

# Helping Myogenic Stem Cells Stand Their Ground against Muscular Dystrophy

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Duchenne muscular dystrophy (DMD) is the most common and severe form of muscular dystrophy. It is an X-linked disorder caused by mutations in the dystrophin gene and rapidly progresses after onset in early childhood. Most affected individuals become wheelchair bound by the age of 12 and succumb to heart or lung failure by the age of 30. Many research programs are currently being pursued to restore dystrophin expression levels in these individuals. One approach employs myogenic stem cell transplant therapy to generate new muscle. This strategy succeeded in a murine model of DMD (*mdx* mice) using syngeneic stem cell transplants. However, it was ineffective in human clinical trials of allogeneic stem cell transplants, because recipients developed immune responses to donor cells. Immunosuppressive reagents have also failed to improve donor myoblast engraftment and may even inhibit this process.

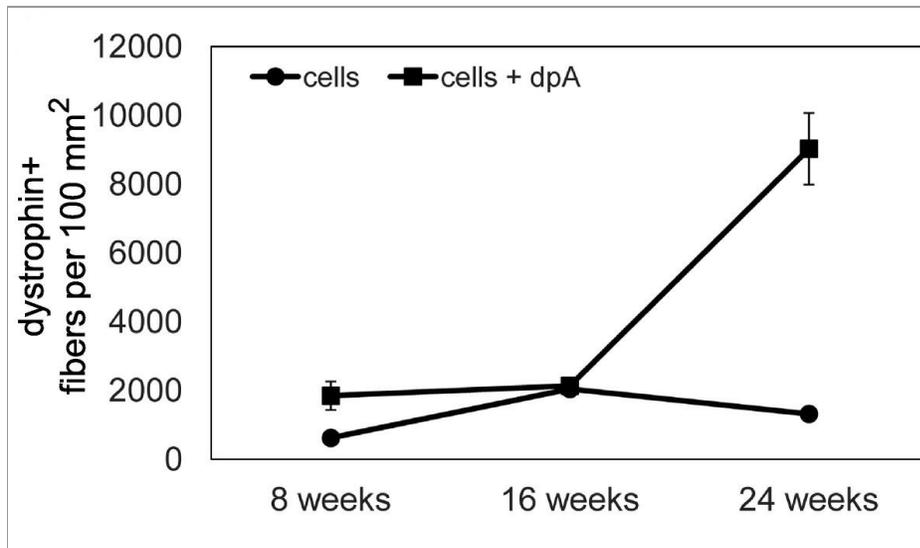
In an effort to ultimately improve the efficacy of myogenic stem cell transplantation in individuals suffering from DMD, postdoctoral fellow Dr. Maura Parker and members of the Storb Lab, in the Clinical Research Division, and members of the Tapscott Lab, in the Human Biology Division, developed a clinical model that utilizes nonmyeloablative hematopoietic cell transplantation (HCT) to establish donor tolerance prior to allogeneic transplantation of myogenic stem cells. Parker and colleagues applied this strategy to a canine model of DMD (*cxmd* dogs) using allogeneic transplants of freshly isolated muscle-derived mononuclear cells. As published in *Molecular Therapy* in 2008, this regimen elevated dystrophin expression levels to 6.48% of wild-type levels and out to 24 weeks. Parker *et al.* then considered whether selection for CXCR4 expression on myogenic stem cells could improve engraftment in canine-to-murine and canine-to-canine transplantation models, given that this approach yielded highly efficient engraftments of murine muscle stem cells in a previous study of *mdx* mice.

Interestingly, they found that sorting on the basis of CXCR4 expression actually reduced engraftment of canine muscle-derived cells in immunodeficient NOD SCID mice. Pre-incubation of non-sorted muscle-derived cells with an anti-CXCR4 antibody prior to engraftment also reduced engraftment. As CXCR4 only has one ligand, SDF-1, and SDF-1 RNA was detected in canine skeletal muscle, the authors reasoned that the anti-CXCR4 antibody might be blocking an interaction between CXCR4 on donor cells and SDF-1 on recipient skeletal muscle. They explored this

hypothesis further, and found that pre-incubation of canine muscle-derived cells with SDF-1 prior to engraftment significantly reduced the number of muscle fibers expressing canine dystrophin in recipient mice by an average of four- to five-fold. Parker *et al.* also found evidence of functional CD26, which negatively regulates SDF-1 binding to CXCR4, in freshly isolated canine muscle-derived cells. Therefore, they treated canine muscle-derived cells with an inhibitor of CD26 (diprotin A) prior to transplantation and observed that the number of murine muscle fibers expressing canine dystrophin increased significantly by two- to 10-fold.

In an immune tolerant canine model, where HCT resulted in >80% donor chimerism for one dog and 3% donor chimerism for another, transplantation of diprotin A-treated allogeneic muscle-derived cells led to 6.8-fold and 2.6-fold increases, respectively, in the number of dystrophin positive muscle fibers 24 weeks later. The authors are currently extending these studies to a human-to-murine xenotransplant model and will be testing the efficacy of an FDA-approved CD26 inhibitor, sitagliptin, to enhance engraftment in various transplantation models, with the hopes that it will contribute to a rapidly translatable treatment for individuals with DMD.

[Parker MH, Loretz MH, Tyler A, Snider L, Storb R, Tapscott SJ.](#) 2012. Inhibition of CD26/DPP-IV enhances donor muscle cell engraftment and stimulates sustained donor cell proliferation. *Skeletal Muscle* 2:4.



Modified from image provided by Maura Parker

Treatment of allogeneic donor muscle stem cells with diprotin A (dpA) improves engraftment by 6.8-fold in a canine model of Duchenne muscular dystrophy (cxmd) that does not express dystrophin. Prior to muscle cell transplantation, cxmd dogs received nonmyeloablative hematopoietic cell transplants (HCT) to induce recipient immune tolerance to donor cells. De novo dystrophin expression (Y-axis) in skeletal muscle biopsies was quantified using an antibody against dystrophin.