FDA Approved Therapy for LAM in Less Than a (20 Year) Decade

By Frank McCormack, MD, LAM Foundation Scientific Director

The FDA-approved sirolimus for use in patients with LAM on May 28, 2015, almost exactly 20 years after The LAM Foundation was founded. The informal tag line for the Foundation back then was 'an effective treatment in under a decade', and the Board's tongue-in-cheek position was that we could 'use our own discretion' to decide when the decade started. I am still not sure when the start date was, but I think we can assign the end date for the first effective treatment for LAM as May 28, 2015.

The FDA effort started a few months before the MILES trial was published in The New England Journal of Medicine in April 2011. We had contacted Pfizer to ask if they would consider pursuing an FDA indication for LAM based on the MILES trial result that sirolimus stabilized lung function. After about three months of internal deliberations, Pfizer replied in June 2011 that they would not approach the FDA about changing the sirolimus label, in part because the product was already commercially available and the resource demand of a submission would be significant against a limited market potential and expiring patent for sirolimus. Pfizer (as its predecessor, Wyeth) had already contributed greatly to the LAM effort by supplying sirolimus and financial support in part for the MILES trial, and under the circumstances their response was not unexpected. At the Summit for Drug Discovery in Tuberous Sclerosis meeting in July 2011, however, one of the panelists mentioned an alternative route to FDA approval, called the Citizen’s Petition. A Citizen Petition is a procedure by which a person or persons can petition the government to request that it take certain actions. In this case, the proposal was to petition the government to change the approved product label for sirolimus, even in the absence of an application from the manufacturer for this change.

With help from Gene Sullivan, MD, a LAM Foundation Board member and former Deputy Director of the Division of Pulmonary and Allergy Products at the US FDA, we contacted the FDA about this approach. After reviewing the matter, based on optimism from the MILES trial publication that sirolimus might be approvable for LAM by a more conventional approach, the FDA decided that the most efficient path would be for Pfizer to submit an application, rather than relying on the Citizen Petition procedure. The FDA then actively encouraged Pfizer to apply in May 2012. An atypical regulatory filing pathway highlighting a collaborative approach with the MILES team was judged to be acceptable by the FDA, in which the MILES data sets would be directly submitted to the IND application that I had submitted for the MILES Trial, and Pfizer would be permitted to cross-reference the data. Under these conditions, Pfizer agreed to pursue an indication for sirolimus in LAM. With the help of Gene Sullivan, and the pro bono assistance of a skilled legal advisor, Frank Sasinoski, of the DC law firm Hyman, Phelps and McNamara, the LAM Foundation successfully filed for Orphan Drug Designation for sirolimus in LAM (granted October 31, 2012) and transferred it to Pfizer to assist with waiver of a large filing fee (~ $1 million) that is typically required of companies.

Upon an initial review of the MILES data sets, the FDA expressed optimism that MILES might well be sufficient to support approval. The randomized and double-blind trial design, rigorously maintained despite the complexities of central drug level monitoring and dose adjustments, helped to make the case for efficacy. The FDA further offered that an Advisory Committee, extensive post marketing studies, additional audits, or an Integrated Safety Sum-

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mary would not likely be required, as long as the FDA review of the full data sets confirmed the summary results. The Cincinnati MILES team, the Data Center in Florida and dozens of people at Pfizer worked for two years on the 2562 page MILES Clinical Study Report (CSR) that was required for filing. The FDA reviewed 3 dataset submissions, and granted Breakthrough Therapy Designation for sirolimus for the treatment of LAM on December 12, 2014, accelerating the review process and providing access to powerful FDA resources for assistance with trial design and regulatory approval. Pfizer submitted the final MILES datasets, the Clinical Study Report and the supplemental New Drug Application (sNDA) to the FDA on Christmas Eve, 2014. Less than six months later, with little activity and few queries, the FDA granted approval.

This stunning outcome exemplifies the remarkable progress that can be made when industry, a clinical investigative team, a patient advocacy group and a regulator put financial considerations and bureaucratic protocol aside to do what is right for patients. The courage and sacrifice of the women who enrolled, considered enrolling, attempted to enroll, wished they could have enrolled, or cheered from the sidelines in the MILES trial made the FDA decision possible. In essence, MILES subjects donated 10-20% of their lung function to get an answer for all LAM patients and for all time; bringing us to this place. There is no question who the heroes are in this story.

Sirolimus is the first drug approved for the treatment of LAM, and one of only a very few drugs approved for a diffuse parenchymal lung disease. What will FDA approval mean for LAM patients? First and foremost, FDA approval is the ultimate endorsement that the ratio of benefit to risk of a therapy is favorable. Physicians will therefore prescribe the drug with greater confidence. Insurers will be more inclined to provide coverage. And finally, the FDA ruling has the potential to facilitate approvals in other countries where patients have had difficulty obtaining the drug. The loss of access to sirolimus for Japanese patients after MILES has been a primary motivator for me personally. As it turned out, Dr. Inoue and Nakata righted that wrong about a year ago, when they obtained Japanese government approval for sirolimus in LAM through submission of MILES data to the Japanese Ministry, launching of their own safety study, and enlistment of the help of a pharmaceutical company. LAM patients in China, Russia, Singapore, Korea and other countries are still struggling to obtain sirolimus, however, and there is more work to do.

We owe a lot of people wine. LAM basic and clinical researchers for providing the scientific basis for MILES; MILES investigators, nurses, coordinators and patients for making the trial a success; Jeff Krischer, Karalyn Hadley, Marisa Couluris and Hye-Seung Lee and the entire team at the Rare Diseases Data Center for assistance with trial design and operations, expert data analyses and seemingly endless responses to FDA, Pfizer and ‘Japanese FDA’ queries; The NIH Rare Diseases Consortium, Bruce Trapnell and all MILES funders; Sheri Selk and the Cincinnati Children’s Translational Research Trials Office staff for 6 years of invaluable MILES trial support; Gene Sullivan for sage advice about trial design and conduct from beginning to end; Matthew Hodgson, Jeannie Bailey and Leslie Korbee for their stellar work as Project Managers for MILES; Leslie also for the pro bono, unfailingly eager and capable assistance she has provided to the LAM community for 8 years; Susan McMahan for her outstanding leadership as the MILES-trialwide coordinator; Frank Sasinowski and Gene Sullivan for all the advice, meetings and document drafting during FDA interactions; Tammy Roads and her coordinators for work on MILES and two years of uncompensated weekend and evening work on the MILES CSR; Eli Katz and Brenda Cooperstone who were early champions at Wyeth and Pfizer for the LAM effort; Sandi See Tai, Dan Levy, and Debi Tran at Pfizer for many months of biweekly CSR conference calls and tireless work on this project; Bob Abraham of Pfizer for his pioneering work on mTOR and his ongoing encouragement; and, last but not least, Sue Byrnes, Tom Laurenzi, Laura Lentz, Sue Sherman and the LAM Foundation Board, donors and staff who provide critical support to the MILES trial, greatly facilitated the FDA approval process and brought the patient voice to every conference table.

Speaking of the FDA—although the agency is not often publicly thanked, I can tell you that Dr. Badrul Chowdhury and his team in the Division of Pulmonary, Allergy and Rheumatology Products bent over backwards for LAM. They proactively encouraged Pfizer to seek an indication, pressured us all to hurry with the completion of the CSR and sNDA filing, and guided us through the shortest regulatory path possible. This has been the LAM story from the beginning; in the end people are people, and whether affected or unaffected; self employed, a member of a multinational company or an official in a federal agency; good people everywhere go out of their way to help when they encounter an eminently worthy cause.
Staying Strong Together
BY SUSAN E. SHERMAN, EXECUTIVE DIRECTOR

“Thanks for all the troops in the trenches who gave so much for others for [an approved treatment]. Thank you for all the women who will benefit from your ceaseless endeavors. Thank you for all your strength and perseverance. You have shown to the world what can be done. You are a shining example of courage. You are my heroines!!”

Phillip Steele, Family member of a LAM patient

This expression of gratitude is one of hundreds of comments posted on social media and sent via email in response to the FDA approval of Rapamune for the treatment of LAM. For me it is a sincere, instantaneous and heartfelt expression of what we are all feeling. Who could have asked for a more exciting development in this, the LAM Foundation’s 20th year? When added to the growth and achievements of the Foundation during its first two decades, this accomplishment underscores the sense that the LAM community was, and continues to be, exceptional. Looking forward, the logical question is, how do we sustain momentum so that we reach our final goal of a cure, as soon as possible? The answer is by instilling a renewed sense of urgency into the fundamentals that have defined the LAM community from the beginning: collaboration, ingenuity, and compassion.

