



Center for Lung Biology Pulmonary NewsLetter

November 2014

Volume 5, Number 1

Senior Faculty

Ronald Allison
Mikhail Alexeyev
Abu-Bakr Al-Mehdi
Diego Alvarez
Jonathan Audia
Ronald Balczon
Stephen Ballard
Paul Brett
William Broughton
Eugene Cioffi
Errol Crook, Chair, Int. Medicine
Benjamin Estrada
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
Silas Leavesley
Ivan McMurtry
Jack Olson, Emeritus
Masahiko Oka
James Parker, Emeritus
Thomas Rich
Troy Stevens, CLB Director
Mary Townsley, CLB Training Dir.
John Vande Waa, Chief, Infect. Disease
Wiltz Wagner
Tony G. Waldrop, USA, President
David Weber

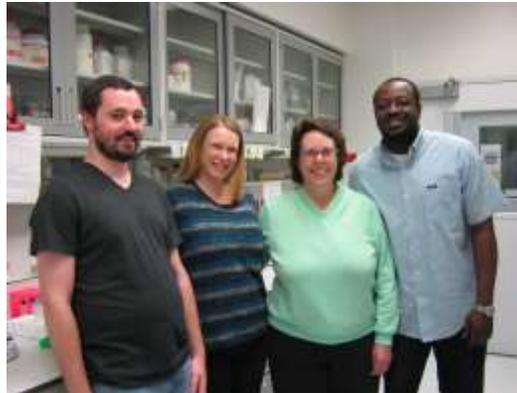
Junior Faculty

Robert Barrington
Natalie Bauer
Mary Burtnick
Donna Cioffi
Kari Dugger
Sarah Gebb
Viktor Pastukh
Wito Richter
Mykhaylo Ruchko
Sarah Sayner
Jon Simmons
Viktor Solodushko
Dhananjay Tambe

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?



D. Cioffi Lab

Left to Right - Caleb Hamilton, Dr. Audrey Vasauskas, Dr. Donna Cioffi, and Pierre Kadeba - Not Shown Rebekah Morrow

The Giles Filley Memorial Award in Respiratory Physiology and Medicine is given to two trainees annually, one from the University of Colorado and one from elsewhere. This award is given in memory of Giles Filley, M.D., who was an internationally renowned pulmonary physician and physiologist. One of his major contributions was the development of a method for measuring the diffusing capacity of the lung. He spent his career in the Pulmonary Division at the University of Colorado. His encyclopedic knowledge and keen mathematical insights were the source of inspiration to all those

around him, especially young scientists in whom he took a special interest. The Filley Award ranks among the most prestigious prizes in the field of pulmonary science.

Donna L. Cioffi was this year's "non-Colorado" Filley Award recipient. Donna received her undergraduate and master's degree in Chemistry from the University of Connecticut and Yale University, respectively, before completing her doctoral degree and postdoctoral fellowship in the Center for Lung Biology at the University of South Alabama. She was the recipient of a K99 fellow-faculty transition award, which helped her to secure a tenure-track Assistant Professor position in the Department of Biochemistry and Molecular Biology, a position she currently holds.

Donna's work has principally focused on resolving the molecular anatomy of endothelial cell store operated calcium entry channels. She has identified the protein responsible for channel gating, partially resolved the stoichiometry of a complex multi-protein channel, and revealed important molecular determinants of ion selectivity through the channel. Calcium influx through this channel is sufficient to disrupt pulmonary endothelial cell barrier integrity, and thus, represents a contributing cause of pulmonary edema. Funding by the Giles Filley Award will enable her to diversify and expand her research program, where she intends to evaluate the glycosylation of anti-endothelial cell antibodies in pulmonary arterial hypertension. Future plans for this new project include development of carbohydrate-based biomarkers for early disease diagnosis.

