1. That we start planning now for how to maintain the momentum of this remarkable organization for the next 25 years.

2. That every LAM patient will take advantage of the opportunity to participate in the solution by attending LAM clinics at least once a year, enrolling in trials, helping to fund research, and offering their time and talents to The LAM Foundation.

3. That our partnerships with the NIH, other rare lung disease organizations, and the FDA will continue to thrive and grow.

4. That we expand the global reach of our clinic network to the 25 most populous cities in the world, so that we can study and serve as many LAM patients as possible, and distribute LAM expertise across the planet.

5. That we continue to attract the most compassionate, intellectually curious, and driven physician scientists to the LAM community.

6. That we can find more efficient and expeditious mechanisms to conduct trials, especially those involving the repurposing of already approved drugs, so that we can shorten the time to the next breakthrough therapy.

7. That all LAM patients will enroll in the MIDAS Registry, which will facilitate future trials and help us capture the interest of pharmaceutical companies.

8. That we find a way for women with LAM who wish to have children of their own to do so safely, with the lowest possible risk to mother and child.

9. That we find remission-inducing therapies that eradicate LAM cells, to improve upon the effective but suppressive therapy that we already have.

10. Until #9 is accomplished, that we will learn how to use mTOR inhibitors in the safest, most effective manner possible.
I saved wish #10 for last, because we have the opportunity to take it off the list shortly after the 25th anniversary arrives. The Multicenter Interventional Lymphangioleiomyomatosis Early Disease Trial (MILED Trial) is designed to determine if we should be starting low dose sirolimus early, so that mild LAM stays that way. In 2019, we simply don’t know how best to treat a patient who presents with mild cystic change in the lung, and who still has normal lung function (defined as FEV1>70%). The LAM Guidelines do not provide guidance on this issue, because there is not enough evidence to make a clear recommendation.

Furthermore, we think that LAM progresses in almost all premenopausal women with the disease (and in many, but not all, postmenopausal women). So why wait for almost inevitable further lung damage to occur before starting what we know to be an effective therapy? After all, we don’t wait for heart or kidney failure to develop before starting treatment for high blood pressure. We start anti-hypertensive therapy early because we want to protect the organs from further damage, and we know that the drugs used are very, very safe. Ah—then the issue becomes whether low dose sirolimus taken over long periods of time is safe. Answering that question is a primary objective of the MILED Trial.

There is a lot of literature about the safety of sirolimus in patients who have undergone transplants and who are taking multiple immunosuppressive drugs simultaneously, including sirolimus. However, there is very little written about safety for patients who are on sirolimus alone (monotherapy), or on sirolimus at low doses. Collectively, LAM Clinic Directors now have a lot of experience with patients who are on low dose sirolimus monotherapy, and several patients who have been on the drug for nearly a decade with an excellent safety profile. In my opinion and that of many LAM clinicians, low dose sirolimus is very well tolerated and very safe, and I am optimistic that the MILED study will support that position.

If the MILED Trial is successful, and confirms our hopes for safety and efficacy of early low dose sirolimus, I think it is possible that in the future we will be recommending that young women start on sirolimus at the first sign of LAM, and that the number of patients requiring transplants will decline over time because we have stopped this disease in its tracks.

I once said that The LAM Foundation had taken LAM from an asterisk in medical textbooks to a juggernaut of progress. In the next 25 years, I hope that the asterisk will be restored to remind us that LAM was a disease that used to threaten the lives of young women.

The MILED Trial is enrolling now.

If you have mild LAM, are not on sirolimus treatment, and would like to know if you qualify for the trial, please write to Susan.McMahan@uc.edu or call her at (513) 558-4831.
This past December, Dr. James Kiley, Director of the Division of Lung Diseases at the National Heart, Lung, and Blood Institute (NHLBI), joined our LAM Education Meeting at the NIH to share progress in LAM research. Dr. Kiley said, “Every little bit helps. As long as we’re communicating and working toward common goals in a constructive and positive way, we can leverage our efforts to achieve more together. Everybody can contribute.”

Since our grassroots beginnings in 1995, The LAM Foundation has proven this statement time and time again. We are now benefitting from several years of intense activity, including innovative conferences, new grant cycles, and fundraising efforts, culminating in a leveraged $50-60 million research impact. There is not only much to celebrate about what we do, but also who we are—a patient-centric organization with an increasingly global reach.

As we look forward to our 25th anniversary, one question arises: What are we going to do next? The answer will come through continuing our incredible momentum in three main areas:

**LAM Research.** We will continue to cultivate new scientists and fund the most promising research to advance the diagnosis and treatment of LAM. At present, The LAM Foundation is funding 12 LAM scientists who are pursuing a wide range of LAM-related projects, from conducting laboratory-based science to exploring the benefits of exercise. More than half of these funded grants go to early-career scientists, who we hope will make LAM research a priority for years to come.

Two additional grants from the UPenn Orphan Disease Center to LAM scientists have been indirectly funded by The LAM Foundation’s efforts. Since December of 2015, the Foundation has awarded or raised funds to support an astonishing 31 grants in the amount of $2,245,000. Many of these have been leveraged into much larger grants from the NIH and other sources, verifying the importance of Dr. Kiley’s words.

**LAM and Rare Lung Diseases Clinics.** We will continue to expand our LAM Clinic and Research Network by adding more locations and global lung disease experts. Twenty-five years ago, there were few options for women with LAM to find accurate information, much less compassionate and informed care.

Under the leadership of our scientific and medical directors, Drs. Frank McCormack and Nishant Gupta, respectively, we share clinical knowledge across a diverse network that now includes more than 60 locations across the US, Australia, China, Japan, Brazil, Canada, the UK, EU and Turkey. Such international collaboration has been important in getting sirolimus approved for the treatment of LAM in more than 38 countries since 2015.

**Patients.** We will continue to seek out every woman with LAM throughout the world, powering clinical trials and offering hope on a global scale. When I first joined The LAM Foundation almost 6 years ago, much of our outreach was carried out through phone calls and letters. Today, through the Internet and social media, we routinely help patients find resources in faraway places such as Malaysia, Israel and Ghana. For women with LAM, distances have little meaning. The LAM family offers resources and hope worldwide.

Historically, The LAM Foundation has planned and hosted vibrant, interactive conferences and educational meetings on both an international and local scale. Looking forward, we will continue to increase the reach and innovation of our recent events in Cincinnati, Los Angeles and Washington DC, aiming to inspire more ideas, more solutions and improved quality of life for every woman living with LAM – while we search for the cure. We now look forward to the 2020 International LAM Research Conference and LAMposium to be held in Cincinnati, Ohio in the spring of 2020. This will mark the 25th Anniversary of the Foundation and a pivotal opportunity to gather the global LAM community.

Over the years, the scale of our efforts has grown, but our mission remains the same. It is now more important than ever to connect and contribute to The LAM Foundation so that we may continue our momentum in all areas. You can join our efforts by attending meetings, connecting online, and sending or encouraging donations. As we share new knowledge of LAM, we empower progress. Thank you for continuing to grow along with us, and for being our source of Hope.
The LAM Foundation is proud to announce the 2018 Grant Award winners, providing funding for three LAM research projects in the amount of $410,000. These projects were peer-reviewed by The LAM Foundation’s Scientific Advisory Board and approved by The LAM Foundation Board of Directors.

- William Stanford, PhD, Ottawa Hospital Research Institute
  **2018 Pilot Award: $50,000 for one year**
  *Inducing Synthetic Lethality in LAM Cells Using Novel Antagomir Biologies*

- Charilaos Filippakis, PhD, Brigham and Women’s Hospital
  **2018 Career Development Award: $180,000 for three years**
  *Therapeutic Targeting of Macropinocytosis-Mediated Nutrient Uptake in LAM*

- Anne Karina Perl, PhD and Yan Xu, PhD, Cincinnati Children’s Hospital Medical Center
  **2018 Multi-PI Established Investigator Award: $200,000 for two years**
  *LAM cells reprogram the epithelial-mesenchymal crosstalk in the alveolar niche*

**LAM Researchers Awarded 2018 MDBR Research Grant Awards**

The Penn Medicine Orphan Disease Center also announced the winners of the 2018 Million Dollar Bike Ride Research Grant Awards. We extend our sincerest thanks to The LAM Foundation’s Easy Breathers Cycling Team and all those who donated to the Million Dollar Bike Ride to make these research projects possible. 2018 was the fifth consecutive year for the Million Dollar Bike Ride (MDBR), which has awarded more than $500,000 to LAM research projects.

- Elizabeth Henske, MD, Brigham and Women’s Hospital
  *TFEB and Lysosomal exocytosis to prevent lung destruction in LAM*

- Hilaire Lam, PhD, Brigham and Women’s Hospital
  *The Mitochondrial Unfolded Protein Response: Roles in the Pathogenesis and Therapy of LAM*
How can we improve the lives of LAM patients in five years or less? This is the question scientists, clinicians, and patients themselves gathered to answer at the first-ever LAM Patient Benefit Conference.

