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SPRING/SUMMER 2016

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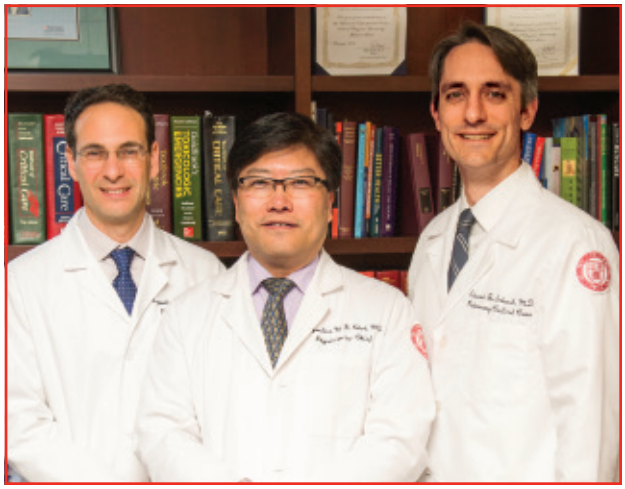
Carbon Monoxide: A Potent Antidote to ARDS?

It is well known that carbon monoxide can be lethal. We guard against running a car in a closed garage and place detectors throughout the house to detect the colorless, odorless, and deadly gas. So it may come as a surprise to learn that research is finding small amounts of carbon monoxide to have healthful benefits, particularly in respiratory therapy.

One proponent of this unusual therapy is **Augustine M.K. Choi, MD**, Physician-in-Chief at NewYork-Presbyterian/Weill Cornell Medical Center, who for more than 25 years has sought to identify effective treatments in lung disease. His research has focused on the regulation and function of stress response genes in response to oxidative stress, and he has extensively examined the molecular regulation/signaling pathways and function of heme oxygenase-1 and gaseous molecule carbon monoxide in a variety of *in vitro* and *in vivo* models of lung and vascular diseases.



Dr. David A. Berlin, Dr. Augustine M.K. Choi, and Dr. Edward J. Schenck

Dr. Choi and his Weill Cornell colleagues in Pulmonary and Critical Care Medicine, **David A. Berlin, MD**, and **Edward J. Schenck, MD**, have

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The Developing Lung: Implications for Therapeutic Advances

"The lung is such a complex and beautiful structure," says **Wellington V. Cardoso, MD, PhD**, a member of the Division of Pulmonary, Allergy and Critical Care Medicine at NewYork-Presbyterian/Columbia University Medical Center and Director of the Columbia Center for Human Development. "There is a multitude of diversity of cells – in fact, it is known to have more than 40 different types."

> **"Even subtle developmental defects from adverse fetal exposures can lead to lifelong deficits in organ function and susceptibility to disease in adulthood."**
> **— Dr. Wellington V. Cardoso**

Dr. Cardoso's perspective is informed by nearly two decades of basic research in lung development. Supported by several R01 NIH grants, Dr. Cardoso continues to focus his scientific acumen on the mechanisms that regulate lung development and regeneration and repair – a path he decided upon after his medical training in Pathology. While studying pulmonary emphysema, he became interested in lung development and growth; since then he has dedicated his career to this line of inquiry, which encompasses his tenure as a Principal Investigator and Director of the Program in Lung Development and Progenitor Cell Biology at the Boston University School of Medicine, and continues now at Columbia University. "A central effort of my lab has been to identify gene regulatory networks that control lung progenitor cell behavior in development and in regeneration-repair, with the ultimate goal of discovering novel therapeutical targets for lung disease."

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Carbon Monoxide: A Potent Antidote to ARDS?

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been examining the therapeutic applications of inhaled carbon monoxide in intubated patients with sepsis-induced Acute Respiratory Distress Syndrome (ARDS) through a multicenter NIH-funded clinical trial. As part of this safety study, they are also testing a delivery device developed by Dr. Choi to administer the gas in controlled and targeted doses.

