering the Latest Combination Product in Asthma Therapy

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The past 2 decades have seen an unprecedented increase in asthma prevalence but also an unexpected decline in asthma mortality. This has been attributed to the advent of fixed combinations of inhaled corticosteroids and long-acting beta-2-agonists (ICS/LABA). Irrespective of whether these drugs are prescribed too frequently their impact on current treatment is enormous. The rationale for combining ICSs and LABAs in one inhaler has many noteworthy arguments: basic research studies (not corroborated clinically) claim that the concurrent administration of ICS/LABA leads to additive effects. The most reasonable explanation for their success, however, is the fact that they improve compliance with ICS since patients would inhale a relevant ICS dose on each occasion they would require a beta-agonist on-demand. Thus, current guidelines recommend ICS/LABAs as the most effective treatment option for people whose asthma uncontrolled with ICS alone. Furthermore, since combining ICS and LABA in a single inhaler might lead to improved adherence compared with separate inhalers, guidelines recommend the use of single-inhaler ICS/LABAs over free combinations. Several ICS/LABA combinations are currently available. Despite of that, asthma control remains poor in the real world. Incorrect handling, poor adherence and persistence to treatment have been identified as contributors to this. *flutiform*[®], which combines fluticasone propionate and formoterol fumarate in a single aerosol inhaler was approved in the EU in June 2012 as the most recent addition to the therapeutic armamentarium in the maintenance treatment of asthma. It is available at three dose strengths and has been shown to be efficacious and safe in randomized double-blind clinical trials as well as in pooled analysis in patients with a range of asthma severities. In these trials fluticasone/formoterol is superior to fluticasone or formoterol monotherapies for improvements in FEV₁ over 12 weeks of treatment and provides greater improvements in asthma control, rescue-medication-free days, awakening-free nights and symptom-free days and a lower rate of exacerbations than fluticasone alone. *flutiform*[®] has comparable efficacy to budesonide/formoterol and fluticasone/salmeterol for lung function and asthma control but a significantly faster onset of bronchodilation than fluticasone/salmeterol. The long-term safety and efficacy of *flutiform*[®] have also been demonstrated over treatment periods of up to 1 year where treatment with *flutiform*[®] is associated with a low incidence of severe exacerbations. Further studies are needed to corroborate the clinical efficacy and real-world effectiveness. Until then Fluticasone/formoterol (*flutiform*[®]) is a new, promising additional treatment option for moderate to severe asthma with a fast onset of bronchodilation.

LS6**How should COPD be treated considering small airway obstruction and adherence?**

Yasuhiro Setoguchi

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COPD is a chronic inflammatory disease that is characterized by persistent airflow limitation. Some studies have shown that inflammation of the small airway is associated with lung function abnormalities, leading to the concept that this lung compartment may be a pivotal target for the pharmacological treatment of COPD.

Bronchodilator therapy is central to the symptomatic management of stable COPD, with long-acting agents preferred over short-acting ones. The specific bronchodilator regimen chosen should depend upon drug availability and individual response. However, if symptoms are not well controlled with a single agent, the GOLD guidelines recommend coadministration of bronchodilators with different mechanisms of action, rather than up-titration of the dose of the single agent. The GOLD guidelines also state that inhalation is the preferred route of administration for bronchodilator therapy in COPD patients. However, elderly patients may have difficulty using inhalers, and may need other methods of administration. Tulobuterol, a short-acting β_2 agonist, can be administered by a transdermal patch, which achieves sustained, and effective systemic levels of tulobuterol lasting for 24 h, and is clinically used as a long-acting β_2 agonist. Moreover, because the maximum blood concentration of tulobuterol is lower when administered via this route than when administered orally. In a study by Fukuchi et al, treatment with transdermal tulobuterol was at least as effective as inhaled salmeterol in improving the symptoms of dyspnea and pulmonary function in stable COPD patients. Furthermore, in another study of a similar design by Ichinose et al, relative to inhaled tiotropium monotherapy, the combination of transdermal tulobuterol plus inhaled tiotropium significantly improved pulmonary function as well as symptoms of dyspnea, resulting from a reduction in pulmonary hyperinflation.

Recently, the impulse oscillation system (IOS) is considered to provide more useful and detailed information regarding the state of the small airways.

IOS-assessed study by Setoguchi et al. demonstrated that transdermal tulobuterol provided additional benefits to patients already established on inhaled tiotropium therapy, in terms of improvements in peripheral airway function. Takahashi H et al. showed that adherence was greater to transdermal tulobuterol than to inhaled salmeterol in elderly COPD patients. Transdermal tulobuterol is a useful medicine for COPD in term of pharmacologic target to small airway and adherence in elderly patients.

LS7-1**Putting the patient first**

Ashley Woodcock

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If followed by physicians and patients, asthma guidelines should ensure good disease control in all but the most difficult-to-treat cases. However, despite the existence of many asthma guidelines and treatment strategy documents, poorly controlled asthma remains very common, even in affluent countries and regions. This presentation will explore the reasons why this is the case.

Guideline-based management is evidence based for a population of asthma patients. But there is increasing acceptance that management needs to be adjusted to an individual patient's circumstances. Comorbidities such as reflux, obesity, rhinitis and smoking need to be taken into consideration.

The evidence base for guidelines comes from randomised controlled trials whose participants are often unrepresentative of the wider patient population, both in their disease and their adherence to treatment. If the data upon which guideline recommendations are based are not applicable to many patients, their relevance to clinical practice is limited. The incorporation of data from innovative real-world studies of a diverse group of patients, such as the Salford Lung Study, could help change the guidelines and, in doing so, make them more patient focused.

Finally, this presentation will examine the patient's role in their asthma treatment and discuss the ways in which patient behaviours, such as poor adherence to prescribed medications, could explain the poor control we so often see in clinical practice.

Zinc code: RECE/RESP/0173/13

Preparation date: October 2013

LS7-2

Future opportunities

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Shown in randomised controlled trials to alleviate asthma symptoms and improve quality of life, guideline-defined asthma control remains an elusive goal for many patients. Research has shown that non-adherence to prescribed medication is widespread, even in severe asthma, and that many patients are dissatisfied with their treatment regimens.

Most guidelines recommend that patients whose asthma is not controlled by inhaled corticosteroids (ICS) alone receive combination treatment with a long-acting beta₂ agonist (LABA) in addition to the ICS. Until recently, all approved ICS/LABA treatments required twice-daily administration.

Fluticasone furoate/vilanterol (FF/VI) is a newly approved inhaled therapy in Japan for the treatment of bronchial asthma in patients requiring concurrent use of ICS and LABA. Both FF and VI have inherent 24-hour activity, making it the first truly once-daily ICS/LABA combination. The duration of action, potency and selectivity of FF and VI have been demonstrated *in vitro* and *in vivo*. This presentation will illustrate these findings and communicate the outcomes of randomised controlled trials of FF, VI and FF/VI in which its effectiveness in improving lung function and reducing allergen response and exacerbation rate has been shown.

