

Strategies for AAV-Based Therapy of Duchenne Muscular Dystrophin

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Gene therapy using the adeno-associated virus (rAAV) to deliver mini/micro- dystrophin is the current promising strategy for Duchenne Muscular Dystrophy (DMD). However, the further transformation of this strategy still faces many “bottlenecks”. Most gene therapies are only suitable for infants with strong muscle cell regeneration and immature immune system, and the treatment depends heavily on the high dose of rAAV. However, high-dose rAAV inevitably causes side effects such as immune response and acute liver toxicity. Therefore, how to reduce the degree of fibrosis and excessive immune response in older patients and uncouple the dependence association between therapeutic effect and high dose rAAV are crucial steps for the transformation of rAAV-based gene therapy.

Duchenne muscular dystrophin

gene therapy

MyoAAV

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorders, with a prevalence rate of 1/3500–5000 newborn boys worldwide ^[1]. The main symptoms of DMD are progressive muscle weakness accompanied by muscle steatosis. Affected boys usually present clinical symptoms between 3 and 5 years old, they lose ambulation ability around 12 years old and die in the second or third decade due to cardio-respiratory insufficiency ^[2].

DMD is caused by a mutation in the *DMD* gene that encodes dystrophin, which is the largest known human gene, comprising 79 exons and spanning 2600 kb, roughly 0.1% of the whole genome. More than 7000 mutations were found in affected boys, including deletion spanning one or multiple exons, which account for 60 to 70% of all DMD cases. The point mutations are responsible for 26% of DMD cases. Exonic duplications account for 10% to 15% of DMD cases ^[3]. Dystrophin is located under the sarcolemma and forms the dystrophin-associated glycoprotein complexes (DGC) with a group of transmembrane proteins. The DGC complexes form a mechanical connection between the intracellular skeleton and the extracellular matrix, which together protect the sarcolemma from the damage caused by the stress generated during muscle contraction ^{[4][5]}. In the absence of dystrophin, the sarcolemma is unable to recruit DGC complexes, and thereby becomes extremely unstable, resulting in muscle fiber necrosis, inflammatory cell infiltration, muscle fiber regeneration, and eventually muscle fiber replacement by connective tissue with progressive muscle sclerosis and loss of contractile function. With the disease continuing to advance, the regeneration ability of muscle fibers decreases and gradually degenerates and disappears, finally involving respiratory muscles and myocardium ^{[6][7]}.

Since the identification of the *DMD* gene in 1986, the search for a cure for DMD has been intense. However, there is currently no effective form of a cure because the significant obstacles include both the large size of the *DMD* gene for gene therapy and that affecting nearly all muscle types (skeletal, smooth and cardiac muscle, which together represent ~40% of the total body mass in males) as well as the limited “treatment window”. Comprehensive analysis found that in addition to health management, drugs targeting different *DMD* mutation types have been developed, but these drugs are only suitable for patients with specific mutation types, and their clinical benefits are very limited. Many studies have demonstrated that gene therapy based on the recombinant adeno-associated virus (rAAV) to deliver mini/micro- dystrophin is the best strategy for the treatment of DMD. However, preclinical and clinical trials have demonstrated that therapeutic efficacy depends on patient age and disease deterioration, and high vector titers that can achieve significant therapeutic efficacy can cause severe liver toxicity. Therefore, maintaining and extending the “window period” of gene therapy and reducing the coupling degree of vector titer and liver toxicity are important bases to ensure the continuous and stable effect of gene therapy, and are strong guarantees to benefit more DMD patients in the whole life cycle.

2. Clinical Development of Systemic AAV-Mediated Mini/Micro-Dystrophin Gene Therapy

rAAV, derived from the wild-type AAVs, are well characterized as potential gene transfer vehicles in the treatment of neuromuscular disorders, with the capacity to transduce the vast majority of the striated musculature with a single administration. AAV is composed of an icosahedral protein capsid of ~26 nm in diameter and a single-stranded DNA genome of ~4.7 kb that can either be the sense or anti-sense strand. The capsid comprises three types of subunit, VP1, VP2 and VP3, in a ratio of 1:1:10 (VP1:VP2:VP3). The genome is comprised of three genes (*Rep*, *Cap* and *aap*), which are flanked by two T-shaped inverted terminal repeats (ITRs) that largely serve as the viral origins of replication and the packaging signal [8]. The *Rep* encodes proteins required for gene replication, *Cap* gene encodes the three capsid subunits and recognizes the host cell surface and the *aap* gene encodes the assembly-activating protein needed for the capsid assembly and nuclear localization for some AAV serotypes [9]. However, rAAV genomes substitute all the AAV protein-coding sequence with therapeutic gene expression cassettes, and just reserve the ITRs, which are needed for gene replication and packaging during vector production. The complete removal of viral coding sequences maximizes the packaging capacity of rAAVs and contributes to their low immunogenicity and cytotoxicity when delivered in vivo [10].

