Chronic Inflammation in Asthma Airway Remodeling

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Abstract

Chronic inflammation has become a dominant factor in our understanding of chronic asthma. For many years, the important role that inflammation played in asthma was not recognized, and pharmacology recommendations were to avoid steroid treatment if at all possible. Today, clinical authorities recommend inhaled steroids for all patients with persistent asthma. However, although many studies of chronic asthma patients treated with long-term steroids show suppression of inflammation in the lung, patients continue to have exacerbations of their disease and relentless decline of FEV1. This progression has been attributed to airway remodeling – structural changes in the airway that obstruct airflow. While experts state that remodeling is triggered by chronic inflammation, the links between inflammation and remodeling and decline in FEV1 are still speculative. We have developed an initial computational model to explore the physiology of airway remodeling. This systems-engineering approach uses physiological modeling and simulation to quantitatively evaluate hypotheses in the progression of the disease. We will present the model with details of how it was developed and how it is being applied to drug development decisions.

Background and Objectives

Asthma - respiratory disease with acute bronchoconstrictive phases occurring over minutes and hours and more chronic decreases in lung function occurring over months and years. The acute bronchoconstriction is often triggered by an event, exposure to an allergen or chemical, dry/cold air, or other stressor, and in many cases can be relieved by currently available drugs.
Chronic asthma is believed to be a result of airway remodeling - fibrosis and other structural changes in the airways which lead to increased obstruction, irreversible in some diseases, but potentially not in others.

A top-down systems approach to chronic asthma can provide a framework for quantitatively dissecting and reconciling multiple conflicting observations and hypotheses, in particular the phenomena of chronic inflammation and airway remodeling and how they may relate to each other. The commonly held viewpoint is that chronic inflammation leads to airway remodeling, however a number of investigators emphasize that this has not been definitively proven. It might be that remodeling causes inflammation, or a single factor causes both processes, or even that the two processes are completely independent. Our objective is to develop model which can assist in exploring these and related issues and eventually provide insights to drug development teams in the field of asthma.

Methods

We are using a top-down approach with layered modules. The initial step in the process is to develop a model of healthy physiology, which can then be modified to by disease and treatment processes.

1. Model healthy physiology. If the biology being modeled is in homeostatic balance, then explicitly represent that homeostasis.

2. Extend the model to represent the disease condition of interest. Recognize that disease conditions are often defined as syndromes or collections of clinical manifestations, and that such clinical observables may be the result of different etiologies in different patients, which in the clinic may be difficult to distinguish.

3. Model interventions in response to each disease etiology. Consider an intervention as a means to (more or less effectively) drive the diseased biology to a state of healthy homeostasis. While in some cases the original state of healthy homeostasis may be attainable, for many disease conditions what can be attained is a different state that while different from healthy homeostasis is preferred to the untreated disease condition.

The initial design is developed graphically and the initial development of the model is being done in JDesigner, a Systems Biology Workbench environment. Initial model development is based solely on literature data.

Modeling Assumptions

There appear to be multiple (at least two major: eosinophilic and neutrophilic) phenotypes of asthma and associated airway remodeling, each of which may have different dominant remodeling processes, thus confounding how clinical observations are interpreted.

The principal anatomical location(s) of increased obstruction and airway resistance remain(s) uncertain.

While some airway remodeling processes can be correlated with a severe asthmatic condition, researchers do not know what causal links might be in effect. Therefore, the sequence of events responsible for structural remodeling is not yet well understood.

These difficulties are exacerbated by the very long time during which airway remodeling occurs and during which treatments must be studied in clinical trials.

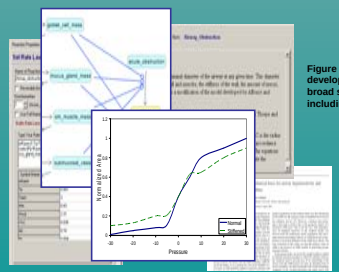

Figure 1. Model development uses a broad selection of data including literature data.

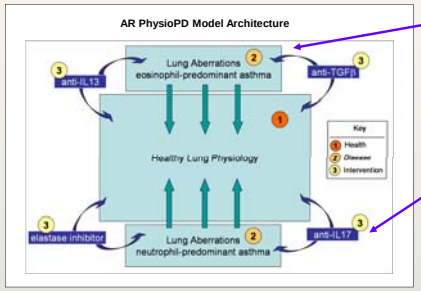

Figure 2. Modular structure of a PhysioPD model of airway remodeling associated with chronic asthma

Disease modules serve two purposes:

A. Disrupt the healthy lung physiology represented by the foundation module

B. Add model components to represent pathophysiological components beyond disruptions of healthy lung physiology.

Intervention modules serve three purposes:

A. Disrupt the pathophysiology represented in the currently active disease module and, in all likelihood, also disrupt the healthy (or disrupted) lung physiology represented by the foundation module

B. Add model components to represent specific treatment-related physiological components that are not already included in the foundation module or the active disease module

C. Add model components to represent the pharmacology needed to, at least approximately, describe the intervention's pharmacokinetics and, in appropriate detail, its mechanism of action.