Additionally, the usability and patient perception of the inhaler through which medication is delivered is important to consider. FF/VI is delivered via a new inhaler, the ELLIPTA® dry powder inhaler, which is a blister-based dry powder device well received by patients in clinical studies.

Zinc code: RECE/RESP/0173/13

Preparation date: October 2013

LS8-1

How omalizumab works: what we know and what we don't

Klaus Rabe

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It is well established that immunoglobulin E (IgE) plays a key role in allergic asthma via its interaction with inflammatory cells, and the induction and maintenance of chronic allergic airway inflammation.¹ It is these mechanisms that provided a rationale for anti-IgE therapy in patients with allergic asthma, and led to the clinical use of a humanized anti-IgE monoclonal antibody, omalizumab, in this setting.²

In this presentation, we will review the role of IgE in the allergic cascade and the mechanism by which it binds to high-affinity IgE receptors (FCεRI) on a variety of cell types²⁻⁴. We will also review the mechanism of action and pharmacodynamic effects of omalizumab, highlighting its impact on pro-inflammatory cytokines, cells and biomarkers, and consider how our knowledge of asthma pathogenesis has contributed to our understanding of omalizumab.^{3,5}

Asthma is clearly a heterogeneous disease. More research is required to further understand its pathogenesis, the role of anti-IgE treatment, and the mechanism by which the effects of omalizumab are elicited.

1. Rabe KF, et al. *Allergy* 2011;66:1142-51.
2. Novartis Europharm Ltd. (2012). XOLAIR. Summary of Product Characteristics. Horsham, UK.
3. Chang TW. *Nat Biotechnol* 2000;18:157-62.
4. Wenzel SE. *Nat Med* 2012;18:716-25.
5. Djukanović R, et al. *Am J Respir Crit Care Med* 2004;170:583-93. GMCC: 169885. NP4: JP1310139838.

LS8-2

The efficacy and safety of omalizumab in asthma

Ken Ohta

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The clinical efficacy of omalizumab, a humanized monoclonal anti-immunoglobulin E antibody, has been well documented in a number of clinical trials involving adolescents and adults with severe allergic asthma. This presentation will summarise the efficacy data from major randomized trials, highlighting the impact of omalizumab on clinical outcomes such as exacerbations, asthma control, symptoms, quality-of-life and healthcare utilization.¹⁻³ For example, clinically significant exacerbations were reduced by 26% vs placebo in the INNOVATE trial ($p=0.042$)¹ and by 25% vs placebo in the EXTRA trial ($p=0.006$)³ over their respective treatment periods. Similar benefits have also been reported in 'real-world' observational studies in Japan⁴ and around the world,⁵ and the EXCELS study⁶ has provided important information on the long-term safety of omalizumab.

Omalizumab was initially approved by the US Food and Drug Administration in 2003 for adults and adolescents (12 years of age and above) with moderate-to-severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids (ICS).⁷ In the European Union, omalizumab is approved for the treatment of patients aged 6 years and over with severe persistent allergic asthma inadequately controlled with ICS and a long-acting β_2 -agonist.⁸ In Japan, omalizumab was approved in 2009 as an add-on therapy for adult patients with severe allergic asthma who are inadequately controlled with high-dose ICS and best standard of care, and has been recently approved for children with severe allergic asthma.

1. Humbert M, et al. *Allergy* 2005;60:309-16.
2. Bousquet J, et al. *Allergy* 2011;66:671-8.
3. Hanaia N, et al. *Ann Intern Med* 2011;154:573-82.
4. Ohta K, et al. *Allergol & Immunol* 2012;19:1798-822.
5. Braunstahl G-J, et al. *Resp Med* 2013;107:1141-51.
6. Long AA, et al. *Ann Allergy Asthma Immunol* 2009;103:212-9.
7. Genentech USA, Inc. (2010). XOLAIR (omalizumab) for subcutaneous use. Prescribing information. South San Francisco, CA.
8. Novartis Europharm Ltd. (2012). XOLAIR. Summary of Product Characteristics. Horsham, UK.

GMCC: 169885. NP4: JP1310139838

LS8-3

Omalizumab in children with allergic asthma

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Asthma is the fourth most common cause of disability-adjusted life-years for children aged 10-14 years;¹ approximately 20% children will be diagnosed with asthma by the age of 10 years.² Most mild/moderate childhood asthma can be controlled by *p.r.n.* short-acting β_2 -agonists and regular inhaled corticosteroids plus, if needed, long-acting β_2 -agonists and anti-leukotrienes.³ However, 5% of children with asthma have chronic symptoms and/or recurrent exacerbations despite maximal treatment with conventional medications.³ There is, therefore, a need for medications to improve asthma control and reduce the associated burden-of-disease in these children.

Omalizumab is a humanized monoclonal antibody against IgE that has been approved for paediatric use in the EU⁴ and, more recently, Japan.⁵ There have been a number of clinical trials and 'real life' studies which have shown that omalizumab can reduce exacerbations and improve asthma control in children, and has corticosteroid-sparing potential.⁶⁻⁸ In study IA05, over 24 weeks, omalizumab reduced the rate of clinically significant exacerbations by 31% vs placebo ($p=0.007$). The number of treated patients needed to prevent one exacerbation was 1.7, confirming that this decrease is not only statistically significant, but clinically relevant.⁶

This clinical relevance is supported by recent 'real life' studies.^{9,10} In a multi-centre observational study assessing asthma control in French children with severe allergic asthma, exacerbation rates were reduced by 72% and hospitalizations by 89% over a year of treatment ($p<0.0001$).¹⁰ These and other data provide consistent evidence supporting the cost-effectiveness of omalizumab when used in the appropriate patient group, with prompt administration. Data reinforcing safety of omalizumab in children (6-<12 years) will also be discussed.¹¹

1. Gore FM, et al. *Lancet* 2011;377:2093-102.
2. To T, et al. *Am J Respir Crit Care Med* 2010;181:337-43.
3. Hedlin G, et al. *Eur Respir Rev* 2012;21:175-85.
4. Novartis Europharm Ltd. (2012). XOLAIR SmPC. Horsham, UK.
5. PharmaAsia News, online article, 2nd September 2013.
6. Lanier B, et al. *J Allergy Clin Immunol* 2009;124:1210-6.
7. Milgrom H, et al. *Pediatrics* 2001;108:e36.
8. Busse WW, et al. *N Engl J Med* 2011;364:1005-15.
9. Brodli M, et al. *Arch Dis Child* 2012;97:604-9.
10. Deschildre A, et al. *Eur Respir J* 2013 Epub Mar 21
11. Milgrom H, et al. *Curr Med Res Opin* 2011;27:163-9.

