ics, and will discuss opportunities and directions for future studies related to early detection of lung cancer. The presenters will also compare the generalizability of the NLST trial results to a parallel ongoing trial in Europe.

CLINICAL AND TRANSLATIONAL SCIENCE AWARDS SYMPOSIUM

The Clinical and Translational Science Awards (CTSA) program was established to transform the local, regional, and national environment and increase the efficiency and speed of clinical and translational research across the country. The pulmonary, critical care, and sleep community is fortunate to have several of its members in a variety of leadership positions among the 55 CTSAAs throughout the country. One of the major symposia will focus on how CTSAAs advance pulmonary, critical care, and sleep medicine research across the entire translational research spectrum. This symposium will give specific examples of how CTSA funding has been used to transform clinical and translational research, including training and pilot support for early phase research and researchers, consultative help in statistics and informatics, the provision of institutional resources to facilitate the practice of human research, and assistance in navigating institutional review boards. Speakers will discuss some of the tools generated by CTSAAs, how they have enhanced research collaborations across institutions, and how the networking of multiple centers is improving the healthcare of our nation.

LATE-BREAKING CLINICAL TRIALS SYMPOSIUM

One of the important goals of the ATS International Conference is to present the most up-to-date advances in pulmonary, critical care, and sleep medicine. For the third year in a row, the International Conference will have a late-breaking clinical trials symposium to present the most recent and important clinical trials in pulmonary, critical care, and sleep medicine. This year's symposium will discuss clinical trials on asthma, tuberculosis, lymphangioleiomyomatosis, chronic obstructive pulmonary disease, and critical illness.

THE PRACTICE OF MEDICINE: INSIGHTS AND UPDATES

Physicians are intensively trained in the practice and art of medicine, but receive little to no training in the business of medicine. All practicing physicians in the United States are required to operate in an environment where business is an integral part of their practice. Knowledge required of physicians ranges from how to effectively code and bill for their services (a process that is continually revised and updated) to how to manage an office, buy equipment, contract with payors, and set a fee schedule, all while working within a scope of practice that is fiscally sound and viable over decades. This year, the Clinical Practice Committee will offer a symposium to address these key concepts for the practicing physician. This symposium will

promote mastery of the "business of medicine" by new clinicians, while more experienced clinicians can update their knowledge to manage their practices more efficiently.

While science is always evolving and the content of each year's conference is unique, many established formats for education, such as poster discussions, sunrise seminars, post-graduate courses, and mini-symposia have remained relatively constant. Over the last few years, the ATS has made a number of changes to the International Conference to maximize the content and learning opportunities at the meeting. Last year, the Society accepted abstracts of unique clinical cases for the first time. Because of the positive response to case reports at the 2010 meeting, the ATS will continue this popular feature at ATS 2011. Based on feedback from last year's participants, the majority of case reports will be presented in interactive Poster Discussion sessions. ATS 2011 will also feature more hands-on learning opportunities than have ever been offered in the past. From performing ultrasound, initiating therapeutic hypothermia, and implementing quality improvement initiatives, attendees will be able to learn by seeing and doing at the International Conference. In addition to practical training, these sessions will provide the essential context for the use of the medical devices, scientific instruments, or clinical protocols to optimize their appropriate use in clinical medicine.

Overall, the International Conference Committee expects that ATS 2011 will be an invaluable opportunity to enhance the education, science, and career development of ATS members and other attendees from around the world. Given the diverse opportunities available for individuals involved in pulmonary, critical care, and sleep medicine, there really will be something to benefit everyone. We look forward to seeing you in Denver

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Polymorphonuclear Neutrophils Move into the Fast Lane in Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is characterized by an abnormal inflammatory response of the lung to inhaled noxious particles and gases. The main risk factor for

COPD in developed countries is cigarette smoke exposure. However, for unclear reasons not all smokers develop COPD. One of the first inflammatory cell types implicated in the pathogenesis of COPD was the polymorphonuclear neutrophil (PMN). PMNs and their products were linked to COPD in the 1960s when severe early-onset emphysema was found to be associated with inherited deficiency of α_1 -antitrypsin (AAT)

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(1), which is an important physiologic inhibitor of the PMN-derived proteinase neutrophil elastase (NE), in the lower respiratory tract. Subsequent studies showed that PMNs are the most abundant inflammatory cell type present in the airways and lung parenchyma of patients with COPD. In addition, airway PMN counts were shown to correlate positively with disease progression and their number increases further during acute exacerbations (2). PMNs contribute to the pathogenesis of COPD by releasing proteinases (especially NE), reactive oxygen species, and proinflammatory mediators that promote lung inflammation and destruction in COPD.

