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MATRIX METALLOPROTEASE-12 INHIBITORS

If you visit the web site of the Pharmas that have, or would like to have, a respiratory portfolio and check out their 'pipeline', you will occasionally see an entity labeled 'MMP inhibitor'. It might or might not be in their respiratory section and the agent will be in Phase I or II. You might also have seen 'MMP' in the title of a research publication. What's this about? The matrix metalloproteases are of interest as potential culprits of connective tissue destruction in a number of chronic inflammatory conditions including emphysema. We are familiar with the protease-antiprotease mechanism that alpha-1 antitrypsin deficiency (AATD) revealed. Only a very small proportion of patients with emphysema have AATD, of-course, so it was reasonable to seek related pathogenetic mechanisms of lung destruction, -other proteases that might play a role in the 99% of patients with emphysema who do not have AATD.

The MMPs are a large family of zinc-dependent peptidases that are secreted by macrophages (among other cells) and that can degrade extracellular matrix proteins including elastin and collagen, as well as a range of bioactive molecules. They seem to be the body's construction workers, being involved in projects like angiogenesis, cell proliferation, migration, differentiation, apoptosis, host defense and tissue remodeling. Some MMPs may be involved in tumor suppression, others possibly in tumor progression. Clearly they are serious players, and alveolar macrophages are packed with them. A trickle slowly becoming a river of animal and human studies in recent years, including one in this Journal (*Wallace AM et al. COPD 2008;5:13–23*), have strongly suggested that MMP-12 in particular can produce emphysematous lung damage; it is released in response to cigarette smoke, its level in sputum is higher in smokers with COPD than in smokers without COPD, and FEV_1 is inversely related to sputum MMP-12 levels. Mice that are deficient in MMP-12 seem to be totally protected from experimental emphysema, and just recently a large human genetic survey found that a single nucleotide substitution in the promoter region of MMP-12 (presumably down-regulating its expression) was associated with protection of smokers against loss of lung function and, intriguingly, in also protecting children with asthma (*Hunninghake GM, et al. NEJM 2009;361:2599–608*). There are also a small number of proof-of-concept studies that experimental inhibitors of MMP-12 can protect against smoke-induced emphysema in animal models. It should be mentioned that other proteases have also been implicated in lung damage although not so strongly, namely MMPs 1 and 3, and cathepsins S and L. There are 4 endogenous tissue inhibitors of MMPs or TIMPs, numbered 1-4, whose role may be analogous to that of AAT in relation to neutrophil elastase. For practical reasons, the TIMPs are not candidates for development as therapeutic agents.

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Small molecule inhibitors of MMP-12 are being synthesized, tested in animal emphysema models, and developed for the clinic. A number of patents have been issued for potential molecules (*Norman P. Selective MMP-12 inhibitors. **Expert Opinion on Therapeutic Patents** 2009;19:1029-34*). I found very few that were already "in humans": Wyeth, now a division of Pfizer, has MMP408 in Phase I, AstraZeneca has AZD1236 in Phase II. Among the several that are in preclinical stages, Arriva has inhaled ilomastat "a potent, broad spectrum inhibitor of matrix metalloproteinases that has been shown to be active in an animal model of cigarette smoke-induced emphysema". Merck-Serono has a selective MMP-12 inhibitor, AS111793, in preclinical.

There are also publications on several MMP-12 inhibitors that have been discovered and worked on by academic groups but that have not been picked up by a pharmaceutical company yet. Industry's interest in MMP inhibitors was dampened some years ago when it was noted that some MMP inhibitors promoted tumor growth, possibly by turning off the synthesis of anti-angiogenesis factors thus permitting angiogenesis in developing malignancies. Other MMP inhibitors may have the reverse effect, so until the field is cleared of mines, industry is understandably nervous about investing heavily in it. However, the number of molecules that have been patented as MMP-12 inhibitors (above) perhaps indicates that industry is still interested in their potential. They seem promising anti-inflammatory agents for COPD and perhaps their day will come.

NEW CLINICAL TRIALS

PhRMA listed 15 initiated studies of 11 drugs for COPD in October and November 2009. I showed a few of these in the last "Pipeline". Other new trials of interest in that group were: **N 30-201**, described as an "S-nitrosothiol therapy that stores and transduces nitric oxide." The development is a collaboration of NitroMed and the corporation known as N30, and the product is aimed at cystic fibrosis and asthma, as well as COPD. The trial is in Phase I and is not listed in clinicaltrials.gov.

Pfizer initiated 2 Phase I COPD drug trials (**PF-3715455**, and -**489791**) and 2 Phase II COPD drug trials (**PF-3635659** and **PH-797804**). I believe 489791 is a vasodilator aimed at PAHypertension. **PF-3635659** was in Ph I last year but has now progressed to Ph II. I was unable to obtain information about its nature, but the design of its Ph II study suggests it is a once-daily bronchodilator. I was not able to discover the nature of the other Pfizer agents.

PT001 is Pearl Therapeutics's glycopyrrolate formulated for HFA-MDI delivery in Phase I-II. Pearl is developing a range of COPD products for delivery by its HFA-MDI technology including a formoterol monotherapy, a formoterol-glycopyrrolate combination and even (according to their website) a triple combination that includes an ICS.