We are extremely proud of Donna and her many accomplishments. Do not hesitate to congratulate her for a job well done. Donna's award adds to a growing list fellow-to-faculty transition awardees from the Center for Lung Biology. Previously, Timothy Moore, Natalie Bauer, Diego Alvarez, and Sarah Sayner all received Parker B. Francis Fellowship Awards.

What's New in Research Training?

We are pleased to report that our proposal requesting a third cycle of funding (2014-2019) was funded! In this cycle the T32 program, co-directed by Drs. Mary Townsley and Troy Stevens, provides support for 6 predoctoral trainees and 4 short term medical student research trainees yearly. Training focus areas include 1) smooth muscle and mechanisms of pulmonary arterial hypertension, 2) endothelial inflammation, infection and acute lung injury, 3) mitochondrial dysfunction and oxidative stress, and 4) ion channels and transport.

Recent Center for Lung Biology "Did you know..." articles, authored by Pierre Kadeba (entitled: *Lung Disease morbidity and mortality in cystic fibrosis*) and Jamie Hill Kuck (entitled *On the 50th anniversary of the first human lung transplant*), are included in this issue of the newsletter.

What's New in Pulmonary & Critical Care?

We recently welcomed our two first-year fellows to the Division, Dr. Brad Pitts and Christopher Williams. 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. The transplant rotation at UAB has been a positive experience for our fellows as has time spent in the Biloxi, MS VA medical / surgical ICU.

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.

We are presently recruiting for two faculty positions as clinical educators and clinician scientists.

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...

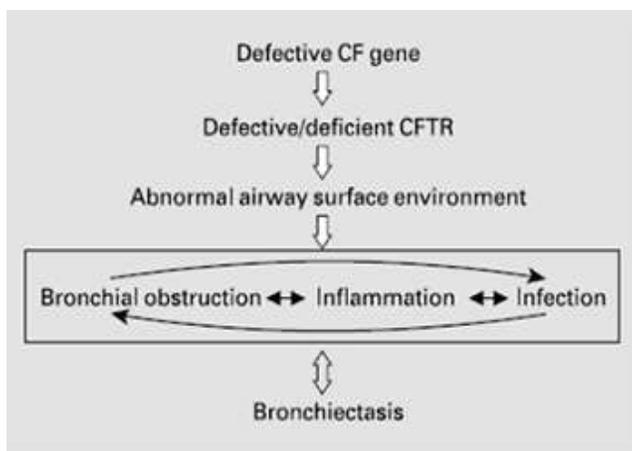


Figure 1. Pathogenesis of lung disease in Cystic

...that lung disease is the main cause of morbidity and mortality in cystic fibrosis (CF)?

CF is one of the most common lethal genetic disorders affecting primarily Caucasians and populations of European descent^{1, 2}. The disease is one of abnormal ion transport. It is caused by mutations in a gene located on the short arm of chromosome 7, which encodes for a glycoprotein known as Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)⁴. In 1985, scientists used a positional cloning approach termed "reverse genetics" to locate the position of the CF gene. The novel molecular tool entailed first identifying the location of a gene, then working backward to understand the physiologic bases of the disease⁵. In 1989, laboratories of Drs. Lap-Che Tsui, John Riordan, and Francis Collins

simultaneously reported in *Science* the identification of the mutated gene present on chromosomes of CF patients compared to normal patients⁶⁻⁸. Today, almost 2,000 mutations have been identified (www.genet.sickkids.on.ca/cftr) with the most common being a deletion of phenylalanine at position

508⁵. The mutations can be ascribed to five categories which encompass reductions in mRNA levels, protein production, protein processing, channel regulation, and channel conduction¹. Physiological results of the mutations are an impairment of salt and water transport across the apical membrane of epithelial cells in sweat glands, reproductive and gastrointestinal systems and the respiratory tract⁹. This results in organ failure and subsequent death, except in the case of sweat glands. Complications from lung disease are the most common cause of mortality. The lung disease profile is a combination of mucus hypersecretion and impaired mucociliary clearance to form an abnormal airway surface environment conducive to chronic airway infections and bronchiectasis.³ (Figure 1).

