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The COPD Pipeline XXXIII

Nicholas Gross, MD, PhD[1]

Abbreviations: chronic obstructive pulmonary disease, **COPD**; phosphoinositide 3-kinase, **PI3K**; muscarinic beta2-agonist, MABA; mitogen-activated protein kinase inhibitor, **MAPKi**; non-invasive ventilation, **NIV**; forced expiratory volume in 1 second, **FEV_1**

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1 University Medical Research, Saint Francis Hospital and Medical Center, Hartford, Connecticut

Address correspondence to:

Nicholas Gross, MD, PhD
grossnicholas1@gmail.com

The Top 25

How are we pulmonologists doing for new COPD drugs? Sales data from 2015 have just been published. Pharmaceutical companies report new drugs for the year, providing information about drugs approved and in the pipeline for each of the "Top 25 Companies."[1] Novartis, the top drug company for some years, had 8 new drugs approved last year, none of which were pulmonary drugs. They also had 4 drugs pending approval and 20 drugs in Phase IIB and beyond. One of the latter was the asthma drug QMF149 (fixed indacaterol/mometasone combination).

Pfizer is next in line with 3 approved drugs in 2015, 3 drugs pending, 12 drugs in Phase IIB, and 15 drugs in early research. But no pulmonary drugs were created in 2015. Next is Sanofi with 3 approved drugs, but no pulmonary drugs in 2015. Then Merck, number 4, and Roche number 5, neither of which provided any pulmonary drugs in 2015. GlaxoSmithKline was number 6, with 2 asthma drugs approved in 2015, Nucala (mepolizumab) and Breo Ellipta (fluticasone furoate/vilanterol) but not for chronic obstructive pulmonary disease (COPD). After Gilead at number 7, and Johnson & Johnson at number 8, we get our first COPD drug: Bevespi Aerosphere™ (AstraZeneca's fixed combination of glycopyrrolate and formoterol fumarate). We have to wait to pharma company number15, Boehringer-Ingelheim, for our next COPD-approved drug which is Spiolto Respimat (a fixed tiotropium bromide/olodaterol combination). All the way through the remaining pharmas to number 25 there is not another COPD drug approved, pending, in Phase IIB or beyond, or in early research. Not only that but not a single one of the COPD drugs in "the pipeline" is for an agent with a new mechanism.

On the brighter side, all of the first 3 reports in this month's Pipeline column (below) deal with novel mechanisms for COPD.

CHF6297

CHF6297 is a "potent and selective inhibitor of human MAP kinase p38."[2] It is being developed as an anti-inflammatory agent for airway diseases among other conditions. NCT02815488 is its first trial in humans and this is a Phase I/II trial. The purpose is to evaluate the safety and tolerability, as well as pharmacokinetics and pharmacodynamics of single and repeat doses of the dry powder. If safety outcomes allow, the trial will progress to a lipopolysaccharide challenge.

GS5745

GS5745 is a matrix metalloprotease-9 (MMP9) monoclonal agent being developed as an anti-inflammatory agent for a variety of disorders, all early phase, including one Phase I trial for COPD (NCT02077465).[3] The medication is administered by 2-weekly intravenous infusions and the primary outcomes are safety and change in pre-bronchodilator FEV_1 percent predicted.

GSK2269557

GSK2269557 is described as "a potent and highly selective inhaled phosphoinositide 3-kinase delta

inhibitor being developed as an anti-inflammatory and anti-infective agent in subjects with activated phosphoinositide 3-kinase (PI3K) delta syndrome."[4] It has been in trials for idiopathic pulmonary fibrosis, and asthma, as well as other disorders and is now being studied as a drug for COPD. Two similar Phase II trials have been completed (NCT02294734[5] and NCT01462617[6]).

AZD8871

AZD8871 is a dual pharmacologic beta-agonist-antimuscarinic, muscarinic beta2-agonist (MABA) from AstraZeneca. Clinical trial NCT02814656 is its first-in-human safety trial.[7] If initial single doses are well tolerated, the trial will progress to an ascending dose format. The formulation is a dry powder. The sponsors state that their aim is a potential treatment for either COPD or asthma (or both) and that, ultimately, a fixed combination of this MABA and an inhaled corticosteroid may be developed, creating what amounts in effect to a triple agent.

Neutrophil Lung Imaging

Neutrophil lung imaging, an interesting and quite original technology, aims to provide objective information about neutrophil retention in the lungs, presumably as an index of inflammation in the lungs, a key aspect of COPD that has been difficult to quantitate. Following injection of labelled neutrophils in healthy individuals or patients with COPD, "the uptake of labelled neutrophils in the lung will be assessed by single-photon emission tomography" (NCT02551614).[8] This is an exploratory study to further develop an imaging platform for the assessment of whole lung neutrophil retention.

Rejuvenair

Rejuvenair, a product of CSA Medical, is a procedure that employs liquid nitrogen to treat inflamed bronchial tissue. Details of the procedure are not provided nor are results of its use. The web site states "...the truFreeze® System is an advance in the proven science of cryoablation that is designed to deliver extremely cold (-196° C) liquid nitrogen spray through a small catheter to apply even thermal injury and flash freeze a variety of tissue surfaces. During this process cells are selectively destroyed while the underlying collagen structure is preserved, providing a scaffold for healthy tissue to re-grow."[9] The Phase II clinical trial will enroll 11 patients with chronic bronchitis and COPD. The primary outcome is safety and feasibility (NCT02483637).[10]

CNTO 7160

CNTO 7160 is a Janssen monoclonal antibody that prevents interleukin-33 from binding to the ST2 receptor (IL-33R); it is expected to be useful in severe asthma via the regulation of inflammatory cells that are key to asthma such as neutrophils and eosinophils.[11] The present trial is a Phase I trial that includes individuals with asthma or atopic dermatitis, but trials in COPD are likely to follow if the drug is well tolerated and effective.