Before the meeting began in November 2017, The LAM Foundation conducted surveys with patients and clinic directors to identify the mental and physical issues that were most important to them. The results determined the mission of the conference: to identify and fund proposals for new products or services that can best meet patients’ needs in the short term.

Several main topics were generated from patient and clinic director feedback. During the Patient Benefit Conference, participants and thought leaders focused on these topics in moderated workshops, generating potential solutions and grant proposals.

Among the many valuable ideas shared, the following proposals have received funding to move forward. Each was chosen for its potential to result in solutions that will positively impact the diagnosis, care, or quality of life of LAM patients by the year 2023.

**Biomarkers and LAM**

“Identification and validation of new biomarkers based on single-cell RNAseq data”

Why do I have this disease, and how will it develop? For LAM patients, this question is often asked, but not always answered. Understanding the origin and development of LAM is dependent on a greater understanding of how disease cells function, interact, and grow.

Anne Karina Perl, MS, PhD, of Cincinnati Children’s Hospital has proposed new methods to identify and validate biomarkers in LAM. Biomarkers give us medical signs of disease presence and severity—and LAM has very few. Serum VEGF-D has shown value as a diagnostic biomarker, but there are other categories of biomarkers we have yet to develop. Prognostic biomarkers can help determine disease progression, and predictive biomarkers can estimate response to treatment.

To identify these biomarkers, Dr. Perl will utilize the powerful, state-of-the-art technology of single-cell RNA sequencing. This method helps us understand how individual cells function and interact with the other cells around them. Dr. Perl plans to use this approach to develop new LAM-specific biomarkers.

Single-cell RNA sequencing has changed the way we interpret disease. The more we understand a cell’s actions, the better we can identify and treat abnormal cell function. Dr. Perl aims to use this method to develop new treatments for LAM.

These approaches can go a long way in advancing research, but the results typically take a longer amount of time to directly benefit patients. But this study will take advantage of a rare opportunity—there
are already multiple LAM samples in existence that
can be used to identify biomarkers. This accelerated
pace of discovery will lead to patient benefit in less
than five years.

“Identification and validation of new biomark-ers based on single-cell RNAseq data”

The MILES study showed that sirolimus can sup-
press lung function decline and improve symptoms in
patients with LAM. But reaction to sirolimus therapy
can also differ among patients—many are responsive
to treatment, while others are resistant. What causes
these reactions, and how can we predict them?

Jane Yu, PhD, of the University of Cincinnati aims
to answer these questions by enhancing our under-
standing of sirolimus therapy in LAM. In studying cell
response to sirolimus exposure, we can discover why
LAM cells evade the actions of sirolimus, leading to a
more individualized approach to treatment.

For all patients, sirolimus treatment must be contin-
uous to sustain benefits—if drug exposure stops, lung
function declines. This means that sirolimus works
by inhibiting growth in LAM cells rather than killing
them. And in some cases, cells can develop resistance
or stop responding altogether. Why are these cells able
to withstand treatment, while others cannot?

Dr. Yu and her team will use single-cell RNA sequenc-
ing techniques to identify the molecules that determine
the behavior of sirolimus-resistant LAM cells. With
these findings, they can develop new biomarkers to
identify which patients may be resistant to sirolimus
therapy. If sirolimus resistance is detected earlier,
new treatment strategies can be implemented sooner,
meaning less lung function decline for these patients.

These insights could aid in the ultimate goal of Dr.
Yu’s laboratory—to develop new treatments that not
only stop the growth of LAM cells, but eliminate them
altogether.

“It’s all in the timing”

We know that symptomatic LAM occurs almost
exclusively in women. We know that symptoms can
intensify with pregnancy. We know that premenopaus-
al patients tend to decline faster than postmenopausal
patients. From these observations, we believe that
hormonal influences play a pathogenic role in LAM—but we do not know for sure.

Adam Gerard Cole, MD, of the University of
Cincinnati aims to find concrete answers to the
questions surrounding estrogen and LAM. By studying
fluctuations in lung function and pulmonary symptoms
during the menstrual cycle, Dr. Cole can provide
strong circumstantial evidence for the impact of
hormones on disease progression.

Home spirometry methods will be used to measure
changes in lung function over time. Patients will per-
form a daily spirometry test, record menstrual cycle
dates, and keep track of ovulation. Researchers will
then determine the variation in lung function for each
patient throughout the course of the menstrual cycle.
Trends in this data will demonstrate whether patients
who experience menstrual variation in symptoms tend
to decline faster than patients who do not.

If this difference is shown, menstrual cycle vari-
ation in home spirometry could become a new way
to identify patients at risk for faster lung function
decline, helping physicians decide when to initiate
treatment. With a better understanding of estrogen
and LAM, these treatments could someday include
hormone-based therapy options.

“Worldwide standardization of cystic lung dis-
ease CT with implementation of ultra-low radi-
ation”

For patients with LAM, CT scans are a necessary
part of life with a cystic lung disease. Diagnosis and
follow-up care depend on regular x-ray imaging. But
the benefits of regular scans also come with a draw-
back—potential carcinogenic effects of continued
radiation exposure.

Dr. Marcus Y. Chen, MD, of the National Institutes of
Health aims to reduce these risks as much as possible.
His research focuses on standardizing CT imaging
protocols so that no patient is exposed to more than
the minimum amount of radiation.

When LAM patients go in for a scan, there is cur-
rently 150-fold variability in the amounts of radiation
used. This means that scans can range anywhere from
a single chest x-ray of 0.1 mSv all the way up to 15
mSv. Because there are no established protocols for
chest scans in LAM, the amount of radiation exposure depends on the model of CT scanner used and the preferences of the local physician.

The basic principal of x-ray imaging is to use the lowest amount of exposure possible. But how low is the lowest? To establish new protocols, Dr. Chen and his research team are going to find out. They will begin by constructing a model of human lungs, complete with cystic abnormalities that are characteristic of LAM patients. These lungs, made of plastic yet medically realistic, will become an invaluable resource for the LAM community.

Individual clinic sites will be able to repeatedly scan the model lungs—something they could not safely do with a patient. Scanners will then be calibrated to the specific requirements of LAM lungs, reducing radiation exposure and optimizing image quality.

Less radiation means a lower risk of patients developing cancer. With these risks decreasing, physicians may decide to lessen the time between follow-up scans. The sooner changes in LAM lungs can be assessed, the earlier changes in therapeutic treatments can be made—leading to better care for all.

“Feasibility study of [11C]acetate PET as an indicator of early response to rapamycin in LAM patients”

Positron emission tomography (PET) scans allow doctors to check for diseases in the body. The scans can help evaluate organ and tissue functions, identify body changes at the cellular level, and detect early onset of disease. Because there are currently no imaging biomarkers for LAM, healthcare providers are unable to detect the disease using these scans. What would it mean for patients if they could?

Carmen Priolo, MD, PhD, of Brigham and Women’s believes that the impact could be essential to improving care for LAM. Her research aims to test the potential for PET scans to detect whole-body tumor burden and metabolic activity in LAM patients.

PET scans use small amounts of radioactive materials called radiotracers to follow molecular activity in the body. [11C]acetate is a radiotracer that is commonly used to detect renal, pancreatic, and prostate tumors. Dr. Priolo hypothesizes that [11C] acetate could be used to follow the metabolic activity of lungs in patients with LAM.

In following the metabolic activity of kidney tumors, the study also aims to reveal a new imaging biomarker for LAM. This activity could help physicians predict how a patient may respond to rapamycin, allowing for more personalized dosages and lengths of treatment. As a low-radiation risk option for imaging in LAM, [11C]acetate PET scans show great promise for both patients and researchers.

Exercise and LAM

“Mobile health to increase patient accessibility to exercise and elucidate exercise & fatigue in LAM”

LAM patients are often instructed to stay as active as possible, but they aren’t often instructed on how to achieve this while dealing with the symptoms of chronic respiratory disease. For many, exercise intolerance and fatigue are everyday realities. How can patients be better equipped to overcome these barriers on their own terms?

Mary Beth Brown, PhD, PT, of Indiana University has proposed a mobile health platform that empowers LAM patients to understand their optimum level of exercise and stick with a regular routine. The user-friendly, web-based platform—“LAmHealth”—will be the first to collect patient data related to exercise and fatigue in LAM.

An activity monitor worn on patients’ wrists integrates with a smartphone app to capture heart rate, physical activity, and sleep metrics. Patients also record data on blood oxygen saturation, pulmonary function, and supplemental oxygen use, along with symptoms of fatigue, emotional wellness, and sleep quality.

