Center for Lung Biology Pulmonary NewsLetter

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Senior Faculty

Ronald Allison
Ronald Balczon
Stephen Ballard
William Broughton
Eugene Cioffi
Errol Crook, Chair, Int. Medicine
Fabien Eyal, Chief, Neonatology
Karen Fagan, Chief, Pulm. and Crit. Care
Brian Fouty
William Gerthoffer, Chair, Biochemistry and Molecular Biology
Mark Gillespie, Chair, Pharmacology
Johnson Haynes, Jr.
Richard Honkanen
Stephen Kayes
Susan LeDoux, Vice Chair, Cell Biology and Neuroscience
Thomas Lincoln, Chair, Physiology
Ivan McMurtry
Jack Olson
James Parker
Kane Schaphorst
Troy Stevens, CLB Director
Mary Townsley, CLB Training Dir.
John Vande Waa, Chief, Infect. Disease
Wiltz Wagner
Glenn Wilson, Chair, Cell Biology and Neuroscience

Junior Faculty

Mikhail Alexeyev
Abu-Bakr Al-Mehdi
Diego Alvarez
Natalie Bauer
John Benjamin
Donna Cioffi
Sarah Gebb
Masahiko Oka
Viktor Pastukh
Thomas Rich
Mykhaylo Ruchko
Sarah Sayner
Victor Solodushko
David Weber
Songwei Wu
Wenkuan Xin
Bing Zhu

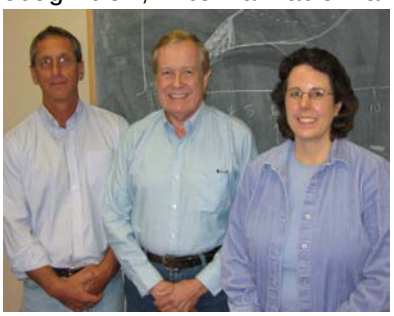
Contact Us

USA Center for Lung Biology
MSB 3340, Mobile, AL 36688
Ph: (251) 460-7086; Fax: (251) 460-7452
http://www.usouthal.edu/clb

What's New in Pulmonary Science?

Endothelium lines the surface of all blood vessels, where it forms a barrier that separates blood from the tissue. Solutes are sieved at the endothelial surface by the carbohydrate fraction of glycoproteins and glycolipids. This vast carbohydrate array displays a staggering molecular complexity, one that investigators have only recently begun to divulge with glycome analysis of oligosaacharides using mass spectrometry. However, plant and animal cells utilize glycoproteins called lectins that discriminate the molecular anatomy of complex carbohydrate surface structures. At the Center for Lung Biology, Drs. Eugene and Donna Cioffi have used lectins to discriminate the complex underpinnings of the lung endothelial cell glycocalyx. Their work has demonstrated that lung capillary endothelial cells possess a unique fingerprint with respect to arterial and vein endothelial cells characterized by the presence of a terminally linked α(2,3)-sialic acid. Work by Dr. Ron Balczon at the Center in collaboration with Dr. Terrance Tumpey at the Centers for Disease Control indicates that some flu viruses uses this terminal α(2,3)-sialic acid linkage as a receptor for recognition, internalization and replication within endothelium. Budding and release of newly replicated viral particles into the circulation requires cleavage of the terminal α(2,3)-sialic acid by neuraminidase. Indeed, the neuraminidase enzyme is widely expressed among virulent pathogens, including the flu virus. New studies by the Cioffi team find that neuraminidase does more than just release virus from the cell; neurominidase cleavage of the terminal α(2,3)-sialic acid is sufficient to cause endothelial cell barrier disruption, resulting in increased permeability. These findings reveal a novel mechanism of edema formation, as the complex carbohydrate surface of capillary endothelium is linked to the intracellular cytoskeletal structure that dictates endothelial cell shape. Moreover, these results suggest that the actions of neuraminidase may contribute to the alveolar edema prominent in viral pneumonia. Look for the forthcoming publications documenting these actions of neuraminidase on pubmed.

Hair-like projections represent the endothelial cell glycocalyx, as shown in *Circ. Res.* 92: 592-594, 2002.



Drs. Ronald Balczon, Eugene Cioffi and Donna Cioffi

What's New in Research Training?

The summer of 2010 arrived along with 28 summer research trainees to work with faculty affiliated with the Center for Lung Biology (CLB). Two high school students, Matthew Robson and Trevor Stevens, returned for a second summer of research. Both Matthew and Trevor presented abstracts at the 2010 ATS Conference. Further, we are excited to learn that both students were named National Semifinalists in the Siemens Competition for Math, Science and Technology (see the press release at http://www.siemens-foundation.org/pool/siemens_competition/2010/2010_siemens_competition_semifinalist_and_regional_finalist_ press_release.pdf). A total of 14 undergraduate summer research fellows came from ongoing summer programs organized by the Center for Healthy Communities' NIH-funded EXPORT program and the University-funded UCUR program. An additional 7 undergraduates were supported by a supplement awarded to the CLB's program project grant, an NSF-funded REU grant, or the summer undergraduate research program in Pharmacology (SURF). Finally, 5 medical student summer research fellows were supported the CLB's T32 short term training program or the College of Medicine. These summer research fellows presented their work in one of several formats: the 37th Annual Medical Student Research Day, the UCUR Conference, or the 4th Annual College of Medicine Research Forum.