GMCC_169885. NP4_JP1310139838.

LS9-1**Pulmonary rehabilitation and pharmacologic therapy: strategy for improving physical activity in COPD**

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Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease in which patients experience a progressive decline in lung function, worsening exercise capacity and frequent exacerbations. Based on clinical evidence, the progression could be modified by focused on 1) earlier diagnosis; 2) risk reduction through smoking cessation; 3) symptom reduction and improving health-related quality of life (HRQOL) with pharmacologic therapy and pulmonary rehabilitation; 4) decreasing complication by reducing exacerbation and mortality.

The new Global Initiative for Chronic Obstructive Lung Disease (GOLD) advocates interventions according to the severity of COPD, patient's symptoms and risk of exacerbations/hospitalizations. Maintenance pharmacologic therapy with inhaled long-acting anti-muscarinic or β -adrenergic agents or combined β -adrenergic agents/inhaled corticosteroid reduces symptoms, improves lung function, improves exercise capacity and HRQOL.

Pulmonary rehabilitation, which includes exercise training, smoking cessation, nutritional intervention, and patient's education, reduces symptom burden, increase exercise capacity, improves HRQOL, and reduces health care utilization, probably reducing through the severity of exacerbations. Because pharmacologic therapy with inhaled long-acting bronchodilators and pulmonary rehabilitation appear to amplify the effect of both therapies each other, combination therapy with pharmacologic therapy and non-pharmacologic therapy, including pulmonary rehabilitation is recommended in COPD management by GOLD and other clinical guidelines.

Patients with COPD are generally very inactive physically, and this physical inactivity is detrimental to their health. Physical inactivity not only impairs HRQOL, it probably shortens life expectancy. Therefore, increasing physical activity should be a prominent goal in treatment of COPD. Physical activity levels correlate better with functional exercise capacity, such as the 6-minute walk distance, than abnormalities on pulmonary function tests. Because functional exercise capacity increases with pulmonary rehabilitation, and other important factors such as motivation and self-efficacy for exercise are also improved, it stands to reason pulmonary rehabilitation should increase activity and participation in extended activities of daily living. Indeed, an emerging medical literature suggests that pulmonary rehabilitation improves physical activity levels in patients with COPD. Recent clinical studies also suggest that maintenance pharmacologic therapy with inhaled long-acting anti-muscarinic or β -adrenergic agents improves physical activity and these bronchodilators appears to amplify the effectiveness of pulmonary rehabilitation. In this regards, combination therapy which includes both pulmonary rehabilitation and pharmacologic therapy is important for improving physical activity in patients with COPD.

In this seminar, I would like to present importance to improve physical activity level and summarize the strategy for improving physical activity in management of patients with COPD.

LS9-2**Importance of the early intervention in the COPD patients**

Peter J Barnes

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COPD is a relentlessly progressive disease in most patients so that disease severity and the need for treatment increases over time. As in many chronic diseases the prospects for therapy are better in earlier stages of the disease, but at present we tend to treat COPD only when it is severe and with a high mortality. Smoking cessation is more effective in early disease than more severe disease, which also suggests a greater reversibility during its early stages. COPD is characterised by a distinct pattern on inflammation in small airways and lung parenchyma that results in small airway fibrosis and emphysema. The pattern if inflammation may change as the disease progresses with increased innate immunity through the disease stages, but also acquired immunity in later stages, perhaps due to bacterial colonisation or autoimmunity. Long-acting bronchodilators are currently the most effective therapy for COPD patients and reduce symptoms by acting on small airways to reduce air trapping. The UPLIFT study shows that the long-acting muscarinic antagonist tiotropium bromide improves spirometry, symptoms and quality of life of COPD patients over a 4-year period and also reduces exacerbations and mortality when added to other treatments including LABA and inhaled corticosteroids. Although overall there is no effect on disease progression, patients with earlier disease (GOLD2) do show reduced disease progression with tiotropium, whereas GOLD 3 and 4 do not. This might be because of reduced exacerbations but could also be explained by reduced fibrosis of small airways through reduction of mechanical forces and also an inhibitory effect on fibroblasts in small airways. The inflammation in COPD is resistant to the anti-inflammatory effects of corticosteroids and the molecular mechanisms for this resistance have now been defined. A reduction in histone deacetylase-2 (HDAC2) as a result of oxidative stress prevents corticosteroids from switching off activated inflammatory genes in COPD airways even in early disease. It is now clear that earlier treatment of COPD would be beneficial in order to prevent the disease progressing and in the future the idea of treating patients before symptoms begin to prevent future problems should be considered, analogous to the treatment of hypertension or hypercholesterolemia.

LS10**Latest news in combinations therapy in asthma**

Alberto Papi

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The goal of asthma treatment is to achieve and maintain control of the disease. In patients with asthma that is not well controlled with an inhaled corticosteroid (ICS) alone, combination therapy with an ICS plus a long-acting β_2 -agonist (LABA) is advocated. It is well recognized that ICS/LABA combination treatment can significantly improve asthma control levels compared with simply increasing a patient's ICS dosage. Fixed-dose ICS/LABA combination therapies offer significant benefits over single inhalers, in terms of facilitating patient adherence to both the ICS and LABA components of the treatment.

There is a clear discrepancy between the efficacy of ICS/LABA products demonstrated in a clinical trial setting and the situation in real-world clinical practice. Although asthma prevalence appears to have stabilized in some European countries, asthma control is still suboptimal and a large proportion of patients continue to experience inadequately controlled disease, even in regions where access to treatment is good. Thus, everyday clinical experience of asthma does not mirror the evidence of improved outcomes promised by randomized controlled trials on the efficacy of current treatments.⁷

Specific treatment attributes are likely to influence a patient's acceptance of and adherence to their regimen. For example, most patients require to perceive immediate relief of asthma symptoms; a treatment with a fast onset of action can provide motivation for patients to adhere to their therapy, which is likely to lead to improved asthma control. A recent survey conducted in Europe highlighted the items considered more relevant by respiratory physicians for an effective ICS/LABA combination treatment. The 5 top ranked characteristics in this survey resulted: efficacy in symptom control, effective anti-inflammatory activity, improvement of lung function, safety/tolerability and rapid onset of action.

A new combination therapy for the treatment of asthma is being developed that brings together the potent ICS, fluticasone propionate (FP), and the rapid-acting LABA, formoterol fumarate (FORM), in a single hydrofluoroalkane (HFA) pressurized metered dose inhaler (pMDI). The safety and efficacy profiles of FP and FORM are well established and the combined pharmacological effects of the two components hold solid evidence in terms of clinical effectiveness. For example, FORM is known to be a rapid-acting LABA, with a speed of onset of action as fast as salbutamol. The anti-inflammatory effects of FP are sustained and rapid and, and it is highly effective in treating asthma.