ARDS, a syndrome of severe acute lung inflammation and hypoxemic respiratory failure, affects some 180,000 patients annually in the U.S. Despite decades of research and recent advances in lung protective ventilator strategies, morbidity and mortality remain unacceptably high. Furthermore, no specific effective pharmacologic therapies currently exist. The lack of specific effective therapies for sepsis-related ARDS indicates a need for new treatments that target novel pathways. Carbon monoxide (CO) represents a novel therapeutic modality in ARDS based on data obtained in experimental models of ARDS and sepsis over the past decade.

The study posits that CO has been shown to be protective in experimental models of acute lung injury (ALI), including hyperoxia and endotoxin exposure, bleomycin, ischemia/reperfusion, and ventilator-induced lung injury. "At low doses, CO has been shown to confer tissue protective effects in these ALI models," says Dr. Choi. "In addition, CO decreases inflammation, enhances phagocytosis, and improves mortality in models of sepsis including endotoxemia, hemorrhagic shock, and cecal ligation and puncture. CO has also been shown to have beneficial therapeutic effects in preclinical models of disease, including pulmonary hypertension, vascular injury, and transplantation."

> **"Carbon monoxide as a treatment tool will hopefully reduce the time that lungs are under stress and reduce the damage done to the lungs."**
>
> **— Dr. Edward J. Schenck**

Furthermore, notes Dr. Choi, multiple human studies have demonstrated that experimental administration of several different concentrations of CO is well tolerated and that low-dose inhaled CO can be safely administered to subjects in a controlled research environment. "Dr. Choi's translational and basic science research has focused on trying to understand the way a human's own carbon monoxide works and how it can help fight certain disease states," says Dr. Schenck, a critical care intensivist with a particular interest in critical care ultrasound. "In small doses, carbon monoxide acts as an anti-inflammatory agent in certain tissues and in certain conditions. The reason why this is such an exciting concept is that ARDS can be secondary to multiple conditions throughout the body, such as severe trauma, burn, pancreatitis, or in response to an infection. Beyond fighting the conditions that create the lung syndrome, there is nothing that has been proven to target the disease itself or the syndrome. Carbon monoxide's anti-inflammatory effect may ameliorate the condition beyond just supporting the body as it heals from the process."

"The key insight as Dr. Choi discovered decades ago is that carbon monoxide, which was known to be produced in normal biological processes in all of us, is an important regulator of inflammation in mammals and an important cytoprotection to cells," says Dr. Berlin, Director of the Medical Intensive Care Unit and Medical Director of Critical Care Services, Pulmonary and Critical Care Medicine at NewYork-Presbyterian/Weill Cornell. "Carbon monoxide turned out to be an important mediator of many regulatory processes and specifically resolving inflammation and preventing excessive proliferation of cells. For that reason CO has been studied in more than a dozen different diseases in animals and in laboratory models. And now it's been studied in shock states and respiratory failure states, organ transplantation, fibrosis of the lung, and pulmonary hypertension."

Evaluating the Efficacy of CO in ARDS

The current trial underway for ARDS seeks to determine accurate dosing levels to ensure that the therapy is creating the desired physiologic effect. "This trial was designed through work at Weill Cornell, Duke University, Massachusetts General, and Brigham and Women's Hospital to develop and validate equations dating back to the 1970s about the way the lung absorbs gases, specifically carbon monoxide," says Dr. Schenck. "Using an equation will help us to predict the way we would administer a dose of this gas going forward."

Variables in dosing depend on height, age, and sex. "The lung gets larger as one grows taller; it doesn't get bigger as a person gets bigger," says Dr. Schenck. "Variables also depend on how well the lung is exchanging carbon dioxide and how sick the patient is from the disease process. Phase I of this trial, which will extend to next summer, is focusing on the administration of low doses of the gas."

"The IRB has been expanded to potentially recruit patients from the surgical ICU. This would include patients who are suspected of having an infection and also have a lung condition," says Dr. Berlin, who along with Dr. Schenck is enrolling patients for the study and administering the CO therapy.

"This treatment as it is proposed would slightly increase the level of carbon monoxide in the patient's blood, targeting levels of hemoglobin that are 4 to 5 percent bound to carbon monoxide," says Dr. Berlin. "Normally we have less than 2 percent of our hemoglobin bound to carbon monoxide. So this is designed to give a low dose of CO to very slightly increase the level of carbon monoxide in a person's blood to assist in the body's own restorative process."

