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Gene therapy for inherited muscle diseases: Where genetics meets rehabilitation medicine

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Abstract

The development of clinical vectors to correct genetic mutations that cause inherited myopathies and related disorders of skeletal muscle is advancing at an impressive rate. Adeno-associated virus (AAV) vectors are attractive for clinical use because (i) AAVs do not cause human disease, and (ii) these vectors are able to persist for years. New vectors are now becoming available as gene therapy delivery tools, and recent preclinical experiments have demonstrated the feasibility, safety and efficacy of gene therapy with AAV for long-term correction of muscle pathology and weakness in myotubularin-deficient canine and murine disease models. In this review, we present recent advances in the application of gene therapies to treat inherited muscle disorders including Duchenne Muscular Dystrophy and X-linked Myotubular Myopathy. Potential areas for therapeutic synergies between rehabilitation medicine and genetics are also discussed.

What is gene therapy and when will it be used in clinical practice?

Gene therapy - the process of introducing foreign genomic materials into host cells to elicit therapeutic benefit - became available for clinical practice on November 2, 2012, when Glybera (alipogene tiparvovec) became the first gene therapy in the Western world to receive market approval for patients with lipoprotein lipase (LPL) deficiency, a rare genetic disease previously without effective treatment(1, 2). Since 1989, gene therapy clinical trials have been undertaken in 31 countries with more than 1800 human trials ongoing, completed or approved worldwide(3). Many of these trials target rare “orphan diseases”. The Orphan Drug Act of 1983 defined an orphan product as a drug intended to treat a condition affecting fewer than 200,000 persons in the United States or a drug that would not be expected to be profitable within seven years following FDA approval(4). Orphan disease designation allows a sponsor to apply for market protection for the product following approval. 2,700 orphan drug designations and more than 400 approvals associated with these designations were approved as of 2012(4). While most gene therapy trials have addressed cancer or cardiovascular disease, a significant number of gene therapy trials have targeted rare monogenic (single gene) diseases (Table 1)(3). These groundbreaking therapies involve the insertion of DNA sequences that encode functional, therapeutic genes into patients to replace mutated dysfunctional genes causing disease. In the case of Glybera, a DNA sequence encodes a therapeutic LPL gene packaged within a vector, in this case an adeno-

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associated virus (AAV). The recombinant AAV is injected into a patient harboring a mutant disease-causing LPL gene. The injected AAV is capable of shuttling the replacement DNA sequence from inside the vector to the cells of the targeted tissue. Once inside, the patient's own cellular machinery works to transcribe the new replacement DNA sequence to produce the therapeutic protein to treat the patient's disease (Figure 1). Besides the success of Glybera, other notable examples of gene therapy successes are highlighted in clinical trials undertaken in rare genetic childhood diseases such as X-linked severe combined immunodeficiency (SCID-X1) and Leber congenital amaurosis (LCA). In the first example, SCID-X1 results in recurrent and often fatal infections caused by genetic deficiency in cellular and humoral immunity. Long-term follow-up of nine SCID-X1 boys treated in a French adenovirus-mediated gene therapy trial reported eight survivors after nearly ten years(5). In the second example, LCA leads to congenital blindness caused by mutations in a retinal gene that causes progressive loss of vision; young patients become completely blind by adulthood. Three independent gene therapy trials for LCA patients have been initiated, and follow-up results indicate improvement in vision for up to 2 years with no serious adverse events(6–8). These and other gene therapy successes have been offset by serious, and rarely fatal, adverse events that lead to early clinical trial "holds". The most famous case was the death of Jesse Gelsinger in 2000, who was the 19th patient enrolled in a gene therapy trial of a deficiency of ornithine transcarbamylase (OTCD)(9). Despite these early setbacks, the field of gene therapy continues to move forward at an extraordinary pace.

Will gene replacement therapy be useful for inherited muscle diseases like muscular dystrophy?

