

Undergraduate Research Seminar  
Wednesday, August 3<sup>rd</sup>, 2016 5:30 p.m.  
Leigh 309

## **Daniela Valero**

Investigating the Molecular Basis of Muscle Phenotypes in Myotonic Dystrophy Type 1

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Myotonic Dystrophy 1 (DM1) is an inherited neuromuscular disease characterized by symptoms including myotonia (inability to relax the muscles), skeletal muscle wasting, cardiac conduction defects, cataracts, insulin resistance, mental retardation, and excessive daytime sleepiness. DM1 is caused by the expansion of CTG repeats in the 3' untranslated region of the gene, *Dystrophia Myotonica Protein Kinase (DMPK)*. Investigations into the mechanistic basis of DM1 revealed that expression of the mutant *DMPK* allele produces a 'toxic' RNA that sequesters the Muscleblind-like (MBNL) splicing factors resulting in global mis-splicing. A couple of these splicing changes have been linked to the skeletal muscle phenotypes associated with DM1. However, a lot is still not known about what cellular processes are disrupted in DM1 that cause the muscle phenotypes observed. To address this, we are using two approaches. First, we are investigating the role of a family of nuclear proteins, called nuclear lamina proteins, in DM1 muscle phenotypes. The nuclear lamina is a structure underlying the nuclear envelope that is important for many cellular processes. Defects in nuclear lamina components result in a group of muscular dystrophies called laminopathies. As the laminopathic muscle and cardiac phenotypes overlap with those observed in DM1, disruption of nuclear lamina function may contribute to DM1 pathology. This hypothesis is further supported by recent work showing that DM1 patient fibroblasts display defects in nuclear shape and structure. In addition, RNA-sequencing analysis of DM1 muscle shows that the expression and splicing profiles of multiple nuclear lamina components is misregulated. We will extend these studies by examining the localization of various nuclear lamina proteins in human DM1 myotubes that are differentiated from fibroblasts as well as in skeletal muscle from mouse models of DM1. The second approach we are undertaking is to determine which of the mis-splicing events in DM1 muscle contribute to disruption of muscle function. By RNA-sequencing analysis of the tibialis anterior skeletal muscle from DM1 patients, we have compiled a list of genes that are significantly mis-spliced in DM1. Of these genes, quite a few are involved in calcium signaling, which is very important in excitation-contraction coupling of muscles. We will continue these studies by analyzing the effect of specific splicing changes in components of calcium signaling on muscle function. Taken together, our studies will not only elucidate the molecular basis of the muscle phenotypes in DM, but will provide critical insights into basic muscle biology.

## **Itai Meiom**

### **Weaning-induced Involution in the Murine Liver is Characterized by Dramatic Changes in Myeloid Populations**

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The rodent liver expands during pregnancy/lactation, most likely in order to facilitate the increased metabolic demands of pregnancy and milk production. Post-weaning, the liver undergoes involution which is characterized by hepatocyte cell death, stromal remodeling, and immune cell infiltration. Specifically, weaning-induced liver involution is characterized by an increase in CD11b<sup>+</sup>F4/80<sup>+</sup> macrophages, CD11b<sup>+</sup>Ly6C<sup>+</sup>Ly6G<sup>-</sup> monocytes, and CD11b<sup>+</sup>Ly6C<sup>+</sup>Ly6G<sup>+</sup> neutrophils in rodents. My project seeks to understand if this increase in myeloid cells during weaning-induced liver involution may be, in part, due to proliferation of resident myeloid populations. Additionally, we would like to identify whether myeloid populations form immune foci and/or develop an immune suppressive phenotype during weaning-induced involution. Liver involution involves hepatocyte apoptosis which contributes to the weight and volume loss of the rodent liver post weaning. Epithelial cell apoptosis typically occurs in the context of immune suppression so as to dampen potential autoimmune T cell responses. Therefore, one explanation for the elevated levels of myeloid populations is a necessity to regulate deviant immune responses targeted towards self. However, we do not currently know if this increase in myeloid populations is due to immune cell infiltration or expansion of resident myeloid populations already present in the liver. Previous studies from the Schedin lab suggest that these myeloid populations may also be forming immune foci and may shift towards an immune suppressive phenotype during weaning-induced liver involution. Increased levels of immune suppressive myeloid populations during weaning-induced liver involution may also be contributing to a pro-metastatic microenvironment in the liver. Data suggests that weaning-induced liver involution establishes a transient pro-metastatic microenvironment which may explain the increased risk for liver-specific metastasis in breast cancers diagnosed after pregnancy. It is currently unknown what role these myeloid populations play in this pro-metastatic microenvironment established in the liver.