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IN THIS ISSUE

TARGETING TUMOURS IN CHILDREN

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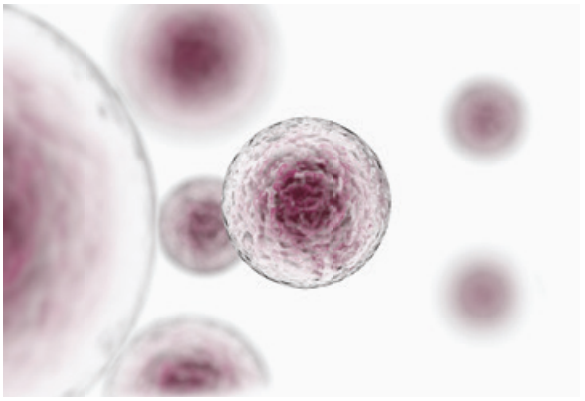

Teaming Up To Target Tumours In Children

Braving little-known territory, a group of researchers from the VIVA-KKH Paediatric Brain and Solid Tumour Programme is seeking breakthroughs in research and clinical care for childhood brain and solid tumours.

Rare, often under-recognised and reported late, brain and solid tumours account for nearly 55 percent of childhood cancers, causing significant physical, psychological and social impact to children and their families.

"Very young children are often unable to report their symptoms accurately, and in later adolescence may hide or be reluctant to come forward," explains Dr Amos Loh, Chairman, Steering Committee, VIVA-KKH Paediatric Brain and Solid Tumour Programme, who is also Consultant, Department of Paediatric Surgery, KK Women's and Children's Hospital (KKH).

"Solid tumours are also more diverse, with far fewer individual tumour numbers as compared to blood cancers. This results in a more challenging accrual process for any clinical protocol and slows the advancement of care for these diseases."

Childhood cancers are the second leading cause of death in children in Singapore and developed countries worldwide. However, despite advances in treatment, outcomes for most childhood solid tumours remain inferior to blood cancers.

In 2015, the VIVA-KKH Paediatric Brain and Solid Tumour Programme was established to pursue advancements in care for childhood brain and solid tumours through translational clinical research, leveraging on the collective strengths and expertise of partner institutions KKH, Viva Foundation for Children with Cancer (VIVA) and St. Jude Children's Research Hospital (SJCRH), USA.

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ARRESTING THE SPREAD

Today, programme collaborators Dr Amos Loh, Dr David Low, Head and Consultant, Neurosurgical Service; Associate Professor Kenneth Chang, Head and Senior Consultant, Department of Pathology and Laboratory Medicine; Dr Soh Shui Yen, Senior Consultant, Haematology/Oncology Service, KKH; and Dr Francis Chin, Senior Consultant, Department of Radiation Oncology, National Cancer Centre Singapore (NCCS), are focusing their attentions on the four most common tumour types in Singapore.

Their sights are set on rhabdomyosarcoma (a type of soft tissue sarcoma), neuroblastoma (the most common sympathetic nervous system tumour), kidney tumours (in particular Wilms tumour), and central nervous system neoplasms (in particular medulloblastoma).

"This group of cancers is often metastatic, in that they spread beyond the primary tumour to affect other parts of the body. Their incidence in Asian countries also appears to differ from the west," Dr Loh says. "Directed research into the epidemiology, clinical outcomes, tumour biology, and socio-economic impact of paediatric cancer in Asian children will allow better interpretation of Western data and applicability to local and regional populations.

Furthermore, studying the differences in incidence, histology and treatment response observed in Asian children may enable the discovery of genetic reasons for the differences observed in different ethnic groups, and hopefully help us to refine or direct novel therapeutic approaches for Asian children."

"Screening for features of cancer predisposition in children can help to give us a better understanding of their presenting profile and a greater awareness of the subtleties of their tumour symptoms."

Dr Soh Shui Yen
Member, Steering Committee, VIVA-KKH
Paediatric Brain and Solid Tumour Programme
Senior Consultant, Haematology/Oncology Service, KKH

IMPROVING CLINICAL CARE

One of the programme's first steps was to establish a dedicated multidisciplinary brain tumour clinic to help patients and their families negotiate the complexities of their care journey, supported by nurse coordinators to enhance the coordination of care from various disciplines at multiple points during the treatment process.

"The continual development and coordination of subspecialty care across multiple disciplines is not only fundamental to providing holistic, comprehensive care to the child and their family, but also absolutely crucial in advancing treatment and outcomes for childhood solid tumours," Dr Soh says.

In collaboration with researchers and clinicians at NCCS and the University of Amsterdam, the team is also implementing a cancer predisposition screening project using three dimensional photography and clinical screening methods to detect facial morphometric features in children with a predisposition to developing brain and solid tumours.

"Early diagnosis is critical in allowing therapy to be initiated when disease burden is low, and minimising the complications of more aggressive therapy while optimising the potential for cure," Dr Soh explains.

"Screening for features of cancer predisposition in children can help to give us a better understanding of their presenting profile and a greater awareness of the subtleties of their tumour symptoms. This is a great step towards mitigating diagnostic delay in children."

INVESTING IN TECHNOLOGY

Further along the care development pathway, A/Prof Chang is in pursuit of a new approach to brain tumour characterisation using cutting edge technology.

"Medulloblastomas are a form of fast-growing brain tumour. More than 70 percent of all paediatric medulloblastomas are diagnosed in children under age 10," A/Prof Chang says. "We are trying to develop a new approach to subtyping paediatric medulloblastomas according to their gene expression signature. This enables us to distinguish tumours according to their biological behaviour even though they may look the same under a microscope."

