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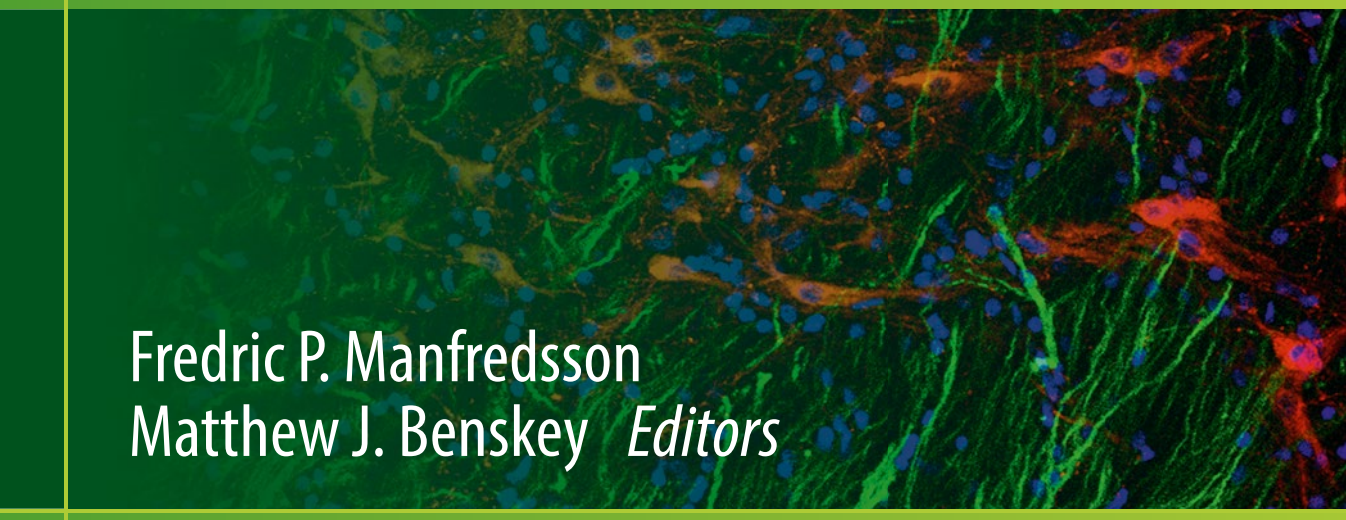

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Viral Vectors for Gene Therapy

Methods and Protocols

Humana Press

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Cover Illustration: AAV5 CAG-GFP (green) transduced fibers of passage traversing tyrosine hydroxylase (red) dopamine neurons of the substantia nigra in the rat brain. Courtesy of Fredric P. Manfredsson and Ivette M. Sandoval.

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Preface

Gene therapy, on a basic level, is defined as the delivery of nucleic acids to a cell in order to produce a desired effect. There are many methods that can be utilized in order to deliver nucleic acids to cells; however, the most efficient and adaptable method is the use of viral vectors. Viruses have naturally evolved over millennia to develop elegant mechanisms used to evade host immunity, gain entry to a cell, deliver their genetic material, and hijack host cell machinery in order to produce progeny virions. Viral vector-based gene therapy harnesses this awesome power of nature in order to efficiently deliver a desired genetic payload to cells of interest. The fundamental concept of a viral vector is relatively simple. First, the genes from the viral genome that are responsible for viral replication or untoward host response (i.e., disease) are removed, leaving only the genetic information that is absolutely essential for viral assembly. Next, the desired genetic payload is inserted into the modified viral genome. Finally, the resulting recombinant viral vector, containing the desired genetic material, is assembled in cultured cells and purified.

In its current state, viral vector gene therapy has become commonplace in both the laboratory and the clinic. Within the laboratory, viral vectors are commonly used as efficient genetic shuttles. The ability of viral vectors to infect a myriad of cells (both dividing and nondividing) and deliver various nucleic acids, which can then be integrated into the host genome or remain episomal, makes them extremely adaptable and powerful tools in biomedical research. Additionally, viral vectors are used in the lab to both model disease and research potential therapeutics. Further down the translational pipeline, viral vectors are being explored in the clinic to treat a wide range of diseases utilizing vastly different therapeutic approaches. This includes viral vectors in the treatment of cancers, neurodegenerative disease, and pulmonary disorders. Moreover, gene therapy is not limited to simple genetic overexpression, but can also accomplish a wide range of modalities such as CRISPR/CAS genome editing or manipulation of the expression of endogenous proteins. The wide range of problems to which viral vectors have been successfully applied underscores not only the tremendous potential of this tool but also how far the technology of viral vectors has grown and continues to grow [1–3]. Indeed, 2017 saw the first viral gene therapy product gain FDA approval (Luxturna©), paving the way for future efforts.

The idea of utilizing a virus to deliver a desired set of nucleic acids to a cell dates back to the early 1970s when researchers discovered that retroviruses were capable of acquiring cellular genes, giving proof in principle to the idea that viruses could be used in order to deliver nonviral genetic information to cells [4]. Not long after this observation, researchers were able to successfully generate recombinant viruses that were also capable of delivering nonviral genetic material to target cells [5–10]. Since these early landmarks in viral vector history, the field of viral vector gene therapy has grown exponentially. With advances in the fields of both molecular biology and virology, researchers have "vectorized" an ever-increasing number of different viruses with different capabilities. Further, researchers are constantly modulating every step of the viral life cycle in order to improve viral genetic delivery, while also expanding the potential repertoire of functions that a virus can perform. In this way science is constantly pushing the envelope of what a virus is able to achieve, with the end result being an unprecedented level of control over an extremely powerful tool.

