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Singapore Scientists Provide New Insights on how Cancers Evade the Immune System

SINGAPORE, 19 April 2017 – A team of scientists from Singapore has discovered new ways in which cancers can escape the body's immune system. Focusing on gastric cancer (GC), the third leading cause of cancer death worldwide, the team's findings may also prove applicable to other major cancers with potential implications for how cancers might be better treated with immunotherapy, one of the most promising classes of anti-cancer drugs today.

Promoters are regions in the genome that regulate the expression of genes, similar to the switch of a light bulb. Using an ultra-sensitive technique called NanoChIP-seq, the team surveyed the promoter landscape for GC to better understand the epigenetic mechanisms contributing to GC development. The team found that in GCs, gene promoters are dysregulated in a way that alters a tumour's antigenic profile to evade the body's immune system. The study, published in the leading journal *Cancer Discovery*, involved scientists and clinicians from Duke-NUS Medical School, Genome Institute of Singapore, Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS), and National Cancer Centre Singapore (NCCS).

"Using the NanoChIP-seq platform invented in Singapore, we created comprehensive epigenetic profiles for both GC and normal tissues," explained team leader Professor Patrick Tan. "Epigenetics is a process by which a cell's DNA is chemically modified by the environment, to change gene expression. By comparing the epigenetic profiles of gastric tumours to normal tissues from the same patient, we were able to identify those promoters specifically altered in GC tissues." Professor Tan is a Faculty Member of Duke-NUS Medical School, Deputy Executive Director of the Biomedical Research Council at the Agency for Science, Technology and Research (A*STAR), and also Senior Principal Investigator at CSI Singapore and Principal Investigator at NCCS.

Just like how a light can be controlled by multiple switches to influence its intensity and colour, the team identified hundreds of genes controlled by multiple promoters, causing alternate versions of that gene to be produced. The team demonstrated that some of these gene variants are capable of stimulating cancer growth. Strikingly, the team also found that many of these alternate gene variants produced in gastric tumours were also less likely to stimulate the immune system compared with their normal counterparts.

"Our data, combining computational, experimental assays, and analyses of human gastric cancers, indicates that the use of these less immunogenic variants may enhance the ability of a tumour to bypass the host's immune system. This process is referred to as tumour immunoediting," added Ms Aditi Qamra, graduate student at the Genome Institute of Singapore and first author of this study. She is also a graduate student with the Department of Physiology at the NUS Yong Loo Lin School of Medicine.

The findings provide important insights into mechanisms used in cancer development and may have implications for cancer immunotherapy. While striking clinical responses have been seen in some patients treated with immunotherapy, these drugs are expensive, associated with side effects, and not all patients respond to the treatment. The team's results suggest that studying the promoter profiles of tumours may possibly identify those patients who would be responsive to immunotherapy. Moreover, the team also identified cellular pathways required by the tumour cell to maintain expression of the less immunogenic gene variants. The team is now exploring if targeting these

pathways, combined with immunotherapy, can increase the proportion of patients that might respond to such drugs.

The team's research was performed as part of the Singapore Gastric Cancer Consortium, supported by the A*STAR, Duke-NUS Medical School, as well as the National Research Foundation Singapore under its Translational and Clinical Research Flagship Programme (NMRC/TCR/009-NUHS/2013) administered by the Singapore Ministry of Health's National Medical Research Council. The team is also working with ETPL, the commercialisation arm of A*STAR, to develop the Nano-ChIPseq platform into a start-up, so that the platform is made available to more academic and industry customers.

Summary of key findings

- Nano-ChIPseq enables the comprehensive identification of promoter elements using small amounts of tissue, opening up the ability to analyse samples obtained directly from patients.
- Altered promoters in GC change the gene expression profile of GC cells and may confer its oncogenic properties, including cell movement and cancer signalling.
- Gene variants associated with GC altered promoters lack immunogenic N-terminal-lacking peptides, enhancing the ability of gastric tumours to evade the native body's immune response.

