Center for Lung Biology Pulmonary NewsLetter

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A Tribute to Dr. James C. Parker…

2012 marks Dr. Parker's 35th year of service at the University of South Alabama, and in this year, he has transitioned from a full time faculty member to emeritus professor. Jim has had an enormous impact on our Center for Lung Biology, the University, and the lung community on the whole. Here, we extend our deep-felt appreciation for his outstanding contributions.

Dr. James Parker at his retirement celebration

Jim grew up in New Orleans in the '50s and '60s. He was recruited to Washington and Lee University, where he was a standout track and swimming athlete, serving as captain of the swimming team in his senior year. Soon after graduation, Jim began as a graduate student at the University of Mississippi Medical School. He first worked with Drs. Elvin Smith and Carl Jones on cardioprotection in ischemic heart disease. He completed graduate studies on this topic, but both of his mentors were recruited elsewhere to chair positions, leaving him to identify a new direction for his postdoctoral work. Jim chose to stay at the University of Mississippi with Dr. Arthur Guyton. At the time, Guyton was interested in mechanisms responsible for pulmonary edema following smoke inhalation injury, and so Jim helped develop approaches to quantify pulmonary edema. He, along with Guyton and Dr. Aubrey Taylor, laid the groundwork for measuring pulmonary filtration coefficient, Kf, an approach used extensively today. During his postdoctoral years, Jim made direct measurements of interstitial pressure, identifying that lung interstitial pressure is negative relative to atmospheric pressure. This work provided experimental support for the concept that fluid filtered into the interstitium is drawn by negative pressure into lymphatics for clearance. It was by all standards a highly productive time.

Jim's association with Dr. Guyton provided unparalleled career opportunities. As part of an International Review of Physiology edited by Guyton, he had the opportunity to write a comprehensive chapter on *Pulmonary Transcapillary Exchange and Pulmonary Edema* (*Cardiovascular Physiology III*, 18: 261-315, 1979). This review gave Jim a voice among the leaders in the field. Soon after, Dr. Taylor accepted the Chair of Physiology position at the University of South Alabama; Jim was his first recruit. Aubrey and Jim worked productively to address fundamental issues pertaining to lung fluid filtration, identifying the principles responsible for fluid filtration across the endothelium, through the interstitium and into lymphatics (*Handbook of Physiology*, Chapter 4, pgs 167-230, 1985). It was with this foundation in lung fluid balance that Jim was able to make his most significant contribution.

In 1984, Jim discovered that alveolar pressure was a determinant of lung injury (*J. Appl. Physiol.*, 57: 1809-1816, 1984). For the first time, his study described a relationship between increasing airway pressure and microvascular permeability, representing one of the key building blocks that led to development of our current protective ventilation practice in the ICU. His subsequent work documented the importance of stretch-induced calcium signals in endothelium, which we now recognize are at least partly due to activation of transient receptor potential 4 channels of the vanilloid subfamily (*Am. J. Physiol.-Lung*, 293: L923-L932, 2007). In fact, this idea has continued to gather momentum, as TRPV4 channels represent putative targets for treatment of pulmonary edema (*Sci. Trans. Med.*, 4: 159ra147, 2012; *Science Trans. Med.,* 4: 159ra148, 2012). Jim's work on ventilator-induced lung injury stands out among his many contributions; through the years he has published in excess of 150 full-length peer-reviewed papers, chapters and texts.

It is a goal for all biomedical researchers to make discoveries that impact the practice of medicine. Jim has been one of the few fortunate scientists who contributed discoveries that have changed medical practice and directed investigation into possibly novel therapeutic options. We remain grateful to Jim: thanks for your efforts Dr. Parker.

What's New in Research Training?

The **Running and Walking Club** provides a coordinated mechanism for CLB members to share in their active lifestyles. We run and walk at area-sponsored 5K, 10K, half marathon and marathon events. The list of these events for the 2011-2012 season is shown at **http://www.usahealthsystem.com/RunningandWalkingClub**. Workout schedules are provided online in the Training Schedule section. The workout schedule is adaptable for any individual's goals. In addition, we provide a summary of recent scientific articles that highlight important health issues in our Science for Health section (see below). The schematic shown on the left illustrates our commitment to a life balanced by mind and body. The Latin words *Alio Valetudo* shown in the banner mean personify health; be healthy and enjoy all life has to offer.