Losmapimod

Losmapimod, an oral p38 mitogen-activated protein kinase inhibitor (MAPKi), targets MAPKs activated in macrophages and endothelial cells that occur as a part of airways inflammation. It has been through trials for a major depressive disorder and coronary vascular inflammation following plaque rupture but outcomes have been mixed. In a previous severe COPD study, the drug failed to meet the primary outcome which was an increase in exercise tolerance.[12] The primary outcome of a recently completed Phase II study was a decrease in acute exacerbations (NCT02299375).[13]

Lebrikizumab

Lebrikizumab is a La-Roche monoclonal anti-IL-33 agent that has shown efficacy in improving the rate of asthma exacerbations and lung function in patients with moderate-to-severe asthma.[14] It is now being tested for an improvement in lung function in a 24 week Phase II trial of COPD. The trial is a randomized, double-blind, placebo-controlled, parallel-group trial. It is enrolling 300 individuals with COPD and a history of exacerbations who are being treated with inhaled corticosteroids and at least 1 long-acting inhaled bronchodilator. The primary outcomes are safety, efficacy, and patient-reported outcome measures. (NCT02546700).[15]

Benralizumab

Benralizumab is a monoclonal from Medimmune directed against IL-5. It is in a Phase II trial with the primary endpoint being the frequency of moderate or

severe acute exacerbations of COPD (NCT01227278).[16] The drug is currently in 56 trials including a wide variety of solid, metastatic, and vascular malignancies, many diverse autoimmune disorders, rheumatoid disease, diabetes mellitus, and some complications of infectious diseases, plus about 20 asthma studies in which the drug has achieved significant decreases in the frequency of acute asthma exacerbations. Finally, the drug has gotten around to COPD.

HOmeVent

HOmeVent is the abbreviation for the "Registry of Stable Hypercapnic Chronic Obstructive Pulmonary Disease Treated with Non-Invasive Ventilation" trial.[17] There is evidence that non-invasive ventilation (NIV) therapy is an effective option for some COPD patients who have been hospitalized for acute respiratory failure and secondary hypercapnia. NIV has improved the survival rate and quality of life in some such COPD patients. It is suggested that these outcomes represent an important advance in the field, and that the use of NIV in patients with chronic hypercapnic COPD should increase, possibly addressing the health care burden incurred by these patients. However, the proportion of stable COPD patients with chronic hypercapnia is unknown. There is a paucity of data regarding NIV usage patterns over time in this setting. The present study, NCT02811588,[17] is a registry that will enroll 300 COPD patients with GOLD stage III and IV. The primary outcome is the prevalence of hypercapnia in patients with COPD. The study is observational, prospective, and not controlled.

Tacholiquine

Tacholiquine, or its active ingredient Tyloxapol is, a mucolytic agent, claimed to have significant anti-inflammatory properties *in vitro*.[18] It has been the subject of a recent 3-week clinical trial sponsored by bene-Arzneimittel GmbH. The purpose was to evaluate the mucolytic activity of tacholiquine compared to saline in chronic bronchitis patients. At 3 weeks the "sputum weight was significantly greater" in the active group than the saline comparison group. Sputum cells were decreased as were sputum IL-1β, IL-6 and IL-8 in the active group. However, lung function tests and standardized clinical questionnaires were unchanged. The authors conclude, "our study demonstrated that inhalation of Tyloxapol by patients with COPD is safe and superior to saline and has some anti-inflammatory effects."[18]

Bezlotoxumab

Bezlotoxumab is a human monoclonal antibody designed for the prevention or recurrence of *Clostridium difficile* infection.[19] A Merck drug, it was approved by the Food and Drug Administration last July after some criticism by experts along the way. It is expected to commence marketing in early 2017 under the trade name ZINPLAVA™.

TD4208

TD4208 Revefenacin is a once-daily, nebulized long-acting muscarinic antagonist in late-stage development for the long-term management of COPD. It is currently in duplicate Phase III trials (NCT02459080[20] and NCT02512510[21]). Its developers, Theravance in collaboration with Mylan, state "the drug could serve as a foundation for combination products and for delivery in metered dose inhaler and dry powder inhaler products."[22]

CHF 5993

CHF 5993 is Chiesi's Phase III triple dry powder inhalation of the fixed combination of beclomethasone dipropionate, formoterol and glycopyrronium bromide via pressurized metered-dose inhaler. It is in a trial versus the combination of fluticasone and vilanterol by dry powder inhaler plus tiotropium by Respimat. The trial is open label and the primary outcome is non-inferiority in the St. George's Respiratory Questionnaire (NCT02467452).[23]

Umeclidinium/Vilanterol with Tiotropium/Olodaterol

The clinical trial NCT02799784 is a Phase IV head-to-head trial of umeclidinium/vilanterol (via the Ellipta delivery device) versus tiotropium/olodaterol (via Respimat).[24] The format is a cross-over with two 8-week terms separated by 3 weeks of washout. The primary outcome is trough forced expiratory volume in 1 second (FEV_1) at the end of each 8 week trial period.

Zephyr EBV valve

The Zephyr EBV valve, Pulmonx's endobronchial valve, is in a multicenter, prospective, randomized trial versus standard of care in individuals with heterogeneous emphysema (NCT02022683).[25] The primary outcome

is change in FEV_1 at 3 months. The trial, predicted for 94 individuals, will be performed entirely in Europe.

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