Using the first and only clinical diagnostic NanoString nCounter® platform in Singapore, the relative amount of genetic 'signal' that each tumour displays is measured in order to characterise it more

Members of the VIVA-KKH Brain and Solid Tumour Programme Steering Committee – (left to right) Dr Amos Loh, Consultant, Department of Paediatric Surgery; Dr Soh Shui Yen, Senior Consultant, Haematology/Oncology Service; A/Prof Kenneth Chang, Head and Senior Consultant, Department of Pathology and Laboratory Medicine; and Dr David Low, Head and Consultant, Neurosurgical Service, KKH. (Not pictured: Dr Francis Chin, Senior Consultant, Department of Radiation Oncology, NCCS)

specifically according to its gene expression signature and biological behaviour.

"We invested in the NanoString nCounter® platform as it has a unique capability to perform tests accurately on material from formalin-fixed paraffin embedded tissues. This is the simplest method of preservation and treatment of human tissues that is performed by laboratories around the world, allowing us to perform advanced genetic tests on specimens from even the most basic of laboratories from surrounding countries, at fairly low cost," A/Prof Chang says. "We have begun to extend these research test panels to our regional collaborators, who have expressed much interest."

The team has established a dedicated research laboratory space in the SingHealth Academia building to cultivate cell line and animal models of solid tumours from paediatric patients at KKH.

"If we are able to validate the test panel, it can be used as a full clinical test in the near future, and even form the basis of a new and better brain tumour treatment protocol," A/Prof Chang adds.

Also underway are multiple projects analysing the molecular signature of paediatric solid tumours. A key study, led by Dr Chen Zhixiong, Principal Investigator, Department of Physiology, National University of Singapore, seeks to understand the prevalence and function of genes involved in cell death mechanisms, and their role in the development of neuroblastomas – a tumour of the sympathetic nerves that occurs in infants.

ADVANCING POPULATION-BASED SCIENCE

Research into rare diseases requires the joint participation and combined experiences of healthcare centres around the world in order to supply sufficient data to power the clinical studies needed to answer critical research questions.

Turning their attention to population-based science, the team has formed a strategic partnership with the Singapore Childhood Cancer Registry (SCCR), enabling them to participate in major cooperative group trials around the world.

"SCCR's comprehensive database has captured more than 3,000 childhood cancer cases diagnosed and treated in Singapore since 1997, of which 60 percent are patients with brain and solid tumours," says SCCR's founding director, Professor Tan Ah Moy, who is also Senior Consultant, Haematology/Oncology Service, KKH.

"By making epidemiological, clinical and prognostic data on childhood cancers in Singapore available to researchers, we can drive epidemiological and outcome studies to help tailor treatment for childhood cancer patients in the future. Research findings will translate into better and more specific drug treatment, minimising side effects and improving survival outcomes at the same time."

BUILDING THROUGH NETWORKS

"Every patient is unique, and this is even more apparent in the field of rare diseases," Dr Loh says. "At times, no more than two or three cases of a particular tumour type may have ever been encountered in the world. To progress, it is vital for healthcare professionals to be able to connect with each other through collaborative networks, to pool insights and build on each other's discoveries."

VIVA has established a platform that links Singapore with other developed nations in the Asia-Pacific region through the VIVA-Asia working groups.

"We are trying to develop a new approach to subtyping paediatric medulloblastomas according to their gene expression signature. This enables us to distinguish tumours according to their biological behaviour even though they may look the same under a microscope."

A/Prof Kenneth Chang
Member, Steering Committee, VIVA-KKH Paediatric Brain and Solid Tumour Programme
Head and Senior Consultant, Department of Pathology and Laboratory Medicine, KKH

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These bring institutions together with the common goal of pursuing clinical and translational research that is relevant to the needs of children with cancer in the Asia-Pacific region.

"Collaborating with international centres of excellence allows researchers and clinicians to tap into the expertise of world experts in the field. This enhances the standards of clinical care and refines research goals," Dr Loh says. "KKH cares for the majority of children with brain and solid tumours in Singapore. Leveraging on St. Jude's knowledge and expertise, and with VIVA's support, we are able to do far more working in concert to combat the scourge of childhood cancer."

"In partnership with our regional colleagues, we want to change the way childhood cancer is understood, diagnosed and treated in Asia."

Dr Amos Loh
Chairman, Steering Committee, VIVA-KKH Paediatric Brain and Solid Tumour Programme
Consultant, Department of Paediatric Surgery, KKH

CREATING THE FUTURE

The team's ultimate goal is to see their research findings translate into changes and adaptations in treatment methods that will improve therapeutic outcomes for children with brain and solid tumours.