Science for Health

Premenopausal breast cancer survivors: exercise to survive! The latest American Cancer Society (ACS) Statistics state that women diagnosed with breast cancer prior to forty years of age have an 84% chance of surviving to 5 years post-diagnosis (www.cancer.org). For young women unlucky enough to be diagnosed with triple negative breast cancer, a highly aggressive form of breast cancer, the survival rate drops to approximately 60%. Although triple negative breast cancer is frequently associated with mutations in the BCAC1 and/or 2 genes, anyone can get triple negative breast cancer. This tumor subtype (ER- PR- Her-2-) is characterized by its rapid growth, predilection for distant visceral and brain metastasis, and poor prognosis (relative to ER+/PR+ tumors). Because triple negative breast cancer lacks the receptors for targeted therapy, post-treatment "survivors" are left without the "safety-net" of maintenance therapies like herceptin (for HER-2 + cancers) or Tamoxifen (for ER+ cancers). Many turn to life-style changes and dietary supplements to delay or prevent metastasis.

One of the most effective life-style changes that a triple negative breast cancer patient can make post-treatment is to exercise. Moderate to intense exercise drives down insulin-like growth factors, and improves immune function.[1] There is also evidence to support that a reduction in insulin-like growth factors can down regulate vascular endothelial cell growth factor signaling.[2] Vascular endothelial cell growth factor is thought to be a key player in recurrence and metastasis of triple negative breast cancer tumors. Regardless of the molecular mechanisms involved, epidemiological studies have illustrated that breast cancer patients in general, regardless of tumor pathology, who exercise have a 34% risk in mortality from breast cancer. To that end, the American Cancer Society recently published new guidelines for breast cancer "survivors", including an exercise minimum recommendation of 150 minutes per week. The American Cancer Society also notes that "exceeding the guidelines is likely to provide additional health benefits."[3]

The key message for young breast cancer survivors is to do as much as you can as often as possible. It just might save your life.

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What's New in Pulmonary & Critical Care?

In the past several months we have been busy reviewing and interviewing candidates for our 3-year Pulmonary and Critical care Medicine. We had an outstanding group of applicants and anticipate that we will match some excellent fellows. 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 we signed an agreement for our second year fellows to go to the University of Alabama Birmingham for one month to rotate on the lung transplant service.

Our Pulmonary Clinics continue to be busy. Recently the USA Sleep Disorders Clinic moved back to the main USA Campus from the West Mobile area. Sleep studies are being performed at Providence Hospital and read by USA physicians.

Clinical research continues to grow in the Division with investigator and industry developed and sponsored activities. We hope to expand further through our recent submission of translational research proposals to the NIH as well as out 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…

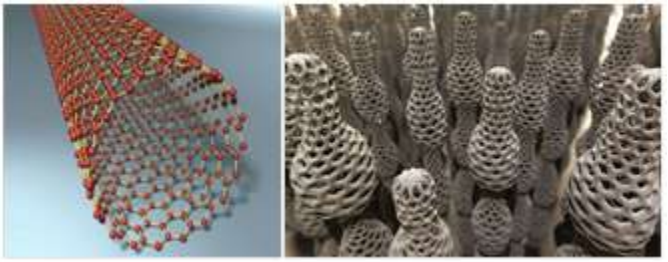

Figure 1. (A.) Artist's cross-sectional image of a carbon nanotube. Image: Digital Art/Corbis. (B.) 3-D renderings of carbon nanotubes of variable diameters and lengths. Image: Joel Brehm, Office of Research and Economic Development, University of Nebraska-Lincoln.

… that the toxicology of carbon nanotubes (CNTs) is hindering their use in the treatment of lung diseases?

