# *In vivo* stem cell-targeted gene therapy enabled by viral engineering

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Stem Cells and Development

FIELD OF ACTIVITY
Stem cell biology

KEY WORDS
Duchenne Muscular Dystrophy, Muscle stem cells, AAV engineering, gene therapy

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**CONTEXT & OVERALL OBJECTIVE:**
Many degenerative diseases are associated with tissue wasting and stem cell decline. Most gene restoration strategies correct terminally differentiated cells in target tissues and can be toxic to unrelated tissues. Moreover, the natural turnover of terminal cells decreases efficacy of gene therapy over time. By contrast, our general *in vivo* stem-cell targeted gene restoration strategy allows sustained efficacy in target tissues while avoiding toxicity in unrelated tissues.

**PROJECT DESCRIPTION:**
Duchenne Muscular Dystrophy (DMD) affects 1/5000 male births, causing muscle wasting and early mortality, due to mutations of the DMD gene encoding the Dystrophin protein. Current DMD gene therapies with adeno-associated viruses (AAVs) face limitations like systemic toxicity and dilution of therapeutic effects, due to preferential targeting of differentiated muscle fibers, which are subject to natural turnover. Unlike existing strategies, our approach aims to correct muscle stem cells (MuSCs), the long-term regenerative source of skeletal muscle, ensuring persistent therapeutic effects with a single intervention. Notably, we have established an engineered AAV platform with the goal to transduce MuSCs directly *in vivo*. We will identify MuSC-specific receptors and corresponding high-affinity ligands, displayed on recombinant AAVs to selectively target MuSCs while avoiding non-target cells (proof-of-principle demonstrated). Combined with CRISPR/Cas9 tools, these vectors will restore Dystrophin expression in DMD models. By harnessing the regenerative potential of MuSCs, our strategy reduces toxicity, minimises viral loads, and enables long-term correction, paving the way for transformative gene therapies for DMD and many other genetic diseases associated with stem cell decline.

**MEDICAL NEEDS / INDICATIONS:**
As of today, there are no cures for DMD, which imposes a lifelong physical, emotional, and financial burden on the patients and their families. The only approved therapies for DMD are used to slow disease progression and do not restore Dystrophin function. There is a critical need to develop a broad and durable stem cell-targeted therapy that can regenerate or repair muscle. This approach can also be used for other genetic muscle wasting diseases, like Becker Muscular Dystrophy, Limb-Girdle Muscular Dystrophy, and many more.

**DEVELOPMENT STAGE:**
TRL 3. Technology development with validations in preclinical models of DMD (mouse).

**PRODUCT:**
A flexible mouse model for *in vivo* assessment of AAV and LNP tropism across diverse cell types and tissues, including stem cells (e.g., MuSCs) and immune cells.

**PUBLICATIONS RELATED TO THE PROJECT:**
Sarde et al., bioRxiv 2025; Hartmann et al., Mol Ther Methods Clin Dev 2018; Mbakam et al., Frontiers in Medicine 2022; Buchholz et al., Trends in Biotechnology 2015; Duan, Mol Ther 2023; Philippidis, Hum Gene Ther 2020; Münch et al., Nature Communications 2015.