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Systemic delivery of adeno-associated viral vectors

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For diseases like muscular dystrophy, an effective gene therapy requires bodywide correction. Systemic viral vector delivery has been attempted since early 1990s. Yet a true success was not achieved until mid-2000 when adeno-associated virus (AAV) serotype-6, 8 and 9 were found to result in global muscle transduction in rodents following intravenous injection. The simplicity of the technique immediately attracts attention. Marvelous whole body amelioration has been achieved in rodent models of many diseases. Scale-up in large mammals also shows promising results. Importantly, the first systemic AAV-9 therapy was initiated in patients in April 2014. Recent studies have now begun to reveal molecular underpinnings of systemic AAV delivery and to engineer new AAV capsids with superior properties for systemic gene therapy.

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Introduction

Many life-threatening diseases affect a number of organs or affect tissues that are widely distributed. A successful gene therapy for these diseases requires a viral vector that can effectively reach all target cells throughout the body. Since our vessels are a built-in and ready-to-use system for bodywide transportation, a convenient strategy to achieve systemic delivery would be infusion of a therapeutic viral vector into the circulation. For this seeming straightforward method to work, a viral vector has to reach the target area, get out from the vasculature and infect the diseased cells.

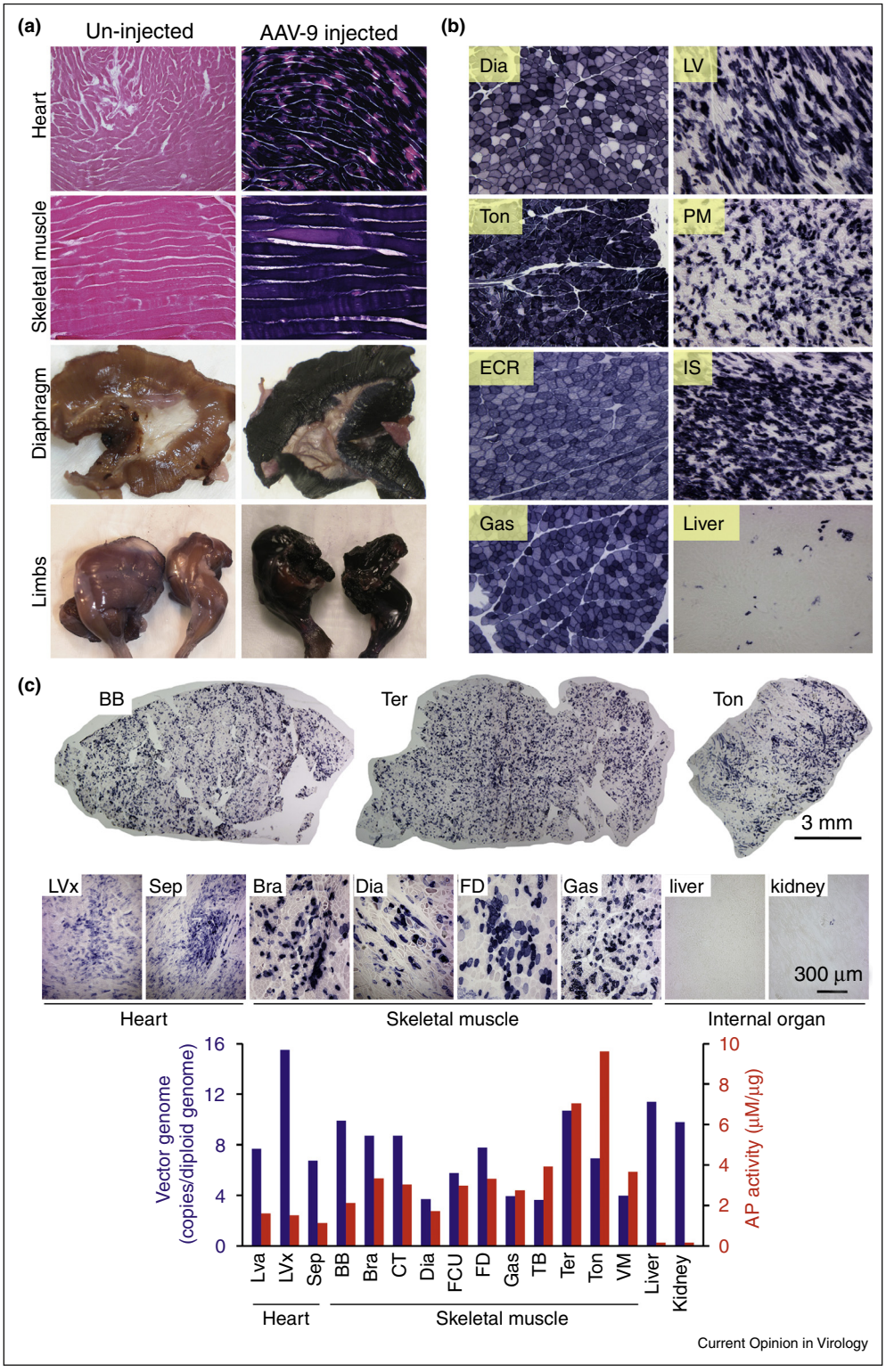
A report in 1992 claimed to have achieved 'widespread long-term gene transfer' to striated muscles in newborn mice using recombinant adenovirus [1]. The authors delivered adenovirus intravenously to 2–5-day-old mice and detected some expression in the liver, lung, heart and skeletal muscle. While the adenoviral vector had indeed spread to various tissues and organs, there were only sporadic transduction in skeletal muscle and ~0.2% transduction in the heart. This is far from 20 to 50% gene transfer efficiency required to treat skeletal muscle disease and cardiomyopathy in diseases like Duchenne muscular dystrophy (DMD) [2,3]. Several strategies were developed to overcome the endothelial barrier for systemic adenovirus delivery. These include the application of the vessel dilator and permeabilizer, hydrodynamic injection and viral capsid modification [4–6]. Despite improved intravascular transduction of a single limb with pressurized infusion and endothelial permeabilization, adenoviral vectors eventually lose the favor for systemic delivery due to severe immune responses and fatal complications [7].

