MOLECULAR, CELLULAR & INTEGRATIVE PHYSIOLOGY
GRADUATE GROUP

WINTER 2014 RESEARCH COLLOQUIUM &
POSTER SESSION

Friday, March 7, 2014
AGR Room, Buehler Alumni and Visitors Center

2:00 – 3:00 p.m. Poster set-up and judging

3:00 – 3:05 p.m. Welcome- Dr. Dietmar Kueltz

3:05 – 3:20 p.m. **Presentation by Bert Frederich**
"Cardiac Progenitor Cell migration is directed by combined chemotactic and electrotactic signaling mechanisms"
Major Professor: Nipavan Chiamvimonvat, MD

3:25 – 3:40 p.m. **Presentation by Tyler Stradleigh, Exit Seminar**
"Improved Preservation of Life-like morphology in Organotypically Cultured Retinal Ganglion Cells"
Major Professor: Andrew Ishida, Ph.D.

3:45 – 4:00 p.m. **Presentation by Mikella Robinson**
"Characterization of mesenchymal stem cell therapy in a novel human iPS cell-derived cardiomyocyte infarct model"
Major Professor: Claus Sondergaard, Ph.D.

4:05 – 4:20 p.m. **Presentation by Shannamar Dewey, Exit Seminar**
"Fluctuating Effects of Diabetes Mellitus Type 1 and 2 on the Ubiquitin Proteasome System in two Rodent Models: Proteasome Inhibition is Not the Magic Answer"
Major Professor: Aldrin Gomes, Ph.D.

4:25 – 4:30 p.m. Closing Remarks & Announcements by Dr. Dietmar Kueltz

4:30 – 5:30 p.m. Poster Session
**INVITED EXIT SEMINARS**

- **Shannamar Dewey:** "Fluctuating Effects of Diabetes Mellitus Type 1 and 2 on the Ubiquitin Proteasome System in two Rodent Models: Proteasome Inhibition is Not the Magic Answer"

**ABSTRACT:** Diabetes mellitus affects more than 370 million people worldwide and heart disease is the leading cause of death among diabetics. While ventricular dysfunction in diabetics can result from multiple cardiac etiologies, a form of idiopathic failure of the diabetic heart has been identified and termed diabetic cardiomyopathy (DbCM). The cellular pathogenesis of this co-morbidity is believed to be complex and multifactorial. The primary diabetic conditions of hyperglycemia, insulinopenia, and hyperinsulinemia have been shown to alter several aspects of cellular homeostasis including calcium handling, metabolism and formation of glycated proteins. Proteases are key players in maintaining cellular homeostasis through both protein quality control and signal cascade regulation and thus could be centrally involved in DbCM pathogenesis. The ubiquitin proteasome system (UPS) is responsible for over 60% of intracellular protein degradation and disturbances in this system have been found to play a role in several diseases including Alzheimer’s, cancer, and ischemia reperfusion injury. Thus it is a possible candidate for interacting with several aspects of pathogenic cellular processes. Evidence presented by three separate groups implicates impairment of the UPS during the development DbCM and one group reported a cardioprotective effect of proteasome inhibition in a murine model of Type 1 Diabetes (T1DM). The overall goal of this thesis was to investigate the UPS in detail in T1DM and Type 2 Diabetes (T2DM) to determine if it is a potential target for limiting the development of DbCM and to understand the effects of both forms of diabetes on this complex system. The data reported here from two separate murine models indicate that the UPS is affected dynamically with disease progression in a manner that is not consistent between T1DM and T2DM. The T1DM Akita mouse model displayed early suppression of proteasome activity and later activation. The T2DM ob/ob mouse model presented early activation of proteasome activity and later attenuation. Treatment of both models with proteasome inhibition did not protect from or reverse muscular atrophy caused by diabetes. Based on these findings, general proteasome inhibition does not seem to be a likely treatment candidate to limit the impact of DbCM. However, several interesting findings within this work suggest effects on the ubiquitin pathway and further investigation into these findings coupled with development of the ability to affect specific substrate delivery to the proteasome could be worth pursuing. Additionally, the final research chapter of this work includes a proteomic study of the T1DM Akita model at 5 weeks of age. One of the surprising discoveries reported here is a detection of cardiac dysregulation at this time point as indicated by measurable cardiac atrophy in these young mice. The proteomic results offer several new pathways of investigation which could be important during the earliest progression of DbCM. Most notably, soluble epoxide hydrolase (sEH) expression was found to increase dramatically with age in these mice. Taken together the conclusions of this work suggest that overall proteasome inhibition is not worth pursuing in terms of limiting the impact of DbCM on diabetic patients but the data included here offers several new interesting avenues of experimentation.

- **Tyler Stradleigh:** "Improved Preservation of Life-like morphology in Organotypically Cultured Retinal Ganglion Cells"