PRESS RELEASE

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NUS and A*STAR scientists identify promising liver cancer-killing compounds with novel drug-screening platform
The compounds which target the cancer gene SALL4, could be used in the development of more effective and personalised cancer treatments

Singapore, 30 December 2019 ⸺ Scientists from the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore, and the Agency for Science, Technology and Research (A*STAR)'s Genome Institute of Singapore (GIS) have discovered four potential drug compounds that target hepatocellular carcinoma (HCC), the most common type of liver cancer. The findings, which were made using a cancer gene-targeting drug-screening platform engineered by the team, are expected to pave the way for new and more effective treatments for liver cancer as well as other cancers.

The study was conducted in collaboration with Brigham and Women's Hospital, Boston, and the Harvard Medical School, and its findings were published in the scientific journal *Gastroenterology* in August 2019.

HCC accounts for 85 per cent of liver cancer occurrence[1]. The lack of effective therapeutic interventions for HCC has also made liver cancer the second leading cause of cancer death worldwide[2]. Current drugs, such as sorafenib and regorafenib, used to treat HCC are not durable, and are typically only used to treat patients with advanced-stage HCC[3]. Advances in therapeutic discovery for HCC are needed to address this unmet need.

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[1] El-Serag HB, Rudolph KL. Hepatocellular Carcinoma: Epidemiology and Molecular Carcinogenesis. Gastroenterology. 2007;132:2557–2576.

[2] Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D.M., Forman, D. and Bray, F. (2015), Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer, 136: E359-E386.

[3] Bruix, Jordi et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: Subanalyses of a phase III trial. Journal of Hepatology, Volume 57, Issue 4, 821 – 829; Bruix, Jordi et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66.

The research team therefore developed a cancer gene-targeting drug-screening platform which tapped on libraries of synthetic molecules and natural compounds, to identify potential drug candidates against SALL4, a cancer gene linked to HCC. These drug candidates can address the unmet medical need for more effective treatments of HCC.

The team found four natural compounds which target SALL4, which is a protein critical for early embryonic development but it is typically silenced in adult tissues. The protein, however, has been found to be reactivated in various cancers and is also expressed in 30 to 50 per cent of HCC tumours[4].

These natural compounds could potentially limit SALL4-linked HCC cancer cell growth. A probe into these compounds revealed that they are inhibitors of oxidative phosphorylation, a metabolic pathway that promotes the growth of cancer cells with high SALL4 expression.

The team further demonstrated that the most potent natural compound identified, oligomycin, had a higher efficacy than existing standard-of-care drug sorafenib in preclinical studies, and displayed little toxicity at effective doses. Oligomycin is produced by streptomyces bacteria[5]. When combined with sorafenib, oligomycin could further reduce the growth of SALL4-linked HCC tumours in vivo.

Oligomycin may also be used to suppress other SALL4-linked cancers such as lung cancer. The findings also collectively suggest that SALL4 serves as a potential biomarker for clinicians to select cancer patients who could benefit from therapies involving oxidative phosphorylation inhibitors that disrupt the metabolism of certain tumour types.

Dr Justin Tan, CSI Honorary Research Fellow and GIS Innovation Fellow, who led the study, said, "Our study has identified a vulnerability in tumours that express cancer gene SALL4, as well as compounds targeting this vulnerability. These compounds have great potential to be further developed into drugs to effectively treat liver cancer and other cancers linked to this gene. Further studies on these compounds can lend deeper insights to bring advancement to precision medicine for SALL4-linked cancers, and to improve the quality of cancer treatments."

Prof Patrick Tan, Executive Director of GIS and Senior Principal Investigator at CSI, said, "Liver cancer is the sixth most common cancer worldwide, affecting about 24 individuals in every 100,000 people a year[6]. Hence, the current lack of therapeutic options for it is a grave concern. With the development of the drug-screening platform, this study aims to address that concern by providing a more efficient drug discovery process. In addition, their discovery of potential drug compounds could pave the way for more effective and personalised liver cancer treatments in the future."

Moving forward, the team plans to further develop the oxidative phosphorylation inhibitors discovered for clinical testing in cancer patients, with the hope of bringing a more effective treatment option to patients with SALL4-linked cancers. The team also aims to expand their innovative drug-screening platform to discover drugs that target other cancer genes in different cancer types.

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[4] Yong KJ, Gao C, Lim JSJ, et al. Oncofetal gene SALL4 in aggressive hepatocellular carcinoma. N Engl J Med 2013;368:2266–2276.

[5] Smith RM, Peterson WH, McCoy E. Oligomycin, a new antifungal antibiotic. Antibiot Chemother 1954;4:962-70.

[6] https://www.singhealth.com.sg/patient-care/conditions-treatments/liver-cancer/overview

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About the Cancer Science Institute of Singapore (CSI 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, haematopoiesis, 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 leukaemia 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 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.a-star.edu.sg/gis.

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 entities, the wider research community and industry. A*STAR's R&D activities span biomedical sciences and physical sciences and engineering, with research entities primarily located in Biopolis and Fusionopolis. For ongoing news, visit www.a-star.edu.sg/.