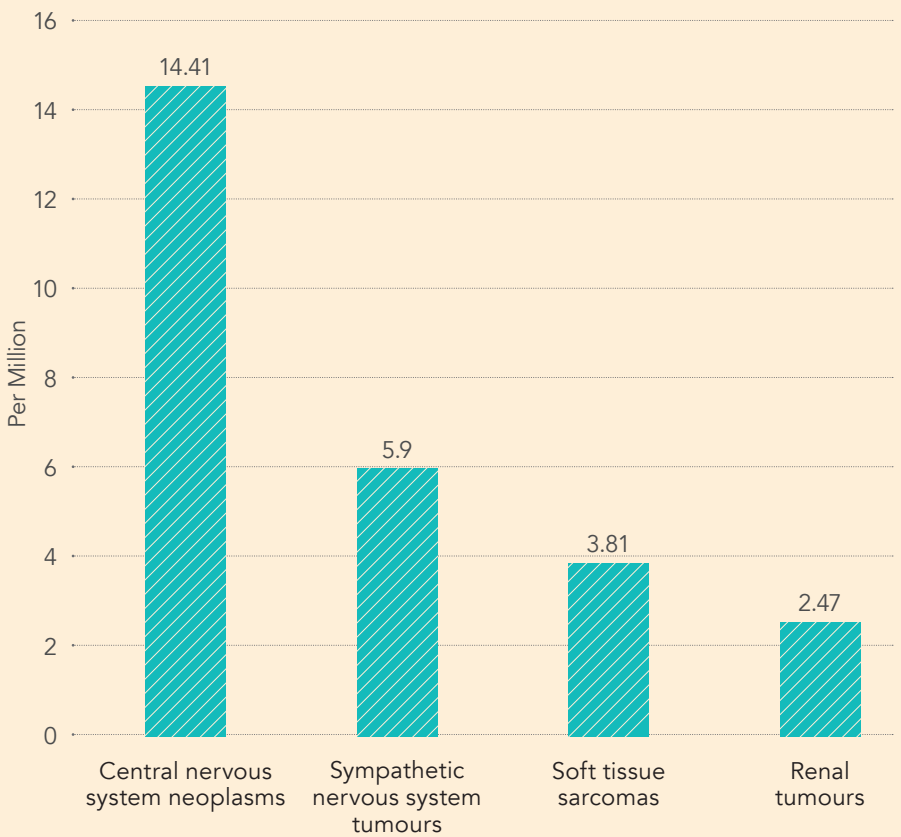
"Up till now, we have had limited perspective into the unique biology and behaviour of Asian children with brain and solid tumours," Dr Loh says. "I believe the clinical and scientific findings from research into our patients will shed light on aspects of their epidemiology, biology, clinical behaviour, and treatment response that are new and unique to the Asian populations.

In partnership with our regional colleagues, we want to change the way childhood cancer is understood, diagnosed and treated in Asia."

The team hopes that the data being gathered today will in the future complement existing knowledge held by other cooperative study groups to provide a more accurate, global picture of childhood disease.

"Children are our future. By unravelling the mysteries of paediatric brain and solid tumours in various ethnic groups, we are well-positioned to improve the future of healthcare and life expectancies for whole populations," Dr Loh notes. "This is the vision that we share as collaborators, and are working towards."

AGE-STANDARDISED INCIDENCE* OF PAEDIATRIC BRAIN AND SOLID TUMOURS IN SINGAPORE (2003 - 2007)



* This refers to age-specific incidence rates of the local population under 15 years weighted according to the age structure of the world standard population.
Source: Singapore Childhood Cancer Registry Monograph 2005-2007.

Deciphering Molecular Clues to Paediatric Urinary Tract Infection

Clinician researchers at KK Women's and Children's Hospital (KKH) are closing in on molecular clues found in urine, which may be able to help predict the risk of kidney damage in children with urinary tract infection (UTI) at an earlier stage.

"Kidney scarring is the ultimate morbidity associated with early childhood UTI, and is an implicating risk factor for hypertension, impaired kidney function and complications of pregnancy in later life," says Principal Investigator, Associate Professor Chao Sing Ming, who is leading the research effort. "Being able to identify patients with UTI who are at risk of kidney damage at an early stage is key to helping us develop better approaches to treatment and prevention."

EXAMINING THE INNATE IMMUNE RESPONSE

UTI is one of the most common bacterial infections in children, and one of the leading causes of febrile illness necessitating hospital admission in infants and young children. While the majority of these patients will have limiting disease with no involvement of the kidneys, up to 25 percent will eventually develop kidney damage and scarring which permanently replaces functioning tissue.

To develop a more accurate and focused approach to management, KKH nephrologists A/Prof Chao Sing Ming, Dr Ng Yong Hong and Dr Indra Ganesan carried out a prospective cohort study, in collaboration with scientists and bioinformatics experts from the Agency for Science Technology and Research (A*STAR) and Lund University, Sweden. The study was supported by KKH's Department of Diagnostic and Interventional Imaging and KK Research Centre, and funded by the Biomedical Research Council.

Using high throughput biotechnology with advanced multiplexing immunoassay, the team examined urine samples from 121 children with febrile UTI, looking for early urinary proteomic signatures that could be implicated in acute kidney infection – also known as acute pyelonephritis (APN) – and the development of kidney scarring.

"To the medical researcher, urine is liquid gold," says A/Prof Chao. "Obtainable without harming or distressing the patient – which is of utmost importance in young children. The analysis of urine also confers immense advantage in the study of renal diseases as urine is in direct contact with the kidney tissues where the disease occurs, and contains valuable downstream biomarkers that can be directly measured and studied."

"Being able to identify patients with UTI who are at risk of kidney damage at an early stage is key to the development of better approaches to treatment and prevention."

A/Prof Chao Sing Ming
Senior Consultant, Nephrology Service, KKH

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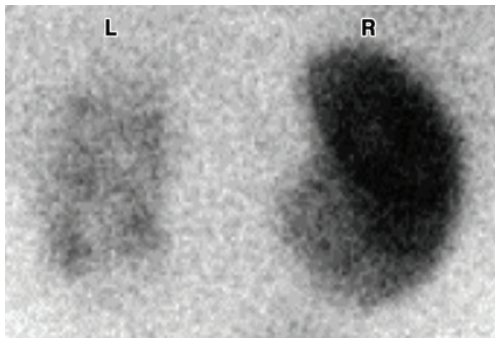


Kidney involvement in UTI assessed by dimercaptosuccinic acid (DMSA), which is the gold standard for diagnoses of acute kidney infection and scarring.

Of the 121 patients tested, 55 percent were diagnosed with APN, of which 43 percent went on to develop kidney scarring. The team further discovered distinguishing proteomic signatures in the urine samples of children with APN as well as proteomic signatures predictive of kidney scarring.

