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EDITORIAL

Towards routine manufacturing of gene therapy drugs

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The great potential for gene therapy to treat a wide range of diseases has led to high expectations with the first marketing approval of an adeno-associated virus (AAV) serotype 1-based gene therapy in 2012 (Glybera for the treatment of lipoprotein lipase deficiency) by the European Medical Agency and the successful completion of a phase 3 clinical trial of an AAV2-based investigational product (SPK-RPE65 for the treatment of Leber's Congenital Amaurosis, LCA2).[1,2] These and other advances have led to an increasing interest by large biopharmaceutical companies to partner in the development of gene therapy approaches for the treatment of human diseases. This interest is driven by the potential to address many serious unmet medical needs for genetic[3] and acquired[4] diseases by gene therapy. Since the first human gene therapy trial in 1990 using a retroviral vector, many different viral vectors have been developed, evaluated *in vitro* and in animal studies, and eventually assessed for human use in clinical trials. These developments have been paralleled by advancements in the technology required for vector production, purification, and quality control. The challenge has been to manufacture gene therapy vectors consistently at the quality level necessary for routine clinical use. Furthermore, the recent breakthroughs in clinic use of gene therapy vectors, *e.g.*, for primary immune deficiencies, lysosomal storage disorders, and cancer with lentiviral vectors, and for lipoprotein lipase deficiency, hemophilias, and retinopathies using AAV vectors, is fueling the need for larger quantities of these vectors.[5] Therefore, manufacturing processes are becoming more scalable and cost effective. More comprehensive characterization and stringent quality control tests are required to support advancing stages of clinical development and prospective product licensure requirements (in this issue reviewed by Clement *et al*.[6] for AAV vectors and by Merten *et al*.[7] for lentiviral vectors).[7]

The promising current upward inflection in the evolution of human gene therapy and clinical gene therapy vector development prompted the Journal to develop a special issue of *Molecular Therapy – Methods & Clinical Development* to provide an update on the state of the art in this field.[8] This issue gives a perspective on future needs for large-clinical scale production and purification methods of "traditional" viral vectors (AAV, lentiviral) that have supported most of the recent human gene therapy clinical protocols, as well as for oncoviral vectors (review by Ungerechts *et al*.[9]). Furthermore, the use of recombinant baculoviruses as potential gene therapy vectors (review by Kwang *et al*.[10]) was included because of the large transgene packaging capacity of this vector platform and its use in gene transfer studies to the eye. Finally, two reviews on nonviral gene therapy based on nanoparticles (review by Chen *et al*.[11]) and aptamers (review by Maier and Levy[12]) were selected for this issue in order to illustrate advances in manufacturing of nonviral vector platforms with potentially advantageous safety features. Equally important, original research articles focused on process development and current Good Manufacturing Practice manufacturing, quality control testing, and establishment of reference materials have been included to showcase cutting edge developments in the production of gene therapy products. The advances in manufacturing technologies made in the gene therapy field in recent years are impressive and resulting in the realization of routine large-scale production of gene-based drugs for the potential treatment of a range of human diseases.

CONFLICT OF INTEREST

OWM is Head of the laboratory for Applied Vectorology of Généthon, and holds patents in lentivirus and baculovirus-based recombinant AAV vector technologies. JFW is a Co-founder and Chief Technology Officer at Spark Therapeutics, and holds patents in recombinant AAV and lentivirus technologies.

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