MediCine

A publication of the Yong Loo Lin School of Medicine • Issue 18 / May 2016

THE TAO OF THE CLINICIAN-SCIENTIST

DEAN'S MESSAGE

Hello Everyone,

As this issue of the School newsletter goes to print, we are finalising the shortlist of applicants who want to study for a medical undergraduate degree here at NUS Medicine.

It is one of the most difficult tasks that our Admissions colleagues perform every year: each one of the more than 2,000 young men and women who apply for a place is an outstanding candidate in his or her own right. They all have keen intellects and participate in or even lead initiatives which aim to help disadvantaged groups in our community. Many are also gifted musically and artistically, and blessed with engaging and charismatic personalities.

Every one of these young men and women is an eligible candidate for admission to NUS Medicine in 2016. But not everyone who applies to study Medicine is given a place. Such is the calibre of the candidates competing for the 300 places in the NUS Medicine programme that we look beyond grades and achievements.

What do we look for in our students? The Governor of the Straits Settlements, Sir John Anderson, put his finger on it when he wrote to the inaugural batch of medical students in 1905. "What I want you to remember is that the course of study you are about to enter upon is not merely a course of study which is intended to earn you a living, but a passport to membership of a very great profession, a profession in many instances, of unselfish devotion and splendid achievement, a profession of lofty ideals and one which calls for all the best qualities, mental and moral, which a man can give. It demands not only freshness and vigour of body, but steadiness and skill of hand and eye. It wants infinite patience and keenest sympathy, and to all these qualities, there has to be added unfaltering courage."

Our selection criteria is not perfect and we will continue to tune it so that the School is able to continue to reliably pick out the most suitable and appropriate candidates. The results speak for themselves, in the generations of alumni that the School has educated and trained.

Research work at NUS Medicine continues to make news: in this issue, clinician-scientist Chng Wee Joo shares what it takes to become a doctor and a scientist. We also take a look at the work on a new genetic test to help doctors adjust drug dosage to optimum levels for paediatric cancer patients. Another group of researchers has developed a hybridised drug that is able to kill artemisinin-resistant malaria.

Happy reading!

Warmest wishes,
Khay Guan

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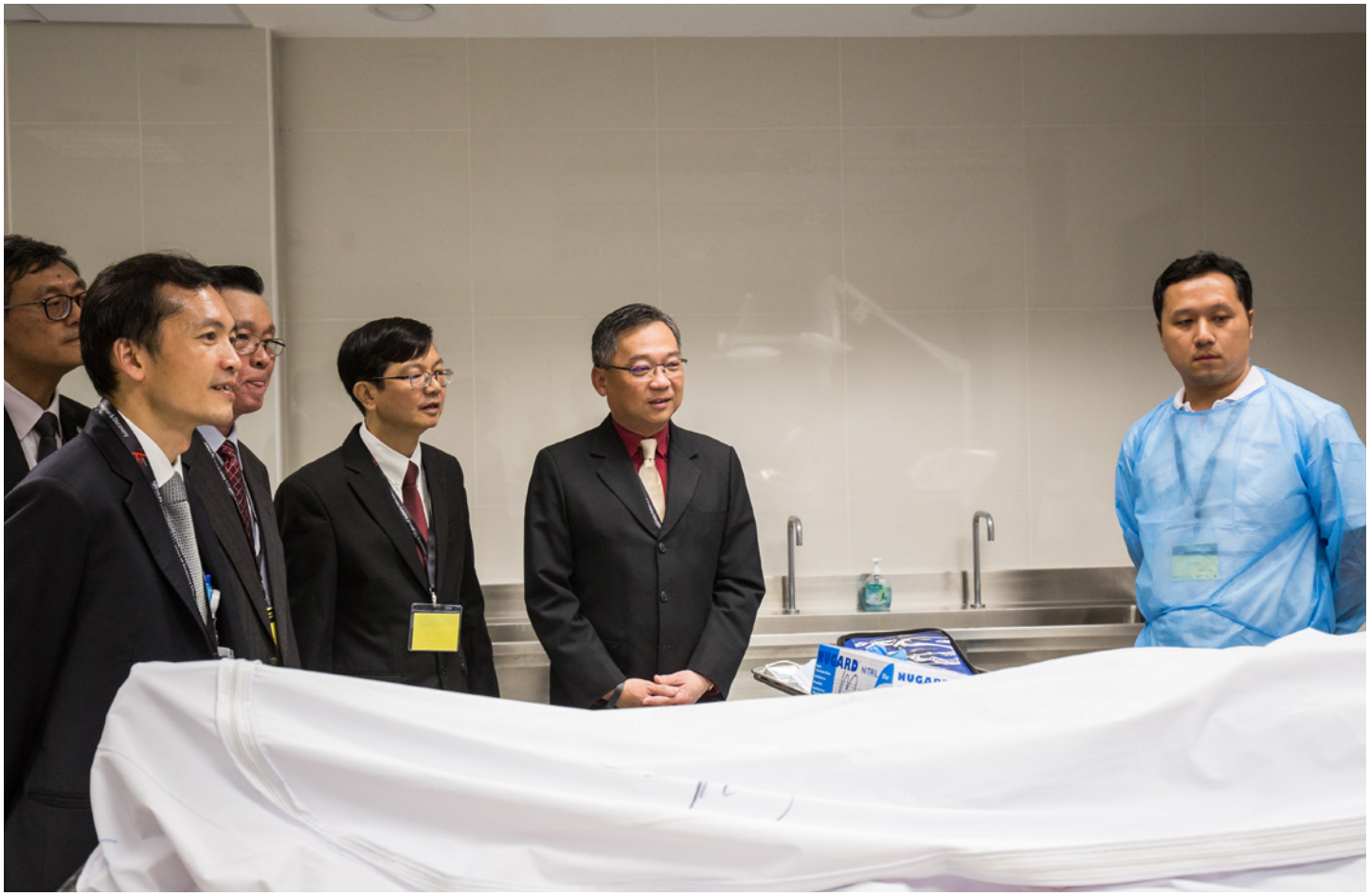


BIGGER, BRIGHTER, BETTER HUMAN ANATOMY TEACHING FACILITY CATERS TO MORE STUDENTS

The study of human anatomical structures has been made easier and more comfortable for NUS medical students and staff, thanks to the improved teaching and learning facilities at the Department of Anatomy of the National University of Singapore's Yong Loo Lin School of Medicine.

