

JOINT NEWS RELEASE

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Chemotherapy fails for some blood cancer patients because of crucial gene mutations, finds study by NTU Singapore and Singapore General Hospital

Mutations in a crucial gene are the key reason that chemotherapy fails in some patients with blood cancer, a study by **Nanyang Technological University, Singapore (NTU Singapore)** and **Singapore General Hospital (SGH)** has found.

Lymphoma, a type of blood cancer, is the fifth most common cancer among males and the sixth most common cancer for females in Singapore, according to latest data from the Singapore Cancer Registry.¹ Broadly divided into Hodgkin lymphoma and non-Hodgkin lymphoma, the cancer is often treated with chemotherapy regimens.

However, majority of patients with aggressive forms of non-Hodgkin lymphoma do not respond to traditional therapy, and a sub-group of patients who respond initially go on to relapse and progress to fatal outcomes.

To unravel the puzzle of why chemotherapy fails in certain patients with non-Hodgkin lymphoma, the research team led by **Assistant Professor Navin Verma** at **NTU's Lee Kong Chian School of Medicine (LKCMedicine)** and **Assistant Professor Nicholas Grigoropoulos, Senior Consultant from the Department of Haematology at SGH**, scrutinised the publicly available genetic database of over a thousand UK patients. In addition, the research team analysed a total of 167 non-Hodgkin lymphoma specimens from patients in the UK in collaboration with research groups at the University of Cambridge, UK.

Through advanced gene sequencing technology, the research team mapped cancer-causing gene abnormalities from samples of patients whose chemotherapy failed. They found that mutations in the gene **DDX3X** - a type of protein responsible for processing and transmitting signals for cell growth – is the possible culprit behind cancer cells' resilience. This was later confirmed using cutting-edge molecular techniques.

¹ <https://www.singhealth.com.sg/patient-care/conditions-treatments/lymphoma>

The team combined their genetic data and those from previous studies and found through advanced analysis that lymphoma patients with DDX3X mutations had a significantly lower survival rate than those without such mutations. They also found that DDX3X mutations cause increased STAT activity – a type of signalling mechanism that allows cancer cells to survive.

Upon further investigations, the team tested the STAT3 inhibitors - a substance and member of the STAT family that interferes with biologic activity including growth and proliferation - and discovered that these inhibitors killed lymphoma cells with DDX3X mutation (or altered DDX3X) more effectively than standard chemotherapy agents.

Although further research is needed, these findings provide hope that new and better drugs could be developed to block STAT activity and therefore improve the chances of survival for non-Hodgkin lymphoma patients with DDX3X mutations. Clinicians may in future be able to test for such mutations to have a better gauge of chemotherapy outcomes for patients with non-Hodgkin lymphoma.

Asst Prof Navin said, “Now that we know DDX3X mutations are what make some cancer cells difficult to kill with chemotherapy, it is possible to identify patients with such mutations through lab tests before treatment starts. Early identification will allow clinicians to have a better understanding of general chemotherapy outcome for this group of cancer patients and enable them to offer personalised therapy from the get-go, buying precious time that would otherwise be spent on futile chemotherapy.”

Published in the scientific journal *Molecular Cancer* in October 2021, the findings shed light on aggressive forms of non-Hodgkin lymphoma and provide insights into possible new therapy options for this group of patients with poor chances of survival.

What is DDX3X?

Located on the X chromosome, the gene *DDX3X* processes cell information and transmits signals for cell growth. While past research studies have associated the gene’s involvement in many types of cancer, its role in non-Hodgkin lymphoma has not been studied at detailed molecular levels until now.

Asst Prof Grigoropoulos said, “We leveraged our extensive clinical experience in treating patients with lymphoma at the Singapore General Hospital to design and execute the research and proved that DDX3X mutation is associated with chemotherapy resistance. But more needs to be done. We are now continuing our research efforts and actively developing new drugs as well as diagnostics to help those with DDX3X mutations, not only in lymphoma, but other common cancers as well.”

First author **Atish Kizhakeyil**, a **PhD student at LKC Medicine** said, “Previously, the exact role of DDX3X gene in lymphoma progression was less known. I believe that our findings on the loss of function of DDX3X would help in improving treatment outcomes of lymphoma patients with DDX3X alteration.”

Professor Dermot Kelleher, Dean of the Faculty of Medicine and Vice-President, Health at the University of British Columbia in Vancouver, Canada, who was not involved in the study, said, “Understanding more about this gene and what specific changes DDX3X mutations lead to the aggressiveness and chemoresistance in lymphoma subtypes will help us to fine tune treatments, which would provide these patients with mutated gene the best possible chance of survival.”

Highlighting the significance of being able to access and use non-Hodgkin lymphoma specimens for their study, the research team said without these specimens, research hypotheses and theories will remain as they are and there will be no treatment or a better way of diagnosing cancers.

The researchers are looking to conduct further research that could lead to the development of new cancer drugs based on their insights into DDX3X, which has the potential to be used as a target for a better cure for lymphoma and beyond.

Note to Editors:

Paper titled [“DDX3X loss is an adverse prognostic marker in diffuse large B-cell lymphoma and is associated with chemoresistance in aggressive non-Hodgkin lymphoma subtypes”](#), published in *Molecular Cancer*, October 16, 2021. DOI: 10.1186/s12943-021-01437-0

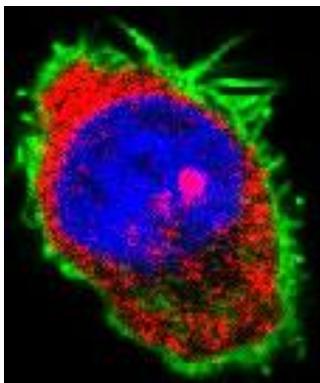


Image: Pictured is a cultured cell of cutaneous T-cell lymphoma. The DDX3X protein is shown in red. Actin and nucleus are shown in green and blue to demarcate cell cytoplasm and nuclear area, respectively.

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About Nanyang Technological University, Singapore

A research-intensive public university, Nanyang Technological University, Singapore (NTU Singapore) has 33,000 undergraduate and postgraduate students in the Engineering, Business, Science, Humanities, Arts, & Social Sciences, and Graduate colleges. It also has a medical school, the Lee Kong Chian School of Medicine, set up jointly with Imperial College London.

NTU is also home to world-class autonomous institutes – the National Institute of Education, S Rajaratnam School of International Studies, Earth Observatory of Singapore, and Singapore Centre for Environmental Life Sciences Engineering – and various leading research centres such as the Nanyang Environment & Water Research Institute (NEWRI) and Energy Research Institute @ NTU (ERI@N).

Ranked amongst the world's top universities by QS, NTU has also been named the world's top young university for the past seven years. The University's main campus is frequently listed among the Top 15 most beautiful university campuses in the world, and it has 57 Green Mark-certified (equivalent to LEED-certified) building projects, of which 95% are certified Green Mark Platinum. Apart from its main campus, NTU also has a campus in Singapore's healthcare district.

Under the NTU Smart Campus vision, the University harnesses the power of digital technology and tech-enabled solutions to support better learning and living experiences, the discovery of new knowledge, and the sustainability of resources.

For more information, visit www.ntu.edu.sg

About Singapore General Hospital

Singapore General Hospital, a member of Singapore Health Services, is the public sector's flagship hospital. Established in 1821, SGH is Singapore's largest acute tertiary hospital with 1,700 beds and national referral centre offering a comprehensive range of 39 clinical specialties on its campus. Every year, about 1 million

Singaporeans benefit from medical care delivered by its 800 specialists. 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.

For more information, please visit: www.sgh.com.sg