Over 20 years since the discovery of the mutated gene, the disease remains uncured. Modern treatments of symptoms, but not the underlying defect, have managed to increase life expectancy to about 37 years¹⁰. The current therapeutic aim is to correct the underlying genetic defect by targeting lung epithelial cells to introduce a normal CFTR gene or to potentiate the CFTR channel conductance using pharmacological agents.^{9, 11} Hope remains to manage the various aspects of the lung disease in an attempt to extend patients' lives to a level comparable to the rest of the population.

References

1. Rosenstein BJ, Zeitlin PL. Cystic fibrosis. *Lancet* 1998;351:277-82.
2. Ratjen F, Doring G. Cystic fibrosis. *Lancet* 2003;361:681-9.
3. Dinwiddie R. Pathogenesis of lung disease in cystic fibrosis. *Respiration* 2000;67:3-8.
4. Tsui LC. The cystic fibrosis transmembrane conductance regulator gene. *Am J Respir Crit Care Med* 1995;151:S47-53.
5. Welsh MJ, Ramsey BW. Research on cystic fibrosis: a journey from the Heart House. *Am J Respir Crit Care Med* 1998;157:S148-54.
6. Kerem B, Rommens JM, Buchanan JA, et al. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989;245:1073-80.
7. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989;245:1066-73.
8. Rommens JM, Iannuzzi MC, Kerem B, et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science* 1989;245:1059-65.
9. Kreindler JL. Cystic fibrosis: exploiting its genetic basis in the hunt for new therapies. *Pharmacol Ther* 2010;125:219-29.
10. Simmonds NJ, Cullinan P, Hodson ME. Growing old with cystic fibrosis - the characteristics of long-term survivors of cystic fibrosis. *Respir Med* 2009;103:629-35.
11. Van Goor F, Hadida S, Grootenhuys PD, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci U S A* 2009;106:18825-30.

Author: Pierre Kadeba

Chief editor: Natalie Bauer, Ph.D., April 2013

Did You Know...

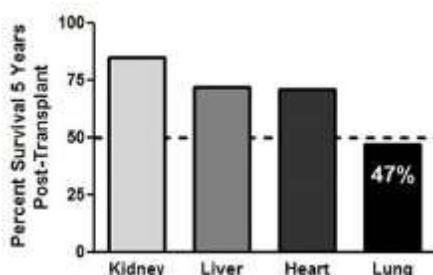


Figure 1. Current 5-year post-transplantation survival rates for kidney, liver, heart, and lung. US Dept. of Health and Human Services, 2009.

...that 2013 marks the 50th anniversary of the first human lung transplant?

In 1963, Dr. James Hardy and colleagues from the University of Mississippi transplanted the left lung of John Richard Russell, a convicted murderer who suffered from an occlusive malignant carcinoma in his left lung, advanced emphysema of his right lung, and renal failure^[1]. For his contribution to science, Russell received a full pardon^[2], but died 18 days after surgery. This landmark procedure proved that lung transplantation was technically feasible.

However, the 5-year post-transplant survival remains low compared to the survival rates of other organ transplants (Figure 1) [3].

In the subsequent twenty years, several attempts at lung transplantation failed. Most patients died within a few weeks due to transplant rejection, and many never left the hospital. The improvement in immunosuppressive therapies was a significant advancement to post-surgery survival. Cyclosporine A, which inhibits the production of the pro-inflammatory cytokine, Interleukin 2 [4], and subsequent T-cell activation, became available clinically in 1983 and was used in the first successful lung transplant that same year [5]. For transplant recipients, cyclosporine A remains a critical ingredient of the triple-drug immunotherapy, consisting of a calcineurin inhibitor, an antimetabolite, and a corticosteroid. This drug combination deters the onset of bronchiolitis obliterans syndrome, a form of chronic graft rejection and one of the leading causes of lung transplant-related mortality [6].