COLLABORATION
First, let’s consider collaboration. The LAM Foundation has shown that encouraging collaboration between scientists, patients, clinicians and families has accelerated both research outcomes and quality of life for women with LAM. Looking forward, we know that providing even more ways for the entire LAM community to share information will keep progress toward a cure on track. This includes producing research conferences and LAMposium, recruiting young scientists, connecting LAM clinicians and patients and partnering with organizations such as the National Institutes of Health. We will also form stronger ties with other rare disease organizations such as the Rare Lung Disease Consortium to assure that the LAM community interests and LAM research are a priority.

INGENUITY
The LAM community, led by The LAM Foundation, has “ingenuity” as its middle name. The endless spirit of volunteerism, scientific curiosity, creative fundraising and altruism are why significant advancements have arrived in 20 short years. It takes unfiltered grit for a family to create a fundraiser out of heartbreak; for a scientist to conceptualize and apply for one more grant in the face of many academic and clinical priorities, and for a strong and confident woman to publically share a personal story of illness and fear. And yet, this ingenuity turns family heartache to the accomplishment of raising thousands of dollars to power LAM research; turns intellectual curiosity into research projects or active clinical trials and transforms women with LAM who share their story from victim to victor. From its inception in a suburban basement in Cincinnati, to being highlighted in the New England Journal of Medicine and receiving recognition from the National Institutes of Health, The LAM Foundation has built a culture of ingenuity and an expectation of results.

COMPASSION
Finally, as we look forward, the LAM success story will only come to its desired conclusion of a cure, if we remain grounded in the compassion that first inspired Frank McCormack, MD, Sue Byrnes and early supporters of the Foundation to take action. Compassion fuels ingenuity and creates a fertile environment for sharing and achieving together. It inspires our LAM Clinic Directors to intervene to help patients beyond providing routine care, answering emails and helping them through the challenges of having a rare disease. Compassion for each other leads women with LAM to volunteer for clinical trials, not for their own benefit, but to help the next generation affected by LAM – as was the case with the MILES trial. Our nearly 35 LAM Liaisons volunteer countless hours to help women diagnosed with LAM, offering hope, education and a shoulder to cry on. They do this in addition to being career women, moms, wives and daughters, not to mention managing their own LAM diagnosis. Compassion is the heart of the LAM community.

What will it take to find better treatments and ultimately a cure for LAM? More collaboration. More ingenuity. Endless compassion. Ask yourself, what can I do? In the pages of this edition of Journeys you will find inspiration and many opportunities to help propel us forward to our next chapter in the LAM success story. Ideas for taking action include:

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Enrollment for the MIDAS Trial launched in March at LAMposium. Within these few short months, the Rare Lung Disease Consortium at Cincinnati Children’s Hospital Medical Center has signed up 100 women with LAM for this extremely important and primarily observational study.

As with any research study, patients have a lot of questions. They want to make certain they qualify and most importantly make certain they understand what is being asked, and that it will fit with their lifestyle.

So I thought I would put together some information and answer some of the frequently asked questions from women with LAM who are interested in enrolling in MIDAS.

The Multicenter International Durability and Safety of Sirolimus in LAM or MIDAS Study is being funded by the Rare Lung Disease Consortium. The study is a long term prospective or observational registry of women with LAM, who are taking or considering taking mTOR inhibitor therapy such as sirolimus or everolimus. The goal of the study is to refine the treatment of patients with LAM by determining if long term suppressive therapy with sirolimus or everolimus is safe and can prevent progression to more advanced stages of LAM.

Here are some of the most common questions discussed with women with LAM, when they call my office:

Q: Do I need to be taking sirolimus?
A: You do NOT need to be on sirolimus or everolimus

Q: Will I need to travel to Cincinnati?
A: No, you do not need to travel to Cincinnati. Even if your LAM Clinic does not become an official Rare Lung Disease (RLD) study site, you can still participate. With your permission we will collect your data from your LAM Clinic after your yearly visit.

Q: What other sites will be opening or is my LAM Clinic going to be a site?
A: We plan to open up 30 RLD sites across the U.S. Please go to the LAM Foundation website to see the complete list of sites.

Q: If go to the NIH, can I participate in this study?
A: Yes

Here are some additional thoughts:

- There are no additional visits required to participate (we will gather your data from your yearly LAM Clinic visit). The only additional information we ask you to provide is a completed questionnaire and completion of home diaries.
- Although there may not be direct benefit, this study provides important information to researchers into the progression of LAM and how long term use of sirolimus effects progression.

When women with LAM call or email me to enroll, I will email a copy of the consent for them to review. If they are interested, I mail them a packet of information, including the consent, HIPAA authorization, diaries, and questionnaires. Once they receive this packet we schedule a time that I can call to discuss the protocol in detail and to review the consent. After I have answered all questions, if they choose to participate, I ask that they sign both copies of the consent and HIPAA document and have them return that to me. We go over the questionnaires and diaries (when to complete, when to return them). I also ask that they contact me before they visit a LAM Clinic so I can request records.

ALL WOMEN WITH A DIAGNOSIS OF LAM CAN ENROLL IN THIS STUDY.

We gratefully acknowledge all of the women who have volunteered to support clinical trials for LAM in the past. These women have advanced the treatment of this disease and the continued hope for a cure.

For more information to enroll contact:
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LAM Foundation Biomarker Innovation Summit: A Model for Engagement and Action

Sometimes slogans like “Stronger Together” are a rallying cry to motivate people to action. Other times a slogan serves to provide a quick vision of who we are. This story is about our slogan in action. Is there truth to our claim that we are, in fact, Stronger Together? Read this story about the LAM Biomarker Innovation Summit and you be the judge. What does Stronger Together really mean?

In 2013, The LAM Foundation Board of Directors, a passionate group of volunteers and leaders wrote a new strategic plan that included the following goal: “Focusing investment on the development of biomarkers that can be used to make the diagnosis of LAM, and to predict disease progression and treatment response.” In pursuit of that goal, the Foundation took the following steps to turn goals into action:

**January 2014:** John Adler, in memory of his wife Vi Adler, provided a major gift to support the planning of the LAM Biomarker Innovation Summit. Industry partners Novartis, Pfizer and Insmed offer sponsorship funds to support meeting.

**March 2014:** At LAMposium in Chicago, a preliminary meeting of interested scientists gathered to consider current LAM biomarker research and next best steps to accelerate the discovery of new biomarkers.

**April 2014:** The LAM Biomarker Summit Planning Committee was formed and met regularly for six months to organize the meeting. It included Frank McCormack, MD, Lisa Young, MD, Lisa Henske, MD, Greg Downey, MD, Laura Lentz, Board Chair, Pat Venter, Board Vice Chair, Sue Sherman, Executive Director and Judy Sheridan, Grants and Research Manager.

**Summer 2014:** Women with LAM participated in a LAM Foundation Survey to guide priorities for scientists to consider at the Summit.

More than 60 international biomarker and LAM scientists are invited to attend the first LAM Biomarker Innovation Summit in Atlanta, GA. LAM Foundation staff coordinated meeting details and logistics.

A Biomarker Summit Fundraising campaign was launched and the LAM community raised an additional $140,000 to support pilot research projects generated at the Summit.

**November 2014:** More than 50 biomarker and LAM scientists gathered in Atlanta, GA, surrounded by the questions the LAM patients prioritized in the survey. With the needs of LAM patients in mind, these scientists participated in a series of presentations and small group discussions focused on the four types of biomarkers: diagnostic, predictive, prognostic and surrogate. From there, new ideas emerged in the areas of imaging, validating diagnostic approaches, composite scoring and new ways to analyze historical data and tissue samples.

**December 2014:** Biomarker Innovation Grant (BIG) was launched, 14 LAM scientists and clinicians sent in letters of intent in search of grant money to begin their LAM biomarker pilot projects.

**February 2015:** Final grant submissions were received and peer-reviewed by The LAM Foundation Scientific Advisory Board (all volunteer board) who discussed and prioritized most promising projects.

**March 2015:** LAM Foundation Board of Directors considered recommendations from the Scientific Advisory Board and six projects were approved and funded.

The first ever LAM Foundation Biomarker Innovation Grants (BIG) were awarded at the Friday Night Awards Banquet at LAMposium. Congratulations to Brian Bartholmai, MD, Elizabeth Henske, MD, Simon Johnson, MD, David Kwiatkowski, MD, PhD, Carmen Priolo, PhD, and Raymond Yeung, MD.

