Lymphatic Malformation Institute

2012 ANNUAL REPORT

This report summarizes the key proceedings of the Lymphatic Malformation Institute's research funding program for the year 2012.

RESEARCH PROJECTS

ACTIVE

Several projects were launched or approved for funding this year, and a total of $585,982.54 was invested in/committed towards research. These projects cover different areas of investigation such as patient-database construction, generation of mouse models, genomics and *in vitro* cell and molecular biology studies:

1. Lymphatic anomalies database

(Cameron C. Trenor III, MD; Boston Children's Hospital)

The main goal of this project is to assimilate and organize the patient data for the large number of vascular anomalies patients seen at BCH into a searchable database. The pilot phase of the project is nearing completion and work on the main project has begun, including defining data elements and building patient questionnaires.

2. Transgenic mouse model to determine the mechanism and treatment of congenital pulmonary lymphangiectasia and lymphangiomatosis

(Donald M. McDonald, MD, PhD; University of California, San Francisco)

This project focuses on the development and characterization of a potential mouse model of lymphangiomatosis. This is being achieved by over-expressing VEGF-C in lungs to test if that leads to over-growth of lymphatic vessels and chylothorax, conditions that will mimic what is seen in patients. Results from these studies will not only help shed light on the mechanism of pulmonary pathology seen in lymphangiomatosis, but will also give to the field its first mouse model of the disease that could be used to pursue additional avenues of investigation.

3. Molecular crosstalk and matrix metalloproteinases in generalized lymphatic anomaly (GLA) and Gorham-Stout syndrome (GSS) patients

(Ramani Ramchandran, PhD and Kelly Duffy, PhD; Medical College of Wisconsin)

The study will investigate signaling between lymphatic endothelial cells (LECs) and osteoclasts to learn if and how the deregulation of this communication causes disease. The pleural cell sample from a patient sent to Dr. Duffy's lab by the LMI in 2011 was successfully cultured, and will be a

The LMI employs a unique, interactive model for funding research – we communicate frequently with our applicants and grantees to brainstorm and shape project ideas. The entire funding process, including the review of grant proposals, is run by the institute's Research Director, Dr. Michael Dellinger and Program Director, Dr. Nupur Garg.

part of the study (*LMI Annual Report 2011*). Overall, this project will be instrumental in developing a cell culture model for studying the disease mechanism *in vitro*.

4. Genetic and genomic analysis in patients affected by Gorham-Stout disease and general lymphatic anomalies

(Juan Carlos Lopez Gutierrez, MD, PhD and Pablo Lapunzina, MD, PhD; Institute of Medical and Molecular Genetics (INGEMM), Madrid, Spain)

In this project, genomic analysis will be conducted on patient samples including blood as well as tissue to uncover potential genetic anomalies behind lymphangiomatosis and/or Gorham's disease. Techniques employed include karyotyping arrays, SNP arrays and next generation sequencing (NGS).

5. Immunohistochemical features of lymphangiomatosis and Gorham's disease

(Erik Eklund, MD, PhD; Lund University, Lund, Sweden)

The work will focus on staining patient tissue samples to visualize and quantify the levels of signaling molecules, cell-surface receptors, and several other proteins. This will help identify candidate targets for further studies whose deregulation is involved in disease pathogenesis.

6. Exome sequencing

(Michael A. Levine, MD; Children's Hospital of Philadelphia)

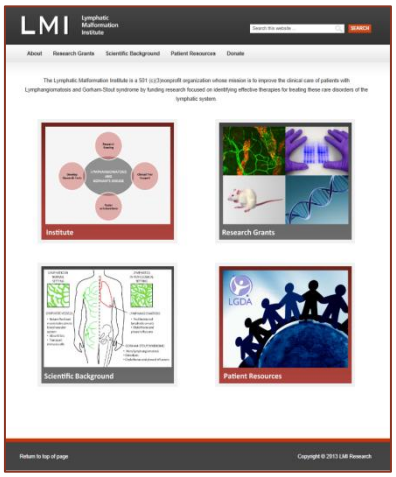
Work on this project, initiated in early 2011, continued during 2012, and involves exome sequencing in a lymphangiomatosis patient's blood samples and lesional tissue. Also included in the analyses are control samples from unaffected family members. Preliminary candidate-data is being further investigated to determine potential significance and contribution to disease.

UNDER CONSIDERATION

Pre-proposals for two new project ideas were received and favorably reviewed. They include investigation of the mTOR and RANKL pathways in disease, and the development of a mouse model for Gorham's disease. Full applications for both projects will be reviewed in the first quarter of 2013.

WEBSITE LAUNCHED

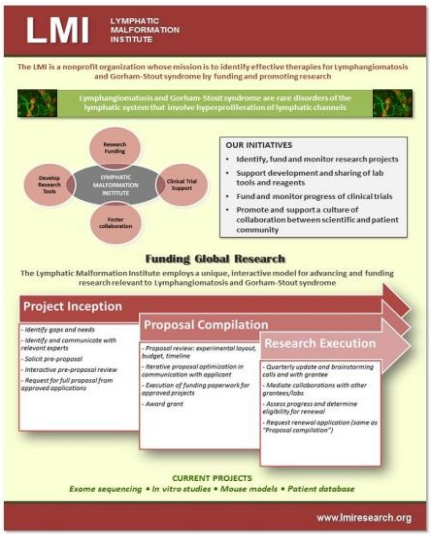
The LMI website**, www.lmiresearch.org**, was launched in September 2012. The site is home to key resources for scientists who are seeking to learn about, and find funding opportunities for research on lymphangiomatosis and Gorham's disease. These include background information on these disorders, descriptions of projects currently funded by the LMI, and detailed instructions for



submitting grant applications. In the few months since its launch, the website has already helped the LMI gain greater visibility amongst the scientific community. By providing up-to-date information, we aim for the website to be a reflection of the institute's growing program and presence.

