Public Abstract
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Duchenne muscular dystrophy (DMD) is a genetically inherited debilitating muscle disorder affecting young boys due to the loss of dystrophin protein in muscle and the heart. Affected individuals lose their mobility and become confined to a wheel chair in early teens. They develop heart disease towards the end stage of the disease. Heart failure or breathing complications leads to death. Currently there is no cure for DMD. Gene therapy has shown great promise to restore the lost dystrophin protein in DMD. During my PhD, I have addressed several important aspects of dystrophin gene therapy. The findings from these studies will benefit development of an effective gene therapy for DMD and will open the door for some important future studies. Here I briefly describe the findings in my research.
In the first study I addressed whether muscle-only rescue affects the heart. I used mice genetically engineered (alias transgenic) to carry dystrophin in skeletal muscle but not in the heart. To more closely mimic the human heart condition, I aged these mice to 23-months, an aged dystrophin-null mice show heart failure similar to that of DMD patients. Evaluation of heart pathology, ECG and pump function revealed that the heart in transgenic mice does not notably differ from the dystrophin deficient mice. In other words, selective muscle only treatment did not improve or heighten heart disease in DMD. In the next study I evaluated whether continuous therapeutic dystrophin expression is essential for muscle and heart health. To evaluate this in a mouse model, I created two mouse models carrying therapeutic dystrophin in the heart or muscle. These mice were engineered in a way that permits intentional removal of the therapeutic gene from the heart or muscle using viral mediated enzyme delivery. I delivered the viral mediated enzyme to muscle or the heart of the respective mouse strain in adult mice. After 12-15 months of therapeutic dystrophin removal, I evaluated muscle and the heart from individual strain. The removal of muscle therapeutic dystrophin resulted muscle deterioration, reduced muscle weight, size and force. The heart pump function was noticeably weakened after removal of cardiac therapeutic dystrophin. These findings indicated that uninterrupted therapeutic dystrophin expression is essential to maintain muscle and heart health. In the third study, I proposed, based on patient data, that dystrophin may contain a heart protection region between repeats 16-19 (R16-19) of dystrophin. I studied this by comparing the heart pathology, ECG and pump function in two transgenic mouse models that express dystrophin in the heart with or without R16-19. In support of my hypothesis, addition of R16-19 completely rescued ECG and corrected an important heart function parameter that were not rescued in mice that lack R16-19. Lastly, I looked at whether very low levels of dystrophin can benefit DMD heart. To test this, I used a mouse model referred to as mdx3cv that was genetically modified using chemical induced mutations. These mice expressed about 3.3% of dystrophin compared to normal mice. The heart of mdx3cv mice showed similar level of damage as dystrophin deficient mice. Surprisingly, ECG and hemodynamic function were improved in mdx3cv mice. These results suggest that marginal level dystrophin expression can still help the heart but it is far from sufficient for full recovery.