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

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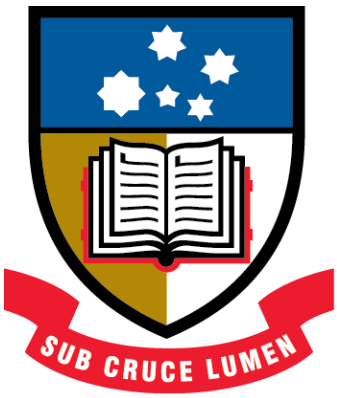
A thesis submitted for the degree of Doctor of Philosophy



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To my parents

Yufeng and Honglu

Declaration

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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 endosmal 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