COLLOQUIUM

Base editing and prime editing: correcting mutations that cause genetic disease in cells, animals, and patients

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DEFY GRAVITY

Virtual Seminar Only	Friday, April 5 10AM All are encouraged to attend!
Attendance Link: https://utoronto.zoom.us/j/86092773171 Meeting ID: 860 9277 3171 Passcode: 802024	

Abstract: In this lecture I describe the development and therapeutic application of two precision gene editing technologies that install or correct targeted mutations without requiring double-strand DNA breaks, thereby minimizing undesired consequences of chromosomal cleavage. We developed base editors, proteins that directly perform chemistry on individual DNA bases in living cells to install or correct mutations at targeted positions in genomic DNA. We recently engineered CRISPR-free, all-protein base editors that enabled the first purposeful changes in the sequence of mitochondrial DNA in living cells. By integrating base editors with *ex vivo* and *in vivo* delivery strategies that deliver therapeutic proteins, we rescued animal models of human genetic diseases including sickle-cell disease, progeria, and spinal muscular atrophy (SMA). Single-AAV base editing systems enhance the safety and practicality of *in vivo* base editing. Our development of engineered virus-like particles (eVLPs) provide additional *in vivo* delivery methods for gene editing proteins that minimize off-target editing and the risk of oncogenic DNA integration. Base editors are in at least seven clinical trials to treat diseases including familial hypercholesterolemia, sickle-cell disease, beta-thalassemia, and multiple types of leukemia, resulting in the first reports of clinical benefit from both *ex vivo* and *in vivo* base editing therapeutics.

I will also describe prime editors, engineered proteins that directly write new genetic information into a specified DNA site, replacing the original sequence, without requiring double-strand DNA breaks or donor DNA templates. Prime editing can mediate any base substitutions, deletions, and/or insertions of up to ~200 base pairs in living cells *in vitro* and *in vivo*, and has been applied to directly install or correct pathogenic alleles that previously could not be corrected in therapeutically relevant cells. We illuminated the cellular determinants of prime editing outcomes, and used the resulting insights to develop new prime editing systems with substantially higher editing efficiencies and product purities.

Most recently, we used phage-assisted continuous evolution (PACE) to evolve a suite of sixth-generation prime editors (PE6a-6g), which each evolved to specialize in different types of prime edits. Prime editing has recently been used to rescue animal models of genetic diseases including sickle-cell disease, metabolic liver diseases, and genetic blindness, and is anticipated to enter clinical trials in the next few months. The combination of prime editing and site-specific recombinases enable programmable gene-sized (>5 kb) integration and inversion at loci of our choosing in human cells. We also developed engineered virus-like particles (eVLPs) that deliver base editor and prime editor RNPs (protein-RNA complexes) to various tissues in vivo with efficiencies sufficient to rescue animal models of genetic disease. Base editing and prime editing enable precise target gene correction, in addition to target gene disruption, in a wide range of organisms with broad implications for the life sciences and therapeutics.

Liu Research Group Site: https://www.liugroup.us/

This seminar will be hosted by Prof. Drew Woolley and will be held on Zoom only.

This talk will be recorded. Please send your request for a recording or any additional information to: chem.reception@utoronto.ca

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