



# 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  
Benjamin Estrada  
Fabien Eyal, Chief, Neonatology  
Karen Fagan, Chief, Pulm. and Crit. Care  
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William Gerthoffer, Chair, Biochemistry  
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Richard Honkanen  
Stephen Kayes  
Susan LeDoux, Vice Chair, Cell Biology  
and Neuroscience  
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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

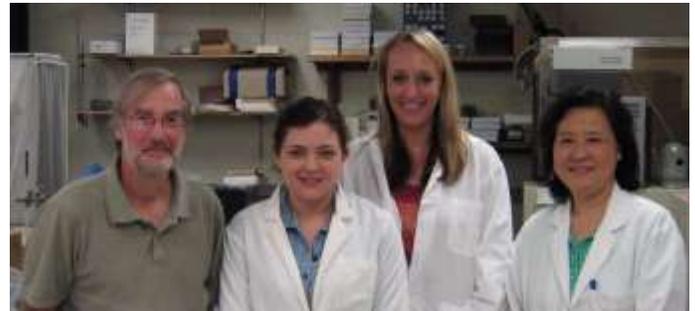
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Sarah Sayner  
Victor Solodushko  
David Weber

## Contact Us

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

## What's New in Pulmonary Science?

Dr. Stephen Ballard's research has centered on cystic fibrosis (CF) lung disease since he first began work in the Department of Physiology at the University of South Alabama as an Assistant Professor in 1989, coincidentally the same year that the cystic fibrosis transmembrane conductance regulator



Ballard's Lab

Left to right - Dr. Stephen Ballard, Jessica Madden, Holly Schwarzbauer, and Lin Cui.

(CFTR), the specific anion channel that is defective in CF disease, was discovered. His focus has been on the mechanism of chloride, bicarbonate, and fluid secretion from airways of the lung and the role played by these processes in the production of the tenaciously thick mucus that obstructs the airways of CF patients. Although much has been learned about salt, biomolecule, and water transport in the airways by studying the lungs of genetically normal mammals, the lack of an appropriate animal model to study the dynamics of secretion in CF airways has been a significant impediment to advancement of knowledge in this area. Genetic models of CF mice have been available for over 20 years, but unfortunately, this model species does not develop the same pattern of lung pathology seen in humans with CF disease. Recent advancements in gene knockout technology from researchers at the University of Iowa have led to the generation of CF swine and CF ferrets, genetic models that do express human-like CF lung disease. These models represent a tremendous advancement in the study and treatment of CF disease. Dr. Ballard, who has 24 years experience in studying ion and fluid transport in swine, has recently obtained funding to acquire and study CF pigs. Dr. Ballard states "This is a remarkable opportunity to make significant advancements in our understanding of CF disease. Hopefully, by studying the disease etiology and progression in these animals, we and others can establish better treatment paradigms for humans with CF disease."

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## What's New in Research Training?

Our major effort related to training this year led to development of a proposal to NHLBI for our T32 renewal. The CLB training grant, currently in its second cycle of funding, has provided critical support for training for 9 years at this point! This program has not been static, but has grown, along with the maturation of the CLB as a whole. In our first cycle of funding (2004-2009), we drew upon the expertise of 14 faculty to provide T32-funded training for predoctoral fellows. We began by supporting 4 trainees, then progressed in years 2-5 to support 6 trainees per year. Our second cycle of funding began in 2009 with 18 faculty. While our primary goal in this cycle has been to provide T32 support to 6 predoctoral trainees each year, we requested and were funded to provide 4 short-term training slots as well per year. At that time, short-term training eligibility included medical students and master's students in engineering. Our proposal requesting a third cycle of funding (2014-2019) was submitted in January 2013. Our T32 faculty has grown again to a total of 25! We have retained the predoctoral/short-term training structure for this cycle, focusing short-term support now solely on medical students due to changes in NIH eligibility criteria. One additional modification in our short-term program was our request to support short-term trainees who progress into the "MD with Research Honors" program.

The program plan for the third cycle retains our strong core curriculum in Lung Biology and an extensive set of enrichment/survival skills courses. The program will be co-directed by Drs. Mary Townsley and Troy Stevens. They will be joined by Drs. William Gerthoffer, Johnson Haynes, and Ivan McMurtry to form the Internal Advisory Committee. External advisors will be chosen annually from experienced investigators among the national lung biology community. The annual CLB Lung Bowl, initiated in 2012, will not only serve as a focal point for introducing new predoctoral and short-term trainees to the CLB community, but as the culmination of our annual external review process.