Most gene therapy clinical trials have targeted genes involved in cancer(3) with fewer trials initiated in monogenic diseases, such as Duchenne muscular dystrophy (DMD). Muscular dystrophies make up only a small percentage of the monogenic diseases (Table 1), notably Becker, Duchenne and Limb Girdle muscular dystrophy. Pompe disease, amongst others listed in Table 1, is not considered a muscular dystrophy even though skeletal muscles of affected patients grow progressively weaker due to accumulation of abnormal proteins within the muscle's contractile tissue. Therapeutic approaches at replacing defective genes in monogenic diseases of muscle, like DMD, include the use of recombinant viral vectors engineered to target specific tissues. In the 1960s, the discovery of naturally occurring adeno-associated virus (AAV) isolates led to the clinical application of recombinant AAV vectors with early successes in clinical trials (10). AAV vectors are attractive for clinical use because AAVs are not associated with human disease(2), the virus persists in the infected host for years and a large "toolkit" of AAV vectors is available as clinical gene therapy delivery tools(11). In addition to muscle diseases, AAV vectors have been used in clinical gene therapy trials targeted to the liver for the treatment of hemophilia B, to the lung for treatment of cystic fibrosis, to the brain for treatment of Parkinson's, Batten's, and Canavan's disease, to joints for treatment of rheumatoid arthritis and to the eye for treatment of LCA(10).

In recent years, AAV–mediated gene replacement has rapidly moved from preclinical studies to clinical trials due to encouraging results from animal models. Major challenges

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surrounding this strategy include: (1) effective delivery methods to target muscles throughout the body, including diaphragm and cardiac muscle, and (2) host immune responses to the therapeutic vector(12). The latter challenge was encountered in a double-blinded, randomized, controlled phase I trial of limb-girdle muscular dystrophy(13, 14), AAV1-MCK.human-alpha-Sarcoglycan (SGCA) was injected locally into the extensor digitorum brevis muscle in 3 patients, and sustained transgene expression was observed in 2 out 3 patients after 6 months. Humoral and cellular immune responses to the AAV capsid proteins were detected in the patient who failed to show expression. Another phase I trial on DMD from Mendell et al (15) also raised the potential of cellular immune responses to either self or non-self dystrophin epitopes. In the study, AAV vectors carrying a truncated but functional dystrophin gene under the control of a CMV promoter were injected into the bicep of 6 DMD patients. None of the patients displayed transgene expression with 4 out 6 patients showing detectable T cell responses against the transgene product. Two of the patients had dystrophin-specific T cell responses before the treatment. Taken together, these trials are informative to emphasize the importance of pre-screening patients for pre-existing immune responses to both AAV capsid proteins and transgene product, and also to develop strategies to circumvent immune responses, such as using a transient course of immunosuppression, shown to be effective in a dog model of DMD(16, 17).

Can genes be repaired?

While AAV-mediated gene therapy is regarded as a gene replacement strategy, another exciting development, termed exon skipping, focuses on gene repair. Approximately 70% of all DMD mutations are due to single or multiple exon deletions. Such deletions disrupt the open reading frame of dystrophin and hence, result in a premature truncated protein. In most cases, selective removal of specific exons can restore the reading frame and produce a partially functional dystrophin protein for clinical benefit(18–21). Antisense oligonucleotides (AOs) targeting pre-mRNA to modulate splicing have been used to induce exon skipping, and the first human phase I trials(22, 23) focused on skipping exon 51, which, if successful, would be able to correct ~13% of DMD patients with specific deletions within exons 42 to 50. A therapeutic exon skipping AO, 2-O-methyl AO termed “PRO051” (23), and AVI-4658, a morpholino conjugated AO(22) that targets an internal sequence of exon 51 was injected intramuscularly into DMD patients. AOs used in these trials were well tolerated, demonstrated successful exon skipping, and all patients demonstrated dystrophin expression to levels between 3–12% and 22–35% by PRO051 and AVI-4658, respectively. Following these initial clinical trials of intramuscular administration, phase I/II trials using systemic delivery of the two drugs were tested for dose, safety and efficacy(24, 25). Dose-dependent restoration of dystrophin expression was observed following weekly administration of the experimental compounds through abdominal subcutaneous injections in two cohorts. While no significant differences was detected in patient’s walking ability following a 12-week long treatment(24), patients treated with weekly PMO-AO (AVI-4658) (25) for 48 weeks demonstrated improvement in stabilization of the muscle and in the six-minute walking distance test (6MWT) (26). A larger confirmatory phase III trial is in the planning for 2014. Clinical trials for skipping other exons are also underway or in planning(18). These “personalized gene therapy medicines” generate hope for DMD

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patients, with the caveat that effective therapy will need to restore dystrophin expression in both skeletal and cardiac muscle, and that treatment will need to be persistent. The future challenge for clinical development with AOs is that current forms have a short half-life, and more than 85% of AOs are cleared from the circulation within 24 hours. This short half-life requires weekly injections to maintain a therapeutic level. Long-term outcomes of these AOs are also unknown. Intramuscular administration of these agents may be limited in treating skeletal muscle, and treating the cardiac muscle will need to be addressed for this strategy to be an effective treatment for DMD associated cardiomyopathy.