With more medical, dental, nursing, pharmacy and life science undergraduate students using its facilities to study human tissue and organ structures over the years, the Department embarked on six months of extensive renovations of its three-decades old teaching facility in February last year. They were opened on 17 March 2016 by the Minister for Health, Mr Gan Kim Yong.

The refurbished Human Anatomy Teaching Facility now includes an enlarged, well-ventilated hall for anatomy prosection classes, during which visuals of dissected specimens can be projected on large TV screens, with commentary delivered via an enhanced audio-visual system. The hall and the new dissection and embalming rooms were upholstered with anti-slip flooring and improved lighting. New-generation trolleys with facilities for connection to efficient downdraft suction systems that minimise exposure to formalin means students and staff are able to work comfortably in the facility, which now includes a completely refurbished mortuary to accommodate more cadavers.

A new reception area for families and loved ones of deceased body donors and other visitors completes the list of works carried out to modernise and upgrade the facility, which is located on the ground floor of the Anatomy Building in the NUS Medicine campus on Lower Kent Ridge Road.

All in, the refurbished facility has expanded its teaching space by 16 per cent from the original 1,050 square metres and can now more comfortably accommodate the 800 Medicine, Dentistry, Nursing, Pharmacy and Life Sciences undergraduate students attending Human Anatomy practicals as well as residents and specialists participating in workshops there, said Prof Bay Boon Huat, the Department's Head.

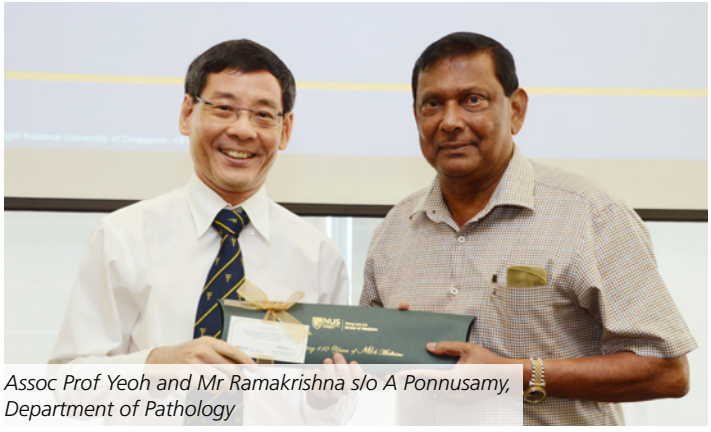
"We separated the dissection and embalming areas from the general teaching area, so that specimen preparation could be carried out in a better work environment for our prosectors. The works are timely, because our student numbers have gone up over the years and we want to provide them and our staff with a more conducive learning and teaching environment.

"The human body is the most essential tool when it comes to learning anatomy. When students work with cadavers, they are able to keenly appreciate the three-dimensional relationships between different body systems, regions and organs. While computer-aided learning has its benefits, many pedagogical studies have shown that practical experience with cadavers remains superior. We are truly grateful to our body donors and their families, because their gifts ensure that our students will continue to receive the in-depth, hands-on training that is so essential for their undergraduate and postgraduate professional development."

IN APPRECIATION OF OUR LONG-SERVING STAFF MEMBERS

Few can claim to have witnessed the evolution of NUS Medicine over the last 110 years, but a special group of academic and administrative staff that have been around for 20 years and more received special recognition at a luncheon earlier this year. Representatives received a NUS Medicine Heritage Tie (for the men) and Heritage Shawl (for the ladies) from the Dean, Associate Professor Yeoh Khay Guan. In all, 251 colleagues from the 18 Departments, two Centres and the Dean's Office who have served between 20 to 60 years at NUS Medicine were recognised.

Emeritus Professor Chan Soh Ha, Department of Microbiology & Immunology, and the Dean, Assoc Prof Yeoh



Assoc Prof Yeoh and Mr Ramakrishna s/o A Ponnusamy, Department of Pathology

Ms Ng Geok Lan, Department of Anatomy, receiving a Heritage Shawl from Assoc Prof Yeoh

