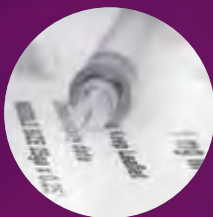
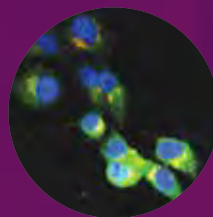


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# RespiratoryExchange

Research and News for Physicians from Cleveland Clinic's Respiratory Institute

Winter | 2015

## TRPV4

Understanding Its Role  
in Mechanosensing,  
Myofibroblast Differentiation  
and Pulmonary Fibrosis

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## Dear Colleagues:

Welcome to the Winter 2015 issue of *Respiratory Exchange*, which presents the latest discoveries and accomplishments of our pulmonary, critical care medicine, allergy and clinical immunology staff in Cleveland Clinic's Respiratory Institute.

This issue highlights our most recent leading-edge innovations and research, including:

- Details of a recent Cleveland Clinic study examining the precise nature, extent and significance of the systemic vascular involvement in pulmonary arterial hypertension
- Research recently published in the *Journal of Clinical Investigation* that identifies TRPV4 as a long-elusive mechanosensor/transducer that mediates myofibroblast differentiation and in vivo pulmonary fibrogenesis
- A prospective study that suggests CoQ10 may be beneficial to pulmonary arterial hypertension patients
- An update on our Respiratory Institute's involvement as a Clinical Center for the new PETAL (Prevention and Early Treatment of Acute Lung Injury) Network, the successor of the Acute Respiratory Distress Syndrome Network (ARDSNet)
- A fascinating case study demonstrating why it is critical to recognize cases of cholinergic urticaria that may mimic exercise-induced anaphylaxis
- A discussion, provoked by recent animal studies, of whether RSV can be transmitted through the placenta into developing fetal lungs

I hope you enjoy the articles in this issue of *Respiratory Exchange*. Inside, you'll also find a listing of our actively enrolling clinical trials as well as a comprehensive listing of our staff and their specialty areas. To learn more about our clinical research activities, please visit [clevelandclinic.org/pulmonary](http://clevelandclinic.org/pulmonary) (where you'll find current and archived issues of *Respiratory Exchange*).

As always, use our toll-free number for physicians, 866.CCF.LUNG (866.223.5864), if you have any questions or would like to refer a patient. We're here to help.

Sincerely,

Herbert P. Wiedemann, MD, MBA  
CHAIRMAN | CLEVELAND CLINIC RESPIRATORY INSTITUTE

### *Respiratory Exchange*

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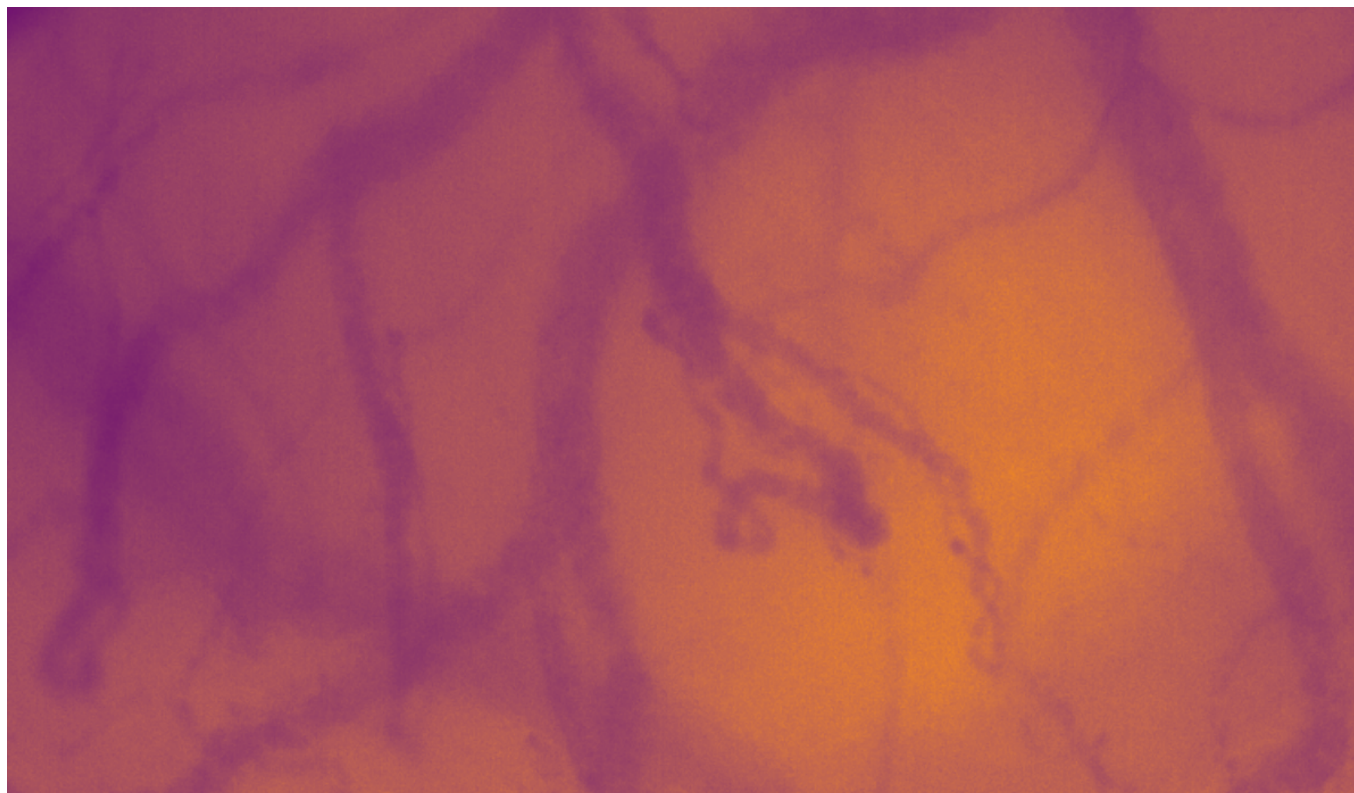
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# Is Systemic Circulation Affected in Pulmonary Arterial Hypertension?

By Adriano R. Tonelli, MD, and Raed A. Dweik, MD



Sublingual capillaroscopy in a patient with PAH. The microcirculation is illuminated with a special light that creates a high-contrast image of flowing red blood cells in these superficial vessels. Red blood cells are seen as dark structures and the white blood cells as gaps. Vessel walls are delineated by the red blood cells.

**P**ulmonary arterial hypertension (PAH) is a condition characterized by narrowing of the pulmonary arterial vessels that, if left untreated, leads to right heart failure and death.<sup>1</sup> Several systemic diseases are known causes of PAH, including scleroderma, cirrhosis with portal hypertension and congenital heart diseases. There are two particular subgroups of PAH — idiopathic and heritable — that have traditionally been associated with an isolated pulmonary vascular involvement. Although it is well-documented that patients with idiopathic or heritable PAH have pulmonary vascular dysfunction, preliminary data suggest that there may be a degree of systemic vascular involvement.

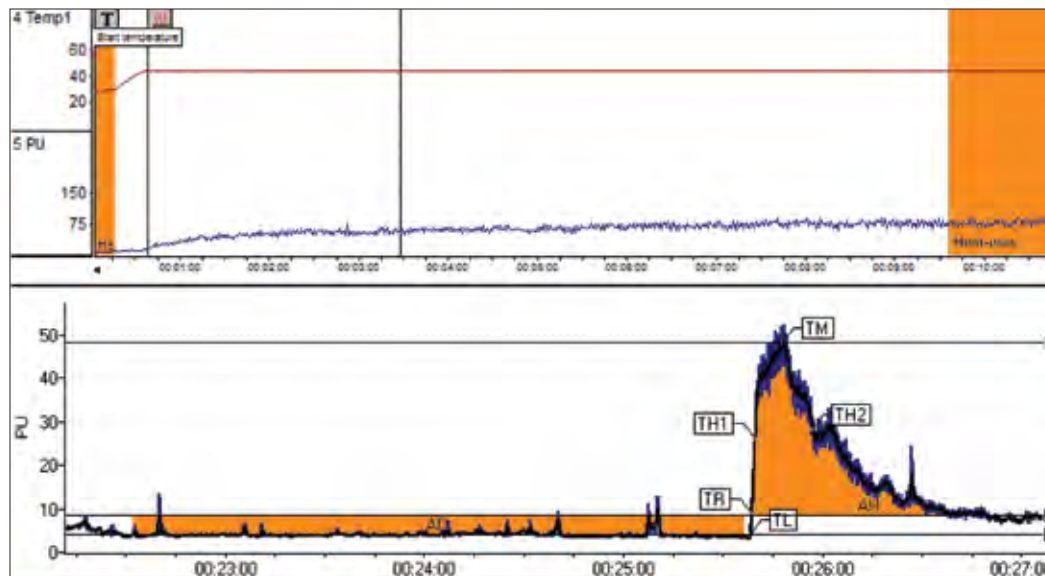
We are particularly interested in studying the precise nature, extent and significance of the systemic vascular involvement in PAH. We have recently shown that the sublingual microcirculation of patients with PAH is characterized by a lower sublingual microvascular flow index (a semiquantitative measure of the capillary flow) and a higher capillary tortuosity when compared with age- and gender-matched healthy controls.<sup>2</sup> The sublingual microcirculation was assessed using a handheld video capillaroscope system, which used oblique profiled imaging (angled illumination with higher-intensity light projected outside the field of view).

We are currently evaluating systemic microcirculation in patients with PAH using laser Doppler. This technology measures the local microcirculatory blood perfusion based on degree of change in the laser wavelength when it hits moving objects, a phenomenon called Doppler shift. For this test, we attach the integrated electrode containing several laser beams to a selected area in the anterior aspect of the forearm. Once baseline microvascular perfusion is obtained, we challenge the local circulation by increasing the skin temperature or occluding flow. Then we rapidly restore the forearm circulation. With increases in skin temperature to 44°C, the

*continued next page* >



*We are currently evaluating systemic microcirculation in patients with PAH using laser Doppler. This technology measures the local microcirculatory blood perfusion based on degree of change in the laser wave length when it hits moving objects, a phenomenon called Doppler shift.*



Cutaneous laser Doppler perfusion measured at the forearm in a patient with pulmonary arterial hypertension.

**Upper panel:** Thermal hyperemia: the temperature of the electrode is increased to 44 degrees centigrade (red line) with an associated increase in perfusion units (PU) (blue line) over 10 minutes.

**Lower panel:** Post-occlusive reactive hyperemia: an arm cuff is inflated for 4 minutes above systemic arterial pressure. Upon rapid deflation, the forearm laser Doppler probe detects a sudden increase in the cutaneous perfusion units (PU). Usual determinations are shown with letters.

microvascular perfusion increases several-fold, and this variation is measured as the percentage change in perfusion units.

In a different area of the same forearm, we determine the microvascular perfusion before, during and after inflation of an arm cuff at 200 mm Hg. During this challenge, the perfusion units decrease during vascular occlusion and increase severalfold above the baseline level when the cuff is rapidly deflated. Several measurements are obtained, including the percentage change in perfusion from the biological zero to the point of perfusion when circulation is occluded and perfusion is absent to peak flow following the release of occlusion, as well as the percentage change in perfusion. The vasodilation noted with hyperemia and immediately after vascular occlusion relies on the local endothelial production of nitric oxide, which is a diffusible gas with a central role in the pathobiology of PAH.<sup>3</sup>

Results of our investigations support the notion that PAH is a systemic vascular disease predominantly affecting the pulmonary circulation. It remains to be defined whether the systemic vascular involvement correlates with disease severity or response to therapy. If the latter were to be the case, it would certainly facilitate the evaluation and treatment of these patients, given that the microcirculation system is more easily accessible than the pulmonary vasculature. ●



Dr. Tonelli is an associate staff member at Cleveland Clinic's Respiratory Institute who is currently supported by a KL2 grant from the NIH. His research interest is in pulmonary hypertension. He can be reached at 216.444.0812 or tonella@ccf.org.