Non-sense stop codon read-through is another method of gene editing, and potentially benefits ~ 13% of DMD boys with premature termination codon (PTC) mutations. Aminoglycoside antibiotics initially demonstrated the capacity to induce ribosomal read through of premature stop codon(27), but not efficient and too toxic to be used for long term treatment. Ataluren (PTC124) was identified to be effective in this matter in *mdx* mice, and subsequently tested in human DMD trials(28–30). The drug was well tolerated in general and the dystrophin protein was detected with treated patients showing improvement in the 6MWT. However, correlation between the level of dystrophin expression and the 6MWT remains unclear. More trials are currently under way and the same treatment strategy could be potentially applied to other muscle diseases including spinal muscular atrophy. Progress in developing other approaches targeting repair of the muscle membrane due to lack of dystrophin is also under development. For example, increasing the level of the compensatory protein utrophin (31, 32), and upregulation of glycosylation of a-dystroglycan to improve extracellular matrix attachment (33).

Can defective genes be completely replaced? Surprising lessons learned from dogs

In 2008, a case report of a 5-month-old Labrador retriever was published in a Canadian veterinary medical journal(34). The dog presented with weakness, muscle atrophy and histopathological changes in skeletal muscle consistent with a centronuclear myopathy. Because male littermates were similarly affected, the authors postulated that the disease was X-linked, giving rise to the possibility that the disorder could be analogous to X-linked myotubular myopathy (XLMTM). It was through the tireless and extraordinary efforts of Alison Rockett Frase, that our research group was able to acquire a first-degree relative, a dog named “Nibs”, a Labrador retriever coming from a line of dogs with a history suspicious for XLMTM. We later discovered that Nibs harbored a canine MTM1 mutation(34), the same gene known to cause myotubular myopathy in patients [reviewed in “The Miracle of Nibs” (35)]. Mrs. Frase recalls the story of her odyssey locating and retrieving the founding carrier dog from a farmer in Canada. The following excerpt describes how a determined mother of an affected child can help shape the future of research for a disorder like myotubular myopathy: “In the fall of 2008, a female Labrador Retriever was discovered to carry the same gene as I do for my son’s muscle disorder called mytubular myopathy (MTM). To date, this was the first MTM large animal ever discovered by researchers anywhere in the world….Nibs was a beautiful Labrador Retriever that was instrumental in giving us puppies that carry the myotubular myopathy (MTM1) gene that

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affects our son Joshua. I am so grateful to Nibs for the initial 12 puppy litter…Our second litter of MTM pups has been born…Knowledge gained from these animals may one day lead to treatments not only for MTM, but other neuromuscular diseases. It will be a miracle for our son Josh and thousands of children like him if our goals are achieved." Joshua Frase passed away on December 24, 2010, less than 2 years after this was written. His legacy, the *Joshua Frase Foundation*, set into motion research that will, hopefully, develop the first effective treatment for this devastating disorder.

XLMTM is an orphan disease, affecting 1/50,000 live male births worldwide(36) with only supportive, palliative care available for patients(37). This inherited muscle disease results from loss-of-function mutations in the Myotubularin 1 gene (*MTM1*) (38) that encodes the founder of a family of 3-phosphoinositide phosphatases acting on the second messengers phosphatidylinositol 3-monophosphate [PI(3)P] and phosphatidylinositol 3,5-bisphosphate [$PI(3,5)P_2$] (39, 40). Although myotubularin is expressed ubiquitously, loss of this enzyme profoundly affects skeletal muscles causing hypotrophic myofibers and structural abnormalities, with associated weakness (41). No effective therapy exists for XLMTM. Management of the disease generally consists of mechanical ventilation, gastrostomy feeding tubes, antibiotics (for respiratory infections), orthotics to prevent skeletal limb contractures and surgical treatment to alleviate severe spinal deformities. In spite of aggressive medical care, the average life expectancy is only about two years and most who survive beyond this age require mechanical ventilation.