Randomized controlled trial and pooled analyses demonstrate the efficacy and tolerability of this the new combination. It has been shown that fluticasone/formoterol is more efficacious than fluticasone or formoterol given alone, and has similar efficacy and tolerability profiles to budesonide/formoterol and fluticasone/salmeterol, with the additional benefit of more rapid bronchodilation than fluticasone/salmeterol. The pharmacological characteristics of fluticasone and formoterol are consistent with the preferences of respiratory experts, who have reported that the potency of the ICS and the speed of onset of the LABA are among the most important features of an ICS/LABA combination product. A rapid onset of action is also an important attribute of an ICS/LABA maintenance therapy for patients and recent studies have suggested that therapies with a rapid onset of bronchodilation may encourage patient adherence to their treatment regimen.

LS11**Latest strategies in the treatment of advanced NSCLC, achieving efficacy with less toxicity**

Ralph G. Zinner

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In this session Dr. Zinner, a primary investigator of PRONOUNCE study, will review advances of NSCLC chemotherapy for recent years as well as the latest clinical trials presented this year which could impact on our daily clinical practice. He will then discuss importance of balancing efficacy and toxicity by showing QOL-related endpoints such as PFS without Grade 4 toxicity (G4 PFS), EQ5D-I/VAS etc. He will also provide some examples of the U.S. practice to maintain patients' QOL in NSCLC chemotherapy.

LS12

Review of the Japanese CAP therapeutic guidelines for adults

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The Japanese Respiratory Society (JRS) Guidelines for the Management of Community-Acquired Pneumonia in Adults was initially developed in 2000 and revised in 2005. I will compare the outline of the JSR Guidelines with the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) Community-Acquired Pneumonia Guidelines 2007.

I will first of all explain why domestic guidelines are necessary and then briefly introduce the outline of the ATS/IDSA Guidelines. At the end, I will explain the current status and etiology of pneumonia in Japan. The characteristics of the etiology of community-acquired pneumonia (CAP) in Japan include: that the incidence of *Streptococcus pneumoniae* is the highest; that the development of resistance to macrolide has been quicker than that to penicillin; that *Mycoplasma pneumoniae* is more common in young people; that the incidence of Legionella pneumonia is lower than in EU and USA; and that indigenous bacteria in the oral cavity and anaerobic bacteria are important because of aspiration pneumonia in elderly people.

The characteristics of the JRS Guidelines include a simple severity classification system, the recommendation to identify causal microorganisms to the best possible extent, the recommendation of oral penicillin medication to treat bacterial pneumonia but a cautious approach to the use of fluoroquinolone, and the recommendation of medication that takes into account pharmacokinetics (PK)/pharmacodynamics (PD). One of the particularly noteworthy characteristics is the differentiation between bacterial and atypical pneumonia. I will describe the background leading to the introduction of the concept behind the differentiation.

Lastly, as the time for revising the JRS Guidelines is approaching, I would like to discuss some issues that need to be addressed in the revision.

ES1-1

The diagnosis and impact of COPD

Tomoko Betsuyaku

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COPD is a common chronic inflammatory disease characterized by persistent airflow limitation, which is preventable and treatable. The burden of COPD is significant and increasing. Based on the epidemiological study conducted in Japan in 2000 (NICE study), it is estimated that there are more than 5.3 million COPD patients in Japan. However, according to the Ministry of Health, Labor and Welfare in Japan, it has been reported that patients who have received treatment of COPD in 2008 was approximately 170,000, which was significantly different from the estimated number of patients. In more recent study, respiratory function test was performed using a hand-held spirometer in 2,067 Japanese patients aged ≥ 40 years old with history of smoking, attending primary care clinics without diagnoses of COPD who experienced repeated respiratory tract infection. The study showed that 19.4% of subjects had airflow obstruction compatible with COPD. In another Japanese study with hand-held spirometer which investigated the prevalence of airflow limitation in outpatients routinely visiting for their cardiovascular diseases and who were aged 40 years or older with a smoking history showed that the prevalence of airflow limitation was 27.0%, and 87.7% of these subjects have not been diagnosed with COPD prior to the study. These reports suggest that significant number of patients is still undiagnosed and raising awareness of the disease is urgently required. Needs of more practical diagnosis and management is also needed to encourage COPD treatment in wider population, especially to primary clinic physicians who are facing these undiagnosed patients.

ES1-2

COPD pathogenesis, mechanism of disease progression and management

Jorgen Vestbo

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COPD is a common chronic inflammatory disease characterized by persistent airflow limitation, which is preventable and treatable. Inflammation of the respiratory tract is a prominent feature, presumably involved in both the development of COPD and subsequent disease progression. Inflammation also plays a role in exacerbations of COPD, where anti-inflammatory treatment has a solid evidence base when it comes to preventing exacerbations. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document, updated in 2013, has proposed a multidimensional approach to assess patients with COPD. It recommends that COPD management and treatment should consider both disease impact, determined by assessment of symptoms and activity limitation, and future risk of exacerbations, determined from airflow limitation and/or exacerbation history. As well as reducing symptoms, reducing risk of is required to prevent progression and mortality. Prevention of COPD exacerbation is recognized as one of the most important aims for achieving a better prognosis. The GOLD combined assessment of COPD results in the grouping of patients into one of four categories: A: low risk, less symptoms; B: low risk, more symptoms; C: high risk, less symptoms; D: high risk, more symptoms. Comprehensive understanding on pathogenesis of the disease, risk factors for disease progression, role of each medications and goal for management of COPD, will guide to optimal management and health outcomes.

ES1-3

COPD management and future possibilities

Paul Jones

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Spirometry has remained the standard method in clinical diagnosis of COPD and for assessing COPD severity. But it is now accepted that FEV1 is an inadequate marker to assess severity of breathlessness, exercise limitation and health status impairment, although it still plays an essential role in the clinical diagnosis of COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document, updated in 2013, advises utilising either the CAT or the mMRC dyspnoea scale in symptom assessment. Unlike the mMRC which is only covers activity limitation due to breathlessness, the CAT is a simple tool that covers a wide range of effects of COPD for quantifying the symptoms and impacts of COPD. Recent work using the CAT suggests that it may have a use in case-finding patients who need spirometry to confirm the diagnosis of COPD.

