PRESS RELEASE

Singapore scientists found a new way to improve treatment outcomes for breast cancer

The research team discovers why cancer drugs stop working and how to make them work again

Singapore, 18 March 2021 — Breast cancer is the most common cancer in women worldwide and the second most common cancer overall[1]. Although it can now be treated with drugs, many of these drugs mysteriously stop working after some time, causing a relapse.

Now a team of researchers from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS), the Genome Institute of Singapore (GIS) under the Agency for Science, Technology and Research (A*STAR) and the National University Cancer Institute, Singapore (NCIS), together with their international research collaborators in Denmark, have found out why this happens.

There are often several molecular pathways that stimulate cancer growth, and most targeted therapies affect only one molecular pathway. Drug resistance often develops because of 'rescue' from the other cancer pathway not targeted by the drug treatment. The researchers found a solution - to administer an additional drug that controls the second pathway.

The team, led by Professor Lee Soo Chin from CSI Singapore and NUS Yong Loo Lin School of Medicine and Professor Yu Qiang from GIS, focused on a protein called HER2 (human epidermal growth factor receptor 2), which when present in excessive amounts stimulates the cancerous growth of breast cells. Drugs that target HER2 are effective against HER2-overexpressing breast cancer cells, but these drugs eventually become ineffective, and scientists did not know why.

Deciphering the resistant mechanisms of breast cancer to HER2-targeting therapy

The scientists used existing data from a biochemical database and tumour samples from 29 patients enrolled into a clinical trial conducted at NCIS, to zero in on an enzyme subunit called PPP2R2B (serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B beta isoform) that seemed to be in short supply in the cancer cells whenever the drugs targeting HER2 failed to work.

The research team discovered that PPP2R2B suppresses cancer by making chemical modifications in a signalling pathway called PI3K/AKT/mTOR. When there is a shortage of

[1] https://www.wcrf.org/dietandcancer/cancer-trends/breast-cancer-statistics

PPP2R2B, HER2-targeted therapy seems unable to suppress the HER2 protein, and the cancer spreads.

Using one drug to help another

The scientists discovered that another enzyme, EZH2 (enhancer of zeste homologue 2), was responsible for suppressing the activity of PPP2R2B. They found that a clinically available drug called EPZ-6348 is able to block the activity of EZH2, allowing both PPP2R2B and the anti-HER2 drugs to resume their work in suppressing the cancer.

Prof Lee who is also Head & Senior Consultant at the Department of Haematology-Oncology at NCIS said, "HER2+ breast cancer comprises 20 per cent to 25 per cent of all breast cancers. It is highly dependent on HER2 signalling and is traditionally treated with drugs that specifically target HER2. Despite initial effectiveness, resistance to anti-HER2 therapy develops almost invariably in patients with advanced cancer, and they will eventually succumb to the disease. This study provides insights on why anti-HER2 drugs eventually fail and offers a solution to restore sensitivity to anti-HER2 treatment, which may prolong the survival of patients."

Prof Yu, Senior Group Leader at GIS, added, "The study discovered a new way in which cancer cells develop resistance to anti-HER2 drugs. Given that a third of HER2 and breast cancer cells have low levels of PPP2R2B, we predict that these cancer patients might benefit from adding EZH2 inhibitor to the anti-HER2 treatment."

The findings were published in the journal *Nature Communications* on 18 November 2020.

Next steps

Moving forward, the research team plans to conduct a clinical trial to test the efficacy of combining a drug that inhibits EZH2 with a standard anti-HER2 drug for treating HER2+ breast cancer. They are also evaluating PPP2R2B as a potential predictive marker to select patients for anti-HER2 therapy.

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About the Cancer Science Institute of Singapore (CSI Singapore)

The Cancer Science Institute of Singapore (CSI) is one of only five Research Centres of Excellence established by the Government of Singapore with funding from the National Research Foundation and the Ministry of Education. Its mission is to better understand the causes of human cancer across Asia, and thereby improve its detection, treatment and prevention for the benefit of the patients. The CSI's outstanding researchers and excellent scientific facilities create an energetic environment for ground-breaking research and world-class training. The CSI is internationally recognized for its innovative research on the biology of cancers prevalent in Asia, and for taking new methods for cancer treatment from the laboratory to the clinic. Through its local and global partnerships, the CSI works with leading minds from multiple scientific and clinical disciplines in Singapore, the USA and Europe, both in academia and in industry.

For more information on CSI Singapore, visit https://www.csi.nus.edu.sg/web/

About A*STAR's Genome Institute of Singapore (GIS)

The Genome Institute of Singapore (GIS) is an institute of the Agency for Science, Technology and Research (A*STAR). It has a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity. Established in 2000 as a centre for genomic discovery, the GIS pursues the integration of technology, genetics and biology towards academic, economic and societal impact, with a mission to "read, reveal and write DNA for a better Singapore and world".

Key research areas at the GIS include Precision Medicine & Population Genomics, Genome Informatics, Spatial & Single Cell Systems, Epigenetic & Epitranscriptomic Regulation, Genome Architecture & Design, and Sequencing Platforms. The genomics infrastructure at the GIS is also utilised to train new scientific talent, to function as a bridge for academic and industrial research, and to explore scientific questions of high impact.

For more information about GIS, please visit www.a-star.edu.sg/gis.

About the Agency for Science, Technology and Research (A*STAR)

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