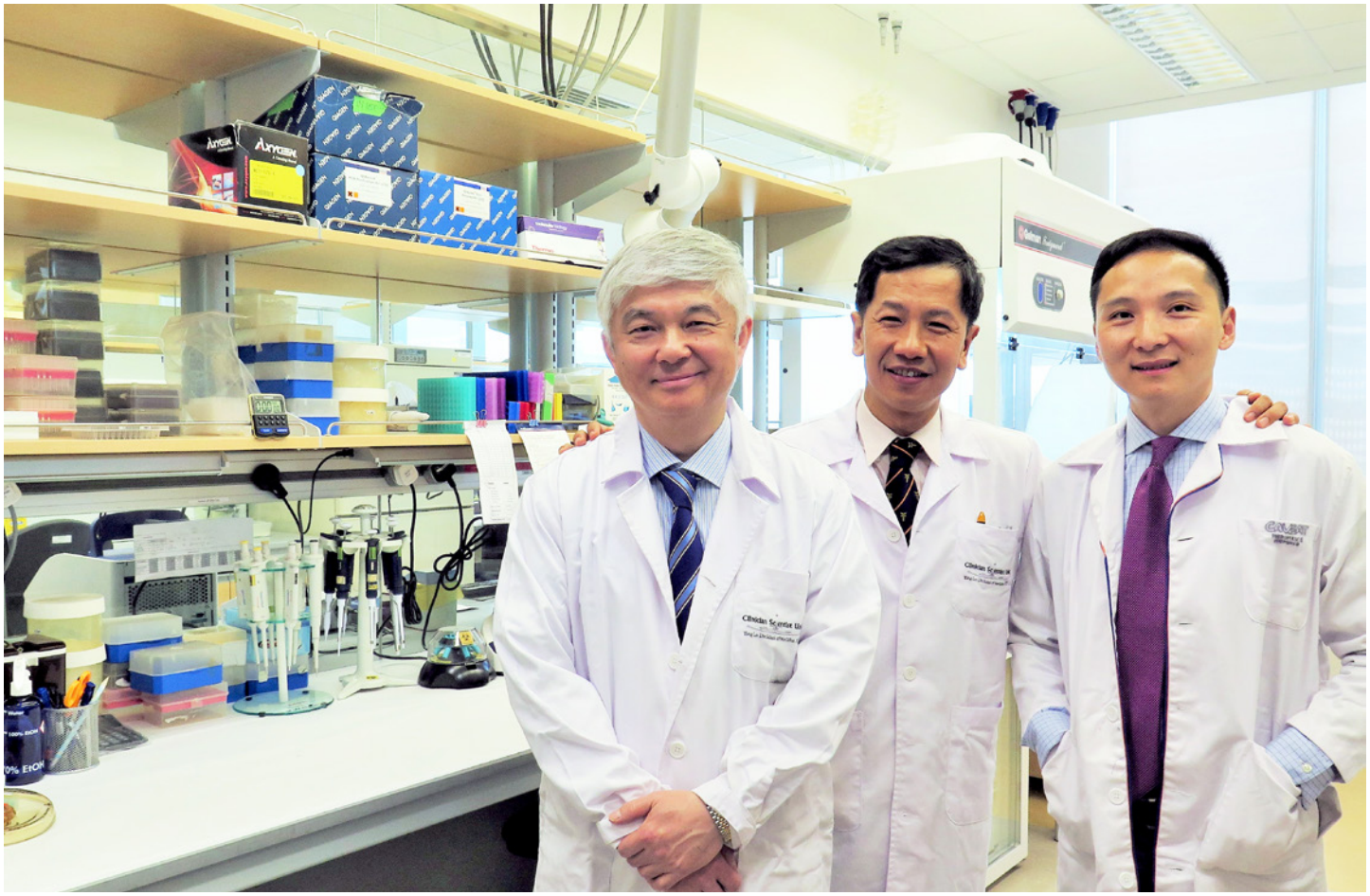
NEW GENETIC TEST HELPS DOCTORS ADJUST DOSE OF POTENTIALLY TOXIC DRUG IN ASIAN PATIENTS

Agnes (not her real name) is a typical 7-year-old in Primary 1, except for one thing: she has acute lymphoblastic leukaemia (ALL). She is also extremely sensitive to the common ALL drug 6-mercaptopurine (6-MP) and its toxic side effects. Shortly after starting treatment with 6-MP, Agnes' blood cell levels plunged, making her susceptible to repeated infections.

Approximately 1 out of 80 ALL patients are hypersensitive to 6-MP like Agnes. For many years, doctors have known that sensitivity to 6-MP and other thiopurine drugs are linked to variations in the TPMT gene in Caucasians. However, Asians appeared to be more sensitive than Caucasians to the drug, and this difference could not be explained by differences in the frequency of TPMT variants.

Now, a study of children with ALL has shown that another gene, NUDT15, is likely to be responsible for the greater sensitivity in Asians than in Caucasians. Published online in Nature Genetics in February, the study was led by Dr Takaya Moriyama and Dr Jun J. Yang, both of St Jude Children's Research Hospital in Memphis, Tennessee in the U.S. The researchers examined variants in the NUDT15 gene in 270 children with ALL in three countries, Guatemala, Singapore, and Japan. The Guatemalan patients were descended from Native Americans, who are genetically related to East Asians. The Singaporean arm, which comprised 69 ALL paediatric patients at NUH, was led by Associate Professor Allen Yeoh of the Department of Paediatrics. Assoc Prof Yeoh is also Agnes' doctor.

The NUDT15 gene normally produces an enzyme that breaks down toxic metabolites of the 6-MP drug into less harmful substances, thus neutralising the drug's toxicity. The study showed that, in all three groups, several variants of the NUDT15 gene made the



enzyme less active. Patients with one variant gene had intermediate enzyme activity and were more susceptible to 6-MP toxicity than patients with no variant genes. Two variant NUDT15 genes multiplied the effect. These patients had low enzyme activity and were extremely sensitive to 6-MP toxicity (see Facts Box).

Based on the findings, NUDT15 gene testing will soon be offered at St Jude Children's Research Hospital and at the new NUS-Viva Centre for Translational Research in Acute Leukaemia (CenTRAL), a $10-million laboratory funded by the Viva Foundation for Children with Cancer.