GOLD recommends that COPD management and treatment should consider both disease impact in terms of symptoms and activity limitation, and future risk of exacerbations. Patients often receive TRIPLE therapy, which adds an anticholinergic to ICS and LABA since in clinical trials this approach been associated with greater improvements in lung function, health status and hospitalisation compared with anticholinergic therapy alone. However it is not known what proportion and which type of patients benefit from single therapy or multiple therapy. More scientific investigation is required, particularly in settings that more closely reflected routine practice, to determine whether a TRIPLE therapy strategy based on symptoms and exacerbation history can improve the management of COPD for the majority of patients.

ES2-1

Next-generation hallmarks of lung adenocarcinoma

Marcin Imielinski

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Lung adenocarcinoma, the most common subtype of non-small cell lung cancer, is responsible for over 500,000 deaths per year worldwide. Massively parallel sequencing technology has enabled the comprehensive characterization of somatic genetic alterations in lung adenocarcinoma at base-pair resolution. A major goal of cancer genome characterization is to identify novel oncogenic alterations that represent potential therapeutic targets and molecular biomarkers of treatment response. The high somatic mutation rate in lung adenocarcinoma (~12 substitutions per megabase) poses serious challenges for statistical “driver” gene discovery, however properly calibrated analytic approaches can distinguish signal from noise. I will present the results of our published study (Imielinski *et al* 2012 Cell) and the ongoing TCGA lung adenocarcinoma effort, comprising over 400 whole-exome sequenced and 50 whole-genome sequenced cases. I will discuss the mutational heterogeneity across this large case set, focusing on substitutions and rearrangements. I will highlight likely driver alterations nominated by our analysis, including recurrent mutations in RNA binding proteins (*U2AF1*, *RBM10*) and the Ras homologue *RIT1*. I will also describe our recent whole genome sequencing analysis of an outlier sorafenib responder that yielded a novel but rare oncogenic alteration and potential marker of sorafenib sensitivity. I will conclude with a discussion of the “driver-negative” landscape and a perspective on future lung adenocarcinoma genome sequencing efforts.

ES2-2

Cutting-edge of Cancer Genome! “Target genome sequence toward clinical application”

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Our knowledge on the genes that are relevant to lung cancer development and treatment is expanding. Efforts are devoted to utilize the knowledge in clinical practice.

Identification of EGFR mutation as a main determinant of the response to gefitinib revealed the importance of genetic information for the treatment of non-small cell lung cancer (NSCLC). However, the access to the lung cancer tissue is not available in many patients, and only a part of patients benefit from the test. Availability of high sensitivity tests solved the problem: they are able to test using cytology samples obtained at the time of initial pathological examination, and thus test samples are readily available from all patients. Concomitantly, the utility of EGFR mutation was clearly demonstrated by NEJ002 and WTJOG3405 studies. The guideline of Japanese lung cancer association recommended performing EGFR mutation test before initiating 1st-line treatment. Currently almost all NSCLC patients are tested in Japan. Guidelines of ASCO and NCCN also recommend EGFR mutation test before the use of EGFR-tyrosine kinase inhibitor (EGFR-TKIs). A large international studies named ASSESS and IGNITE are in progress: they are exploring the power of high sensitivity tests performed using cytological samples or even plasma.

During the effort of clinical application of EGFR mutation test, the list of genes that may have clinical utility has been expanding. They include somatic mutations like ALK, ROS, RET fusion genes, and BRAF mutations, as well as germ-line variants in BIM gene and the gene to which a close association was observed with the development of fatal interstitial pneumonitis by EGFR-TKIs. Testing individual genes one by one is not practical in clinical medicine: the medical costs may become enormous and only the limited amount of samples is available for the test. One of the solutions is the use of high-speed sequencer testing all genes simultaneously. A huge number of sequence reads available have enough room to accommodate all necessary genes, while the incorrectness of the reads is considered a major challenge for the use in clinical application. Our system called MINTs that uses MiSeq sequencer is able to detect somatic mutations from clinical samples with cancer cell-content less than 1% with both false-positive rate and false-negative rates less than 0.01.

Detailed genetic information on cancer cells as well as patient normal cells will promote individualized medicine in lung cancer treatment.

ES3-1**Asthma and COPD in Asia Pacific**

Christopher KW Lai

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Asthma and COPD are amongst the most common chronic medical conditions worldwide. A recent Canadian study showed that about 1 in 4 and adults over the age of 35 years might develop COPD during his/her lifetime, and about 1 in 3 might develop asthma. This talk will focus on the burden and management issues related to these 2 diseases.

In the most recent International Study of Asthma and Allergies in Childhood (ISAAC Phase III), the global prevalence of asthma symptoms (wheeze in the past 12 months) amongst adolescents was 14.1%. In Asia Pacific, the prevalence for this age group was 8.8%, ranging from 0.8% in Tibet (China) to 29.5% in Ho Chi Minh City (Vietnam). Although asthma mortality has shown a downward trend in many developed countries worldwide, the disease is still causing significant morbidity, with about 1 in 3 patients with uncontrolled asthma. This poor control is likely the consequence of under-usage of inhaled steroid and over-estimation of control, both on the part of the patients and physicians. Uncontrolled asthma, as defined by GINA, is associated with a higher risk of exacerbation that requires urgent health care utilization, including emergency room attendance, unscheduled medical visits and hospitalization. Tackling these issues related to poor asthma control may help reduce the burden of disease to society.

COPD has increasingly become one of the biggest health burdens to society, owing to a combination of an ageing population and worsening outdoor air quality in developing countries. In Asia Pacific, the prevalence of moderate to severe COPD may range from 5 to 20%. Patients with COPD are more likely to utilize health care services including hospitalization, emergency department visits, ambulatory care visits, homecare visits & long-term care residence. Unfortunately, the disease is often not diagnosed and inadequately managed. In a recent survey, 16 to 78% of GPs in Asia Pacific claimed they did not follow the guidelines in managing COPD patients, and only 10 to 48% used spirometry for diagnosing the disease. Despite being an important determinant for COPD treatment, exacerbation history was ignored by up to 2/3 of GPs. Thus early recognition of the disease with appropriate treatment may help reduce the disease burden.

ES3-2**Phenotypes of asthma/COPD and exacerbation**

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In spite of the heterogeneity of asthma, symptoms in most of the patients with mild to moderate diseases can be controlled with inhaled corticosteroids and long-acting bronchodilators, possibly due to the wide range of anti-inflammatory activities of corticosteroids. In contrast, severe asthma is difficult to control with such a simple strategy, and individualization of the treatment is mandatory. That is why "phenotypes" of severe asthma has accumulated the interests of researchers and clinicians during the past 5 years. Phenotype identification with unsupervised cluster analysis has especially been a hot topic, demonstrating some clinically important phenotypes such as non-eosinophilic asthma in obese women. More than 10 cluster analyses have been reported, and exacerbation frequency is one of the major determinants of severe asthma phenotypes.

