Research Directions/Projects of Professor Steven C. George

Overview

There are two overriding areas of research in my lab, both of which focus on understanding the biology and physiology of the lungs: 1) nitric oxide metabolism, and 2) wound healing and tissue remodeling. Our approach is to consider the lung as an integrated whole organ, combining both cellular and whole organ studies as well as both experimental and theoretical techniques. For example, exhaled nitric oxide is a potential useful biomarker of inflammation, yet in order to interpret this signal one must understand the exchange dynamics at the both the cellular and whole organ level. The cells of the lungs are the source of nitric oxide; thus, one must understand what changes in the local biochemical environment (i.e., inflammatory cytokines) alter these events. For nitric oxide to appear in the exhaled breath, it is advected through the larger airways of the lungs. This involves understanding the fluid mechanics of bifurcating tubes, mass transfer coefficients, and lung mechanics. New mathematical models must be developed to interpret the exhaled nitric oxide signal, and new models have unknown parameters, which must be estimated from experimental measurements. This combined approach to studying the lungs demands many skills, but provides exciting and challenging opportunities in the more general areas of signal processing, heat and mass transfer, parameter estimation, drug delivery, reaction kinetics, and tissue engineering. Below is a more detailed description of the individual projects.

Specific Projects

Characterizing Endogenous and Exogenous Nitric Oxide Exchange in the Lungs.

In the past decade years, the importance of NO as a physiological messenger has progressively increased. NO has important roles in regulation of smooth muscle tone, neurotransmission, coagulation, and host defense response, and has been described in nearly every mammalian organ system. More recently, NO has been detected in the exhaled breath of humans. The magnitude and shape of the exhalation profile depends strongly on factors such as exercise and the presence of inflammatory diseases such as asthma. This project will combine experimental and theoretical techniques aimed at understanding and interpreting the exchange dynamics of NO.

(Project currently undertaken by Hoon Sung Jeh, Hye-won Shin, and Federico Perez)
Building a Respiratory Simulator

In the past year, sequencing the human genome was completed creating a vast array of knowledge which must be placed in the larger context of cell and whole organ function. A similar, but vastly more complicated project, has been termed the human "physiome" which would include a complete description of human physiology. This is incredibly more complicated than the genome project, as it includes not just a sequence of nucleotide base pairs, but the time and spatial varying interactions of the proteins, cells, and organs which are the product of the genome. One step towards building a human physiome is to begin with each organ, and develop an intelligent platform by which existing and future knowledge can be integrated into a dynamic model of the organ. At any given point in the development, the "respiratory simulator" could be used to make new predictions regarding an array of lung functions and could play an important role in quickening the pace of new therapeutic developments.

(Project currently undertaken by Yeo Hong Yoon)

Wound Healing and Extracellular Matrix Remodeling in the Lungs

The goal of this project is to investigate wound healing and extracellular matrix remodeling in the lung as it applies to diseases such as asthma and pulmonary fibrosis. The lung is not ordinarily considered an organ which is "injured", yet this is exactly what occurs during acute asthmatic exacerbations, for example. In asthma, the wound healing process results in abnormal extracellular matrix production, or "scarring", which can accelerate the progression of the disease. This project utilizes a co-culture of human fibroblasts and human bronchial (or alveolar) epithelial cells in a manner that simulates the respiratory mucosa. We can then injure the engineered tissue in a fashion that simulates an acute asthmatic exacerbation to improve our understanding of the cellular and molecular events of wound healing. Characterization of the tissue engineered model will be accomplished by a variety of techniques including ELISA, and two-photon microscopy.

(Project currently undertaken by Angelie Agarwal, Steven Evans, and Sergio Sandoval)

Transport of Nitric Oxide, Nitric Oxide Donors, and Peptides in the Lungs

Simultaneous diffusion and reaction of small molecules in lung tissue is critical to understanding the fundamental transport dynamics of nitric oxide, nitric oxide donors, and therapeutic peptides. The goal of this project is to investigate the transport properties of nitric oxide, S-nitrosothiols, diazeniumdiolates, and small peptides in the bronchial mucosa, to design new therapeutic strategies to deliver pharmacologically active molecules locally in the lungs as well as systemically. Experimentally, the project will
utilize Ussing-type diffusion chambers and the tissue engineered mucosa described above to measure overall mass transfer coefficients across different cellular layers, rates of production (in the case of NO), and rates of consumption (NO and peptides). The project will also use theoretical studies to identify important and rate-limiting parameters that can be used in the drug design strategy.

(Project currently undertaken by Wei-yang Wu, Peter Condorelli, Hoon Sung Jeh, and Hye-won Shin)

Cytokine-induced Production of NO by Lung Cells

The production of NO by lung cells is strongly influenced by inflammatory cytokines such as tumor necrosis factor-a (TNF-a), interleukin 1b (IL-1b), and interferon-g (INF-g). These cytokines interact with each other in a complex fashion during the induction of NO production. The mechanism of this synergistic action is poorly understood. The goal of this project is to understand this mechanism of synergy by studying the induction process at different levels including mRNA transcription, translation, and stability, as well as protein (iNOS) stability and function.

(Project currently undertaken by Soonjo Kwon and Joy Lau)