"Our study findings led us to conclude that urinary proteomic signatures could serve as early markers of kidney infection, and help to predict the risk of kidney scarring in a child with UTI," says A/Prof Chao.

"These biomarkers could potentially be used as a non-invasive means to stratify the risk of children developing kidney damage following UTI, fuelling the development of more precise and targeted management, and sparing the majority of patients unnecessary distress and costs of further investigations and management."

The study was awarded the Best Oral Presentation Award at the triennial 17th Congress of the International Paediatric Nephrology Association in September 2016.

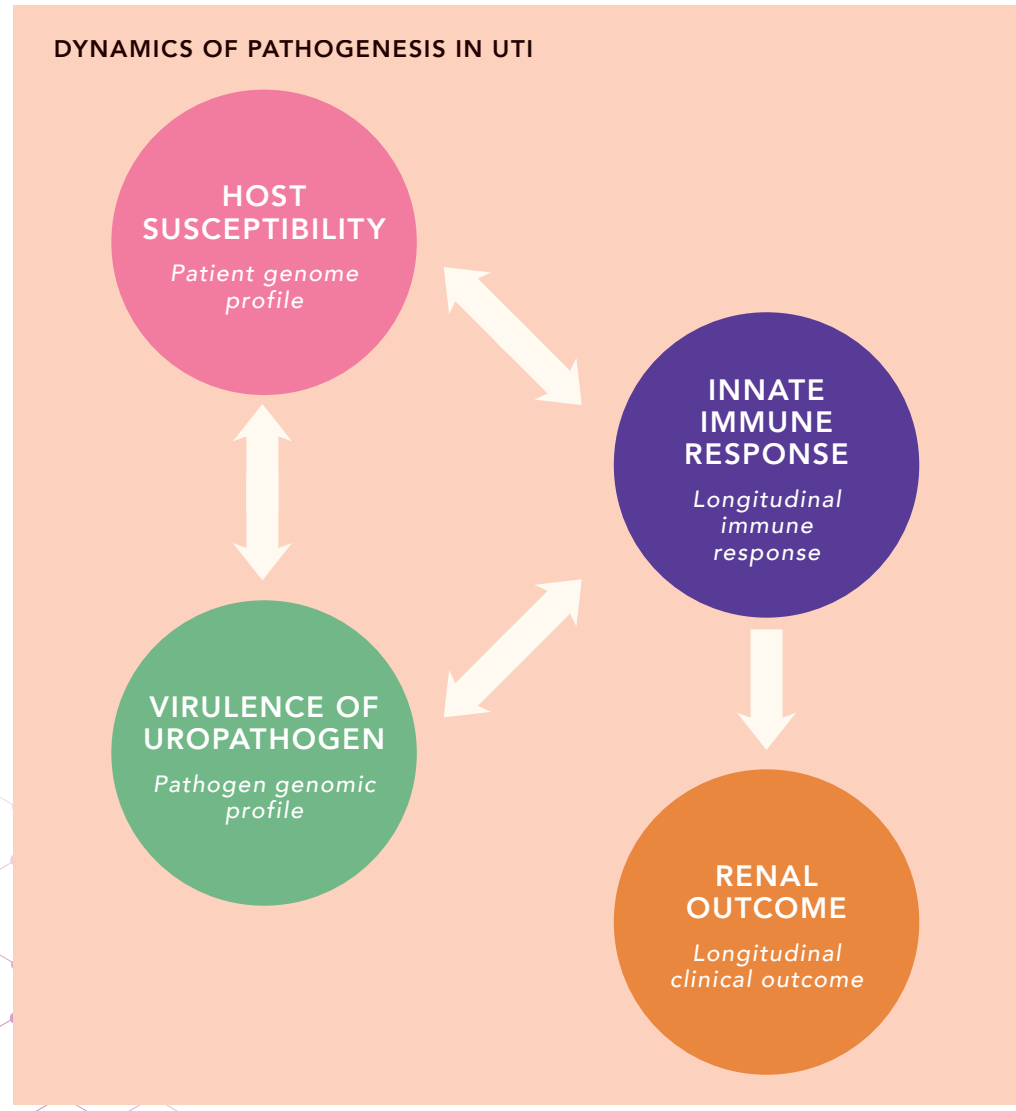
PURSUING A DEEPER UNDERSTANDING OF PATHOGENIC DYNAMICS

Already forging ahead, A/Prof Chao and the team have widened their research efforts in pursuit of a deeper understanding of the whole pathogenetic dynamics of UTI at a molecular level – including host genetic susceptibility and genetic polymorphism, uropathogen genomics, the longitudinal immune response and the resultant longitudinal clinical outcome.

"In order to harness the rapidly developing advanced technologies relevant to research, it is necessary for the clinicians to collaborate with biomedical scientists and bioinformatics experts," asserts A/Prof Chao.

"KKH has in place well-established clinical pathways, a well-curated patient cohort and standardised management protocols, which are paramount for clinical data accuracy."

"We are fortunate to have access to A*STAR's expertise in biotechnology, enabling the simultaneous and accurate analysis of large batches of bio samples. With advancements in bioinformatics software, large amounts of raw multidimensional data that used to take years to be modelled and integrated can now be transformed into relevant information within a much shorter period of time that can help us better understand, anticipate and ultimately combat the disease."