More sophisticated screening and storage techniques are critical to further increase 5-year survival. Currently, a transplant surgeon determines whether to operate solely by surveying the exterior of donor lungs [7]. Once approved, lungs can be stored in 4°C for up to 3 hours, which is a potentially damaging process [8]. Additionally, exhaustive eligibility criteria are established for both donors and recipients. Lung transplantation is absolutely contraindicated in patients with malignancy or dysfunction of another major organ system [9]. Under the current guidelines, John Russell would have never received a new lung. While several advances have been made in the field of lung transplantation, more research is necessary to further improve 5-year survival.

References

1. Hardy, J.D., et al., *Lung Homotransplantation in Man*. JAMA, 1963. **186**: p. 1065-74.
2. Press, A., *Pardon to Reward Convict in Rare Lung Transplant*, in *The Fort Scott Tribune*. 1963: Fort Scott.
3. Services, U.S.D.o.H.a.H. *Patient Survival*. 2009.
4. Snell, G.I. and G.P. Westall, *Immunosuppression for lung transplantation: evidence to date*. *Drugs*, 2007. **67**(11): p. 1531-9.
5. Cooper, J.D., et al., *Unilateral lung transplantation for pulmonary fibrosis*. *Toronto Lung Transplant Group*. *N Engl J Med*, 1986. **314**(18): p. 1140-5.
6. Todd, J.L. and S.M. Palmer, *Bronchiolitis obliterans syndrome: the final frontier for lung transplantation*. *Chest*, 2011. **140**(2): p. 502-8.
7. Kron, I.L., et al., *Successful transplantation of marginally acceptable thoracic organs*. *Ann Surg*, 1993. **217**(5): p. 518-22; discussion 522-4.
8. Sanchez, P.G. and F. D'Ovidio, *Ex-vivo lung perfusion*. *Curr Opin Organ Transplant*, 2012. **17**(5): p. 490-5.
9. Orens, J.B., et al., *International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation*. *J Heart Lung Transplant*, 2006. **25**(7): p. 745-55.

Author: Jamie Hill

Chief editor: Sarah Sayner, Ph.D., October 2013

Have you found us on Facebook?

<https://www.facebook.com/pages/USA-Center-for-Lung-Biology/243653778980604>

Find us on Facebook



USA Center for Lung Biology

3rd Annual Lung Bowl

Lung Bowl 2014



The CLB and the Pulmonary and Critical Care division held its 3rd annual Lung Bowl on August 8, 2014. Six teams competed in this year's event, which was held in the College of Medicine's active learning facility. Teams were comprised of various combinations of pulmonary fellows, postdoctoral fellows and 2nd-5th year graduate students. Each team had 4 members. As detailed below, we had 2 different stems, 2 speed rounds (one question for every person on the team), and one final jeopardy question.

Participants competed to answer questions pertaining to 2 different stems. Each stem had 5 questions. Individual team members were given 10 minutes to answer the 5 questions, and responses were turned in and graded. Correct individual answers were worth 1 point, meaning that each team could accrue a maximum of 20 points (1 point per question x 5 questions x 4 team members) for correct answers. Teams were then given an additional 15 minutes to provide the team response. Correct team answers were worth 10 points per question, meaning that each team could accrue a maximum of 50 points (10 points per question x 5 questions). Every stem was therefore worth a total of 70 points, so after all the stems have been completed; teams had the potential to earn 140 points (70 points per stem x 2 stems).

