Peripheral artery disease (PAD) is a common manifestation of atherosclerosis and is characterized by an accumulation of plaque within the arteries supplying blood to the lower extremities. Due to the occlusion of the artery, the lower limbs lack a sufficient amount of blood (ischemia) to maintain adequate muscle health. When the skeletal muscle lacks oxygen and nutrients, it becomes damaged and non-functional, which leads to negative disease outcomes such as exercise intolerance, pain and muscle tissue death. I am interested in studying the role of the endothelial cell (the cell that comprises all blood vessels) in regulating the regenerative time-course of skeletal muscle ischemia. The endothelial cell (EC) within the skeletal muscle can coordinate blood-flow recovery (through the growth of new vessels) but can also contribute to inflammation and muscle regeneration. PAD is strongly associated with other comorbidities such as insulin resistance and diabetes (often outcomes of high fat (HF) diet-induced obesity) that worsen the regenerative response to skeletal muscle ischemia. HF diet and obesity are shown to cause low-grade systemic inflammation, impair blood vessel growth and skeletal muscle adaptations that may impact ischemia outcomes. We hypothesized that HF diet would impair the regenerative capacity of ischemic muscle. Male mice were fed a HF or normal chow (NC) diet (9 weeks). To mimic PAD, HF and NC mice underwent femoral artery ligation surgery that reduced blood flow to the lower leg and muscle regeneration was assessed at early and later time-points. Surprisingly, ischemic muscle from HF fed mice exhibited multiple signs of improved recovery, including blood vessel growth, blood flow recovery, inflammatory resolution and skeletal muscle maturation. Our data suggest that moderate duration HF diet promotes a more favorable tissue environment that potentially improves the regeneration of ischemic muscle. Although it is commonly believed that HF diet can impede the regeneration of ischemic muscle, these results provide a new perspective on how the effects of HF diet can promote beneficial PAD outcomes. From a clinical perspective, this knowledge can potentially be utilized in developing therapeutic strategies to improve the wellbeing of patients suffering from PAD.