A frequent-exacerbator phenotype is also present in COPD, as reported in a 2009 study by ECLIPSE investigators. Although exacerbations become more frequent as COPD progresses, the best predictor of exacerbation is a history of exacerbations. Based on this finding, 2013 update of global strategy for the diagnosis, management, and prevention of COPD (GOLD) has incorporated exacerbation frequency as an indicator of COPD risk, independently of the severity of airflow obstruction. Other studies report that lung emphysema, bronchial wall thickening, persistent inflammation, but not bronchodilator responsiveness or annual change in pulmonary function, are associated with the frequency of exacerbation.

It is now clear that physicians should be aware of the presence of frequent exacerbators among patients with severe asthma and COPD. Further studies would be required to characterize the phenotype in more detail and develop an individualized treatment for these patients.

ES3-3

Correlation between exacerbation and peripheral airway in asthma & COPD

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Main inflammatory lesion of bronchial asthma is more peripheral non-cartilagenous lesion of bronchus. Especially in the nocturnal asthma patient, during mid-night eosinophils are not distributed in the proximal bronchi but distributed more peripheral near the alveolar lesions (1). Activated eosinophils (EG2) and major basic protein (MBP) positive cells distributed more narrow (<2mm diameter) non-cartilagenous airways compared with more wide (>=2mm diameter) airways (2). These asthmatic patients easy to occur asthma attack. To prevent the exacerbation of asthma, we have to deliver inhaled corticosteroids (ICS) bronchodilators to more peripheral lesion. Many devices have developed for the adequate deliver of agents to more periphery.

In COPD patients the main lesion of inflammation was also peripheral bronchioles.

The characteristic inflammatory cells are neutrophils. The experimental guinea pig of COPD, anti-cholinergics Tiotropium inhibit neutrophil numbers both in the cartilagenous and non-cartilagenous airways (3). It also decrease collagen content in non-cartilagenous airways. Anti-cholinergics-Tiotropium will be effective to reduce the neutrophilic inflammation in experimentally induced COPD.

In humanbeing, main inflammatory lesion is also more-peripheral lesion and inflammation is mainly induced by neutrophils. It was said that beta-adrenoceptors distributed more peripheral lesion and anti-cholinergic receptors (muscalinic acetylcholine receptors) distributed more proximal lesion of bronchi. Recent study showed that not a few M3 muscalinic acetylcholine receptors distributed more periphery (4). Anti-cholinergics might work more peripheral, non-cartilagenous main inflammatory lesion. So we should use another device to deliver Tiotropium more peripheral lesion.

Respimat mist distributed whole bronchi and lungs. It was equally safe compared with prototype device (HandiHaler) (5). Handling of this device is easier and most of COPD patients prefer Respimat to HandiHaler (6).

The main stem of inflammatory lesion of both bronchial asthma and COPD is more peripheral airways. To prevent exacerbation, we have to choose devices deliver drugs more peripheral lesion of airways.

- (1) Kraft M., et al. AJRCCM 1996; 154: 1505-1510.
- (2) Tulic MK., et.al. Chest 2003; 123: 348s-355s.
- (3) Pera T., et al. Eur Respir J 2011; 38: 789-796.
- (4) Ikeda T., et al. Br J Pharmacol. 2012; 166: 1804-1814.
- (5) Wise RA., et al. N Engl J Med. 2013, DOI: 10.1056/NEJMoa1303342.
- (6) Kato M., et al. Pharma Medica 2011; 29: 135-140.

ES3-4

Future direction of inhaled anticholinergic drugs for airway obstructive diseases: lesson from TIOSPIR trial

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There are two kinds of inhaled bronchodilator such as β_2 agonists and anticholinergic drugs to treat obstructive airway diseases; COPD and bronchial asthma. Cumulative data show that anticholinergic drugs and β_2 agonists have been used as the first line of bronchodilator to treat COPD patients and asthma patients, respectively. In recent years, however, it was reported that more than half of COPD patients show airway reversibility by using a combination of a short-acting anticholinergic drug (SAMA) and a short-acting β_2 agonist (SABA) and that a newly developed long-acting β_2 agonist (LABA) show the effective bronchodilation in COPD patients as much as anticholinergic drugs do. From these data, the Japanese guideline for the diagnosis and management for COPD describes that a long-acting anticholinergic drug (LAMA) and LABA are equally positioned as long-acting bronchodilator for management of stable COPD patients. As for the effect of bronchodilators on asthmatic patients, SAMA are useful to treat nocturnal asthma and exacerbation of asthma to relief symptoms, and other data on clinical usefulness of anticholinergic drugs in asthma patients are also reported. In current asthma guideline, although SABA for the reliever and LABA with inhaled corticosteroids (ICS) for management of stable asthma patients are positioned, and SAMA are positioned as the reliever of exacerbation of asthma, LAMA are expected for positioning as controller drugs for management of stable asthma in addition to ICS or a combination of ICS and LABA.

Concerning tiotropium, LAMA for COPD, in recent years, a lot of evidence about clinical efficacy and usefulness in management of COPD has been reported, the effects of tiotropium on cardiovascular systems, which have been indicated by some researchers, were negated, and its safety was confirmed.

In this symposium, we will review the history of how anticholinergic drugs and β_2 agonists became the mainstream for treatment of COPD and bronchial asthma, respectively, and discuss the application of tiotropium for the treatment obstructive airway diseases in the future from the latest data of tiotropium.

CB1-1**Uncovering the burden of COPD**

Christine Jenkins

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Chronic obstructive pulmonary disease (COPD) places a considerable burden on patients and healthcare systems worldwide and is a growing issue in the Asia-Pacific region. People with COPD use large and disproportionate amounts of health services. For example, in China, COPD is associated with a high economic burden with the cost per patient accounting for up to 40% of an average family's income.¹ Most of the direct costs of COPD are attributed to outpatient services, hospitalizations and medicines, added to which is a considerable financial burden due to indirect costs. Data discussing the impact of COPD, particularly on patients of working age, including lost productivity, will be presented.

The personal impact of COPD includes restrictions to daily activities such as washing and dressing, going shopping and participating in sport. Morning is the worst time of day for COPD patients, who report that breathlessness, cough and phlegm are most troublesome at this time.² Dyspnea in particular has important effects on daily activity, quality of life and participation at work. Patients report depressive symptoms, poor sleep quality and diminished social functioning, alongside a broad array of physical limitations (e.g. weaker muscle strength, reduced exercise capacity) that worsen as lung function declines,³ indicating the need for early intervention.