Phase II of the trial is expected to begin next year and will focus on not only validating the equation on dosing, but also setting dosages to achieve a target in the blood that will enhance efficacy.

"Other types of therapies have been tried in the past, such as beta-agonists, varying doses of steroids, and other gaseous therapies such as inhaled nitric oxide," says Dr. Schenck. "They have not really panned out. Carbon monoxide potentially could be the first targeted therapy for ARDS."

Reference Material

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The Developing Lung: Implications for Therapeutic Advances

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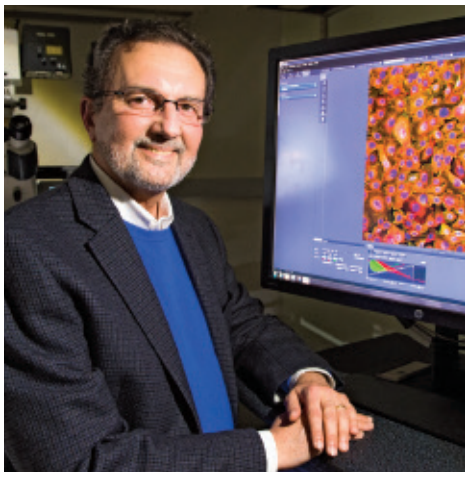
A Myriad of Research Directions



Dr. Wellington V. Cardoso

Dr. Cardoso underscores a point often overlooked in adult medicine that even subtle developmental defects resulting from adverse exposure of the fetus to maternal smoking, alcohol, or dietary deficiencies can lead to lifelong deficits in organ function and susceptibility to disease in adulthood. Two years ago, Dr. Cardoso and colleagues at Boston University and Rutgers published a study that, for the first time, established evidence in an experimental model of a link between prenatal Vitamin A deficiency and airway hyperresponsiveness postnatally. Their data showed that transient exposure of the fetus to a Vitamin A-deficient intrauterine environment did not disturb overall lung formation or growth but led to the development of aberrant overly differentiated smooth muscle in airways. The defect persisted postnatally regardless of the adult Vitamin A status and made these mice hyperresponsive to spasmogenic stimuli, as seen in human asthma. "The study uncovered a requirement for Vitamin A in preventing excessive, precocious formation of smooth muscle in developing airways," says Dr. Cardoso. In a recent review article on this topic that includes clinical studies, Dr. Cardoso and Dr. Hector Marquez emphasize the importance of additional studies to further explore therapeutic avenues of inquiry.

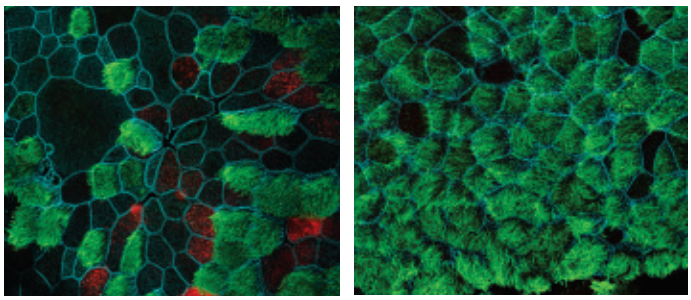
More recently, Dr. Cardoso's group, along with his collaborators at Boston University, published a series of studies that reveals an unexpected role for the Hippo pathway and its effector Yap in the lung. Although known to be associated with cancer and control of organ size, the role of Hippo-Yap in lung development was elusive. "Early during lung development distinct regulatory programs are activated in epithelial cells to give rise to the conducting airways and future distal gas-exchange of the lung," explains Dr. Cardoso. "We discovered the existence of a small population of progenitor cells between these two regions in which Yap activates a developmental program that generates the conducting airways. Without Yap these cells are unable to integrate growth-factor signaling for specification and do not form airways."

The study also showed that once airway progenitors are specified, Yap undergoes a dramatic nucleocytoplasmic shift. This shift is necessary to initiate differentiation of these progenitors both in embryonic and adult airways during regeneration. "Our group is currently exploring the involvement of this pathway in pulmonary remodeling and fibrosis," says Dr. Cardoso.