Dr. Dweik, Director of the Pulmonary Vascular Program, can be reached at 216.445.5763 or dweikr@ccf.org.

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# CoQ10 Shows Promise in Benefiting Pulmonary Arterial Hypertension Patients

By Jackie Sharp, CNP

**P**ulmonary arterial hypertension (PAH) is a disease that affects the blood vessels of the lungs, causing high pressure that leads to heart failure. Abnormalities of the intracellular organelle, the mitochondria, are present in the blood vessels of patients with PAH. The mitochondria are the cell's powerhouse, producing energy, but also are required for producing the heme that is used in hemoglobin in red blood cells. Coenzyme Q (CoQ10) is a vitamin cofactor that is essential for mitochondrial functions.

Recently, CoQ10 has been shown to improve cardiac function in heart failure patients through the effects it has on the mitochondria, so we hypothesized that CoQ10 might improve mitochondrial functions in energy and heme production and thus benefit PAH patients.

We conducted a prospective study in which eight PAH patients and seven healthy controls were supplemented with oral CoQ10 (100 mg, three times a day) for 12 weeks. CoQ10 levels were similar among PAH and control individuals at baseline. However, PAH patients had higher CoQ10 levels than controls after taking CoQ10.

Many studies have identified abnormalities in iron metabolism and red blood cells in pulmonary hypertension patients. In our work, we found similar abnormalities in patients at baseline, but also found that CoQ10 improved the hemoglobin content of red blood cells that increased in the PAH patients. These changes were not seen in healthy subjects. In fact, hemoglobin decreased slightly in healthy controls. CoQ10 improved right heart function in PAH subjects, but exercise and other markers of heart failure, such as serum brain natriuretic peptide levels, did not improve over the course of the three-month study.

Equally important, CoQ10 was well-tolerated in this study, confirming the minimal side effects of supplementation. The decrease in immature red blood cells, improvements in heart function by echocardiogram and increased red cell hemoglobin at 12 weeks suggest that trials of longer duration and/or higher doses of CoQ10, may demonstrate benefit for patients with PAH. ●



Jackie Sharp is a certified nurse practitioner in the Pathology Department at Cleveland Clinic Lerner Research Institute. She can be reached at 216.636.0000 or [sharpj@ccf.org](mailto:sharpj@ccf.org).

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Sharp J, Farha S, Park M, Comhair SA, Lundgrin EL, Tang WH, Bongard R, Merker M, Erzurum SC. CoQ supplementation in pulmonary arterial hypertension. *Redox Biology* 2014;2:884-891.



# Could **RSV** Be Transmitted Through the Placenta into Developing Fetal Lungs?

Animal studies demonstrate vertical transmission in utero, paving way for potentially paradigm-shifting human studies

By Giovanni Piedimonte, MD

**R**espiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and young children. Strong epidemiologic evidence suggests that when infants are infected, they are predisposed to chronic respiratory dysfunction and asthma, possibly due to persistence of the virus or its effects on lung development.

For many years, it has been generally accepted that the pathophysiology of RSV bronchiolitis is driven by the inflammatory response mounted by horizontal (i.e., interpersonal) transmission of the virus in the first few months after birth.

However, my colleagues and I recently published an animal study in PLOS ONE<sup>1</sup> that has brought to the forefront a striking new idea: RSV may be transmitted vertically from the respiratory tract of the mother to the lungs of the fetus. Until now, we believed that when a pregnant woman got a cold, the developing fetus was protected by the placenta from RSV and other respiratory viruses.

## INTRIGUING FINDINGS: TRANSPLENTAL TRANSMISSION AND BEYOND

In our study, pregnant rats were inoculated with recombinant RSV. The RSV genome was subsequently found in 30 percent of fetuses (Figure 1) and in the lungs of 40 percent of newborn rats and 25 percent of rats born to inoculated mothers when tested in adulthood (10 weeks after birth). These data support transplacental transmission of RSV from mother to offspring and the persistence of vertically transmitted virus in the lungs after birth.

*If our findings can be confirmed in human studies, we may have to rewrite the books on RSV transmission.*

Notably, we also found that exposure to RSV in utero changes the way that lungs function through dysregulation of neurotrophic pathways, thereby predisposing the subject to the postnatal airway hyperreactivity that is the hallmark of asthma.

## RETHINKING RSV TRANSMISSION

While this is the first time to our knowledge that vertical transmission of RSV — or any common respiratory virus — has been reported, a number of infectious agents, including herpesviruses and retroviruses, have been shown to cross the placenta and establish persistent infection in offspring.

### Our research was driven by two key factors:

- Human and animal research showing that while RSV primarily targets the lungs, the virus can spread to extrapulmonary sites, which can have systemic implications. We postulated that if RSV can spread beyond the lungs, it is possible that the virus also could penetrate the placenta.
- The possibility that some infections, such as RSV, once regarded as temporary may be longer-lasting and more pervasive than we thought. While the acute phase of an RSV infection typically resolves in a few weeks, my colleagues and I found in a separate study that RSV's molecular signature persists in the bone marrow long after the virus has cleared — even well into adulthood.<sup>2</sup> This finding has implications for both mother and fetus in terms of the potential for in utero transmission and its sustained effects.

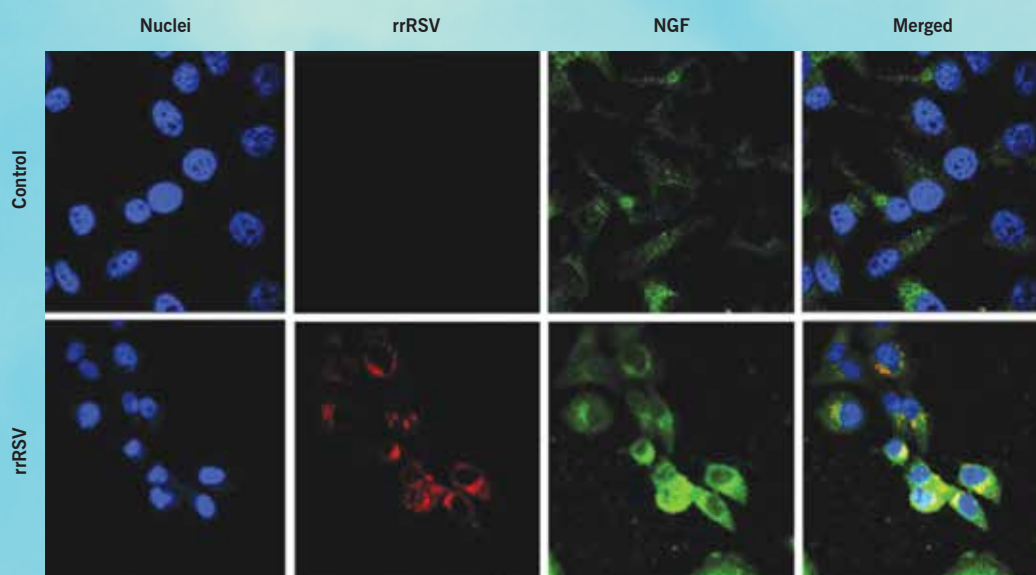
## POTENTIAL IMPLICATIONS: A NEW FOCUS ON PREVENTION IN PREGNANCY?

If our recent findings can be confirmed in human studies, we may have to rewrite the books on RSV transmission. The general idea we have been working under for decades in pulmonology is that nothing bad happens in the lungs until the baby is born — even with serious conditions such as cystic fibrosis. This study suggests that a certain percentage of patients who develop asthma may do so because of viral exposure in utero.





This study suggests that a certain percentage of patients who develop asthma may do so because of viral exposure in utero.



**Figure 1.** Propagation of vertically transmitted RSV in the rat. Magnified at 60 $\times$ , extracts of whole fetuses are shown that were delivered from dams inoculated with recombinant RSV (rrRSV; bottom row) or from pathogen-free controls (top row) and cocultured with human airway epithelial cells. The micrographs show red fluorescence in the cytoplasm of cells exposed to fetal extracts from rrRSV-infected dams, confirming the presence of actively replicating infectious virus associated with markedly increased green nerve growth factor (NGF) immunoreactivity. Reprinted from Piedimonte et al., *PLOS ONE*.<sup>1</sup>

The next step in our research will be to see if these observations are replicated in ex vivo studies of human cells. Eventually, research will focus on in vivo human studies in mothers naturally infected with RSV. Cleveland Clinic Children's plans to work closely with our colleagues in Cleveland Clinic's Ob/Gyn & Women's Health Institute to carefully administer these studies.

If human studies replicate our findings from animal models, our understanding of the pathogenesis of RSV infections would be completely changed. It would turn back the clock of respiratory developmental diseases by months and mean that we would need to start thinking about lung development and pathology during pregnancy rather than at birth. This could create a paradigm shift by extending our focus on prevention from the first few years after birth to also include the last few months before birth. ●

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# Understanding the Role of **TRPV4** in Mechanosensing, Myofibroblast Differentiation and Pulmonary Fibrosis

By Mitchell A. Olman, MD

**I**diopathic pulmonary fibrosis (IPF) is a fatal fibrotic lung disorder with marginally effective medical treatment. Myofibroblasts are critical to the fibrogenic lung repair process through their ability to produce collagen, secrete pro-fibrotic cytokines and contract tissue. Although myofibroblasts require active transforming growth factor- $\beta$  (TGF- $\beta$ ), and a mechanical signal for their generation, the nature of the mechanical signal and the mechanism by which the mechanical signal is sensed have remained elusive.

In a search through the literature, my team noted that a calcium-permeable cell membrane ion channel named transient receptor potential vanilloid 4 (TRPV4) was activated upon plasma membrane stretch and thus could act as a mechanosensor. Thus, we investigated whether TRPV4 plays a role in myofibroblast differentiation and/or in vivo lung fibrosis.

In work recently published in the *Journal of Clinical Investigation*,<sup>1)</sup> we show that inhibition of TRPV4 by small molecule inhibitors and/or downregulation/deletion of TRPV4 using molecular or genetic techniques resulted in an almost complete blockade of both the calcium influx response as well as the myofibroblast differentiation response to TGF- $\beta$ .

*Successful manipulation of TRPV4 channel activity may be a novel therapeutic approach for fibrotic diseases of the lung and other organs.*

## Reference

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Moreover, TRPV4 exhibited its mechanosensing and myofibroblast-differentiating effect under conditions of matrix stiffness in the range of normal and fibrotic lung (1-25 kPa), suggesting it can sense changes in matrix stiffness during the fibrogenic process. Using a model assay system developed in our laboratory, we also noted that TRPV4 blocked the myofibroblast differentiation response to actual fibrotic lung tissue. Furthermore, TRPV4 deficiency protects mice from in vivo lung fibrosis in an experimental murine model.

