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The COPD Pipeline XXXIV

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Abbreviations: research and development, **R&D**; adipose-derived cellular stromal vascular fraction, **AD-cSVF**; chronic obstructive pulmonary disease, **COPD**; phosphoinositide 3-kinase, **P13K**; EXAcerbations of Chronic pulmonary disease Tool, **EXACT**

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The Pharmaceutical Industry

Inevitably, we are interested in the industry with which we interact every day. A very short report of its state is of interest (a more detailed report can be found elsewhere[1]). Among the top 15 pharmaceutical companies, overall Research and Development (R&D) spending worldwide remains consistent at a collective total of about $70 billion a year. In order of annual revenue (for 2015), Roche was at the top for R&D, followed in order by Johnson and Johnson, Novartis, Pfizer, Merck, Bristol-Myers Squibb, AstraZeneca, Sanofi, Eli Lilly, GlaxoSmithKline, AbbVie, Amgen, Celgene and Takeda.[1] R&D spending by the top 3 is close to each other, each being about $9 billion per year; the last 3 are about $3 billion each. As a percentage of overall revenue, the proportion of investment in R&D is around a disappointing 15%-20% for most pharmas, the exceptions being Bristol-Myers at 36% and Celgene at 40%. For us pulmonologists, one looks to Novartis (near the top), and AstraZeneca and GlaxoSmithKline (middle of the pack). Looking to the future is difficult because much of the really innovative work is done by small companies which belong to the "big boys" and that will only be brought into the major company when and if the small companies show some real promise, a strategy that protects the shares of the major players.

Adipose-Derived Cellular Stromal Vascular Fraction (AD-cSVF)

The use of stem cells to restore the activity of failing organs has a history of controversy that is in part related to ethical concerns. However, the availability of autologous stromal cells opens up the possibility that autologous cells can be harvested from patients and re-infused in the expectation that the infused cells can repopulate failing organs and achieve improved function.[2] An outline of a new clinical trial is available (NTC02946658).[3] In the words of the investigators "this study includes microcannula harvesting of subdermal adipose tissues, incubation, and isolation of AD-cSVF. This stromal pellet is then suspended in normal saline and deployed via...intravenous route."[3] A Phase 1 study is for safety outcomes and a Phase 2 study will enroll 100 individuals with severe chronic obstructive pulmonary disease (COPD), the outcome being lung function.

GSK2269557

GSK2269557 is described as "a potent and highly selective inhaled phosphoinositide 3-kinase (PI3K) delta inhibitor being developed as an anti-inflammatory/anti-infective agent in subjects with activated PI3K delta syndrome."[4] It has been in trials for idiopathic pulmonary fibrosis and asthma as well as other disorders. Two similar phase 2 trials have just been completed (NCT02294734 and 01462617).

SB681323

SB681323 also known as dilmapimod, is a mitogen-activated protein (MAP) kinase inhibitor from GlaxoSmithKline. It has been the subject of studies in

rheumatoid arthritis, neuropathic pain, coronary artery disease and now COPD. The trial (NCT00564746) is a Phase 1 study in healthy individuals and is now completed. A previous Phase 2 COPD trial was completed but there do not seem to be any reported results.

Danirixin

Danirixin, a GlaxoSmithKline agent, is a small molecule reversible C-X-C chemokine receptor-2 antagonist with high-affinity and selectivity. Two trials have been completed, one being in healthy individuals, a second in patients with COPD. One ongoing randomized, placebo controlled study is in phase 2. The trial aims to recruit 600 individuals with moderate or severe COPD. The individuals will receive placebo or drug twice daily by mouth for 24 weeks. The primary outcomes include pulmonary function, pulmonary symptoms as determined by a subset of the EXAcerbations of Chronic pulmonary disease Tool (EXACT), and adverse events (NCT03034967).[5]

AQX-1125

AQX-1125, an Aquinox agent, is an activator of SHIP1, the agent that controls the PI3K cellular signaling pathway. Activation of SHIP1 reduces the migration of immune cells and thus reduces inflammation.[6] A new trial will enroll a total of 400 individuals with severe or very severe COPD. The agent (or placebo) will be administered orally, once daily, and will be maintained for 12 weeks. The primary outcome is a change in current symptoms as measured by the EXACT tool (NCT 01954628).[7]

PEP03

PEP03 is an orally active 5-LO inhibitor being developed in Taiwan. Its action is to block both cysteinyl leukotrienes and leukotriene B4. Clinical studies (unpublished) indicate that it is capable of improving lung function in asthmatic patients. Because there is evidence that leukotrienes may also contribute to the pathology of COPD,[8] the present study has been initiated (NCT00219648). It is a phase 2 randomized double-blind, placebo-controlled, dose-finding, 12-week trial in COPD individuals. The primary and secondary outcomes are not stated; the status of the study is unknown according to ClinicalTrials.gov.[9]

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