Pulmonologist Nick ten Hacken reflects on COPD and the role of the BDC in pulmonary medicine.

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in the world and represents an important public health challenge that is both preventable and treatable. COPD is a major cause of chronic morbidity and mortality throughout the world: many people suffer from this disease for years and die prematurely from its complications. Globally, the COPD burden is projected to increase in the coming decades because of continued exposure to COPD risk factors and aging of the population.[1]

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for the disease (*e.g.* smoking). Spirometry is a lung function test that is required to make the diagnosis in this clinical context, and particularly the FEV_1/FVC ratio is an important parameter. The presence of a post-bronchodilator FEV_1/FVC ratio < 0.7 confirms the presence of persistent airflow limitation and thus of COPD. [1] FEV_1 is relatively easy to obtain, highly reproducible and tracks health outcomes in COPD. Therefore, FEV_1 has been the gold standard biomarker for COPD for many decades. However, there are also disadvantages, as FEV_1:

1. does not give information about underlying disease activity or pathological processes;
2. can not separate the various phenotypes of COPD;
3. is not specific for COPD as it is modified by other lung diseases;
4. is relatively unresponsive to known therapies that prolong survival or other clinical outcomes of COPD.[2]

With the recognition that COPD is a heterogeneous disease with different phenotypes and different underlying pathologies, there is a growing need for personalized treatment based on objective biomarkers. With the growing awareness of COPD as a systemic disease, there has been a shift in the emphasis of biomarker discovery towards blood specimens. Indeed, a large number of candidate blood biomarkers has been put forward, however most of them lack a clear relationship with important health outcomes. With respect to this, a large 3-year observational controlled multicenter international study (ECLIPSE[3]) was initiated that aimed at defining clinically relevant subtypes of COPD and identifying novel biomarkers and genetic factors. A number of promising biomarkers in blood was identified, but none fulfilled the criteria of being an excellent biomarker. A few years later, the COPD Biomarker

Qualification Consortium (CBQC[4]) was initiated in collaboration with the FDA, COPD Foundation, National Heart & Lung Institute and scientists from the pharmaceutical industry and academia. This consortium listed a number of potential blood biomarkers for COPD that should be validated and replicated in large studies. However, the CBQC lacks the technical knowledge and utilities to optimize accurate blood assays with high sensitivity, specificity, and repeatability that can be used across academic centers worldwide.

In that perspective, the Biomarker Development Center (BDC) in my opinion is a unique opportunity. This extensive public-private partnership in close collaboration with clinicians, industry and patient stakeholder associations, aims to bring promising biomarkers towards commercial applications based on stringent and transparent criteria. The mission statement of the BDC is to narrow the biomarker development gap by professionalizing the validation of biomarker candidates through an end-user-driven approach. In other words, the above described CBQC could be seen as a potential end-user. On the other hand, the CBQC could have a consultant function for the BDC in prioritizing candidate biomarkers for further validation. Moreover, because pharmaceutical industries and the FDA are involved in the CBQC consortium, this could help in raising money for future COPD biomarker validation studies.

The role of BDC in pulmonary medicine is difficult to predict. This will depend on the successful meeting of a number of challenges like:

- being able to work together in a consortium, showing that collaboration between public-private partners is productive;
- finding creative solutions for all technical complications in the lab;
- getting access to specimens from large cohort studies of well characterized patients;
- storing data from these studies in big databases and performing adequate statistics taking the right clinical confounders into account;
- raising money to perform large biomarker validation studies.

If the BDC consortium is able to take these hurdles, a number of unmet needs in the diagnosis and management of COPD can be supported, although this would take at least 5-10 years in my opinion. We then could have biomarkers that are able to predict which smokers will develop COPD later in life; which COPD patients frequently exacerbate; which COPD patients have a fast decline in lung function; and which patients respond well to inhaled

corticosteroids. Being able to answer these clinical questions will inevitably have a great impact on COPD medicine and particularly on the lives of many patients suffering from COPD.

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD: update 2015. Available at: http://www.goldcopd.org/.
2. Sin DD, Vestbo J. Biomarkers in chronic obstructive pulmonary disease. Proc Am Thorac Soc 2009; 6(6): 543-545.
3. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints. ECLIPSE website. Available at: http://www.eclipse-copd.com/.
4. COPD Foundation. COPD Biomarker Qualification Consortium information page. Available at: http://www.copdfoundation.org/Research/COPD-Biomarker-Qualification-Consortium/Learn-More.aspx.

Nick ten Hacken received his PhD in 1998 and has been working as a pulmonologist since 1994. He was appointed Associate Professor in 2005. He is currently working at the Department of Pulmonary Diseases of the University Medical Center Groningen and is involved in the BDC as Principal Investigator of the "COPD Demonstrator Project". His ambition in research focuses on phenotyping obstructive airway diseases, developing new biomarkers, exploring the role of small airways, modifying life style factors (physical activity, smoking, obesity), understanding exercise physiology and studying systemic inflammation and multi-morbidity. Furthermore he is closely involved in studying innovative endobronchial intervention techniques for COPD and asthma. In the following, Nick ten Hacken reflects on COPD and the role of the BDC in COPD medicine.