NUDT15 is one more gene in the expanding arsenal of genes that have been linked to specific functions. For example, in ALL, Assoc Prof Yeoh has characterised other genes that help to predict treatment response and outcome.

After close monitoring and multiple dosage adjustments, accompanied by bouts of infection, Assoc Prof Yeoh was able to find a dose that controlled Agnes' cancer without causing severe side effects. NUDT15 gene testing could reduce or even eliminate this difficult period of adjustment. Since 6-MP is prescribed for the second phase of treatment (5 weeks after initial treatment with another drug), patients can be tested to determine an appropriate 6-MP dose before even starting the drug. As Dr Yang sees it, NUDT15 gene testing represents a step towards "turning imprecision medicine into precision medicine."

FACTS BOX

How NUDT15 Gene Testing Can Help to Determine 6-MP Dosage

Result (No. of NUDT15 Variants)	NUDT15 Activity	6-MP Dosage Adjustment
0	Normal	None (normal dose)
1	Intermediate	Lower dose (eg, half-dose)
2	Low	Much lower dose (eg, 10% of normal dose)

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1. Moriyama T, Perez-Andreu V, Nishii R, et al. NUDT15 polymorphisms and individualization of thiopurine therapy. Nat Genet. 2016 Feb 15. [Epub ahead of print]

2. Lu Y, Kham SK, Ariffin H, et al. Host genetic variants of ABCB1 and IL15 influence treatment outcome in paediatric acute lymphoblastic leukaemia. Br J Cancer. 2014;110:1673-1680.

NEW HYBRID DRUG PLUGS HOLE IN MALARIA DRUG RESISTANCE

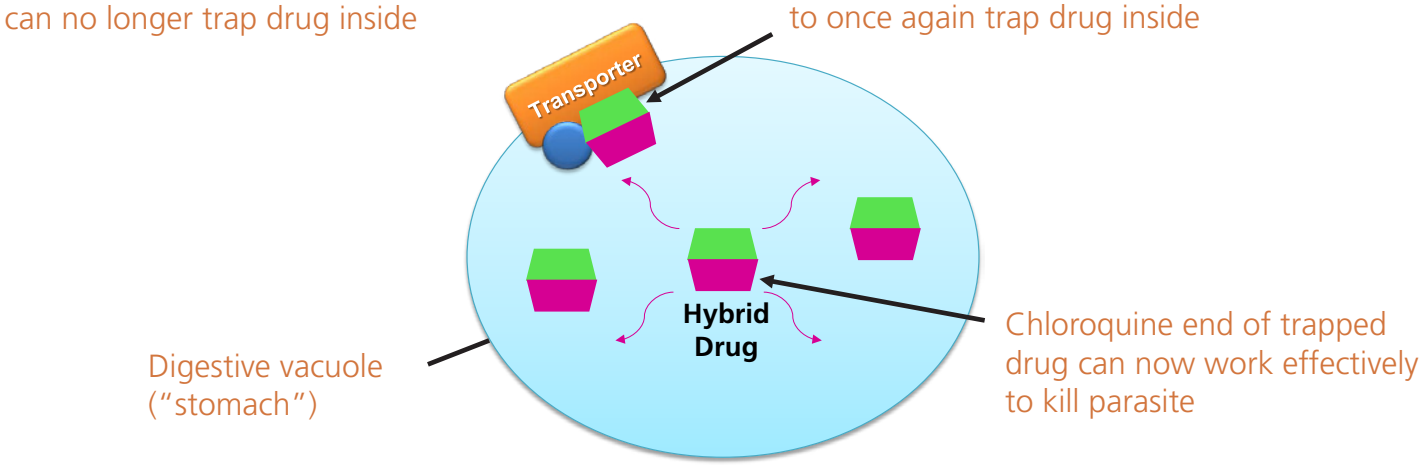
A combination of artemisinin and another drug (artemisinin combination therapy, ACT) is currently the best malaria treatment recommended by the World Health Organization. In early 2015, artemisinin-resistant malaria was confirmed in five countries in Southeast Asia: Cambodia, Laos, Myanmar, Thailand, and Vietnam. Even more worrying, malaria cases that are resistant to practically all drugs have begun to emerge along the Thailand-Cambodia border. Such cases do not respond to ACT; thus, new therapies that are effective for resistant malaria are urgently needed.

For a therapy to be effective, it needs to counteract the resistance of malaria to existing drugs. Malaria drugs, such as chloroquine and artemisinin, work within the digestive vacuole of the malaria parasite, which serves as its stomach. The killing action of chloroquine is better understood than that for artemisinin. Once chloroquine enters the parasite's "stomach," the stomach membrane traps the drug inside (similar to a window closing and locking) and the high levels of drug can then effectively kill the parasite. However, in a resistant malaria parasite, the stomach membrane is mutated so that it cannot keep the drug inside the stomach, just like a window with a broken lock. Since the drug is no longer concentrated inside the stomach, it can no longer kill the malaria parasite effectively.

Associate Professor Kevin Tan of the Department of Microbiology & Immunology and Associate Professor Brian Dymock of the Drug Development Unit and the Department of Pharmacy have now developed a hybrid drug that combines parts of chloroquine and a chemoreversal agent. This gives the hybrid drug a "dual acting" mechanism: a killing factor (chloroquine-derived) and a second component that acts on that faulty window of the parasite's stomach so it can now close again (the chemoreversal agent). The drug becomes concentrated inside the stomach of the drug-resistant parasite, killing it.