Since the discovery of CNTs in 1991 by Sumio Iijima (1), these nanoscaled carbon sheets rolled into hollow tubes and capped at both ends, have caught the attention of biomedical scientists (Figure 1). However, CNTs are hydrophobic and insoluble in aqueous solution, and tend to aggregate due to strong van der Waals interactions (2). In order to make CNTs more compatible with biological systems, the insolubility and aggregation issues have been overcome by the attachment of functional groups to the external surface of CNTs in a process known as functionalization (3). Indeed, in 2001, Chen et al. (4) functionalized CNTs with molecules containing reactive side-chains extending from their surface. These reactive side-chains were then modified to bind proteins. In 2004, Pantarotto et al. demonstrated that functionalized CNTs (f-CNTs), modified with a fluorescent probe, readily permeate plasma membranes (5). Thus, the synthesis of f-CNTs enables the simultaneous immobilization of small biomolecules (e.g. imaging sensors to track

delivery) and biomarkers (e.g. antibodies) in addition to drugs or nucleotides thereby enabling selective targeting of CNTs with their associated cargo to certain molecules or cells. Thus, f-CNTs are promising tools as targeted drug carriers to treat a wide variety of diseases, including diseases of the lungs.

Despite the promise of f-CNTs in drug delivery, studies investigating health risks associated with worker-exposure during the manufacturing process revealed lung toxicity from both inhalation and intravenous delivery routes. In 2004, rodent studies demonstrated that intratracheal instillation of CNTs produced inflammation and led to the formation of granulomas (6, 7), which became progressively worse with increasing CNT dose (9). Toxicity was not only attributed to CNT aggregation, but also due to their biopersistence (8, 9). In 2009, Ryman-Rasmussen demonstrated that inhalation of aerosolized CNT led to subpleural fibrosis in mice but noted the pathology was different from asbestos-associated fibrosis (10). Intravenous delivery of CNTs in mice induced low toxicity in the liver, spleen and lungs mediated by oxidative stress (11). In the lungs, an inflammatory response was observed and CNTs aggregates accumulated in the capillaries. Despite the associated inflammatory risks, CNTs have shown therapeutic promise in a human lung carcinoma animal model, where direct intratumoral delivery of f-CNTs carrying siRNA sequences promoted cell death, reduced tumor volume, increased tumor necrosis, and prolongs animal survival (12).

Though the negative findings are a setback for the use of CNTs as targeted drug carriers to the lung, researchers remain cautiously optimistic. Functionalization is the key to CNTs as a safe drug delivery system. CNTs can be modified to make them more dispersable and discourage aggregation. We now appreciate that while long, thin CNTs behave like asbestos, short or curly CNTs do not (13), suggesting safer CNTs can be made. Indeed, CNTs of variable diameter and length can now be synthesized (Figure 1B). CNTs could also be functionalized to render them more biodegradable, so that they do not persist in the lung for an extended period of time (14). In summary, the current toxicological profile of CNTs in the lung hinders their use as targeted drug carriers to the lung. However, functionalization of CNTs to reduce aggregation and promote biodegradability as well as altering the aspect ratio of CNTs could decrease lung toxicity. The technology of targeting drugs to the specific site of disease must be further explored in order to reduce undesirable wide-range systemic effects of a drug and facilitate targeting to the pulmonary circulation.

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The Inaugural Lung Bowl…

The CLB and Pulmonary and Critical Care division held its first annual "Lung Bowl" competition on June 1, 2012 at the University of South Alabama faculty club. Five teams competed in the event. Teams were comprised of a pulmonary fellow, post-doctoral fellow, and 2rd-5th year graduate students; teams had a total of 4-5 members.

Teams competed to answer story problem questions, speed round questions and a final jeopardy question. The competition began with the story problem round, where 4 different stems were tested, each with 5 questions. Individual team members were given 10 minutes to answer the 5 questions, and these responses were turned in and graded. Correct individual answers were worth 1 point, meaning that each team could accrue a maximum of 25 points (1 point per question x 5 questions x 5 team members) for correct individual 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 worth a total of 75 points, so once all the stems were completed, teams had the potential to earn 300 points (75 points per stem x 4 stems). A running point total was kept by our volunteer score keepers. Teams assessed their standings after each stem.

The speed round followed the stems. We had 5 speed rounds in total. In the speed round, participants – 5 at a time (i.e. one per team) - walked to the front of the room with a lung bowl paddle. A question about the pulmonary sciences was read, and the first person to raise their paddle was given a chance to answer. Ten seconds was allocated to respond. If no one responded within 10 seconds, then we moved on to an alternative question. Correct answers earned 10 team points. With incorrect answers, 10 team points were deducted. A total of 50 points was awarded in this round.