To circumvent the difficulty in AAV packaging with the full-length dystrophin gene, mini/micro-dystrophin therapies has been developed. The notion of miniaturized dystrophin was based on a Becker muscular dystrophy patient, who remained ambulatory for seven decades despite a deletion of nearly half of the *DMD* gene [11]. Recently, mini-dystrophin incorporating different spectrin repeats (SRs) and hinges (**Figure 1**) delivered by different AAV serotypes are undergoing assessment of safety and efficacy in three simultaneous gene therapy trials (**Table 1**) [12] sponsored by Sarepta Therapeutics, Pfizer, and Solid Biosciences.

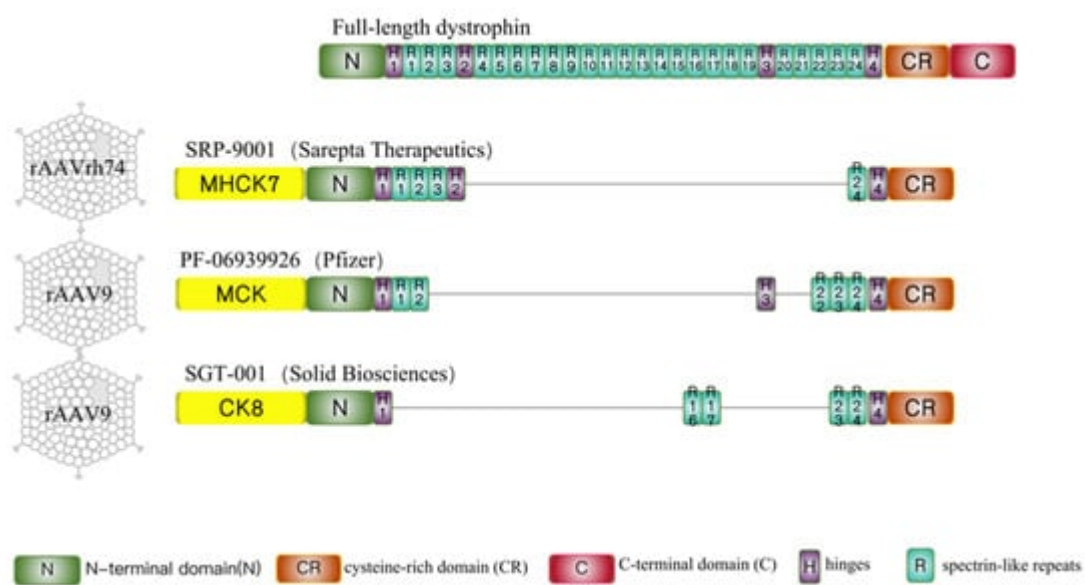


Figure 1. Full-length dystrophin and micro-dystrophins designed in 3 clinical trials. Full-length dystrophin contains an N-terminal domain (N), 24 spectrin-like repeats (R1 to R24), four hinges (H1 to H4), a cysteine-rich domain (CR), and a C-terminal domain (C). SRP-9001(Δ R4-R23/ Δ C) is the candidate drug developed by Sarepta Therapeutics and regulated by the MHCK7 promoter. PF-06939926(Δ R3-R21 + H3/ Δ C) is used in clinical trials sponsored by Pfizer and driven by the MCK promoter. SGT-001 (Δ R1-R22 + R16R17/ Δ C) is a type of micro-dystrophin designed by Solid Biosciences and regulated by the CK8 promoter. The common characteristics of these three micro-dystrophins are the preservation of the N-terminal domain, cysteine-rich domain, and portion of spectrin-like repeats and hinges and the absence of C-terminal domain. The differences are in the central hinges and the R16/17 nNOS-binding domain. SRP-9001 contains hinge 2 and PF-06939926 contains hinge 3, only SGT-001 carries the R16/17 nNOS-binding domain.