The new hybrid drug killed malaria strains grown in the laboratory as well as malaria parasites from patients in Thailand. Importantly, the drug was very effective against malaria that was resistant to both chloroquine and artemisinin. For example, it was three times more effective than chloroquine at killing both chloroquine-resistant and artemisinin-resistant strains. The researchers are continuing to refine the hybrid drug to make it an even more effective therapy for resistant malaria. This work was recently published in the scientific journal Antimicrobial Agents and Chemotherapy.

Although malaria drugs and chemoreversal agents have been used to treat drug-resistant malaria before, this is the first time that a hybrid of chloroquine and a newly discovered chemoreversal factor has been used in a single novel molecule for this purpose. A single therapy has several advantages that make it a promising new weapon against drug-resistant malaria. Besides being more convenient to take, it has less risk of drug-drug interactions, may be better absorbed and distributed in the body, and could result in slower development of new resistant strains of malaria.



How the Hybrid Drug Works in Digestive Vacuole ("Stomach") of Malaria Parasite to Reverse Drug Resistance

TRI-GENERATIONAL HOMECARE TRANSFORMS THE FUTURE OF EDUCATION AND HEALTHCARE IN SINGAPORE

The rapidly ageing population in Singapore is set to create challenges in her healthcare system. The elderly, especially those suffering from chronic diseases will require multi-disciplinary clinical management and long-term medications. Some of them will have added social issues such as lack of family support and many may come from low income families. Under this climate, it is a possibility that they become more susceptible to depression and many find it difficult to grow old in Singapore.

With a strong desire to serve the elderly, a group of NUS Medicine students decided to act as advocates for these vulnerable and less fortunate people in our community. Tri-Generational HomeCare @ North West is a groundbreaking student-led community project where students provide holistic medical and social care to vulnerable seniors via regular home visits. They see themselves playing some of the roles of loved ones in assessing the needs of the elderly, meeting these needs and coordinating the care of the elderly.

In collaboration with Alexandra Health System's (AHS) Ageing-In Place (AIP) Programme and North West Community Development Council (NWCDC), NUS students from Nursing, Medicine, Pharmacy and Social Work lead small teams of secondary school students to visit homes of elderly patients over a span of six to seven months. One of the aims is to provide opportunities for secondary school students to be equipped with theoretical knowledge and practical skills in the care of the elderly through the workshops planned. More importantly, they hope to inculcate important values such as compassion and respect in students. This project is based on the service-learning concept where community service is used as an opportunity to enrich classroom learning. During these visits, these two generations of students engage the senior generation of patients by building rapport, assessing their home environment and providing patient education, amongst other patient-centric care measures.

To prepare for the home visits, healthcare professionals and specialists from AHS's AIP Programme and NWCDC impart communication and caregiving skills to the NUS students who then share what they have learnt with their secondary school juniors. Learning comes full circle after the home visits are completed when students present their feedback and recommendations to the healthcare professionals at multi-disciplinary meetings.

Such teaching and learning, where students from different disciplines step out of their classrooms into the community to acquire knowledge and skills while serving the needs of the elderly population, is inter-professional education and authentic learning at its finest.

From identifying the healthcare needs in the community, to collaborating with community and healthcare partners, to training secondary school youths – our NUS students have created a refreshing synergy of partnerships at multiple social and institutional levels. This bottom-up and community-based approach towards education and healthcare, whereby members of the community step up to teach and care for each other, provides a promising future for Singapore's education and healthcare landscape. Due to the resounding success of the project, there are plans to expand this initiative to other institutions such as the National University Health System. As the demographic landscape of Singapore evolves to be one where aged dependency is growing against a declining fertility rate, Tri-Generational HomeCare @ North West paints a unique and optimistic picture of how students and community actors in education and healthcare can address these demographic concerns.

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2. Ministry of Health, Singapore, (18 August, 2015), "Opening Speech by Mrs Tan Ching Yee, Permanent Secretary (Health) at the Singapore Healthcare Management Congress, 18 August 2015", MOH Press Room News Highlights. Available here

PARTNERS IN THE PROCESS

Tey Min Li & Teri Danielle Yeoh You Ying

MEDICAL STUDENTS GET A FIRSTHAND TAKE ON THE JOURNEY TO RECOVERY THAT PATIENTS FACE THROUGH THE LONGITUDINAL PATIENT EXPERIENCE.

He has walked through fire. Literally.

G, a 27 year old gentleman, sustained a devastating 70 percent burns injury from a workplace accident. Through the Longitudinal Patient Experience programme, we have been privileged to journey with Mr G on his path to recovery.

We are introduced to G in the SGH Burns Ward. Sitting up on a chair, he is having his lunch as his mother and aunt keep him company. As second year medical students, he is the first burns patient we have encountered. He shares how only his feet, garbed in work boots, had been largely spared from the fire.

In our subsequent visits, we gradually get to know G better.

G details the many months he was in hospital - his fading consciousness in the HDU, his inability to communicate while on the ventilator. The numerous operations and skin grafts. It has been an arduous process, for both him and his family, who have played no small part in G's road to recovery. In spite of the long road ahead, G retains a charming sense of humour in relation to his condition. With a small laugh, he cheerfully comments how surprised he was, after waking up from yet another reconstructive facial operation, that he now has double eyelids courtesy of the plastic surgeon.

Despite the devastating effects of the accident, G has continued to take things positively, and his sheer fortitude and optimism has been most humbling and inspiring for us. He is keen on contributing to activities in the Burns Support Group – from providing guidance to recent burns victims, to speaking with conviction about the need for more awareness regarding skin donation in Singapore.

