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The COPD Pipeline XIV

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This column begins with more research that addresses the most important unmet need in COPD, -a means of turning off the ongoing inflammation in COPD airways. Some of the projects mentioned here and in previous "Pipelines" are beyond the horizon having not even reached the preclinical stage. However, one hopes that some of them will bear fruit in our lifetimes.

Multispecific Antibodies

While monoclonal antibodies have found uses in some disorders, e.g. omalizumab for asthma, their success in disorders where there is no single target tends to be limited or short-lived. Malignant diseases are examples, to which one might add inflammatory diseases. To address this problem, several biotech companies are working on multispecific antibodies. These are antibody drugs that either combine 2 or more monoclonals in fixed combinations, or, more likely, by synthesizing a fusion product that addresses two or more targets, -a multispecific antibody (1).

Some of the larger pharmaceutical companies have already acquired biotech companies that have promising agents or expertise in the area. One such agent is catumaxomab, a trifunctional antibody which binds both tumor cells and T cells. The agent, manufactured by Fresnius Biotech GmBH and named Removab®, has been approved to treat malignant ascites in some European countries. It has orphan drug status in USA and clinicaltrials.gov lists 12 trials, mostly in Phase II.

In a previous Pipeline, I reported on "broad spectrum chemokine inhibitors", one of which, FX125L, was in clinical trials (2). Its rationale, analogous to that for multispecific antibodies, was that redundancy within the immune system required a solution that would shut down multiple inflammatory pathways. One hopes that the identification of some key pro-inflammatory agents in COPD will enable the development of a multispecific antibody that will arrest the ongoing inflammation. As always, the key is to discover the basic pathobiology of COPD inflammation to the extent that we know what potential targets to aim at.

RNA interference

This is a process that moderates the activity of genes, usually suppressing or silencing a gene by inactivating its mRNA product. In brief, a message can be degraded before it is translated by the introduction of a small RNA molecule that is complementary to a part of the mRNA. The double-stranded RNA molecule is recognized by a specific RNAse which cleaves it, preventing it from instructing the translation into a protein. The biological function of RNAi is believed to be a defense against viral infections. Employed as a research tool since its discovery in the 1990's, RNAi is now being looked at for its potential uses in medicine, respiratory syncytial virus infection being one. In laboratory models, it is a powerful and highly specific way to limit the expression of a target protein. However

at least two main obstacles to its wider exploitation exist. The first is the identification of a key target which, as stated above, is a big question in COPD. The second is a means to deliver the silencing double-stranded RNA into the cell, -a problem that is similar to that of correcting genetic defects with gene therapy. Another potential concern is the accidental silencing of off-target genes that happen to have sequences similar to the target's gene.

The problem of delivery has been addressed by wrapping the RNA in fat-like molecules called lipidoids, a technique that has been successfully employed in mice with a variety of models of inflammation (3). The target molecule was CCR2, the chemokine receptor that inflammatory monocytes require to localize to inflammatory sites. When the CCR2-specific silencing RNAi was administered systemically to the mice, it accumulated in spleen, bone marrow and monocytes. Efficient degradation of CCR2 mRNA in monocytes occurred and prevented their accumulation at the sites of inflammation. Essential functions of the innate immune system were spared, thus limiting unwanted effects. One can envision a similar molecular approach being used to turn off the persistent inflammation in COPD. As always, there will be other problems to overcome, but although it is several years off, the therapeutic application of RNAi holds great potential for the treatment of COPD as well as other chronic inflammatory disorders.

PUR118 is described by its maker Pulmatrix as a 'calcium-based dry powder' inhalation which has anti-inflammatory properties. Studies in smoke-challenged mice suggest it may reduce the frequency of acute exacerbations. There is one listing in clinicaltrials.gov (NCT01333904), -a phase I study the endpoints of which include sputum markers of inflammation and mucociliary clearance.

Hemolung, an Extracorporeal CO_2 Removal System

An alternative to mechanical ventilation in patients with hypercapnic respiratory failure has been sought for many years. A less invasive method for the removal of CO_2 from the circulation was innovated by Hattler 10 years ago. It uses a single intravenous catheter to remove up to 100ml CO_2/min and has been validated in experimental animal models. The system, Hemolung, has now been applied to 5 patients with acute on chronic respiratory failure (4). The $PaCO_2$ was lowered from a mean of 83 mm Hg to 69 mm Hg in the first hour and to 60 mm Hg over the next 11 hours. The patients reported a reduction in dyspnea. Apart from local bleeding no serious adverse events were experienced. The authors conclude "the Hemolung may be a safe and effective extracorporeal CO_2 removal technique."

