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New Hope for Treatment of Duchene Dystrophy by Employing Dystrophin Expressing Chimeric Cells – Studies Published in *Stem Cell Reviews and Reports*

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Duchenne muscular dystrophy (DMD) is X chromosome linked recessive a severe type of muscular dystrophy due to mutation in the gene that encodes protein dystrophin that is important to maintain the muscle fiber's cell membrane [1]. This fatal disorder has been described 200 years ago and is inherited in 70% of cases from parents, however in approximately 30% cases is a result of a de novo mutation. DMD affects one in 4,000–5,000 males at birth and it usually begins in young 3–4 years old boys and symptoms worsens quickly. Females who are carrying a single mutant gene on one of their X chromosomes at locus Xp21 - located on the short arm of the X chromosome, may show mild symptoms. Since in females one of the two X chromosomes undergoes physiological inactivation, the clinical picture depends on a pattern of X-chromosome inactivation in the muscle tissue. In contrast DMD is more severe in boys who have one single mutated gene at X chromosome at locus Xp21 and is clinically presented by muscle loss in legs and pelvis and subsequently disease spreads to the upper arms. As result of this affected young males are not able to walk at age of 12 years. The average life expectancy does not exceed 25 years. With efficient medical care males are often living into their 30s. One of severe complications that requires assisted ventilation is weakness of breathing due to dystrophy of respiratory muscles [1].

Unfortunately, so far it is no cure for this devastating disorder and available treatment is generally aimed at controlling in DMD suffering patients the onset of symptoms and to maximize their quality of life. The most common drugs include corticosteroids, anticonvulsants to control risk of seizures as well as selected immunosuppressants. Thus, it is an urgent need to develop more efficient treatment strategies. The current approaches include i) exon-skipping strategy employing antisense oligomers to skip faulty parts of dystrophin during transcription of dystrophin gene DNA to mRNA, allowing to produce truncated functional protein, ii) application of skeletal muscle satellite stem cells or pericytes, iii) to replace mutated gene by employing CRISP/Cas9-mediated genome editing, and iv) delivery of synthetic dystrophin gene, called microdystrophin, by employing adeno-associated viral (AAV) vector mediated gene transfer [2]. In particular, this latter therapeutic strategy proposed by Solid Biosciences Inc. as phase I/II clinical trial using SGT-001 AAV vector carrying microdystrophin has been recently stopped by U.S. Food and Drug Administration due to serious side effects in first treated patient that produced onset of thrombocytopenia, anemia and activation of complement cascade (https://www.fiercebiotech.com/biotech/solid-bio-s-dmd-gene-therapy-graduates-from-partial-hold-to-full-fda-clinical-hold). This indicates need to improve safety of gene delivery [3].

In this context the novel promising strategy employing dystrophin expressing chimeric cells (DEC) in murine model of DMD (mdx) proposed by Dr. Siemionow group from University of Illinois at Chicago that has been published in our journal deserves special attention [4, 5]. In the first paper published in April issue of SCRR murine DEC were generated via ex vivo fusion of normal donor and dystrophin-deficient myoblasts from mdx mutant mice using polyethylene glycol [4]. These chimeric cells were transplanted into the gastrocnemius muscle of mdx mice and therapeutic effect was assessed 30 days post-transplant by muscle functional tests. As reported 30 days post-transplant of DEC dystrophin expression in gastrocnemius muscle of injected mdx mice increased to ~40% and this correlated with improvement of muscle strength and function [4]. In the second follow up paper published in a

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current issue of SCRR Dr. Siemionow developed two dystrophin expressing chimeric (DEC) cell lines created by ex vivo fusion of human myoblasts derived from two normal donors, and normal and DMD donors [5]. In vitro studies, DEC created by Dr. Siemionow group displayed phenotype and genotype of donor parent cells, expressed dystrophin, and maintained proliferation and myogenic differentiation. In vivo study, local delivery of both DEC lines to the gastrocnemius muscles of mdx/scid mice restored dystrophin expression by ~17% and 23% for cells derived from two normal donors, and normal and DMD donors, respectively. This chimerism correlated at 90 days after DEC transplant with significant improvement of muscle force, contraction and tolerance to fatigue [5].

In conclusion, this interesting studies established DEC strategy as a potential therapy for DMD and other types of muscular dystrophies. We are looking forward to see application of DEC cells in clinical trials to treat this fatal and devastating disorder.

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