Animal models of the disease currently exist in zebrafish, mice and notably, in dogs (41–43). The murine phenotype resembles human XLMTM, with similar pathology and early mortality. In a mouse knockout model of XLMTM, local delivery of the wild-type myotubularin gene (*MTM1*) via an AAV vector reversed characteristic pathological features and rescued the function of injected limb muscles(44). Buj-Bello et al were the first to report a gene therapy success in the *Mtm1* knockout mouse in 2008. That same year, the *Joshua Frase Foundation* provided our research group access to a female Labrador retriever harboring an *MTM1* gene mutation that was later proven by Beggs et al to cause a canine version of the human disease(45). From this single founding female our group established a canine breeding colony to study effects of the disease in dogs. Initial data revealed that affected males display a phenotype directly analogous to human XLMTM: progressive and severe muscular weakness(46) leading to the inability to walk, weak ventilatory muscles leading to respiratory impairment(47) and early death. Based upon the early experience with gene replacement in the *Mtm1* knockout mouse(44), a similar gene replacement strategy was initiated in the XLMTM dog in 2011.

For eventual gene therapy of XLMTM patients, our goal was to use a predictive large animal model (the XLMTM dog) to refine the delivery system, to assess critical safety parameters such as the potential host immune response to vector and transgene, and to optimize efficacy measurements. In collaboration with the French non-profit institute, Généthon(48), cohorts of *Mtm1* knockout mice were first tested for response to systemic *Mtm1* gene replacement via tail vein injection. Results indicated that a single systemic treatment with AAV-*Mtm1* sufficed for long-term (at least one year) survival and essentially complete amelioration of symptoms of mice with myotubularin-deficient muscles(49).

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Using the same AAV vectors produced by Généthon scientists and tested in mice, our collaborative research group confirmed that local gene replacement therapy, delivered intramuscularly into the hind limb of young XLMTM dogs, reversed pathological changes in myotubularin-deficient skeletal muscles. Remarkably, the treated muscles also showed nearly normal strength at six weeks post-injection, compared to very weak muscles (only 20 percent of normal strength) in saline-injected contralateral limbs. In subsequent experiments, intravascular administration of AAV8-*MTM1* at the same dose used in mice was well tolerated in dogs, rescued the skeletal muscle pathology and respiratory function, and prolonged life for over one year (Figure 2). Together these initial studies demonstrated the feasibility, safety and efficacy of gene therapy with AAV for long-term correction of muscle pathology and weakness observed in myotubularin-deficient mouse and dog models, and paved the way to clinical trials aimed at correcting this devastating disease in patients.

Rehabilitation and gene therapy

As highlighted in the discussion above, research on the role of gene therapy in the treatment of muscular disorders has undergone impressive growth over the course of the past decade, with a considerable portion of this research being focused on inherited myopathies such as DMD and XLMTM. Gene replacement therapy in such disorders, however, represents only a fraction of the spectrum of muscular disorders addressed in rehabilitation medicine that might benefit from application of a gene therapy approach. Equally significant are inquiries into the genetic regulation of age-related muscle atrophy, muscle breakdown in hypercatabolic states (as seen with malignancy or infection), as well as recovery from muscle injuries associated with mechanical trauma, ischemia or denervation.

Investigation of potential gene therapy strategies to enhance muscle regeneration and/or counteract the effects of muscle atrophy and degeneration is underway to elucidate (and experimentally manipulate) molecular events at the transcriptional, translational and post-translational stages. Examples include research on the bioavailability of growth factors such as TGF1-3(50, 51), IGF-1(52, 53) and growth-differentiation factors such as GDF8/myostatin(54, 55) that play a role in the proliferation and differentiation of muscle stem cells (reviewed in this supplement by Jasuja and LeBrasseur). The ability to therapeutically regulate expression of these factors has the potential to prevent muscle loss and enhance muscle recovery, and thus is aligned with key concerns in the area of rehabilitation medicine. To date, however, much of the research in these areas has remained within the molecular and cellular biology domains, with limited dissemination to the rehabilitation research community. Translational research on the rehabilitation applications of these therapies remains in the nascent stages, though advocacy for advancement of research to define the cellular and molecular mechanisms that are induced and/or enhanced by rehabilitation therapies continues to grow(56).

