

Editorial

Challenges of turning nucleic acids into therapeutics

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“Frustrations are life’s gestures, through which we grow in knowledge” [1]. Failure in turning nucleic acids into therapeutics has led many gene therapy companies into bankruptcy, but the endeavor continues. Gene therapy is a new biomedical discipline that is still in its infancy. In the last decade, enormous progress has been made in various aspects of gene therapy, including gene transfer in animal models. However, to realize its full potential to treat a variety of diseases, much basic science research and pre-clinical studies will be needed to rigorously establish efficacy and safety in relevant animal models of specific diseases. As biologic responses in cultured cells and animals may not always reflect what will actually happen in humans, there can be no substitute to clinical testing of the new treatment modalities in patients. There were also serious setbacks, especially with the death of Jesse Gelsinger, a young volunteer, in a gene therapy trial in September, 1999, at the University of Pennsylvania in Philadelphia [2]. However, creating an accurate understanding of the potential benefit and limitations of gene therapy among the public, regulators and financial community will allow us to begin moving

up the shattered expectations of gene therapy into reality [3].

In this issue of *Advanced Drug Delivery Reviews*, we have attempted to illustrate the recent advances and bottlenecks in the use of plasmid DNA, ribozymes and peptide nucleic acids (PNA) for gene therapy. This issue has attempted to cover the most exciting areas in the science of gene transfer with the articles contributed by leaders of their respective fields of study.

Gene therapy is a method for the prevention, correction or modulation of genetic and acquired diseases that uses genes to produce therapeutic proteins [4]. David Dean overviews the possible use of peptide nucleic acids (or PNAs) as antisense and antigene compounds that inhibit both transcription and translation. PNA has also been used to link specific targeting ligands or peptides to plasmids to circumvent barriers, such as cell-targeting and nuclear localization for enhanced gene transfer. Leonidas Phylactou discusses the use of ribozymes to down-regulate or repair un-wanted gene expression by RNA cleavage and RNA *trans*-splicing, respectively. Watanabe and Sullenger discuss the strategy that uses a therapeutic repair approach to correct a mutation by modifying the altered nucleic acid sequence within the cells. Natural living cells often modify their genetic instructions at the mRNA

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level. Splicing and editing can add, delete, or rewrite parts of mRNA transcripts to generate mature mRNAs needed to translate into required proteins. RNA repair has the potential to revert mutations to wild type, and therefore is more suitable than conventional gene replacement therapy.

Ronald Scheule discusses CpG motifs-mediated immunostimulation with recent results in the field of gene therapy. The simple dinucleotide sequence 5'-cytosine-guanosine-3' or CpG present in bacterial DNA has immense importance in cancer, antisense therapy and gene therapy. Parkes and Hart discuss the use of cell adhesion molecules for the development of targeted gene delivery systems. Targeting of adhesion molecules as receptors for gene transfer has several advantages over other receptor-mediated delivery. One of such advantages is the ability of these receptors to mediate the internalization of large particles, which will allow efficient cellular uptake of DNA molecules of unrestricted size. Uherek and Wels overview the possible use of nuclear structural proteins, recombinant viral capsid components and modular fusion proteins to achieve enhanced cellular uptake and intracellular delivery of plasmid DNA. A better understanding of how these proteins employ endogenous cellular transport processes to enter and leave individual cell compartments will be of great help in identifying proteins and protein domains suitable to use as DNA-carriers.

The spatial and temporal control of gene expression of therapeutic proteins plays an important role in therapeutic index. Restriction of gene expression to the tumor cells will ensure both efficacy of tumor eradication and preservation of surrounding normal tissues. Vile and associates discuss the strategies to control gene expression at the transcription level as well as the importance of using tissue and tumor-specific promoters in cancer gene therapy.

The inability to deliver growth factors locally in a sustained manner is a substantial barrier to tissue regeneration. Systems capable of sustained localized gene delivery should be well suited for growth factor

therapeutics. Jeffrey Bonadio updates the current status and future prospects of gene delivery systems for bone regeneration, in which plasmids encoding tissue-inductive proteins or growth factors are physically entrapped in polymer matrices (gene activated matrix, GAM) of poly(lactide-co-glycolide) or some other biodegradable polymers. Implantation of GAM at sites of bone injury has been shown to produce sustained gene expression and induce new bone in a dose- and time-dependent manner.

A better understanding of gene therapy will also lead to the treatment of chronic inflammatory disorders not easily treatable by conventional therapies. Mary Lynne Hedley overviews the common features of immune related inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, bowel diseases and asthma, with emphasis on how to develop gene-based drugs for these indications.

I am grateful to all the authors for their contribution to this issue of the *Advanced Drug Delivery Reviews*. Despite early setbacks, we need to reach equitable scientific resolutions and make every effort to reach our goal in treating diseases using gene medicines as pharmaceuticals. I hope that this issue provides stimulation for innovative approaches and look forward to further development in this fascinating field. We must maintain a strong competitive edge and work together in areas of mutual benefit.

References

- [1] T. Tulku, *Gesture of Balance: A Guide to Awareness, Self-healing and Meditation*, 9th Edition, Dharma Publishing, Berkeley, California, 1996, p. 15.
- [2] S.L.C. Woo, Presidential address of the 3rd Annual Meeting of the American Society of Gene Therapy (2000) <http://www.asgt.org>.
- [3] B.F. McGraw III, Commentary on the challenges of establishing gene medicines as a new class of therapeutics, *J. Drug Target.* 7 (1999) 245–248.
- [4] R.I. Mahato, L.C. Smith, A. Rolland, Pharmaceutical perspectives of gene therapy, *Adv. Genet.* 41 (1999) 95–156.