What we found particularly hard-hitting was how G's position was so relatable to us. Getting to know G, he shared with us anecdotes of his time in university, his time spent abroad on student exchanges, and even his work-study experience in the United States. He also shares with us how he took the photograph that hangs behind him, adorning the living room wall - a beautiful panorama from a Greek island. The accident has put on hold, but in no way derailed G's travel plans. G speaks animatedly of looking forward to a short trip in the future, when he has regained more of his strength. He repeatedly urges us to explore the world and seize opportunities to go overseas where possible.

Yet, in spite of all that we've taken away from our conversations and that little friendship we've developed with G, we sometimes still struggle to understand how we could best communicate with G – there were times we simply ran out of conversation topics, or fell short in terms of knowing how to demonstrate our empathy.

There were times we didn't quite know what we should be doing to make G feel most comfortable, and there were occasions where we felt like we were really taking away more from our conversations with him than he was from them. Yet, this is perhaps what the art of medicine is all about, and we are really just students who are still trying to learn and grow by the day. Perhaps one of the greatest takeaways we've had from the Programme thus far, too, is realising how life is about many journeys coming together. We have just embarked on our journey to learn to be good doctors in future. G, too, is on a long journey that is hopefully headed towards gradual recovery and healing.

We've also come to see first-hand through this little friendship we've built that sometimes, medicine is not just about delivering quick cures or fast solutions. For all the progress modern medicine has come to make in terms of being able to eradicate diseases and conditions, it is important for us to realise that sometimes, recovery is not always swift. Sometimes, recovery can be a very long journey we have to struggle to make.

The road is never easy, and we may sometimes encounter road blocks, false starts and stops, detours, and potholes along the way. And sometimes, when we think there's nothing else we can prescribe, it's often an extra dose of compassion and empathy that counts.

THE STROKE PATIENT - WEAKENED IN BODY, UNDIMINISHED IN SPIRIT

Lai Kah Ho and Lee Xing Ni Janice

Forlorn, debilitated and dependent – these are common and stereotypical views of stroke patients. Participating in the Longitudinal Patient Experience programme has helped to change those views for my partner and me. We met our first patient, Mr Lim, at Ang Mo Kio – Thye Hua Kwan Hospital, along with our mentor Dr Loh Yong Joo. As we followed Mr Lim on his journey to recovery, we witnessed first-hand the joys and struggles that he as well as his caregivers underwent throughout a year.

Prior to the stroke episode, Mr Lim was a chef and the sole breadwinner for the family. Post-stroke, he was declared unfit for work and had to accept the reality that he would no longer be able to continue with his role as provider.

Throughout our time with Mr Lim and his wife, we saw how he continued to strive, wanting to make more progress in recovery. Although he was limited by his physical disability, he makes it up with his mental and emotional strength and tries his best to regain his daily functions. He engages in exercises recommended by his physiotherapists and occupational therapists and does his daily walks along his HDB corridor. He also puts in great effort to communicate with us despite having difficulty finding the words to express himself. When Dr Loh told Mr and Mrs Lim that his recovery would plateau eventually, he was not fazed by the news; instead, he remained positive about recuperation.

We also gained a clearer perspective of outpatient care for patients with chronic physical disabilities, their daily struggles and the treatment dilemmas they faced. Botox injections were recommended to Mr Lim for temporary relief of muscle spasms, which could allow him to exercise and possibly make better progress. However, the effects wore off after three months and both he and his spouse felt that his condition had deteriorated slightly post-treatment. They were then faced with the dilemma of paying for another dose of Botox, of which the effects are uncertain, or to decline Botox treatment and proceed with rehabilitation.

Another important lesson we learned about handling chronic patients is that it does not merely require clinical expertise. Just as important are the inputs from other healthcare professionals and the final outpatient care plan put together by the entire healthcare team.

As Dr Edward Trudeau so aptly put, "To cure sometimes, to relieve often, to comfort always." Medicine has a limited capacity to restore patients to their original healthy state, and such is unquestionably the case for Mr Lim. Fortunately, he draws comfort from the unwavering support of his wife and Dr Loh, who have fought alongside him through the toughest initial challenges. In our eyes, Mr Lim is the absolute epitome of a motivated patient, and witnessing his progress certainly was a humbling experience for us.

A FAMILY'S LOVE AND SUPPORT VITAL FOR HEALING

Soo Jiunn Jye Roy and Too Jia Yu Sarah

Having just entered medical school, we were bright-eyed students fresh out of Junior College. We knew little of medicine, our knowledge confined to the "science medicine" we learnt in lecture theatres and anatomy hall sessions. We were unfamiliar with the perspectives of patients and the importance of communication, distant from the wards and clinics where medicine was actually practised. While we were taught the science of medicine in school, we saw the opportunity to learn the art of healing in this Longitudinal Patient Experience programme.

We had the fortune of working with our dedicated mentor, Dr Soh Shui Yen, who had vast experience specialising in paediatric oncology at the KK Women's and Children's Hospital. With her kind advice and assistance, we were given the opportunity to meet with and learn from a child, Jayden, who was only 6 years of age. He had been battling neuroblastoma and, after a year of intensive treatment, was on the path of recovery. We were told of the hardships endured by his family while he went through chemotherapy, and even after. He would be extremely irritable, lashing out at the family's domestic worker, even hitting his mother. He was unable to attend school and thus had to drop out of the mainstream education curriculum. Thankfully, with the assistance of social workers, he was enrolled in a special school where he could learn and mingle with children his age.

We still remember Dr Soh's words clearly – that illnesses like these not only affect the patient, but his or her family as well. Jayden's parents would put in a significant amount of effort, taking him to and from school and the hospital for his weekly reviews. We could only imagine the stress on the family, who had two younger sons to look after.