This presentation will highlight the importance of effective symptom management in COPD. Together with degree of airflow limitation and risk of exacerbations, symptom assessment is crucial for evaluating disease impact and severity and for monitoring response to treatment in the 2013 GOLD management paradigm.⁴ There are now several effective strategies to improve COPD symptoms. Evidence will be presented to highlight the rationale for the use of long-acting bronchodilators, which are recommended either alone or as a component of first-line treatment for symptom management in all but the very mildest disease.⁴

References

1. He et al. Chinese Journal of Tuberculosis and Respiratory Diseases 2009; 32:253-7.
2. Partridge et al. Curr Med Res Opin 2009;25:2043-8.
3. Eisner et al. Am J Epidemiol 2008;167:1090-101.
4. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). Updated 2013. Available from: <http://www.goldcopd.org/> (last accessed 19 September 2013).

GMCC_168053. NP4_JP1310142392.

CB1-2**Low risk, more symptoms, what are the options?**

Marc Miravittles

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Bronchodilators are essential for the management of chronic obstructive pulmonary disease (COPD) symptoms. By relaxing smooth muscle, bronchodilators reduce bronchoconstriction, hyperinflation and air trapping. Lung function deteriorates more rapidly during the less severe, early stages of COPD¹ and therefore early intervention in COPD may be effective for improving outcomes.

This presentation will review the clinical data for the inhaled once-daily long-acting β_2 -agonist (LABA) indacaterol and once-daily long-acting muscarinic antagonist (LAMA) glycopyrronium, both delivered via the Breezhaler[®] device. These long-acting bronchodilators have demonstrated significant ($p < 0.05$) improvements in lung function, exercise endurance, symptoms and exacerbations compared with placebo in patients with moderate-to-severe COPD.^{2,3} In addition, in patients with moderate-to-severe disease, dyspnea and health-related quality of life were significantly improved ($p < 0.05$) with indacaterol 150 μg versus tiotropium 18 μg ,⁴ and the onset of bronchodilation following the first dose was significantly faster with glycopyrronium 50 μg versus placebo and tiotropium 18 μg (open-label).⁵ Overall, these agents have demonstrated good safety profiles, comparable to placebo and tiotropium.^{2,3}

Many patients remain symptomatic despite receiving a single bronchodilator⁶ and additional therapy may be required. Current guidelines recommend adding a second bronchodilator as airflow obstruction becomes more severe, to optimize symptom benefit for patients.⁷ The once-daily LABA/LAMA combination QVA149 (indacaterol/glycopyrronium) has been shown to improve lung function versus the monocomponents (indacaterol 150 μg and glycopyrronium 50 μg) and placebo.⁸ Hence, some patients may benefit from combining bronchodilators of different pharmacologic classes (i.e. LABA plus LAMA).

References

1. Decramer, Cooper. Thorax 2010;65:837-41.
2. Jones et al. Prim Care Respir J 2011;20:380-8.
3. Buhl, Banerji. Int J COPD 2012;7:729-41.
4. Buhl et al. Eur Respir J 2011;38:797-803.
5. Kerwin et al. Eur Respir J 2012;40:1106-14 (New Drug Application Dossier).
6. Dransfield et al. Prim Care Respir J 2011;20:46-53.
7. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). Updated 2013. Available from: <http://www.goldcopd.org/> (last accessed 19 September 2013).
8. Bateman et al. Eur Respir J 2013;3:199-209.

GMCC_168053. NP4_JP1310142392.

CB2-2**Acute exacerbation in IPF-Treatment approach to this life-threatening complication-**

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The clinical course of idiopathic pulmonary fibrosis (IPF) is usually chronic, but some patients may experience episodes of acute respiratory worsening. Although these episodes may occur secondary to common conditions such as pneumonia, pulmonary embolism, pneumothorax or cardiac failure, the term acute exacerbation of IPF (AE-IPF) has been used when a cause cannot be identified for the acute respiratory worsening. This presentation will focus on the diagnostic and management issues for AE-IPF. A universally agreed definition of an AEx-IPF has not been established. In 2007, a consensus definition for AEx-IPF was proposed by an expert committee sponsored by the IPF Clinical Research Network: previous or concurrent diagnosis of IPF, with (a) unexplained worsening or development of dyspnea within 30 days, (b) high-resolution computed tomography with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern, (c) no evidence of pulmonary infection by endotracheal aspirate or BAL, (d) exclusion of alternative causes. Japanese criteria for AE-IPF in 2004 includes above criteria and following additional criteria: (e) deterioration of PaO₂ more than 10mmHg under same condition, with minor criteria of (i) elevation of CRP, LDH, (ii) elevation of KL-6, SP-A, SP-D. Treatment of AE-IPF has generally consisted of high-dose corticosteroids usually in pulse doses, but there are no data from controlled trials to prove their efficacy. In Japan, cyclosporin A has been frequently used, but no convincing evidence of benefit has been demonstrated. A neutrophil elastase inhibitor, sivelestat, has been reported to be effective for AE-IPF in a small case reports. The efficacy of recombinant human soluble thrombomodulin that acts by reducing thrombin-mediated clotting and enhancing protein C activation has been reported. A few studies demonstrated possible therapeutic effect of direct haemoperfusion with a polymyxin B immobilized fiber column (PMX-DHP) on AE-IPF. The protective effect of antifibrotic therapies such as pirfenidone for AE is still unclear, and needs further investigation. The effect of nintedanib, a tyrosine kinase inhibitor, on the progression of IPF and on AEx-IPF has been reported in Phase II trial. Mechanical ventilation is often used in patients with AE-IPF, but the data on its effects on outcomes are mixed. Noninvasive positive pressure ventilation is a viable option for AE-IPF

CB3**Acute Respiratory Distress Syndrome: A Case-based Approach for a Heterogenous Pathophysiological Condition**

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Acute Respiratory Distress Syndrome (ARDS) is an acute hypoxic condition that develops in patients with various underlying diseases and injuries, shows bilateral lung infiltrates on chest X-rays, and is not attributable to heart failure or overhydration. Pathological findings specific for ARDS are referred to as diffuse alveolar damage (DAD), which includes intra-alveolar edema, fibrin deposition, hyaline membrane formation, and destruction of type I alveolar epithelial cells. Uncontrolled neutrophil-dominant inflammation and increased permeability of lung microvascular endothelial cells and alveolar epithelial cell layers are common pathophysiological features of ARDS, which clinically leads to non-hydrostatic pulmonary edema.

Diagnosis of ARDS has long been based on the American-European Consensus Conference (AECC) definition, but a new Berlin definition was published in 2012 to improve the specificity of clinical diagnosis (JAMA 2012; 307:795-803). However, even with the new definition, exclusion of other diseases with similar clinical findings, especially those with established therapy, is still a matter of critical importance.

