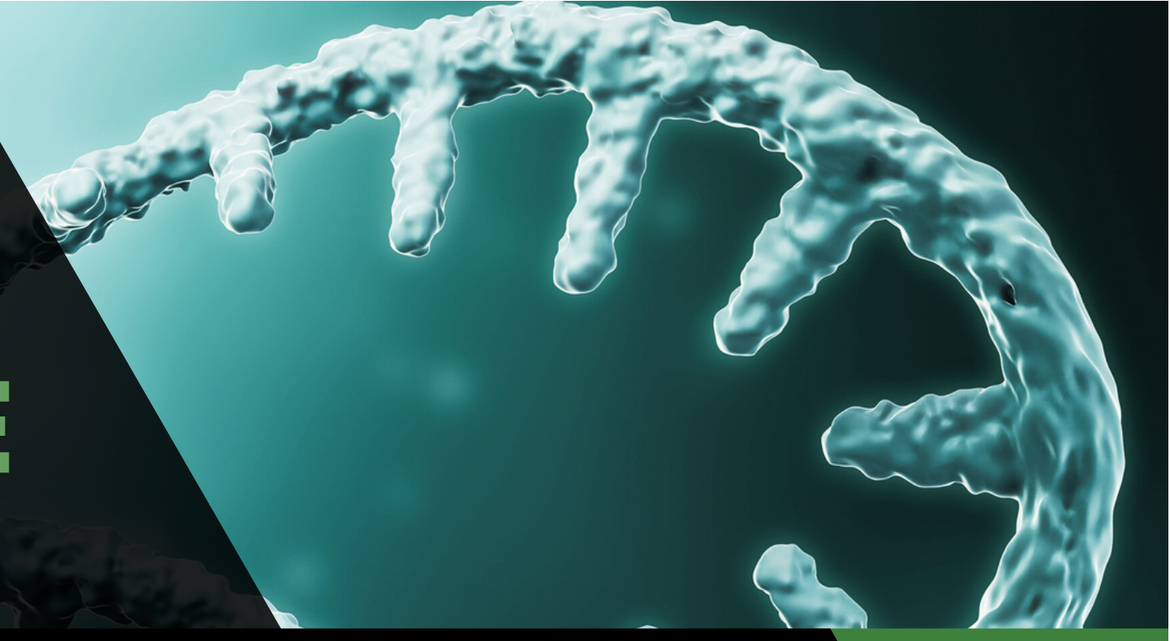
SINGAPORE RNA
SEMINAR SERIES



ACTIVATION OF THE VIRAL MIMICRY RESPONSE BY TRANSPOSABLE ELEMENTS IN CANCER

Tuesday 19 August 2025
9.00am (SGT , GMT+8)

Via Zoom

About the speaker

Kate Chiappinelli is an Associate Professor in the George Washington University Department of Microbiology, Immunology and Tropical Medicine and the GW Cancer Center, where she started her independent laboratory in 2017. Dr. Chiappinelli received her PhD from Washington University in St. Louis and pursued postdoctoral studies at Johns Hopkins University with Dr. Stephen Baylin where she and her colleagues discovered that inhibiting DNA methylation causes an immune response in cancer through transcription of transposable element RNA. Her independent laboratory, funded by NIH and DOD grants, studies the epigenetic changes in cancer and how epigenetic drugs can reverse these, specifically focusing on noncoding regions of the genome and the anti-tumor immune response. A major focus of her research is epigenetic regulation of transposable elements in cancer and how they contribute to innate immunity. A translational goal of this work is learning how to optimally combine epigenetic and immune therapies to fight cancer, with a focus on ovarian cancer. Kate is passionate about community science outreach, with extensive experience working with high school students in St. Louis, Baltimore, and Washington, DC to introduce them to hands-on science.

Dr. Kate Chiappinelli
Associate Professor of Microbiology, Immunology, & Tropical Medicine
The George Washington University

About the seminar

Transposable elements (TEs) comprise the majority of the human genome. In most somatic tissues, TEs are silenced by DNA methylation and histone modifications. Tumors exhibit changes in DNA methylation including global loss of methylation at regions that are silenced for genome stability, like TEs, and gain of methylation at the promoter regions of tumor suppressor genes. We showed that low doses of DNMT inhibitors (DNMTis) activate type I interferon signaling by reducing methylation and increasing expression of TEs that activate dsRNA sensors. DNMTis increase TEs in murine models of cancer, activating interferon signaling and recruiting CD8+ T cells to kill cancer cells and sensitize to immune checkpoint blockade therapy.

We performed a genome-wide analysis of the response to DNMTi in a panel of ovarian cancer cell lines. Alu elements, which directly bind to the dsRNA sensor MDA5, are the most significantly demethylated TEs after DNMTi treatment. Our RNA-sequencing analyses indicated that A-to-I RNA editing of TEs by the RNA editing enzyme ADAR1 was increased after DNMTi treatment. This A-to-I editing makes TE RNA less immunogenic and inhibits the immune response to DNMTi. We find that combining ADAR1 knockdown and DNMTi treatment significantly increases type I interferon signaling and cancer cell secretion of downstream cytokines, including CCL5 and CXCL10. Further, this combination increased recruitment and activation of host immune cells and significantly improved survival in the aggressive ID8 Trp53-/- murine model of ovarian cancer. CITE-Seq (cellular indexing of transcriptomes and epitopes, a type of single-cell RNA sequencing that utilizes antibody tagging of each cell type before sequencing) demonstrated significantly higher infiltration of T and B cells in the tumor microenvironment.

To understand the immune cell types causing the DNMTi anti-tumor response, we used antibodies to deplete CD8 T cells and NK cells in the ID8 Trp53-/- model with ADAR1 knockdown and DNMTi treatment. In addition, we performed these experiments in the C57BL/6-Tg(IghelMD4)4Ccg/J mice, which only produce antibodies against “Hel” antigen and have no other B cell responses. Of these lymphocyte populations, depleting T cells had the biggest effect and we observed specific killing of tumor cells by T cells isolated from the mice. We performed immunopeptidomics on cancer cell lines with and without DNMTi and showed that DNMTi upregulate TE peptide presentation by MHC molecules on the surface of tumor cells. Using a novel immuno-engineering approach, we are able to generate antigen-specific T cells targeting TEs and other antigens in murine and human cancer cell line models. These T cells specifically recognize (produce IFNgamma and TNFalpha) and kill the target tumor cells. As DNMTi have also been shown to demethylate genes crucial for T cell function, including IFNgamma and TCF7, we are currently combining these T cells with DNMTis for a novel cell therapy against cancer.

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