Table 1. Current status of systemic AAV mini/micro-dystrophin clinical trials.

Sarepta	Pfizer	Therapeutics Solid Biosciences	
Trial name	An open-label, systemic gene delivery study using commercial process material to evaluate the safety of and expression from SRP-9001 in subjects with Duchenne muscular dystrophy (ENDEAVOR)	A phase 1b multicenter, open-label, single ascending dose study to evaluate the safety and tolerability of pf-06939926 in ambulatory and non-ambulatory subjects with Duchenne muscular dystrophy	A randomized, controlled, open-label, single-ascending dose, phase I/II study to investigate the safety and tolerability, and efficacy of intravenous SGT-001 in male adolescents and children with Duchenne muscular dystrophy
ClinicalTrials.gov Identifier	NCT04626674	NCT03362502	NCT03368742
Study nature	Phase-1b trial	Phase 1b, open-label, trial	Phase 1/2, open-label, trial

Sarepta	Pfizer	Therapeutics Solid Biosciences	
Drug name	SRP-9001	PF-06939926	SGT-001
AAV-serotype	rAAV-rh74	rAAV9	rAAV9
Dose	1 dose (1.33×10^{14} vg/kg) for cohort 1	2 doses (1.0×10^{14} vg/kg, 3.0×10^{14} vg/kg)	2 doses (5.0×10^{13} vg/kg, 2.0×10^{14} vg/kg)
Patient number	38	22	16 (estimated enrollment)
Patient average age	3 years and older	4 years and older	4~17 years
Disease stage	Ambulatory and non-ambulatory subjects	Ambulatory and non-ambulatory subjects	Ambulatory and non-ambulatory subjects
Corticosteroid use	3 months on stable weekly dose of oral corticosteroids for cohort 1	Daily glucocorticoids for at least 3 months	Stable daily dose (or equivalent) of oral corticosteroids ≥ 12 wks
Dystrophin gene mutation	Any mutation	Any mutation	Any mutation
Pre-Nab to AAV	Negative	Negative	Negative
Primary outcome	The change in micro-dystrophin expression in DMD patients treated with SRP-9001.	Safety and tolerability	Safety
Secondary outcome	Adverse events, vector shedding, and the development of antibodies to AAVrh74.	Micro-dystrophin expression in biopsy	
SAE	Increased transaminases that required corticosteroid treatment. Nausea and vomiting that required intravenous treatment (cohort 1).	More than 40% of patients suffered vomiting, nausea, decreased appetite, and pyrexia.	Complement activation, reduced platelet count, liver dysfunction, and acute kidney injury

Sarepta Therapeutics used rAAVrh74 (a serotype very similar to AAV-8) to delivery of the micro-dystrophin driven by MHCK7 promoter [\[13\]](#), named as SRP-9001. MHCK7 promoter (~770 bp), a novel regulatory cassette based on enhancer/promoter regions of murine muscle creatine kinase (CK) and α -myosin heavy-chain genes, can direct high-level expression comparable to cytomegalovirus and Rous sarcoma virus promoters in fast and slow skeletal and cardiac muscle, and low expression in the liver, lung, and spleen [\[13\]](#). According to the phase 1/2 open-label, safety, and tolerability trial (ClinicalTrials.gov: NCT03375164), 4 DMD boys, mean age 4.8, with mutations between exons 18 and 58, took prednisolone for ≥ 12 weeks but the AAVrh74 total binding antibody titers $< 1:400$ were enrolled [\[14\]](#). The subjects received a daily dose of 1 mg/kg prednisone for 30 days before the 2.0×10^{14} vg/kg SRP-9001 was injected. After 12 weeks, therapeutic efficiency was assessed. Compared to the baseline, the

gastrocnemius muscle biopsy showed a mean of 81.2% muscle fiber expression of micro-dystrophin, and the mean expression level was 74.3%. Serum CK remained decreased in all subjects (range 46–85%), with functional improvement by a mean 5.5 points in the North Star Ambulatory Assessment (NSAA) at 1 year. Meanwhile, the adverse event (AE) profile was minimal. The transient elevation of γ -glutamyltransferase in three patients was resolved with corticosteroids and the most common was vomiting (50%), which was considered to be not correlated with the AAV immunity. Currently, the treated patients average over 9 years old and in the predicted steep decline phase of disease they did not decline, but demonstrated a 7-point increase above their pre-treatment baselines on NSAA, and a 9.9-point (unadjusted means) and 9.4-point (least squared means) improvement versus a propensity-weighted external control ($p = 0.0125$) [15].