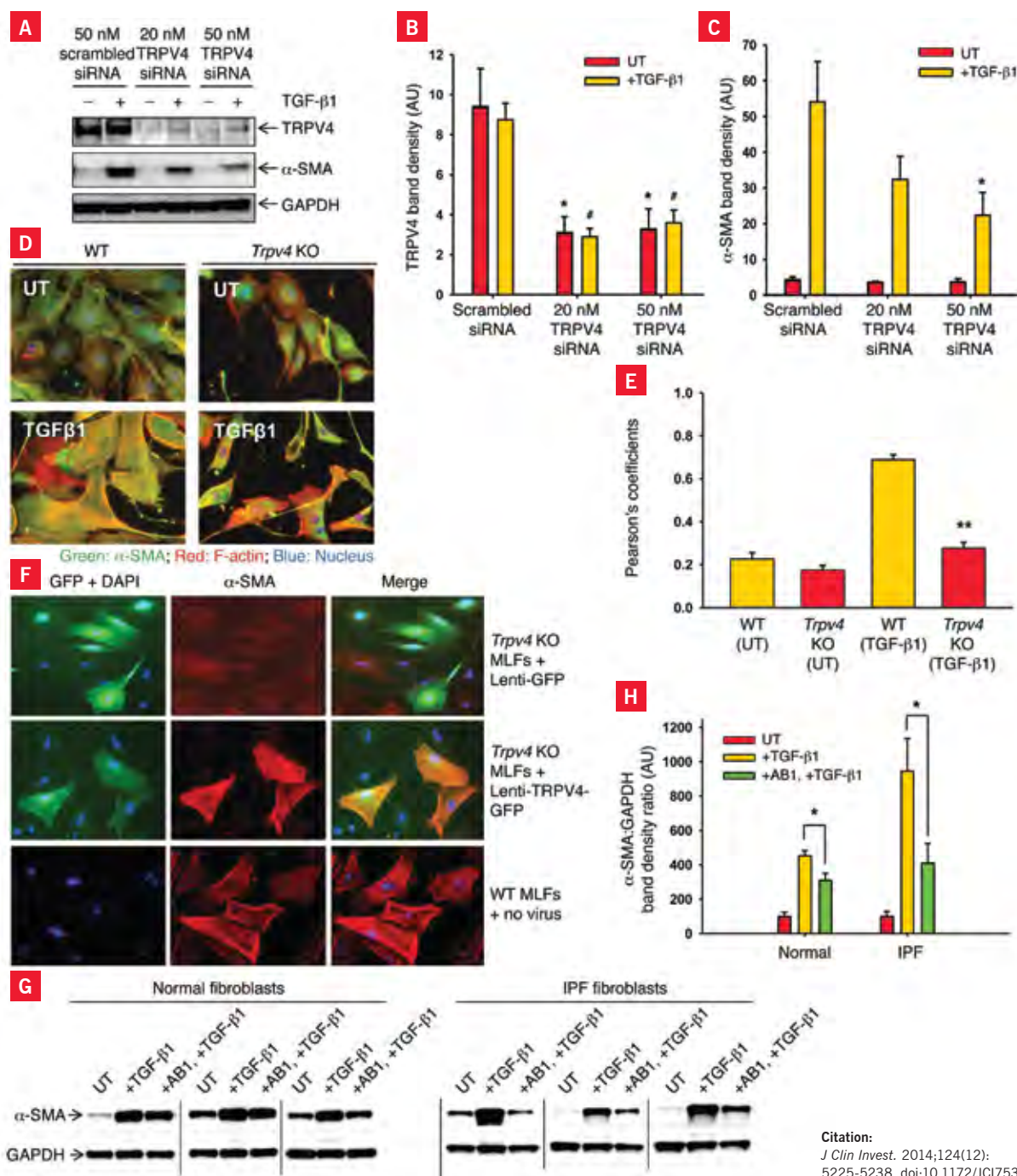
These data identify TRPV4 as a long-elusive mechanosensor/transducer that mediates myofibroblast differentiation and in vivo pulmonary fibrogenesis. Successful manipulation of TRPV4 channel activity may be a novel therapeutic approach for fibrotic diseases of the lung and other organs. TRPV4 has also recently been shown to be involved in other disorders associated with pulmonary parenchymal stretch including ventilator-induced lung injury, and a TRPV4 inhibitor for pulmonary edema due to pulmonary venous hypertension is undergoing Phase I trials.

In other work in our group, we are studying the role of TRPV4 in macrophage function (with Rachel Scheraga, MD), and the role of nonmuscle myosin in inducing the pro-fibrotic fibroblast phenotype (with Brian Southern, MD). ●



Dr. Olman is a staff physician in the Respiratory Institute with a primary appointment in the Department of Pathobiology. Contact him at 216.445.7191 or [olmanm@ccf.org](mailto:olmanm@ccf.org).





**Figure. TRPV4 is required for TGF- $\beta$ 1-induced lung myofibroblast differentiation.**

HLFs were plated on fibronectin-coated (10  $\mu$ g/mL plastic wells and incubated with or without TGF- $\beta$ 1 (2 ng/mL, 24 hours), TRPV4 siRNA or scrambled siRNA. (A) Representative immunoblots show knockdown of TRPV4 proteins by TRPV4-specific siRNA and blocking of TGF- $\beta$ 1-induced  $\alpha$ -SMA expression under conditions of TRPV4 knockdown. (B and C) Quantification of (B) TRPV4/GAPDH and (C)  $\alpha$ -SMA/GAPDH protein bands from A. \* $P$  < 0.05 scrambled vs. TRPV4 siRNA-treated cells, # $P$  < 0.05 TGF- $\beta$ 1-treated cells treated with scrambled siRNA vs. TRPV4 siRNA;  $N$  = 3. (D) Representative fluorescence micrographs (original magnification,  $\times$ 20). Myofibroblast differentiation is reduced in fibroblasts from TRPV4 KO mice (colocalization of  $\alpha$ -SMA and F-actin, orange). (E) Quantification of results from D by Pearson's coefficient analysis. \*\* $P$  < 0.01; TGF- $\beta$ 1-treated WT vs. *Trpv4* KO cells;  $N$  > 18 cells per group. UT, untreated. (F) Reconstitution of TRPV4 into *Trpv4* KO mouse lung fibroblasts (MLFs) using a *Lentivirus* expression system (lenti-TRPV4-GFP) restores myofibroblast differentiation in response to TGF- $\beta$ 1. Lenti-GFP-infected *Trpv4* KO mouse lung fibroblasts were used as negative controls; uninfected WT mouse lung fibroblasts were used as positive controls. Original magnification,  $\times$ 20. (G) TRPV4 blockade has a greater inhibitory effect on myofibroblast differentiation ( $\alpha$ -SMA/GAPDH band density in immunoblots) in fibroblasts from patients with IPF than in normal fibroblasts. (H) Quantitation of results from G. \* $P$  < 0.05;  $N$  = 5 per group. Results are expressed as mean  $\pm$  SEM.

# CASE STUDY: A 19-year-old College Athlete: Cholinergic Urticaria Masquerading as Exercise-Induced Anaphylaxis

By David M. Lang, MD



## INTRODUCTION

A college athlete was referred to Allergy/Immunology for further evaluation and management of recurrent episodes of anaphylaxis.

## CASE PRESENTATION

Three episodes had occurred in the six weeks prior to evaluation — each requiring emergency department management:

➤ **Episode 1** (six weeks earlier): During the third mile of a five-mile run, the patient developed palmar and plantar pruritus, nausea, throat and chest constriction, tongue swelling, and shortness of breath. Prior to exercise, she had consumed taco soup with avocado, ground beef, taco seasoning, black beans and tomato. She was taken to an emergency department, where she received epinephrine, oxygen, aerosolized bronchodilator and methylprednisolone; she was discharged with a prescription for a prednisone burst/taper. Her serum tryptase was 11.0 ng/mL.

➤ **Episode 2** (two weeks earlier): During the latter portion of a five-mile interval training exercise (sprint/jog/walk), she developed palmar/plantar tingling with nausea and a sensation of tongue swelling. Prior to exercise, she had consumed mussels, calamari and a hamburger on a sesame seed bun. She was taken to an emergency department, where she received epinephrine, oxygen, aerosolized bronchodilator and methylprednisolone. Her serum tryptase was elevated at 25.5 ng/mL.

➤ **Episode 3** (six days prior to evaluation): During high-intensity fitness training, she developed palmar/plantar tingling, throat tightness and tongue swelling. She consumed several teaspoons of liquid diphenhydramine and self-administered intramuscular epinephrine. EMS was called, and four more doses of intramuscular epinephrine were administered in the field. She received two more doses of epinephrine after arrival in an emergency department. Prior to this episode, she had consumed apples, strawberries, green pepper, bread and an oatmeal raisin Luna Bar® (containing rice, soy and other items). Serum tryptase was obtained, but the specimen was mishandled such that the result was not determined.

The patient had engaged in strenuous exercise at other times in the weeks prior to initial visit without experiencing any episodes. A diagnosis of exercise-induced anaphylaxis — possibly related to wheat, had tentatively been made. The above episodes were unrelated to menses or taking aspirin or aspirinlike drugs.

She denied wheezing, coughing or shortness of breath. Previous trials of inhaled steroid monotherapy or inhaled steroid combined with a long-acting beta agonist were not beneficial.

The patient experienced mild rhinitis symptoms in the spring/summer and fall months, for which she did not require regular medication. For a number of years, she had exhibited a tendency for flushing, pruritus and pencil eraser-size or smaller urticarial lesions provoked by heat expo-

sures — including being in a hot tub for more than 10 to 15 minutes or in association with hot showers.

Remarkable wheal/flare reactions to tree and weed pollens had been observed on inhalant skin testing.

Skin testing for foods had shown remarkable wheal/flare reactions to peanuts, mango, celery, pistachio, cashew and grape; she had previously tolerated these foods without untoward reaction, with the exception of pistachio and celery, which had been associated with tongue and throat itching on separate occasions.

## CLEVELAND CLINIC EVALUATION

Upon physical examination, the patient was in no acute distress and there were no remarkable findings. Cutaneous examination revealed no urticarial lesions, and there was no dermatographia evident with light stroking. Skin testing was performed, and revealed no remarkable wheal/flare reactions to wheat or soy.

She was instructed to avoid rigorous exercise in hot weather or in remote areas, or exercising without a partner and a cellphone. A tentative diagnosis of cholinergic urticaria, which may masquerade as exercise-induced anaphylaxis<sup>1</sup> was made.

The patient returned for a treadmill challenge. After provocation of profuse sweating, she developed erythema, pruritus and “pinpoint” urticarial lesions typical for cholinergic urticaria on her posterior torso, left lower extremity and distal upper extremities. At that point, the exercise challenge was terminated.



### CLINICAL COURSE

The patient was advanced on a regimen of combination H1 and H2 antihistamines with an anti-leukotriene drug. Levocetirizine and cetirizine were gradually increased, respectively, to 20 mg and 30 mg at HS.

- Cetirizine 10 mg at HS (advanced to 30 mg at HS)
- Levocetirizine 5 mg at HS (advanced to 10 mg at HS)
- Fexofenadine 180 mg in a.m.
- Ranitidine 150 mg BID
- Montelukast 10 mg daily

Despite daily use of the above medications, she continued to experience episodes of anaphylaxis that included urticaria/angioedema with exercise. Several episodes required administration of epinephrine and emergency department management. Ultimately, her tendency to experience these episodes progressed such that they occurred with routine activity.

She experienced an episode while standing outdoors on a warm day, without engaging in strenuous exertion. She was told that her face appeared swollen. Subsequently, she developed throat discomfort, had difficulty swallowing and felt lightheaded. She received two doses of intramuscular epinephrine. A third dose was administered

when EMS arrived. She improved while riding in an ambulance to the nearest emergency department. Despite being discharged on a course of oral steroids, she experienced recurrence of mouth swelling that evening, and then 48 hours later had swelling of her eyes, lips and tongue. A trial of doxepin was proposed, but this was not prescribed as she described lassitude that affected her school performance. Her cetirizine dose was reduced to 20 mg at HS.

