PRESS RELEASE

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Discovery paves the way for potential genetics-guided precision medicine for paediatric leukemia patients

Singapore, 4 March 2016 – One in five Singaporean children undergoing chemotherapy for acute lymphoplastic leukemia (ALL) has an inherited genetic variation that makes them sensitive to standard doses of chemotherapy. These children – along with other Asian children – were found to suffer excess side effects such as prolonged fever and infections when given mercaptopurine – a chemotherapy drug that is the cornerstone of successful paediatric ALL treatment – even at dosages much lower than the recommended levels in the United States.

These findings came in an international study involving 270 children from Singapore, Guatemala and Japan with ALL. Scientists found that inherited NUDT15 gene variants in the children lead to severe side-effects. The study is a collaboration among the National University of Singapore Yong Loo Lin School of Medicine (NUS Medicine), Unidad De Oncologia Pediatric in Guatemala, the Japanese Pediatric Leukemia/Lymphoma Study Group and St Jude Children's Research Hospital in United States. The findings were published online in Nature Genetics on 15 February 2016.

The discovery has paved the way for potential genetics-guided precision medicine for ALL patients. By screening for NUDT15 variants in children with ALL, doctors can potentially personalise their chemotherapy doses based on their genotype and avoid toxicity without compromising treatment effectiveness.

Gene variants found that cause chemo-drug intolerance

The researchers found four NUDT15 variants that alter the metabolism of mercaptopurine - a member of a class of chemotherapy medication that is widely used as anti-cancer and immunosuppressant drugs, and which is crucial for curing ALL, the most common childhood cancer. Patients with these genetic variants are particularly sensitive to the drugs. They are intolerant of standard drug dosages and are at risk for treatment-disrupting toxicity. This is very common among Asians, with one in 5 Singaporean children and up to 1 in 3 Japanese children at risk. The scientists also found that the genetic variations

are also common in other populations across Asia and those of Hispanic ethnicity.

The research in Singapore involved 76 ALL patients and was led by Associate Professor Allen Yeoh from the NUS Medicine's Department of Paediatrics. Most Asian children are particularly sensitive to mercaptopurine, tolerating only two-thirds of the dose of mercaptopurine used for American children, explained Assoc Prof Yeoh, who is also a senior consultant in the Division of Paediatric Haematology-Oncology at the National University Cancer Institute, Singapore.

"About 20% of Singaporean children tolerate even lower doses - about one third of the dose used in America, while 1 in 80 children are extremely sensitive tolerating only 5% of the usual dose. For many years, dosing Asian children with mercaptopurine was very much a hit-and-miss, causing unnecessary side effects of infections and fever in the sensitive ones and probably under-dosing the majority because of fear of side effects."

NUDT15 variants associated with reduced enzymatic activity and imbalance of mercaptopurine metabolism

A St Jude's news announcement on the findings said the researchers have shown that the NUDT15 enzyme helps to balance mercaptopurine activity by reducing the supply of the active drug metabolite that triggers cell death. This check-and-balance mechanism helps to prevent the excessive death of white blood cells that put patients at high risk for infections and other serious complications. The study team showed the high-risk NUDT15 variants cause a 74.4% to 100% loss of NUDT15 function and a toxic build-up of the drug at standard doses.

"This study is key to the development of more effective, personalised mercaptopurine therapy because it provides a clear explanation of how variations in the NUDT15 gene change drug metabolism and cause toxicity in patients," said Dr Jun J. Yang, an associate member of the St Jude Department of Pharmaceutical Sciences, who led the international effort, which included clinicians and researchers in Asia, Central America, Europe and the United States. "We are planning clinical studies to move these findings from the laboratory to the clinic with the hope to guide individualised therapy in the future," Dr Yang added.

"While it was clinically recognised that patients of Asian ancestry often cannot tolerate mercaptopurine dosages commonly used in the United States and Europe, the pharmacological basis was unknown," added Dr Ching Hon-Pui, Chair of the St Jude Department of Oncology. "This exciting study breaks down a critical barrier to further tailoring the use of this important drug and will likely aid the implementation of precision medicine approaches to improve the quality of care in children with ALL."

Laboratory findings showed that all four of these NUDT15 variants were associated with lower levels of enzymatic activity and imbalance of mercaptopurine metabolism.