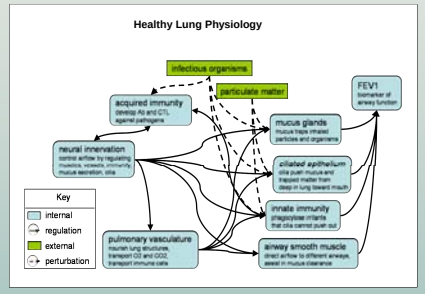

Figure 3: Key elements to be considered in a model of the healthy lung

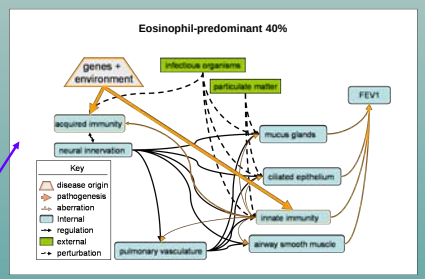

Figure 4: Key elements to be considered in modeling eosinophil-predominant airway remodeling

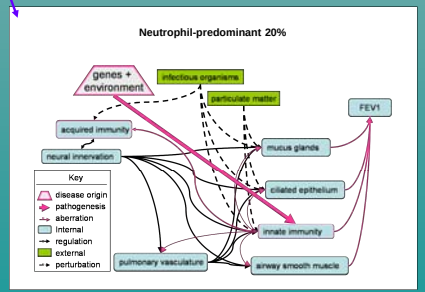

Figure 5: Key elements to be considered in modeling neutrophil-predominant airway remodeling

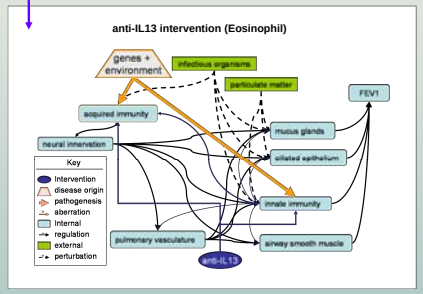

Figure 6: Anti-IL13 therapy interacts through an individual's acquired and innate immunity and may be best for patients with eosinophil-predominant airway remodeling

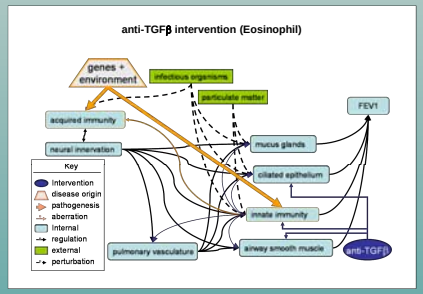

Figure 7: Anti-TGFβ therapy interacts primarily through an individual's innate immunity and may be best for patients with eosinophil-predominant airway remodeling

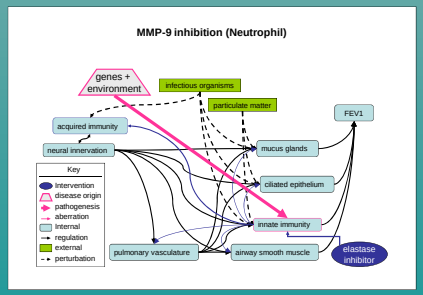

Figure 8: Elastase inhibitor therapy interacts primarily through the individual's innate immunity and may be best for patients with neutrophil-predominant airway remodeling

Results

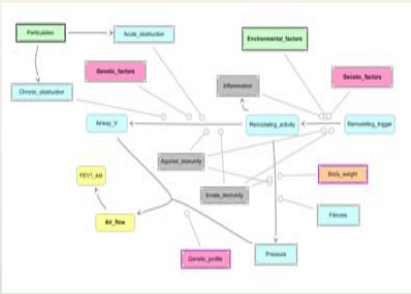

Figure 9: Top level architecture

In the context of asthma and FEV1 decline, remodeling has always been found with inflammation, however inflammation has been found in other lung diseases without the characteristic remodeling of asthma. In addition, in the few studies examining generalized systemic inflammation and asthma, no direct link has been found thus arguing that specific immune activation in the lung is required. In terms of factors that would directly affect FEV1, certainly airway remodeling is involved, but nonspecific lung inflammation and specific immune activation probably influence FEV1 over the long-term via changes in airway remodeling rather than through direct effects of immune or inflammatory cells on air flow. Hence remodeling influences FEV1 directly in the model, and lung inflammation and specific immunity affect remodeling.

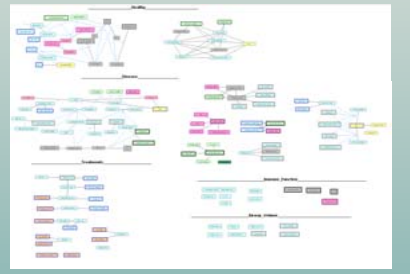

Figure 10: Bird's eye view

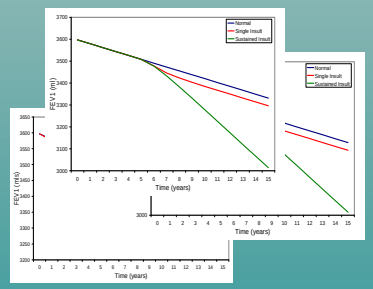

Figure 11: Testing hypotheses with the model

Conclusions

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