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ADVANCES IN PULMONOLOGY

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IPF: Looking to the Microbiome for New Treatments

Idiopathic pulmonary fibrosis (IPF) is a devastating chronic lung disease of unknown cause occurring primarily in middle-aged and older adults. IPF is characterized by progressive scarring in the lungs and affects some 200,000 people in the U.S. each year. Though uncommon, its incidence appears to be on the rise and is expected to increase with the aging population. IPF has a high mortality with a median survival of three to five years.

Robert J. Kaner, MD

Despite years of investigations, the origin of IPF has remained elusive, with possible roles played by alveolar epithelial injury, the microbiome inducing immune activation, a genetic predisposition, cigarette smoke, or any combination thereof.

"While two-thirds of people who have the disease are former smokers, the cause for this disease is not certain," says **Robert J. Kaner, MD,** a pulmonologist in the Division of Pulmonary and Critical Care Medicine at NewYork-Presbyterian/Weill Cornell

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Sleep and Cardiovascular Risk: A Causal Relationship?

Sleep is increasingly recognized as an important contributor to health, yet many Americans – particularly women – regularly do not get enough sleep. To learn if inadequate sleep increases their risks of heart disease, **Sanja J. Jelic, MD**, Division of Pulmonary, Allergy and Critical Care Medicine; **Lori J. Mosca, MD, MPH, PhD**, and **Brooke Aggarwal, EdD, MS, CHES**, Division of Cardiology; and **Marie-Pierre St-Onge, PhD**, Division of Endocrinology, NewYork-Presbyterian/Columbia University Irving Medical Center, have come together to study the relationship between sleep habits and cardiovascular risk factors in three separate, but synergistic, investigative phases.

Sanja J. Jelic, MD

"Sleep restriction today is very prevalent and most people curtail their sleep thinking that it is nothing," says Dr. Jelic, a pulmonologist and expert in sleep apnea. "They tend to be very cavalier about it. They lead busy lives and have to get things done. However, we think that this lack of sleep does have some negative consequences on cardiovascular health."

"Multiple studies have found associations between short sleep duration and sleep disorders and heart disease, but the evidence is not quite there yet," says Dr. Mosca, a vocal leader in women's heart health for more than two decades. "It's been a big debate among researchers in the field. We're not sure if lack of sleep causes the increased risk or if the two are just correlated."

In 2016, Columbia University was named one of five American Heart Association's Go Red for

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IPF: Looking to the Microbiome for New Treatments *(continued from page 1)*

Medical Center, whose clinical expertise focuses on interstitial lung diseases. "We believe there is definitely a genetic predisposition; about 5 percent of patients will have a first-degree relative who also has this disease. However, how the genetic predisposition interacts with environmental and other factors is not well understood at this point."

Currently, two FDA-approved drugs are available to slow the progression of the worsening of lung function – nintedanib and pirfenidone. Surgical therapy with lung transplantation is available to only a small minority of patients. As IPF gradually progresses, an individual becomes more impaired in terms of dyspnea, cough, and ability to exercise and carry out activities of daily living, requiring supplemental oxygen.

> **"Fifty years ago, it was thought that lung tissue was sterile. Now we know that there is a specific microbiome signature that correlates with increased risk of disease progression in idiopathic pulmonary fibrosis."**
>
> **— Dr. Robert J. Kaner**

"This disease causes widespread scarring throughout the lungs, with a prognosis that is not much better than lung cancer," says Dr. Kaner. "Because the two drugs we have now are not curative, we desperately need new approaches."

A possible answer to a new treatment for the disease, says Dr. Kaner, may reside in recent research suggesting that the lung microbiome correlates with outcome in IPF, either by initiating fibrosis or as a trigger in exacerbations. "Two small studies conducted overseas, one in India and one in the United Kingdom, looked at treating IPF with antibiotics in which patients appeared to have better outcomes. This suggests that the microbiome may be relevant."