**September 2016:** Projected final reports on outcomes of BIG projects.

Collaboration = Funded research and new discovery. This is the equation and meaning behind STRONGER TOGETHER!
Dr. Larkins is a woman’s health physician and expert in menopause and helping women manage hormone issues. She offers her expert advice to women with LAM related to these women’s health questions.

Dear Dr. Larkin:
I am a woman with LAM and have experienced multiple bladder infections. The prescribed treatment includes vaginal estrogen (Estrace, 2 grams, 2x/week). I asked my urologist if he could do a blood test for estrogen before I started and then while using the cream to see how much estrogen was getting into the blood. He said the tests were too inexact. He was unfamiliar with LAM.

You must have lots of LAM patients—older women with bladder infections. I asked for the smallest amount of estrogen possible. The 2 grams seems like a lot. Is there something better from the point of view of LAM that I could be using? The Estrace (plus lots of water) seems to be doing the trick.

Signed
Wary of Estrogen

Reply: Dear Wary of Estrogen:

You are wise to pay attention to your estrogen levels. Here are some points that may help you:

1. The dose you have been prescribed is correct. One gram (1 gm) of CREAM is only 0.1 mg of estradiol. It is the cream VEHICLE that is being measured. The cream is still very low dose. Using 2 gms of cream two times per week mean you are using 0.4 mg of estradiol per week, or about 20 mg of estradiol per year. That is equivalent to 20 birth control pills IF all of the cream was absorbed (which it is not). It is still a small amount; I predict that you would do fine with decreasing to 1 gram of cream 2 times per week. Vagifem tabs are even lower in estrogen—the standard prescription is one 10ug tab 2 times per week which equates to 1mg estradiol per year, the equivalent of one birth control pill a YEAR. The Estring is 2 mg of Estradiol per 90 days or 8mg per YEAR (8 birth control pills).

2. When a patient uses vaginal estrogen, the first few DAYS to 1-2 weeks there might be a MINIMAL increase in serum estradiol levels. There is a little more absorption when the vagina is very atrophic (a tree will soak up tons of water very quickly if the ground has been very dry for a long time) but as soon as the vagina is well estrogenized, the absorption is MINIMAL. In fact there are several studies that document that serum estradiol levels do not change, and remain in the post-menopausal range with vaginal estrogen use.

3. It IS possible to measure serum estradiol levels before and after vaginal estrogen use—this is commonly done to reassure breast cancer patients that their levels do not change. I think it is very reasonable to do this. A suggestion would be to only measure the estradiol level before use and then wait about 4 weeks before measuring the level again (the estradiol needs to use it regularly for those 4 weeks to estrogenize the vagina).

4. A recommended regimen for this patient would be an ESTRING in the vagina every 90 days) and then a tiny pea size amount of estradiol placed directly on the urethra at bedtime a few times per week. The cream is perfectly reasonable, but the ESTRING delivers the estrogen slowly over 90 days and there is no peak or trough. Oncologists like it the best of the 3 options adding the drop of cream will help to prevent the UTIs you need to estrogenize the tip of the urethra (to allow for the mucous barrier to return) and the ring does not get estrogen to the urethra.
Causes of Chylothorax in LAM: It is Not (Always) What you Think.

BY MAXIM ITKIN, MD, PHILADELPHIA VA MEDICAL CENTER AND FRANK MCCORMACK, MD, LAM FOUNDATION SCIENTIFIC DIRECTOR

The lymphatic system is a one-way circulatory network, which returns tissue fluid to the blood circulation, transports immune cells to lymph nodes, and assists with absorption of dietary fat and other nutrients. Our lymphatic system begins as a network of tiny channels at the tips of fingers and toes, and proceeds to larger and larger vessels analogous to small creeks becoming streams and finally a river that flows toward the abdomen. Once in the abdomen, nutrients are dumped into the flow for transport into our blood stream. The fats from our foods are packaged into small particles called chylomicrons, which give chyle its characteristic white color. Chyle originates in cells that line the small bowel and is transported through intestinal lymphatic vessels in the bowel wall and support structures, and is then transported into the cisterna chyli and thoracic duct. The thoracic duct transports chyle through the chest cavity to the great veins in the neck. If the lymphatic system becomes blocked at any point with LAM cells, chyle can “reflux” or flow backwards into other areas. Leakage of the chyle into the chest cavity results in a pleural effusion, which just means fluid in the chest, called chylothorax, which occurs in about a third of patients with LAM. Leakage of chyle into the abdomen (chylos ascites) or pericardium, the walled sac containing the heart, are complications of LAM.

Conventional wisdom once held that the injury or obstruction of the lymphatic channels above the diaphragm is the primary cause of chylothorax. For that reason, interventional therapies were directed toward the interruption of the flow in the thoracic duct by surgical thoracic duct ligation (tying of the thoracic duct) or obliteration of pleural cavity by pleurectomy (a procedure that adheres the outside of the lung to the inside of the chest cavity). Because more recent advances in the imaging of the lymphatic tree have revealed that chylothorax from sub-diaphragmatic causes occurs with some frequency in LAM, alternative approaches to this problem are required.

The key to understanding the pathophysiology of body fluid flow disorders is imaging. Until recently the imaging of the lymphatic system lagged behind the imaging of the vascular systems, primarily because of difficulties introducing contrast material into the lymphatic vasculature. Conventional lymphangiography, in which the dye is used to produce an X-ray image of the lymph vessels and nodes, and lymphoscintigraphy in which a radioactive material is used for the same purpose, are outdated methods that lack sufficient spatial resolution and robustness for imaging the entire lymphatic system.

The recent development of improved technology for imaging of the lymphatic system and image-guided interventions have provided an opportunity to better understand and address the causes of non-traumatic chylothorax. A widely available, non-invasive procedure called non-contrast MRI lymphangiography utilizes heavy T2 weighted MRI (an MRI view that almost any scanner can produce, like changing your camera setting from color to black and white) sequences to allow visualization of the thoracic duct and abnormal lymphatic structures such as extra-pulmonary LAM. Contrast enhanced MR lymphangiography is a new technique in which contrast material (gadolinium) is injected into the groin lymph nodes during MR imaging. This technique allows dynamic imaging of the flow of the lymph, lymphatic leaks, and abnormal perfusion patterns.

Using these imaging techniques over the last few years, we have learned that there are three anatomic origins for non-traumatic chylothorax:

1. Chylous ascites (chylo leaks into the abdomen)
2. Occlusion of the thoracic duct
3. Leakage from the retroperitoneal lymphatic masses (extra-pulmonary LAM)

In cases in which chylothorax arises from chylous ascites (chyle leaks into the abdomen) chyle migrates into the chest through tiny holes in the diaphragm. The existence of the communications between the abdominal cavity and chest through the holes in the diaphragm has been known for many years. Negative pressures in the chest during normal breathing cause chyle to be suctioned from the abdomen into the pleural cavity.

When lymphatic channels are blocked by LAM cells or masses, the lymphatic system bypasses the blockage by development of a system of collateral lymphatic vessels. If one of these collateral vessels courses near the lining of organs in the chest or abdomen, it can rupture and cause a chylous leak into a potential space such as the peritoneal, pleural, or pericardial cavities.

Retroperitoneal lymphatic masses are often present in patients with LAM. Chyle leaking from these masses can migrate through tissue planes and spaces in the abdomen and chest and appear as chylothorax.

The key for successful treatment of non-traumatic chylothorax is an understanding of the source of the specific chyle leak. Interruption of the flow in the thoracic duct below the leak by surgery or percutaneous embolization can cure chylothorax. However, that strategy can make chylous leaks worse in patients with weeping retroperitoneal masses or chylous ascites.

The preferred treatment of chylothorax originating in abdominal LAM masses is the injection of agents that close off lymphatic channels with glue or scar. Due to complex structure and interconnected nature of these masses, the main challenge to effective treatment is locating the leak. The “trial and error” treatment approach can take many hours and several sessions to complete.

Interventional or surgical treatment of chylous ascites remains a significant treatment challenge due to difficulty in visualization of the intestinal lymphatic ducts and the leak. In essence, the dye injected into the gut to find the leak does not course upstream into the feeding tributaries that are draining the leaking masses, so it is difficult to “see” the source of the leak.