Mining the Medical Image

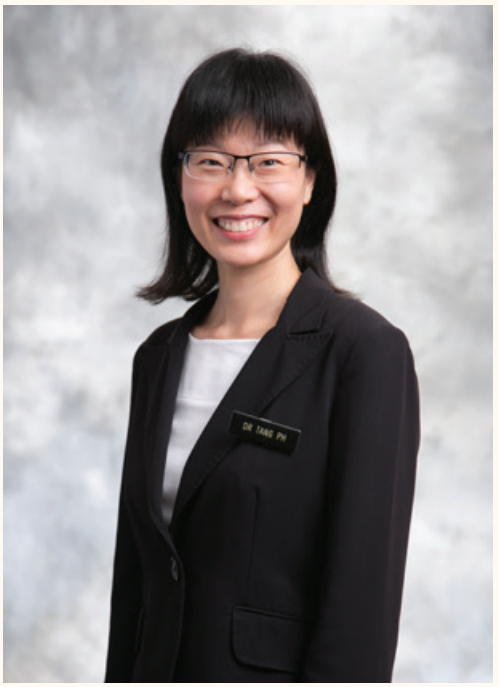
Researchers at KK Women's and Children's Hospital (KKH) are pursuing advancements in medical imaging that can provide physicians objective and measurable information about disease progression and patient response to treatment, and even predict functional outcomes.

Dr Tang Phua Hwee, Senior Consultant, Department of Diagnostic & Interventional Imaging, KKH, has been investigating the use of advanced imaging technology to improve healthcare for women and children for more than a decade.

"Within the field of medical research, imaging is often utilised as an objective marker for diagnoses, and for monitoring disease progression and the patient's response to treatment. Therefore, it is critical for new and experimental imaging techniques to be thoroughly trialled to establish their accuracy and reliability before being incorporated into clinical management," Dr Tang says.

Technological advancements in recent years have given rise to new imaging capabilities. "Similar to the smartphone consolidating the functions of a calculator, camera, diary and phone into one device, medical imaging technology has progressed to the stage where we can not only assess structure, such as size and shape, but also discern the integrity of connecting white matter tracks and metabolite profiles using magnetic resonance imaging," Dr Tang describes.

"Experimental imaging research may not be directly targeted at preventive chronic diseases such as diabetes and hypertension; however it plays a vital role in providing the physician objective and quantitative measurements of the degree of disease progression, and the patient's response to treatment."



Pursing a valuable image – Dr Tang Phua Hwee, Senior Consultant, Department of Diagnostic and Interventional Imaging, KKH, is investigating experimental imaging techniques to improve clinical management and outcomes.

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MRI research team members from the Department of Diagnostic and Interventional Imaging at KKH. Back row from left – Senior Consultant, Dr Tang Phua Hwee; research officer, Mr Toh Zhe Han; senior radiographer, Ms Serena Teo; and research officer, Ms Khine Nwe Win. Front row from left – research assistant, Ms Karen Kek; and senior research technologist, Ms Mudun Kotuwage Punya Damayanthi Arunoda.

DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI)-based neuroimaging technique which makes it possible to visualise the location, orientation, and quantify the anisotropy of the brain's white matter tracts, providing researchers insights into brain network connectivity.

Using DTI, Dr Tang and her team conducted magnetic resonance imaging on young judo athletes (mean age of 19 years) with normal body mass index (BMI) who practice judo at least twice a week, each session lasting two hours. These results were compared against the brain images of normal healthy children with normal BMI who are not known to engage in sports activities regularly.

"The young athletes' brains showed comparatively greater white matter connectivity in the anteroposterior, craniocaudal and transverse directions," Dr Tang says. "Further, the DTI technique was able to reliably quantify the degree of increased white matter connectivity in these children, which visual inspection of MRI images would not be able to identify. It provides objective evidence that regular exercise is good for the brain's structural connectivity."

The robustness of DTI's capability to provide insights into the brain has led Dr Tang to further explore its use in children with muscle disorders. In collaboration with paediatric neurologist Dr Wendy Liew, Consultant, Neurology Service, KKH, who secured research grants from the National Medical Research Council and SingHealth Duke-NUS Paediatric Academic Clinical Programme, the team is looking at a myriad of factors ranging from genetic material to muscle enzymes and imaging data.

Dr Tang enthusiastically shares that results from the preliminary data look very promising and the team has recently submitted four abstracts based on the preliminary data alone for the International Society for Magnetic Resonance in Medicine (ISMRM) 2017 conference.

INSPIRING NEW APPLICATIONS

Dr Tang is also investigating new research techniques such as arterial spin labelling (ASL), where blood flowing in the neck carotid arteries is labelled and a signal is acquired when the labelled blood reaches the brain. In September 2016, she presented on the "pain network on arterial spin labelling MRI in post hysterectomy women" at the 16th World Congress of Anaesthesiologists, garnering the second prize in the pain category.

"While ASL is not ready for routine clinical use yet, this technique holds potential advantages, such as enabling cerebral perfusion to be done without having to inject the patient with an intravenous contrast agent," Dr Tang shares.

She further envisions that the applications for advanced imaging will continue to multiply, citing fellow researcher and anaesthetist Dr Sng Ban Leong's work in elucidating the brain's response to pain through MRI technology. Dr Sng is also Deputy Head and Senior Consultant, Department of Women's Anaesthesia, KKH; and Director, KK Research Centre.

"Modern advances in imaging technology show much potential to give healthcare professionals valuable additional information in understanding, treating and even pre-empting potential complications. As a result, we are also seeing an increase in the use of imaging to meet the rising demand for objective and quantifiable biomarkers," says Dr Tang.

Together with her team, Dr Tang continues to work closely with clinicians to ensure that imaging answers their clinical questions and new technology is tailored to add value to clinical outcomes for patients.

"There are so many advances happening; it is only by testing these out in the local context that you can truly evaluate objectively which ones will enhance your management protocols, and which one is really going to be useful and benefit the patient."

RESEARCH INVOLVING CHILDREN

Since 2013, Dr Tang's research team has scanned and analysed the images of more than 140 patients and healthy volunteers, both adults and children, as part of an ongoing study into the development and testing of MRI and spectroscopy methods using a three Tesla MRI scanner.