The CLB T32 program has been successful in our view – since 2004 we have supported a total of 22 predoctoral trainees, 23% of whom have been from under-represented groups. Five of these predoctoral trainees accrued individual fellowship funding subsequent to T32 support. Of our T32 alumnae who have completed the PhD, 75% are active in academia and/or research careers. Our proposal was favorably reviewed, so we hope to report initiation of third-cycle funding in April 2014.

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## What's New in Pulmonary & Critical Care?

We recently welcomed our two first-year fellows to the Division, Dr. James Dean and Ji Lee. We had an outstanding applicant pool and were delighted to have these outstanding applicants join us. We continue our efforts to provide the highest quality clinical and research training to our fellows through ongoing assessment and restructuring of the program. Recently one of our second year fellows went to the University of Alabama Birmingham for one month to rotate on the lung transplant service. Future endeavors include opportunities for Fellows at the VA in Biloxi, MS.

Our Pulmonary Clinics continue to be busy and growing. We continue to look for opportunities to better serve the health needs of our community.

Clinical research continues to prosper in the Division with investigator and industry developed and sponsored activities. We hope to expand further through our ongoing research in the Pulmonary Hypertension Center and the Center for Lung Biology.

Overall, the Division continues to provide outstanding pulmonary and critical care to patients in the northern Gulf Coast with active, productive research and educational programs for the region. We hope to be the major resource for expert clinical care and research in Pulmonary and Critical Care Medicine in the area.

## Did You Know...



**Figure 1.** Click on the following link to view ultrasound footage which shows a fetus breathing and hiccupping:<http://www.prenatalanswers.com/fetal-respirationspractice-breathing/>

### ...that a fetus practices breathing for months before birth?

Fetal breathing movements are episodic and irregular, interspersed with periods of apnea<sup>1</sup>, and in humans they become detectable by ultrasound at 10-11 weeks gestation<sup>2, 3</sup>. Fetal breathing movements become more regular and uniform as gestational age increases<sup>4</sup>. Breathing movement frequency increases until the 10 weeks before birth, when periods of apnea increase<sup>5, 6</sup>.

General fetal movement has been used for centuries to monitor fetal well being. Hippocrates believed that movement began 70-90 days after conception, and that males moved more vigorously than females<sup>7</sup>. Paré, a 16th century French surgeon and obstetrician, recognized that absence of fetal movement could be a sign of intrauterine death<sup>7</sup>. The first recorded observations of intrauterine breathing movements in a

human fetus were made in 1888 by the German doctor von Ahlfeld. He and his student, Weber, used a kymograph to record 'periodic, rhythmic intrauterine fetal movements' that they attributed to breathing motions<sup>8</sup>. Many of their contemporaries dismissed the theory that these were fetal breathing movements because no one had ever visually observed such movements in a fetus. In 1911 another German scientist, Reifferschied, published simultaneous kymograph recordings of fetal breathing movements, maternal respiration, and maternal pulse<sup>8</sup>. He noted that these actions all occurred at different rates. Although the scientific community remained skeptical, his measurements would later prove to be remarkably accurate.

It was not until the 1970s that two landmark studies answered the question of whether fetal breathing movements normally occurred in vivo. The work was performed by two groups - Merlet and her colleagues from France, and British scientists led by Dawes. In 1970 and 1972, these groups published papers with data obtained from fetal lambs in utero. The authors showed that breathing movements normally occur during gestation and do so at irregular intervals<sup>1, 9</sup>. Later work with animals proved that eliminating fetal breathing movements results in immature, underdeveloped lungs<sup>10, 11</sup>.

More recent in vitro studies have investigated the signaling pathways between fetal breathing movements and lung development. Fetal breathing movements stretch the lungs and move fluid in and out of the lungs. Mechanical stretch upregulates the release of serotonin via mechano-sensitive channels<sup>12</sup>, which promotes differentiation of epithelial cells. Stretch also increases epithelial cell proliferation<sup>13, 14</sup> and stimulates secretion of lung surfactant lipids from type II epithelial cells<sup>15</sup>. Parathyroid hormone-related protein (PTHrP) is the product of a stretch sensitive gene expressed by the lung which is essential for normal lung development<sup>16</sup>. In the absence of PTHrP, lipofibroblasts spontaneously transdifferentiate into myofibroblasts<sup>17</sup>. Lipofibroblasts are the source of the lipids necessary for surfactant synthesis. Overdistension of alveolar epithelial cells caused loss of PTHrP mRNA<sup>17</sup>, resulting in a less mature lung phenotype and mirroring the effects of ventilation in premature infants.

While the importance of fetal breathing movements is now widely accepted, the underlying mechanisms of lung development dependent on these movements are still being revealed with both in vivo and in vitro studies. These scientific results will hopefully lead to improvements in patient care, as they show that fetal breathing movements in utero are vital for postnatal lung function.

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Author: Rebekah Morrow

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