Although most studies have focused on enumerating PMNs or their products in the lung and airways of human patients with COPD and experimental animals with emphysema, studies dating back to the late 1980s reported that circulating PMNs in patients with COPD have functional abnormalities that could potentially contribute to COPD pathogenesis. These studies reported that smokers and patients with COPD have increased lung retention of PMNs due to increased PMN margination and reduced PMN deformability within the pulmonary vasculature, and this process increases during acute exacerbations of COPD (3, 4). It has been shown that PMNs from patients with COPD have increased extracellular proteolytic activity and increased capacity to migrate to formyl-methionyl-leucyl-phenylalanine (fMLP) in Boyden Chamber assays when compared with cells from healthy smokers and nonsmokers (5). Other studies reported that PMNs from patients with COPD have dysregulated levels of cell adhesion molecules, chemokine receptors, and intracellular tyrosine kinases that participate in PMN adhesion and migration (6, 7). However, the abnormalities in PMN migratory responses were not fully characterized and the aberrant signaling pathways responsible for them were not identified in these earlier studies.

The article by Sapey and coworkers in this issue of the *Journal* (pp. 1176–1186) builds upon this prior literature by using novel technologies to more completely characterize the abnormal migratory responses of PMNs from patients with COPD (8). This article also provides novel insights into the aberrant intracellular signaling pathway that contributes to the abnormal migratory responses of PMNs from patients with COPD. The authors used shallow chemotaxis gradients in modified Dunn Chambers and time lapse video microscopy to compare the real-time migratory velocity, migration accuracy, and morphology of PMNs from patients with COPD with normal plasma levels of AAT (“common garden variety” COPD) to that of cells from age-matched healthy nonsmokers and healthy smokers to various chemoattractants *in vitro*. The authors also studied cells from patients with AAT deficiency having similar airflow obstruction and smoking histories and taking similar medications (including inhaled corticosteroids) as the patients with COPD to control for the potentially confounding effects of these variables on PMN function. They showed that PMNs from patients with “common garden variety” COPD migrated with much greater speed than cells from the control groups, but the migration accuracy of COPD PMNs to chemoattractant gradients was impaired. The PMNs of patients with COPD took more circuitous and less efficient routes toward the stimuli. This migratory abnormality was associated with reduced PMN pseudopodia formation (reflective of the reduced migratory accuracy) but normal expression of key chemokine receptors, including CXCR1, CXCR2, and the fMLP receptor, FPR1. This PMN migration defect did not occur in patients with AAT deficiency having similar pulmonary function as the COPD group. Surprisingly, the migratory abnormalities of COPD PMNs did not correlate with disease severity (as assessed by GOLD stage) and were present even in

patients with GOLD 1 stage disease. The authors implicated abnormal phosphatidylinositol-3-kinase (PI3K) signaling in the abnormal migration pattern of PMNs from patients with COPD since incubating COPD PMNs *in vitro* with low concentrations (1 nM) of a synthetic PI3K inhibitor (Ly294002) reversed the migratory defect in COPD cells but had no effect on the migratory responses of PMNs from the other subject groups. The authors concluded that in patients with COPD there is excessive but highly inaccurate migration of PMNs to chemotactic stimuli, which may not only hinder clearance of bacteria from the lung but may also promote excessive lung destruction in patients with COPD. This latter concept is supported by observations that when chemoattractants activate PMNs to migrate, PMNs translocate serine proteinases and matrix metalloproteinases from their intracellular granules to the cell surface in proteinase inhibitor-resistant forms and also release high concentrations of proteinases into the pericellular environment; these proteinases transiently overwhelm the local proteinase inhibitor defense (9–11).

The concept that excessive and inaccurate PMN migration is linked to COPD pathogenesis and might be amenable to therapeutic intervention is novel. One limitation of the article is that the authors implicated the PI3K signaling pathway in this migratory defect exclusively by testing the efficacy of a synthetic PI3K inhibitor on PMN migration *in vitro* (8). PI3Ks are a family of proteins that catalyze the phosphorylation of the 3-OH position of phosphoinositides and generate lipids that control a wide variety of intracellular signaling pathways involved in cell growth, proliferation, motility, and survival. PMNs express several PI3K isoforms, including PI3K δ and PI3K γ , which have different biological activities. Not only is LY294002 not selective for different PI3K isoforms, it also has activities on other lipid kinases and other unrelated proteins such as NF- κ B, which is activated in leukocytes in patients with COPD (12). PI3K-independent motility responses have also been reported in human PMNs (13). Future studies could confirm that the PI3K pathways are contributing to the migratory defect observed in COPD PMNs and identify the isoforms involved.