A running point total was kept by our volunteer score keepers. Teams were able to assess their standings after each stem. A speed round followed each of the first two stems. Team members had one opportunity per speed round. In the speed round, participants – 6 at a time (i.e. one per team) - walked to the front of the room and were handed a paddle. A question about the pulmonary sciences was read, and the first one to raise their paddle was given a chance to answer. Ten seconds were allocated to raise the paddle. If no one responded to the question within 10 seconds, then we moved on to an alternative question. A correct answer earned 10 team points. With an incorrect answer 2 team points were deducted. If incorrect answers were given, we moved on through a list of possible questions until a correct answer was provided. A total of 50 points was awarded in each speed round.

After all of the stem and speed rounds had been completed, teams met for one final question. This was the "final jeopardy" round, where teams evaluated their position in the overall standings and wagered any number of points against a final answer. Teams designated the number of points for the question before the question was received. If the question was answered correctly, then the designated number of points was added to the team total. If the question was answered incorrectly, then the designated number of points was subtracted from the team total. Scores were tallied after the final jeopardy round and the coveted *Lung Bowl Champion* was declared.

CLB faculty was responsible for the accuracy of the questions and answers in this year's Lung Bowl; each question and answer pairing had been carefully vetted. There was no opportunity to challenge the accuracy of the answer during the competition. Questions, and the accuracy of the answers, were discussed during the social gathering after the competition was completed.

The Game

Participants arrived at 2:00 pm on June 8, 2014 to discover the make-up of their team. As a first order of business, team names were announced, including:

The Pulmonettes: Priyanka Vyas, Audrey Vasauskas, Ningyong Xu, Naga Annamdevula

US Airways: Zakiya Douglas, Michael Francis, Phoibe Renema, Thomas Yarbrough

Happythelial Cells: Ji Young Lee, Jared M. McLendon, Jamie Kuck, Kristal Webb

The Lobe Trotters: Adam Morrow, Leslie A. Hargett, Pierre Kadeba, Kathleen McClinton

The Pulmonators: Christopher Williams, Lauren Hartman, Ed Crockett, Kaori Oshima

The Denver Bronchus: William "Brad" Pitts, Andrew Ferretti, April Scruggs, Ashley Lindsey

Once team names were announced, the competition began.

Stems related to gas exchange, blood gases, and the pulmonary circulation. The first sequence of questions was asked by Dr. Stevens. The Pulmonettes took the early lead coming out of the first stem with 52 points, followed closely by The Pulmonators with 51 points. The first speed round questions were offered by Dr. Townsley. These questions focused on historical figures in the pulmonary sciences, with some histology and anatomical questions mixed in. The Pulmonettes maintained their lead, with 72 points, while The Lobe Trotters moved into second place with 67 points. Dr. Fouty's stem and questions followed. Here, teams were required to solve blood-gas problems, and interpret the results in physiological and clinical settings. The Pulmonettes extended their lead after Dr. Fouty's questions, heading the pack with 120 points. Dr. Fagan composed questions for speed round 2. These questions were a crowd favorite, as they were focused on "Celebrity Lung Disease." Happythelial Cells made an impressive surge in this category, bringing their score to 130 alongside The Pulmonettes. Heading into the jeopardy round, The Pulmonettes and Happythelial Cells led the way followed by The Denver Bronchus with 123 points. U.S. Airways, Happythelial Cells, and The Pulmonators waged all of their points on the final jeopardy round, whereas The Pulmonettes waged 0 points. Teams were not aware of the final jeopardy question going in, so team points were at risk. The final question, listed below, was a 2-part question. The Lobe Trotters scored full credit on their final answer, surging to the win with a grand total of 161 points.

Final Jeopardy Question

Which two 18th century scientists are widely acknowledged for the discovery of oxygen? (Who was the first person to report the discovery of oxygen, and who was the first person to describe its "true nature?")

Bonus Points (10)

Where were these discoveries made? Identify the countries where these scientists worked.

When all was said and done, it was a great time for participants and fans alike. We're looking forward to next year's competition!



**Our Winning Team:
The Lobe Trotters**

From left to right: Adam Morrow, Leslie A. Hargett, Kathleen McClinton, Pierre Kadeba