Recent pathological findings in the lung support this path of investigation. "Fifty years ago, it was thought that lung tissue was sterile," says Dr. Kaner. "Now we know that there is a host microbial community that can be identified by studies of bacterial DNA. Those studies have been done with bronchoalveolar lavage, a procedure by which a bronchoscope is passed into the airways enabling the collection of epithelial lining fluid. From those studies has come the recognition that there is a specific microbiome signature that correlates with increased risk of disease progression in idiopathic pulmonary fibrosis."

CleanUP IPF

Following that lead, in 2016 the National Institutes of Health launched CleanUP IPF, a multicenter clinical trial to evaluate an antimicrobial approach to improving the outcome of individuals with idiopathic pulmonary fibrosis. The study is under the leadership of **Fernando J. Martinez, MD, MS**, Chief of Pulmonary and Critical Care Medicine at Weill Cornell, and a renowned clinician and translational investigator who specializes in fibrotic lung disease and airway disorders.

CleanUP IPF aims to enroll 500 patients across approximately 30 medical centers across the U.S., including Weill Cornell. The unblinded phase 3 study, the first pragmatic study in IPF ever performed, seeks to determine if antimicrobial therapy in addition to standard care compared to standard care alone in individuals with IPF will improve clinical outcomes, such as the length of time to a rehospitalization. Patients will be randomized to receive co-trimoxazole or doxycycline – off patent and readily available antibiotics – and remain in the trial for up to 42 months with three clinic visits over two years and follow-up phone calls.

"This is a pragmatic clinical trial designed to make it as easy as possible for participants to follow," says Dr. Kaner. "Patients will know upon randomization if they are assigned to the antibiotic arm or usual care arm. Even if assigned to the antibiotic arm, they also can choose to remain on their usual care for idiopathic pulmonary fibrosis, which in most cases will include the FDA-approved drugs."

With an enrollment goal of 15 patients, the Weill Cornell investigators hope to conduct a bronchoscopic sub-study, including the collection of lung samples comparing the microbiome and lung immune cells before and after administration of antibiotics, as well as gene expression in the distal airways. "We are planning to propose this sub-study working with **Dr. David Artis** and **Dr. Laurel Monticelli,** Weill Cornell immunologists, to correlate the changes in the microbiome with changes in innate lymphoid cells," says Dr. Kaner.

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Selected Clinical Trials

To learn more about CleanUP IPF and other clinical trials underway in the Division of Pulmonary and Critical Care Medicine at NewYork-Presbyterian/Weill Cornell, contact:
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CleanUP IPF for the Pulmonary Trials Cooperative
The purpose of this study is to compare the effect of standard care versus standard of care plus antimicrobial therapy (co-trimoxazole or doxycycline) on clinical outcomes in patients diagnosed with IPF.

Idiopathic Pulmonary Fibrosis Prospective Outcomes Registry (IPF-PRO)
This registry is collecting data on the strategies used to achieve a diagnosis of idiopathic pulmonary fibrosis and the treatment and management efforts applied throughout study follow-up, clinical outcome events, and patient reported outcome data.

Pulmonary Fibrosis Foundation Registry
This registry is collecting data on at least 2,000 patients with interstitial lung disease (ILD) at approximately 40 clinical sites in the U.S., and is targeting enrollment of approximately 60% of the 2,000 participants to have idiopathic pulmonary fibrosis. The aim of the registry is to create a cohort of well-characterized patients with ILD for participation in retrospective and prospective research.

Sleep and Cardiovascular Risk: A Causal Relationship? *(continued from page 1)*

Women Strategically Focused Research Network Centers. The Center's $3.7 million funding supports multifaceted research projects over four years looking at sleep and cardiovascular risk across women's life stages. "We believe there is substantial evidence suggesting that lack of sleep, poor sleep habits, and poor quality of sleep are risk factors for cardiovascular disease," says Dr. Mosca, Executive Center Director. "We wanted to study the problem of lack of sleep and sleep patterns in women because they have unique life stages that put them at high risk for abnormal sleep patterns. The study goal is to use three scientific approaches – population-based science, clinical science, and basic science – to determine which women are at risk for sleep problems and to determine if there is a causal relationship with heart problems."

