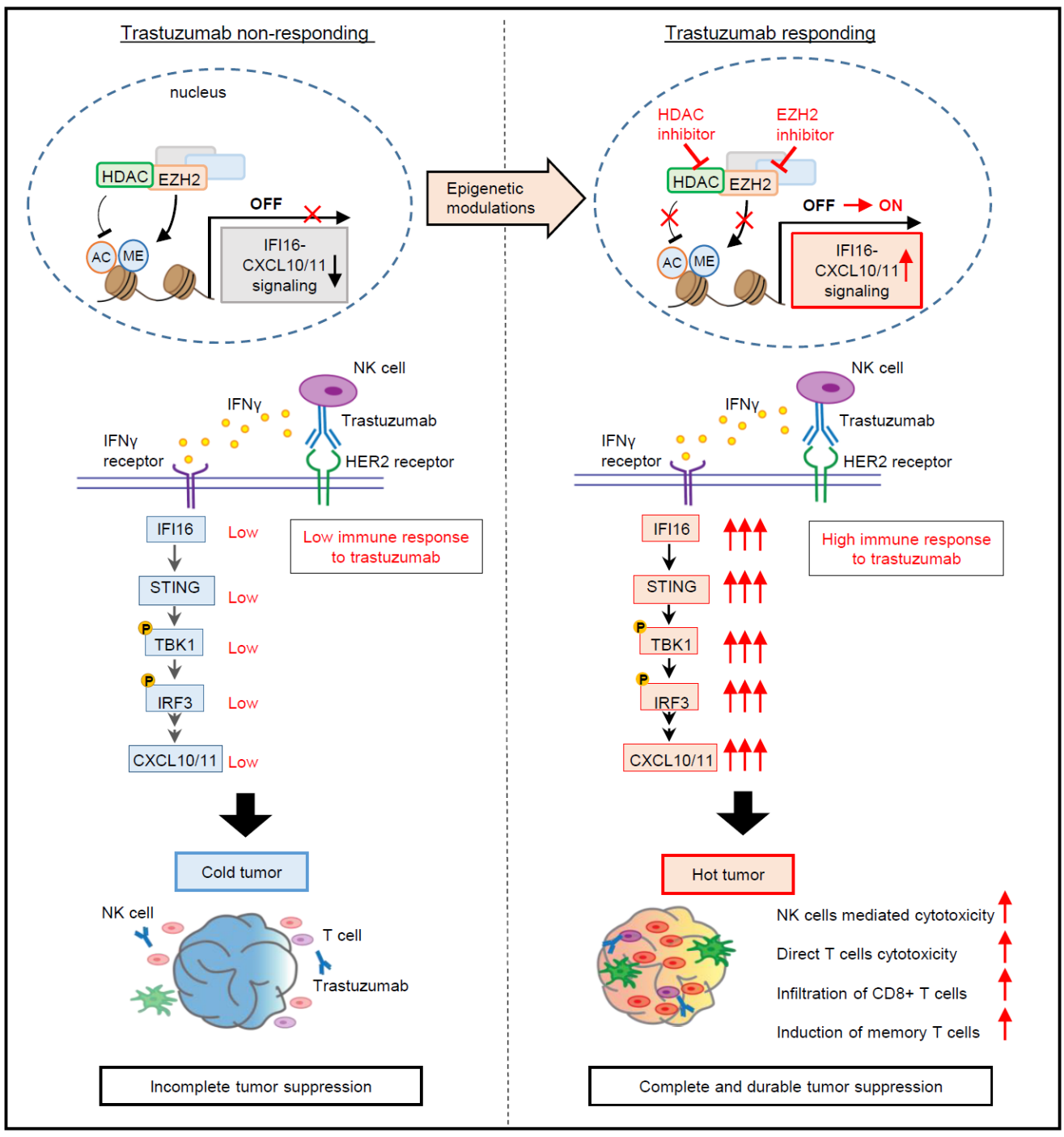
EPIGENETIC THERAPIES AND BIOMARKERS BEHIND IMMUNE RESISTANCE TO HER2+ BREAST CANCER TREATMENT



Model illustrating the proposed epigenetic drug mechanism-of-action. The combination of EZH2 and HDAC inhibitors reactivates IFI16-mediated immune responses, thereby sensitizing anti-HER2 antibody (trastuzumab) anti-tumour responses in HER2+ breast cancer patients. The reactivation of IFI16-CXCL10/11 signalling converts the immunosuppressive "cold tumour" to an immunocompetent "hot tumour", with increased CD8+ T cell infiltration and memory T cells within HER2+ tumours. This improves the clinical outcomes of trastuzumab treatment, leading to complete and durable tumour suppression. (Copyright: Genome Institute of Singapore)

2 August 2022 –HER2-targeted antibody treatment, such as trastuzumab (Herceptin), has significantly increased the clinical responses of HER2+ breast cancer. However, up to 50% of HER2+ breast cancer patients develop resistance to the treatment, followed by disease progression, relapse, and metastasis.

Our research has pinpointed the IFI16-dependent STING immune signalling pathway as a crucial immune factor contributing to trastuzumab resistance and breast cancer relapse. It also serves as a biomarker signature that identifies HER2+ patients with the potential of developing resistance to the antibody-targeted treatment. Restoring this pathway through epigenetic drugs (EZH2 and HDAC inhibitors) reactivates the immunotherapeutic efficacy of trastuzumab. The combinatorial treatment promotes IFI16-mediated CXCL10/11 signalling for complete tumour eradication, and promotes long-term T cell memory in HER2+ breast cancer.

This research was published in the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* on 26 July 2022.

"Our research work discovered an immunosuppressive pathway contributing to trastuzumab resistance, and provided a viable therapeutic approach for effective and durable trastuzumab treatment. "

Dr Ong Li Teng, Research Associate,
Laboratory of Precision Cancer Medicine, GIS

"Cancer is one of the leading causes of death worldwide. Immunotherapy has shown promising results in curing various cancers, but a relatively low number of patients respond to it or achieve long-term remission. Our research work reveals the mechanisms behind unsuccessful HER2-targeted treatment, and provides an actionable treatment strategy to improve the current clinical challenges.

We are now collaborating our work on the verification of the biomarkers and epigenetic therapeutic strategies with the National University Health System (NUHS). Hopefully, this could be a bench-to-bedside project that helps patients in need."

Dr Yu Qiang, Senior Group Leader
Laboratory of Precision Cancer Medicine, GIS