It is also still unclear whether the PMN migratory defect identified in this study occurs exclusively in patients with COPD, since patients with lung diseases other than COPD and AAT deficiency were not studied (8). In this respect it is noteworthy that stimulated PMNs from both patients with COPD and patients with asthma release increased amounts of reactive oxygen species when compared with cells from healthy subjects (14). Furthermore, PMNs from patients with respiratory diseases other than AAT deficiency should be studied in light of a recent finding that PMNs from AAT-deficient patients have abnormal chemotactic responses due, in part, to loss of AAT-mediated regulation of the biological activity of IL-8 (15). It is not clear whether the defect in COPD PMN migration responses to chemoattractants is a primary defect in PMN function in a subset of smokers at risk from progression to COPD or secondary to systemic abnormalities occurring in COPD, since patients with COPD have increased circulating levels of regulators of leukocyte function such as TNF- α , IL-8, IL-1 β , and IL-6 (16). However, the lack of correlation between COPD severity and the PMN migratory defect argues against the latter possibility (8). The contribution of the excessive and inaccurate migration of COPD PMNs to COPD progression also is not clear. Patients with COPD have other PMN functional abnormalities, including defective phagocytosis of bacteria (17) and increased production of oxidants (14), and also have functional abnormalities in other leukocytes germane to COPD pathogenesis, including macrophages and T lymphocytes (18, 19). Nevertheless, the study by Sapey and colleagues confirms

the utility of studying the functional characteristics of peripheral blood PMNs as a surrogate for airway and lung PMNs.

The study by Sapey and coworkers (8) is timely, since it identifies PI3K inhibition as a novel therapeutic strategy for COPD. Components of the PI3K pathway play a crucial role in the expression of inflammatory mediators, inflammatory cell recruitment, and immune cell function in COPD (20). In addition, the PI3K pathway has been successfully targeted to reverse corticosteroid insensitivity in leukocytes from patients with COPD and in the lungs of experimental animals with COPD (21, 22). The study by Sapey and colleagues thus adds weight to the argument that selective PI3K inhibition might have antiinflammatory potential in patients with COPD.

