Dr. Howard Worman

”Emery-Dreifuss muscular dystrophy (EDMD) is caused by mutations in genes encoding proteins of the nuclear envelope. Autosomal EDMD results from mutations in LMNA, which encodes A-type lamins, and X-linked EDMD from mutations in EMD, which encodes emerin. Mutations in genes encoding nesprins and SUNs have also been associated with the EDMD phenotype. The proteins encoded by these genes are involved in connecting the inside of the nucleus to the cytoplasm, forming or associating with the LINC complex. We have shown that LMNA mutations causing autosomal EDMD, as well as deficiency of A-type lamins, block cytoplasmic actin-dependent nuclear movement by disrupting anchoring of the nucleus to structures known as TAN lines, which are composed of SUN2 and nesprin-2. Loss of emerin, as occurs in X-linked EDMD, additionally blocks nuclear movement by altering retrograde cytoplasmic actin flow that drives it. Depletion of SUNs and nesprins also leads to defective nuclear movement by altering TAN line function. In cells lacking A- type lamins, inhibition of ERK1/2, which is activated by alterations in lamins, emerin, SUNs and nesprins as well as in striated muscle of animal models of autosomal EDMD, reverses the nuclear movement defect. We now propose to test the hypothesis that there is a link between genetic alterations that cause EDMD and the nuclear movement defects and ERK1/2 activation they create. To test this hypothesis, we will utilize an innovative fibroblast-based assay to mechanistically dissect defects in nuclear movement and then extend the findings to cultured myoblasts and skeletal muscle *in vivo*. In Aim 1, we will examine the relationship between LINC complex function, ERK1/2 activity and nuclear movement, with a focus on how hyperactivated ERK1/2 prevents nuclear movement. In Aim 2, we will examine the temporal relationship between nuclear movement and ERK1/2 activity during physiological activation of the kinase and perform a series of biophysical experiments to directly test if moving the nucleus regulates ERK1/2 signaling. In Aims 3 and 4, we will extend our studies into muscle cells, examining how LINC complex proteins and ERK1/2 affect nuclear movement in migrating myoblasts and determining if A-type lamins and emerin affect proper nuclear positioning in muscle, in mouse models of EDMD with alterations in lamins or emerin. Overall, this research will provide novel insights into the cellular pathology of EDMD and simultaneously uncover new information about nuclear movement, a cellular function of broad significance to basic cell biology.”