CONTINUES ON NEXT PAGE >
The data comes together in the mobile health platform to give us a better understanding of the factors that affect physical activity for LAM patients. Armed with this knowledge, we can provide evidence-based guidance for optimal exercise approach—meaning that no LAM patient will have to base their decisions on trial and error.

Still, the guesswork that comes with developing an unguided exercise routine isn’t the only barrier to consider. Traditional, medically-supervised programs require regular trips to pulmonary rehabilitation centers. When schedules are busy, wait lists are long, and transportation options are limited, it can be difficult for patients to participate in these programs.

Home-based rehabilitation, however, offers greater flexibility for patients to follow their own schedules and preferences. More control over where and when exercise occurs means less obstacles to accessing and maintaining care. When patients are given the means and the tools to take charge of their own exercise routines, they can make major improvements in their own health.

**Supplemental Oxygen and LAM**

The realities of LAM may mean that some patients use supplemental oxygen devices, but this doesn’t mean that they stop being active. So why is there a lack of supplemental oxygen therapies that fit an active lifestyle?

In the initial surveys from the LAM Patient Benefit Conference, women with LAM clearly expressed their frustration with the limitations of supplemental oxygen devices. Survey results showed that these devices were often inconsistent in quality and difficult to access.

One of the Patient Benefit Conference workshops focused on improving the quality and technology of supplemental oxygen therapy to address this patient need. Through discussion between both patients and clinicians, the group generated ideas for making supplemental oxygen devices easier to use, less burdensome, and more appropriate for living an active lifestyle.

The “EasyOX” is the resulting idea that won the most votes for the Patient Choice Award. This digitally-controlled device can remotely adjust oxygen flow, improving the function and mobility of an oxygen tank.

Funds have been reserved to support further research and product development for the “EasyOX” device. The LAM Foundation is pursuing academic programs in biodesign and technology in hopes of identifying a program that will adopt this project.

**Mental Wellness and LAM**

The physical manifestations of LAM are, by necessity, the primary focus of care. But for women coping with the everyday realities of this disease, the effects do not simply stop at the surface. How can we improve care for the whole person—inside and out?

Patients and clinicians thoughtfully addressed this sensitive and important need in a dedicated workshop. The discussion included topics of anxiety, fear, and depression. Patients expressed the stress and worry that comes with financial burden on their families. They also shared the challenges of dealing with the limitations in life with LAM.

In 2019, The LAM Foundation will develop a new webpage on www.thelamfoundation.org to address these topics. Patients will then have a designated place to access content and resources for mental health needs. Dr. Sian Cotton and Stacy Sims, experts in integrative medicine and mindfulness, will author this new content.
In an effort to better understand the natural history of lymphangioleiomyomatosis (LAM), the National Heart, Lung, and Blood Institute (NHLBI) established a LAM Registry in 1997. Approximately 250 women with LAM enrolled at six different centers across the United States and attended annual study visits from 1998 through 2003. The baseline data collected from this Registry provided a comprehensive overview of LAM clinical characteristics, and the publication that resulted helped advance our understanding of the disease. However, the most important analysis, determination of the natural history of LAM progression, was abandoned due to a lapse in funding.

Nearly 20 years later, we rescued the Registry data from obscurity and obtained outcome data on all participants from the National Death Index (NDI) and the United Network for Organ Sharing (UNOS) databases. The Centers for Disease Control (CDC) maintains the centralized NDI database of U.S. death record information, and UNOS collects detailed information on every U.S. transplant. By combining data from all sources, we were able to determine which of the patients in the Registry had ultimately died or undergone lung transplantation, and evaluate the disease features (e.g. menopausal status, extent of cystic change on baseline CT, rate of lung function decline) that predict favorable and unfavorable outcomes.

The key findings from our study include the following:

1. The average rate of decline in forced expiratory volume in one-second (FEV1) in patients with LAM is approximately 90mL/year, about 3-4 times faster than the normal age-related decline (which is about 20-30 mL/year). Put another way, the typical FEV1 in a woman with moderate LAM can be represented as the volume of liquid in a 2-liter Coke bottle, and the typical annual rate of loss is equal to removing about 6 tablespoons (tbsp) per year.

2. Premenopausal women decline at a faster rate compared to postmenopausal women (118mL/year vs. 74mL/year or about 8tbsp/year vs. 5tbsp/year).

3. The rate of decline in lung function was not impacted by the baseline features of the patient history that include number of pneumothoraces, the use of supplemental oxygen, presence or absence of angiomyolipomas, or type of LAM (tuberous sclerosis complex associated LAM vs. sporadic LAM).

4. The average survival among all LAM patients was more than two decades from the time of diagnosis. At 5 years post diagnosis, the number of patients who were alive and who had not been transplanted was 94%, at 10 years: 85%, at 15 years: 75%, and at 20 years: 64%.

5. Menopausal status and baseline lung function (FEV1 and diffusion capacity of the lung for carbon monoxide (DLCO)) affect future progression to death or lung transplantation. Patients with more normal FEV1 and DLCO at baseline had improved survival as compared to patients with abnormal lung function at baseline (Figure). Patients who were postmenopausal women at baseline had a lower risk of progression to death or lung transplant.

This analysis was the largest prospective natural history study of women with LAM, and the only one to include rigorously validated pulmonary function testing, survival, and transplantation endpoints. In addition, these data represent perhaps the last opportunity to understand disease progression in the pre-sirolimus era and will be useful for future studies designed to determine the impact of sirolimus therapy on survival.
Ultimately, we hope to develop a LAM-specific disease severity calculator to assist with treatment decisions and to use the banked serum specimens linked with clinical information, including serial lung function parameters and outcome data, to develop and validate novel disease-specific biomarkers for LAM.

This priceless resource was made possible by the selfless efforts of almost 250 women with LAM, who made personal sacrifices to travel to Registry sites once or twice per year for up to 5 years, and complete questionnaires, perform pulmonary function tests and provide blood samples. Dr. Taveira DaSilva and Dr. Moss and the rest of the team at the NIH played a central role in the success of the program, along with the investigators at the other five sites: Dr. Jay Ryu (Mayo Clinic, Rochester, MN), Dr. Stephen Ruoss (Stanford University, Palo Alto, CA), Dr. Geraldine Finlay (New England Medical Center, Boston, MA), Kevin Brown (National Jewish Health, Denver, CO), and Jeffrey Chapman (Cleveland Clinic, Cleveland, OH). We would also like to acknowledge the advocacy efforts of The LAM Foundation that played a pivotal role in the commission of this Registry by the NHLBI.

Ultimately, the number of deaths and transplants that occurred over the two decades since the NHLBI LAM Registry was founded is a sobering reminder to all of us that our work is not yet done. The good news is that through our strong patient physician partnership we have taken another step toward improving our understanding of LAM disease progression and the ultimate goal of achieving a cure for LAM.

Figure: Kaplan-Meier curves showing death/lung transplantation as outcome after segregating LAM patients on the basis of: A) menopausal status, B) baseline FEV1, and C) baseline DLCO. Postmenopausal patients and patients with more normal FEV1 and DLCO at baseline had reduced risk of progression to death/lung transplantation.
I was excited when I heard that the MILED Trial was finally going to be enrolling patients. The MILED Trial was the one drug study that I had been waiting to join. It was my hope that a low dose of sirolimus would allow me to continue living my life rather than waiting for my LAM to progress.

Soon after I was diagnosed with LAM in fall 2009, I began hearing about the idea for the MILED Trial. The MILES Trial enrollment period had already closed when I received my diagnosis. As time went on and MILES was so successful in showing effectiveness of sirolimus in LAM, I was even more anxious for the MILED trial to enroll. Every time I had a clinic appointment, I would ask about the status of the MILED Trial. Every LAMposium I attended, I would seek out information about the status of the trial. It would have been an understatement to say that I was ready for this trial to get off the ground.

The idea of the MILED Trial seemed perfect for me. It seemed to my husband and I that if the MILED trial was successful, I could continue to live a good quality of life without making too many concessions to my LAM disease as I got older. The idea of less severe side effects—or possibly no side effects—from a lower dose was also appealing. If I had been prescribed a larger dose of sirolimus at an earlier time, the side effects alone could have potentially interfered with my ability to continue working full-time.

It is important to note that while I was anxious to participate in the MILED Trial, the decision to participate is a personal decision for each of us. Patients in drug trials have a responsibility to do their part—participation involves more than just taking the drug. You must complete a daily diary so that researchers can track your symptoms. You must remember to contact the clinical research coordinator if you have to undergo certain medical procedures. You must also consider the potential side effects and how they could impact your quality of life.

For me, my quality of life guides how I make my decisions. In this trial, there was a potential to receive the placebo rather than the trial drug. I knew that if my lung function started to decline, I could withdraw from the trial and re-evaluate my medical options—including going on a full dose of Sirolimus. The fact that my overall health was my doctor’s primary concern help put me at ease with participating in a double-blind study.