Over the years, we have developed an algorithm to diagnose and treat non-traumatic chylous effusions. We first perform non-contrast and contrast enhanced MRI in order to identify presence of chylous ascites, to visualize the thoracic duct and lymphatic malformations, and to determine the patterns of the lymphatic flow. These studies can be completed at the referring institution for patients that require consultation or who are being considered for a future lymphatic intervention. We then perform intranodal lymphangiography in order to confirm the MR findings and direct the treatment. In cases of occlusion of the thoracic duct or thoracic duct leak, thoracic duct embolization can cure chylothorax. If thoracic duct flow is normal, thoracic duct occlusion should be avoided. Often, the simple introduction on an oil-based contrast agent can facilitate closure of the leak.
Low Dose or Not Low Dose, That is the Question—But What is the Answer?

BY BRIAN BARTHOLMAI, MD, ASSOCIATE PROFESSOR OF RADIOLOGY, DIVISION CHAIR FOR RADIOLOGY INFORMATICS, MAYO CLINIC, ROCHESTER, MINNESOTA

For both the initial diagnosis of pulmonary disease and the monitoring of changes over time radiologic imaging is key. Chest radiography (x-ray) is a low-cost and low radiation dose tool that provides a highly useful overview of the chest. However, radiography provides images with numerous overlapping structures. Often, radiography cannot demonstrate subtle changes or differentiate pathological changes definitively. Computed tomography (CT) also uses x-rays, but this technology makes numerous high-resolution 'slices' that can be less than 1 mm thick and show small blood vessels, airways, lung tissue and changes due to disease in exquisite detail. The brightness values of the CT pixels represent the density of materials such as air, fat, water, calcium and metal that be measured, tracked over time and may be helpful in predicting prognosis. [1]

One of the drawbacks of radiography and CT is the potential risk from radiation. Some radiation, measured in milliSieverts (mSv), is unavoidable. Average annual background exposure is around 3 mSv. The radiation for a two-view chest x-ray is extremely low, about .05 mSv, while a chest CT scan is around 5-7 mSv. [2]

Extremely high doses of radiation can cause immediate tissue damage, such as with radiation therapy, but the direct effects of radiation are not typically evident. Increases in cancer for people exposed to radiation following Hiroshima and Nagasaki demonstrates that radiation can cause genetic damage. However, a 2006 National Research Council report [3], notes that “At doses of 100 mSv or less, statistical limitations make it difficult to evaluate cancer risk in humans.” For monitoring of known disease such as changes in pulmonary cysts, fibrosis or some types of infection, low dose technique should allow sufficient quality to answer the diagnostic question. In general, for characterization of disease at baseline, detection of subtle or very small abnormalities and or evaluation of potentially life-threatening problems such as blood clots in the pulmonary vessels, a scan obtained with the highest quality imaging at regular dose is reasonable. Advances in CT technology in the last few years have allowed for improved image quality at lower dose. A 'low dose' chest CT can be performed with 5-10 times less radiation than 10 years ago, around 1-2 mSv. For lung nodule detection, a next-generation CT scanner administers a mere 0.06-mSv, nearly equivalent to a radiograph. [4]

The key questions for patients with LAM are most commonly: When is a chest x-ray or CT scan is needed? Should the CT scan be routine or low-dose technique? The answer depends on the individual and reason for the test. Obviously, for both cost considerations and radiation risk, no procedure should be performed that is not medically necessary. It is essential to keep in mind that the risk of death from diagnostic medical radiation remains much less than other common activities such as driving a car or walking across a street. [5]

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The International LAM Research Conference: Basic Science Overview
BY VERA KRYMSKAYA PHD, MBA, ASSOCIATE PROFESSOR OF MEDICINE, PERELMAN SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA

There were five general basic science themes covered:
1. Advancing mTORC1 signaling
2. Lymphatics and inflammation in LAM
3. Hormonal regulation in LAM
4. Lung destruction in LAM
5. LAM cell of origin

ADVANCING MTORC1 SIGNALING

Brendan Manning, PhD (Harvard University’s School of Public Health and the Dana-Farber/Harvard Cancer Center) studies how the mTOR signaling network coordinates nutrient availability with metabolic responses and how dysregulation of this network contributes to cancer and other diseases, including TSC and LAM. Dr. Manning’s presentation was focused on defining the role of TSC complex in the suppression of LAM. The mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) has the ability to sense and integrate growth signals in various forms, including intracellular nutrients and energy, growth factors, and cellular stresses. Multi-site phosphorylation of the TSC2 protein, within a complex with TSC1 and TBC1D7, downstream of distinct signaling pathways appears to account for much of mTORC1’s signal-integrating capacity. Through unbiased genomic and metabolomic approaches, he has found that, in addition to its established role in promoting protein synthesis, mTORC1 stimulates changes in specific metabolic pathways to promote anabolic cell growth and proliferation.

Kun-Liang Guan, PhD (University of California, San Diego) studies signaling mechanisms of cell growth, organ size control and tumorigenesis, particularly focusing on the mTOR and Hippo pathways. He presented on mTOR signaling in nutrient signaling and autophagy regulation. The AMP activated kinase (AMPK) and the mechanistic target of rapamycin (mTOR) are key intracellular signaling molecules that are regulated by nutrient status. AMPK is activated whereas mTORC1 is inhibited by nutrient limitation. They display opposite effects on cellular metabolism and growth. AMPK promotes autophagy while mTORC1 inhibits autophagy. Investigation of the mechanism of mTOR regulation by amino acids demonstrated that different amino acids use different mechanisms to activate mTOR. Leucine and glutamine act through Rag GTPases and Arf1 GTPase, respectively, to activate mTOR. Dr. Guan’s study showed that AMPK and mTORC1 regulate the autophagy initiating protein kinase ULK1 and the autophagy machinery VPS34, which is a lipid kinase critically important for intracellular vesicle trafficking and autophagosome formation. Further, his study revealed a molecular link from nutrient status, to intracellular nutrient sensor/integrator and eventually the regulation of autophagy.

John Blenis, PhD (Weill Cornell Medical College) is focused on defining critical signal transduction mechanisms and how altered cellular signaling promotes carcinogenesis. Dr. Blenis presented on mTORC1/S6K1 control of tumor metabolism. The mTOR Complex 1 (mTORC1) signaling pathway has evolved to sense and respond to cellular energy status, nutrient availability and surrounding oxygen concentrations. In addition, mTORC1 can be further activated by mitogen- and hormone-activated AGC kinases including Akt and RSK, and suppressed by mTORC1 and/or S6K1 via a variety of negative feedback loops. The integration of these multiple inputs control the strength and duration of downstream signaling, which is important in differentially regulating a variety of mTORC1 dependent processes. He has investigated the mTORC1 phosphoproteome and metabolome using mass spectrometry-based analysis. These studies have identified many novel targets that are revealing new connections between mTORC1, S6 kinase and various links to gene expression, mRNA metabolism, protein production and cell metabolism; biological processes critical to the control of cell growth. He discussed the characterization of new molecular targets and biological processes and also provided evidence that targeting nutrient metabolism in cancer cells with activated mTORC1 may provide an important therapeutic opportunity.

Marina Holz, PhD (Yeshiva University and the Albert Einstein College of Medicine) presented that resveratrol in combination with rapamycin reduces TSC2-null xenograft tumor growth. Dr. Holz’s study demonstrated that the addition of resveratrol to rapamycin treatment may be a promising option for selective and targeted therapy for diseases with TSC2 loss and mTORC1 hyperactivation.
Melody A. Swartz, PhD (University of Chicago) is trained as a bioengineer and she uses quantitative approaches in cell biology and physiology, including biotransport and biomechanics, to investigate the role of the lymphatic system in immunity and pathophysiology, particularly in cancer metastasis. Dr. Swartz presented on deciphering the complex roles of lymphatic vessels in modulating immunity. In tissues, interstitial fluid flow is mechanically coupled to lymphatic drainage, and both are often increased in inflammation as well as in the tumor microenvironment. It has long been assumed that local lymph formation is driven primarily by pressure gradients generated by downstream lymphatic pump function, but she found that vesicular transendothelial transport also contributes significantly to lymph formation and is actively regulated by the lymphatic endothelium according to inflammatory stimuli, allowing fine-tuning of the transport of antigens, cells, and chemokines to the local lymph node. But why does lymphatic transport need to be actively regulated, if its primary function is to merely drain excess fluid from the interstitium to prevent swelling? In exploring this question, she is finding lymphatic transport to play fundamental roles in fine-tuning immune responses and regulating the presentation of abundant self-antigens for deletion of autoreactive T cells. At the same time, inflammatory lymphangiogenesis coupled with increased interstitial flow drives fibroblast activation and stromal changes that promote matrix alignment and stiffening as well as, simultaneously, immune suppression. In the tumor microenvironment, these factors synergize to promote escape from host immunity, which is presumably necessary for metastasis. Together, her findings help to define new immunomodulatory roles for lymphatic vessels in inflammation and cancer.

