

2010 Grant Recipients

Hélène Maby-El Hajjami, Ph.D.

University Central Hospital, Switzerland

"Development of transcriptional differentiation approaches for treatment of lymphedema-distichiasis syndrome"

The lymphatic vasculature maintains normal tissue fluid balance by transporting fluid and macromolecules from tissues back to the blood circulation, and it also plays an important role in human diseases such as lymphedema, inflammation and cancer. Lymphatic vasculature is a hierarchically organized network, composed of two functionally and molecularly distinct types of vessels: capillaries and collecting vessels. One of the outstanding questions in lymphatic vascular biology is how this hierarchy of lymphatic vessels is initiated and maintained. Answering this question has profound clinical implications, as damage to the collecting lymphatic vessels causes the majority of lymphedemas, which affects up to 30% of long-term breast cancer survivors. We focus our research on a rare hereditary form of lymphedema, lymphedema-distichiasis, caused by mutated form of forkhead transcription factor FOXC2. Here we propose to study the mechanisms and potential treatment approaches of collecting lymphatic vessel failure in lymphedema by identifying the regulators of FOXC2 transcription in lymphatic endothelium and by developing the transgenic mouse model to study the ability of FOXC2 to promote the differentiation of lymphatic vessels in vivo. We expect that our results will provide novel fundamental knowledge about the regulation of vascular specification during vertebrate development, and will help to design novel treatment strategies for primary and secondary lymphedema.

Li-Chin Yao, Ph.D.

University of California San Francisco, United States

"Development and maintenance of lymphatic endothelial cell specializations in mouse respiratory tract"

Lymphatic endothelial cells are gatekeepers of fluid and cell clearance from tissues. Defective lymphatic transport induces lymphedema and impairs immune responses to infection. To date, there is no effective cure for lymphedema and treatment is limited to manual lymph drainage therapies. Knowledge of the structure and function of lymphatics has lagged far behind corresponding studies of blood vessels. Our laboratory recently discovered that endothelial cells in initial lymphatics have discontinuous junctions uniquely different from the continuous junctions in collecting lymphatics and blood vessels. Junctions are also abnormal in tips of new lymphatics growing during inflammation. The functional significance of these unexpected changes is unknown.

The overall goal of this proposal is to extend our knowledge of the structure and function of specialized lymphatic endothelial junctions in development, health and disease. I hypothesize that the molecular composition of the specialized junctions determines the proper function of initial lymphatics and that abnormal lymphatic junctions are functionally defective, contributing to the pathophysiology of inflammation and development of lymphedema.

My three specific aims are to determine: (1) when specialized lymphatic endothelial junctions develop during pre/postnatal development; (2) whether endothelial junctions develop abnormally in new lymphatics that grow during inflammation; (3) whether treatment of sustained inflammation restores the normal junctional structure of initial lymphatics.

I will take advantage of our well-established mouse model of chronic inflammation induced by airway infection with the pathogen *Mycoplasma pulmonis*. Transgenic overexpression of VEGF-C will be also used. I will use confocal microscopy to determine the distribution of immunohistochemical markers of junctional molecules in lymphatics of mouse airways and lungs in three conditions: normal developmental; in inflammatory conditions; and during reversal and resolution of inflammation after treatment with antibiotics or anti-inflammatory drugs. These structural studies will be supported by functional and molecular biological studies of lymphatics, including transport of fluid and cells and qRT-PCR expression studies.

My long-term goal is to advance our understanding of the role of lymphatic vessels in chronic inflammation by elucidating the development and plasticity of endothelial junctions in initial lymphatics,. Such knowledge may suggest new strategies and therapeutic targets in human inflammatory diseases.

Guy Malkinson, Ph.D.

Weizmann Institute of Science, Israel

"Genetic analysis of lymphatic system development in zebrafish"

The lymphatic system is a network of blind-ended capillaries that protects and maintains the homeostasis of the body by filtering and draining lymphatic fluid. Lately, the lymphatic endothelium has become the subject of great interest especially because of its important role during pathological processes, such as the dissemination of tumor metastasis and lymphedema. Despite the importance of lymphangiogenesis, little is known about the mechanisms that control the early formation and differentiation of lymphatic vessels. Progress in understanding the development of the lymphatic system has been hampered by difficulties in observing lymphatic cells in-vivo and performing defined genetic and experimental manipulation of lymphatic endothelial cells.

Using multiphoton time-lapse imaging of living embryos, we previously demonstrated the existence of a bona-fide lymphatic vascular system in the zebrafish, and established this as an important new experimental and genetic model organism for studying lymphangiogenesis. In this proposal, we will draw on our previous experience characterizing the fish lymphatic vasculature to elucidate novel molecular and cellular mechanisms regulating early lymphangiogenesis. Specifically, we propose genetic and in-vivo imaging studies aimed at characterizing y114- a novel zebrafish mutant that fails to develop lymphatic vessels. Our specific aims are as follows:

1. Phenotypic characterization of y114: We will use long-term time-lapse imaging of homozygous mutants with EGFP-labeled endothelial cells to identify the specific steps of lymphangiogenesis affected by the mutation.
2. Identification of the mutated locus: We will identify the mutated locus responsible for the mutant phenotype by a combination of positional cloning and candidate gene approaches.
3. Functional characterization of y114 during lymphatic development. Studies in support of this aim will include spatiotemporal analysis of y114 expression as well as initial loss- and gain-of-function studies aimed at elucidating the function of the newly identified locus during lymphatic development.

Taken together these studies promise to offer key insights into the genetic programs and cellular behaviors that help shape the lymphatic vasculature. The analysis of the newly defined locus should shed light on previously uncharacterized lymphangiogenic components and possibly provide new drug targets for the treatment of pathological lymphatic conditions that lead to inflammation, autoimmunity and cancer.

2008 Grant Recipients

Xabier Lopez Aranguren, Ph.D.

Katholieke Universiteit Leuven, Belgium

"Molecular Biology and Therapeutic Potential of Multipotent Adult Progenitor Cell (MAPC) Derived Lymphatic Endothelial Cells"

Damien Gerald, Ph.D.

Beth Israel Deaconess Medical Center, United States

"Investigation of RhoB's Function in Lymphatics: a Model to Improve Lymphedema Therapy"

Sunkuk Kwon, Ph.D.

Baylor College of Medicine, United States

"Near-infrared Fluorescence Optical Imaging of Lymph Function in a Preclinical Murine Model"

2006 Grant Recipients

Rawad Mounzer, M.D.

Yale University School of Medicine, United States

"Lymphangiogenesis in Acute and Chronic Models of Inflammation"

Zhanna Nepiyushchikh, M.D.

Texas A&M University, United States

"Functional Roles of Myosin Light Chain in Lymphatic Pumping Activity"

Martin Schneider, M.D.

University of Leuven, VIB, Belgium

"Xenopus Laevis as a Model to Study Lymphangiogenesis in Health and Disease"

R Sathish Srinivasan, Ph.D.

St. Jude Children's Research Hospital, United States

"Lineage Tracing to Identify the Sources of Lymphatic Endothelial Cells"

Additional Support for NIH-funded Postdoctoral Fellows in Lymphatic Research Awards

Gregory Lam, M.D.

Duke University Medical Center, United States

"The Role of Tie2 and the Angiopoietins in EPC Biology"