I believe that the MILED Trial is extremely important because of its huge ramifications for future treatment options in mild patients. The idea that a woman who is newly diagnosed with LAM could start treatment sooner and potentially slow down progression earlier is wonderful. Patients could be at ease knowing that there is a course of treatment for those who are experiencing mild disease.

When I was first diagnosed, the hardest part was knowing that there is not a treatment plan that would work for my mild disease. All we could do was wait and watch for signs of progression. With the results of this trial, that could change. All LAM women, regardless of disease progression, could have the opportunity to benefit from MILED.

There are several MILED study sites across the country including Cincinnati, Philadelphia, Atlanta, Boston, Stanford, Chicago, Nashville, and Denver. If you would like to learn more about the study or see if you may be eligible, please call Susan McMahan at 513-558-4376, or email susan.mcmahan@uc.edu.
What was it like for you to go through the lung transplantation process?

My transplant journey began in 2003, about seven years before I officially listed for transplant. My pulmonologist had encouraged me to go through the evaluation process and list for transplant. At that time, rank on the waiting list was determined by length of time spent on the list, rather than by the Lung Allocation Score (LAS) in place today.

However, I didn’t feel at all ready to make that decision. So I stepped back from the decision and did not revisit it until six years later when the writing was on the wall, so to speak—my lung function had significantly declined, my daily activity was severely restricted, and my weight and strength were no longer at a functional level. Because my lung function was so low, starting Rapamune off-label was not a viable option for me. In short, I could no longer deny my need for a lung transplant.

Throughout this process—and during the year leading up to listing—I felt a great deal of fear, trepidation, and ambivalence.

Throughout this process—and during the year leading up to listing—I felt a great deal of fear, trepidation, and ambivalence. I was especially fearful of the unknowns. This was also a lonely time for me, not all that different from when I was first diagnosed in 1993, prior to finding The LAM Foundation. I now found myself in an even smaller subset of an already very small set of women who are diagnosed with LAM, and I craved real, honest conversation with others who had already navigated the transplant experience.

Thankfully, Sue Byrnes and Dr. Frank McCormack put me in touch with a few amazing women—women diagnosed with LAM who were living wonderfully full post-transplant lives—and the conversations began. Right alongside the difficult emotions, a bit of excitement and hope gradually found its way into my thinking.

What if the transplant were a success? What if I could extend my life? What if I could attend my daughter’s college graduation? What if I could again fully participate in life with not only my mind and my heart, but also with my physical being?

How did the idea for the Circle of Hope Transplant Support Program come about?

The need to expand The LAM Foundation’s support to women facing transplantation was first presented to Sue Sherman, our CEO, by Sally Lamb, our then-Patient Services Director. Sally recognized the unique concerns and challenges presented to our patients in need of a lung transplant. The idea percolated in Sue’s mind, and over time a plan began to take shape.

In late 2015, Sue reached out to me, asking if I would be interested in being involved with such a program. I didn’t skip a beat in saying yes! Given my own experiences, I had no doubt this program was needed and that it would be a valuable addition to our patient support services. Early the following year, I

Dunn three weeks post-transplant with surgeon Michael S. Mulligan, MD, of the University of Washington Medical Center.
drew up a preliminary vision statement and timeline for implementation.

In 2017, Katie Jensen, our Development Director, and Anne McKenna, who at the time was our Patient Services Director, took the project to the next level and ultimately worked their grant writing magic. The resulting grant from Global Genes enabled us to launch the Circle of Hope Transplant Support Program in 2018. Like many projects within The LAM Foundation, the program has been a labor of love by many.

What are the biggest needs that the program addresses?

The Circle of Hope program addresses that craving for real conversation—a connection with other women who have been through the transplantation process, who have navigated both the most wondrous and the most difficult of days. It’s all about support and education.

In addition to providing patient support, the program also supports our dedicated researchers. By educating patients about the opportunity to donate their explanted lung tissue at the time of transplant, we are able to provide our researchers the essential resource they need to find a cure for LAM: fresh lung tissue.

Our women with LAM have always been eager to participate in research, so it’s no surprise that our patients have responded generously and enthusiastically to this opportunity. Tissue donation is a powerful experience and a tremendous gift to the entire LAM community.

How has the program impacted women with LAM so far?

Since launching the program just under a year ago, we have already touched many lives. Our Circle of Hope participants now cover the full range of the transplant process—we have women who are currently in evaluation, women who are through evaluation and waiting on the list, and women who are less than a year post-transplant. Some of our women were not previously involved with The LAM Foundation, but reached out when we announced the Circle of Hope.

The stories that have evolved from these connections fill my heart on a daily basis. When I receive an email or a phone call from a woman thanking me for the program, well, it just doesn’t get any better than that. As a beautiful surprise, I have also received those same messages from our mentors, expressing their gratitude for the opportunity to be involved and to share with others what they’ve learned and experienced. Our mentors are a dedicated and compassionate group of women, and they are making a difference every day. Without them, we wouldn’t have a program.

I’ve always believed in the power of connection. We have witnessed this power for years at our regional gatherings and, of course, LAMposium. Now, to witness this power spreading within our transplant population—it almost leaves me speechless. I am beyond-words blessed to be a part of the Circle of  
SEXUAL HEALTH IN POST-MENOPAUSAL WOMEN WITH LAM

BY LISA LARKIN, MD, FACP, NCMP, IF FOUNDER AND CEO, MS. MEDICINE & FOUNDER AND CEO, LISA LARKIN MD AND ASSOCIATES FOUNDER AND EXECUTIVE DIRECTOR, CINCINNATI SEXUAL HEALTH CONSORTIUM MEMBER, BOARD OF TRUSTEES, NORTH AMERICAN MENOPAUSE SOCIETY

LAM patients understand the link between estrogen and LAM progression. For this reason, women with LAM and their clinicians may look forward to menopause anticipating a slowing of lung function loss. Unfortunately, the onset of bothersome symptoms can make menopause for women with LAM a mixed blessing. These symptoms include hot flashes and night sweats, significant sexual health changes, increased anxiety and depression, cognitive and memory complaints, hair and skin changes, sleep disturbances, and weight gain. Menopause symptoms, especially sexual dysfunction after menopause, negatively impact a woman’s quality of life, self-esteem, relationships, and overall health. The good news is there are safe and effective treatments available for all women, including women with LAM.

Sexual function changes dramatically at menopause. Up to 88% of women 8 years beyond menopause report sexual dysfunction. For most women, sexual concerns are never discussed or addressed. This is especially true in women with health conditions associated with estrogen, such as LAM and breast cancer. Clinician and patient discomfort with discussing sexual health concerns, lack of provider training in evaluating and managing sexual health issues, and lack of knowledge about available treatment options are all known contributors to this gap in care. We must do more!

Sexual dysfunction at menopause is largely due to the loss of estrogen. Although this may be good news for LAM disease progression, estrogen loss is associated with the development of vaginal atrophy, renamed Genitourinary Syndrome of Menopause (GSM). Symptoms include vaginal dryness, irritation, pain with intercourse, lack of lubrication, and recurrent urinary tract infections. GSM is a progressive condition that worsens with time when untreated. Fifty percent of post-menopausal women are affected by GSM, and it is the most common reason they may stop having sex. Still, only 7% of women with GSM are ever treated. Along with the development of GSM, post-menopausal women often note a decline in libido (desire) and a decrease in genital sensation and orgasm. Estrogen loss, declining testosterone, and pelvic floor health all contribute to these issues.

The good news for all women—including those with LAM or a history of breast cancer—is the availability of safe and effective therapies to address sexual health issues, including several new FDA-approved options. Clinicians, however, are not uniformly comfortable with or knowledgeable about these newer options, especially in women with hormone-sensitive health conditions. Even gynecologists may not be comfortable with bringing up the topic of sexual health. Women must speak up and ask their clinicians for help and guidance. If your provider is uncomfortable with addressing your sexual health concerns or offering therapy, ask for a referral to a specialist!

Sexual dysfunction in women with LAM, as with all women, requires a thorough sexual history and a physical exam. Not all sexual dysfunction in menopausal women is related to biology or hormones. Relationship issues, lack of privacy, cultural beliefs, past trauma, and stress can impact sexual functioning and must be explored. Sex therapy and couples’ therapy are important parts of a treatment plan. When sexual history suggests menopause and GSM as the cause, a physical exam is required to confirm the diagnosis.

Published guidelines by the North American Menopause Society (NAMS) and the American College of Obstetricians and Gynecologists (ACOG) support a stepwise approach in the management of GSM for all women. The goal of therapy is to alleviate symptoms, preserve sexual function, and prevent UTIs. The initial approach encourages regular sexual activity,
use of vaginal dilators, pelvic floor physical therapy, and use of over-the-counter vaginal moisturizers and lubricants. All women should be encouraged to use vaginal moisturizers regularly, as data supports that they can be very helpful for many women.