Increasingly demonstrated in rehabilitation medicine literature is research on how mechanical stimuli such as stretch or compression affect intracellular signaling and gene expression (i.e. “mechanotransduction”)(57–59). Studies on up-regulation of growth factors in response to tensile and/or compressive loading have been undertaken in tendon (showing up-regulation of IGF-1)(60, 61), as well as muscle (showing up-regulation of MGF)(58, 62).

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The mechanisms underlying mechanotransduction are still being elucidated, and appear to involve not only chemical signaling pathways, but also direct physical coupling via cytoskeletal elements between membrane structures and nuclear structures. Less understood are the effects of mechanical stimulus on gene therapy delivery and efficacy; Prior studies have shown that cyclical mechanical stretch enhances AAV2 mediated gene transfer to cultured vascular smooth muscle cells(63), but to our knowledge, effects of mechanical stretch on AAV gene transduction have not been reported in skeletal muscle. Our research group is investigating effects of passive stretch in cultured skeletal muscle on the uptake and expression of various AAV serotypes, a process thought to occur via clathrin-dependent endocytosis(64). A series of follow-on studies will examine the effect of exercise on gene therapy uptake/efficacy *in vivo*. Rehabilitation research is needed using similar paradigms along with measures of motor recovery in human subjects undergoing gene transfer.

In other emerging areas of research on gene therapy for treatment of muscular disorders, the interplay of genetic factors and cellular factors is central (e.g. up-regulating expression of growth factors and the availability of responsive precursor cells that retain the ability to differentiate into functionally mature excitable tissues such as nerve and muscle). Indeed in some cases, the means for delivery of gene therapy relies directly upon transplant of cells that have been transfected with the genetic elements of interest. The importance of this synergistic interplay is underscored in a 2008 study by Haastert et al(65) in rats with sciatic nerve injury to determine whether voluntary exercise enhances the effects of gene therapy delivered via Schwann cells over-expressing FGF-2. These authors found that rats treated with FGF-2 gene therapy plus exercise showed enhanced regeneration of myelinated axons in comparison to sedentary animals, and furthermore that mRNA levels of regeneration associated proteins in lumbar spinal cord were significantly higher in exercised vs. sedentary animals. Gene therapies and cellular therapies are each important tools in the emerging era of biologic therapeutics. While cellular and gene therapies each have independent potential as treatments to combat muscular dystrophy, congenital myopathies, and muscle damage, the potential for synergistic therapies is also an important aspect of future treatment strategies. Moreover, as demonstrated by the work of Hasstert et al above, further potentiation of cellular and gene therapies may be effected by the strategic use of exercise interventions, thus positioning rehabilitation researchers and clinicians to offer significant contributions in the development of these important therapeutic advances.

Areas for future research: Where Rehabilitation meets Genetics

As we continue to explore how rehabilitation medicine and genetic medicine complement each other, we can begin to define potential therapeutic synergies by combining rehabilitation and genetic approaches. Areas for further research that emerge at the intersection of these two clinical/research domains are presented in Figures 3 and 4. In this review, we have already discussed advances in the application of gene therapies to treat inherited muscle disorders such as Duchenne Muscular Dystrophy and X-linked Myotubular Myopathy. Specific inquires that should be addressed in the future include whether a dose-response effect for therapeutic exercise in the rehabilitation of inherited muscle disorders exists, and if so whether a minimal effective exercise “dose” (versus toxic “dose”) can be defined. Similarly for gene therapy, dose-response curves need to be established and

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examined with an eye toward minimizing both potential costs and side effects associated with the delivery of large inocula. An intriguing possibility, built on the principles of mechanotransduction discussed earlier, is that by targeting gene therapy delivery to elements over-expressed in muscle after mechanical loading, we may be able to facilitate an activity-dependent up-regulation of therapeutic gene products. Rehabilitation researchers and clinicians thus stand to offer important insights on how gene therapies may be potentiated by the strategic manipulation of exercise timing and intensity. This could have implications, for example, in myopathic patients weaning from chronic ventilator support, where gene replacement therapy might be coupled with a pulmonary rehabilitation/exercise program. Ongoing dialogue about the interplay of biological and behavioral interventions will be essential in moving gene therapy for muscle disorders forward in the coming decade, and will constitute a central focus in the evolving field of Regenerative Rehabilitation.

