NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

ON-SITE BIOLOGY COLLOQUIUM

Friday, 8 May 2026 | 4 pm | S3 05-02 Conference Room 1

Hosted by Prof Antonia Monteiro & Assoc Prof Cynthia He

Map to Block S3

AlphaFold-Guided Design Meets Directed Evolution: Engineering Compact Base Editors and Large Gene Insertion Tools

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Cytosine base editors hold tremendous promise for precision genome medicine, but their clinical translation is limited by the large size of commonly used deaminases such as APOBEC1, which constrains packaging into viral delivery vectors. SsdAtox, a DNA deaminase toxin from Pseudomonas syringae, is approximately two-thirds the size of APOBEC1 and thus an attractive scaffold for compact base editors, yet in its native form it suffers from poor C-to-T editing efficiency and high cytotoxicity. To overcome these limitations, we developed a two-stage engineering strategy. First, using AlphaFold3- and CASTpFold-guided alanine scanning, we identified K31 as a key gatekeeping residue whose substitution enlarges the DNA-binding pocket and boosts editing activity up to ten-fold. Second, to simultaneously optimize activity, reduce indel formation, and minimize cytotoxicity, we developed Trinity-Screen, a novel E. coli-based three-in-one directed evolution platform enabling multiparametric selection in a single scalable workflow. The resulting compact base editor variants demonstrate substantially improved performance relative to BE4max benchmarks. This integrated computational-experimental framework establishes a generalizable pipeline for next-generation base editor development with broad applications in both research and therapeutic genome editing. In the second part of the talk, more recent developments of a novel Bridge RNA system using AlphaFold tools and microbiome databases will be discussed.

About the Speaker

Jungjoon K. Lee is an Assistant Professor in the Department of Biochemistry and at NUS Synthetic Biology for Clinical & Technological Innovation (SynCTI) at the National University of Singapore. He trained at the University of Cambridge (B.A./M.Sci.) and Stanford University (Ph.D.), and leads the GRIT Lab (www.grit-lab.org), which focuses on engineering next-generation genome editing tools including high-fidelity Cas9 variants, compact base editors, genome editing tools for large gene insertion, and off-target profiling methods.