"Another major current challenge is the elucidation of what are the cells that make the stem cell compartment of the lung, how this compartment forms, and how these cells transition to initiate specific programs of differentiation, particularly in airways," adds Dr. Cardoso. "The differentiated cells that line the airways are constantly replenished by undifferentiated progenitors, which include basal and parabasal cells. Basal cells give rise to parabasal intermediate progenitors, which then are thought to differentiate into the multiple cell types of the airway epithelium. However, the specific molecular mechanisms governing the production and role of parabasal cells in the lung remain unknown."

Recently, Dr. Cardoso and his colleagues found that parabasal cells can be distinguished from the other progenitors by selective activation of NOTCH3-Jagged signaling. Moreover, they showed that NOTCH3 controls the balance between basal and parabasal progenitor cells in airways. Using genetic and pharmacological approaches to disrupt or activate NOTCH3, they demonstrated that affecting this balance alters differentiation and the architecture of the airway epithelium.

"Notably," continues Dr. Cardoso, "individuals with chronic obstructive pulmonary disease were found to exhibit NOTCH3 hypoactivation and an expanded basal progenitor pool. Moreover abnormal expansion of basal cells is associated with metaplastic lesions seen in chronic pulmonary diseases and in premalignant conditions. Dr. Cardoso points out that advancing knowledge in this area will open opportunities to further understand mechanisms that control plasticity of the lung and lead to aberrant patterns of differentiation in disease.



Notch controls the balance of ciliated and secretory cells in adult airways. Left: Under normal conditions both secretory (red) and ciliated (green) cells are present. Right: Antagonizing Notch pharmacologically: absence of secretory cells and excess of ciliated cells.

Dr. Cardoso also raises the issue of balance between the numbers of ciliated cells versus secretory cells. How is this established? What are the pathways involved in making a secretory cell? "First we had to learn the rules that guide the making of one type of cell over the other," says Dr. Cardoso. "And then we set up a system to determine relationships between them, looking at what makes it possible to adapt the system to different environments – for example, one that receives more pollutants and particulates compared to one that doesn't." To illustrate, Dr. Cardoso uses the example of cigarette smoke causing lung injury in the postnatal life. "Cigarette smoke brings on an enormous amount of secretion and can lead to chronic bronchitis," explains Dr. Cardoso. "By knowing the pathways that make a cell become a secretory cell, we can then identify pathways that are hyperactivated in response to injury, providing potential targets for intervention."

The concept was demonstrated in a genetically engineered mouse. "When you remove that particular pathway, in this case

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signaling by all Notch receptors, the developing airways of the mouse did not develop any secretory cells, only ciliated, neuroendocrine, and basal cells," notes Dr. Cardoso. "But in a study from another group, in which Notch was hyperactive, there was an excess of secretory cells. These results collectively indicate that this pathway could be a target for chronic bronchitis in patients."

Searching for the Translational Counterpart

"Many of the observations reported in animal models are begging for a translational counterpart," he says. "In my example of lung injury brought on by cigarette smoke, we did not start with the idea of looking for something that would influence chronic bronchitis. We began with the basic question of what is it that makes those secretory cells come about at a certain stage of development."

Although mouse models are powerful tools, there are obviously differences between mice and humans that need to be taken into account when correlating results. With this in mind, Dr. Cardoso points to the importance of integrating information from multiple models, from cell systems to large animal models, when studying human development and disease. Each system or model provides information about a specific aspect of the problem; conclusions are thus achieved through integration of a multidisciplinary approach.

Dr. Cardoso reinforces the beauty of being able to seamlessly integrate basic science with clinical perspectives through the Columbia Center for Human Development. "The Center is a research hub in the Department of Medicine that brings together basic and clinical scientists across the Columbia campus to advance knowledge on mechanisms of organ development and the understanding of the developmental basis of human disease," says Dr. Cardoso. "Human development intersects with many other worlds that are of particular interest nowadays – stem cell research, regenerative medicine, chronic diseases, and pediatric medicine. Understanding organ development will provide insights into congenital diseases and inform us about how aberrant patterns of growth and differentiation influence disease. This can be potentially powerful in the discovery of potential therapeutic targets for intervention in adult disease. Thus our interest goes beyond embryonic development for fetal medicine; we're talking about integrating this knowledge with different aspects of human biology covering a spectrum from birth to old age."

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