Dulera for COPD?

Dulera, Merck's fixed combination of mometasone furoate plus formoterol fumarate, was approved for asthma in 2 dosage formulations last year. Two 26-week Phase III trials aimed at a COPD indication were recently completed. Both formulations, 200 mcg of mometasone plus 10 mcg formoterol b.i.d. and 400 mcg mometasone plus 10 mcg formoterol b.i.d., were superior to mometasone monotherapy or placebo by area under the FEV_1 curve ($AUC_{0\text{-}12}$) at 13 weeks. However, the other co-primary, morning predose FEV_1 versus formoterol monotherapy, was missed by both formulations in one of the 2 studies. Extensions to 1 year for safety evaluation were performed. The NDA for the COPD indication will shortly be reviewed by the FDA.

RPL554 is a long-acting inhibitor of both phosphodiesterase (PDE) 3 and PDE4 that is being developed by Verona Pharma and studied in both asthma and COPD. The rationale for this unusual combination of actions is that while PDE4 is the predominant PDE of lung inflammatory cells, its inhibition results in only modest bronchodilation. PDE3 inhibition, however, mediates airway smooth muscle relaxation. The combination of both actions in a single molecule is expected to have both meaningful bronchodilatory and anti-inflammatory actions. Although PDE3 inhibition is not entirely free of possible cardiac tachyarrhythmia concerns, the inhalation route of administration of RPL554 may mitigate this side effect. It may also mitigate the gastro-intestinal side-effects commonly seen with PDE4 inhibition (5).

The company's latest press release (November 10, 2011) states that the recently completed phase IIa in moderately severe COPD patients was successful and showed bronchodilation of "up to 10% over placebo" and that no cardiovascular or other safety issues were observed. No trials of this agent are listed in clinicaltrials.gov.

SEL-068 is a "nicotine vaccine candidate for smoking cessation and relapse prevention" under development by Selecta Biosciences, Inc. The company has a novel Synthetic Particle Vaccine (SVP) platform that "elicits vigorous immune responses to a wide array of relevant antigens, including small molecules, peptides, oligosaccharides, and proteins". SEL-068 is fully synthetic and induces a high and specific antibody response to nicotine, avoiding the off-target response to biologic carriers inherent in conventional vaccines. The aim is to avidly 'mop up' nicotine in the circulation preventing it from reaching the brain etc. This is their first such vaccine in clinical development and is currently in Phase I (NCT01478893). "Universal" HPV and influenza vaccines are also in development.

Frequent Amendments to Ongoing Clinical Trials

Clinical trials are expensive. Tufts Center for the Study of Drug Development studied the frequency of trial amendments, which can contribute to costs, and found that across all clinical trials there were, on average, 2.3 amendments per trial protocol, each requiring 6.9 protocol changes, leading to delay and unplanned expense (6). Undoubtedly, some of these were safety-related. One of the study investigators commented "..sponsors can minimize [amendments] through better initial study design.." Agreed, however the study also found that 43% of protocol amendments occurred before

the first subject was enrolled. This seems to confirm what I and some other investigators experience, which is that the clinical research organizations, CRO's that conduct almost all pharmaceutical studies nowadays, are anxious to lock in commitments from study sites as quickly as possible. To this end, they send out the protocols before they have been finalized so that investigators at the sites can obtain approval from their respective Institutional Review Boards. In due course, the finalized protocol arrives and must be approved again. Why else would 43% of protocols need to be amended before the study has even begun? The work and expense entailed falls on the investigators and the research sites.

The Unpipeline

Geron Corp. is bowing out of the stem cell field it pioneered citing the long, costly path embryonic stem cells will have to face to become real-world products. It had been working on a stem cell-based treatment for spinal cord injury and one hears that a possible emphysema program was being weighed (7). No major research problems precipitated their decision but Geron estimated it would be at least a decade before approval and the company acknowledged it could make more money by completing two experimental cancer drugs that are already in mid-stage testing. Osiris Therapeutics's Prochymal™ stem-cell preparation is being studied as a treatment for COPD and recently completed Phase II (NCT00683722). As far as I know there is no other on-going stem cell program for COPD.

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