After all of the stem and speed rounds were completed, teams met for one final question. In this "final jeopardy" round, teams wagered any number of the points accrued against a final answer. With the correct answer the designated number of points were added to the team total, and with the incorrect answer the designated number of points were subtracted from the team total. Scores were tallied after the final jeopardy round and a team winner was declared.

The Game

Stems for the competition were emailed to all participants May 31, giving the competitors just 24 hours to prepare for the questions that lie ahead. Participants arrived at the faculty club at 2:00 pm on Friday,

June 1, ready to test their wicked lung skills. They arrived to find team pairings. The first order of business was to generate team names.

"The PEEPs": Karl Schroeder, Abdallah Alzoubi, Sachin Joshi, Ningyong Xu, and Ed Crockett
"Inspiration": Meshann Fitzgerald, Salina Gairhe, Pierre Kadeba, Peter Favreau, and Courtney Rothrock
"Da Bronchos": Phil Almalouf, Rebekah Morrow, Jamie Hill, and Leslie Hargett
"Alveolocos": Samer El Zarif (absent), Christiaan Ochoa, Ashley DeCoux, Terrance Platt
"The Pulmonauts": Ali Riaz, Audrey Vasauskas, Jared McLendon, Patricia Villalta

Once organized, the competition began. The first stem was provided by Dr. Brian Fouty, entitled "Altitude". Five questions arose from the following:

Normal Values:

$\mathbf{P_B}$ (barometric pressure, Denver) = 630 mmHg

$\mathbf{P_B}$ (barometric pressure, sea level) = 760 mmHg

$\mathbf{P_{H2O}}$ (water vapor pressure) @37C= 47 mmHg

$\mathbf{P_AO_2} = (P_b - P_{H2O})\ F_IO2 - P_aCO2/R$

$\mathbf{P_aCO_2}$ (Denver) = 35 mmHg

$\mathbf{R}$ = 0.8

You are living in the Florida Keys, working as an online high altitude medicine expert fielding questions from around the world. On a particularly busy Tuesday you are presented with the following questions….:

Calculators were smoking as participants determined A-a gradients and causes of arterial hypoxemia in a COPD patient, a trekker in the Himalayan Mountains, and a climber ascending Denali in Alaska. After the dust settled from the first round, **Alveolocos** took the early lead with 52 points, followed closely by **Da Bronchos** with 51 points.

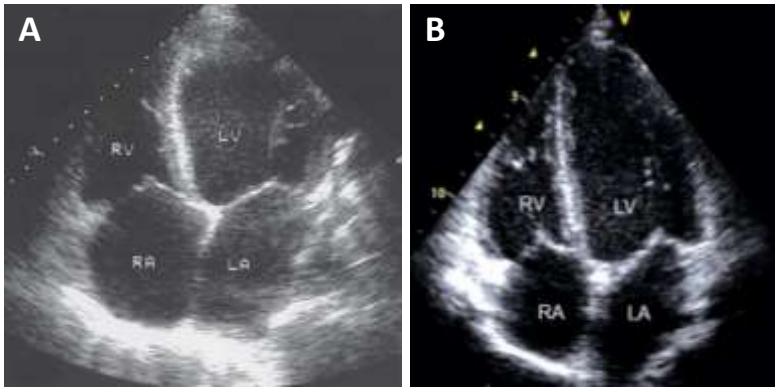
The second stem was written by Dr. Townsley, entitled "The Stock Broker". Five questions were asked based upon the following:

> A 55-year-old stockbroker in New York City began to experience fatigue and shortness of breath with exercise (golf) about 5 years ago. Although these symptoms have become progressively worse, with occasional ankle swelling and increasingly limited exercise tolerance, he did not seek medical advice. In the past month, it typically would take him 6 minutes or more to cross the 200 meter stock exchange floor. Even that limited exercise stress resulted in severe dyspnea. On a particularly alarming morning, he struggled across

the exchange floor, then collapsed with crushing chest pain. His breathing was more labored than normal and he started coughing up pink frothy fluid. As he dimly heard one of his fellow brokers call 911, he finally conceded that he had a problem.