In view of an interval course implying that her threshold for reaction had changed and that she was at risk for serious episodes not only with exercise but also during routine activities, a trial of omalizumab was proposed. She and her parents agreed to proceed. She initially received omalizumab at a dose of 150 mg q 4 weeks. There was partial but definite improvement. Omalizumab was advanced to 300 mg q 4 weeks, which was associated with a definite and sustained benefit.

### DISCUSSION

High-quality evidence supports administration of omalizumab for patients with antihistamine-resistant chronic urticaria/angioedema.<sup>1</sup> However, in four randomized, controlled trials demonstrating the efficacy of omalizumab for chronic urticaria/angioedema, patients with physical urticaria/angioedema syndromes were excluded from participation.<sup>2</sup>

This case highlights the importance of recognizing cases of cholinergic urticaria that may mimic exercise-induced anaphylaxis. Cholinergic urticaria can be confirmed by provocative challenges that raise core body temperature, such as exercise or hot water immersion.<sup>3</sup> A step-care approach for the diagnosis and management of chronic urticaria/angioedema has been recommended, based on best evidence, in recently released guidelines.<sup>1</sup> ●



Dr. Lang is Chair of the Department of Allergy and Clinical Immunology, Co-Director of the Asthma Center and Director of the

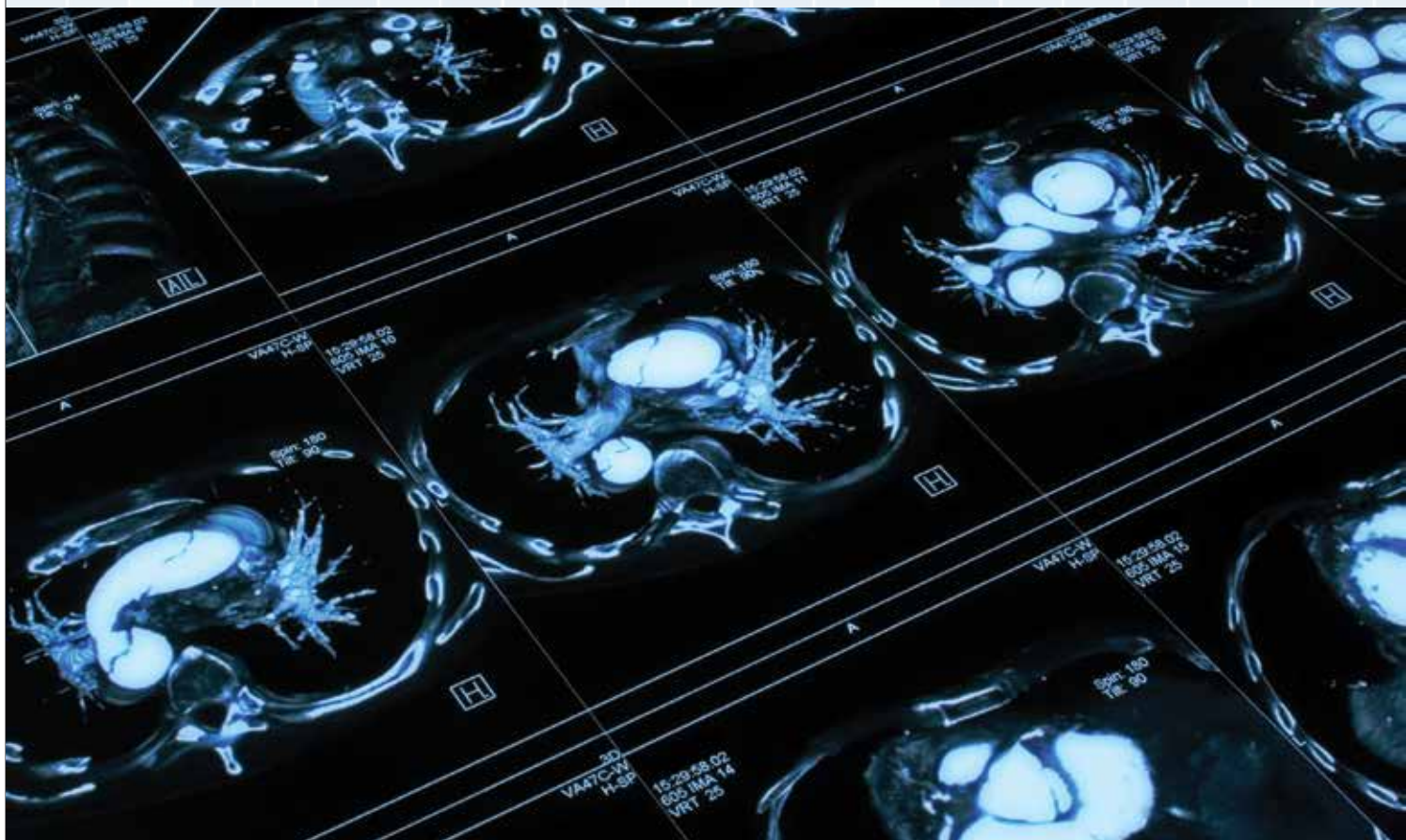
Allergy/Immunology Fellowship Training Program in the Respiratory Institute at Cleveland Clinic. He can be reached at 216.445.5810 or [langd@ccf.org](mailto:langd@ccf.org).

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# Network-based ARDS Research at Cleveland Clinic Enters Third Decade

By R. Duncan Hite, MD



In spring 2014, Cleveland Clinic was named as one of 12 primary awardees to serve as a Clinical Center for the new PETAL (Prevention and Early Treatment of Acute Lung Injury) Network sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The PETAL Network is considered by most as the next generation of the Acute Respiratory Distress Syndrome Network (ARDSNet), which served as a model for clinical research networks and performed groundbreaking clinical trials on ARDS since its inception in 1994. Landmark projects completed by ARDSNet include trials that provided the initial Phase III evidence demonstrating improved clinical outcomes from the “lung protective (low tidal volume) ventilation strategy” and “conservative fluid management.” Each has dramatically impacted patient outcomes and reshaped the standards of care in many aspects of critical care medicine over the past 10 to 15 years.

## A HISTORY OF INVESTIGATIONS TO IMPROVE CARE

As one of only a few Clinical Centers moving forward, Cleveland Clinic has been a primary awardee and enrolling center for both the ARDSNet and now PETAL since their inception more than 20 years ago.

Herbert Wiedemann, MD, Chairman of the Respiratory Institute, provided leadership for the Cleveland Clinic ARDSNet center from 1994 to 2014, and its achievements were the result of the collective efforts of an impressive cast of players. One key contribution by the Cleveland Clinic site was Dr. Wiedemann's role as co-primary investigator of the Fluids and Catheters Treatment Trial (FACTT), which demonstrated that a conservative fluid management approach is superior in acute lung injury and ARDS to a wet or liberal strategy.



#### A NEW ERA, BUILDING ON PAST SUCCESSES

In 2013, I joined Cleveland Clinic's staff as the inaugural Chair of the newly formed Department of Critical Care Medicine. Since 2000, as a faculty member at Wake Forest University Health System, I served as a leader for the Wake Forest Clinical Center in ARDSNet. With that valuable experience, I have now assumed the role of primary investigator for Cleveland Clinic's PETAL Clinical Center as well as head of the critical care research program within the Respiratory Institute.

In addition to maintaining our long history of success in ARDSNet, we have already begun efforts to expand the program's scope to include a broad variety of critical illnesses, and to expand the program's reach to include all patients across the community hospitals within Cleveland Clinic's health system.

#### HOW PETAL WILL DIFFER FROM ARDSNet

The PETAL Network will function in a manner very similar to ARDSNet, but there are many important and exciting differences that will present both challenges and opportunities over the next several years.

As its title suggests, PETAL will shift some of its ARDS research to focus on earlier aspects in disease progression, including (a) recognition and treatment of patients within the first several hours (early) of the onset of ARDS and (b) recognition and utilization of preventive approaches in patients with conditions that predispose to ARDS. This new approach has been long-considered, but the creation of PETAL is the first strong indication of its national priority to NHLBI.

To achieve these goals, all PETAL Clinical Centers now represent strong multispecialty collaborations between intensivists who provide the care for these patients in the ICU and those who provide care to those patients "at risk," including emergency medicine and surgery. Enrollment in PETAL's initial prevention and treatment trials are anticipated in late spring 2015. The effort that has already been made developing those trials' protocols clearly demonstrate the benefits and future potential of this new collaborative network.

Our involvement in PETAL has led to the development of some ambitious goals, including solicitation of novel therapeutic approaches from sources both within and outside the network, introduction of a central institutional review board to the network's infrastructure, enhancements to the process of surrogate consent in critically ill patients, and expanded coordination with ancillary projects generated by the entire ARDS research community.

To achieve these ambitious goals and to complete patient enrollment, the PETAL Network's Clinical Centers are generally made up of three to four contributing medical centers. The Clinical Center anchored by Cleveland Clinic includes invaluable contributions from co-investigators at The Ohio State University Wexner Medical Center, the University of Cincinnati Medical Center and the Summa Health System (Akron, Ohio). This impressive collection of investigators and their respective clinical research teams is now known as the Ohio Consortium. Our initial meetings have fueled rousing enthusiasm and anticipation for the finalized PETAL protocols. In addition, we envision this infrastructure serving as an excellent opportunity for promoting statewide collaborations on projects from any of the four contributors while simultaneously maintaining our focus on PETAL projects.

We are both excited and proud to continue the firmly established history and tradition of success in ARDS research at Cleveland Clinic. The novel and groundbreaking approaches within the PETAL Network will be high priorities, and we are confident that this program will facilitate the development of important collaborations across multiple specialties within the Cleveland Clinic enterprise as well as with other medical centers in Ohio and throughout the U.S. ●



Dr. Hite is Chair of the Department of Critical Care Medicine in Cleveland Clinic's Respiratory Institute. He can be reached at 216.445.3099 or [hited@ccf.org](mailto:hited@ccf.org).

## Respiratory Institute Selected Clinical Trials

Consider offering your patient enrollment in a leading-edge clinical research trial at our Respiratory Institute. Further information can be obtained by contacting the study coordinator or principal investigator.

### SARCOIDOSIS AND INTERSTITIAL LUNG DISEASE

#### STX-100 in Patients with Idiopathic Pulmonary Fibrosis (IPF)

Sponsored by Stromedix Inc., this randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study is examining a humanized monoclonal antibody targeting integrin  $\alpha v \beta 6$  in IPF patients.

**ELIGIBILITY:** Patients age 50-84 years, IPF diagnosis prior to screening via HRCT showing UIP pattern, FVC > 50% of predicted value, DLco > 35% of predicted value, oxygen saturation > 90% on room air at rest, residual volume < 120% of predicted value, FEV1/FVC ratio 0.65 after use of bronchodilator. Ages 18-49 are eligible if they have a diagnosis of UIP based on surgical lung biopsy.

**PRINCIPAL INVESTIGATOR:**  
Daniel Culver, DO

**STUDY COORDINATOR:**  
Tani Martin, BSN, RN | 216.444.9975

#### A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of GS-6624 in Subjects with Idiopathic Pulmonary Fibrosis (RAINIER)

Sponsored by Gilead Pharmaceuticals, this is a Phase 2, randomized, double-blind, placebo-controlled study of a subcutaneous monoclonal antibody (simtuzumab), once a week. Simtuzumab is a humanized mAb with an immunoglobulin IgG4 isotype directed against human LOXL2 (lysyl oxidase-like 2), an ECM enzyme that promotes cross-linking of proteins. The primary objective is to determine the effect of simtuzumab on

progression-free survival as determined by either a categorical decline in FVC or all-cause mortality.