We are greatly obliged to Marshall Matheson of WTWH Media for designing and constructing the website. WTWH Media has been a longtime supporter of the LMI, and we thank them for their continued assistance in advancing our goals.

CONFERENCES ATTENDED



Flyer highlighting LMI's program for distribution at conferences

The following scientific conferences were attended by the LMI staff in 2012:

1. Rare Bone Disease Research Summit

This meeting was held at Johns Hopkins, Baltimore, MD from September 18-19, 2012. It was attended by Tiffany Ferry and Jack Kelly. Both LMI and LGDA provided sponsorship for the meeting. It featured talks on lymphangiomatosis and Gorham's disease presented by Drs. Matthew Warman, and Cameron Trenor III, both of whom were invited to the meeting by the LMI and LGDA.

The following three meetings were attended by Dr. Michael Dellinger who introduced the LMI's research funding program to, and initiated dialogues with several investigators at them:

2. Gordon Research Conference: Molecular Mechanisms in Lymphatic Function& Disease

This meeting was held in Ventura, CA from March 4-9, 2012.

3. International Society for Study of Vascular Anomalies' (ISSVA) 19th International Workshop on Vascular Anomalies

This meeting was held in Malmo, Sweden from June 16-19, 2012.

4. North American Vascular Biology Organization's (NAVBO) Workshop in Vascular Biology
The workshop was held in Monterey, CA from October 14-18, 2012.

COLLABORATIVE ACTIVITIES WITH LGDA

The LMI continues to work very closely with the LGDA on several fronts. This section summarizes the key activities that were led by the LGDA and supported by the LMI during 2012. They revolve around the need to establish well organized systems for collecting and consolidating patient clinical data and samples for catalyzing both basic as well as clinical research. We thank Jack Kelly and Lisa Klepper, RN of the LGDA for their leadership and commitment to these efforts.

1. Global Rare Diseases Patient Registry and Data Repository (GRDR)
The LGDA was one of handful of organizations chosen by the NIH's Office of Rare Diseases Research (ORDR) for its two-year pilot program to collect patient clinical information and build a patient registry that can be used for data analyses and to facilitate future clinical trials. Work on building the registry was initiated in August, shortly after obtaining the approval. The LMI supported the LGDA in this vital endeavor through Dr. Nupur Garg's participation in brainstorming calls during the application process and in the period following the launch.

2. Tissue banking discussions
The LMI and LGDA conducted several conference calls to explore how arrangements can be made for collection, banking and subsequent usage of patient clinical samples such as pleural fluid and tissue sections. This is critically needed to prevent wastage of surgical samples and ensure their availability as material for research. These calls were conducted with individuals/organizations with strong experience in establishing and running tissue banks: Daniel Remer, Rare Disease Program Manager at the National Disease Research Interchange (NDRI), Clinical and Translational Science Institute Biorepository (CTSI Biorepository) at the University of Florida, Dr. Joel Moss at NHLBI, and Jeffrey Kaufman, Executive Director of the Adenoid Cystic Carcinoma Research Foundation (ACCRF). The main goal behind these calls was to understand the complex consent and IRB issues that are involved in setting up tissue banking and sharing. We hope to transform the knowledge gained into concrete action items in the very near future.

3. LGDA brochure
The existing LGDA brochure was revised and updated to incorporate new information. The brochure is intended to highlight background information on lymphangiomatosis and Gorham's disease, as well as provide patients and families with overviews of LGDA's patient registry, their physician-finding program, available treatment options, and other support services. By distributing

it amongst patient and clinical community, particularly at conferences, a key goal is to boost patient recruitment by increasing awareness about these disorders.

SUPPORT FOR THE FAST ACT

The LMI was one over 150 rare disease organizations that Dr. Emil Kakkis, of the EveryLife Foundation, organized to make a coordinated effort to support the ULTRA Act (Unlocking Life Saving Treatments for Rare Diseases Act), and that was eventually adapted into the FAST Act (Faster Access to Specialized Treatments Act) and signed by President Obama in the fall of 2012. The FAST act will expand on the FDA's existing Fast Track and Accelerated Approval pathways for drugs.

CONCLUDING REMARKS

The LMI's research program grew significantly from last year with the funding of several new projects. In addition, planning for an international research conference to be held in mid-2013 has also begun. This meeting will bring together experts from the fields of lymphatics as well as bone biology, and will help identify and address key knowledge-gaps by generating novel ideas for investigation. By forming and strengthening partnerships with labs around the world, we hope that the LMI will continue to gain momentum in the coming year, and establish itself as a pivotal player in lymphangiomatosis and Gorham's disease research.