PRESS RELEASE

SINGAPORE LEADS MAJOR INTERNATIONAL RESEARCH IN DISCOVERING POTENTIAL TARGETED TREATMENTS FOR BILE DUCT CANCER

- Researchers report largest ever genomics study of bile duct cancer, involving 489 patients from 10 countries including liver-fluke (food-borne parasites) and non-liver fluke related cases
- Analysis of different types of molecular data revealed four bile duct cancer subtypes with distinct molecular features

Singapore, 3rd August 2017 – An international study on bile duct cancer or cholangiocarcinoma (CCA), a rare but highly lethal form of liver cancer, has discovered that tumours in the bile duct may be made up of different cancer subtypes. This finding suggests the potential of offering different targeted treatments based on the genetic features of the different disease subtypes.

The research, which is led by the National Cancer Centre Singapore (NCCS), Duke-NUS and Duke University Medical Schools, A*STAR's Genome Institute of Singapore (GIS) and NUS' Cancer Science Institute of Singapore, is a major international effort as part of the International Cancer Genome Consortium (ICGC). This is the first time Singapore is taking the lead on such a large-scale, multinational cancer genomics project. Besides Singapore, the work was also co-led by investigators from Thailand's Khon Kaen University, Japan's National Cancer Center, and the USA.

The study analysed genomic and epigenomic molecular data of 489 CCA cases from 10 countries, including Singapore, Thailand and Japan. These 489 cases included both liver fluke-induced (food-borne parasites) CCA and non-liver fluke related CCA. Through analysis of different types of molecular data, the team identified four subtypes, each revealing distinct molecular behaviours with potential therapeutic opportunities. It was observed that one subtype, which comprised mostly non-liver fluke related tumours, showed potential in responding to immunotherapy. Other subtypes were potentially amenable to targeted therapies currently available or in development for other cancers.

"There are no targeted treatments catered for CCA patients, leading to a dismal prognosis. Our study showed that a third of CCA patients may be potentially treated by targeted therapies, including immunotherapy, HER2 inhibitors, or FGFR inhibitors," said Professor Teh Bin Tean, co-Principal Investigator of the study and Deputy Director (Research) at

NCCS. He is Professor of the Cancer & Stem Cell Biology programme at the Duke-NUS Medical School.

The results also demonstrate that development of CCA involves interactions between genetics, epigenetics and environmental carcinogens, which generate distinct molecular subtypes of CCA in different countries. For example, some patients in fluke-endemic areas suffered long periods of fluke infection and bile duct inflammation leading to the onset of cancer, while other patients without liver fluke infection showed genetic alterations that disrupted the cells' ability to regulate themselves. "Such distinct pathways to cancer illustrates the roles of different risk factors leading to CCA, and highlights the need to identify and manage different risk factors in different regions of the world," said Professor Patrick Tan, co-Principal Investigator of the study and Professor of the Cancer & Stem Cell Biology Programme at Duke-NUS Medical School. Prof Tan is also Deputy Executive Director of the Biomedical Research Council at the Agency for Science, Technology and Research.

The study was enabled by state-of-the-art sequencing techniques, allowing the investigation of the entire genomes of tumours rather than just genes which have been traditionally studied in cancer genetics. While mutations in genes are important processes in cancer, genes represent only 2% of the genome. "Our study showed that changes in the other 98% of the genome, including structural variations and noncoding mutations, also contribute to CCA tumorigenesis. The whole-genome sequences of CCAs that we generated in this study is the largest among CCA studies to date, and represent a valuable community resource for further research in this field," said Professor Steve Rozen, co-Principal Investigator of the study and Director of the Centre for Computational Biology at Duke-NUS Medical School. Somatic mutations in noncoding regions have been proposed to play crucial roles in cancer by affecting gene regulation, as opposed to gene sequences. "The large scale of our CCA study allowed us to develop a new method for identifying sets of genes dysregulated by somatic noncoding mutations. Our method is applicable to any cancer type with available whole-genome data," said Professor Raluca Gordan, co-Principal Investigator of the study and Assistant Professor at Duke University Medical School.

The study also showed that leveraging molecular profiles to classify CCA may be useful in the clinical setting, compared to the current approach which uses the anatomical location of the tumour. While CCAs in different anatomical sites do not differ in prognosis or treatment options, the subtypes discovered by the researchers showed significant differences in prognosis and treatment options.

CCA is a cancer involving uncontrolled growth of the bile ducts, the part of the liver that drains bile into the intestine. It is the second most common primary hepatic malignancy accounting for 10-20% of deaths from hepatobiliary cancers, and the incidence of CCA is rising worldwide. Patients diagnosed with CCA have a dismal prognosis as the disease is considered incurable. Surgery is the only proven treatment modality for this disease. Clinical trials evaluating targeted therapies in unselected CCA populations have shown minimal benefits.

The paper of the study was recently accepted by the Cancer Discovery journal in June 2017. This research was supported by the National Research Foundation Singapore under its Singapore Translational Research Investigator Award (NMRC/STaR/0006/2009) and Clinician Scientist-Individual Research Grant (NMRC/CIRG/1422/2015), and the Singapore

Ministry of Health National Medical Research Council (MOH NMRC) under its Singapore Translational Research Investigator Awards (NMRC/STaR/0024/2014 and NMRC/STaR/0026/2015) and Centre Grant (NMRC/CG/012/2013). The work was also supported by the Genome Institute of Singapore, Duke-NUS and Duke University Medical Schools, Cancer Science Institute of Singapore, National University Health System, National Institutes of Health of the United States of America, and a philanthropic gift from the Bronsveld Foundation.

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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

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 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 Center 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 programs; Cancer Biology & Stem Cells, Experimental Therapeutics, and the RNA Biology Center; these programs 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.

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

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