Enhancement of Gene Therapy by Exploring Functional Gene Vectors Based on Chitosan Modification

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A thesis submitted for the degree of Doctor of Philosophy

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August 2013
To my parents

Yufeng and Honglu
Declarati

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Acknowledgements

I gratefully acknowledge my supervisors Dr Jingxiu Bi and Associate Prof. Sheng Dai, for their invaluable guidance, encouragement and constructive criticism during my candidature period. The knowledge that I learnt from my supervisors is not only just valuable for my PhD, and will benefit for my whole academic career.

I am so lucky to study under the guide of professor Shizhang Qiao. Thanks a lot for his guidance, suggestion and supporting. What I learnt from Prof. Qiao is beyond the science and will support me for my whole academic career and life.

I am particularly grateful to Dr. Hu Zhang for not only giving research supports but also polishing the submitted and published journal papers in the past three years.

Many thanks go to Dr Zheyu Shen and Dr Xin Du for supervision and cooperation on exploring of functional gene delivery system.

Many thanks go to my all lab members and the staff of the School of Chemical Engineering for their individual help and support.

I would like to specially thank the China Scholarship Council (CSC) and The University of Adelaide, who provided me this scholarship to support my PhD.

Finally, I would also like to thank my parents, for their endless love and encouragement throughout my life.
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Abstract

Gene therapy is a broad term that encompasses any strategy to treat a disease by transferring an exogenous gene, gene segments, or oligonucleotides into patient’s cells to manipulate the defective genes or encoding the correct proteins. Gene therapy is becoming more efficient and has been successfully used in the treatment of genetic diseases such as cancers, infectious diseases, vascular diseases due to the rapid development of knowledge in elucidating the molecular basis of genetic diseases, as well as the availability of the complete sequence information of the human genome. However, it is difficult to obtain satisfactory efficiency by using naked nucleic acid without carrier/vectors since gene transfer in eukaryotic cells is a multiple-step process, in which naked nucleic acid can easily be digested. Therefore, the development of safe, efficient and specific delivery vectors for transporting appropriate genes to specific cells or tissues, where they can replace or regulate defective genes, is one of the key strategies in gene therapy.

In my PhD project, a serial of functional polymers, named chitosan supported imidazole Schiff-base (CISB), N-imidazolyl-O-carboxymethyl chitosan (IOCMCS), folic acid factionalized Schiff-base linked imidazole chitosan (FA-SLICS), have been designed and successfully developed as gene carriers based on the modification of chitosan. Additionally, a new strategy for promoting endoplasmic gene delivery and nucleus uptake has been proposed by developing pH-sensitive Schiff-base linked imidazole biodegradable polymers. This delivery system can efficiently load nucleic acids at a neutral pH, release imidazole-gene complexes from the polymer backbones at intracellular endosomal pH, transport nucleic acids into nucleus through multiple-stage intracellular gene delivery, and thus leads to a high cell transfection efficiency.

These smart polymers display good biocompatibility, multiple-functions, and efficient
gene delivery efficiency as gene carriers. Hence they have promising potential applications in future gene delivery and enhance the development of gene therapy.

Key words: Gene delivery, chitosan, pH sensitive, cancer therapy