There have been many efforts to develop new therapies for ARDS, but only low tidal volume ventilation and placement in a prone position have been shown to be effective. The failure of other approaches may be due to previous clinical trials including all patients who met the AECC diagnostic criteria without careful exclusion of other diseases. Clinical findings and courses vary among ARDS patients, depending on the time after onset and underlying diseases and injuries, and pathophysiological conditions and responses to treatment may be heterogenous. Thus, clinical trials in a subgroup of ARDS patients with a more homogenous pathophysiological background may be preferable. In this lecture, representative cases in each subgroup of ARDS will be presented together with the evidence for each case.

CB4**Cough, asthma, and cysteinyl-leukotrienes**

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Asthma is a chronic inflammatory disease of the lower airways, involving various cells such as eosinophils, and cytokines and mediators. Cysteinyl-leukotrienes (cys-LTs) are one of the chemical mediators that play major pathophysiological roles in asthma. They are produced by eosinophils and mast cells, and induce bronchoconstriction, mucous hypersecretion, microvascular leakage, eosinophil chemotaxis and airway remodeling. Anti-leukotrienes, including leukotriene receptor antagonists (LTRAs) which block cysLT1 receptors, exert both bronchodilatory and anti-inflammatory effects and are utilized as second- to third-line controller medication of persistent asthma.

Cough is a major symptom of asthma, and cough variant asthma (CVA) is an asthma phenotype that solely presents with coughing. Sputum levels of cys-LTs are increased in patients with CVA. Antitussive effects of monotherapy with LTRAs in patients with CVA have been reported. We have recently demonstrated that 4 weeks' treatment with an LTRA montelukast exerted anti-inflammatory effect as proved by a decrease of sputum eosinophils, in addition to attenuation of cough VAS and capsaicin cough sensitivity, as reported previously. Spirometry, airway responsiveness, and impulse oscillation indices (respiratory resistance and reactance) were unchanged. These results suggested that the antitussive effect of montelukast in CVA might be attributable to its anti-inflammatory ability rather than bronchodilation (Takemura M et al. *Respiration* 2012).

The treatment did not affect sputum levels of mediators (cys-LTs, LTB₄, PGD₂, PGE₂, PGF_{2a}, and TXB₂). Since inhaled corticosteroid does not seem to affect cough sensitivity while attenuating cough in patients with CVA, LTRAs may involve different mechanism(s) from that of corticosteroid.

LTRAs must theoretically be effective against cough of asthmatic subjects through its "anti-asthma" effects, while evidence supporting direct antitussive effects of cys-LTs on "cough receptors" is scarce. An important clinical question is that whether LTRAs involve non-specific antitussive effects. While a definite answer is not available yet, this possibility seems unlikely at the moment, although some secondary anti-inflammatory properties have been reported for montelukast. This issue needs to be clarified by future research.

CB5**Regulation of airway cleaning in inflammatory airway diseases**

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Airway cleaning is an important non-specific host defense mechanism in the lungs, whereby locally produced biological debris and trapped inhaled particles are removed from the conducting airways of the respiratory tract. Airway cleaning function depends on ciliary motility of airway epithelial cells, coordination of ciliary beating, and rheological properties of airway surface fluid. There are several ways to enhance airway cleaning, including to activate airway ciliary motility, to reduce production of viscous mucus, bronchodilation, and to attenuate airway inflammation. There is accumulating evidence that macrolide antibiotics have a variety of anti-inflammatory activities, such as inhibitions of chemotaxis of inflammatory cells, cytokine production, reactive oxygen species production, and adhesion molecule expression, and are therefore used as a biologic response modifier. In this session, I will demonstrate that the role of 14-membered macrolides, erythromycin and clarithromycin, in the management of airway cleaning dysfunction. First, we measured ciliary beat frequency (CBF) of human airway epithelium by a photoelectric method *in vitro*. Exposure of epithelium to CAM and EM caused rapid increases in CBF, and the maximal increase from the baseline values in response to CAM was 13%, and the concentration required to produce a half-maximal effect (EC₅₀) was 24 nM, which is a physiological concentration in the airway after taking the drug orally. The mechanism of the stimulation of ciliary motility remains unclear, but these results suggest that the use of CAM and EM may result in the improvement of airway clearance. Second, we studied human bronchial epithelium looking at mucus glycoprotein expression by PAS/Alcian blue staining. LPS stimulated the mucin protein expression, and this effect was reduced by EM. Furthermore, the LPS-induced increase in MUC5AC protein expression was inhibited by EM and CAM but not by AMPC, suggesting that the effect is specific for macrolides. We also studied MUC5AC gene expression by *in situ* hybridization, and found that the LPS-induced upregulation of the gene expression was inhibited by pretreatment of cells with CAM. In addition, phosphorylation of I κ B α was observed after the stimulation with LPS, and this effect was inhibited by EM and CAM. Finally, we studied mucociliary transport function by the transport rate of Evans blue dye that had been placed on the tracheal mucosa of mechanically ventilated rabbits *in vivo*, and found that Intravenous administration of CAM accelerated the transport rate in a dose-dependent manner. Taken together, macrolides favorably cause improvements in airway cleaning in chronic airway inflammatory diseases.

CB6-1

Update of the International Multidisciplinary Classification of the IIPs: Roles of Biomarkers

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The idiopathic interstitial pneumonias (IIPs) were classified to 7 diseases by ATS/ERS, which are sufficiently different from one another to be designated as separate disease entities. They can be distinguished from other forms of diffuse parenchymal lung disease by clinical methods including history, physical examination, chest radiology and laboratory studies, and pathology (AJRCCM, 165: 277, 2002). In 2013, the ATS/ERS classification of IIPs was updated and just published (AJRCCM. 188, 733-748, 2013). IIPs were classified to 6 major IIPs and 2 rare IIPs, and Unclassifiable IIP. In addition, molecular biomarkers, including KL (Krebs von den Lungen)-6, SP (surfactant)-D, and SP-A, were shown in the manuscript.

In Japan, serum KL-6, SP (surfactant)-D, and SP-A were approved as clinical use for the diagnosis of interstitial pneumonias, which were described in the current Japanese guide for the diagnosis and treatment of IIPs (The 2nd ed., 2011). In routine practical settings these biomarkers have been widely used in Japan to distinguish interstitial pneumonias from non-interstitial pneumonias, and to distinguish IIPs from special interstitial lung diseases such as hypersensitivity pneumonias and pulmonary alveolar proteinosis.

In this seminar, the updated classification of IIPs will be briefly shown and the role of serum biomarkers, especially KL-6, will be presented.

CB6-2

Role and expectation of serum biomarkers including KL-6 in ILD

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KL-6 are commonly used to diagnose interstitial lung disease in Japan, but is still not widely known and used in overseas.

New international multidisciplinary classification of idiopathic interstitial pneumonia is published by the ATS/ERS in 2013, biomarkers has been introduced in consensus statement.

In this seminar, we ask specialists to provide the latest findings in the diagnosis of interstitial lung disease, focusing on KL-6.