However, as the maxim states, with great power comes great responsibility. Indeed, in order to achieve optimal results using gene therapy, it is the responsibility of the researcher to control for every aspect of the experiment. For years, the requisite knowledge necessary to properly control and conduct a successful gene therapy experiment has been the sole privilege of a handful of highly specialized laboratories or clinicians around the world. However, as the overall success of gene therapy has grown, so has the availability of these powerful tools. Today, the wide availability of viral vectors has made them accessible to virtually any scientist with the desire.

In spite of this increase in the availability of vectors themselves, the requisite knowledge that is absolutely essential to conducting a successful gene therapy experiment has not been made equally available. To successfully utilize viral vectors to their full potential, a large number of decisions must be made; in some instances prior to even obtaining the vector itself. It is the goal of this book to provide a comprehensive list of theoretical knowledge and detailed protocols necessary for researchers, clinicians, and students to successfully utilize viral vectors for a wide range of gene therapy applications. To begin, an introductory chapter will provide an overview of basic gene therapy modalities. Subsequent chapters will delve more deeply into specific protocols, ranging from vector production to delivery methods, which can be used as step-by-step instructions to successfully execute your desired gene therapy application.

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References

1. Tuszynski MH, Thal L, Pay M, et al. (2005) A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer disease. Nature Medicine 11:551–555. doi: 10.1038/nm1239
2. Rainov NG, Grp GIS (2000) A phase III clinical evaluation of herpes simplex virus type 1 thymidine kinase and ganciclovir gene therapy as an adjuvant to surgical resection and radiation in adults with previously untreated glioblastoma multiforme. Hum Gene Ther 11:2389–2401. doi: 10.1089/104303400750038499
3. Flotte TR, Zeitlin PL, Reynolds TC, et al. (2003) Phase I trial of intranasal and endobronchial administration of a recombinant adeno-associated virus serotype 2 (rAAV2)-CFTR vector in adult cystic fibrosis patients: A two-part clinical study. Hum Gene Ther 14:1079–1088. doi: 10.1089/104303403322124792
4. Finer M, Glorioso J (2017) A brief account of viral vectors and their promise for gene therapy. Gene Ther 24:1–2. doi: 10.1038/gt.2016.71
5. Shimotohno K, Temin HM (1981) Formation of infectious progeny virus after insertion of herpes-simplex thymidine kinase gene into DNA of an avian retrovirus. Cell 26:67–77.
6. Wei CM, Gibson M, Spear PG, Scolnick EM (1981) Construction and Isolation of a Transmissible Retrovirus Containing the Src Gene of Harvey Murine Sarcoma-Virus and the Thymidine Kinase Gene of Herpes-Simplex Virus Type-1. Journal of Virology 39:935–944.
7. Tabin CJ, Hoffmann JW, Goff SP, Weinberg RA (1982) Adaptation of a retrovirus as a eucaryotic vector transmitting the herpes simplex virus thymidine kinase gene. Mol Cell Biol 2:426–436
8. Samulski RJ, Berns KI, TAN M, Muzyczka N (1982) Cloning of adeno-associated virus into Pbr322—rescue of intact virus from the recombinant plasmid in human-Cells. PNAS 79:2077–2081

9. Hermonat PL, Muzyczka N (1984) Use of Adeno-associated virus as a mammalian DNA cloning vector—transduction of neomycin resistance into mammalian tissue-culture cells. PNAS 81:6466–6470
10. Yu SF, Rüden von T, Kantoff PW, et al. (1986) Self-inactivating retroviral vectors designed for transfer of whole genes into mammalian cells. PNAS 83:3194–3198

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Part I

Introduction

Chapter 1

Basic Concepts in Viral Vector-Mediated Gene Therapy

Matthew J. Benskey, Ivette M. Sandoval, Kathryn Miller, Rhyomi L. Sellnow, Aysegul Gezer, Nathan C. Kuhn, Roslyn Vashon, and Fredric P. Manfredsson

Abstract

Today any researcher with the desire can easily purchase a viral vector. However, despite the availability of viral vectors themselves, the requisite knowledge that is absolutely essential to conducting a gene therapy experiment remains somewhat obscure and esoteric. To utilize viral vectors to their full potential, a large number of decisions must be made, in some instances prior to even obtaining the vector itself. For example, critical decisions include selection of the proper virus, selection of the proper expression cassette, whether to produce or purchase a viral vector, proper viral handling and storage, the most appropriate delivery method, selecting the proper controls, how to ensure your virus is expressing properly, and many other complex decisions that are essential to performing a *successful* gene therapy experiment. The need to make so many important decisions can be overwhelming and potentially prohibitive, especially to the novice gene therapist. In order to aid in this challenging process, here we provide an overview of basic gene therapy modalities and a decision tree that can be used to make oneself aware of the options available to the beginning gene therapist. This information can be used as a road map to help navigate the complex and perhaps confusing process of designing a successful gene therapy experiment.

Key words Viral vector, Gene therapy, Adeno-associated virus, Lentivirus, Adenovirus, Herpes-simplex virus

1 Introduction

Viral vector-based gene therapy was originally conceived in order to accomplish a simple goal, to transfer genetic material to a target cell. Although simple, achievement of this goal produced profound results. The ability to manipulate gene expression within any desired cell revolutionized the biomedical field. However, with the continual improvement of viral vectors, expression cassettes, and delivery methods, gene therapy has evolved far beyond the ability to simply transfer a foreign gene to a cell, now enabling researchers and clinicians to accomplish an astounding number of sophisticated cellular and molecular manipulations. For example,

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