Caroline Le Poole, PhD (Loyola University Medical Center) presented on modeling LAM therapy by chimeric antigen receptor (CAR)-transduced T cells in mice. Dr. Le Poole’s study identified GD3 as a surface molecule up-regulated on LAM cells. Up-regulation may be a direct consequence of mTOR dysregulation in TSC mutant cells. This also holds true for cell line LAM10224, derived from a patient with mild disease whose diagnosis of LAM was confirmed by HMB45 immunostaining of lung biopsy tissue. GD3 thus offers a potential target for immunotherapy. In vitro and in vivo data suggest that the treatment potential of CAR transduced T cells can well be assessed in human LAM cell challenged SCID/beige mice. If proven effective and safe in repeat experiments, adoptive transfer of CAR transduced T cells may be readily translatable to the treatment of human LAM.

Elena Atochina-Vasserman, PhD, MD (University of Pennsylvania) presented on how pharmacological targeting of VEGFR signaling inhibits TSC2-null lesion growth in the lung. LAM severity correlates with the degree of lymphatic vessel density in the lung and up-regulation of serum VEGF-D, a predictor of the LAM prognosis and potential response to treatment. The VEGF-D activates VEGFR2/3, which has not been targeted therapeutically in LAM. FDA-approved axitinib is a small-molecule inhibitor of VEGFR1, VEGFR2/3. Dr. Atochina-Vasserman’s data demonstrate that pharmacological inhibition of VEGFR signaling with axitinib has a potential beneficial effect in decreasing VEGF-D levels, lymphangiogenesis, inflammatory lung response, and Tsc2-null lesion growth, and suggests a potential therapeutic benefit of targeting of VEGFR signaling for treatment of LAM.

Yang Sun, PhD (Harvard Medical School and Brigham and Women’s Hospital) presented that Pg and E2 synergistically promote the lung metastasis of TSC2-deficient cells in a preclinical model. His data indicate that estradiol and progesterone synergistically increases the metastatic potential of TSC2-deficient LAM patient-derived cells in vitro and lung metastasis in vivo. Thus, targeting both of estradiol and progesterone-mediated signaling events may have therapeutic benefit for LAM and possibly other hormonally dependent cancers.

Jeanine D’Armiento, MD, PhD (Columbia University Medical Center) presented her recent findings leading to insight into lung physiology and pathology through understanding the mechanisms altering lung injury and repair and translating these findings into practical clinical solutions. Recent collaborative studies between her group and Dr. Paul Eklington (Southampton, UK) have shown that in tuberculosis the expression of MMP-1 is critical for the development of cystic lesions. Animals that do not express MMP-1 do not develop destructive cystic lesions. Investigators have shown that the proliferating smooth muscle cells in Lymphangiomymomatosis secrete a variety of proteases. Her group investigated whether the LAM cell expressed collagenolytic enzymes, hypothesized to be necessary for cyst formation. Interestingly, LAM cells express two collagenolytic enzymes, MMP-1 and MMP-14, which are not found in the healthy lung. Given the known importance of collagenolytic enzymes in cyst formation of other lung diseases it is likely that these enzymes are contributing to the destructive lung lesions seen in LAM. Based upon...
these findings in disease, inhaled inhibitors of the collagenolytic metalloproteinases are actively being developed in her laboratory with anticipation that delivery of such compounds will protect the lung from destructive injury in the chronic disease state.

Victoria Stepanova, PhD (University of Pennsylvania) presented on urokinase type plasminogen activator (uPA) in the pathogenesis of LAM. Her data implicate uPA as a novel mediator through which TSC2-null tumors destroy lung parenchyma, identify new approaches to regulate expression of uPA in TSC-compromised cells, and position uPA as an attractive target for potential combinational therapy to enhance the effectiveness of rapamycin monotherapy in LAM patients.

Maya E. Kumar, PhD (Stanford University School of Medicine) presented on defining a mesenchymal progenitor niche at single cell resolution. Most vertebrate organs are composed of epithelium surrounded by support and stromal tissues formed from mesenchyme cells, which are not generally thought to form organized progenitor pools. She described the use of clonal cell labeling with multicolor reporters to characterize individual mesenchymal progenitors in the developing mouse lung. Through such single cell labeling, she observed a diversity of mesenchymal progenitor populations with different locations, movements, and lineage boundaries. Airway smooth muscle (ASM) progenitors map exclusively to mesenchyme ahead of budding airways. Progenitors recruited from these tip pools differentiate into ASM around airway stalks; flanking stalk mesenchyme can be induced to form an ASM niche by a lateral bud or by an airway tip plus focal Wnt signal. Thus, mesenchymal progenitors can be organized into localized and carefully controlled domains that rival epithelial progenitor niches in regulatory sophistication.

Debbie Clements, PhD (University of Nottingham, UK) presented on recruitment of fibroblasts in pulmonary LAM. She demonstrated CXCR4-dependent recruitment of fibroblasts by TSC2-/- cells, and identified proteases which may be activated via the interaction between these cell types. Dr. Clements will use her established 3D models of LAM to further investigate the regulation of proteolytic activity in these co-cultures.

Magdalena Karbownikczek, MD, PhD (Texas Tech University Health Science Center) presented on the neural crest origin of angiomyolipoma and leads to phenotype spreading. Her study suggests that AML cells are predestinated NC-derived neurons lacking capability to achieve terminal differentiation as a result of Notch/Rheb/miR34.

The International LAM Research Conference: Clinical Science Overview

BY JEFF SWIGRIS DO, MS, LAM CLINIC ASSOCIATE DIRECTOR, NATIONAL JEWISH HEALTH, DENVER

Four general clinical themes were covered during the scientific sessions:
1. Imaging LAM
2. Patient contributions to advancing knowledge in LAM: from cells to perceptions
3. Biomarkers for LAM
4. LAM pathogenesis

Joel Moss, MD, PhD (National Institutes of Health (NIH)) kicked off the scientific meeting with a talk focusing on two topics: 1) heterogeneity among patients with LAM; and 2) quantifying LAM-related findings on high-resolution computed tomography (HRCT). Dr. Moss discussed the variability LAM cells possess in their morphology, surface receptor expression, and genetics and how this variability likely plays a large role in phenotypic heterogeneity—how LAM manifests in a particular patient and whether/how well it responds to rapamycin (or rapamycin analogs). Dr. Moss spent the second half of his talk discussing recent work from his lab on HRCT, and how he and his co-investigators are using HRCT to quantify cyst burden, pneumothorax and subtle parenchymal abnormalities adjacent to cysts. Most interesting, microscopically, in LAM, the peri-cystic parenchyma is emphysematous; this is a finding that is impossible to appreciate when viewing the HRCT with the naked eye but can be captured with sophisticated software-directed texture analysis of the HRCT. This software, developed by Dr. Moss and his NIH collaborators,
allows quantification of these metrics while exposing patients to a fraction (10% or less) of the radiation they would be exposed to if undergoing a “standard” HRCT. Dr. Moss’s lab is now working to make this software available at LAM centers outside the NIH and to better understand what these quantified metrics can teach us about how a patient’s LAM will behave over time.

Maxim Itkin, MD (University of Pennsylvania) talked about imaging and treating leaks in the lymphatic duct. Dr. Itkin described how he injects contrast into inguinal lymph nodes and then uses MR imaging to follow the contrast as it navigates its way up the thoracic duct. This technology produces clear images of tortuous lymphatic ducts and branches; aberrant vessels; reflux of lymph fluid into the lungs; leakage of lymph into the thorax, pericardium or peritoneum and other lymphatic-related, extrapulmonary manifestations of LAM. His talk included incredible video clips of lymphatic leaks identified on chest imaging and how he intervenes to correct them. He described his technique of using “coil and glue” to embolize the lymphatic duct and sclerotherapy to permanently close off leaking and non-leaking collateral lymphatic vessels. Dr. Itkin’s pioneering work has helped make such percutaneous techniques the gold standard in treatment of chylous leaks.

Yuen-Yi (Moony) Tseng, PhD (The Broad Institute) gave a talk on building next-generation patient derived models to elucidate LAM pathogenesis. Dr. Tseng described the ambitious goals of her team to generate fully-characterized, completely genotyped cell models for many tumor types, including LAM and angiomylipoma (AML). She described the process they use to collect samples, develop single cell suspensions, grow cells in a “cell nursery” and then conduct verification studies to assess the purity of the model before banking. She aims to use these techniques to fully develop a “cell line factory” to serve the scientific community. Dr. Tseng painted a picture of the future in which a physician could collect a biospecimen from a patient and send it to the “factory” where the cell would be grown and immortalized, allowing for testing of various therapeutic agents on it. At present, she has 8 LAM and 21 AML samples at various stages in the “factory”.