Unfortunately, for women with severe symptoms, vaginal moisturizers and lubricants are frequently inadequate. Over-the-counter products do not address the cellular changes or the increase in vaginal pH associated with estrogen loss. FDA-approved vaginal estrogen therapy is the gold standard for treatment of GSM. Vaginal estrogen therapy is highly effective, eliminates symptoms, improves lubrication, decreases pain with intercourse, and reduces urinary tract infections. These products all carry the FDA-mandated estrogen class label, warning women of an increased risk of breast cancer, uterine cancer, cardiovascular disease, stroke, and dementia, although there is no data to support this label for local vaginal estrogens.

So, is local vaginal estrogen therapy an option for women with GSM and LAM or a history of breast cancer? Despite the FDA-mandated class label, available data supports safety, and I would argue YES! Consider the dosing of vaginal estrogen compared to systemic estrogen. The commonly prescribed 10mcg vaginal estradiol tablet (Vagifem or Yuvalfem) used for an entire year equates to 1mg of estradiol—the amount in one single birth control pill. The dosing is so low with vaginal estrogen that serum estrogen levels do not appreciably change and remain in the menopausal range.

Since 2014, three new and novel therapies have been approved to treat painful sexual intercourse associated with GSM. These include ospemifene (Osphena), prasterone (Intrarosa), and estradiol gel caps (Imvexxy). Ospemifene is an oral non-estrogen SERM (selective estrogen receptor modulator) taken daily. Prasterone (Intrarosa) is a non-estrogen daily vaginal DHEA insert and does not carry the boxed estrogen warning. Estradiol 4mcg Gel Caps (Imvexxy) are the lowest-dose vaginal estradiol formulation available. All three of these products are FDA-approved, effective, and can be considered in LAM patients with GSM who have failed other nonprescription therapies, although none have specifically been studied in LAM patients. For some women who are reluctant to use any vaginal therapy, vaginal CO2 laser treatment may be a preferred option. Small clinical trials support efficacy, although long-term studies are lacking. Cost may be a barrier for many women—the initial series of 3 treatments ranges from $2,000–$3,000.

Treatment of low desire in post-menopausal women is more complex and nuanced than management of GSM, and women with bothersome low desire may benefit from referral to a specialist. Flibanserin (Addyi), a daily oral medication that works to balance neurotransmitters in the brain that influence desire, is currently the only FDA-approved treatment for women with low desire. Flibanserin is approved for premenopausal women only; prescribers must be certified, and it is contraindicated with alcohol. Testosterone therapy for low desire is supported by data in post-menopausal women, but there are no FDA-approved testosterone products available for these women, and use in women with estrogen-sensitive conditions is controversial. Finally, bremelanotide, a non-hormonal, injectable, on-demand medication to treat low desire will likely be approved in early 2019, but has not been studied in LAM patients.

Bottom line—women should not suffer in silence. Sexual health is an important part of overall health, and there are safe and effective therapies available—even for women with LAM. If you have sexual health concerns, and your provider does ask, speak up! And if your clinician is uncomfortable with addressing your sexual health needs, ask for a referral.

INSIGHTS FROM NEW LAM CLINIC: UF GAINESVILLE
BY CLINIC DIRECTORS ALI ATAYA, MD & MARK L. BRANTLY, MD UNIVERSITY OF FLORIDA HEALTH, GAINESVILLE

It has been remarkable to see the advances happening in the field of LAM research and patient care over the last two and half decades. In a short period of time, the medical community and The LAM Foundation have worked together to help us better understand the cause of LAM. They have developed new methods of diagnosis, paved the way towards the first FDA-approved therapy to slow disease progression, and improved the quality of life for women with LAM.

We have had the unique privilege of caring for patients with LAM and other forms of rare lung diseases at University of Florida Health. The strategic location of our institute in Central Florida provides us with an opportunity CONTINUES ON NEXT PAGE >
How did you become interested in studying LAM?

When I began my medical training, I naturally gravitated to the challenge of patients with complex health problems. This led me to training in critical care, advanced/rare lung diseases, and lung transplantation. During my training, I was blessed to have several amazing mentors who were considered experts in these fields, including Dr. Lynch, who followed a large number of LAM cases at UCLA. Through him, I had the opportunity to meet and help care for many patients with LAM.

Time and again in my early career, I saw patients with LAM who had been misdiagnosed, had delayed diagnoses, or were inappropriately treated by community physicians who had never seen a case of the disease (or in some cases, had never heard of it). I saw a clear need and special opportunity to improve the care of patients with this fascinating condition.

As I reviewed the rapidly growing medical literature and the history of The LAM Foundation, I also saw the remarkable success that can come from a unique intersection between a group of well-organized and informed patients and dedicated scientists and clinicians. Quite simply, I needed to be a part of this.

Why was it important for you to join the Rare Disease & LAM Clinic Network?

In the clinic, you need to see a condition many times before you feel comfortable treating patients; in a research trial, you need large numbers of enrolled subjects to ensure that your findings are statistically reliable. Both in clinical practice and in research, patient volume is critical in making progress and developing expertise. Because LAM and many other diseases of interest are rare, this is perhaps the greatest obstacle to better medical care and scientific advances.

Any historian of LAM and the progress that has been made understands the importance of organization and open dialogue. Without both a network of well-organized patients and a connected medical/research community, we wouldn’t have sirolimus or anywhere near our current understanding of LAM biology. Countless lives have been saved as a result.

Our hope is that a stronger bond with the RLDC and LAM Clinic Network would ultimately help improve the care and health of our patients. We want patients who visit the clinic to have no doubt that they are receiving comprehensive and cutting-edge care. We want them to have better and ongoing, cutting-edge clinical trials.

As part of the International LAM Clinic Network, we will now collaborate with other clinics and experts around the country to change and improve the way we take care of patients with LAM, contributing to patient education and research. We believe that this accreditation will help us further achieve our clinic mission goals and provide the best possible care to those who need it.

To learn more about the LAM Clinic at University of Florida Health, visit https://pulmonary.medicine.ufl.edu/. To schedule an appointment, call (352) 273-8740.
more convenient access to potential clinical trials. We want to make it easier for them to have direct access to the latest developments in the field. If we encounter a complex clinical scenario that even experts have rarely seen, we want them to rest assured that their doctor can reach out to the larger community for additional advice.

How will you benefit patients in your new role as LAM Clinic Director?

As a co-director of the UCLA LAM Clinic, I have several goals moving forward, all of which are ultimately to ensure our patients get the very best care. Building stronger ties to the RLDC, LAM Clinic Network, and The LAM Foundation is high on my list of goals.

I plan to improve our clinic’s organization by creating a clearer database or record of the patients we have followed. Because we see patients who may travel large distances and may not be able to see us frequently, I hope to improve outreach to referring doctors in the community and build better lines of communication with these referrers. Finally, I plan to participate in more upcoming multicenter clinical trials so that interested patients can have better access to trial enrollment.

To learn more about the UCLA LAM Clinic, visit: https://www.uclahealth.org/pulmonary-and-critical-care-medicine. To schedule an appointment, contact Olivia Lupian at (310) 794-9938 or olupian@mednet.ucla.edu.
Novel Techniques for Evaluating Pathogenesis of LAM

CyTOF as a Discovery Technology in Lung Disease

PRESENTER: JEFFREY ATKINSON, MD, ASSOCIATE PROFESSOR, DIVISION OF PULMONARY AND CRITICAL CARE MEDICINE, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE IN ST. LOUIS

Mass cytometry, or CyTOF, is a novel technique marrying flow cytometry and mass spectroscopy. CyTOF utilizes antibodies labelled with rare heavy metals instead of fluorophores. It allows for the combination of multiple antibody specificities in a single sample, permitting detection of >30 different intra- and extracellular proteins in human clinical specimens without spillover between channels. The workflow is similar to traditional flow cytometry, but low background on frozen specimens allows for specimens to be stored or shipped and then run in batch, thereby limiting run variability.

Disadvantages of CyTOF include an inability to return live cells after analysis and slower rate of analysis (2 million cells/hour compared with 20-60 million cells/hour with conventional cytometry). In addition, the presence of iodine (in amiodarone), barium and gadolinium (in imaging contrast), and cerium (lighter flint) can interfere with common metal labels.

Dr. Atkinson presented data demonstrating an ability to look at multiple cell types in human lung digests from patients with IPF, COPD, and normal lungs. CyTOF allows for simultaneous quantification and comparison of NK cells, lymphocytes, B cells, and alveolar macrophage. His data suggests that unique subsets of CD206+ lung macrophages which co-expressed CD36 and CD123 were present in IPF, but not in COPD or normal lungs.

