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Gene Therapy for DMD: From Bench to Bedside

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This presentation will detail a 25-yr effort on gene therapy for Duchenne muscular dystrophy (DMD). Duchenne muscular dystrophy (dys) is a single gene defect that is X-linked and primarily only affects males. This gene codes for a mRNA that is over 14 kb in size and therefore too large for many of the viral vectors more specifically for AAV packaging capacity of 5 kb. To circumvent this concern, mini dys transgene cassettes were designed to fit in the AAV packaging constraints and tested in MDX mouse model for efficacy. Following design of functional transgene cassettes, an effort was focused on AAV capsids that would provide global transgene transduction without toxicity. Phase 1 studies of direct muscle injection were carried out in 2006 to validate the safety of this transgene cassette. These studies were further extended with Phase 1 safety trials evaluating "limb infusion" studies completed in 2009. Finally, monkey and canine studies refined the vector design to a novel clinical vector carrying 1) muscle specific promoter, 2) optimized mini dys transgene, 3) packaged in an AAV serotype and chimeric capsid (AAV9 and AAV2i8) for systemic delivery. IND enabling studies followed by FDA approved tox bio-distribution experiments resulted in approval for transitioning into Phase1/2 clinical trials that have commenced this spring. The supporting studies and early clinical results will be presented as a case study of developing "bench to bedside" gene therapy.