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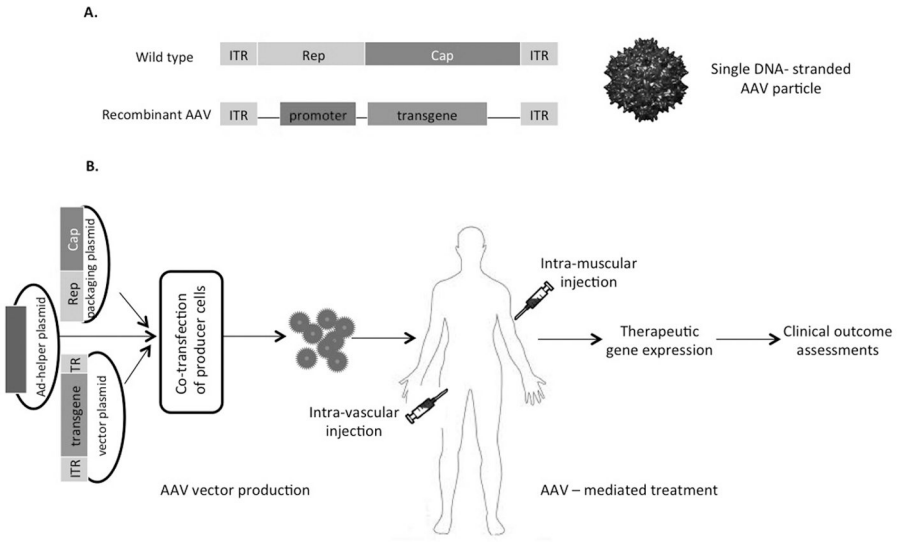

Figure 1.

AAV mediated gene therapy. A, Genome structure of wild type AAV, a linear single-stranded DNA. ITR, inverted terminal repeats, act in *cis* and important for AAV replication, genome packaging and transcription; Rep, *rep* gene produces 4 Rep proteins act in *trans* in all phases of AAV life cycle; Cap, capsid gene, produces 3 viral capsid proteins; Genome structure of recombinant AAV vector, AAV *rep* and *cap* genes are replaced by transgene of interest under the control of a promoter of interest. B, AAV vector production, delivery and assessments of clinical outcome. Co-transfection of AAV production cells such as HEK293 cells with 3 plasmids: (1) an AAV ITR-containing plasmid carrying the gene of interest; (2) a plasmid carrying the AAV *rep* and *cap* genes; and (3) a plasmid providing the helper genes isolated from adenovirus (Ad). Recombinant AAV vectors will be administrated via intramuscular or intra-vascular or other routes into subjects, up-taken by target cells, transgene will be expressed and clinical outcomes will be measured as a result of functions of the transgene product.

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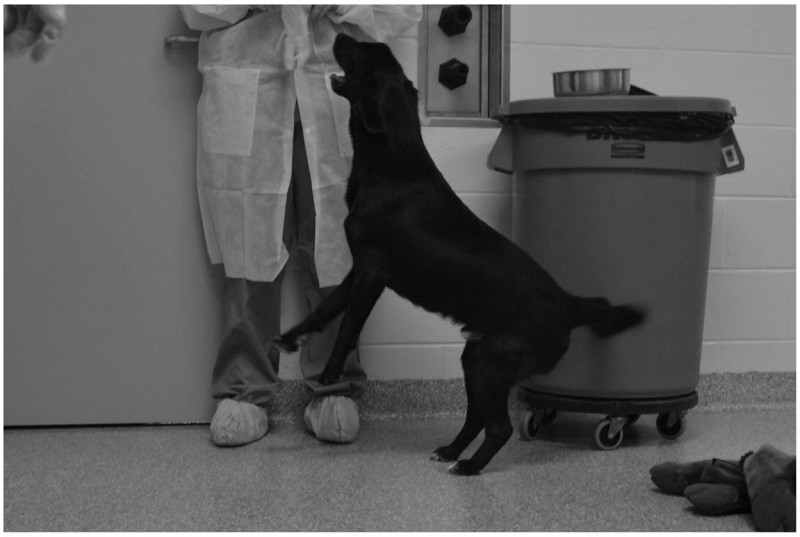

Figure 2.