As this relates to LAM, Dr. Krymskaya’s work indicated that PD-1/PD-L1 immunomodulation is a potential target for LAM therapy. Difficulty defining PD-L1 in highly autofluorescent macrophage populations may require techniques like CyTOF. Cytometry represents a relatively underutilized technique in rare lung disease research, and CyTOF may have high potential as a future translational tool.

Potential Therapeutic Targets for LAM

Glycoprotein-NMB Serves as Both a Marker and Regulator of Tumor Progression in Lymphangioleiomyomatosis

PRESENTER: MANISHA TAYA, PHD CANDIDATE, UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY

Taya showed that in a model of uterine-specific TSC2 deficiency, there are metastatic tumors in 50% of animals, and that these tumors are estrogen- and rapamycin-sensitive. Using RNAseq of these TSC2-deficient cells, the lab identified genes that were estrogen-sensitive, including the melanocytic marker glycoprotein-NMB (GPNMB). GPNMB was expressed in Tsc2 null uterus and in lung tumors. Importantly, human LAM lung lesions highly express GPNMB.

Glycoprotein-NMB is a transmembrane molecule that is expressed in melanocytes and in different cancer cells. Silencing GPNMB in human-derived AML cells (621-101) resulted in decreased proliferation, migration, and invasion of these TSC2-deficient cells. Moreover, data showed that ADAM10 is responsible for cleavage and secretion of GPNMB. The data also showed that silencing GPNMB results in decreased expression of matrix metalloproteinases MMP-2 and MMP-9. These effects are believed to be linked to the shed GPNMB.

The overall hypothesis is that GPNMB has important intracellular effects on the secreting cell and paracrine effects at distance in the pathogenesis of LAM, and could potentially serve as a therapeutic target.
Novel mTOR-Independent Signaling Pathways Attenuating Renal Angiomyolipoma Cell Survival

PRESENTER: UCHENNA UNACHUKWU, PHD, MS, MA, ASSOCIATE RESEARCH SCIENTIST, COLUMBIA UNIVERSITY MEDICAL CENTER

Dr. Unachukwu presented data investigating alternative therapeutic strategies for LAM and TSC. Platelet Derived Growth Factor Receptor (PDGFR) was shown to be phosphorylated in renal angiomyolipoma and pulmonary LAM tissue. Data showed that, in UMB1949 renal angiomyolipoma cells, Imatinib a PDGFR inhibitor resulted in decreased cell proliferation and viability in a dose-dependent manner. In contrast, rapamycin was cytostatic with no effect on cell death.

The effects on cell death were investigated with 2 different PDGFR inhibitors—Nilotinib and Imatinib—and results showed that the effects on cell death were independent of mTOR signaling. Single cell RNAseq of rapamycin or tyrosine kinase inhibitor (TKI)-treated AML cells showed enrichment in cell death and survival pathways in TKI-treated cells. Moreover, the expression of mitogen-activated protein kinase phosphatase 1 (MKP-1) was induced only in the rapamycin-treated cells. These differential effects are predicted to result in inhibition of ERK1/2, which could in turn explain the differential effects on TSC2-deficient cell survival.

iPSC in LAM

PRESENTER: WILLIAM STANFORD, PHD, SENIOR SCIENTIST, REGENERATIVE MEDICINE PROGRAM, OTTAWA HOSPITAL RESEARCH INSTITUTE

Dr. Stanford presented his laboratory’s work centered on developing novel human stem cell models of LAM which would accelerate the identification of drug targets. Primary LAM cells are hard to culture, and the cell of origin in LAM is unknown. However, multiple lines of evidence suggest a neural crest origin of the LAM cell.

Dr. Stanford’s laboratory developed iPSC from fibroblasts isolated from facial angiofibromas of subjects with TSC-LAM. The data showed that the presence of TSC2 is necessary for iPSC reprogramming. TSC2 heterozygous iPSC were then injected into mice, with subsequent tumor development. Tumors were then harvested, and cells grown under smooth muscle differentiation conditions. The resulting cells presented a phenotype reminiscent of LAM cells.

Dr. Stanford then presented novel data investigating biomimetic 3D cell culture based on hyaluronic acid (HA) backbone. These HA hydrogels can, for instance, be cross-linked with MMP-degradable peptides, which can be processed by LAM cell-secreted MMPs. When placed in these hydrogels and compared to culture in plastic dishes, TSC2+/- cells show a marked decrease in TSC2 expression, elevated levels of MMP, and increased invasive properties that were not responsive to rapamycin.

To understand why LAM is restricted to women, CRISPR/Cas9 was used to generate homozygous and heterozygous mutations in both male and female cell lines, which were then differentiated into neural crest-derived smooth muscle cells. Xenografts of these TSC2 mutant cells were then able to migrate to the lungs. Work is underway to understand through in vitro, in vivo, and RNAseq analyses differences between male- and female-derived cells.

Finally, the laboratory used these new tools to identify novel therapeutic targets. First, in a drug repurposing screen using HA-hydrogel invasion as an endpoint and screening 800 FDA-approved compounds, Dr. Stanford and his laboratory identified Dacarbazine (an FDA-approved compound for the treatment of melanoma) as a cytotoxic drug in the absence of rapamycin. Other compounds, such as HDAC inhibitors, are also being investigated. Last, a CRISPR synthetic lethal screen identified multiple RNA, miRNA, and LncRNA as potential targets.

In summary, novel in vitro models of LAM have been developed and used in high throughput screens to identify potential therapeutic targets.

LAM clinical trials: past, present and future

PRESENTER: SIMON JOHNSON, DM, FRCP, HEAD OF THE DIVISION OF RESPIRATORY MEDICINE, UNIVERSITY OF NOTTINGHAM SCHOOL OF MEDICINE

Dr. Johnson reviewed the history and current landscape of clinical trials in LAM. The design of future LAM clinical trials is met with many challenges, including the phenotypic differences of LAM patients, the many candidate targets, and outcomes that are centered around lung function.

CONTINUES ON NEXT PAGE >
endpoints. Designing randomized controlled trials with a lung function endpoint results in expensive and long studies. In addition, the availability of multiple targets leads to competing trials and recruitment difficulties. Since rapamycin is an established therapy, the design of new trials could be a non-inferiority design (which will require a large number of patients) or a combination of rapamycin and another agent.

Target selection is critical and can be enhanced by the quality of the pre-clinical data. This can include surrogate endpoints that could be more sensitive than lung function, such as lung destruction, disease activity, or monitoring for target engagement.

While a randomized placebo-controlled trial may be necessary for drug approval, other trial designs should be considered at least initially to efficiently investigate new therapies. These “adaptive trial designs” would require a smaller number of subjects by incorporating pre-specified protocol alterations that would permit enriching trial arms, dose-finding, and withdrawal of treatment arms. Further, master protocols would allow testing of multiple therapies under the same protocol, with the clear advantage of screening patients for multiple trials and sharing control groups amongst the trials. Adaptive trial designs and master protocols require investment in robust clinical trial infrastructure.

Much work remains to be done in phenotyping patients with LAM, identifying biomarkers, and establishing novel trial designs. However, Dr. Johnson stressed causes for optimism, including the committed patient population, network of clinics, and strength of the basic sciences in LAM.

**Urokinase-Type Plasminogen Activator (uPA) System Contributes to Abnormal Lymphatics in LAM-Like TSC2-Null Tumors**

*Victoria Stepanova, PhD, Research Associate Professor of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania*

Urokinase-type plasminogen activator (upa) is a serine protease that cleaves peptide bonds in proteins. It is also known as urokinase. Upa is involved in remodeling of the extracellular matrix and has been implicated in tumor cell migration and proliferation.

Dr. Stepanova reported that human LAM tissues express high levels of upa. Using fibroblasts from tsc1-/- and tsc2-/- knockout mice, she showed that upa overexpression results from loss of either tsc1 or tsc2. Furthermore, inhibition of upa expression reduces tsc2-null cell growth and invasiveness while increasing susceptibility to apoptosis.

Interestingly, Dr. Stepanova presented data indicating that sirolimus treatment not only failed to reverse upa expression in tsc2-null human cells, but also resulted in enhanced upregulation of upa expression. Fortunately, she presented in vitro data showing that the sirolimus-induced upa expression in tsc2-null cells was reversed by induction of the glucocorticoid receptor-mediated signaling pathway using dexamethasone, pharmacological inhibition of forkhead box (foxo) 1 and 3, and a upa inhibitor, uk122.

Lastly, Dr. Stepanova was able to demonstrate a reduction in tumor growth in vivo through inhibition of ipa expression using upa shRNA, and pharmacological inhibition of upa using amiloride in mouse models of LAM tumorigenesis. These findings—although still pre-clinical and in need of further characterization—suggest that pharmacotherapy targeting upa-dependent pathways may attenuate LAM disease progression, particularly in patients who are unresponsive to, or intolerant of, sirolimus.