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For media queries, please contact:

Ms Ong Yen May
Duke-NUS Medical School
Email: yenmay.ong@duke-nus.edu.sg
Tel: (65) 9841 1321

Ms Joyce Ang
Senior Officer, Office of Corporate Communications
Genome Institute of Singapore, A*STAR
Email: angjj@gis.a-star.edu.sg
Tel: (65) 6808 8101

Ms Carolyn Fong
Associate Director, Media Relations
Office of Corporate Relations
National University of Singapore
Email: carolyn@nus.edu.sg
Tel: (65) 6516 5399

Ms Rachel Tan
National Cancer Centre Singapore
Email: Rachel.tan.c.h@nccs.com.sg
Tel: (65) 9754 0842

About Duke-NUS Medical School

The Duke-NUS Medical School (Duke-NUS, 杜克 — 新加坡国立大学医学院) was established in 2005 as a strategic collaboration between the Duke University School of Medicine, located in North Carolina, USA, and the National University of Singapore (NUS). Duke-NUS offers a graduate-entry, 4-year MD (Doctor of Medicine) training programme based on the unique Duke model of education,

with one year dedicated to independent study and research projects of a basic science or clinical nature. Duke-NUS also offers MD/PhD and PhD programmes. Duke-NUS has five Signature Research Programmes: Cancer and Stem Cell Biology, Neuroscience and Behavioural Disorders, Emerging Infectious Diseases, Cardiovascular and Metabolic Disorders, and Health Services and Systems Research.

Duke-NUS and SingHealth have established a strategic partnership in academic medicine that will guide and promote the future of medicine, tapping on and combining the collective strengths of SingHealth's clinical expertise and Duke-NUS' biomedical sciences research and medical education capabilities.

For more information, please visit www.duke-nus.edu.sg

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 will pursue the integration of technology, genetics and biology towards academic, economic and societal impact.

The key research areas at the GIS include Human Genetics, Infectious Diseases, Cancer Therapeutics and Stratified Oncology, Stem Cell and Regenerative Biology, Cancer Stem Cell Biology, Computational and Systems Biology, and Translational Research.

The genomics infrastructure at the GIS is 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.gis.a-star.edu.sg

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

The Agency for Science, Technology and Research (A*STAR) is Singapore's lead public sector agency that spearheads economic oriented research to advance scientific discovery and develop innovative technology. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit society.

As a Science and Technology Organisation, A*STAR bridges the gap between academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by contributing to societal benefits such as improving outcomes in healthcare, urban living, and sustainability.

We play a key role in nurturing and developing a diversity of talent and leaders in our Agency and Research Institutes, the wider research community and industry. A*STAR oversees 18 biomedical sciences and physical sciences and engineering research entities primarily located in Biopolis and Fusionopolis.

For more information on A*STAR, please visit www.a-star.edu.sg

About Cancer Science Institute of Singapore

CSI Singapore is a state-of-the-art university research institute affiliated with, and hosted at the National University of Singapore. It was established in 2008, with a “Research Centre of Excellence” grant, one of only five in Singapore, by the National Research Foundation and the Ministry of Education. Professor Daniel G. Tenen, MD, a leader in the field of transcriptional regulation, hematopoiesis, and cancer, was named its founding director.

The institute is an anchor for research expertise in three broad programmes; Cancer Biology & Stem Cells, Experimental Therapeutics, and the RNA Biology Centre; these programmes form expansive platforms for CSI Singapore’s focus on key cancer disease cancers in gastric, liver, lung and leukemia which are endemic in Asian populations. CSI Singapore aims to position Singapore as a global-leader in the field of Biomedical Sciences. Its mission: to conduct a multifaceted and coordinated approach to cancer research, extending from basic cancer studies all the way to experimental therapeutics and in so doing improve cancer treatment.

For more information on CSI Singapore, visit www.csi.nus.edu.sg/ws/

About National Cancer Centre Singapore

National Cancer Centre Singapore (NCCS) provides a holistic and multi-disciplinary approach to cancer treatment and patient care. We treat almost 70 per cent of the public sector oncology cases, and they are benefiting from the sub-specialisation of our clinical oncologists. NCCS is also accredited by the US-based Joint Commission International for its quality patient care and safety. To deliver among the best in cancer treatment and care, our clinicians work closely with our scientists who conduct robust cutting-edge clinical and translational research programmes which are internationally recognised. NCCS strives to be a global leading cancer centre, and shares its expertise and knowledge by offering training to local and overseas medical professionals. www.nccs.com.sg