Kristen Holm, PhD, MPH (National Jewish Health, Denver) delivered a talk on patient-reported attitudes and beliefs about supplemental oxygen. Dr. Holm presented her work on developing instruments aimed at capturing chronic obstructive pulmonary disease (COPD) patients’ attitudes and beliefs around supplemental oxygen (O2). Specifically, she seeks to determine how decisional balance (a weighing of the pros and cons), teamwork standards (is O2 use viewed by patients and their partners using a “team” approach or a “patient-only” therapy), and health-related social controls (e.g., nagging by a loved one) affect oxygen adherence among patients with COPD. Although her work is in patients with COPD, not LAM, she drew on a subset of her data (from the young females in her cohort) to shed light on some of the attitudes and beliefs that LAM patients who need O2 might have. She noted that young females in her study were less likely than other patients to be adherent with using O2; and young females were less likely to perceive “pros” of using O2, and are more likely to perceive “cons” of using oxygen. Thus, she concluded that when it comes to encouraging patients with LAM to adhere to O2, it likely will be more effective to focus on the anticipated benefits—rather than the potential downsides (e.g., social stigma) of O2.

Jeffrey Swigris, DO, MS (National Jewish Health, Denver) discussed health-related quality of life (HRQL) in LAM. He described how, on average, patients with LAM have impaired HRQL in various domains, including those in the physical health and emotional well-being domains. He discussed his lab’s ongoing efforts to develop a LAM-specific instrument to assess HRQL called ATAQ-LAM (A Tool to Assess Quality of Life in LAM). His goal is to have ATAQ-LAM be included as an endpoint in future trials of novel therapy for LAM.

Kuniaki Seyama, MD, PhD (Juntendo University School of Medicine, Japan) talked about circulating endothelial growth factors in LAM. He began by reviewing the vascular endothelial growth factor (VEGF) family and then showed data on how VEGF-D levels in patients with LAM are markedly higher, VEGF-C levels in patients with LAM are somewhat higher and VEGF-A levels in patients with LAM are no different from normal controls. He reviewed how VEGF-D levels in chyle are two times greater than levels in the blood in patients with LAM. Dr. Seyama showed some data to suggest that LAM cells produce VEGF-D. He showed how treatment with sirolimus decreases VEGF-D but not VEGF-C levels. He capped off his talk by showing how, in 10 LAM patients, pregnancy did not change FEV1 slope.

Lisa Young, MD (Vanderbilt University Medical Center) spoke on VEGF-D as a biomarker in LAM. Vascular endothelial growth factor-D (VEGF-D) is a lymphangiogenic growth factor that plays a key role in tumor metastasis and is now regarded as a serum biomarker in LAM. Specifically, serum VEGF-D levels are elevated in most (but not all) patients with LAM, and levels correlate
with certain measures of disease severity. Why serum VEGF-D levels are normal in a significant minority of women with LAM is not clear. She reviewed diagnostic test performance characteristics of VEGF-D and its utility as a prognostic marker. She sees potential for VEGF-D as a surrogate outcome measure of treatment response. Dr. Young reminded the audience that although data on VEGF-D in LAM continue to grow, there remain many unanswered questions about LAM pathogenesis and the role of VEGF-D. In 2011, serum VEGF-D quantitation became available as a clinical test in the United States.

**LAM PATHOGENESIS**

Vera Krymskaya, PhD, MBA, (University of Pennsylvania) gave a talk on VEGF-D, lymphangiogenesis, and airspace enlargement. Clinical evidence demonstrates that LAM severity correlates with the degree of lymphatic vessel density and with serum levels of the pro-lymphangiogenic vascular endothelial growth factor D (VEGF-D). Although, LAM disease has been linked to up-regulation VEGF-D, and therapy with sirolimus leads to reductions in serum VEGF-D, it is unclear whether upregulation of VEGF-D plays a protective or pathogenic role in LAM. Dr. Krymskaya offered up excessive lymphatic vessel sprouting as a process contributing to—or driving—lung remodeling processes that underlie airspace enlargement and lung destruction. She reminded the audience that three very important key questions remain to be answered in this arena: 1) what is the mechanism of VEGF-D up-regulation in LAM, 2) do abnormal lymphatics contribute to cyst formation characteristic of LAM, and 3) can VEGF-D signaling and neo-lymphangiogenesis be targeted therapeutically?

Cheryl Walker, PhD (MD Anderson) gave a talk on how the combination of a person’s genes and the environment in which they have lived (or things to which they have been exposed) can determine whether and when a disease might occur later in life. This gene-environment interaction (G by E; or G x E) influences (and in certain cases, inappropriately modifies) the “reading,” “writing” and “erasing” of our epigenome and creates a specific genetic program for an individual. Dr. Walker highlighted that, amazingly, exposures that occur perhaps very early on in development can dictate survival/disease susceptibility in adult life. She went on to explain how these findings are applicable to TSC gene-related diseases, like LAM: (from her abstract) the penetrance of a TSC2 gene defect is profoundly affected by exposures to endocrine disrupting chemicals (EDCs) during development. In the uterus, this reprogramming causes estrogen responsive genes to become hyper-responsive to hormones, exaggerates the effects of normal levels of ovarian hormones on this tissue, and dramatically increases the penetrance of a TSC2 defect. Very little is known about the contribution of environmental exposures to TSC-linked diseases, and these studies point to the importance of both the epigenome and the environment as determinants of penetrance, and perhaps severity, of diseases such as LAM that occur in TSC patients.

Jane Yu, PhD (Brigham and Women’s Hospital) gave a talk on the dysregulation of prostaglandin metabolism and action in LAM progression. Prostaglandin (PGE2) biosynthesis is upregulated in TSC2-deficient, LAM patient-derived cells and in women with pulmonary LAM. Dr. Yu and members of her lab aimed to identify the cellular impact of PGE2 and its receptors (EP1-4). Expression of the PGE2 receptor, EP3, was upregulated in TSC2-deficient LAM patient-derived cells compared to TSC2-addback cells, and she found abundant accumulation of EP3 in LAM lung lesions compared to adjacent normal tissues. Importantly, a specific EP3 antagonist, L-798106, suppresses the growth of TSC2-deficient cells in a dose-dependent manner. In vivo, L-798106 treatment resulted in a reduction of lung colonization of TSC2-null ELT3 cells using non-invasive bioluminescent imaging. Dr. Yu’s innovative work raises the question of whether targeting the prostaglandin pathway—with agents like aspirin or celecoxib—could yield a viable therapeutic option for patients with LAM.

Guillermo Oliver, PhD (St. Jude’s Children’s Hospital) spoke on the lymphatic vasculature in health and disease. He reminded the audience that most lymphatic vessels do not contain smooth muscle and that large—but not small—lymphatic vessels are surrounded by pericytes. Lymph vessel cell progenitors actually start their lives in the walls of veins and migrate from the vein wall to form lymphatic vessels. Proxl is a specific lymphatic endothelial cell marker, and if this signal is removed, lymph vessel cells will migrate back to blood vessel walls. Interestingly, Proxl heterozygote mice (most die at birth with chylosus ascites and/or chylothorax, but some live) develop late onset obesity. Dr. Oliver described how vascular endothelial cells are heterogeneous—they express different surface markers in different organs, within different regions in the same organ, and within the same organ at different stages of development. Emerging data from his lab suggest the same is true for lymphatic endothelial cells. He reminded the audience that lymphatics play a significant role in immune function, inflammation and metabolism—leaky lymphatics promote visceral adiposity. Before closing, he commented on how further study of Schlemm’s Canal, a hybrid lymph/blood vessel in the eye, may hold the key to better understanding and treating glaucoma.
Lisa Henske, MD (Brigham and Women’s Hospital) closed the scientific session with a talk on the role of microRNA in LAM pathogenesis and therapy. MicroRNAs (or miRs) are recently discovered, non-coding RNA fragments that can fine-tune gene expression by silencing messenger RNA by destabilizing or destroying it. Small changes in miR levels, even as little as 1.2-fold, can have large downstream effects, since a single miR can regulate dozens of genes. Selected miRs, termed “oncomiRs” appear to promote cell survival, growth, proliferation, migration, and invasion in benign and malignant diseases. The role of miRNA in TSC and TSC therapeutic responses represents a key knowledge gap. Dr. Henske’s lab has discovered that many miRs are regulated by mTORC1 and that several miRs are up-regulated in the presence of rapamycin. She discovered that miR-21 (microRNA-21) is the miR most elevated in response to rapamycin. She calls miR-21 and the other rapamycin-dependent microRNA “RapaMiRs.” Dr. Henske postulated that miRs could play a role directing the effects of rapamycin on cell growth and survival in LAM, and ongoing work in her lab seeks to determine if miRs could serve as biomarkers of rapamycin response.

