

Press Release

For Immediate Release

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FOUND: GENE THAT FORETELLS SURVIVAL LIKELIHOOD OF PAEDIATRIC LEUKEMIA PATIENTS AT THE ONSET OF DIAGNOSIS

A team of cancer researchers at the National University Health System (NUHS) has identified a gene, microRNA 335 (miR-335), that can foretell which child suffering from leukemia is at a higher risk, and allow doctors and parents to know what the survival prospects of their child are, at the beginning when the disease is diagnosed. When combined with other diagnostic methods, this genetic indicator enables doctors to better plan treatment strategies for paediatric leukemia patients.

In addition, a patient's miR-335 level also affects his or her resistance to prednisolone, a key chemotherapeutic drug. Discovery of this particular drug resistance thus enables doctors to use other medicines that can overcome this resistance, which potentially improves cure rates for children with leukemia.

Prognostic indicators crucial in treatment of ALL

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. The intensity of treatment that ALL patients undergo is based on risk classification using a variety of prognostic factors. This has led to close to 90% cure rate, while the remaining 10% have not fared as well, mainly due to resistance to chemotherapeutic drugs. However, multiple bone marrow tests are required and these tests can only be done during the treatment process. Thus, prognostic factors that are associated with relapse risk and which can be detected earlier, at initial treatment stage, are necessary for clinical application and development of more appropriate therapeutic approaches.

There is also growing evidence that microRNAs play crucial roles in cancer and that specific microRNAs have also been associated with clinical outcomes. Until this finding by the NUHS team - comprising scientists and doctors from the National University Cancer Institute, Singapore (NCIS) and the National University Hospital (NUH) - few studies had looked at microRNAs in relation to clinical response and survival in ALL patients.

Press Release

MiR-335 as an independent prognostic biomarker

Samples from 136 paediatric leukemia patients were tested to find the particular microRNAs that are significantly associated with clinical outcomes. The Principal Investigator of the study, Associate Professor Chng Wee Joo, Head of the Division of Haematology, NCIS and Senior Principal Investigator, Cancer Science Institute of Singapore (CSI Singapore), explained, “Comparing the patients who are cured and those who have adverse outcomes, we looked for genes that are of significantly different expression levels in these two groups, which would be potential markers for clinical outcome. Indeed this was how we found that patients with adverse outcomes have much lower expression levels of miR-335.”

Further tests showed that this effect is independent of other known prognostic factors, for example the US National Cancer Institute (NCI) criteria (age and white blood cell count at diagnosis). This confirmed that miR-335 is an independent prognostic biomarker in predicting final outcome and for risk-stratifying patients.

Combining miR-335 with current prognostic factors can further improve stratification efficiency, added Assoc Prof Chng. “This is important because we can potentially use this information to identify which patients will do badly right at the beginning of treatment and hence may benefit from a different treatment approach.”

But why would a patient with a low miR-335 expression level have a poor clinical outcome?

Assoc Prof Chng explained, “MiR-335 controls the MAPK pathway, which is important for the therapeutic effectiveness of prednisolone. When miR-335 is at a low level, the MAPK pathway is activated and this leads to resistance to prednisolone, which explains the poorer clinical outcome.” In other words, high levels of miR-335 may inhibit MAPK1 activity. Regulation of MAPK1 will also increase sensitivity to prednisolone in ALL cells.

Improving survival rates for high-risk patients

Added Associate Professor Allen Yeoh, Co-Investigator of the study and Senior Consultant, Division of Paediatric Haematology-Oncology, NUH, “When we add a drug that inhibits the MAPK pathway in cells with low miR-335 expression level, sensitivity to prednisolone is restored. This is clinically important because the level of miR-335 not only identifies patients with poor outcome, but also opens ways to restore sensitivity to therapy.

Press Release

This can improve treatment outcome for paediatric ALL patients, and potentially increase their survival rates.”

Moving forward, researchers plan to further validate the prognostic value of miR-335, and explore the addition of a MAPK inhibitor to the therapeutic strategies for the treatment of high-risk patients with low miR-335 expression levels in clinical trials. The researchers will also work on adapting this paediatric treatment protocol for adult cancer trials, though this will take some time.

The findings, as well as the work underway, are the result of the strong collaboration among the different entities within the NUHS, Assoc Prof Yeoh added. “The work that we are doing here at the NUH, the NCIS and also the CSI Singapore is a very good example of the adult-paediatric capabilities and synergies that the NUHS is able to deploy as an academic medical centre.”

