Patient and Scientist Collaboration through Clinical Trials

Frank McCormack, M.D.
Scientific Director, The LAM Foundation
Professor and Director, Division of Pulmonary, Critical Care and Sleep Medicine
The University of Cincinnati
Why do 200 of the world's best scientists cross the globe for a meeting about two very rare disorders?

There is a pervasive optimism that this problem is scientifically tractable and potentially solvable in our lifetimes.
Patients organize

Engage, motivate scientists

Engage NIH

Fund research

Volunteer for trials

TARGET

Preclinical studies

Pilot trial

Pivotal trial

Effective therapy

FDA approval
Compared to other diseases that scar the lung, LAM has several assets

• We understand a lot about the cause of LAM
• We have many ideas for drugs to test based on sound science
• LAM science is moving as quickly as any in pulmonary medicine
• We have a motivated, intelligent, organized patient population
<table>
<thead>
<tr>
<th></th>
<th>Cause known?</th>
<th>Effective therapy?</th>
<th>Molecular targets for trials?</th>
<th>Diagnostic biomarker</th>
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</thead>
<tbody>
<tr>
<td><strong>Sarcoid</strong></td>
<td>no</td>
<td>no</td>
<td>few</td>
<td>no</td>
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<tr>
<td><strong>LAM</strong></td>
<td>yes</td>
<td>yes</td>
<td>many</td>
<td>yes</td>
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</table>
LAM
Accumulated Assets

• Our organized, motivated patient community
• Our rich understanding of the molecular basis of LAM
• Networks of expert centers
  – For Clinical care
  – For Research
    • Registry
    • Tissue bank
    • Data center
• An effective suppressive therapy
• A useful diagnostic, predictive and prognostic biomarker
• Invaluable partnerships
  • with the TSC community
  • the National Heart, Lung, Blood Institute and UK NHS
  • among international LAM communities
    • specially Japan, US and UK
Finding treatments for LAM

Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people and ways to improve health.
Examples of diseases that can be controlled and sometimes cured because clinical trials were done properly

- AIDS
- Leukemias
- Lymphomas
- Hepatitis
- Breast cancer
Bottom line on the importance of human trials in LAM

There simply is no ideal animal model for LAM, and human studies are the only way to be sure that ideas from the laboratory are sound.
But
Clinical trials

• Clinical trials often pose risk
What LAM patients have earned through participation in trials and studies so far

• The genetic cause of LAM
• An effective suppressive treatment
• A diagnostic blood test (VEGF-D)
• A blood test that predicts benefit of therapy (VEGF-D)
• A sound approach to management of pneumothorax
• The utility of HRCT and transbronchial biopsy in the diagnosis of LAM
• Protection from ineffective treatments with doxycycline and progesterone
• Safety information for hydroxychloroquine, letrozole, and (soon) statins in preparation for larger trials
What do we need from future trials and studies

• Remission inducing therapies
• Refining our approach to sirolimus therapy
• Better diagnostic tests
• Tests for personalizing therapy
• Ways to predict progression and response
• Ways to measure total body LAM cell burden
• Where LAM cells come from
• Why women are selectively affected
LAM is the simplest, most decipherable neoplasm in all of creation

- Most cancer cells have dozens of DNA mistakes that enable them to:
  - disregard all the rules
  - grow beyond their boundaries
  - destroy remote tissues

- LAM cells acquire cancer-like capabilities with a single DNA mistake

- Because it’s so simple, the study of LAM provides insight into cancer’s Achilles heel
The study of LAM is rewriting biochemistry textbooks
mTORC1 induces purine synthesis through control of the mitochondrial tetrahydrofolate cycle

Issam Ben-Sahra, Gerta Hoxhaj, Stéphane J. H. Ricoult, John M. Asara, Brendan D. Manning

ACKNOWLEDGMENTS

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Trials

• Completed trials
  – MILES  sirolimus  mTOR pathway
  – RADx2201  everolimus  mTOR pathway
  – Doxycycline  doxycycline  Matrix remodeling
  – The SAIL Trial  hydroxychloroquine  autophagy
  – The TRAIL Trial  letrozole  estrogen axis
  – MSTLS trial  sirolimus  mTOR pathway