The first XLMTM dog treated with intravascular gene replacement therapy (AAV8-MTM1) given at 9 weeks-of-age. Untreated XLMTM dogs do not survive beyond 6 months of age, and succumb to severe muscle weakness and respiratory insufficiency. Shown here, is an affected dog one year post-infusion with AAV8-MTM1. Systemic treatment resulted in amelioration of the severe muscle pathology and weakness observed in untreated dogs.

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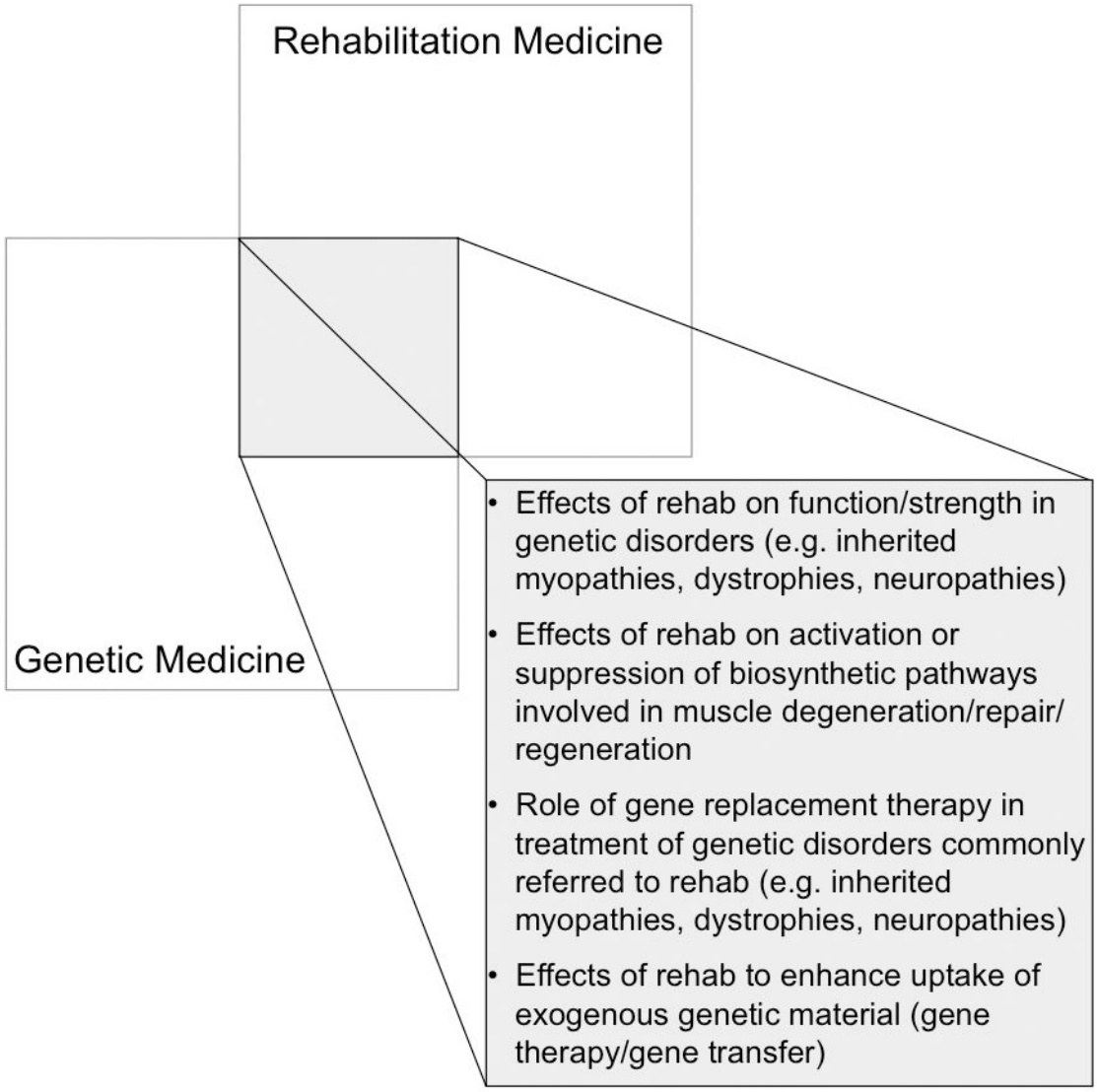

Figure 3.
Areas for future research at the interface of rehabilitation medicine and genetic medicine.