Details of this research were published in a paper entitled “Deregulated MIR335 that targets MAPK1 is implicated in poor outcome of paediatric acute lymphoblastic leukaemia”, in the British Journal of Haematology in July 2013.

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For more information, contact:

Sharon Aw
Senior Assistant Manager, Communications
Tel: 6772 3987
Email: sharon_aw@nuhs.edu.sg

Press Release

About the National University Cancer Institute, Singapore

The National University Cancer Institute, Singapore (NCIS) offers a broad spectrum of cancer care and management covering both paediatric and adult cancers, with expertise in prevention, screening, diagnosis, treatment, rehabilitation and palliative care. The Institute's strength lies in the multi-disciplinary approach taken to develop a comprehensive and personalised plan for each cancer patient and his or her family. NCIS draws on the expertise of its specialists in the fields of haematology-oncology, radiation oncology, gynaecologic oncology, paediatric oncology, surgical oncology, oncology nursing, oncology pharmacy, palliative care, pathology, radiology, medical specialties including gastroenterology and hepatology, infectious diseases, pulmonary and critical care, psychiatry, epidemiology and public health as well as other allied health sciences. NCIS's strength in research allows patients to access drugs and devices before they are commercially available. NCIS is also closely affiliated with the Cancer Science Institute of Singapore, National University of Singapore.

For more information about the NCIS, please visit www.ncis.com.sg

About the National University Hospital

The NUH is a tertiary hospital and major referral centre for a comprehensive range of medical, surgical and dental specialties including Cardiology, Gastroenterology and Hepatology, Obstetrics and Gynaecology, Oncology, Ophthalmology, Paediatrics, Orthopaedic Surgery and Hand and Reconstructive Microsurgery. The Hospital also provides organ transplant programmes for adults (in kidney, liver and pancreas) and is the only public hospital in Singapore to offer paediatric kidney and liver transplant programme.

Staffed by a team of healthcare professionals who rank among the best in the field, the NUH offers quality patient care by embracing innovations and advances in medical treatment.

In 2004, the NUH became the first Singapore hospital to receive the Joint Commission International (JCI) accreditation, an international stamp for excellent clinical practices in patient care and safety. Today, patient safety and good clinical outcomes remain the focus of the hospital as it continues to play a key role in the training of doctors, nurses and allied health professionals, and in translational research which paves the way for new cures and treatment, offering patients hope and a new lease of life.



Yong Loo Lin School of Medicine
Faculty of Dentistry
Saw Swee Hock School of Public Health

Press Release

A member of the National University Health System, it is the principal teaching hospital of the NUS Yong Loo Lin School of Medicine and the NUS Faculty of Dentistry.

For more information, please visit www.nuh.com.sg

About the National University Health System (NUHS)

The National University Health System (NUHS) groups the National University Hospital, the NUS Yong Loo Lin School of Medicine, the NUS Faculty of Dentistry and the NUS Saw Swee Hock School of Public Health under a common governance structure to create synergies for the advancement of health by integrating clinical care, research and education.

The enhanced capabilities and capacity enable the NUHS to deliver better patient care, train future generations of doctors more effectively and bring innovative treatments to patients through groundbreaking research.

Visit www.nuhs.edu.sg

About the Cancer Science Institute of Singapore

The Cancer Science Institute of Singapore (CSI Singapore) was officially launched on 15 October 2008. CSI Singapore aims to position Singapore as a global leader in the field of Biomedical Sciences. Its mission is to conduct a multifaceted and coordinated approach to cancer research, from basic cancer studies extending all the way to experimental therapeutics and in so doing, improve cancer treatment.

CSI Singapore is a state-of-the-art university research institute affiliated with, and hosted at the National University of Singapore. In 2008, it was awarded a \$172 million “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, was named its founding director. Professor Tenen is a leader in the field of transcriptional regulation, hematopoiesis, and cancer.



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Press Release

The institute is an anchor for research expertise in two broad programmes - Cancer Biology & Stem Cells, and Experimental Therapeutics; these programs form expansive platforms for CSI Singapore's focus on key cancers in gastric, liver, lung and leukemia which are endemic in Asian populations.

For more information, please visit www.csi.nus.edu.sg