In the emergency department he was severely dyspneic. His skin was pale and clammy. His blood pressure was 110/65 mmHg, while pulse rate was 100 beats/min. On auscultation of the chest, rales (crackles) could be heard at the bases of both lungs posteriorly. His neck veins were engorged and he had ankle edema. A chest radiograph showed blotchy bilateral opacities. Arterial blood gases, measured while he was breathing room air, showed a PO_2 of 59 mmHg, PCO_2 of 35 mm Hg, and pH of 7.35, while the HbO_2 saturation was 80%. The CBC was relatively normal, with a hemoglobin of 14 g/dL, though cardiac enzymes were elevated. During a protracted accumulation of his medical history, he claimed to have never smoked, but did admit to a history of heavy alcohol use which he attributes to the stress of his job.

After admittance to the cardiac care unit, his left ventricular function was assessed by echocardiography. A 4-chamber apical view for this man at end-diastole (A), shown at right, is compared to that in a normal individual (B). LV ejection fraction, as assessed on echo, was 38%.



Questions about oxygen delivery, shunt fractions, and oxygenation in a chronic heart failure patient dominated stem 2. **Da Bronchos** made a strong push through stem 2, taking a 13 point lead over **Alveolocos**, who in turn, opened a 12 point margin over **The PEEPs**.

Stem 3 was written by Dr. Stevens in a topic that dealt with the cardiorespiratory response to exercise, entitled "The Runner". The following stem served as the basis for the next five questions:

At age 32, you have relocated to Portland to begin your independent academic career at the University of Oregon Health Sciences Center. In an effort to meet new friends and continue with your healthy, active lifestyle you join the Oregon Road Runners Club. The club meets twice a week, on Tuesday and Thursday evenings, for group runs at the Cleveland High Track. This is the perfect place to try out your new heart rate and ventilatory rate chest monitor, and so you show up well hydrated and ready to run on June 30th - your first Tuesday in Portland.

This week's workout includes successive mile, 800-meter, 400-meter, 800-meter, and 400-meter runs, each with 2-minute rest intervals in between. Three groups are formed based upon estimated times. Although you've been active for the past 10 years, you haven't run a 5K since college. You're thinking you may want to start competing in some weekend 5K runs to help you meet people, and so you set out a goal to run a 5K (3.1 miles) in 18:40, at 6-minute per mile pace. Based upon this loose idea, you join a group whose goals seem to be in line with yours. As the group takes off you realize in the first 200 meters that the pace is outstripping your usual runs. You run in the middle of a pack of 10 runners for the first lap. Although you make it through the first lap without much problem, as you begin the turn into your second lap, you can feel your breathing is becoming heavier, with regular, deep inspirations. You make it around the second lap at a time of 2:45, which is on pace for a 5:30 mile, much faster than you have run since college. You feel a stomach pang as you head into the third lap. Your breathing is very deep and labored now, and you notice a significant increase in breathing frequency as you round the third lap and head into the final 400 m. Sweat is pouring off your head while your heart pounds in your chest. You cross

the line marking 200 meters to go, but it's beginning to feel like you won't make it. Your breathing becomes erratic, very heavy and even more labored. With just 100 meters to the finish line you are pushing with all of your effort just to keep the pace, but to no avail. Your pace drastically drops off and you fall out of the pack in the final 50 meters. As you cross the line you grab your knees with both hands, breathing deeply against a queasy stomach. You have crossed the line in 5:45, 15 seconds faster than you've run the mile in 10 years. The monitor on your wrist displays a heart rate of 185 and a ventilatory rate of 45. You stagger around for what seems like seconds, and before you know it the group is back on the line to run an 800-meter interval. You decide to sit this one out, and jump into the slower group for the next 400-meter interval.

Metabolic factors that control minute ventilation, the impact of carbon dioxide on alveolar gas, and oxygen extraction at near maximal exercise dominated the questioning for stem 3. Again, calculators were smoking. **Da Bronchos** maintained their lead after the third round with 148 points, but **The PEEPs** made a strong move into second place.

