NUS National University of Singapore
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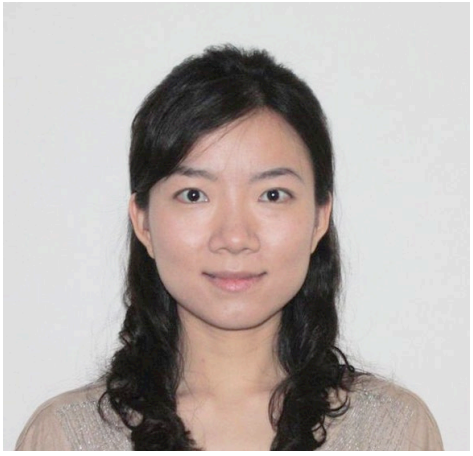
Mon, 15 Sep 2025 | 3 pm | S3-05-02 Conference Room 1

Hosted by Assistant Prof Hu Chunyi

Without the guide? ApoCas9 senses CRISPR RNA abundance to regulate bacterial immune memory formation



By Yan Zhang

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Prokaryotes create adaptive immune memories by acquiring foreign DNA snippets, known as spacers, into the CRISPR array. In type II CRISPR-Cas systems, the RNA-guided effector nuclease Cas9 also assists the acquisition machinery by selecting spacers from protospacer adjacent motif (PAM)-flanked DNA. Here, we uncover the first biological role for apoCas9 that is independent of its dual RNA partners. Following depletion of CRISPR RNA (crRNA) and/or tracrRNA, *Neisseria* apoCas9 stimulates spacer acquisition efficiency. Physiologically, Cas9 senses low levels of crRNA in cells with short CRISPR arrays – such as those undergoing array neogenesis or natural array contractions – and dynamically upregulates acquisition to quickly expand the small immune memory banks. As the CRISPR array expands, rising crRNA abundance in turn reduces apoCas9 availability, thereby dampening acquisition to mitigate autoimmunity risks associate with elevated acquisition. While apoCas9's nuclease lobe alone suffices for stimulating acquisition, only full-length Cas9 responses to crRNA levels to boost acquisition. Finally, we show that this new activity is evolutionarily conserved across multiple type II-C Cas9 orthologs. Altogether, we report an auto-replenishing feedback mechanism in which apoCas9 safeguards CRISPR immunity depth by acting as both a crRNA sensor and a regulator of immune memory homeostasis.

About the Speaker

Dr. Zhang received her BS from Peking University and PhD from the University of Wisconsin Madison. She completed postdoctoral training with Erik Sontheimer at Northwestern University and the University of Massachusetts Medical School, supported by an AHA postdoc Fellowship and an NIH K99/R00 award.

She established her lab at the University of Michigan in 2017 and was promoted to Associate Professor in 2023. Dr. Zhang is an internationally recognized leader in CRISPR biology and gene editing. She is best known for pioneering a major class of non-Cas9 CRISPR (aka Type I) systems for human genome engineering, and for uncovering a novel role for apoCas9 in regulating CRISPR immune memory. She received honors including the prestigious NSF CAREER Award (2023), NIH Maximizing Investigators' Research Award (2020), and NIH Pathway to Independence Award (2016). She is an inventor on multiple patents in Cas9, Cas3, and anti-CRISPR technologies.