**ELIGIBILITY:** Patients age 45-85 with definite IPF using HRCT/SLB in past 3 years. However, if diagnosis is less than 3 years but clinically deteriorating, they can be screened for participation. RA sat  $\geq$  89% at rest, able to walk > 50 meters, FVC 35%-90% of predicted, DLco > 25% of predicted. Exclusions include use of supplemental  $O_2$  > 6 L with activity; FVC > 90% of predicted; history of aortic aneurysm  $\geq$  3.5 cm in diameter; obstructive lung disease by PFTs or HRCT; respiratory hospitalization within past 26 weeks; treatment with immunosuppressive, cytotoxic or anti-fibrotic drugs (NAC is OK); chronic use of moderate- or high-dose oral corticosteroids (> 10 mg/day); and being listed for lung transplant.

**PRINCIPAL INVESTIGATOR:**  
Joseph Parambil, MD

**STUDY COORDINATOR:**  
Ron Wehrmann, RRT | 216.445.0574

#### Safety and Efficacy of a Lysophosphatidic Acid Receptor Antagonist in Idiopathic Pulmonary Fibrosis (SEAL)

Sponsored by Bristol-Myers Squibb, this is a double-blind, placebo-controlled, Phase 2 study of the safety and efficacy of lysophosphatidic acid receptor antagonist (BMS-986020). The primary efficacy outcomes assessment is rate of change in FVC from baseline to week 26.

**ELIGIBILITY:** Patients ages 40-80, 6 months > UIP dx > 48 months, FVC 50%-80% of predicted, DLco 50%-80% of predicted, able to walk 150 meters. Exclusions include

ratio < 80% after administration of BD at screening, + BD response with spirometry, having a family or personal history of long QT syndrome and/or torsades de pointes, QTcF > 450 ms.

**PRINCIPAL INVESTIGATOR:**  
Daniel Culver, DO

**STUDY COORDINATOR:**  
Ron Wehrmann, RRT | 216.445.0574

#### A Double-Blind, Placebo-Controlled Phase 2 Dose-Ranging Study of the Effects of ARA 290 on Corneal Nerve Fiber Density and Neuropathic Symptoms of Subjects with Sarcoidosis

Sponsored by Arafim Pharmaceuticals, the primary objective of this study is to determine the safety and efficacy of 1 mg, 4 mg or 8 mg of ARA 290 administered subcutaneously for 28 consecutive days vs. placebo on corneal nerve fiber density.

**ELIGIBILITY:** Patients ages > 18 and < 70 with neuropathic symptoms and diagnosed with sarcoidosis; who meet both of the following two criteria: score of 4 or greater on BPI and discomfort defined as distal pain/discomfort; and either of the following two criteria: corneal nerve fiber density reduced compared with normal or a previous skin biopsy showing a reduced intraepidermal nerve fiber density; BMI  $\leq$  40 kg/m<sup>2</sup>. Exclusion criteria include abnormal history of physical and mental health, abnormal laboratory results, abnormal ECG, history of serious malignancy in the past 5 years, anti-TNF therapy, other biological anti-inflammatory agents or immunoglobulins administered within 3 months, use of erythropoiesis-stimulating agents within 2 months, history of severe allergies.



## PRINCIPAL INVESTIGATOR:

Daniel Culver, DO

## STUDY COORDINATOR:

Tani Martin, BSN, RN | 216.444.9975

### Use of Roflumilast to Prevent Exacerbations in Fibrotic Sarcoidosis Patients

Sponsored by Forest Research Institute, the primary objective of this study is to determine the effectiveness and toxicity of roflumilast in treating fibrotic sarcoidosis, including reducing episodes of acute exacerbations.

ELIGIBILITY: Patients ages > 18 and < 70 with sarcoidosis, FEV1/FEV ratio < 80%, fibrosis on CXR or HRCT, at least two exacerbations of sarcoidosis in the past year, stable dose of corticosteroids and other agents at least 4 weeks prior to first visit. Exclusion criteria include hypersensitivity to theophylline or pentoxifylline (patients will not be able to take theophylline or pentoxifylline during the time of the study), serum creatinine > 3 mg/dL, moderate or severe liver disease, unstable cardiac disease, noncutaneous malignancy treated in the past 2 years.

## PRINCIPAL INVESTIGATOR:

Joseph Parambil, MD

## STUDY COORDINATOR:

Mary Beukemann | 216.445.8651

### FibroGen FGCL-3019-067: Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG-3019, a Fully Human, Recombinant DNA-Derived, IgG1 Kappa Monoclonal Antibody that Binds to CTGF in the N-terminal Domain

The primary objective of this study, sponsored by FibroGen Inc., is to determine the effect of FG-3019 on FVC % predicted in patients with usual interstitial pneumonia (UIP).

ELIGIBILITY: Patients 40-80 years old with < 48 months dx of UIP; FVC 55%-90%

of predicted; DLco > 30% of predicted. Exclusion criteria include DLco < 30% of predicted (corrected); FVC > 90% predicted; evidence of obstructive lung disease by any of the following criteria: RV/TLC < 80%, or RV > 120% of predicted, or extent of emphysema on HRCT greater than the extent of fibrosis on HRCT; treatment with immunosuppressive, cytotoxic or anti-fibrotic drugs (NAC is OK); history of cancer of any type in the 5 years preceding screening visit 1, excluding nonmelanomatous skin cancer, localized bladder cancer, or in situ cervical cancer; upper or lower respiratory tract infection of any type within 4 weeks of Screening visit 1; planned elective surgery during the study including 4 weeks following the final dose of study drug; body weight > 130 kg; inadequate IV access; listed for lung transplant.

## PRINCIPAL INVESTIGATOR:

Daniel Culver, DO

## STUDY COORDINATOR:

Ron Wehrmann, RRT | 216.445.0574

### Investigation of the Efficacy of Antimycobacterial Therapy on Pulmonary Sarcoidosis Phase II Randomized, Double-Blind, Placebo-Controlled Trial (CLEAR)

The objective of this NIH-supported study is to assess the efficacy and safety of oral CLEAR therapy in patients with confirmed progressive pulmonary sarcoidosis.

ELIGIBILITY: Selected inclusion criteria include patients with sarcoidosis as defined by the ATS/ERS/WASOG statement on sarcoidosis; biopsy demonstrating granulomas, and no alternative for the cause of the granulomas; evidence of disease progression; positive peripheral immune responses to ESAT-6 as a biomarker of response to CLEAR regimen; possess evidence of parenchymal or nodal disease on chest radiograph.

## PRINCIPAL INVESTIGATOR:

Daniel Culver, DO

## STUDY COORDINATOR:

Meredith Seeley | 216.445.9557

### Ocular Sarcoidosis: Open Label Trial of ACTHAR Gel

Sponsored by Questcor, this study will investigate whether treatment with ACTHAR Gel will result in a reduction of ocular inflammation in patients with active ocular sarcoidosis that requires systemic immunosuppressant therapy.

ELIGIBILITY: Selected inclusion criteria include patient with sarcoidosis as defined by ATS/ERS/WASOG guidelines; any posterior, intermediate or panuveitis of sufficient severity to warrant therapy, in the opinion of the treating physician OR anterior uveitis requiring 4 or more daily applications of topical corticosteroids to maintain control of inflammation, or uncontrolled with topical therapy; persistent disease activity (active uveitis) at the time of screening.

## PRINCIPAL INVESTIGATOR:

Daniel Culver, DO

## STUDY COORDINATOR:

Meredith Seeley | 216.445.9557

### HEREDITARY HEMORRHAGIC TELANGIECTASIA

#### A Phase II Study to Evaluate the Effects of up to 12 Weeks of Pazopanib Dosing on Bleeding in Patients with Hereditary Hemorrhagic Telangiectasia

Sponsored by GlaxoSmithKline, this study will investigate whether pazopanib can reduce epistaxis and improve anemia in subjects with hereditary hemorrhagic telangiectasia at a dose that is well-tolerated.

ELIGIBILITY: Selected inclusion criteria include subjects ages 18-75 years of age inclusive; diagnosis of definite or possible HHT by the Curacao criteria; severe epistaxis over previous 4 weeks, as defined as an average of at least 3 nosebleeds per week AND a total duration of greater than 15 min per week AND requiring iron therapy (oral and/or IV) or moderate or severe iron deficiency anemia (Hgb < 11 g/dL); epistaxis is considered to be clinically stable during the 4 weeks prior to screen-

ing; subject agrees not to undergo laser ablation of nasal telangiectasias or take any experimental therapies for HHT other than the study drug; QTc < 450 msec or QTc < 480 msec in subject with BBB.

PRINCIPAL INVESTIGATOR

Joseph Parambil, MD

STUDY COORDINATOR:

Mary Beukemann | 216.445.8951

## ASTHMA

### A 26-Week Randomized, Double-Blind, Active Controlled Study Comparing the Safety of Mometasone Furoate/Formoterol Fumarate MDI Fixed Dose Combination vs. Mometasone Furoate MDI Monotherapy in Adolescents and Adults with Persistent Asthma

Sponsored by Merck/Schering-Plough Research Institute, this study has been designed to compare the incidence of serious asthma outcomes in subjects treated with MF/F MDI BID vs. those treated with MF MDI BID. To demonstrate the risk/benefit of MF/F compared with MF in the same study population, this study also evaluates whether the addition of F to MF reduces asthma exacerbations.

ELIGIBILITY: To qualify for inclusion, patient must report using one of the following asthma therapies: (a) ICS or ICS with one or more adjunctive therapies (LABA, LTRA or theophylline) at a stable dose for at least 4 weeks prior to randomization, (b) leukotriene receptor antagonist (i.e., LTRAs such as montelukast, zafirlukast or pranlukast) OR xanthines (e.g., theophylline) as monotherapy at a stable dose for at least 4 weeks prior to randomization, or (c) daily albuterol/salbutamol (used on most days) without any other asthma controller, in the 4 weeks prior to randomization. Subject must be able to discontinue his/her current asthma medication (e.g., SABA, LTRA, theophylline, ICS or ICS/LABA) and must report a history of at least one asthma exacerbation between 4 and 52 weeks prior to randomization. Key exclusion criteria include unstable asthma;

COPD, cystic fibrosis or other significant, nonasthmatic lung disease; cumulative history of smoking > 10 pack years; an asthma exacerbation within 4 weeks of randomization; and reporting > 4 separate asthma exacerbations within last 52 weeks.

PRINCIPAL INVESTIGATOR:

David Lang, MD

STUDY COORDINATOR:

Elizabeth Maierson, RRT | 216.444.2901

### Severe Asthma Research Program (SARP)

Sponsored by the NHLBI, this multicenter, 36-month study is designed to evaluate the pathology of asthma longitudinally.

ELIGIBILITY: Individuals (6-65 years old) who have been clinically diagnosed with asthma and are prescribed oral corticosteroid or high-dose inhaled corticosteroid and long-acting beta agonist or other controller medication. Participants must demonstrate FEV1 bronchodilator reversibility  $\geq 12\%$  or airway hyper-responsiveness reflected by a methacholine PC20  $\leq 16$  mg/mL. Exclusion criteria include smoking history > 10 pack years if  $\geq 30$  years of age, or smoking history > 5 pack years if < 30 years of age, and no smoking within the past year.