"We are seeking to validate and use new imaging techniques, first in adults and then in children, and initially in healthy volunteers before moving onto patients. Now that the reliability of DTI has been firmly established both in the brain and in muscle and we can see that DTI gives additional information not readily available on visual inspection, the next step is to assess whether it can enhance the current standard clinical imaging protocol and help us provide better and more cost-effective care."

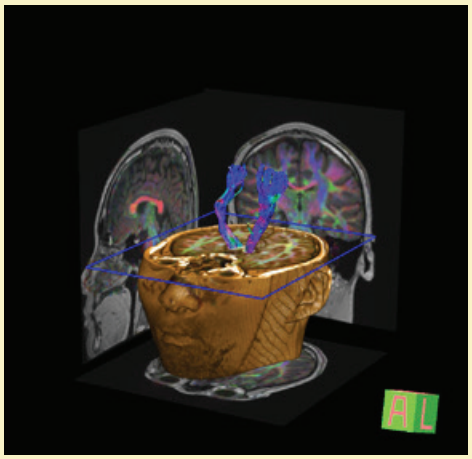
Dr Tang and her team remain on the lookout for healthy children with normal BMI who are willing and able to participate in an hour-long MRI scan for research purposes, with parental consent. To assist with defraying the costs of transportation, reimbursement up to $50 is provided.

SUPPORT MEDICAL IMAGING RESEARCH

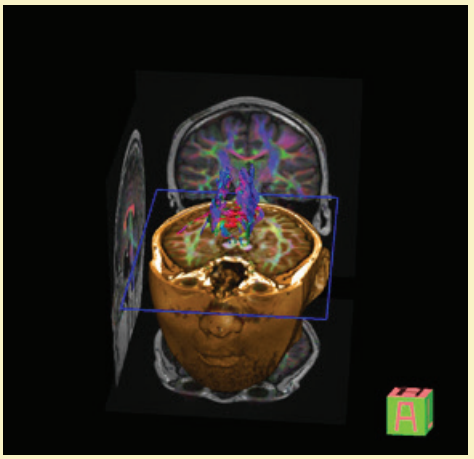
For more infromation about Dr Tang's research and how you can support medical imaging research at KKH, please contact **+ 65 9820 1394**.

POST-PROCESSED DTI IMAGES

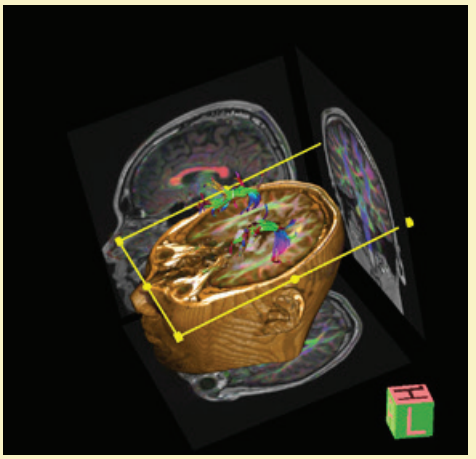
Post-processed DTI images generated from the MRI scanner show the white matter tracks that facilitate brain connectivity. The tracks are colour-coded and superimposed on the subject to facilitate clearer identification.



In blue – motor tracks descending from the brain into the spine.



In red – corpus callosum tracks connecting the right and left sides of the brain.



In green – superior longitudinal fasciculus tracks in the right and left hemispheres connect the front areas to the back.

SAVING CHILDREN WITH RARE DISEASES

A first successful case reported in published literature of haploidentical stem cell transplant for a child with Hoyeraal-Hreidarsson Syndrome.

Stem cell transplantation (also known as bone marrow transplant) was first performed in medical practice in 1957. In step with advancements in the knowledge of basic science, the 2000s saw immense improvements in stem cell transplantation techniques.

In conjunction with better diagnostic facilities and knowledge of the human immune system and haematopoietic stem cells, advancements in stem cell transplantation are continuing to significantly improve the clinical outcomes and prognosis for children with rare diseases.

By Dr Rajat Bhattacharyya

INHERITED BONE MARROW FAILURE SYNDROMES

Children with inherited bone marrow failure syndromes (IBMFS) are seeing particular benefit from advances in stem cell transplantation. Comprising disorders such as dyskeratosis congenita and Fanconi anaemia, IBMFS are a group of very rare congenital diseases that have a diverse clinical presentation.

Primary presenting features can include physical abnormalities, immune deficiency or even development of cancers. Blood count abnormalities can surface very early in life, but may not do so until adulthood in some cases, making the diagnosis of these diseases challenging.

Further, diagnosis is often clinical and may not be confirmed by currently available genetic mutation testing as new mutations are being discovered regularly. Newer techniques, such as whole exome sequencing, are immensely helpful in these situations to establish the genetic basis of such rare diseases.

The only available cure for IBMFS currently remains allogenic stem cell transplantation. Successful engraftment can cure bone marrow failure and any associated immune deficiency; however it does not improve associated problems such as organ dysfunction and cancer predisposition.

Nevertheless, early and definite genetic diagnosis is of paramount importance in informing long term prognosis and also enabling the clinician to take appropriate management steps, such as stem cell transplants if required.

HOYERAAL-HREIDARSSON SYNDROME: A FIRST CASE

A baby of Chinese ethnicity, who was born at 30 weeks gestation and weighed 800 grams at birth, was noted to have mild deficiency of blood platelets at birth. The baby's platelet count normalised, only to become deficient at three months of age associated with a respiratory infection. Soon after, the baby developed progressive deficiency of red and white blood cells and platelets, requiring frequent transfusion.

