

# **Intracellular Microenvironment Responsive Nanogels for Gene Delivery**

Bingyang Zhang

A thesis submitted for the degree of Master of Philosophy



School of Chemical Engineering

The University of Adelaide

Adelaide, Australia

October, 2015

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## **Acknowledgements**

I would like to express my gratitude to all those who helped me during my study period at the University of Adelaide as a Master candidate.

First and foremost, my deepest gratitude goes to my supervisors Associate Prof. Jingxiu Bi and Associate Prof. Sheng Dai for the constant encouragement and guidance. A. Prof. Bi has walked me through all the stages of the experiments and the writing of this thesis. She has always been willing to discuss with me on academic problems and personal matters. A. Prof. Dai has helped a lot with my project design and management with his broad theoretical and experimental knowledge. The knowledge I learnt from him is not only benefiting my Master project but will benefit my whole academic career.

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

Finally, my thanks would go to my beloved family for their loving considerations and great confidence in me all through these years.

## **Abstract**

Gene therapy is a modern technology applied by using therapeutic nucleic acids to treat or prevent diseases. The therapeutic nucleic acids can either be expressed to recombinant proteins for disease treatments or correct the genetic mutations in gene therapy for the treatments of various diseases. However, the development of gene therapy is greatly impeded by the limitation of gene delivery systems. Delivery of gene to eukaryotic cells is a multi-step process. Several barriers including cell membrane, nuclear pore complex (NPC) and intracellular enzymes have inhibited the transfection efficiency of gene. Therefore, the exploring of safe and high efficient gene carriers is essential for the development of gene therapy.

In this thesis, one of the widely studied cationic polymers, polyethyleneimine (PEI), was employed for modifications in the gene delivery application. High molecular weight PEI (HMW PEI) is able to perform high efficient gene transfection to eukaryotic cells due to its good buffering capacity. However, it also has high cytotoxicity to cells owing to its non-biodegradability and its molecular weight related high positive charge density. On the other hand, low molecular weight PEI (LMW PEI) such as PEI800 shows negligible cytotoxicity to cells, but has low transfection efficiency.

In order to reduce the cytotoxicity of PEI-based gene carrier while keep or improve the transfection efficiency, two biodegradable PEI-based gene carriers have been designed and successfully synthesized. The physical and chemical properties of both synthetic carriers were measured. The gene delivery performances of both carriers were also evaluated against HeLa and HEK 293 cells. The synthetic biodegradable gene carriers display good gene binding ability, low cytotoxicity and good buffering capacity. In addition, both carriers are able to perform gene transfection with high efficiency.

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