• Open trials
  – The SOS Trial  simvastatin  apoptosis
  – The SLAM Trial  saracatanib  EMT/autophagy
  – MIDAS  sirolimus  observation
  – Cox2  Celecoxib  apoptosis

• Pending trials
  – MILED  sirolimus  mTOR pathway
  – Inhaled rapa  sirolimus  mTOR pathway
  – Imatananib trial  Gleevec + sirolimus  apoptosis
  – RESULT  resveratrol + sirolimus  apoptosis
Exciting emerging basic LAM directions

• Immune targeting of LAM
  – PD-1/PD-L1 inhibitors

• Targeting metabolic vulnerabilities
  – purine analogues, drugs that affect sirol
Other ideas for upcoming trials

- mizorbine, methotrexate, mycophenylate
- Kaytruda and other immune checkpoint inhibitors
- anti-VEGFR3, anti-VEGF-D, axitinib, pazopanib
- metformin
- anti-estrogen therapies
How do I know if my LAM is going to progress?

• The best indicator is the way it has behaved before
  – FEV1 decline
    • Fast-200 cc/year
    • Typical-70-100 cc/year
    • Slow-30-40 cc/year

• Menopausal status has a big effect
  – Premenopausal-faster (200 cc FEV1 loss/year)
  – Postmenopausal-slower (40 cc FEV1 loss/year)

• VEGF-D level
  – Higher level, faster decline
  – Higher level, better treatment response
Lung function measures, imperfect as they may be, are far and away our best current biomarker. It's important not to overreact to a single down value.

![Graph showing FEV1 prebd over days]

FEV1 prebd

days
How are we currently using sirolimus?

• We treat
  – Patients with abnormal lung function.
    • FEV1 or DLCO< 70% predicted
  – Patients who are declining rapidly and approaching the abnormal range
    • Even when lung function is still normal
  – Patients with problematic effusions or other lymphatic complications
What dose of sirolimus are we using?

- Because sirolimus is taken for long periods, and has side effect, we must strive to find the lowest effective dose
- 1 mg per day keeps most of my patients stable — but not all—need to check FEV1 frequently to verify stability
- In my opinion, low dose sirolimus appears to be very safe.
What I tell new LAM patients

• There is every reason to be optimistic
  – We have an effective therapy
  – Sirolimus effectively suppresses LAM in the same way as blood pressure medicine suppresses hypertension or statins suppress cholesterol
    • It is ‘effective’ not ‘partially effective’
  – The best scientists in the world are interested in the LAM pathway and rate of progress is astounding
For Andrea Slattery, sirolimus stopped the decline in lung function.
What to do when sirolimus does not seem to be working?

- Consider alternative explanations (drug interactions, asthma)
- Consider increasing the dose
- Consider enrolling in trials
VEGF-D testing can save people from need for biopsy and

• To make the diagnosis in patients who have typical lung cysts but no other clues
  – Works more than 50% of the time

• As one tool for decision-making about when to start treatment

https://research.cchmc.org/translationalcores/ttdsl
How do we hope to be able to use VEGF-D and other biomarkers in the future?

• To dose sirolimus properly
• To get an early idea of whether sirolimus will work well in a given individual
• To make trials faster
What’s Next?
We need a way to image and estimate the total body burden of LAM cells.
NHLBI Registry

• 243 patients enrolled in NHLBI Registry between 8/98 and 10/01 followed every 6-12 months for 5 years at six centers
  – CCF, NIH, NJH, NEMC, Stanford, Mayo

• Two papers published
  – Ryu J et al. NHLBI Registry-Characteristics at Enrollment AJRCCM 2006. 173; 105-111

• Longitudinal paper never published
NHLBI Registry Longitudinal Study

- NHLBI transferred all data and samples to National Disease Research Interchange (NDRI) where it is publicly available
- Nishant obtained all NHLBI clinical data on 250 patients and 435 NDRI serum samples
- Nishant submitted social security numbers to the CDC National Death Index (NDI) and the United Network for Organ Sharing (UNOS) to obtain death/transplant status
Linking NHLBI Registry data to death/transplant outcomes

• In the 15 year interval since the last of 240 Registry patients was enrolled there have been
  – 53 transplants
  – 43 deaths (including 15 post transplant)

• With such a large number of events, we should be able correlate many disease features with outcomes of death/transplant
  – Menopausal status
  – Baseline FEV1, DLCO
  – Rate of decline in FEV1, DLCO
  – VEGF-D
  – Your favorite biomarker
With the NDRI/NDI/UNOS data, we will be able to develop a LAM Risk Score Calculator.