**Circulating Biomarkers from the Phase I Trial of Sirolimus and Autophagy Inhibition for Patients with LAM (SAIL)**

*Anthony Lamattina, MS, Senior Technical Research Assistant, El-Cemaly Lab at Brigham and Women’s Hospital*

Lamattina presented the results of a large-scale biomarker analysis of the SAIL trial. The SAIL trial is a phase I dose-escalation study of rapamycin and hydroxychloroquine (an autophagy inhibitor) in rapamycin-naive women with LAM.

Serum analyte concentrations (279 analytes) of potential biomarkers of therapeutic response were assessed longitudinally over a 24-week period of dual sirolimus and hydroxychloroquine treatment, followed by 24 weeks of treatment cessation. Network analysis identified acetyl-Co-A carboxylase complex and coagulation factor II as potential upstream nodes regulating analytes that changed with treatment.

Decreases in vascular endothelial growth factor receptor (VEGFR)-3 and CCL21 were associated with increases in FEV1, indicating that these analytes could serve as endpoints in future clinical trials. Comparing subjects who received high dose (400mg) versus low dose (200mg) hydroxychloroquine suggested that changes in vitronectin and
visfatin were likely hydroxychloroquine- and perhaps autophagy-dependent.

**IGF2 as a Potential Novel Therapeutic Target for Rapamycin-Insensitive LAM Patients (IGF2 in Sirolimus-Resistant LAM)**

**PRESENTER: KSENIYA OBRAZTOVA, PHD, POSTDOCTORAL FELLOW, PERELMAN SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA**

IGF2 is a pro-oncogene essential for normal cell proliferation. Upregulation of IGF2 has been linked to a number of cancers.

Drs. Obraztsova and Krymskaya have previously demonstrated that IGF2 overexpression contributes to LAM cell survival. More recently, they were able to show that STAT3 binds to the IGF2 promoter region within computationally predicted STAT3 binding sites in mouse and human LAM cells. This suggests that STAT3 acts as a direct transcriptional activator of IGF2 gene expression and that IGF2 overexpression is, at least in part, STAT3-dependent.

Furthermore, through identification of LAM cell IGF2 imprinting patterns, their data indicates that increased levels of IGF2 in LAM cells occurs independently of gene dosage. Most importantly, treatment of LAM cells with mTOR inhibitors showed that expression levels of both IGF2 gene and protein products were mTOR-independent. This mTOR-independence suggests that IGF2 inhibition may be a potential pathway for future targeted therapy of sirolimus-insensitive LAM patients.

**Origin of LAM Cells**

**PRESENTER: ELIZABETH HENSKE, MD, DIRECTOR, CENTER FOR LAM RESEARCH AND CLINICAL CARE, BRIGHAM AND WOMEN’S HOSPITAL**

Macropinocytosis is an endocytic pathway for internalization of extracellular fluid via large endocytic vesicles called macropinosomes. It also functions as a nutrient-scavenging pathway in cancer cells.

Dr. Henske was able to demonstrate that Tsc2-deficient cells have a 3-fold increase uptake of dextran, a polysaccharide internalized via macropinocytosis, relative to Tsc2-expressing cells. This upregulation of macropinocytosis was shown to occur via a Vps34 lipid kinase-dependent mechanism. Macropinocytosis was further increased in Tsc2-deficient cells lacking autophagic mechanisms. Autophagy is a degradative cellular process important for responding to nutrient stress and involves proteolytic degradation of cytosolic components at the lysosome.

Using Vps34 inhibition in synergy with an autophagy-deficient cell line, Dr. Henske was able to selectively inhibit proliferation of Tsc2-deficient cells. Furthermore, she was able to show that genetic downregulation of Vps34 inhibited tumor growth in an in vivo xenograft model of TSC. This dependence of Tsc2-deficient cells on Vps34 and macropinocytosis for survival, in vitro and in vivo, suggest that novel metabolic-based approaches to therapy of LAM may be possible.

**Checkpoint Inhibitors in LAM**

**PRESENTER: VERA KRYMSKAYA, PHD, MBA, FCPP, PROFESSOR, PERELMAN SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA**

LAM is characterized by loss of function in tuberous sclerosis complex 2 (TSC2) with resultant upregulation of mTOR signaling. Currently, the only effective therapy for mTOR inhibition is sirolimus. While sirolimus effectively slows disease progression, it is only tumorstatic, and lung function declines upon treatment withdrawal.

Checkpoint inhibitor blockade is a form of immunotherapy directed at proteins in the immune system responsible for downregulation of immune activity. Checkpoint inhibitors target protein interactions between PD-1 and PD-L1, and between B7 and CTLA-4. Blockade of these interactions reverses immune system inhibition, augmenting immune system function and increasing cancer killing activity.

Dr. Krymskaya demonstrated both strong PD-L1 expression and T-cell infiltration in human lung LAM lesions, suggesting that modulation of the PD-1/PD-L1 immune axis is a potential treatment strategy for patients with LAM. Using an orthotopic mouse model of LAM, she found high levels of antigen-presenting cells expressing PD-L1, as well as PD-1-expressing T cells in immunocompetent murine lungs containing Tsc2−/− tumors.

Dr. Krymskaya was able to show that treatment with anti-PD-1 antibody improved survival in an immunocompetent mouse model of LAM. Dr. Krymskaya’s work is a robust starting point for investigating the potential of checkpoint immunotherapy in the treatment of LAM in human subjects.
I am a stem cell biologist, and I have worked for more than 20 years modeling human disease using the mouse or human cells in culture. About 8 years ago, I started developing human stem cell models of LAM. I come to LAMposium each year because I learn so much each time. This year was certainly no different.

For example, one of the most important tools we have in the lab to study disease is known as next generation sequencing, or NGS. We use NGS to identify disease-causing mutations, and to learn how mutations in genes like TSC2 affect the expression of the 20,000 genes encoded by our DNA. I have used NGS for many years, but never had the opportunity to attend a lecture and chat with one of the leaders of this field, Dr. Cole Trapnell of the University of Washington. Dr. Trapnell gave a primer on the technologies associated with single cell sequencing, including new computer programs his lab developed to interpret the massive amount of data generated by this technology.

Other highlights of the scientific talks included learning about glycoprotein NMB as a marker of LAM, a lively discussion on the best preclinical models in which to study LAM, and two talks about the evidence that immunotherapy can be used to treat mouse models of LAM. The research conference ended with an illuminating discussion on how to translate the exciting LAM research to the clinic.

Beyond the cutting-edge research, I learn more each year about the clinical manifestations of LAM not only from the physicians who treat LAM patients but through the presentations by LAM patients. Each year, I leave LAMposium tired but inspired to continue our research that we hope will contribute to the development of new treatments for women with LAM.
LAMposium 2018 has come and gone, and what a conference it was! If someone were to ask me to describe the experience in one word, I’m not sure which word I would choose. Wonderful, awesome, amazing, electric, inspiring, exhilarating… they all fit, but they don’t do justice to how much I took away from this year’s conference.

Hearing about the advancements being made in research is always informative and interesting. Working the fundraising table with other volunteers is something that never gets old. Connecting with people from all parts of the world who have the same goal is phenomenal! Being a part of the Breath of Hope Gala that raised over $271,000. I am truly connected to a community that continually offers “a breath of hope.”

Going to LAMposium is one of the best weekends of the year for me. I get to meet up with old friends and make new ones. I get to see lots of smiles and hear laughter everywhere. This year, I got the chance to welcome several first-time attendees to the LAM family during the Rose Ceremony, and that was very special for me. It is inspiring to see so many people come together for the same cause.

While staying connected through text messages, Skype, and FaceTime is great, there’s something special about getting hugs and more hugs from my LAM family. Each LAMposium has created wonderful memories for me, and this year was no exception.

If you attended LAMposium for the first time this year, you got the chance to experience something special: A community of diverse individuals coming together for a few days to laugh, cry, build each other up, offer strength and encouragement, and give “a breath of hope.”

My name is Dr. Sofya Tokman. I am a transplant pulmonologist and LAM Clinic Director at St. Joseph’s Hospital and Medical Center in Phoenix, Arizona.

I had the opportunity to participate in the Rose Ceremony, to connect with other clinicians, and to meet several women with LAM and their families. I was struck by the sense of community among conference attendees and by the generosity of donors at the Breath of Hope Gala. Although I observed many acts of kindness both big and small, Vineet Venugopal’s gift to Sharlene Dunn during the auction certainly stood out.