LAMposium 2015

This year’s International LAM Research Conference and LAMposium is being described as an exceptional, unique and inspiring conference. Nearly 120 women with LAM - from 8 different countries gathered for a second year in Chicago, IL, and 17 of those patients attended for the very first time. Also in attendance were 120 family members and friends along with 108 scientists and clinicians. If you look at these numbers closely, you will see the ratio of patient to scientist/clinician is 1:1; remarkable for a rare disease conference.

Here are some of the fabulous highlights from the conference:

REMEMBRANCE ROOM

LAM Liaison, Sharlene Dunn Brells organized the inaugural Breath of Hope Remembrance Room, a quiet place to reflect and share memories of the courageous and beautiful LAM women who have passed before us. Sharlene’s inspiration for this room was the memory of her friend Patricia Marie Hovis.

FIRST TIME ATTENDEE ORIENTATION

Cheerleader and LAM Liaison, Marla Hamlin did a lovely job of getting women with LAM, who are new to the conference, up to speed on everything LAMposium. “Marla was a warm, welcoming speaker, perfect for this audience. I counted 25 significant bits of information delivered efficiently and effectively. Bravo!” said a LAM patient attendee.

STRONGER TOGETHER: OPENING CELEBRATION

“A good way to create a ‘sisterhood link’ with audience participation”, was a quote offered about our Stronger Together: Opening Celebration. LAM Foundation Executive Director, Sue Sherman and LAMposium Medical Advisor, Dr. George Pappas, welcomed everyone by offering highlights for the weekend, giving Foundation news and community updates. The introduction of all women with LAM in the room gave everyone a chance to “put a face with a name”.

Congratulations to Andrea Byrnes, who inspired her Mom, Sue Byrnes, to create The LAM Foundation! Andrea was presented with this year’s LAM Quilt.

Thank you to Stacey Wheelus for assembling the 2015 LAM Quilt. Stacy and 35 women lent their “hands” to the beautifully hand sewn quilt.

Money donated to the quilt will go to the LAM Family Network (LFN) which supplements travel expenses for women with LAM who want to attend LAMposium but otherwise could not afford to. Read more about the LAM Family Network (LFN) on page 20.
LAM LIAISON MEETING

Our LAM Liaisons, from across the country, had an opportunity to get together for a working lunch. The Liaisons participated in a communication and an advocacy presentation to help in their efforts to raise LAM awareness. Jackie Reau, a PR Consultant, worked with the Liaisons on building awareness and enticing media attention for LAM. Christina Hamilton, The LAM Foundation Advocacy Board Chair, talked with the Liaisons about how to focus their LAM story with local, state and federal government officials.

Our LAM Liaisons work within their regions to gather women with LAM, family and friends for educational and social meetings. We hope you get a chance to join a regional meeting.

We would like to welcome some new LAM Liaisons to the group. Region 15, Texas, New Mexico and parts of Oklahoma now have LAM Liaisons; please welcome Maria Teniente and Frances Saldivar. Region 9, Indiana, Kentucky, Ohio, and West Virginia now have an additional LAM Liaison, Melaney Parrish. Welcome back Carmen Iglesias to Region 13 our Great Plains Region that covers Iowa, Kansas, Missouri and Nebraska. Welcome Reina Endo who will work with Sharlene Brels Dunn in Region 18 which covers Alaska, Oregon and Washington. And finally, Elena Perez Blair is going to start a new region, Region 21 in Puerto Rico. Thank you for being a part of this great group of volunteers!

A special Thanks goes to Lincare Respiratory Specialists who donated their time and O2 to our conference. For two days, women on oxygen therapy could talk with the Lincare specialists about new technologies in O2 therapy. They could also refill their oxygen tanks and re-charge their oxygen equipment. For some women, this meant they did not need to go back to their hotel rooms to refill their tanks.

RED CARPET PHOTOS

Everyone can be a star in front of our Red Carpet Banner. The Foundation now has a branded banner available for photos. We are not certain how many photos were posted, but the Red Carpet Banner was “the place to be and be seen” on Facebook, Twitter, Instagram and other social media outlets.

DISTINGUISHED FUNDRAISING AWARD WINNER REBECCA NISSLY

At the Friday Night Awards Banquet, Rebecca Nissly was recognized with the Distinguished Fundraising Award for initiating a $100,000 donation from Metamucil’s, “Do More Than You Think” campaign. 22,000 votes were cast, and Rebecca’s winning essay about The LAM Foundation received more votes than the seven other charity organizations. Women with LAM, families and friends around the world cast the winning votes.

A landslide victory for Rebecca and for LAM Research!

LAM LEADER AWARDS

2014 offered an extraordinary list of LAM Leader candidates including women with LAM who put together regional and community fundraisers; women with LAM who quietly changed the lives of others through their compassion and empathy, and those who selflessly volunteered for clinical trials and made their annual trips to the NIH. Every year –women with LAM have pursued hope, faced LAM with courage and cared for their sisters and families. Because of this, all women with LAM received this year’s LAM Leader Award.
International LAM Research Conference

Over 108 physicians and scientists attended two days of exceptional presentations and research updates at The International LAM Research Conference.

A significant moment for one professional was, “Hearing the patients share their experience during the scientific sessions.” Women with LAM inspire scientists and clinicians as they work to find better treatments, diagnostics and ultimately, a cure.

International LAM Research Conference Highlights:

This year, all nine LFSAA recipients were present. Seated left to right: Frank McCormack, MD; Elizabeth Henske, MD; Vera Krymskaya, PhD; Simon Johnson, Professor of Respiratory Medicine

Standing left to right: Yoshikazu Inoue, MD, PhD; Koh Nakata, MD, PhD; David Kwiatkowski, MD, PhD; Joel Moss, MD, PhD; Kuniaki Seyama, MD, PhD

Research grants for 2014 LAM studies were presented to:

Debbie Clements, PhD, from Nottingham University for her Pilot Award study, Investigating the Cross Talk Between LAM Cells and Recruited Stromal Fibroblasts.

Lisa Young, MD, from Vanderbilt University for her three year study on Lymphangiogenesis and Estrogenic Milieu and LAM Biomarkers.

Khalid Almoosa, MD, from University of Texas Health Center for his one year special project, Does Variability of Care Exist Among LAM Specialty Clinics.

Andrey Parkhitko, PhD, from Harvard Medical School for his 3 year Fellowship Award on A Cross-Species Approach to the Discovery of Genes Accelerating TSC/LAM Tumor Growth.

Raymond Yeung, MD, from University of Washington for his one year Pilot Award on Serum Metabolites in LAM.

The first-ever LAM Foundation Biomarker Innovation Grants (BIG) were awarded to:

David Kwiatkowski, MD, PhD
Carmen Priolo, MD, PhD
Elizabeth Henske, MD
Brian Bartholmai, MD
Simon Johnson, Professor of Respiratory Medicine
Raymond Yeung, MD

These grants were awarded as a result of the LAM Biomarker Innovation Summit held in November 2014. The LAM community and The LAM Foundation awarded a total of $185,000 in grants to these six recipients.

MDBR Grant Awardees

Congratulations go out to Million Dollar Bike Ride Grant Awardees, Vera Krymskaya, PhD, from University of Pennsylvania and Aris Astreinidis, PhD, from Texas Tech Health Sciences Center. LAM Foundation Donors met the UPenn matching funds challenge, for a total raised of $120,000 for the 2014 Million Dollar Bike Ride. Drs. Krymskaya and Astreinidis both received $60,000 for their LAM pilot studies.

Poster Awards went to:

Debbie Clements, PhD, best basic science poster award
Yang Sun, PhD, best translational science poster
Mariana Sponholz Araujo, MD, best clinical science poster

Congratulations and Thank You to all the scientists and clinicians who could join us at the conference, we are Stronger Together.
Stronger Together

The LAM Foundation is celebrating its 20th Anniversary and adopted the theme, “Stronger Together”. When Sue Byrnes created The LAM Foundation in 1995, she knew that hope starts with a conversation. Because of her courage and perseverance, today we are a global community of women with LAM, their families, scientists, clinicians, and external partners who have come to be…Stronger Together.

