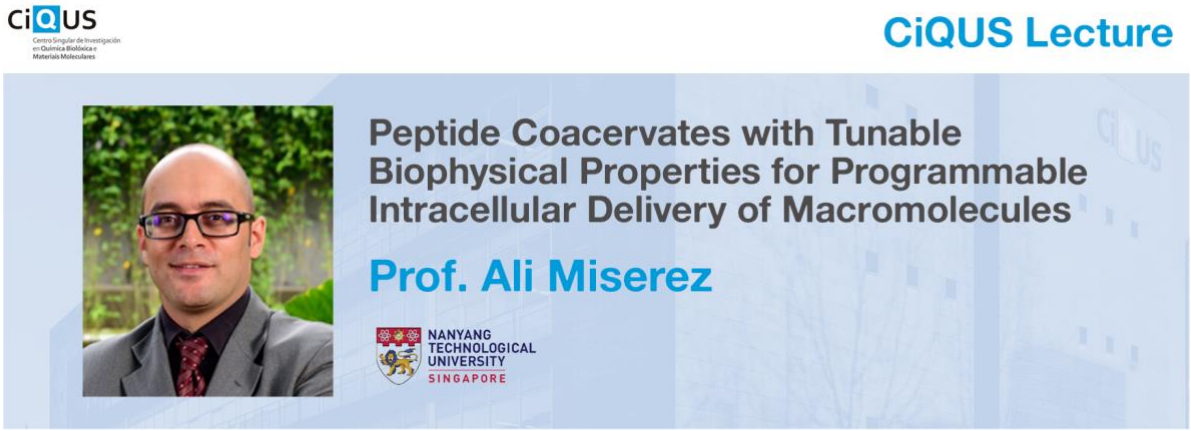

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Abstract

Biomacromolecular therapeutics (*e.g.*, proteins, DNA, mRNA, antibodies, gene editing tools, etc…) hold vast therapeutic potential across human disease states by addressing intracellular targets that have proven refractory to traditional approaches. However, a common hurdle to the deployment of these modalities lays in their inability to cross the cell membrane, which has prompted intense research into the development of safe delivery vehicles capable of packaging large biomacromolecules and deliver them intracellularly. A promising type of delivery vectors that we have recently pioneered are phase-separating peptide (PSP) coacervate microdroplets (CMs) produced by liquid-liquid phase separation (LLPS)[1,2]. CMs are simple to synthesize, non-cytotoxic, and can recruit a wide range of modalities (proteins, pDNA, mRNA, gene editing tools [3], etc…) using aqueous-phase preparation procedures. While we have demonstrated that PSP CMs are able to cross the plasma membrane of mammalian cells and deliver their payload, the properties of CMs that regulate their cell uptake and cargo release kinetics remains poorly understood.

In this talk, I will present our recent studies[4] showing that cell uptake and cargo release kinetics efficacy can be modulated by controlling the materials and biophysical characteristics of CMs, which can be achieved by simple mutations of PSPs. I will then discuss how optimized PSP sequences can yield remarkable delivery efficacy of a broad range of therapeutics, including proteins, antibodies, genes, mRNA, siRNA, and CRISPR-Cas9 modalities, all of which can be transfected into cells with an efficacy that surpass currently available commercial delivery systems, including in hard-to-transfect cells such as primary cells, immune cells, and macrophages. The work opens exciting possibilities in gene and cell therapies.

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Biosketch

Ali Miserez is a Full Professor of Biomimetic and Bioinspired Materials at Nanyang Technological University (Singapore), which he joined in 2009, with joint appointments in the School of Materials Science and Engineering and the School of Biological Sciences. He obtained his PhD (2003) from EPFL (Switzerland) in the field of composite and mechanics of materials. From 2004 to 2009, he was a post-doctoral fellow at UC Santa Barbara, where he expanded his research towards biomimetic engineering and biochemistry of extra-cellular tissues. Miserez's research aims at revealing the molecular, physico-chemical, and structural principles from unique biological materials, and at translating their molecular design into novel biomimetic materials, including for healthcare applications. At NTU, he is currently the founding Director of the "Center for Sustainable Materials".

His interdisciplinary research has been published in about 150 articles in a wide range of journals across the Physical and Life Sciences, including in Science, Nature Materials, Nature Biotechnology, Nature Chemical Biology, Nature Chemistry, Biomacromolecules, ACS Nano, Acta Biomaterialia, Advanced Materials, J. Biological Chemistry, Polymer Chemistry, etc. He has delivered numerous invited talks, including at Gordon Research Conferences in the field of bioinspired materials, biointerfaces, biomineralization, and intrinsically disordered proteins.