New Collaborations Aim to Speed Drug Development in COPD

Written by Anne Jacobson

Drug discovery and development is a complex and expensive process. Clinical trials are major investments for industry and for academic researchers but also for patients, many of whom could undergo repeated clinical, radiographic, and laboratory assessments without the promise of therapeutic benefit.

One option for streamlining drug development includes ending the development of less effective drugs earlier in the development process. This requires the use of surrogate markers that better predict clinical efficacy and safety. Novel biomarkers, for example, may serve as intermediate outcome measures in patients with chronic obstructive pulmonary disease (COPD). Another option involves identifying the specific population of patients who are most likely to benefit from a particular drug—the right drug for the right patient at the right time. Specific patient populations could be determined by patient profile (phenotype), including factors, such as age, gender, x-ray CT findings, blood biomarkers, and genetic or clinical profile. Target populations could also be restricted to certain disease stages, such as early versus late disease or previously untreated versus treatment-refractory COPD.

In this session, presenters described two major research collaborations that are aimed at advancing the discovery and development of new treatments for COPD.

The COPD Biomarker Qualification Consortium

Biomarkers play a prominent role in every stage of drug development. In preclinical studies, biomarkers can be used to determine whether therapeutic targets are relevant in disease pathology. In Phase 1 studies (healthy volunteers), biomarkers can be used to explore mechanism of action, pharmacology, and optimal dosing. In Phase 2 and 3 studies (patients with disease), biomarkers are essential for assessing clinical outcomes. As an example of biomarkers in COPD, the forced expiratory volume in 1 second (FEV_1) has been instrumental in characterizing airflow obstruction and determining efficacy of bronchodilator-based therapies. However, COPD is a heterogeneous disease, and a single biomarker is not sufficient to evaluate the potential efficacy of promising drug candidates across diverse patient phenotypes.

Qualifying a novel biomarker requires a large volume of preclinical and clinical data, which is difficult for individual research programs to amass. The COPD Foundation launched the COPD Biomarkers Qualification Consortium (CBQC), a new collaboration of government agencies, academic medical centers, and pharmaceutical companies that will share data on the identification and validation of COPD biomarkers. Ruth Tal-Singer, PhD, GlaxoSmithKline, King of Prussia, Pennsylvania, USA, and Industry Chair for the CBQC, described the goals of the new initiative.

Table 1. COPD Biomarker Qualification Consortium: Example Biomarkers.

Biomarker Candidate	Role in COPD
St. George's Respiratory Questionnaire for COPD (SGRQ-C)	A rating scale for health status and disease impact
6-minute Walk Distance (6MWD)	A marker to stratify risk of mortality
Plasma Fibrinogen	A marker to stratify risk of mortality and hospitalization

Biomarker qualification is the process of evaluating the clinical utility of biomarkers. According to the United States Food and Drug Administration (FDA), a biomarker is qualified when the scientific, medical, and regulatory communities agree that its measurement is analytically valid. In addition, when

Highlights from the
American Thoracic Society 2011 International Conference

a qualified biomarker is evaluated, the test result can be relied upon to provide specific physiological, toxicological, pharmacological, or clinical meaning. Early candidates for biomarker qualification in COPD are listed in Table 1.

The CBQC was launched in October 2010, with three specific goals. The first is to qualify biomarkers through the FDA and European Medicines Agency (EMA) to facilitate the development of new treatments for COPD. Second, the CBQC aims to identify biomarkers for which sufficient data already exist in industry, academic, and government databases to warrant consideration for qualification. The third mission of the CBQC is to identify and fill any additional gaps in biomarker development by facilitating collaborations within the international research community.

The SPIROMICS Collaborative Study

The Subpopulation and Intermediate Outcome Measures in COPD Study (SPIROMICS) is an ongoing collaboration that is led by the National Heart, Lung, and Blood Institute (NHLBI) to evaluate the heterogeneity of COPD. Tom Croxton, PhD, MD, NHLBI, Bethesda, Maryland, USA, described the background, design, and goals of the SPIROMICS initiative.

Smoking is the primary risk factor for the development and progression of COPD. However, in the COPD Genetic Epidemiology (COPDGene) Study, smoking history correlated only weakly with lung function in patients with COPD [www.COPDGene.org]. The lack of a dose-response relationship between pack-years of smoking and FEV_1 was a surprising finding that underscores the complexity of COPD. Indeed, other recent studies have revealed many diverse factors that influence the natural history of COPD, including systemic inflammation, infectious colonization, and immune dysregulation. At the cellular level, mucous metaplasia, apoptosis, and matrix degradation also contribute to COPD.

According to Dr. Croxton, the SPIROMICS collaborative study arose from the recognition that developing effective pharmacotherapies for COPD requires a comprehensive understanding of the disease process, which can only be realized through the analysis of a wide spectrum of characteristics, including phenotypic, biomarker, genetic, genomic, and clinical data.

SPIROMICS has two main objectives. The first objective is to identify subpopulations of COPD patients who are pathogenetically and mechanistically homogenous, based on clinical characteristics, biomarkers, genotypes, and imaging studies. The second objective is to identify practical surrogate markers of COPD severity that can be incorporated into future clinical trials, including early-phase proof-of-principle and dose-ranging studies. The goal is to accelerate the development of new COPD therapies by identifying potential intermediate outcome measures for use in COPD research.

SPIROMICS will recruit approximately 3200 individuals across a range of age groups and ethnic backgrounds, comprising 2400 patients with COPD, 600 smokers with normal lung function, and 200 never-smokers. To maximize the applicability of study findings to the COPD patient population, there will be few restrictions on study eligibility. Patients will undergo annual assessment of lung function and biochemical measures for at least 3 years (Table 2). In addition to the core longitudinal study, SPIROMICS will also include substudies that are related to bronchoscopy, COPD exacerbations, and mucus clearance.

Table 2. SPIROMICS: Patient Assessment Measures.

Year	Assessment Measures	
0	• Questionnaires • Bronchodilator spirometry • 6-minute walk test	• Blood collection • Sputum collection • CT imaging
1	• Questionnaires • Bronchodilator spirometry • 6-minute walk test	• CT imaging • Blood collection • Sputum collection
2	• Questionnaires • Blood collection	• Bronchodilator spirometry
3	• 6-minute walk test • Blood collection	• Questionnaires • Bronchodilator spirometry

The SPIROMICS initiative also represents a new model for prospective collaboration in COPD research. Through SPIROMICS, participating medical centers will build a rich repository of biochemical specimens for ongoing research projects. SPIROMICS will also develop bioinformatics resources that will facilitate the sharing of clinical, biomarker, radiographic, and genetic data across participating sites and external investigators. Medical centers that are currently involved in the SPIROMICS project include Columbia University, Johns Hopkins University, University of California at Los Angeles, University of California at San Francisco, University of North Carolina at Chapel Hill, University of Utah, Wake Forest University, and University of Michigan.

Through unprecedented collaborative efforts, the CBQC, SPIROMICS, and similar global public-private partnerships have the potential to discover new biomarkers and therapeutic agents that can improve the diagnosis, monitoring, and treatment of COPD while expediting the development of novel therapies. Preliminary reports from these research groups may have clinical implications on COPD management in the near future.