The Department of Chemical & Biomedical Engineering

presents

On Supramolecular Assembly and Subcellular Biochemistry: Mechanistic Principles for Design and Delivery of Therapeutics

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9:30 – 10:30 A.M.
Room A113 – CBE Seminar Room

Abstract:
Subcellular trafficking mechanisms maintain normal cell physiology by regulating endogenous traffic and influencing the stability, accumulation, recycling and elimination of exogenous agents. Accordingly, therapeutics can be formulated to harness such cellular biochemistry to improve treatment efficiency. To do so, supramolecular assembly made possible via non-covalent interactions has become an important design component. I present two examples of such assemblies that result in optimal therapeutic strategies taking advantage of subcellular mechanisms:

1) Viruses are supramolecular building blocks with applications in gene therapy and have specific mechanisms to initiate uptake and navigate trafficking within the cell. Using non-infecting retrovirus-like particles (RVLPs) as a template, assembly of lipid-based or polymeric supramolecular ultrastructures around RVLPs not only revived their transduction capability\(^1\) but also modulated the trafficking pathway and kinetics.\(^3\) Specific lipid compositions and polymer ultrastructures surrounding the RVLP core mediated varied types of endosomal vesicular transport.

2) Crystals are ordered supramolecular assemblies. Clofazimine (CFZ) is a weakly basic drug that bioaccumulates and crystallizes specifically within macrophages as Biocrystals. Upon detailed chemical and biological characterization, the crystal structure of the biocrystals was identified to be that of CFZ-HCl, a hydrochloride salt of CFZ elucidating the critical role of subcellular chloride channels in drug biocrystal synthesis.\(^4\) The biocrystals also up-regulated macrophage-associated anti-inflammatory mechanisms while inhibiting pro-inflammatory mechanisms.\(^5\) To extend applications of CFZ biocrystals, biomimetic versions can be applied for macrophage-tracking in clinical flow cytometry\(^6\) and photoacoustic diagnosis\(^7\) and macrophage-targeted theranostic treatment of inflammation in various disease models. Most importantly, this study illustrates the concept of therapeutic agents formulated as non-toxic, stable supramolecular crystalline assemblies as a promising design strategy given the need for sustained, targeted therapy in chronic diseases.

Overall, the interaction of cell-specific biochemical processes and supramolecular structures such as crystals and therapeutic delivery vehicles can provide key mechanistic insights for designing optimal cell-targeted theranostics.

Speaker References
5. GS Yoon, S Sud, RK Keswani, T1 Standford, KA Stringer & GR Rosania, “Phagocytosed Clofazimine Biocrystals Can Modulate Innate Immune Signaling by Inhibiting TNFα and Boosting IL-10A Secretion”, *Molecular Pharmaceutics*, (2015), 12 (7), 2517-2527 (link).

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