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**PAH RISK SCORE CALCULATOR**

For more information go to www.pah-app.com

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<tr>
<th>WHO Group I Subgroup</th>
<th>WHO Group II</th>
<th>WHO Group III</th>
<th>WHO Group IV</th>
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<td>+1</td>
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| Vital Signs               | | |
|----------------------------|---|
| BSB ≤110 mm Hg            | +1 |
| BB ≤82 BPM                | +2 |

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<tr>
<th>6-Minute Walk Test</th>
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<td>≤140 m</td>
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<td>&gt;140 m</td>
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<tr>
<td>&gt;10 pg/mL</td>
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<td>% pred. DLco ≤60</td>
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<tr>
<td>% pred. DLco ≥80</td>
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<th>Right-heart Catheterization</th>
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<td>mRAP ≤20 mm Hg within 1 yr</td>
<td>+1</td>
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<tr>
<td>PVR ≤32 Wood units</td>
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**SUM OF ABOVE**

(Starting Score) + 6

=RISK SCORE

Risk scores range from 0 (lowest risk) to 22 (highest risk)

- **LOW RISK**: Score 1–7
- **AVERAGE RISK**: Score 8
- **MODERATE HIGH RISK**: Score 9
- **HIGH RISK**: Score 10–11
- **VERY HIGH RISK**: Score ≥12

<table>
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<tr>
<th>PREDICTED 5 YEAR SURVIVAL</th>
<th>95%–100%</th>
<th>90%–95%</th>
<th>85%–90%</th>
<th>70%–85%</th>
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<td>RISK SCORE</td>
<td>1–7</td>
<td>8</td>
<td>9</td>
<td>10–11</td>
<td>≥12</td>
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Priorities for mTOR inhibitors

– Refine the approach to use of mTOR inhibitors
  • Provide access to drug for all
    – Regulatory approval around the world, PMDA, FDA and beyond
  • Personalize dosing
    – Determine the lowest effective dose for each individual
  • Determine if early treatment prevents progression
  • Determine if the drug can be safely given over long periods
  • Find markers that allow us to determine who will progress and who will respond
MIDAS Registry

• An NIH funded natural history study for all LAM patients (whether they are are on sirolimus or not)
• Strictly observational-does not involve extra testing
• Currently have about 200 LAM patients enrolled in U.S.
• Will eventually extend to international sites
MIDAS

• Who is eligible for MIDAS?
  – Every woman with TSC, cysts or not
    • must attend a TSC or LAM Clinic at least once per year
  – Every woman with LAM
    • must attend a LAM Clinic at least once per year
MIDAS Registry

– Examples of what could we learn from MIDAS
  • Where sirolimus continues to work over long periods
  • Whether sirolimus is safe over long periods
    – Unusual side effects (such as ovarian cysts) may emerge
  • Whether sirolimus improves quality of life
  • Whether sirolimus improves survival
  • The natural history of LAM in a community cohort
  • Whether VEGF-D predicts development of LAM in women with TSC
MIDAS Sites

• 8 sites are open and enrolling
  – UCincinnati, Stanford, Vanderbilt, Cleveland Clinic, UT Houston, UPenn, UUtah, UMich

• 10 sites will soon open
  – MayoFL, Oregon, Minor/James, Harvard, URochester, St. Louis, Charleston, Emory, Loyola National Jewish

• 15 other sites are considering
MIDAS Registry

• Our hope is that MIDAS will live on in perpetuity, and will be a platform for future research
• My hope is that every LAM patient will enroll, and every woman with TSC will enroll
To explore participation in MIDAS

