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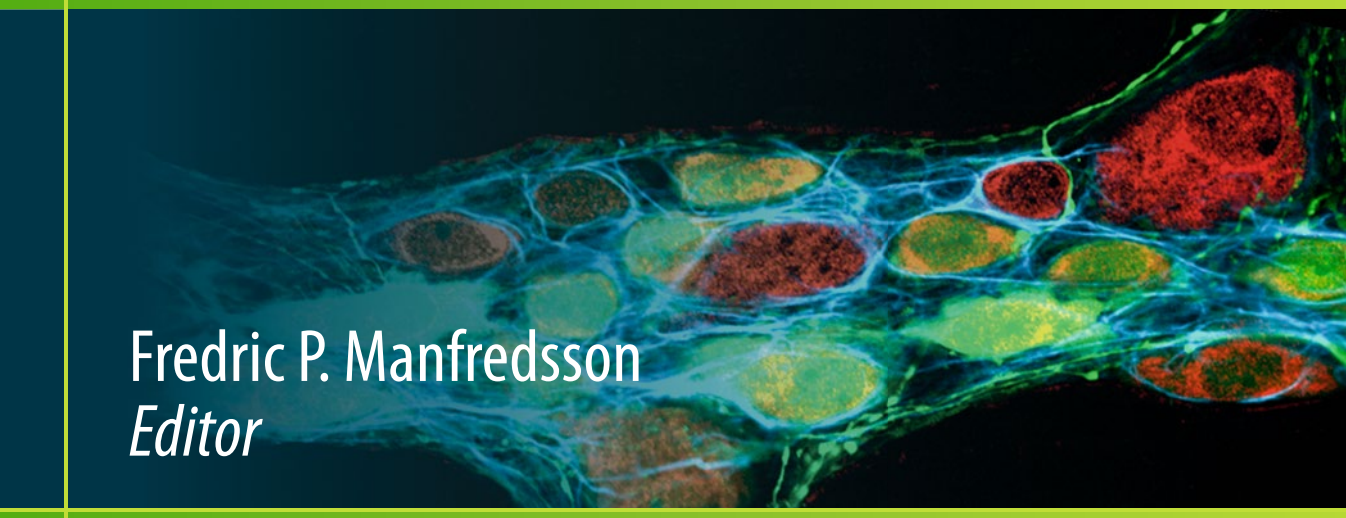

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Editor

Gene Therapy for Neurological Disorders

Methods and Protocols

Humana Press

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Gene Therapy for Neurological Disorders

Methods and Protocols

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Preface

Gene therapy of the nervous system, a technique once utilized by a few select laboratories, is now a commonplace research tool used around the world. Not only is gene therapy a useful utility in treating and creating preclinical models, but this technology has also demonstrated success in the clinic, in terms of both safety and efficacy [1, 2].

Gene therapy is a valuable tool that is being increasingly utilized to model neurodegenerative disorders [3]. One reason for this is the inherent ability of gene therapy to control genetic expression in both a spatial and temporal manner. For example, using this precision of gene therapy to model neurodegenerative disorders enables researchers to overcome any developmental compensations that may occur with germ line manipulations [4, 5], to create lesions that are restricted to one hemisphere or specific circuits, and to easily titrate the genetic material of interest [6], among other benefits. Of course, these benefits of gene therapy also translate to the use of gene therapy for the delivery of therapeutic genes in preclinical models of neurological disorders [7–11]. That being said, after over 15 years of experience in gene therapy, it has become clear to me that a significant amount of crucial knowledge necessary to design and execute a *successful* gene therapy experiment often fails to be disseminated in a normal format (i.e., via scientific manuscripts). Rather, this esoteric, yet essential knowledge is either briefly mentioned or solely propagated via word of mouth. Therefore, it is all too common that studies involving gene therapy manipulations produce results that vary between investigators (e.g., Ref. 12). Although such discrepancies are not the result of any wrongdoing, their occurrence adds to the "mysticism" sometimes associated with gene therapy and could serve to reduce the enthusiasm for taking on similar projects in the future. Thus, one purpose of this book is to dispel any confusion and provide a clear and detailed road map of how to successfully design and execute a gene therapy experiment in order to obtain consistent results.

As science progresses and new discoveries are made, the boundaries of gene therapy are rapidly expanding: Gene therapy vehicles are continuously undergoing development and are becoming more readily available, delivery methods are continuously being developed, and transgene cassettes are becoming more and more refined. This leaves the researcher with a plethora of decisions that must be considered before undertaking a gene therapy experiment. In this volume I have invited experts from around the world to share their expertise in finite areas of neurological gene therapy. The compilation of protocols and instructive chapters in this book are intended to give researchers, clinicians, and students of all levels a foundation upon which future gene therapy experiments can be designed. When one designs experiments involving gene therapy of the nervous system, several aspects need to be considered before experiments are designed: What delivery vehicle do you use? Will you produce this vector? How will you ensure that your vector retains stability? What expression system best fits your needs? What route will you choose to deliver your gene therapy agent? How will you model the neurodegenerative disorder that you aim to investigate, and what are the proven methods to treat these disorders in preclinical models? This book is aimed to address all these important considerations as well as to disseminate the

aforementioned bits of arcane information that are very important to consider during the course of experimentation.

Finally, the penultimate goal for many gene therapists is to see their product eventually end up in the clinic as a treatment for neurological disorders. Although gene therapy has progressed to the clinic, this is not a straightforward path as several variables such as age and disease status have to be considered. Several chapters in this volume will also discuss special considerations that need to be addressed when translating experimental approaches to the clinic.

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