Researchers in Singapore have found a common therapeutic vulnerability for a genetically diverse and deadly leukaemia

The findings may play a critical role in preventing and treating blast crisis chronic myeloid leukaemia.

SINGAPORE, 17 March 2020 – Scientists and clinicians from Duke-NUS Medical School, the Agency for Science, Technology and Research's (A*STAR's) Genome Institute of Singapore (GIS), and the Singapore General Hospital (SGH), have devised a novel drug combination that could treat a particularly deadly form of leukaemia, known as blast crisis (BC) chronic myeloid leukaemia (CML). The team has also developed strategies that may identify patients with early stage or chronic phase (CP) CML who are at increased risk of developing BC, and potentially preventing disease progression.

CML is a blood cancer that can be controlled by continuously taking an expensive type of medicine called a tyrosine kinase inhibitor (TKI). In almost all patients, stopping TKI treatment results in recurrence of CML. While most CML patients respond well to life-long TKI usage, about 10 per cent of patients become resistant to TKIs, and progress to late-stage or blast crisis (BC) CML. Patients with BC almost always die from their disease. While many genetic mutations are known to be associated with BC progression, the mechanisms by which they and other factors cause BC remain largely unknown. This knowledge gap prevents clinicians from identifying which CML patients are at risk of BC progression, and treating BC when it occurs.

"To fill these critical gaps, we employed the latest molecular approaches to establish that the so-called 'polycomb repressive complex', or PRC, alters the regulation of a set of genes which drive BC progression," said Dr Tun Kiat Ko, Research Fellow at Duke-NUS' Cancer and Stem Cell Biology (CSCB) programme. He also added, "We found that the consequences of altered PRC activity were common to the majority of BC cases, regardless of the different leukaemia-causing mutations we also found in them."

Using this increased understanding, the team devised novel drug combinations, which reverse the downstream effects of the PRC in BC. At the same time, they also developed methods to identify CML patients who were at increased risk of developing TKI-resistance and progressing to BC.

"Our discovery is like finding the 'one ring that rules them all'. Since there are many cancer-causing genetic mutations that occur when chronic phase CML transforms to blast crisis, it has been very challenging to determine which ones are critical to BC, and therefore important to target. By discovering this 'one ring' and how to 'destroy' it with a novel drug combination, we open the door to treating this deadly cancer with the same combination of drugs regardless of the myriad mutations that exist in any particular patient. In addition, our study demonstrates the ability of scientists and clinicians to make exciting discoveries that can be translated to the improved health of patients all over the world, as well as Singaporeans," said Associate Professor Ong Sin Tiong from the Duke-NUS CSCB programme and corresponding author of this study.

"The multi-omics approach was critical to the success of the study. Each layer of information provided us corroborative evidence and insight into the dysfunction of the polycomb repressive complex leading to the progression to blast crisis stage of CML," asserted Asif Javed, co-corresponding author of the study.

"This study is another example of how interdisciplinary research leads to new insight," says Axel Hillmer, Group Leader at the GIS who led the genomics part of the project.

Patrick Tan, Executive Director of GIS, adds, "Due to technology advancements over the last years, it is now possible to apply more complex genomic analyses to translate such findings into routine diagnostics."

"As a haematologist treating patients with advanced blast crisis CML, it is disheartening when we run out of treatment options for them. And that is why we are very encouraged by the study findings and certainly hopeful that our patients may one day benefit from the efforts of our collaboration," Associate Professor Charles Chuah, Senior Consultant, Department of Haematology, SGH.

The team is currently working on approaches to identify CML patients who are at risk of BC transformation, and also to determine why the key PRC-related events occur in the first place.

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Reference: *Ko TK, Javed A, Lee KL, Pathiraja TN, Liu X, Malik S, Soh SX, Heng XT, Takahashi N, Tan JHJ, Bhatia R, Khng AJ, Chng WJ, Sia YY, Fruman DA, Ng KP, Chan ZE, Xie KJ, Hoi Q, Chan C, Teo ASM, Camacho OV, Meah WY, Khor CC, Ong CTJ, Soon WJW, Tan P, Ng PC, Chuah C, Hillmer AM and Ong ST (2020). An integrative model of pathway convergence in genetically heterogeneous blast crisis chronic myeloid leukemia. Blood. DOI:*

About Duke-NUS Medical School

Duke-NUS is Singapore's flagship graduate entry medical school, established in 2005 with a strategic, government-led partnership between two world-class institutions: Duke University School of Medicine and the National University of Singapore (NUS). Through an innovative curriculum, students at Duke-NUS are nurtured to become multi-faceted 'Clinicians Plus' poised to steer the healthcare and biomedical ecosystem in Singapore and beyond. A leader in ground-breaking research and translational innovation, Duke-NUS has gained international renown through its five signature research programmes and eight centres. The enduring impact of its discoveries is amplified by its successful Academic Medicine partnership with Singapore Health Services (SingHealth), Singapore's largest healthcare group. This strategic alliance has spawned 15 Academic Clinical Programmes, which harness multi-disciplinary research and education to transform medicine and improve lives.
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.a-star.edu.sg/gis.

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The Agency for Science, Technology and Research (A*STAR) is Singapore's lead public sector R&D agency, spearheading 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.

About Singapore General Hospital

Singapore General Hospital, a member of Singapore Health Services, is the public sector's flagship hospital, with more than 1 million patient visits each year. Established in 1821, SGH has close to 1,600 beds and is Singapore's largest acute tertiary hospital and national referral centre that offers a comprehensive range of medical care by its 800 specialists from over 40 clinical sub-specialties on campus. As an academic healthcare institution and the bedrock of medical education, SGH plays a key role in nurturing doctors, nurses and allied health professionals, and is committed to innovative translational and clinical research in her continual strive to provide the best care and outcomes to her patients. www.sgh.com.sg

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