



## Preface

Gene regulation for effective gene therapy<sup>☆</sup>

Gene therapy holds great promise for treating both genetic and acquired diseases, such as cancers, tissue damages and diabetes among others and thus it is one of the fastest growing fields with enormous research efforts. However, several barriers must be overcome before gene therapy can be used in the clinical settings. The widespread clinical applications of gene therapy are being hampered due to its safety concerns such as un-controlled gene delivery and expression. While significant progress has already been made in designing non-toxic gene carriers, regulation of gene expression still needs great attention. Some therapeutic genes have deleterious side effects if they are expressed by non-target cells and tissues. For example, a growth factor gene may induce tumor formation when it is expressed in non-target normal tissues. Therefore, gene expression should be carefully regulated to avoid these dangerous side effects.

This theme issue aims at bringing together several key scientists to discuss the emerging trends in gene regulation and its application for effective gene therapy. This issue can be divided into four sub-themes: (i) gene regulation by transcription factors, (ii) gene regulation by promoters, (iii) stimuli responsive gene regulation, and (iv) RNA interference (RNAi) for gene regulation. Gene expression can be regulated at transcriptional, translational, and post-translational levels. Regulation of transcription controls when transcription occurs and how much RNA is created. Since cis-regulatory elements and trans-regulatory proteins are involved in transcriptional regulation, gene regulation can be achieved by modifying cis-regulatory elements or trans-regulatory proteins. A transcription factor is a protein that binds to specific DNA sequences and thereby controls the transfer of genetic information from DNA to RNA. Transcription factors bind to either enhancer or promoter regions of DNA adjacent to the genes that they regulate. In many disease states, transcription factors play important roles in enhancing the expression or silencing of specific genes. Therefore, it is crucial to understand the transcription factors which are involved in these processes. In addition, the transcription factors may be used as therapeutic reagents. Hideaki Kaneto and co-authors discuss about the role of MafA in differentiation of pancreatic  $\beta$ -cells as a strong transactivator for the insulin gene. The possible applications of MafA for the production of insulin-producing  $\beta$ -cells are discussed. Another important example of transcriptional regulation in a disease is the role of transcription factors in transdifferentiation of hepatic stellate cells (HSCs), which is involved in the liver fibrogenic process. Jelena Mann and Derek Mann describe the transcriptional factors of HSCs in this process.

Transcription factors can be modified to respond a physiological condition or increase promoter activity. An artificial transcription

factor is a chimeral protein designed for modulating gene transcription. The artificial transcription factors with zinc-finger motifs have been produced for specific recognition of the target sites in chromosome, which results in inducing specific proteins. Takashi Sera describes the design and applications of artificial-zinc finger proteins. Transcription factors are also modified to respond to a specific external drug, such as tetracycline, rapamycin and steroids. Tetracycline-inducible regulatory system can function as a potent trans-modulator to regulate gene expression in mammalian cells *in vitro* and in animal models. Fabienne Rolling and colleagues discuss the current progress of the tetracycline-inducible gene expression systems.

Cis-regulatory elements can be used for transcription regulation. Specific promoters have been studied to limit gene expression to target tissues. Recent advances in molecular biology of gene regulation provide important information about various promoters, which are applicable to gene therapy. These regulatory promoters can be divided into two groups: tissue specific promoters and physiology responsive promoters. Both promoters can restrict gene expression specifically to target tissues. Furthermore, the combination of both systems can increase disease specific gene expression.