Stronger Together was evident at this year’s International LAM Research Conference, LAMposium and Breath of Hope Gala.

Take a look at the numbers:
• Over 350 women with LAM, family, friends, scientists and clinicians attended
• 16 countries were represented
• 118 LAM patients attended along with 120 family and friends
• 17 LAM patients attended the conference for the very first time
• 108 physicians and scientists attended and were inspired to help move LAM research forward faster
• An astounding 1:1 Patient to Scientist-Clinician ratio
• More than $210,000 was raised for LAM Research at the Breath of Hope Gala. 100% of which will directly fund LAM research
• 285 direct story links to medical and news websites who shared the inspiration of the International LAM Research Conference and LAMposium story and our partnership with Loyola University Health Center; resulting in…
• 59,667,276 media impressions

There were some new events added to this year’s conference. Thursday evening women with LAM, family and friends attended the annual social. It was also a great opportunity for first time attendees to make new connections and place a friendly face with those they met online.

The conference moved into full gear later that evening as Jeffrey Swigris, DO, MS, from National Jewish Health, gave the Conference Kick-Off presentation. His presentation, “Incorporating Patient-Centered Outcomes into LAM Research”, was well received. Newly diagnosed and first time attendee, Melaney Parrish took the time to share her story with everyone. Her vision of raising LAM awareness in her West Virginia hometown and across the US inspired the audience.

Combined breakfasts and lunches, throughout the weekend prompted conversations about exciting new LAM research and new connections were made while sharing a meal.

JOINT SESSION: WOMEN’S HEALTH FORUM

Hormones and the LAM patient is a topic of interest for professionals and women with LAM alike. This was the topic of a joint session panel discussion, Women’s Health Forum: Hormones and LAM Across a Lifetime. LAM Foundation Board Member, Geraldine Finlay, MD, moderated a panel of experts including MeiLan Han, MD, MS, University of Michigan; Kathleen Haegeger, MD, MPH, University of Rochester Medical Center; Lisa Larkin, MD, University of Cincinnati Medical Center; and Steven Hammes, MD, PhD, University of Rochester Medical Center.

BREATH OF HOPE GALA PLATINUM ANNIVERSARY CELEBRATION

It was the most successful year ever for the Breath of Hope Gala Platinum Anniversary Celebration. The Silent Auction cocktail party was a hit for everyone. The paparazzi did not arrive, but that did not stop everyone from taking a turn at the Red Carpet Banner.

A lovely dinner was served and the program was filled with many emotional highlights.

We celebrated 20 years of progress and pursuing a cure with three stories that demonstrate the real impact of what Sue Byrnes and Dr. Frank McCormack created when they started The LAM Foundation. Brian Kleps, emeritus board member, shared his story of participating in early letter writing campaigns and fundraising in memory of his wife, whom he lost to LAM before the Foundation was created.

Shelby and Zack Garner shared their experiences of fear and uncertainty which turned to hope and optimism when Shelby responded well to treatment -- an outcome from the groundbreaking MILES Trial that was supported by the Foundation and women with LAM during our second decade.

CONTINUES ON NEXT PAGE >
More than 100 women with LAM came to the dance floor to accept a rose and have their picture taken; they then donated their roses back to a nearby Chicago nursing home. Roses were distributed by LAM Clinic Directors, Robert Kotloff, MD, George Pappas, MD, Steve Ruoss, MD and Joel Moss, MD, PhD, from the NIH.

The rose ceremony ended with Dr. Clark Baxter playing the bagpipes in tribute to the 242 women who lost their battle with LAM. Their memories and friendship lives on in our hearts.

Funding for LAM research was accelerated as the Emcee for the night, Sherry Truhlar, entertained with an extremely generous Fund – A – Cure auction. Once the audience’s paddles were exhausted, applause for raising over $210,000 for LAM research erupted from the room.

And of course the night would not be complete without the party going into the late evening as the celebration continued with dancing and casino games.

When asked what was the most significant moment experienced at the LAMposium and the Breath of Hope Gala, one attendee said, “There were so many moments; it is hard to identify one. My husband attended with me and we are amazed at the collaboration and enthusiasm shown by everyone.”

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**Save the Date!**

Join us for the 2016 International LAM Research Conference and LAMposium at the Cincinnati Marriott at Rivercenter Covington, Kentucky

**September 22 – 25, 2016**
Thank you to our Loyal Sponsors for Their Support

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The LAM Foundation appreciates your generous gifts and is proud to have you as our partners in the fight to cure LAM.
Announcing The LAM Foundation’s 20|20|20 Campaign!

The 20|20|20 Campaign is a fundraising drive of The LAM Foundation which brings together families, friends, and communities to heighten awareness of LAM – a progressive lung disease – and to fund a breakthrough therapy for LAM...faster.

As recognition of the Foundation’s 20th anniversary, friends, families, and co-workers are inspiring 20 people in their communities to join them in giving $20 a month for 20 months. During this 20 month period, we will seek local, state, regional, and national attention for The 20|20|20 Campaign and the LAM Foundation. The initial sign-up for this first-ever 20|20|20 Campaign began on June 1, 2015 and continues through September 30, 2015.

Through the 20|20|20 Campaign, we will

- Heighten awareness of LAM across larger community circles
- Identify and provide support for more women with LAM
- Fund a breakthrough therapy for LAM...faster!

We are taking steps to create a world without LAM. Join us today!

Visit www.thelamfoundation.org and click on the 20|20|20 icon for details to:
- Launch your 20|20|20 Campaign.
- Support a 20|20|20 Campaign.
- Make your personal donation to the 20|20|20 Campaign.

You Can Bring More Women to LAMposium with $1:$1 Match

Generous donations to the LAM Family Network (LFN) make it possible for women with LAM to travel to the International LAM Research Conference, LAMposium and Breath of Hope Gala. This year, just over $11,000 in travel grants were awarded to 21 women with LAM who would not have attended without LFN support. Grants are awarded based on financial need and previous conference attendance.

The LFN Fund is generously supported each year by donors and proceeds from the LAM Quilt Project. For the first time ever, an anonymous donor has offered a dollar for dollar match, up to $10,000 to replenish the LFN Fund. That gives us the opportunity to raise $20,000 to bring more women to the 2016 LAMposium in Cincinnati.

If you are inclined to support women with LAM in their search for education, expert clinical advice, clinical trial opportunities and the empathy and support of the LAM Community, please consider donating to LFN between now and October 31, 2015. Traveling to the conference can be a remarkable experience for women who are newly diagnosed with LAM or who have never attended. Many women have never met someone else who has LAM and may not have access to LAM clinicians. By giving to the LFN Travel Fund you are giving these women a chance to connect and engage in community.

You can give three different ways:

1) Online at thelamfoundation.org by clicking on the DONATE NOW button and choosing LAM Family Network (LFN) in the drop down menu.

2) Use the Journeys donation envelope attached; indicate LFN MATCH on the Occasion Line.

3) Mail a check to The LAM Foundation and indicate LFN MATCH. Or call The LAM Foundation at 877.CURE.LAM (877.287.3526) or send an email to info@thelamfoundation.org.
The LAM Foundation would like to thank our many generous donors for their support.

This list reflects gifts made between July 1, 2014 and December 31, 2014

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The pink feather denotes donors who have included The LAM Foundation in their charitable estate plan. By doing so, they are now members of the Breath of Hope Legacy Society. To learn more, please contact The LAM Foundation at info@thelamfoundation.org. If you have made a planned gift to the Foundation, please let us know so we can recognize your name with a pink feather.

The MG denotes companies that offer matching gifts. If your company has a matching gift program, please contact your HR Department to find out how to request a matching gift donation to The LAM Foundation.
Lymphangioleiomyomatosis (LAM) is a rare lung disease that occurs almost exclusively in women. It affects mainly the lungs causing excessive growth of smooth muscle cells that progressively destroy lung tissue and diminish lung function. Although research is ongoing, there is currently no cure for LAM. For some patients lung transplantation is their only means of survival.

Monday, June 1, 2015 has been designated as the 5th Worldwide LAM Awareness Day by the WLPC (Worldwide LAM Patient Coalition). Please see the links below for details of your national organization.

The Fifth Annual Worldwide LAM Awareness Day was held officially on Monday, June 1, 2015. Thank you to those of you who have and continue to promote awareness, raise funds offline, and have set up online fundraising pages. At The LAM Foundation, online WWLAD Campaigns are open and will continue through December 31, 2015.