The Center for Lung Biology's "Did you know..." series published its latest on-line article on pulmonary arterial hypertension and mortality risk of during pregnancy, authored by Salina Gairhe (November, 2010). The complete text of Salina's article is included in this issue of the newsletter.

What's New in Pulmonary & Critical Care?

The Division of Pulmonary and Critical Care Medicine in the Department of Medicine at the University of South Alabama continues to provide outstanding pulmonary and critical care to patients in the northern Gulf Coast. We continue to have active inpatient consultative services in both pulmonary and critical care medicine, coordinate critical care delivery for patients at two major hospitals, and operate a busy sleep and advanced lung physiology laboratories.

In addition, the Division has significantly increased its clinical research programs opening three new clinical trials in pulmonary hypertension as well as several (new and continuing) translational projects in pulmonary hypertension and acute lung injury. USA Pulmonary is increasingly sought after to participate in research owing to the diversity of our patients and the expertise of our faculty. Members of the Division continue to be productive in publishing results of their original research as well as presenting research results at international meetings.

The other major focus of the Division is the training of future Pulmonary and Critical Care Medicine physicians. Training focuses on providing outstanding clinical training and focused research training with the goal of training physician investigators (in basic science and clinical research). The current training program has 2 fellows per year for a total of three years of training. The recruitment for the fellows starting in 2012 will be underway soon. We anticipate a group of outstanding candidates again this recruitment period. Research training for these fellows remains an important priority to help develop the next generation of physician scientists. Several fellows were very successful in research this year with half the fellows presenting original research at international meetings over the past year.

Did You Know...

...that women with pulmonary arterial hypertension (PAH) have an elevated risk of mortality during pregnancy? PAH is characterized by an increase in the mean pulmonary artery pressure from 15 mmHg to greater than 25 mmHg at rest. The elevated pressure intensifies the work load of the right ventricle leading to right ventricular hypertrophy and right heart failure[1] (Figure). PAH of unknown etiology is classified as idiopathic PAH which is not only associated with a female predominance, but is also exacerbated during pregnancy.

Women of childbearing age are 2-3 times more susceptible to PAH compared to age-matched males[1] . The

first clinical description of idiopathic PAH was in 1951 by Dresdale *et al.* who reported 60% of patients in their study were female[2] . Similarly, in the study by Evans *et al.*, 8 cases of confirmed idiopathic PAH, which they called "solitary pulmonary hypertension," were all female[3] . In 1957, Shepherd and coworkers similarly described a female predominance and suggested that amniotic embolism during pregnancy could precipitate the disease[4] . In an extensive literature review of 602 cases, Wagenvoort and Wagenvoort in 1970 reported 27 definitive cases (4.5%) of PAH associated with pregnancy[5] . In a 1986 study by Dawkins *et al.*, 6 out of 73 women (8%) with idiopathic PAH referred for heart-and-lung transplantation, described onset of symptoms either during pregnancy or postpartum[6] . Indeed, considerable maternal physiological changes take place during pregnancy and the peripartum period that can exacerbate PAH, yet it is uncertain whether pregnancy causes PAH.

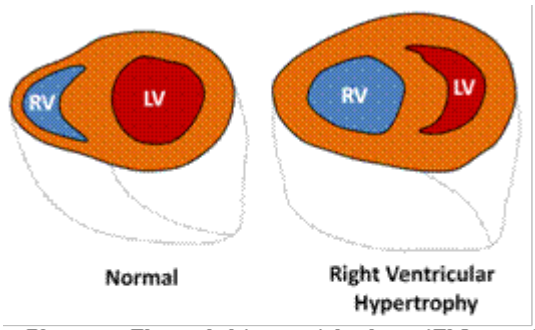


Figure. The right ventricular (RV) wall becomes thickened with PAH. Normally, the RV is thin walled and compliant in comparison to left ventricle (LV). With the onset of PAH, the RV becomes muscular and less compliant thus unable to manage the cardiopulmonary changes that occur during pregnancy.

The large increase in blood volume during pregnancy is not well tolerated by PAH patients. Cardiac output increases by approximately 50%[7] , but the right ventricle of patients with PAH is poorly adapted to cope with these changes. The hypertrophied and dilated right ventricle of these patients is insufficient to manage the elevated heart rate and after-load as the cardiac output rises. Recruitment of the pulmonary circulation that normally facilitates the increased cardiac output may be prevented by the constricted and remodeled pulmonary arteries of PAH patients[8] . The cardiac output rises again during the second stage of labor and immediately postpartum as uterine blood flow returns to the general circulation[8] . The pathology of idiopathic PAH also involves *in-situ* thrombosis; therefore, the elevated coagulation state experienced during pregnancy may further promote thrombus formation in the lung. In addition, the remodeled vessels will be less tolerant to thromboemboli. This may be further aggravated by the postpartum hypercoagulative state. Thus, the circulatory and haemodynamic changes of pregnancy present significant risk to the PAH patient. In case studies from 1979 to 1996, maternal death rates of 30-56% were reported in women with PAH[9] . Most of these maternal deaths occurred within 35 days postpartum[9] . With the evolution of new therapies to treat PAH coupled with a multiprofessional approach to pregnancy, maternal mortality rates in the period from 1997-2007 have declined to 17-33%[10] . Although new therapies, such as vasodilators, prostaglandin analogues, phosphodiesterase 5 inhibitors have improved outcomes, some of these drugs, such as endothelin antagonists, are teratogens and must be avoided during pregnancy. Therefore, PAH patients are strongly counseled to avoid pregnancy.

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Author: Salina Gairhe
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