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References

- Laurell C-B, Eriksson S. The electrophoretic alpha-1-globulin pattern of serum in alpha-1-antitrypsin deficiency. *Scand J Clin Lab Invest* 1963; 15:132–140.
- Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, Cherniack RM, Rogers RM, Sciurba FC, Coxson HO, *et al*. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–2653.
- MacNee W, Wiggs B, Belzberg AS, Hogg JC. The effect of cigarette smoking on neutrophil kinetics in human lungs. *N Engl J Med* 1989; 321:924–928.
- Selby C, Drost E, Lannan S, Wraith PK, MacNee W. Neutrophil retention in the lungs of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;143:1359–1364.
- Burnett D, Chamba A, Hill SL, Stockley RA. Neutrophils from subjects with chronic obstructive lung disease show enhanced chemotaxis and extracellular proteolysis. *Lancet* 1987;2:1043–1046.
- Yamagata T, Sugiura H, Yokoyama T, Yanagisawa S, Ichikawa T, Ueshima K, Akamatsu K, Hirano T, Nakanishi M, Yamagata Y, *et al*. Overexpression of CD-11b and CXCR1 on circulating neutrophils: its possible role in COPD. *Chest* 2007;132:890–899.
- Yanagisawa S, Sugiura H, Yokoyama T, Yamagata T, Ichikawa T, Akamatsu K, Koarai A, Hirano T, Nakanishi M, Matsunaga K, *et al*. The possible role of hematopoietic cell kinase in the pathophysiology of COPD. *Chest* 2009;135:94–101.
- Sapey E, Stockley JA, Greenwood H, Ahmad A, Bayley D, Lord JM, Insall RH, Stockley RA. Behavioural and structural differences in migrating peripheral neutrophils from patients with COPD. *Am J Respir Crit Care Med* 2011;183:1176–1186.
- Owen CA, Campbell MA, Sannes PL, Boukedes SS, Campbell EJ. Cell-surface-bound elastase and cathepsin G on human neutrophils: a novel, non-oxidative mechanism by which neutrophils focus and preserve catalytic activity of serine proteinases. *J Cell Biol* 1995;131: 775–789.
- Owen CA, Hu Z, Barrick B, Shapiro SD. Inducible expression of tissue inhibitor of metalloproteinases-resistant matrix metalloproteinase-9 on the cell surface of neutrophils. *Am J Respir Cell Mol Biol* 2003;29: 283–294.
- Campbell EJ, Campbell MA, Boukedes SS, Owen CA. Quantum proteolysis by neutrophils: implications for pulmonary emphysema in alpha₁-antitrypsin deficiency. *J Clin Invest* 1999;104:179–190.
- Gharbi SI, Zvelebil MJ, Shuttleworth SJ, Hancox T, Saghir N, Timms JF, Waterfield MD. Exploring the specificity of the PI3K family inhibitor LY294002. *Biochem J* 2007;404:15–21.
- Chodniewicz D, Zhelev DV. Chemoattractant receptor-stimulated F-actin polymerization in the human neutrophil is signaled by 2 distinct pathways. *Blood* 2003;101:1181–1184.
- Teramoto S, Shu CY, Ouchi Y, Fukuchi Y. Increased spontaneous production and generation of superoxide anion by blood neutrophils in patients with asthma. *J Asthma* 1996;33:149–155.
- Bergin DA, Reeves EP, Meleady P, Henry M, McElvaney OJ, Carroll TP, Condron C, Chotirmall SH, Clynes M, O'Neill SJ, *et al*. Alpha-1 antitrypsin regulates human neutrophil chemotaxis induced by soluble immune complexes and IL-8. *J Clin Invest* 2010;120:4236–4250.
- Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009;33:1165–1185.
- Prieto A, Reyes E, Bernstein ED, Martinez B, Monserrat J, Izquierdo JL, Callol L, de Lucas P, Alvarez-Sala R, Alvarez-Sala JL, *et al*. Defective natural killer and phagocytic activities in chronic obstructive pulmonary disease are restored by glycoprophosphopeptical (immunoferron). *Am J Respir Crit Care Med* 2001;163:1578–1583.
- Hodge S, Hodge G, Ahern J, Jersmann H, Holmes M, Reynolds PN. Smoking alters alveolar macrophage recognition and phagocytic ability: implications in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2007;37:748–755.
- Hodge SJ, Hodge GL, Reynolds PN, Scicchitano R, Holmes M. Increased production of TGF-beta and apoptosis of T lymphocytes isolated from peripheral blood in COPD. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L492–L499.
- Ito K, Caramori G, Adcock IM. Therapeutic potential of phosphatidylinositol 3-kinase inhibitors in inflammatory respiratory disease. *J Pharmacol Exp Ther* 2007;321:1–8.
- Marwick JA, Caramori G, Casolari P, Mazzoni F, Kirkham PA, Adcock IM, Chung KF, Papi A. A role for phosphoinositide 3-kinase delta in the impairment of glucocorticoid responsiveness in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2010; 125:1146–1153.
- Marwick JA, Caramori G, Stevenson CS, Casolari P, Jazrawi E, Barnes PJ, Ito K, Adcock IM, Kirkham PA, Papi A. Inhibition of PI3Kdelta restores glucocorticoid function in smoking-induced airway inflammation in mice. *Am J Respir Crit Care Med* 2009;179:542–548.

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A Metabolic Window into Acute Respiratory Distress Syndrome

Stretch, the “Baby” Lung, and Atelectrauma

Protective ventilation strategies are central to the conventional management of patients with the acute respiratory distress syndrome (ARDS). Experimental studies (1) suggest two main mechanisms of ventilator-induced lung injury: volutrauma, injury from excess distension; and atelectrauma, local shear injury from tidal opening and closing. Lung distension and tidal opening result from a balance of recruitment and tidal volume, but the

contribution of each is unpredictable. Thus, while sound principles exist for population-based recommendations—avoid excess lung stretch—the specifics remain polemic.

In this issue of the *Journal*, Bellani and coworkers (pp. 1193–1199) report that, in patients with ARDS, the metabolic activity—likely reflecting inflammation—in aerated lung regions was correlated with the tidal volume delivered to those regions, as