NCT03769116 is a randomized double-blind placebo-controlled phase 2 trial assessing the efficacy of SRP-9001 in 41 males with DMD. DMD patients between the ages of 4 and 7 and who have been taking oral corticosteroids for at least 12 weeks prior to the study were enrolled as participants. Participants were treated with a single intravenous injection of either SRP-9001 or a placebo. Primarily, the outcomes analyzed the change in the baseline NSAA score after 48 weeks and the micro-dystrophin expression after 12 weeks. Secondary outcomes assessed the time of the 100 m timed test, time to rise from the floor, and time to ascend four steps, as well as further quantifying micro-dystrophin using IF. After 48 weeks, patients in the treatment group were moved to the placebo group and vice versa, and all patients were treated with intravenous injection once again. The analysis reoccur 48 weeks after this second round of treatment, followed by a 3-year open-label extension for all patients. In January 2021, topline results for the first 48-week period were released [16]. Participants injected with SRP-9001 demonstrated significantly increased micro-dystrophin expression at 12 weeks compared to the baseline (mean expression of 28.1%), and no new safety concerns arose. However, there was no significant improvement of the NSAA score compared to the placebo after 48 weeks. Sarepta suggested that this discrepancy was due to poor randomization, which assigned patients with a higher baseline NSAA to the placebo group, who thus had a better natural history.

In late 2019, Sarepta announced another clinical trial, NCT04626674, known as the ENDEAVOR trial [17]. Thirty-eight patients with the same criteria as in NCT03375164 were confirmed as participants. Interim data from the first 11 patients in this study were released at the World Muscle Society Virtual Congress in September 2021 [18]. These data indicated that the SRP-9001 treatment was associated with robust micro-dystrophin expression localized to the sarcolemma and suggest that the level of expression was related to the vector genome copy number. In addition, adverse effects were consistent with previous studies, and all treatment-related adverse effects were temporary and manageable. Shortly after these data were presented, Sarepta released the results of the integrated analysis of the across studies 101, 102, and 103 at the target dose. At one year, SRP-9001 treated patients improved by 3.1 points (unadjusted means) and 2.4 points (least squared means) on NSAA versus the propensity-weighted external control ($p \leq 0.0001$) [19]. Therefore, these provide further support to reinforce confidence in our ongoing Phase 3 Study SRP-9001-301, EMBARK, which is a randomized double-blind placebo-controlled trial designed to assess the efficacy of SRP-9001 treatment for patients with DMD [20].

2.2. Pfizer-PF-06939926

At the American Society for Gene and Cell Therapy (ASGCT) meeting on May 15, 2020, Pfizer's press released the preliminary results of its ongoing clinical trial (ClinicalTrials.gov: NCT03362502) [21]. This is an open-label study to primarily evaluate the safety and tolerability of PF-06939926. PF-06939926 is a recombinant AAV9 carrying the mini-dystrophin under the control of a minimized murine muscle creatine kinase (MCK) promoter [22]. The preliminary results were collected from nine DMD patients of 4 years and older taking daily glucocorticoids for at least 3 months, with no pre-existing neutralizing antibodies to AAV9 before the injection of PF-06939926. Three patients received a low dose of 1.0×10^{14} vg/kg, and six patients received a high dose of 3.0×10^{14} vg/kg. Immunofluorescence (IF) and liquid chromatography mass spectrometry (LCMS) were used to assess the expression of mini-dystrophin. The data indicated that comparing to the normal, 2 months was 20% and 12 months was 24% ($n = 3$). At a high dose, the expression was 35% ($n = 6$) at 2 months and 52% ($n = 3$) at 12 months. Three subjects demonstrated a median improvement of 3.5 points from the baseline in NSAA at 12 months. Fat fraction demonstrated a reduction of 8% at a high dose ($n = 3$) and was unchanged at a low dose at 1 year, estimated by MRI. However, more than 40% patients suffered vomiting, nausea, decreased appetite, and pyrexia. Furthermore, three serious adverse events requiring urgent intervention were observed in the first two weeks following treatment, persistent vomiting, resulting in dehydration, acute kidney injury involving atypical hemolytic uremic syndrome (aHUS)-like with complement activation requiring hemodialysis and eculizumab. All three events were effectively treated and had resolved completely within 2 weeks. Then, the trial was originally put on hold by Pfizer to enable protocol amendments.