Tissue specific promoters have been applied to cancer gene therapy, which usually utilizes cytotoxic gene products to inhibit cell proliferation and induce cell death. Therefore, without the use of regulatory promoters, gene therapy may harm normal cells. To minimize toxic side effects to normal cells, gene expression should be regulated to target cancer cells. Zhihong Dong and Jacques Nör describe transcriptional targeting of tumor endothelial cells. Tumor cells actively secrete angiogenic factors and endothelial cells grow and migrate fast in response to this signal. Therefore, tumor endothelial cell-specific gene expression system is an effective approach to target cancer cells. Tumor specific promoters can be used to produce oncolytic virus, which actively replicates in host cells. The proteins, which are required for replication, can be regulated by tumor specific promoters. Therefore, replication of oncolytic virus is limited to cancer cells. The tumor specific replication of oncolytic virus eventually induces the death of the infected tumor cells. Dominik Dorer and Dirk Nettelbeck review tumor specific promoters for oncolytic virus. Also, Yi Lu discusses different strategies of transcriptionally-regulated gene therapy with tissue specific promoters for treating prostate cancer.

The major obstacle to gene therapy of central nervous system (CNS) neurological disorders, such as Parkinson's disease, Alzheimer's disease, Huntington's disease and others is the need to deliver and express therapeutic genes to specific cell types in the CNS. Diverse types of cells constitute the brain parenchyma, in which neurons, astrocytes, oligodendroglia, microglia, and epithelial cells consist of complex, three-dimensional networks. Shu Wang and colleagues discuss the new advances in the area of transcriptional targeting to brain cells, with a particular focus on engineering gene cassettes to

<sup>☆</sup> This preface is part of the *Advanced Drug Delivery Reviews* theme issue on "Gene Regulation for Effective Gene Therapy".

augment cell type-specific expression with a neural cell-specific promoter.

Numerous cellular barriers hinder nuclear translocation of plasmid vectors in non-dividing cells and there is paucity of methods that can restrict transgene expression to specific cell types. Aaron Miller and David Dean discuss the role of tissue-specific transcription factors in mediating the nuclear entry of plasmid vectors in a cell-specific manner.

Hypoxia is a pathological condition in which a region of the body is deprived of adequate oxygen supply. For example, solid tumors have the region with low oxygen tension, hypoxia. Also, coronary heart disease or stroke induces hypoxia in the myocardium and brain, respectively. Hypoxia-inducible factors (HIFs) are transcription factors that respond to changes in available oxygen. Some genes have hypoxia response elements in their regulatory regions and thus are induced by specific transcription factors under hypoxic conditions. The hypoxia specific regulatory regions have been applied to ischemia specific gene therapy. Masahiro Hiraoka and colleagues discuss the application of hypoxia inducible systems to cancer therapy. Minhyung Lee and colleagues review hypoxia inducible systems for ischemic diseases such as stroke, spinal cord injury and ischemic heart disease.

Glucose response gene expression may be useful for diabetes gene therapy with the high glucose concentration inducible genes such as the insulin gene. Glucose responsive gene expression for gene therapy is discussed by Kyung Soo Ko and associates. Heat is another physiological condition for inducible gene expression. Local application of heat activates heat shock promoters and induces gene expression specifically in the target tissue. Wolfgang Walther and Ulrike Stein discuss current development of heat responsive gene expression systems for gene therapy.

RNA interference (RNAi) is currently the field of extensive research. Small interfering RNA (siRNA) has a promising future as a nucleic acid small drug. For tissue specific and regulatable RNAi gene therapy, conditional RNAi gene therapy systems have been designed. Sang-Kyung Lee and Priti Kumar provide an excellent review on conditional RNAi.

The combined use of targeted delivery systems and gene regulation systems increases specificity and efficiency of gene therapy.

Also, side effects of gene therapy will be minimized with gene regulation systems. With rapid advances in molecular biology of gene expression, more and more sophisticated regulatory systems will be available. With this progress, gene therapy will be safer and more efficient and eventually a clinical option for various severe and debilitating diseases. This theme issue on gene regulation for effective gene therapy is timely and may provide stimulation for developing efficient and safer gene regulatory systems.

Finally, we would like to express our sincere thanks to all the contributors of this issue of the Advanced Drug Delivery Reviews. We hope that their outstanding contributions provide greater insight into the emerging trends in gene regulation for effective gene therapy. We hope this issue provides stimulation for innovative approaches and further development in this fascinating field. We also hope that this issue will be helpful to the researchers who are planning tissue specific gene therapy.

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