As medical students, we merely saw patients in clinics and hospitals and failed to realise that there was more to a family and their struggles outside a hospital setting. Visiting them in their home allowed us an intimate understanding of the challenges the family faced in caring for such a young patient. The father was providing for the family by working two jobs, while the mother held the fort at home by tending to their three young children. We saw the immense struggle the parents had to endure in caring for the children. In the short span of half an hour, the three sons fought, cried, laughed and bonded over toys. It took a lot of patience, cajoling, and pacifying to keep the boys in check. Through it all, the parents' love for their children shone through and moved us immensely.

In medical school, we learn about the roles of doctors and nurses in providing patients with essential medical care. Through this programme, we have seen and understood for ourselves the importance of love in caring for the sick. We have gleaned from Jayden's parents that loving care has its place alongside medicine in the management of patients. Therefore, as much as we should know how to treat with medicine, we should also know how to heal with love.

Acknowledgement: Dr Soh Shui Yen, Department of Pediatrics, KK Women's and Children's Hospital

THE TAO OF THE CLINICIAN-SCIENTIST

BECOMING ONE IS TO TREAD A LONG AND WINDING ROAD THAT IS LESS TRAVELLED, BUT MOST FULFILLING, SAYS PROFESSOR CHNG WEE JOO IN A RECENT NUHS GRAND ROUNDS TALK.

Very often the question is asked, "What is a clinician-scientist (CS)?" The definition is muddled. The National Medical Research Council will give you one definition; our own doctors will give you another. Is it embedded in the qualifications of the individual, type of research that he or she performs, or the practice that the individual is in? For example, Cancer Science Institute director Dan Tenen is medically qualified, he does a wide range of research (that is more basic and mechanistic) but is no longer a practicing clinician. I'm medically qualified, I do clinical translational research while also delving into the mechanistic basic components of this translational research, and I continue to practice clinically.

What is a true clinician-scientist then? I don't think there is a single definition. The way I look at it is this: what is the mindset of the person doing the research? Must he be medically qualified, so that he has insight into the clinical problems and is able to then identify what matters most for the patient? Does he need to be a practicing clinician? It will help. But then again, if he is always thinking about how to improve gaps in clinical management, in improving understanding of disease biology so as to find solutions to help patients, I think that would suffice as well. And I think importantly, he or she should also be a very important and effective link between clinicians and basic scientists (BS).

THE JOURNEY MATTERS AS MUCH AS THE DESTINATION

Very often, collaboration between scientists and clinicians fails because they don't understand each other. The CS should be well-versed in the scientific methods and thinking processes required and act as the link (between clinicians and basic scientists). I don't just focus on the translational end or clinical end of the research, because I know that a translational project may take many years to bear fruit. There are different phases to the work – from discovery to understanding of the mechanism, to identifying a treatment, to conducting clinical trials to get the treatment into the clinic eventually. In Singapore, we are often in a hurry. We want someone to come up with a KPI in three years. If that's the situation, you'd pretty much be forcing everyone to do work only to fulfill this objective. I think that is a waste because there are many unique diseases of the Asian phenotype that we need people in our region, in Singapore, in NUS to research. It can be a clinician-scientist and of course it can be a basic scientist as well, but we need to not forget about the entire process (that goes into translating research discoveries into clinical application).

I didn't have all these things in my mind when I started my journey. All journeys have a beginning and mine wasn't really very promising. I decided in secondary school and in JC that I really wanted to do medicine. I guess, many people then wanted to do

medicine. It was a very popular degree to go for. I wanted to help people get better and I was interested in science and chemistry and so this provided a good mix. So I applied as most Singaporeans do, to NUS Medicine. Most applicants don't get into NUS – and I was one of those. It wasn't a very promising start, but I always look at the silver lining and the light at the end of the tunnel. There's always a positive twist to something that appears disappointing at the beginning.

AT LEEDS

I ended up going to Leeds University medical school in the UK. At that point the only thing I knew about Leeds was the Leeds Football Club. I didn't know much about the medical school though I knew a few Singaporeans studying medicine there who had pretty good feedback on the school. It turns out that Leeds does have a very strong programme in haematology, a strong pathology department and the medical school made some early discoveries on surgical techniques and tools. And so, this became one of the first lessons that I learned – a CS must be able to take rejection as well as criticism in his/her stride, because you will face much hardship in your career. But it was at Leeds that the seeds were truly planted and I became interested in research and translational-type research. I realised going through medical school that many of the important advances in medicine and treatment were through key scientific discoveries. Some of it were quite amazing, e.g. the discovery of penicillin and some vaccines. I also realized that just learning what is in the textbooks will not make things better for the patient, because there are too many diseases that have poor treatment options and outcomes. We are just starting to understand and describe some of those.

THE AWAKENING

Indeed, there is plenty of research still to be done. In my last year at medical school I joined the radiology department on an elective to do research. This led to my first publication, the year I graduated, looking at PSA. It was not by intent but I was doing a project on Cancer and the Gleason score in predicting the stage of newly diagnosed prostate cancer. The topic itself was not the main thing; it was the participation and getting my feet wet that I really liked. Some people will find the process very laborious and unexciting, but I find that the excitement is in finding out something – in the joy of discovery. So I was developing an interest to do this kind of work. Then after graduation I went to another historic place, York, where I did two years on a general medicine rotation that was supposed to prepare me for the MRCP exam. It was during this period that I encountered haematology. I wrote a case report when I was there and the combination of lab-based enquiry with clinical care connected particularly with my personal interest in diagnostics and problem-solving. So this was where my interest initially started.