PRINCIPAL INVESTIGATOR:

Serpil Erzurum, MD

STUDY COORDINATOR:

Marybeth Boyle | 216.445.1756

### KIA

Sponsored by the NIH and Brigham and Women's Hospital, this is a 30- to 34-week, treatment-randomized, double-blind, placebo-controlled study of the effects of cKIT inhibition by imatinib in patients with severe refractory asthma (KIA).

ELIGIBILITY: Patients age 18-60 years, diagnosed with asthma for at least one year, ACQ 1.5 at VI and V3, pre-bronchodilator FEV1 40% of predicted, > 80% compliance with PEF recording and diary recording during the run-in period.

PRINCIPAL INVESTIGATOR:

Serpil Erzurum, MD

STUDY COORDINATOR:

Jackie Sharp, CNP | 216.636.0000

### Alternate Day Diet (ADD)

Sponsored by the NHLBI, this study is looking at the effects of a calorie-restricted diet in asthmatics.

ELIGIBILITY: Participants must be between the ages of 18 and 65 with a diagnosis of asthma. Healthy individuals will also be enrolled for comparison. Exclusion criteria include diabetes (fasting blood sugar >110 mg/dL), lactose intolerance, BMI > 32 kg/m<sup>2</sup>, pregnancy and inability to maintain ADD diet. Low-calorie "shakes" will be provided to participants.

PRINCIPAL INVESTIGATOR:

Serpil Erzurum, MD

STUDY COORDINATOR:

Megan Park | 216.445.1756

## LUNG CANCER

### The Evaluation of Exhaled Breath in Disease States

The pattern of chemicals (volatile organic compounds) in exhaled breath of people with particular diseases seems to be different than in the breath of those without the disease. Advances in chemical sensing devices allow the detection of these patterns. This study assesses the ability of sensors to detect the presence of a disease by analyzing subjects' exhaled breath. This stage of the study focuses on breath samples from subjects who are at a high risk of developing lung cancer and those with proven lung cancer.

ELIGIBILITY: Patients ages 40-90 years,  $\geq 10$  pack-year history; untreated, tissue-confirmed lung cancer, or high suspicion of lung cancer; evaluation of an indeterminate lung nodule with a maximum diameter of 3-20 mm. Exclusion criteria include any cancers within the last 5 years, any history of lung cancer, immunosuppressive or continuous supplemental oxygen use.



**PRINCIPAL INVESTIGATOR:**

Peter Mazzone, MD, MPH

**STUDY COORDINATOR:**

Mary Beukemann | 216.445.8651

**Early Diagnosis of Pulmonary Nodules Using a Plasma Proteomic Classifier**

A prospective, multicenter, blinded observational study to collect blood specimens and clinical data in association with patients with a newly diagnosed lung nodule who have been referred for pulmonary consultation to guide diagnostic decision-making and clinical management. The study, sponsored by Integrated Diagnostics Inc., will explore the clinical hypothesis that the lung nodule test demonstrates performance parameters, such as negative and positive predictive values, which would substantiate the test's use in clinical decision-making for individual patients presenting with new lung nodules.

**ELIGIBILITY:** Patients age  $\geq 40$  years, undergoing diagnostic evaluation for a new lung nodule with maximal dimensions identified by CT scan  $\geq 8$  mm and  $\leq 30$  mm. Exclusion criteria include previous nodule diagnostic procedures, nodule detected by previous CT scan 60 days prior to current CT scan, prior diagnosis of any cancer within 2 years of lung nodule detection, except for nonmelanoma skin cancer, and administration of blood product.

**PRINCIPAL INVESTIGATOR:**

Peter Mazzone, MD, MPH

**STUDY COORDINATOR:**

Mary Beukemann | 216.445.8651

**Lung Cancer Blood and Urine Bank Development**

The purpose of this study is to gather blood and urine samples from people who are either at risk of having lung cancer, or have been proven to have lung cancer, so that these samples can be used to develop lung cancer tests. The tests developed might be able to predict who will develop lung cancer in the future, or could help doctors diagnose

lung cancer. Blood and urine will be collected and stored at  $-70$  degrees Celsius pending worthy projects. Freezer space has been obtained in the lab of Daniel Culver, DO.

**ELIGIBILITY:** (1) Patients ages 40-90 years,  $\geq 10$  pack year history; (2) untreated, tissue-confirmed lung cancer, or high suspicion of lung cancer; (3) high risk for lung cancer due to smoking, family history and COPD. Exclusion criteria include any cancers within the last 5 years, any history of lung cancer, immunosuppressive or continuous supplemental oxygen use.

**PRINCIPAL INVESTIGATOR:**

Peter Mazzone, MD, MPH

**STUDY COORDINATOR:**

Mary Beukemann | 216.445.8651

**LUNG TRANSPLANT****Immune Mechanism of Rejection in Human Lung Allografts**

To determine mechanisms by which pre-existing immune responses to self-Ags increase PGD leading to augmented alloimmune responses resulting in chronic rejection following human LTx, subjects will be recruited who have high PRA percentages prior to transplant. Serum and BAL samples will be collected prior to lung transplant as well as post-transplant. This study is sponsored by the NIH and Washington University in St. Louis.

**ELIGIBILITY:** Patients awaiting LTx at Cleveland Clinic who undergo desensitization if there is sensitization to HLA and self-Ags using the standard desensitization protocol with rituximab and IVIG.

**PRINCIPAL INVESTIGATOR:**

Marie Budev, DO, MPH

**STUDY COORDINATOR:**

Chenett Greer | 216.445.9287

**Lung Transplant and Cognitive Impairment**

This is a prospective study that is intended to further investigate the incidence, preva-

lence and risk factors for neurocognitive impairment in a cohort of lung transplant recipients. All patients who agree to participate will undergo a series of selected neurocognitive tests on the day of their standard outpatient post-transplant appointment. Patients will not be asked to come in for a separate appointment or day to participate in the research study. In a confidential, one-on-one testing method in a private exam room, each study participant will undergo the Montreal Cognitive Assessment Test and a series of neurocognitive tests, referred to as a neurocognitive battery (NB), to evaluate domains of cognitive function/dysfunction.

**ELIGIBILITY:** Patients 18 or older who are  $\geq 12$  months from their transplant surgery.

**PRINCIPAL INVESTIGATOR:**

Marie Budev, DO, MPH

**STUDY COORDINATOR:**

Chenett Greer | 216.445.9287

**LUNG VOLUME REDUCTION****Lung Function Improvement After Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves Used in Treatment of Emphysema (LIBERATE)**

Sponsored by Pulmonx, the purpose of this study is to assess the safety and effectiveness of bronchoscopic lung volume reduction (BLVR) using the Pulmonx Endobronchial Valve (EBV) in treated study participants compared with control participants to support a premarket approval application to FDA. One hundred and eighty-three patients who are found to qualify for the study during a bronchoscopy procedure will be randomly assigned to either the study treatment group or the control group. Approximately two-thirds will be randomly assigned to the EBV treatment group and one-third randomly assigned to the control group.

**ELIGIBILITY:** Completed a supervised pulmonary rehabilitation program  $< 6$  months prior to the baseline exam or is regu-

larly performing maintenance respiratory rehabilitation if initial supervised therapy occurred > 6 months prior; baseline evaluation occurred < 90 days after screening exam; signed written informed consent to participate in study using a form that was reviewed and approved by the IRB; continued nonsmoking between initial screening and baseline exams; FEV1 > 15% or < 45% of predicted value at baseline exam; 6-minute walk distance of < 400 meters at baseline exam.

PRINCIPAL INVESTIGATOR:

Michael Machuzak, MD

STUDY COORDINATOR:

Yvonne Meli, RN | 216.445.4215

## PULMONARY HYPERTENSION

### Pulmonary Vascular Complications of Liver Disease-2 (PVCLD2)

Sponsored by Perelman School of Medicine at the University of Pennsylvania as a subcontract of the NHLBI, the purpose of this study is to determine if certain genes, hormones or other factors predict the risk of developing lung vessel disease in patients with liver disease and whether they determine outcome.

ELIGIBILITY: Patients age  $\geq 18$  years with chronic portal hypertension from intrinsic liver disease or portal vein disease, documented by clinical history or liver biopsy, referral for evaluation for liver transplantation (LT) or portopulmonary hypertension (or a known diagnosis of portopulmonary hypertension). Exclusion criteria include having an active infection, active or recent (< 2 weeks) gastrointestinal bleeding, lung transplant or LT recipients, being pregnant.

PRINCIPAL INVESTIGATOR:

Gustavo Heresi, MD

STUDY COORDINATOR:

Kasi Timmerman | 216.444.2140

### A Multicenter, Open-Label, Single-Arm, Phase 3b Study of Macitentan in Patients with Pulmonary Arterial Hypertension to Psychometrically Validate the PAH-SYMPACT Instrument

Sponsored by Actelion Pharmaceuticals Ltd., this study is to demonstrate the psychometric characteristics of reliability and construct validity of the PAH-SYMPACT instrument and its ability to detect change.

ELIGIBILITY: Patients age 18-80, diagnosis of PAH in WHO Functional Class II-IV and belonging to a subgroup of the Dana Point Clinical Classification Group 1, mPAP > 25 mm Hg, PVR > 240 dyn·s/cm, PCWP < 15 mm Hg, 6-minute walk test > 150 m. Exclusion criteria include TLC < 60%; FEV1/FVC < 70%; FEV1 < 65%; life-threatening diseases with a life expectancy of < 12 months; recently started or planned cardiopulmonary rehabilitation program based on exercise; treatment with ERAs, riociguat, IV or subcutaneous prostacyclin or prostacyclin analogs within 3 months prior to visit 2; CYP3A inducers within 4 weeks prior to visit 2.

PRINCIPAL INVESTIGATOR:

Joseph Parambil, MD

STUDY COORDINATOR:

Kasi Timmerman | 216.444.2140

### Pulmonary Arterial Hypertension Treatment with Carvedilol for Heart Failure (PAHTCH)

Sponsored by the NIH, this is a 6-month double-blind, randomized, controlled intervention with three arms preceded by an open-label, 1-week run-in period of the effects of carvedilol in patients with pulmonary arterial hypertension.

ELIGIBILITY: Age 18-65; PAH Class 1 (Dana Point 2008); NYHA/WHO Class I-III; stable on PAH medications for the last 30 days; women of childbearing age must use a double-barrier local contraception until completion of the study.

PRINCIPAL INVESTIGATOR:

Serpil Erzurum, MD

STUDY COORDINATOR:

Emir Roach, MD | 216.445.7706

### RISE-IIP: A Randomized, Double-Blind, Placebo-Controlled Phase II Study to Investigate the Efficacy and Safety of Riociguat (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg and 2.5 mg TID) in Patients with Symptomatic Pulmonary Hypertension Associated with Idiopathic Interstitial Pneumonias (IIPs)

Sponsored by Bayer HealthCare AG, this study aims to evaluate the safety of treatment with oral riociguat at various doses and the effect on 6-minute walking distance in patients with PH associated with IIP.

ELIGIBILITY: Men and women age 18-80 with a diagnosis of major IIPs or rare IIPs as per ATS/ERS/JRS/ALAT guidelines; FVC  $\geq 45\%$ ; 6MWD 150-450 meters; diagnosis of PH confirmed by RHC with mPAP  $\geq 25$  mm Hg, PCWP  $\leq 15$  mm Hg at rest. Exclusion criteria include acute lung infection or exacerbation, active smoking, reasonable likelihood of receiving lung transplant during the 26-week study period, and PH-specific treatment within 3 months of screening.

PRINCIPAL INVESTIGATOR:

Gustavo Heresi, MD

STUDY COORDINATOR:

Kasi Timmerman | 216.444.2140

### A Multinational, Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults with Pulmonary Arterial Hypertension (PAH)

This study, sponsored by Pfizer, will compare treatment with sildenafil 80 mg TID, 20 mg TID and 5 mg TID with respect to time to mortality, time to clinical worsening and effect on 6MWD.