Further investigations showed hypocellular bone marrow aspirate and cerebellar hypoplasia which, combined with a history of prematurity and intrauterine growth retardation, confirmed a clinical diagnosis of Hoyeraal-Hreidarsson Syndrome – a severe variety of dyskeratosis congenita, an IBMFS.

All common gene tests for dyskeratosis congenita were negative; however whole exome sequencing identified a biallelic RTEL1 (regulator of telomere elongation helicase 1) mutation, further confirming the genetic basis of the disease. This particular genetic anomaly has been previously described in only 18 children worldwide, according to a recently published review[1].

The baby had extremely low red and white blood cell and platelet counts, causing him to be at risk of severe infection, and necessitating very frequent blood and platelet transfusions. In view of these factors, an urgent stem cell transplant was necessary.

The baby's father was chosen as the stem cell donor, as he was identified as NK (natural killer) cell mismatched through KIR (K immunoglobulin receptor) genotyping. NK cell mismatched haploidentical donors are ideal as the risks of the recipient experiencing non-engraftment, graft versus host disease (GVHD), viral infections and also leukaemia relapses post-transplant have been shown to be reduced compared to donor-recipient pairings which are not NK cell mismatched.

A haploidentical stem cell transplant was performed using reduced intensity chemotherapy conditioning and peripheral blood stem cell processing using the T Cell Receptor (TCR) Alpha Beta and CD19 depletion technique. Prompt engraftment was noted within 15 days post-transplant with no major infection or complication. The baby eventually achieved excellent immune reconstitution.

More than two years post-transplant, the child is cured of bone marrow failure and maintains a stable blood count. The non-haematological components of the disease remain. This is the first case reported in published literature of a child with Hoyeraal-Hreidarsson Syndrome undergoing a successful haploidentical stem cell transplant.

TECHNOLOGICAL ADVANCEMENTS IN DONOR CELL SELECTION

Haploidentical ('haplo' referring to half tissue matched family members) stem cell transplant using T cell depletion was first introduced in the early 1990s, and initial transplants using CD34 positive selection achieved high rates of engraftment. However, patients with leukaemia experienced high rates of virus infection and subsequent relapse.

In recent years, the knowledge that only a specific fraction of T cells mediate T cell alloreactivity – and others are beneficial in mediating antiviral and anti-tumour effects – has led to advancements in the methods of selective T cell depletion in clinical practice, such as the TCR alpha beta and CD19 depletion technique.

This technique allows the selective depletion of alloreactive T cells and B cells, reducing them to levels of clinical insignificance. Doing so significantly reduces the recipient's risk of GVHD, negating the need for post-transplant immunosuppression.

Large amounts of CD34 positive stem cells are also retained through this technique, which help to facilitate rapid and high rates of engraftment.

Moreover, the method of T cell depletion helps to retain the donor's gamma delta T cells and NK cells, which would normally require about four months to proliferate and mature from the donor's stem cells.

Immediately post-infusion, these beneficial cells help to fight virus-infected cells and host dendritic cells, thereby contributing to infection control and reducing the risk of graft rejection in the patient. They also provide anti-tumour (or anti-leukaemia, in the case of a patient with leukaemia) effects.

BOOSTING THE IMMUNE SYSTEM THROUGH CELL MANIPULATION

The increased understanding of NK cell alloreactivity has played an intriguing role in revolutionising allogenic stem cell transplantation. NK cells are so named, as they are natural killers of infected cells and cancer cells. This effect is mediated by excitatory and inhibitory NK cell receptors called KIRs, and their interaction with the particular human leukocyte antigen (HLA) allele combination between donor and recipient – a phenomenon known as NK cell alloreactivity.

Advances in KIR genotyping technology now enable clinicians to select haploidentical stem cell donors with higher levels of NK cell mismatch (alloreactivity) with the patient, which can help in reducing the patient's risk of graft rejection, viral infections and relapse (in the case of leukaemia).

The immune system can be further boosted by manipulating the donated stem cells to deplete naïve T cells (CD45RA positive lymphocytes) which cause GVHD, while selecting and infusing memory T cells (CD45RA negative but CD45RO positive lymphocytes) which help to kill virus infected cells and also leukaemia cells. Moving forward, we are looking to design even better grafts from haploidentical donors through combinations of various cell manipulation techniques.

As the knowledge of basic science continues to advance, new clinical applications in stem cell transplantation will continue to emerge, giving us more precise and powerful tools to cure rare and life-threatening diseases.

References:

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Dr Rajat Bhattacharyya, Consultant, Department of Paediatric Subspecialties, Haematology/Oncology Service, KKH

Dr Rajat Bhattacharyya obtained his MBBS MD (Paediatrics) from Calcutta Medical College, India, and has more than 13 years of specialist training and experience with leading medical centres including Bristol Children's Hospital and St James Hospital, United Kingdom; and British Columbia Children's Hospital, Canada.

Dr Bhattacharyya is a Fellow of the Royal College of Paediatrics and Child Health, and the Royal College of Pathologists, United Kingdom. His subspecialty interests include paediatric stem cell transplantation, leukaemias and benign haematological disorders.

KKH Sets Guinness World Record

for Largest Reunion of People Born at the Same Hospital

On 16 October 2016, KK Women's and Children's Hospital (KKH) made history yet again when 2,241 people gathered at Bishan Stadium to set a Guinness World Records™ title for the world's largest reunion of people born at the same hospital.

The youngest participant was seven and the oldest was 84 years old. A community family carnival was held on the same day, with more than 3,000 people joining in the festivities.

"We are very heartened and humbled by the strong show of support from those born in KKH," said Associate Professor Tan Heng Hao, Chairperson of the Born in KKH Steering Committee, and Deputy Chairman, Division of Obstetrics and Gynaecology, KKH.