The St Jude announcement added that researchers checked patients enrolled in the study and found that the NUDT15 variants predicted enzyme activity and mercaptopurine tolerance.

For example, patients in Singapore and Japan with the two highest risk variants had the lowest level of enzyme activity. "These patients had excessive levels of the active drug metabolites per mercaptopurine dose, which suggests we may reduce the drug dose to achieve the level necessary to kill leukemia cells without causing toxicity," said Dr Yang. He added that the NUDT15 variants have no other known health consequences so far.

The scientists checked leukemic cells from 285 children newly diagnosed with ALL and found those with NUDT15 variants were also more sensitive to mercaptopurine. "That suggests we can screen for NUDT15 variants and potentially plan mercaptopurine doses according to each patient's genotype before the therapy starts. This way, we hope to avoid toxicity without compromising treatment effectiveness," Dr Yang said. He added that the findings may also benefit patients prescribed the drugs for inflammatory bowel diseases, such as those with ulcerative colitis and Crohn's disease.

Future studies are needed to figure out exact mercaptopurine doses needed for patients with different NUDT15 variants. At the moment, Assoc Prof Yeoh and his team will continue testing children with ALL for the NUDT15 variants at the new VIVA-NUS Centre for Translational Research in Acute Leukaemia (CenTRAL) located at the NUS Medicine's Centre for Translational Medicine, and adjust the mercaptopurine dosages to ensure that the children are treated effectively with the least possible side effects.

"Patients with ALL on the study will undergo comprehensive tests that will accurately stratify their risk of relapse so that appropriate doses of chemotherapy can be given. In addition, we will determine upfront if they can tolerate the normal doses of mercaptopurine. Through additional grants, young adults will also benefit from the programme. The National University Hospital (NUH), Singapore General Hospital and Tan Tock Seng Hospital will also enrol young adults on a national protocol here based on our successful treatment in children for the first time," added Assoc Prof Yeoh, a senior consultant at the Division of Paediatric Haematology and Oncology at NUH.

Meanwhile, the search continues for variants in NUDT15 or other genes that influence chemotherapy effectiveness and safety.

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About the National University of Singapore (NUS)

A leading global university centred in Asia, the National University of Singapore (NUS) is Singapore's flagship university, which offers a global approach to education and research, with a focus on Asian perspectives and expertise.

NUS has 17 faculties and schools across three campuses. Its transformative education includes a broad-based curriculum underscored by multi-disciplinary courses and cross-faculty enrichment. Over 38,000 students from 100 countries enrich the community with their diverse social and cultural perspectives.

NUS has three Research Centres of Excellence (RCE) and 26 university-level research institutes and centres. It is also a partner in Singapore's fifth RCE. NUS shares a close affiliation with 16 national-level research institutes and centres. Research activities are strategic and robust, and NUS is well-known for its research strengths in engineering, life sciences and biomedicine, social sciences and natural sciences. It also strives to create a supportive and innovative environment to promote creative enterprise within its community.

For more information on NUS, please visit www.nus.edu.sg.

About the NUS Yong Loo Lin School of Medicine

Established in 1905, the NUS Yong Loo Lin School of Medicine is the first institution of higher learning in Singapore and the genesis of what would become the National University of Singapore.

The School offers one of the finest undergraduate medical programmes in the Asia-Pacific region and commands international recognition and respect. The Times World University Subject Rankings 2015-2016 list NUS Medicine as Asia's leading medical school, while the Quacquarelli Symonds (QS) World University Rankings by Subject 2015 placed NUS Medicine 21st globally.

The School admits 300 students to its medical undergraduate degree programme annually. Its principal missions are to educate and train the next generation of healthcare professionals, and foster research that will help to transform the practice of medicine. It also plays a pivotal role in producing future leaders in healthcare delivery, discovery and public service as well as in Singapore's Biomedical Sciences Initiative.

The School's 18 departments in the basic sciences and clinical specialties work closely with the Centre for Medical Education and the Centre for Biomedical Ethics to ensure that teaching and research are aligned and relevant to Singapore's healthcare needs.

For more information about the NUS Yong Loo Lin School of Medicine, please visit http://medicine.nus.edu.sg/corporate/