ELIGIBILITY: Patients age 18-75 with idiopathic pulmonary arterial hypertension (IPAH), PAH secondary to connective tissue disease (CTD) or PAH with surgical repair of congenital defects at least 5 years previously; mPAP  $\geq 25$  mm Hg, PCWP or LVEDP  $\leq 15$  mm Hg, PVR > 4 Wood units; 6MWD



> 50 meters. Exclusion criteria include acutely decompensated heart failure within 3 months, history of pulmonary embolism, treatment with bosentan within 3 months, treatment with PDE-5 inhibitors for PAH, TLC < 70% of predicted, FEV1 < 60% of predicted, history of malignancy or HIV within past 5 years.

PRINCIPAL INVESTIGATOR:  
Gustavo Heresi, MD

STUDY COORDINATOR:  
Kasi Timmerman | 216.444.2140

## CRITICAL CARE MEDICINE

### Study of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure (GRAIL)

An NHLBI-supported study to evaluate whether administration of ganciclovir reduces serum IL-6 levels (i.e., reduction between baseline and 14 days post-randomization) in immunocompetent adults with severe sepsis or trauma-associated respiratory failure.

ELIGIBILITY: Selected inclusion criteria include patients age 18 years or older; CMV IgG seropositive; report that patient has previously been tested and found to be CMV seropositive at any time; intubation and requiring mechanical positive pressure ventilation (including acute lung injury/ARDS (EA consensus definition); meets criteria for either (a) severe sepsis within a 24-hour time period within the 120-hour window, or (b) trauma with respiratory failure and an ISS score > 15 within a 24-hour time period, and within the 120-hour window (where mechanical ventilation is not due solely to a head injury).

PRINCIPAL INVESTIGATOR:  
R. Duncan Hite, MD

STUDY COORDINATORS:  
Michelle Ferrari, RN, BSN | 216.445.1939

Danijela Djureinovic, RN, BSN |  
216.445.3960

### Vitamin C Infusion for Treatment in Sepsis-Induced Acute Lung Injury

The objective of this NIH-supported study is to assess the efficacy of a 96-hour intravenous vitamin C infusion protocol (200 mg/kg per 24 hours) in patients with established acute lung injury (ALI) from sepsis.

ELIGIBILITY: Selected inclusion criteria include patients age 18 years or older with a suspected or proven infection, and meeting 2 out of 4 of the criteria for systemic inflammatory response (SIRS) due to infection, and accompanied by at least 1 criterion for sepsis-induced organ dysfunction (defined as fever > 38°C (any route) or hypothermia < 36°C (core temp only); tachycardia heart rate > 90 beats/min or receiving medications that slow heart rate or paced rhythm; leukocytosis (> 12,000 WBC/ $\mu$ L) or leukopenia (< 4,000 WBC/ $\mu$ L or > 10% band forms); respiratory rate > 20 breaths per minute or PaCO<sub>2</sub> < 32 or on invasive mechanical ventilation).

PRINCIPAL INVESTIGATOR:  
R. Duncan Hite, MD

STUDY COORDINATORS:  
Michelle Ferrari, RN, BSN | 216.445.1939

Danijela Djureinovic, RN, BSN |  
216.445.3960

### Impact of Aggressive Empiric Antibiotic Therapy and Duration of Therapy on the Emergence of Antimicrobial Resistance During the Treatment of Hospitalized Subjects with Pneumonia Requiring Mechanical Ventilation

The primary objective of this NIAID-sponsored study is to demonstrate a low rate of emergence of antibiotic resistance in *P. aeruginosa* and *Acinetobacter spp* during the treatment of hospitalized patients with pneumonia requiring mechanical ventilation treated with PD-optimized meropenem administered as a prolonged infusion in combination with a parenteral aminoglycoside plus tobramycin by inhalation (group 1) compared with therapy with meropenem

alone (group 2, control arm).

ELIGIBILITY: Selected inclusion criteria include hospitalized males or females,  $\geq$  18 years, with respiratory failure requiring mechanical ventilation and clinical suspicion of HAP, HCAP or VABP; onset of exacerbation of pneumonia at least 72 hours after admission to an acute care facility or onset of pneumonia in a nursing home or rehabilitation facility with subsequent transfer to an acute care facility.

Within 48 hours before starting empiric therapy, a subject's chest radiograph should show the presence of a NEW or progressive infiltrate, cavitation or effusion suggestive of pneumonia.

PRINCIPAL INVESTIGATOR:  
R. Duncan Hite, MD

STUDY COORDINATOR:  
Michelle Ferrari, BSN, RN | 216.445.1939

### A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Assess the Safety and Efficacy of ART-123 in Subjects with Severe Sepsis and Coagulopathy

Sponsored by Asahi Kasei Pharma America Corp., this study is designed to determine whether ART-123, when administered to subjects with infection complicated by at least one organ dysfunction and coagulopathy, can reduce mortality, and to assess the efficacy of ART-123 in the resolution of organ dysfunction.

ELIGIBILITY: Selected inclusion criteria include receiving treatment in an ICU, or in an acute care setting with documented orders to transfer to the ICU; clinical evidence of bacterial infection and a known site of infection; and all of the following: currently receiving treatment with antibiotics, WBC > 12,000/mm<sup>3</sup> or < 4,000/mm<sup>3</sup> or bandemia > 10%, platelet counts in the range of > 30,000/mm<sup>3</sup> to < 150,000/mm<sup>3</sup>; fever with core temperature of < 36°C or > 38°C; subjects with inflammatory changes due to sepsis defined by receiving vasopressors to maintain mean arterial pressure  $\geq$  65 mm Hg.

## PRINCIPAL INVESTIGATOR:

Jorge Guzman, MD

## STUDY COORDINATORS:

Michelle Ferrari, BSN, RN | 216.445.1939

Danijela Djureinovic, BSN, RN |

216.445.3960

**A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Colistin in Patients with Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE)**

Sponsored by Achaogen Inc., this study is designed to demonstrate the superiority, in terms of all-cause mortality at 28 days, of a plazomicin-based regimen compared with a colistin-based regimen in the treatment of BSI or nosocomial pneumonia due to CRE.

ELIGIBILITY: Selected inclusion criteria include positive blood or lower respiratory tract culture  $\leq$  72 hours prior to randomization meeting any of the following criteria: direct susceptibility testing on a blood or lower respiratory tract isolate suggesting a carbapenem-resistant member of the Enterobacteriaceae, isolation of a carbapenemase-producing member of the Enterobacteriaceae from blood or lower respiratory tract culture, final susceptibility testing on blood or lower respiratory tract isolate demonstrating a carbapenem-resistant member of the Enterobacteriaceae. Diagnosis of BSI or nosocomial pneumonia in a ventilated patient as follows: all clinical components defining the infection at baseline must have been present within 72 hours: fever (oral or tympanic temperature  $\geq$  38°C or core body temperature  $\geq$  38.3°C) or hypothermia (core temperature  $<$  35°C); new-onset arterial hypotension as defined by systolic blood pressure (SBP)  $<$

90 mm Hg, mean arterial pressure (MAP)  $<$  70 or an SBP decrease  $>$  40 mm Hg in the absence of other causes of hypotension; elevated total peripheral white blood cell (WBC) count  $>$  10,000 cells/mm<sup>3</sup>,  $>$  15% immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count  $<$  4500 cells/mm<sup>3</sup>.

## PRINCIPAL INVESTIGATOR:

Jorge Guzman, MD

## STUDY COORDINATORS:

Michelle Ferrari, BSN, RN | 216.445.1939

Danijela Djureinovic, BSN, RN |

216.445.3960

**Randomized Trial of Ticagrelor for Severe Community Acquired Pneumonia (TCAP)**

Sponsored by Vanderbilt University via a contract through AstraZeneca, this study is designed to assess the efficacy and safety of 90 days of oral ticagrelor in patients hospitalized with severe community acquired pneumonia (CAP).

ELIGIBILITY: Selected inclusion criteria include the presence of community acquired pneumonia (CAP) AND admission or planned admission to an ICU for severe respiratory distress or arterial desaturation OR mechanical ventilation (invasive or noninvasive) OR vasopressors AND at least two of the following within the past 7 days: recent increase in dyspnea, increased sputum production, change of character of sputum, WBC  $>$  12,000 or  $<$  4,000 cells/mm<sup>3</sup> or  $>$  10% bands, body temperature  $>$  38°C or  $<$  36°C.

## PRINCIPAL INVESTIGATOR:

R. Duncan Hite, MD

## STUDY COORDINATORS:

Michelle Ferrari, BSN, RN | 216.445.1939

Danijela Djureinovic, BSN, RN |

216.445.3960

**A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Safety and Efficacy Study of H.P. Acthar® Gel (Acthar) in Subjects with Acute Respiratory Distress Syndrome (ARDS)**

Sponsored by Questcor Pharmaceuticals Inc., this study is designed to evaluate the potential efficacy and safety of Acthar in subjects with ARDS. Acthar is hypothesized to have direct effects to attenuate lung injury and/or promote injury resolution.

ELIGIBILITY: Selected inclusion criteria include ARDS as defined by PaO<sub>2</sub>/FiO<sub>2</sub>  $<$  200 mm Hg with PEEP  $>$  5 cm H<sub>2</sub>O, bilateral opacities on chest radiography not explained by atelectasis, effusions, nodules or pre-existing disease; requirement for positive pressure ventilation via an endotracheal tube; respiratory failure not fully explained by cardiac failure or fluid overload. Inclusions must occur within the same 24-hour period. Enrollment between 24 hours and 10 days after ARDS criteria are met.

## PRINCIPAL INVESTIGATOR:

R. Duncan Hite, MD

## STUDY COORDINATORS:

Michelle Ferrari, BSN, RN | 216.445.1939

Danijela Djureinovic, BSN, RN |

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# NewsBriefs

## Atul C. Mehta, MD, Receives Highest Honor in the Field of Interventional Pulmonology



**Atul C. Mehta, MD**, received the 2014 Gustav Killian Centenary Award at the 18th World Congress for Bronchology and Interventional Pulmonology in Kyoto, Japan.

Killian performed the first-ever bronchoscopy in 1897 to remove an endobronchial foreign body. This award was created in his honor and is considered the highest recognition in the field. It recognizes a bronchologist whose achievements and clinical practice have made a significant impact on the art and science of bronchology.

Nine other individuals, including Shigeto Ikeda (inventor of the flexible bronchoscope), Jean-Francis Dumon (pioneer of interventional pulmonology) and Ko-Pen Wang (inventor of TBNA), have been recipients of this award.



Dr. Mehta has spent his entire career in the field of bronchoscopy. He is one of the founders of the American Association for Bronchology, the *Journal of Bronchology* and the new field of interventional pulmonology. He has been the editor-in-chief of the *Journal of Bronchology* for 11 years. During his tenure, the journal was included in the National Medical Library. Dr. Mehta has published more than 350 peer-reviewed papers and 80 book chapters and edited 13 books. His contributions are in the areas of lung transplantation, tracheal stenosis, TBNA, infection control, and in the repair and maintenance of the bronchoscope.

His numerous awards include recognition as a Master Educator, Cleveland Clinic (2006); Clinical Educator of the Year, American Thoracic Society (2006); American College of Chest Physicians Presidential Citation Honor Lecture (2006); and the Pasquale Ciaglia Memorial Lecture by the American College of Chest Physicians for his contributions in the field.