"The encouraging response which we have received from the community for this event is a true testament to their appreciation for the holistic medical care and compassion that we provide to our patients every day."

The event also celebrated the 50-year anniversary of another world record set by KKH. From 1966-1976, the hospital had held the Guinness World Records title for being the largest maternity hospital in the world – with a record 39,835 babies born in a year at its peak in 1966.

Honoured guests at the event included Deputy Prime Minister and Coordinating Minister for National Security, Mr Teo Chee Hean; Minister of State, Ministry of Health, Dr Lam Pin Min; Member of Parliament for Bishan-Toa Payoh Group Representation Constituency, Mr Chong Kee Hiong; Member of Parliament for the Bukit Batok Group Representation Constituency, Mr Murali Pillai – all of whom were born in KKH – and Senior Minister of State, Prime Minister's Office, Ministry of Foreign Affairs and Ministry of Transport, Mrs Josephine Teo.

NEW FUND LAUNCHED CHAMPIONING WOMEN'S HEALTH RESEARCH AND EDUCATION

In celebration of KKH's 156 years of excellence and commitment to women's and children's health, the event also hosted the launch of the Women's Health Research and Education Fund under the SingHealth Duke-NUS Obstetrics and Gynaecology Academic Clinical Programme (OBGYN ACP).

This newly established fund supports medical research and education advancing areas relating to women's cancer, pregnancy and childbirth, fertility and parenthood, and women's health conditions (menopause, endometriosis and incontinence), leading to potential breakthroughs in clinical care for the future generations of women in Singapore and beyond.

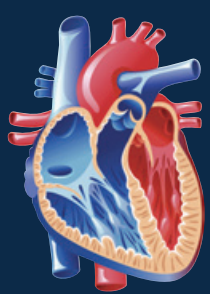
50-year-old local heritage snack foods company Tai Sun Food Industries pledged their commitment through a contribution of $50,000 to the newly launched fund.

"We are honoured that Tai Sun has recognised our commitment to providing innovative and compassionate care for women, and thank them for their support in enabling advances in healthcare and helping us make a difference to the lives of women now and for generations to come," said Professor Bernard Chern, Academic Chair, OBGYN ACP, who is also Chairman, Division of Obstetrics and Gynaecology, KKH.

A woman wearing a yellow tag identifying that she was born in KKH waves from the crowded grandstand at Bishan Stadium, where 2,241 people gathered to set a Guinness World Records title for the world's largest reunion of people born at the same hospital.

SUPPORT WOMEN'S HEALTH RESEARCH AND EDUCATION AT KKH

To give to the Women's Health Research and Education Fund, please visit **https://www.academic-medicine.edu.sg/OBGYNACP** or contact Linda Tay at **+65 6394 5019** or **linda.tay.lp@kkh.com.sg**.



BETTY WU LEE-KKH PAEDIATRIC CARDIAC CARE FELLOWSHIP

Impacting paediatric medical training across the region

With the vision to improve the lives of children with heart conditions across Southeast Asia, the paediatric cardiac care team at KK Women's and Children's Hospital (KKH) has launched a fellowship to train and mentor regional paediatric doctors in specialist cardiac care for children.

Named in honour of benefactor Mrs Betty Wu Lee, the Betty Wu Lee - KKH Paediatric Cardiac Care Fellowship programme provides doctors from regional countries the opportunity to undergo training in paediatric cardiology and/or cardiothoracic surgery at KKH and the National Heart Centre Singapore.

The fellowship is part of KKH's collaborative regional efforts to share expertise with medical professionals in neighbouring countries, resulting in a healthy exchange of ideas with long-term impact and an increased capacity to provide care and to strengthen their healthcare system in the long run.

"The Betty Wu Lee - KKH Paediatric Cardiac Care Fellowship will provide opportunities for specialist medical training to these paediatric doctors, and ensure maximum sustainable impact on the quality of healthcare accessible to children with heart conditions across the region," says Dr Loh Yee Jim, Head and Consultant, Cardiothoracic Surgery Service, KKH.

"We are deeply grateful to Mrs Betty Wu Lee for standing with us in enhancing care for children – in Singapore and beyond."

Announcement of GUINNESS WORLD RECORDS attempt result for Largest Reunion of People Born at the Same Hospital. (L-R: Dr Lam Pin Min, Minister of State, Ministry of Health; Mr Rishi Nath, GUINNESS WORLD RECORDS adjudicator; Mr Teo Chee Hean, Deputy Prime Minister and Coordinating Minister for National Security; Professor Kenneth Kwek, CEO, KKH; Mrs Josephine Teo, Senior Minister of State, Prime Minister's Office, Ministry of Foreign Affairs and Ministry of Transport; Professor Alex Sia, Chairman, Medical Board, KKH; Mr Ang Hak Seng, CEO, People's Association.

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ABOUT KK WOMEN'S AND CHILDREN'S HOSPITAL

Founded in 1858, KK Women's and Children's Hospital (KKH) is a recognised leader in Obstetrics, Gynaecology, Paediatrics and Neonatology. The 830-bed academic medical institution is Singapore's largest tertiary referral centre for high-risk women's and children's conditions. More than 600 specialists adopt a multi-disciplinary and holistic approach to treatment, and harness compassion, medical innovations and technology to deliver the best medical care possible.

Accredited as an Academic Medical Centre, KKH is a major teaching hospital for all three medical schools in Singapore, Duke-NUS Medical School, Yong Loo Lin School of Medicine and Lee Kong Chian School of Medicine. The Hospital also runs the largest specialist training programme for Obstetrics and Gynaecology and Paediatrics in the country. Both programmes are accredited by the Accreditation Council for Graduate Medical Education International (ACGME-I), and are highly rated for the high quality of clinical teaching and the commitment to translational research.

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