During a subsequent update at the Muscular Dystrophy Association's (MDA) Scientific and Clinical Conference in March 2021, Pfizer announced that it had dosed another 10 patients with PF-06939926, for a total of 19 [23]. Thankfully, there were no more serious AE presented at this extended cohort, which Pfizer attributed to the implementation of a glucocorticoid-based mitigation plan inspired by its previous interim results. A total of 30% of patients in the larger cohort experienced the previously mentioned minor AE, and improvements in NSAA scores were consistent with the previous findings. Based on these promising findings, PF-06939926 received a fast-track designation from the FDA to begin phase-3 trials in late 2020 (NCT04281485) [24], and the first participant was been dosed in in Barcelona, Spain on December 29, 2020. However, in September 2021, three patients were reported to have experienced serious treatment-related muscle weakness, two of whom also suffered from myocarditis, leading to the exclusion of patients who have mutations in exon 9 through 13 or both exon 29 and 30 from all trials [25]. Unfortunately, in December 2021, Pfizer reported the death of a patient being treated with PF-06939926 [26]. No further details have been provided by Pfizer at this point, and both NCT03362502 and the recruitment for the upcoming phase 3 NCT04281485 have been put on hold pending an investigation.

2.3. Solid Biosciences-SGT-001

Solid Biosciences initiated a phase 1/2 open-label clinical trial (ClinicalTrials.gov: NCT03368742) designed to assess the safety and preliminary efficacy in DMD patients treated with SGT-001. SGT-001 was the candidate drug using AAV9 and a CK8 muscle-specific promoter to deliver and drive micro-dystrophin carrying the R16/17 neuronal nitric oxide synthase (nNOS) binding domain, which is considered to allow sufficient blood perfusion in the working muscle [27]. Participants in this study are DMD patients who are males between 4 and 17 years,

negative for the AAV9 antibodies, and who have used oral corticosteroids for at least 12 weeks prior to beginning the trial. Interim data from the first six patients were made available via a press release from Solid Biosciences in March 2021. Six subjects were treated by SGT-001 with a low dose (5.0×10^{13} vg/kg, $n = 3$) and high dose (2.0×10^{14} vg/kg, $n = 3$). IF and Western blotting (WB) were used to estimate the expression level of micro-dystrophin. In a patient with the low dose, the micro-dystrophin was below the 5% level of quantification by WB and approximately 10% of fibers by IF. However, in the other two subjects, micro-dystrophin was detected at very minimal levels by IF and none by WB. However, in the three subjects of the high dose, the micro-dystrophin expression ranged from approximately 5–17.5% of the normal dystrophin by WB and 10–70% of positive muscle fibers by IF at day 90. Several days later, the non-ambulatory adolescent DMD patient demonstrated a platelet count reduction, followed by a red blood cell count reduction and transient renal impairment. Patients in the low-dose cohort had a mean NSAA score increase of 1.0, while patients in the high-dose cohort had an increase of 0.3. Patients in the untreated control group experienced a 4-point decline in the same time frame, indicating an initial clinical benefit associated with the treatment with SGT-001. Patients in both dose groups achieved clinical improvements on the 6-min walk test and vital capacity test, as well as meaningful improvements as assessed by patient-reported outcome measures (PROMs). The AEs were serious and the repeated complement activation has resulted in two clinical holds by the FDA. The first was related to thrombocytopenia in 2018 and the second was in October 2019 because of a more widespread complement activation affecting red blood cells (RBCs) and causing renal damage and cardiopulmonary insufficiency [28][29]. Due to the small number of patients tested and the difficulties Solid Biosciences faced in this trial, firm conclusions regarding the safety or preliminary efficacy cannot be drawn from this study at this time. An in vitro study suggests that the AAV capsid not only interacted with various components of the complement system, but also directly activated the complement system in a dose-dependent manner [30].

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