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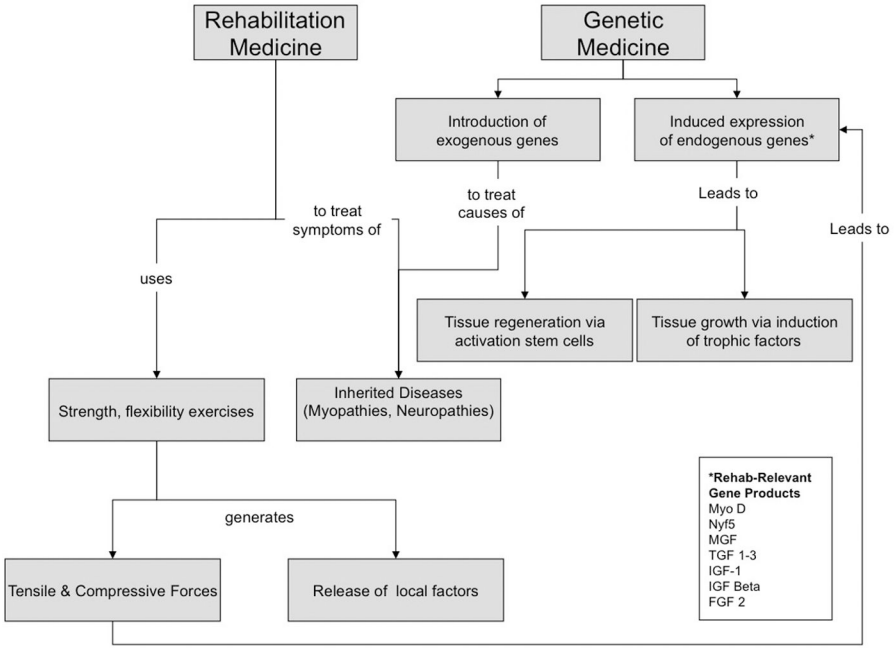

Figure 4.
Conceptual framework for areas of overlap between rehabilitation and genetic medicine.

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Table 1

Monogenic disorders reported in gene therapy clinical trials

Adrenoleukodystrophy
α-1 antitrypsin deficiency
Becker muscular dystrophy
β-thalassaemia
Canavan disease
Chronic granulomatous disease
Cystic fibrosis
Duchenne muscular dystrophy
Fabry disease
Familial adenomatous polyposis
Familial hypercholesterolaemia
Fanconi anaemia
Galactosialidosis
Gaucher's disease
Gyrate atrophy
Hemophilia A and B
Hurler syndrome
Hunter syndrome
Huntington's chorea
Junctional epidermolysis bullosa
Late infantile neuronal ceroid lipofuscinosis
Leukocyte adherence deficiency
Limb girdle muscular dystrophy
Lipoprotein lipase deficiency*
Mucopolysaccharidosis type VII
Ornithine transcarbamylase deficiency
Pompe disease
Purine nucleoside phosphorylase deficiency
Recessive dystrophic epidermolysis bullosa
Sickle cell disease
Severe combined immunodeficiency
Tay Sachs disease
Wiskott–Aldrich syndrome

*Glybera approved in Europe

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Table 2

Transcription factors in skeletal muscle potentially responsive to rehabilitation strategies

Factor	Description
Myo D	Transcriptional regulatory protein, induced during muscle regeneration(66)
Myogenic factor 5 (Myf5)	Transcriptional regulatory protein induced during muscle regeneration(67–69)
Mechano growth factor (MGF)	A splice variant of IGF-I that leads to muscle hypertrophy via activation of satellite cells(70)
Myogenic regulatory factor 4 (Mrf4)	Myogenic regulatory factor induced during muscle regeneration(71–73)
Myogenin	Myogenic regulatory factor induced during muscle regeneration(74–76)
Transforming growth factor beta (TGF-beta)	Considered a key signaling molecule in cardiac hypertrophy and failure, among others (77–79)
IGF-1 (Insulin-like growth Factor-1)	Implicated in the control of skeletal muscle growth, differentiation, survival, and regeneration, and considered a promising therapeutic agent in staving off the advance of muscle weakness (80–84)