Preface

Scene 1. The year was 1890. A young couple brought their 5-year-old son to their physician. Unlike his peers, the boy had a hard time walking and his muscles were getting weaker. “What is the problem? Can you treat it?” the couple implored the physician. In the face of these serious questions from the apprehensive couple, the physician told them he had very little to offer. All he could tell them was that this was a muscle wasting disease commonly seen in young boys. A French physician named Duchenne de Boulogne described this disease in 1868 and it has been dubbed Duchenne muscular dystrophy. Six years later, the young boy succumbed to his disease.

Scene 2. A century later, it was 1990. A 2-year-old boy caught the attention of his physician. On physical examination, the physician noticed signs of delayed neuromuscular development. Laboratory testing revealed abnormally high blood creatine kinase levels. The clinical findings reminded the physician about a landmark study published in 1987. Louis M. Kankel and his colleagues had cloned the first human disease gene called dystrophin. Mutations in the dystrophin gene have been identified as the culprit for Duchenne muscular dystrophy. A muscle biopsy and genetic testing are ordered immediately. It did not take long before the physician found that a small fragment of the dystrophin gene was indeed missing in the boy. “I am very sorry,” the physician told the parents, “Your child suffers from Duchenne muscular dystrophy, the most common lethal muscle disease in boys. The genetic testing confirms the diagnosis.” “Can you fix the mutated gene and cure the disease?” The worried parents asked. “I can put him on steroids and my colleagues can provide you with genetic counseling. But I am afraid that is all we can do.” The boy died at age 20.

Scene 3. Another hundred years have passed and it is 2090. A young couple is anxiously waiting for the results of the whole genome sequencing for their newborn boy. The physician comes in, “I’m afraid there is bad news. We found a mutation in the dystrophin gene of your son. But don’t worry, we will put him on gene therapy”. The boy receives his treatment and lives a long active and healthy life thereafter.

Muscle diseases, such as Duchenne muscular dystrophy (DMD), have afflicted humans for thousands of years as depicted in relief paintings of ancient Egyptian tombs. Quality of life is severely reduced and lifespan is shortened. Little was
known about the inner world of these diseases until the arrival of the molecular biology era. The discovery of the dystrophin gene in 1987 stands out as one of the great breakthroughs. Many more muscle disease genes have been cloned since then. Collectively, gene hunting has transformed the clinical practice by allowing accurate genetic diagnosis. Yet, a far more reaching implication of disease gene deciphering is gene therapy. Researchers now have the opportunity to tinker with the genetic tools to either repair or replace the defective gene.

The concept of therapeutic gene transfer was born within a decade of the discovery of the DNA double helix by Watson and Crick. The seminal studies of Kunkel and colleagues immediately generated great euphoria and hype among both researchers and the general public. It seems that a cure for muscular dystrophy by gene therapy is just around the corner. In reality, the development of muscle gene therapy has been far more challenging and frustrating.

DMD gene therapy started soon after the discovery of the gene, albeit with minimal knowledge of gene function, molecular pathogenesis or gene delivery vehicles. In the early 1990s, proof-of-principle successes were achieved by several groups using strategies from direct muscle injection of a plasmid carrying the full-length dystrophin expression cassette to retrovirus or adenovirus-mediated expression of a minimized dystrophin gene. Since then, enormous effort has been directed towards the development of an effective gene therapy for Duchenne muscular dystrophy and many other muscle diseases. We now know much more about the disease, the gene, the gene delivery vectors and the host immune response. Yet, the magic cure remains elusive.

Where are we? Is gene therapy ever going to work for muscle diseases? What is hindering muscle gene therapy? Can muscle gene delivery be used for treating other diseases? What is the clinical status of muscle gene therapy? With these questions in mind, this book was born. This is the first book entirely dedicated to muscle gene therapy. It encompasses a comprehensive and up-to-date evaluation of muscle gene therapy by leaders in the field.

Animal disease models have been extremely valuable in testing novel therapies. Preclinical studies in animals offers critical reassurance. For this reason, the book is started with a chapter on the animal models of muscle diseases. What follows are 15 chapters covering different aspects of muscle gene therapy.

Two chapters provide the current perspective on the design and application of antisense oligonucleotide-mediated exon skipping. This strategy aims at repairing the defective gene. It is not an imminent cure, but will significantly reduce the severity. Over the last decade, this technology has rapidly moved from encouraging findings in the rodent models to the large animal model and now human patients. The encouraging results from phase I human trials, as well as the exciting news on systemic exon skipping in dystrophic dogs, have greatly raised the hope that a clinical reality for muscle gene therapy is in sight.

Another major stride in the field is the development and application of adeno-associated viral vector (AAV) for muscle gene therapy. Approximately 40% of our body is made of muscle. Unlike many other tissues that have a restricted anatomic location, muscles are all over the place. For a long time, body wide gene delivery
has been a great challenge for muscle gene therapy. With the help of novel AAV serotypes, this obstacle has now at least been solved in rodents and dogs. For this and many other reasons, AAV has become the most favorite muscle gene delivery vehicle. It is thus not surprising that many chapters have elaborated on this highly promising technology.

One of the greatest lessons we have learned over the years is how our body’s immune system responds to the gene delivery vehicle and the therapeutic protein produced by the vector. This is a hurdle we have to overcome in order to translate gene therapy efficacy from the bench to the bedside. This issue is addressed by a chapter on modulating immune response for muscle gene therapy.

Several chapters have also been included to address special issues in muscle gene therapy. These include gene therapy for respiratory and cardiac muscles, in utero gene therapy, delivering large therapeutic genes to muscle and the combinatorial approaches for muscular dystrophy gene therapy.

Gene therapy is a rapidly evolving field. It has benefited greatly from breakthroughs in basic biomedical research, such as RNA interference and stem cell research. Two chapters deal with these fascinating advances. These new tools expand the horizon of muscle gene therapy to diseases that were considered unapproachable previously. Also noteworthy are two chapters that describe the applications of muscle gene transfer to treat diseases that mainly affect other tissues or even using muscle as a target for genetic vaccine. Collectively, the possibilities of muscle gene therapy are endless.

The book concludes with a chapter on clinical trials of muscle gene therapy. When gene therapy was initially brought up as a concept, its simplicity and intuitive nature led many to believe that it would be a homerun. However, the road of dream chasing has been quite bumpy and full of unpleasant surprises. The death of a patient volunteer in a phase I clinical trial for a metabolic disease at the end of the 1990s made many people believe that gene therapy was merely a fancy toy for scientists which would never reach patients. As demonstrated by many encouraging examples in our final chapter, I have every reason to believe that muscle gene therapy has finally come of age. At the same time, I have no doubt that the road ahead of us is not straightforward. Painstaking effort will be needed to make the Scene 3 described at the beginning of this preface a reality. Nevertheless, tomorrow will be better.

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