Population-Based Study In the first year, the Center's population-based research project, led by Dr. Brooke Aggarwal, a behavioral scientist in the Division of Cardiology, recruited 500 women between the ages of 20 and 79 to examine sleep patterns and cardiometabolic risk at different stages of life. "We're looking to see if a woman's reproductive life stage modifies any relationship that we may find between sleep and cardiovascular health," says Dr. Aggarwal. "Close relationships are generally thought to be beneficial, but negative relationships might increase the risk of heart disease. One's perception of social support – such as feeling cared about, valued, and loved – may be more important than the simple presence of a spouse or partner."

Clinical Trial In the Center's second project, participants from the population cohort are being invited to enroll in a clinical trial in which they are asked to restrict their sleep by 90 minutes each night for six weeks; an accelerometer worn on their wrists tracks hours of sleep. Dr. Marie-Pierre St-Onge, a nutrition scientist and obesity researcher, serves as the Principal Investigator of this arm of the study, which is comparing the impact of sleep restriction on diet, exercise habits, amounts of body fat, and cardiometabolic risk factors to baseline sleep patterns to determine if lack of sleep is a causal factor in the development of heart disease. "If the answer is yes, that means we should include lack of sleep as a major lifestyle risk factor in standard screening guidelines for heart disease, just as we include smoking, physical activity, and diet," says Dr. St-Onge, Center Director, who served as Chair of an American Heart Association major scientific statement on sleep and cardiometabolic risk published in *Circulation* in November 2016.

Basic Science Dr. Sanja Jelic is the Principal Investigator of the basic science component examining the molecular changes that occur when premenopausal and menopausal women restrict sleep and how those changes raise the risk of heart disease. All of the women who are enrolled in the clinical project are also enrolled in the basic science project. Dr. Jelic believes that the effect of sleep restriction on endothelial dysfunction can lead to cardiovascular risk. She has developed a novel technique to directly assess abnormal activation of these cells, which she previously used to study obstructive sleep apnea. "The goal here is to see whether sleep deprivation affects vascular function at all and to determine the mechanisms," she says. "Knowing mechanisms may ultimately lead us to new ways to improve vascular health in people who do not get sufficient sleep."

Dr. Jelic collects the endothelial cells via a small intravenous catheter similar to a modified blood draw. "We're currently looking into pathways that regulate inflammation and nitric oxide bioavailability and oxidative stress that may play a key role in vascular dysfunction," explains Dr. Jelic. "We are also seeking to determine the impact of sleep restriction on endothelial apoptotic rate and repair capacity."

Marie-Pierre St-Onge, PhD, and Lori J. Mosca, MD, MPH, PhD

Dr. Jelic's preliminary data seems to indicate that some of the molecular pathways are being altered. "It's well known that lack of sleep alters the activity pathway and affects a person's ability to make decisions or perform complex tasks or operate machinery," says Dr. Jelic. "These are mostly behavioral observations. What we are focusing on are hardcore cardiovascular changes that we think are going to be affected by this behavior."

The researchers emphasize that their work seeks to call attention to the importance of adequate sleep to metabolic and general health. "One of our main motivations is to contribute to the evidence base that will allow for sleep habits and sleep disorders to be routinely screened for in the physician's office," says Dr. Mosca. "We all screen for cardiovascular risk factors, such as cholesterol and blood pressure. We often ask about diet and exercise. Given the strong correlation between sleep habits and cardiovascular risk, we want to put this on the radar of every physician to start screening for sleep disorders and poor sleep patterns and refer their patients to pulmonologists – many of whom are sleep specialists – for evaluation and possible treatment."

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