BioPharm Insight listed 11 (different) new trials for COPD agents in November and December, namely:

MN-221 Medicinova says MN-221 is a novel, highly selective ß2-adrenergic receptor agonist in Phase I being developed for the treatment of exacerbations of asthma/COPD. (It is also being developed for the treatment of premature labor).

AZD-9668. AstraZeneca described this oral, b.i.d. agent as an anti-inflammatory in a Ph I trial in April 2008. It is now described as a neutrophil elastase inhibitor for COPD as well as CF and bronchiectasis. Three new studies were initiated, - two were Phase 1 bioavailability studies and one was a Ph II study to assess efficacy and safety on a background of budesonide/formoterol co-administration.

GSK-573719 is a GSK LAMA in a repeat Phase II dose-finding study.

Erdosteine is described as a "thiol agent..a multifactorial drug" with antioxidant, anti-inflammatory, antitussive-mucolytic properties (*Moretti M. **Expert Opin Drug Metab Toxicol 2009;5:333-43***). According to the sponsor, Edmond Pharma, there is suggestive evidence it is able to restore beta-adrenergic responsiveness in COPD and scavenge reactive oxygen species. The drug which is taken orally twice daily is in Phase III in Italy (NCT01032304).

BI-1744 is a Boehringer-Ingelheim once-daily LABA that will be paired with tiotropium (and, one suspects, an ICS as well). Five new studies of this agent were initiated in Dec 09, a Ph II dose-ranging study of the LABA in combination with the standard dose of tiotropium, a pair of 24-hr spirometric studies of tiotropium combined with either of two alternative doses of the LABA, and finally a pair of 6-week studies of tiotropium combined with either of two alternative doses of the LABA.

NEW DRUG APPROVALS FOR 2009

This column is being written in early 2010, -a good time to review drug approvals in the previous year. There are different sources, Nature Reviews Drug Discovery reports that 25 "new" drugs were approved in the United States (Nature Reviews Drug Discovery 2010*;9: 8–92*). Of these, 19 were for new chemical entities (NCEs), and 6 were for 'biologics'. None of the drugs on their list was for a respiratory indication, let alone COPD. There were an additional 75 approvals for drugs which were not new entities.

The FDA, in close agreement, reports 99 new drug approvals for USA in 2009 on their website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu). However, only 18 of these qualify as NCEs (none are for a COPD indication). The remainder are classified as being merely a different salt, or ester of an already approved product, or a new formulation, combination, manufacturer, indication, or switch to over-the-counter of an approved product and, therefore, not considered to "represent an advance over available therapy," according to FDA, -"me-toos" in common parlance. The only two approvals for a respiratory indication were tadalafil (Eli Lilly) and treprostinil (United Therapeutics), both for Pulmonary Artery Hypertension indications.

Two observations, apart from the dearth of new COPD therapies: the ratio of new indications for existing drugs to new chemical or molecular entities, about 3:1 this year according to both *Nature* and the FDA, has been steadily increasing for some years. On the other hand, 2009 has been called 'a good year for biologics' where 4 of the NME agent approvals were for monoclonals, and 3 were for orphan drugs. Some predict that 2009 signals the beginning of the era of biologic medicine and therapeutics.

STEM CELLS FOR COPD?

Osiris Therapeutics in collaboration with Genzyme has been developing an adult 'mesenchymal stem-cell' (MSC) line for COPD as well as some other chronic inflammatory disorders. The cells were derived from healthy, adult, human bone marrow donors who had been appropriately pre-screened for the usual transmissible agents. The MSCs are "..naturally immune privileged cells..and escape immune surveillance" due to "low levels of expression of major histocompatability complex (MHC) class I antigens, and being negative for MHC class II and co-stimulatory molecules CD40, CD80, and CD86" (*Newman RE et al. Inflamm Allergy Drug Targets 2009;8:110-23)*. By way of background, over the past several years animal models of lung damage, including emphysema models, have served to provide proof-of-concept. In these studies, infused mesenchymal cells home to the lungs, replace damaged cells and reduce inflammation. One presumes that Phase I safety studies of the MSC line, called 'Prochymal', in humans have been successful as the agent is now in a Phase II randomized, placebo-controlled trial in 62 patients with moderate or severe COPD (NCT00683722).

Patients receive 4 intravenous infusions of Prochymal or placebo and will be followed for 2 years. The infusions were well tolerated according to a press release of June 2009. The same release also provided some interim 6-month results stating that the primary outcome, the demonstration of safety, was being met. Lung function was not improved, but some inflammatory indicators, -CRP was cited, -were reduced in the active arm vs placebo arm. (The sponsors state they have not published or submitted any clinical results as of the time of writing, March 2010). The trial will conclude about the end of 2010. The agent is also in Phase III studies for Crohn's disease, and GvHD, for which FDA has given it orphan drug status and in Phase II for acute myocardial infarction, type 1 diabetes, and acute radiation syndrome. As far as I have been able to discover, there is no other stem-cell product in development for therapeutic use in humans.

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