Interim Progress Report for 2019 ISHLT/Enduring Heart Transplant Longevity Research Award

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We would like to thank the Enduring Hearts Foundation for its generous support of our research program, entitled “Leukotriene B4: A Potential Mediator and Biomarker for Cardiac Allograft Vasculopathy (CAV)”. The overall aim of our work is to translate findings from preliminary animal and human CAV models into clinically useful biomarkers and novel targets for therapeutics to prevent and treat CAV. Our overall hypothesis is that LTB4, an inflammatory lipid mediator, is a key molecule involved in the development of CAV, that LTB4 level can be used as a biomarker for early CAV detection, and that the LTB4 signaling pathway is an important target for novel drugs that prevent and/or treat CAV.

***Specific Aim 1:* Define the involvement of Leukotriene B4 (LTB4) in an experimental model for CAV.**

Rationale: LTB4 is produced by macrophages through the conversion of LTA4 to LTB4 via the enzyme leukotriene A_4 hydrolase (LTA4H) and induces vascular endothelial cell apoptosis and smooth muscle cell proliferation. To assess the role of LTB4 during CAV development, we will inhibit LTA4H with the drug Bestatin (also known as ubenimex), and assess lesion formation and local inflammation, as a surrogate for CAV formation, in a well-established rat aortic transplant model.

Progress to-date: The experiments for Specific Aim 1 are being conducted by Dr. Sonja Schrepfer’s group in the Laboratory of Transplant Surgery and Immunology at UCSF. In the six months since receipt of the first installment of grant funding, Dr. Schrepfer’s group has performed 15 of the 30 planned rat aortic transplants. The remaining 15 rat aortic transplants will be performed by March 2020. Subsequently, histopathological analysis of CAV development will be performed, as well as the immunohistochemistry, immunofluorescence, ELISPOT, and CyTOF/mass cytometry assays described in the proposal.

***Specific Aim 2:* Determine plasma LTB4 levels in HT recipients with CAV and correlate with clinical activity to determine whether plasma LTB4 levels can be used as a non-invasive CAV biomarker.**

For this aim, we will enroll 20 adult heart transplant and 10 pediatric heart transplant recipients with CAV, as well as age- and sex-matched controls without CAV. Blood is being drawn at study enrollment, and after 6 months, to measure plasma LTB4 and NT-proBNP levels. We are also recording New York Heart Association functional class and echocardiographic measurements in our study database.

Enrolled participants are screened prior to their standard-of-care follow-up clinic visits at Stanford Hospital. Angiograms are reviewed by study staff and the principal investigator. Once diagnosis is confirmed, study coordinator consents participants in clinic, blood is drawn, then processed and banked at research center.

All blood samples will be batched and sent to MD Biosciences for measurement of LTB4 levels. NT-proBNP levels are being run by the Stanford Clinical Laboratory.

The following tables and charts summarize patient enrollment to-date, as well as demographic and clinical characteristics. We started out by focusing on adult heart transplant patient enrollment, and will now focus our attention on pediatric enrollment. We are very confident that we will be able to enroll the remaining patients in year 2. We have been in active discussion with the pediatric team and they are identifying appropriate patients for enrollment.

In summary, we have made substantial progress towards achieving our study goals and objectives since receipt of the first year of study funds in April 2019, and we look forward to continued progress towards achieving our two main study aims in the coming year, with continued support from the Enduring Hearts Foundation.

	Enrollment Goal	**Current Enrollment**
Single-organ adult heart transplant recipients CAV (+)	20	20
Single-organ adult heart transplant recipients CAV (-)	20	3
Single-organ pediatric heart transplant recipients CAV (+)	10	2
Single-organ pediatric heart transplant recipients CAV (-)	10	0