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LECTURE: NEW INSIGHTS LEADING TO IMPROVED DESIGNS OF MICRO-DYSTROPHINS FOR USE IN ADENO-ASSOCIATED VIRUSES VECTORS

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Adeno-associated viruses (AAVs) containing versions of truncated dystrophin (micro-dystrophins) are being delivered to patients with Duchenne muscular dystrophy (DMD) in clinical trials. DMD is a progressive, childhood onset muscle wasting disease caused by mutations in the DMD gene that result in the loss of dystrophin protein in all muscle types (1). These clinical gene therapies aim to overexpress a truncated version of dystrophin in striated muscle capable of achieving partial correction of the disease. To avoid the immune response that is due to the inclusion of N-terminal segments of dystrophin being present in the micro-dystrophins, we have examined a strategy that uses the N-terminal region of utrophin combined with C-terminal components of dystrophin. We have evaluated a series of such constructs that include different C-terminal components using a severe mouse model of DMD, the D2.mdx mouse (2-4), and a rat model of DMD (Figure 1). We administered doses of AAV comparable to those used in clinical trials. We observed improvement in both the skeletal muscle and cardiac muscle disease progression. We report on our continued progress in designing an approach that should not provoke an immune response and benefit the heart as well as skeletal muscle.

Keywords: *Duchenne muscular dystrophy, AAV, gene therapy, cardiomyopathy.*

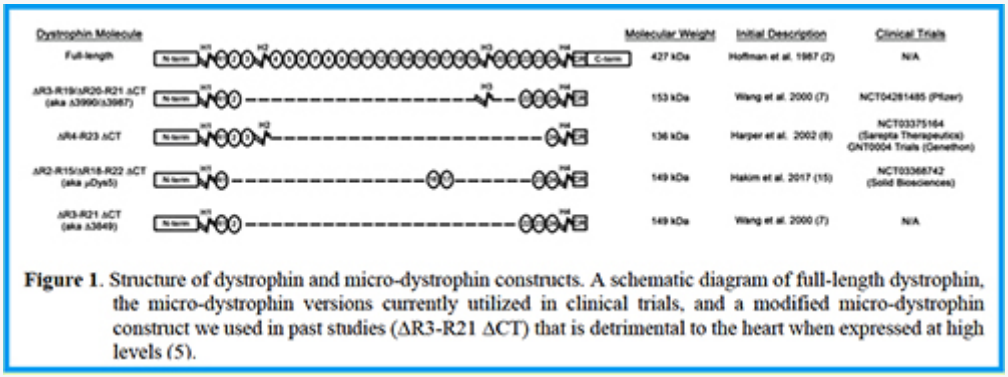

Figure 1. Structure of dystrophin and micro-dystrophin constructs. A schematic diagram of full-length dystrophin, the micro-dystrophin versions currently utilized in clinical trials, and a modified micro-dystrophin construct we used in past studies (ΔR3-R21 ΔCT) that is detrimental to the heart when expressed at high levels (5).