## Cleveland Clinic Wins 2014 CHEST Challenge

Cleveland Clinic proudly captured the CHEST Challenge Championship at this year's American College of Chest Physicians annual meeting in Austin, Texas.

Our team of fellows, including Dhruv Joshi, MBBS, Anupam Kumar, MBBS, and Tanmay Shashank Panchabhai, MD, racked up more than 15,000 points in the popular game-show-style challenge to take the top prize in the 13th annual event — designed to be a fun educational event for fellows. Cleveland Clinic Critical Care Medicine Fellowship Training Program Director Rendell Ashton, MD, was presented with a check for \$5,000.

# Respiratory Institute Staff Directory



**Herbert P. Wiedemann, MD, MBA**  
Chairman, Respiratory Institute  
216.444.8335  
Specialty Interests: critical care (including adult respiratory distress syndrome and sepsis), general pulmonary medicine

## Departments of Pulmonary and Critical Care Medicine



**R. Duncan Hite, MD**  
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Chairman, Department of Pulmonary Medicine  
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Specialty Interests: general pulmonary medicine, lung transplantation



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Specialty Interests: general pulmonary medicine, neuromuscular diseases, sleep medicine, long-term ventilator care



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216.444.6506  
Specialty Interests: pulmonary function lab, asthma, lung cancer



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Specialty Interest: lung transplantation



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Specialty Interests: critical care, general pulmonary medicine



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216.444.1908  
Specialty Interests: advanced diagnostic and interventional bronchoscopy



**Rendell Ashton, MD**  
Associate Director, MICU; Director, Pulmonary and Critical Care Fellowship Program  
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Specialty Interests: critical care, medical education, interstitial lung disease



**David Berzon, MD**  
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Specialty Interests: general pulmonary medicine, critical care



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Specialty Interest: general pulmonary medicine



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Specialty Interests: lung transplantation, pulmonary hypertension, gender-specific pulmonary issues



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Specialty Interests: critical care, general pulmonary medicine



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Specialty Interests: critical care, lung cancer



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Specialty Interest: critical care



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Specialty Interests: advanced diagnostic bronchoscopy, general pulmonary medicine



**Daniel Culver, DO**  
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Specialty Interests: sarcoidosis, interstitial lung disease, hypersensitivity pneumonitis



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Specialty Interest: critical care



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Specialty Interest: critical care



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Specialty Interests: asthma, pulmonary hypertension, chronic beryllium disease, critical care, bronchoscopy, nitric oxide in lung physiology and disease, exhaled markers in lung disease



**Serpil C. Erzurum, MD**  
Chair, Department of Pathobiology, Lerner Research Institute; Director, Cleveland Clinic General Clinical Research Center; Co-Director, Asthma Center  
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Specialty Interests: asthma, pulmonary vascular disease, respiratory physiology





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Specialty Interests: lung transplantation, pulmonary hypertension, critical care, sleep medicine



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Specialty Interests: critical care, sleep medicine



**Thomas R. Gildea, MD, MS**  
[Head, Section of Bronchoscopy](#)  
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Specialty Interests: interventional bronchology, lung transplantation



**Jorge Guzman, MD**  
[Director, MICU; Medical Director of ICU Operations, Cleveland Clinic Health System](#)  
216.445.5765  
Specialty Interests: critical care, sepsis, shock



**Tarik Hanane, MD**  
216.445.2747  
Specialty Interest: critical care



**Umur Hatipoglu, MD**  
[Quality Improvement Officer](#)  
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Specialty Interests: asthma, acute respiratory distress syndrome, general (diagnostic) pulmonary medicine, critical care



**Gustavo Heresi, MD**  
[Medical Director, Pulmonary Thromboendarterectomy Program](#)  
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Specialty Interests: acute respiratory distress syndrome, pulmonary hypertension, sepsis



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Specialty Interest: critical care



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Specialty Interests: critical care, general pulmonary medicine



**Sumita Khatri, MD, MS**  
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Specialty Interest: asthma



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Specialty Interest: critical care



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Specialty Interests: lung transplantation, critical care



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Specialty Interests: general pulmonary medicine, critical care



**Michael Machuzak, MD**  
[Medical Director, Center for Major Airway Diseases](#)  
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Specialty Interests: rigid and flexible bronchoscopy, endobronchial ultrasound, laser, electrocautery, stent placement, bronchoscopic lung volume reduction, transtracheal oxygen catheter placement, lung cancer, pleural diseases, COPD



**Peter Mazzone, MD, MPH**  
[Director, Lung Cancer Program](#)  
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Specialty Interests: lung cancer, critical care, physician education



**Glenn Meden, MD**  
[Chief, Division of Pulmonary and Critical Care Medicine at Hillcrest Hospital; Director, ICU at Hillcrest Hospital](#)  
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Specialty Interests: general pulmonary medicine, critical care



**Reena Mehra, MD, MS**  
[Joint Appointment with Sleep Center](#)  
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Specialty Interests: general pulmonary medicine, sleep medicine



**Atul C. Mehta, MD**  
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Specialty Interests: lung transplantation, endobronchial and bronchoscopic procedures and interventions, transtracheal oxygen therapy



**Eduardo Mireles-Cabodevila, MD**  
[Director, Critical Care Fellowship Program](#)  
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Specialty Interests: critical care, neuromuscular diseases



**Ajit Moghekar, MD**  
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Specialty Interest: critical care



**Kathrin Nicolacakis, MD**  
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Specialty Interest: general pulmonary medicine



**Jennifer Ramsey, MD, MS**  
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Specialty Interest: critical care



**Sonali Sethi, MD**  
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Specialty Interests: advanced diagnostic and interventional bronchoscopy, lung cancer



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Specialty Interests: general pulmonary medicine, cystic fibrosis



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[Joint Appointment with Emergency Medicine](#)  
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**David Skirball, MD**  
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Specialty Interests: critical care, general pulmonary medicine



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[Joint Appointment with Pathobiology](#)  
216.445.6025  
Specialty Interest: interstitial lung disease



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Specialty Interests: general pulmonary medicine, critical care



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Specialty Interest: interstitial lung disease



**Beverly V. O'Neill, MD**  
[Vice President, Medical Operations, Euclid Hospital](#)  
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Specialty Interests: general pulmonary medicine, long-term ventilator patients



**Anita Reddy, MD**  
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**Leah Spinner, MD**  
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**Aman Pande, MD**  
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Specialty Interests: general pulmonary medicine, sarcoidosis, ILD



**James K. Stoller, MD, MS**  
[Executive Director, Leadership Development; Chairman, Education Institute](#)  
216.444.1960  
Specialty Interests: clinical epidemiology, alpha 1-antitrypsin deficiency, respiratory therapy



**Joseph G. Parambil, MD**  
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Specialty Interest: general pulmonary medicine



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Specialty Interests: critical care, lung transplantation



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Specialty Interests: asthma, allergic disorders



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#### **CLEVELAND CLINIC FLORIDA RESPIRATORY CENTER**

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Specialty Interests: critical care, general pulmonary medicine, sleep medicine



**Maryam Valapour, MD, MPP**  
[Director, Lung Transplant Outcomes](#)  
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Specialty Interest: lung transplantation



**Sandra Hong, MD**  
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Specialty Interests: allergic disorders, asthma



#### **Cleveland Clinic Florida Pulmonary and Critical Care Medicine**



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Specialty Interests: critical care, general pulmonary medicine



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#### **Department of Allergy and Clinical Immunology**



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**Vesselin Dimov**  
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**Section of Thoracic Imaging**



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**Michael Bolen, MD**  
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**Rahul Renapurkar, MD**  
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**Pulmonary Pathology**



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Specialty Interests: pathology of interstitial lung disease; pleural and pulmonary tumors



**Sanjay Mukhopadhyay, MD**  
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**Thoracic and Cardiovascular Surgery**



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Specialty Interests: lung and heart-lung transplantation



**Douglas Johnston, MD**  
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Specialty Interest: lung and heart transplantation



**Kenneth McCurry, MD**  
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Specialty Interests: lung and heart transplantation, ventricular assist devices, heart failure surgery, lung and heart ischemia-reperfusion injury



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Specialty Interests: heart surgery, surgical treatment of heart failure, heart transplantation, mechanical heart assist devices



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Specialty Interests: lung and heart-lung transplantation, pulmonary thromboendarterectomy



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**Section of General Thoracic Surgery**



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**Siva Raja, MD, PhD**  
216.445.6860  
Specialty Interests: lung cancer and esophageal cancer



**Daniel Raymond, MD**  
216.636.1623  
Specialty Interests: general thoracic surgery, lung cancer

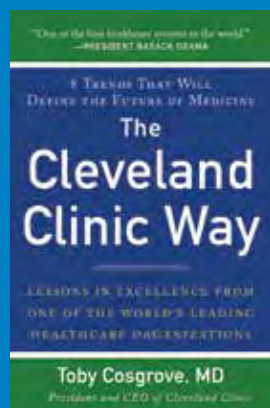


## Consult QD

### PHYSICIAN BLOG

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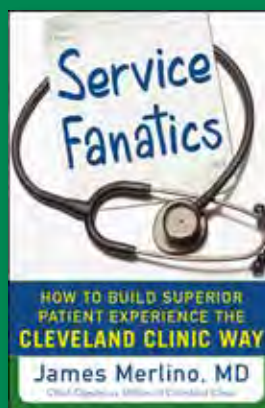
[consultqd.clevelandclinic.org](http://consultqd.clevelandclinic.org)



## The Cleveland Clinic Way

By Toby Cosgrove, MD  
CEO and President of Cleveland Clinic

Great things happen when a medical center puts patients first. For details or to order a copy, visit [clevelandclinic.org/ClevelandClinicWay](http://clevelandclinic.org/ClevelandClinicWay).



## Service Fanatics:

How to Build Superior Patient Experience the Cleveland Clinic Way

By James Merlino, MD  
Chief Experience Officer,  
Cleveland Clinic

Understand the important role patient experience should play in every industry — using a world-class hospital as a backdrop for the lesson. **Available at amazon.com, or wherever books are sold.**



The Cleveland Clinic Foundation  
Respiratory Institute / AC311  
9500 Euclid Ave.  
Cleveland, OH 44195

## RESPIRATORY EXCHANGE RESEARCH AND NEWS FOR PHYSICIANS FROM CLEVELAND CLINIC'S RESPIRATORY INSTITUTE

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[clevelandclinic.org/Refer123](http://clevelandclinic.org/Refer123)

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[clevelandclinic.org/staff](http://clevelandclinic.org/staff)

##### Same-Day Appointments

To help your patients get the care they need, right away, have them call our same-day appointment line, 216.444.CARE (2273) or 800.223.CARE (2273).

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Establish a secure online DrConnect account at [clevelandclinic.org/drconnect](http://clevelandclinic.org/drconnect) for real-time information about your patients' treatment.

##### Critical Care Transport Worldwide

To arrange for a critical care transfer, call 216.448.7000 or 866.547.1467. [clevelandclinic.org/criticalcaretransport](http://clevelandclinic.org/criticalcaretransport)

##### Outcomes Data

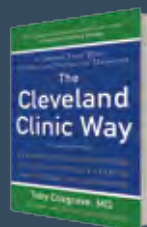
View Outcomes books at [clevelandclinic.org/outcomes](http://clevelandclinic.org/outcomes).

##### CME Opportunities

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##### The Cleveland Clinic Way

By Toby Cosgrove, MD, CEO and President, Cleveland Clinic

Great things happen when a medical center puts patients first. Visit [clevelandclinic.org/ClevelandClinicWay](http://clevelandclinic.org/ClevelandClinicWay) for details or to order a copy.