The fourth stem was written by Dr. Fagan, entitled "Ms. X", with five questions based on the following:

Ms. X, age 41, was walking up a short incline to her apartment carrying her groceries. Approximately ¾ of the way, she developed substantial shortness of breath. After several hours her symptoms improved with rest. While at work as a receptionist the next week, she had a similar event while walking across the office to the mailroom. Her coworkers called 911 and she was taken to the emergency room. On questioning she reported that she had had about one year of increasing shortness of breath and had quit singing in church because of it. She reported that she had had several episodes of bronchitis in the past few years with shortness of breath and occasional coughing. She had no other medical history. In the emergency department her vital signs were normal as was her pulse oximetry. Her heart rhythm was normal. Her lung sounds were clear. Routine labs were also normal. A CXR did not reveal any infiltrates. She was not pregnant. Toxicology testing was negative. She was discharged with follow up with her PCP.

Two weeks later she had another episode of bronchitis and saw her primary care physician who obtained spirometry demonstrating normal airflow. Since the spirometry was normal, her PCP referred her to a cardiologist for an evaluation.

Stress testing was negative for ischemia. An echocardiogram demonstrated a normal ejection fraction and moderate tricuspid regurgitation.

Here, questions about pulmonary vascular resistance, the cause of dyspnea, and treatments for pulmonary hypertension dominated the action. After the completion of our fourth stem, **Da Bronchos** held the lead with 188 points, followed by **The PEEPs** with 172 points, **Alveolocos** with 164 points, **The Pulmonauts** with 133 points, and **Inspiration** with 110 points.

Next, we headed into the speed round. **The Pulmonauts** and **Inspiration** were looking for a big push to garner points for the final jeopardy round. **The Pulmonauts** had their breakthrough, earning 30 points in the round, bringing them into close contention. Sample speed round questions are shown below:

Who was the first to describe cardiogenic pulmonary edema? Hyppolyti Francisci Albertini

The ATS standard for diagnosing obstructive disease is: FEV1/FVC < 0.7

Who developed the stethoscope? René Laennec

Who discovered the pulmonary capillaries? Malpighi

Normal total lung capacity in an average-sized adult male is? 6 Liters

Resting cardiac output is: 5 L/minute

In calculating the alveolar gas equation, the partial pressure of water vapor is assumed to be: 47 mm Hg

In calculating the alveolar gas equation at sea level, the respiratory exchange ratio (RER) is generally assumed to be: 0,8

Normal tidal volume is approximately: 500 mL

Respiratory exchange ratio (RER) is determined by the ratio of: VCO_2/VO_2

The oxygen carrying capacity of 1 gram of hemoglobin is: 1.34 mL
The hemoglobin content of blood is: 15 g/dL

The normal mean pulmonary artery pressure range at sea level is: 12-16 mm Hg.

Who received a Nobel prize in physiology or medicine for their studies on right heart catheterization and assessment of pulmonary pressure? Andre Cournand, Dickinson Richards, 1956

Moving into the final jeopardy round, **Da Bronchos** maintained the lead. Yet, all of the five teams were in contention, each having enough points to win the contest. **Inspiration** had 110 points heading into the final round, and they wagered all 110. **The Pulmonauts** had 163 points, and they wagered 100 points. **Alveolocos** came in with 164 points, and they risked just 50 points. **The PEEPs** earned 182 points, and they risked it all. **Da Bronchos** had 188 points, and they placed 183 at stake. Now was the moment of truth. Having made their wager, they were presented with the final jeopardy question, which was:

"…Based on work done at Pike's Peak Colorado, this famous respiratory physiologist hypothesized that at altitude, oxygen transfer from the lungs into the bloodstream was due to *active secretion*, not passive diffusion. This was later proven to be incorrect, but the correction was never acknowledged by the physiologist to be valid.

Hint: His name is attached to the observation that deoxygenated blood has an increased ability to carry carbon dioxide (CO_2)…

Answer: Haldane

The question was difficult, but the hint helped considerably. Correct answers were given by **Inspiration**, **Alveolocos**, and **The Pulmonauts**. When final scores were tallied, it was **The Pulmonauts** who came from behind to grab the win. **Inspiration** ended in second place followed by **Alveolocos**. After leading for almost the entire game, **Da Bronchos** finished in fourth, followed narrowly by **The PEEPs**.

After the game was completed, all teams retired to food and drinks. The event was great fun. We are already looking forward to next year's follow-up.

Congrats to the 2012 Lung Bowl Champions
The Pulmonauts

Audrey Vasauskas, Jared McLendon, Patricia Villalta, Ali Riaz


University of South Alabama