RLDC 2018 was an incredible source of education for clinicians like DJ and me. The conference improved my understanding of the biology of LAM and gave me hope for a brighter future for women afflicted with this condition. RLDC also offered an opportunity for me to get to know women with LAM outside the clinical setting, giving me a glimpse into the everyday challenges they face.
The time I spent with Meg was particularly enlightening. I typically see Meg in my office, sporting a petite portable concentrator and wearing a fabulously bright-colored jacket. Being with her outside the office at RLDC gave me insight into how much effort it requires for her to attend each appointment. I came away with a renewed sense of vigor and purpose to work toward a more holistic approach to care for women with LAM.

When I think of my time spent at LAMposium, the first word that comes to mind is family. This may sound bizarre when speaking of a medical community, but the gathering of patients, family members, medical professionals, and The LAM Foundation staff most certainly provides an atmosphere of caring, understanding, knowledge, growth, and empathy. This is a group of people who love and support one another, and to me, that feels like family.

This past year was my second LAMposium (of many to come, I’m sure). Being able to sit and discuss any and every aspect of such a rare disease with the leading medical professionals in the field is invaluable. Where else can you sit and eat breakfast and chat with scientists that are working night and day on a cure for you? It’s almost unheard of, and it is such a luxury that we have as LAM patients.

There are so many highlights of the conference, it’s hard to select just a few! For me this year, I would choose seeing patients who have had recent lung transplants—who were oxygen-dependent just last year—with no need for a tank this year! It really brought tears to my eyes to see them experiencing this new life.

Another highlight, year after year, is the Breath of Hope Gala and its fundraising accomplishments. It is moving to see so many people donate their hard-earned money to help fund a cure for the disease that plagues us—in an inspirational and FUN way! This year, not one, but two people that won items during the auction donated their wins (an entire vacation and a beautiful purse!) to other LAM patients. In a world where it’s sometimes hard to find the good, we are surely surrounded by it in our little LAM community.
The Breath of Hope Yoga & Social was inspired by two of my passions: Practicing yoga and finding a cure for LAM. I believe that we are very close to reaching this goal, which makes raising money critical at this point. My LAM sisters who organize great fundraising events in different regions have also been a huge source of motivation. Their dedication and strength inspire me every day to stand strong and fight this disease by contributing towards fundraising.

The community around me has been very kind. I am grateful to everyone who has helped support the Foundation via this event. We all know that different people have different skill sets. I reached out to my friends and coworkers who are designers, videographers, and content writers. We helped leverage their skills for the event, and they enjoyed doing what they love and raising money for LAM at the same time.

My favorite part of organizing these fundraisers is developing new and meaningful relationships. The event inevitably comes to an end every year, but what stays are my relationships with those who helped me put it together. I also really enjoy the whole process of planning the event and seeing it spring from my imagination, alive and real. All the actions leading up to the event build my excitement to see it succeed.

Planning an event is an experience in itself—there is so much I have learned. The Breath of Hope Yoga & Social has helped me overcome my inhibitions and share my story. It has helped me become confident about my condition and love myself for who I am. It has helped me feel empowered and think positively. It has helped me explore an altogether different me who believes in fighting and not giving up, both in terms of the event and my LAM diagnosis. This is my contribution towards finding a cure, and I feel very proud.

Fundraising is so important because the funds raised are ultimately used towards finding a cure for LAM. In 24 years, we have progressed from not knowing what LAM is to finding a treatment for LAM. All this was made possible with the support of fundraising in the background. Researchers and scientists need appropriate resources to study further, and this requires funding. We all share the duty of finding a cure by stepping forward, sharing our story, and fundraising.

There are three pieces of advice that I would give to my sisters who are looking to fundraise:

1. Find your passion. It could be something as simple as painting, yoga, wine tasting, or sports.
2. Attend events in your city that cater to your passion. This will not only give you the opportunity to have fun, but also to learn and implement ideas for your own event.
3. Reach out to friends and family for help. Most people want to support a good cause. By tapping into your community, you are not only contributing your own efforts, but also giving others an opportunity to give.

All in all, organizing a fundraiser and raising money towards finding a cure for LAM has been a life-changing experience for me. It has given me joy that cannot be described. My dream is to see a cure for LAM one day, and I am hopeful that I will see it in my lifetime. By working together, we can help the LAM community grow in leaps and bounds.

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FUNDRAISING SPOTLIGHT: THE BREATH OF HOPE YOGA & SOCIAL

BY NIKITA RATH

Nikita Rath is a LAM patient and host of the annual Breath of Hope Yoga & Social event in Chicago, IL.
In August 2018, Rachel Faleide, MSN, FNP-C, was diagnosed with LAM. In September 2018, she decided to share her diagnosis with friends and family by starting a Facebook fundraiser for LAM. This is what she wrote:

“In one week, I will turn 34. I used to hate birthdays, but now I appreciate each one I have. At the end of July, I had my gallbladder removed. During my CT scan, they found suspicious nodules all over my lungs. Two weeks later, I was diagnosed with lymphangioleiomyomatosis (or LAM) at the Mayo Clinic.

Two weeks ago, my husband and I gained hope and a better prospective on the disease. We attended the LAMposium conference in Cincinnati. We met the top doctors and scientists from around the world dedicated to helping us find better ways to manage this disease, and hopefully someday, a cure. We also met, laughed, and cried with other amazing women of all ages (some older, some younger, some doing better, and some doing worse). We learned how important fundraising is for our disease to help fund further research. I will soon be going out to the National Institutes of Health in Maryland to do my part and contribute my body to research, because if those of us with the disease don’t help solve it, no one will. No one else can.

Rachel’s initial goal was to raise $500. In just weeks, she smashed that goal by raising over $5,000. Here, she shares the story behind her fundraising success.

What gave you the idea to start fundraising on Facebook?
Facebook allows you to donate money to a charity of your choice on your birthday. On my birthday, my diagnosis was relatively new. I knew that I would eventually need to start telling people, so I used this fundraiser to tell my extended friends and family about my diagnosis.

How did it feel to open up to your community about your diagnosis?
Initially I was very scared to tell anyone in my community. As one of the only nurse practitioners for my little community, I didn’t want them to worry about me leaving or feeling deserted by another medical provider (which were already scarce). But the community’s response was overwhelming! I recall posting the fundraiser and then going outside to mow my lawn. By the time I came back in, over $2,000 had been raised. Many of my patients sent cards and flowers as well as words of support. My community really rallied for me.

Did anything surprise you along the way?
Yes, I was surprised by the dollar amount that was raised. I could not believe one little post that took me 30 minutes to write had the ability to raise so much money in such a short amount of time. It was incredible! The fundraiser also raised so much awareness for the disease and the LAM community.

What advice would you give to other patients about Facebook fundraising?
I have fundraised for many projects over the years, and this was as easy as it gets. I do feel that it’s a simple way to share your story and connect with others.

Why did you choose to raise money for The LAM Foundation?
I was diagnosed in August 2018. It was devastating. The hardest part was not knowing what to expect due to the rarity of this condition. In September 2018, my husband and I attended our first LAMposium. The experience completely changed our whole outlook. Suddenly, we realized that we are NOT ALONE, and people are working on research for us every day! After meeting with several other Lammies, I saw how supportive and wonderful this organization was. It felt like this incredible sorority. Raising money to help fund further research and to help my sisters will be something I continue to do for years to come.
On November 15, 2018, Andrea and Quint Slattery hosted “Life Experiences for LAM” in Philadelphia. Guests were dazzled by a dinner, live auction, and raffle to benefit The LAM Foundation amidst the beautiful setting of the Merion Golf Club.

Starting the evening off with purpose, Lyndsay Hoy and Andrea Slattery both gave moving speeches about the importance of funding LAM research. Guests then took the opportunity to do just that as Sherry Truhlar of Red Apple Auctions worked the room to auction off fabulous packages. These “life experiences” included trips to Jackson Hole and Mexico, a New York Fashion Week shopping excursion, a home entertaining event, golfing at six of the country’s best courses, and a girl’s day out. The night’s most coveted prize of all—$12,000 worth of shoes at Neiman Marcus—went to LAM patient Marjorie Hirshorn as the raffle winner!

Andrea and Quint pulled together family and friends to help make the night a success, including a dedicated steering committee, generous event sponsors, and auction donors who provided the wonderfully creative “life experiences.” Despite blizzard-like conditions, the sold-out event was packed with enthusiastic friends, family, and members of the LAM community. By the end of the night, “Life Experiences for LAM” had raised over $415,000 for The LAM Foundation.

Thank you to all who attended, donated, sponsored, and helped to make this evening a smashing success, and to Andrea and Quint for their efforts and dedication!
BREATH OF HOPE GIVING CLUBS

Thank you for your continued support of The LAM Foundation. This list recognizes Breath of Hope Giving Club standings as of March 30, 2018.

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Thank you!
INDIVIDUAL GIVING
January 1, 2018 through December 31, 2018

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* Gifts marked with an asterisk are made posthumously by members of the Breath of Hope Legacy Society.

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