Preface

From a drug development perspective, gene transfer technology is relatively new and evolving at a rapid pace. Recombinant adeno-associated viral (rAAV) vectors have become more widely investigated and improved in their short history [1, 2]. Although wild-type AAV was studied for decades, the work of Xiao Xiao and R. Jude Samulski published in 1996 represents the first evidence that rAAV can be directly administered in situ resulting in efficient, remarkably tolerated, and long-term gene transfer in the mouse skeletal muscle following a single injection [3]. That year was also the year of the lentivirus vector capable of transducing resting neurons after intracerebral injection in the murine model [4]. Yet, 1996 was only 1 year after the Orkin and Motulsky report [5] emphasizing the need for better vectors. Today, progress in rAAV-mediated gene transfer is so robust that long-term, efficient, and regulatable transgene expression is reproducibly achieved in large animal models. For example, (1) the entire limb of hemophilia dogs and primates can be efficiently transduced resulting in long-term phenotypic correction [6, 7] and very recently in hemophilia B patients [8]; (2) rAAV administered once in nonhuman primate muscle shows sustained regulatable transgene expression for more than 5 years [9, 10]. Simultaneously, the discovery of new AAV serotypes [11] along with the ability to encapsidate either "self-complementing" or "single-stranded" vector DNA [12] has turned this vector system into an extremely powerful and versatile tool with preferential organ transduction patterns depending on the AAV capsid origin and/or the vector DNA used. Finally, considerable improvements have been made in the availability of clinical grade rAAV stocks [13] a critical issue, even though large-scale production remains problematic despite the existence of potentially powerful new biotechnological approaches (hybrid viruses such as herpes, baculovirus, and stable packaging cell lines). rAAV vectors and their use in gene transfer are multidisciplinary syntheses requiring the expertise of virologists, physical chemists, chemical engineers, geneticists, epigeneticists, physiologists, and immunologists as well as veterinarians, pharmacists, regulatory affairs specialists, manufacturers, analytical scientists, and medical doctors. The complexity of gene transfer agents in the context of their clinical use requires investigators to have an – or at least an appreciation of – the regulatory environment and constraints that affect vector design, manufacturing, preclinical testing, and clinical use, with an emphasis on patient protection. In this volume, we have invited experts in the field from the USA and Europe to contribute current knowledge from this multidimensional field relating to the biology of AAV, rAAV vector design, vector manufacturing and product testing, performance of rAAV vectors in major organs, rAAV-related immunological issues, design of animal and clinical studies, and clinical experience.

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