• Contact the research coordinator in Cincinnati or at your local site.
• A consent form will be mailed to you to read before you visit the site.
• The site investigator will explain the risks and benefits of the study to you.
• To enroll, you must sign the consent in the presence of the site personnel
• Write to me
  – frank.mccormack@uc.edu
Multicenter International LAM Efficacy of Sirolimus Trial (MILES Trial)
If MILED is wildly successful

- In the future, when a woman with no symptoms is diagnosed with early LAM we will be able to arrest the disease in its tracks before the lung is further damaged
The Low Dose Used in MILED will limit Sirolimus Side Effects

- Mouth ulcers
- High cholesterol
- Lung inflammation
- Low platelets
- Acne-like lesions
- Diarrhea
- High blood pressure
- Protein in the urine
- Suppression of the immune system
- Swelling
- Hypertension
- Pericarditis
- Pericardial effusion
- Skin cancer
- Latent malignancy
- Death
MILED
Who is eligible

- Definite LAM based on ATS/ERS criteria
- Normal FEV1
- Some evidence that LAM might progress
  - oxygen need with sleep or exercise
  - prior progression based on historical pfts
  - premenopausal status + RV or DLCO abnormal on pfts
  - elevated VEGF-D + RV or DLCO abnormal on pfts
  - more than 20 cysts on carinal cut of CT
The MILED Trial is:

- Placebo-controlled
  - Some patients get sirolimus 1 milligrams and some patients get a placebo (sugar pill)
- Randomized
  - The computer ‘flips a coin’ to determine who gets placebo or sirolimus
- Double-blind
  - neither the doctor or the patient knows who is taking the drug or the placebo
MILED
Why does there have to be a placebo arm?

• Without a placebo, it is very easy to be fooled.
  – pulmonary test results vary with how hard patients try
  – patients who are hopeful they are on an effective drug may try harder
Who is ineligible for MILED?

• Patients who have
  – an FEV1 >70% predicted
  – a DLCO less than 60% predicted
  – a resting oxygen requirement
  – large chylous collections
How many patients will be enrolled in the MILED trial

• 60 total
  – 30 in the placebo arm
  – 30 in the sirolimus arm

Study may be ended early after interim analysis is completed if sirolimus is effective
MILED

Where are the sites?

- University of Cincinnati
- Cleveland Clinic
- Vanderbilt
- Loyola Chicago
- Stanford
- University of Pennsylvania
- National Jewish Hospital
- Emory University
- UT Houston
- Brigham and Women’s
- Minor/James Seattle
Who is sponsoring the MILED Trial?

• National Institutes of Health
  – NHLBI (National Heart Lung and Blood Institute)

• The LAM Foundation

• Pfizer
MILED

What will be expected of me?

• You must be willing to be randomly assigned to the placebo or the sirolimus arm
• 7 visits over 2 years
• Travel will be compensated
• Pulmonary function tests, questionnaires and blood tests are done on all visits
• Chest xrays are done at the beginning and the end.
• No CT scans or MRI
• If your lung function declines, you will exit the study and be offered drug
How to explore participation in MILED

• Contact the research coordinator in Cincinnati or at your local site.
• A consent form will be mailed to you to read before you visit the site.
• The site investigator will explain the risks and benefits of the study to you.
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FAQ MIDAS and MILED

• 1. Can I be in both MILED and MIDAS?
  – Yes

• 2. Can I be in other trials and be in MIDAS?
  – Yes

• 3. In MILED, can I learn whether I was in the placebo or treatment group?
  – Yes, after the trial is over
Innovation
LAM Meeting Schedule

2015
- LAMposium 2015
  - Chicago

2016
- RLDC 2016
  - Cincinnati

2017
- TSC/LAM
  - DC

2018
- LAMposium 2018
  - Chicago

Biomarker 2014
- Atlanta

Patient Benefit
- West Coast
What can I do?

• Enroll in trials!
• Donate research data and samples
• Get online and answer LAM Foundation queries
• Attend a LAM clinic at least once per year
Enough said