

Pre-Clinical models of respiratory disease

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The incidence of respiratory diseases like asthma and chronic obstructive pulmonary disease (COPD) continue to rise and despite academic and pharmaceutical endeavours, no new drug class has entered the market that has revolutionized the treatment of these diseases in the past 40 years. This is a particularly concern in COPD where no drug class reduces the rapid decline in lung function. Beta2-adrenoceptor agonists and glucocorticosteroids are the major treatments in asthma and are increasingly being used as combination therapy which offers the advantage of improved pharmacodynamics and patient compliance. Furthermore, the industry is moving toward increasing the duration of action of these drugs in order to reduce the frequency of drug administration and improved clinical effectiveness. Similarly, beta2-agonists and anticholinergic drugs form the mainstay of the treatment of COPD with a greater emphasis on combination therapy and increased duration of drug activity.

There are well over 100 potential bioactive mediators that are found within the milieu of the lung under inflammatory conditions and the goal of targeting individual mediators in the hope of developing novel disease modifying drugs have to date met with disappointment. The era of genomics and proteomics have only underscored this complexity and attempts to use a bioinformatics approach to unravel the complexity of these diseases is hailed as the white knight which will usher in a new era of drug development. One of the major stumbling blocks to this area of drug development has been the ability to model these physiological complex diseases. Animal models have been very successful in the development of the current drug classes used in the treatment of asthma and COPD, however, their role in faithfully recapitulating all of the features of these diseases has come under some criticism. However, it is the manner in which these models are used and how the results are being interpreted that needs to be challenged. A number of animal models had shown the failure of targeting single mediators in the context of delivering new anti-asthma drugs. For example, some models showed that eosinophils, the archetypal inflammatory cell type found in the airways of asthmatic subjects, was not necessary for the development of bronchial hyperresponsiveness, and consequently when anti-IL5 treatments failed in the clinic, the translatability of the animal models rather than the original concept was called into question. Similarly, one of the major issues for the physiological 'systems biologist' is how to measure respiratory lung mechanics in order to understand the mechanism of bronchial hyperresponsiveness, particularly in mice. Much of the discordance in the literature is a failure to properly measure this physiological parameter.

In the context of COPD, destruction of alveoli is thought to be a consequence of an imbalance between proteinase and anti-proteinase levels in the lung. Proteinases such as neutrophil elastase and matrix metalloproteinases (MMP)1,9,12 have been implicated in this tissue destruction. Various inhibitors of neutrophil elastase and MMP's have been developed although an investigation of their effectiveness in models of COPD is often difficult to interpret since there is no suitable animal model of COPD and lung function is not routinely measured. Enormous challenges remain to recapitulate emphysema in an animal model. Nonetheless, animals chronically exposed to cigarette smoke, exhibit features of tissue destruction which can be retarded by inhibitors of proteinases, however, the inability of these inhibitors to fully reverse the structural deficits highlights the problems of selective targeting of single proteinases. Moreover, the failure of MMP inhibitors in cancer is a salutary reminder that a greater understanding of the role of individual MMP's in disease progression in COPD is urgently required in order to test the hypothesis of whether MMP inhibitors will be of utility in this disease.

In conclusion, animal models can be invaluable in evaluating potential drug targets but the information provided must mimic the prevailing clinical evidence for a particular drug target and an iterative process between animal models and clinical models could provide a rationale basis for the discovery of novel drug targets and potentially novel therapeutic agents.