The Chinese University of Hong Kong
Department of Biomedical Engineering

Graduate Seminar – PhD Oral Defence

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Date	***:***	31 July 2025
Time	***:***	10:00 am
Venue	***:***	Room 1118, William M W Mong Engineering Building, CUHK

Title: A Worm-like Nucleic Acid Nanostructure for Gene Delivery and Endosomal Escape

Nanoparticle (NP)-based gene delivery can enable therapeutic applications with lower cytotoxicity than viral vectors, but its efficacy is often hampered by endosomal entrapment. Since 2019, there have been only 14 out of >38000 research articles reporting a correlation coefficient <0.2 between the NP-gene complex and endolysosomes. The two mainstream gene carriers for endosomal escape are cationic and lipid-based NPs. Cationic NPs escape endosomes via the “proton sponge effect”, but their positive charge induces toxicity. Lipid-based NPs escape endosomes via “membrane destabilization”; yet, lipid screening and engineering can be challenging, and lipids can induce inflammation. Nucleic acid nanostructures offer a promising alternative for gene delivery and are widely utilized in preclinical (and recently clinical) applications due to the mitigated cytotoxicity and immunogenicity given their negative surface charge. However, their endosomal escape is inefficient; unlike cationic and lipid-based NPs, nucleic acid nanostructures lack an intrinsic mechanism for doing so. Incorporation of cationic groups, cell-penetrating peptides, or external stimuli that paradoxically undermine their original merits. Innovative nanostructures with an intrinsic mechanism for endosome escape remain to be desired.

This thesis presents a nucleic acid nanotechnology approach to circumvent this delivery bottleneck by adsorbing therapeutic nucleic acids (DNA, siRNA, miRNA, or mRNA) to a gold-polydopamine nanoworm template, thereby assembling a three-dimensional worm-like nucleic acid nanostructure. Devoid of cationic groups, lipids, or mechanical stimuli, this nanostructure naturally activates the chloride voltage-gated channel 3 (ClC3) ion exchanger in endosomes given its worm-like shape; in turn, ClC3 mediates endosomal H^+ and Cl^- accumulation and eventual membrane rupture for cytosolic release, contributing to robust endosomal escape with a correlation coefficient <0.2 between the nanostructure and endosomes. This nanostructure enables in vitro miRNA-enabled macrophage polarization and siRNA-enabled stromal cell differentiation, ex vivo mRNA-enabled cell-based therapy for reducing kidney fibrosis, and in vivo mRNA delivery to hepatocytes for treating liver injury, outperforming Lipofectamine (a commercial transfection agent) in efficacy.

***** ALL ARE WELCOME *****

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