Over the last two decades, adeno-associated virus (AAV) has emerged and now become the most preferred vector for gene therapy [8•,9•,10•,11]. AAV is a single stranded DNA virus discovered in 1965 [12]. It persists mainly as episomal molecules in infected tissues [13–15]. More than 12 different serotypes and hundreds of capsid variants have been isolated from adenoviral stocks and animal tissues or engineered in laboratories. In contrast to adenovirus, intramuscular injection of recombinant AAV serotype-2 (AAV-2) resulted in yearlong robust transduction with nominal cellular immune responses [16,17]. Strategies that have been shown to enhance adenoviral intravascular delivery (such as pharmacological vessel permeabilization and forced extravasation) also resulted in uniform whole limb muscle transduction by AAV-2 [4,18]. However, there remains a significant gap to achieve whole body gene transfer from peripheral vessels. A bona fide breakthrough in systemic gene delivery has to wait until new AAV serotypes are isolated.

Systemic gene delivery with AAV in rodents

In early days of AAV vector development, most studies are focused on AAV-2. Isolation of new serotypes has greatly expanded the repertoire [19–21]. Rutledge *et al.* isolated AAV-6 from an adenovirus stock [22]. Gao *et al.* isolated AAV-8 and AAV-9 from tissues of rhesus monkey and human, respectively [23••,24]. These three serotypes open the door to a successful systemic delivery. Gregorevic *et al.* showed efficient whole body striated muscle transduction in mice after tail vein

Figure 1



Systemic AAV delivery results in bodywide gene transfer in rodents and large mammals. Peripheral vascular delivery provides a method that allows an AAV vector to reach most, if not every, part of the body. **(a)** Bodywide muscle transduction in mice following tail vein delivery of an alkaline phosphatase (AP) reporter gene AAV-9 vector. **(b)** Robust and persistent (up to one year) skeletal muscle and myocardial transduction after jugular vein injection of an AAV-8 AP vector in a neonatal dog. **(c)** Tyrosine mutant AAV-9 results in whole body striated muscle transduction in young adult dystrophic dogs. Top panel, representative full-view images from selected skeletal muscles; middle panel, representative

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