After I finished my training as a Senior House Officer in the UK, I had to decide whether to stay and train as a specialist. I was already married then and the wife said, "Enough time overseas, better get home" because she had parents who were growing older. I came back. I interviewed with Endocrinology first because that was the one job that was advertised in the BMJ and Endocrinology was one of my potential choices. But I really wanted to do haematology. SGH didn't have a position at that time and the NUH was only starting its haematology traineeship and this wasn't advertised. A friend in the Ministry of Health connected me with the Head of Haem-Onc at that time, Lim Hong Liang. Hong Liang took me in for an interview with Liu Te Chih, who took a chance on me. So I joined NUH Haematology.

During that time, I had a colleague who was also interested in doing research studies and writing up case reports, and we encouraged each other on. I think environment is really important. At that time, I wrote up a case series on using cyclosporine to treat patients with renal failure who developed pure red blood cell aplasia due to EPO treatment. This was very topical at that time. The paper still remains highly referenced because people do use cyclosporine to treat this condition. I learned from my seniors at that time – Dr Liu and Dr Tan – that we truly ought to be observant and look at the clinical problem of our patients to obtain ideas and clues on what are the important things that we need to do for them, in terms of understanding what may help them.

THE PREPARATION

As a trainee in the wards, I published quite regularly – small time publications like case reports and small studies. I was getting grants from the NMRC to do some small-scale research, so I was already ramping up towards a CS career path. But there wasn't a really clear career track for clinician-scientists in Singapore in the early 2000s. Most people ended up as clinicians. But as with most things in life, sometimes you will need to have a bit of luck and timing. At that time, Singapore needed more CSs and A*STAR was offering an international fellowship to overseas institutions for two years of funded research training.

The idea at that time was that they don't want to give you time for you to get a PhD – 2 years only; not 3 years, not 4 years. Because they want you to have enough training but not too much time away, so that you can come back straightaway to do your research in Singapore. So I was fortunate enough to get one of these and I went to the Mayo Clinic. Before I went, I actually had no idea how to do lab-based research, and that was the research that I wanted to do, because I realised that there were a lot of exciting things happening in the areas of genomics and genetics. This was the time when microarray technology and the genome project were emerging. I felt that it was an important frontier and I needed the skills for basic research to be effective at the Mayo Clinic, so I had to prepare in advance in order to hit the ground running.

I had understanding chiefs who allowed me to work at a research lab for three months. I am very thankful to Prof Ito and A/Prof Motomi Osato, one of the senior scientists in Prof Ito's lab at that time. I spent 3 - 4 months with them learning how to use a pipette, how to do PCRs, cloning, cell cultures etc. Nothing came out of that experience in terms of publications but it was very much an eye-opener.

Once, I sat in on one of their lab meetings. I could not believe how tough it is to truly be a good scientist. The postdoc who was giving a presentation was literally being picked apart for over-stating the interpretation of the data and Prof in his usual quiet but stern manner pointed out to him that what he said was incorrect. The difference is subtle. To my untrained mind at that time, I thought, "Wow, you mean this is so important?" But I learned that in science, we have to be very precise, and this is one of the problems that many of our graduate students have. In their theses, they state all sorts of conclusions and claims which their data is not exactly saying.

THE COMMITMENT

I had an opportunity to go overseas at an early stage. Very often young doctors come up to me and tell me they want to do a PhD. I see it differently; I do agree that we want more MD-PhDs, but I believe we ought to be flexible and give advice based on what kind of research the person wants to do in the end. I am not convinced that it's always worthwhile to take the time to do a PhD if your work doesn't require that kind of training.

So it's the end in mind that is important. Those aspiring to do research on databases, analyse data or publish don't need a PhD. We have other opportunities such as the Master of Public Health (MCI) – shorter courses, more focused, targeted towards that area. I think if you do need to do work that is mechanistic and more scientific, understanding of basic mechanisms and in the lab, then the discipline of doing a PhD may be useful. But again, what does the PhD study entail? The components of it are also important.

So if you ask me, on hindsight, I did do a PhD. Did I find it useful? If I had not done it, would my three years (one year at the Mayo Clinic) be enough for me to be where I am today? I would say yes. The most important component of that PhD were the three years of research discipline in the lab under good supervision. If I had not submitted a thesis and got a PhD, I wouldn't have acquired the skills I need for the work I do today.

Many international professors observe that our PhD programme doesn't focus on research; it focuses on coursework and finishing modules and attaining the required Cumulative Academic Points (CAP). You don't really have a lot of time doing research. So whether learning on the job is enough or you need the formal certification, what is the formal qualification/education required?

I did a PhD at that point. I thought, why waste the time? It's always useful to have a paper qualification in Singapore. I was lucky also to have the help of A/Prof Evelyn Koay, at that time the Director of the Molecular Diagnosis Center (MDC), who was willing to take me on as a student. I did a part-time PhD. I did my research at the Mayo Clinic first before coming back to do my 1-year of courses/modules here as an Associate Consultant, running clinics and attending classes, taking exams etc. A/Prof Koay was very helpful and taught me that for scientific writing, you have to be quite meticulous. I was quite careless, and she would hand back the thesis to me with her comments in red ink.

A TURN IN THE ROAD

My journey had many twists. I wanted to go to Rochester to do myeloma research. Myeloma is a clinical entity that intrigues me. It's a very complex problem that has interesting diagnostic dilemmas. Patients present with all kinds of multifactorial problems. However, nobody in Singapore then was really into myeloma and this was an area of very active growth in terms of drug development. Through one of my seniors, I was connected to the Mayo Clinic and they accepted me. I was going to do genomics and myeloma with Prof Rafael Fonseca, who was emerging as a very important person in this field at that time.

I was expecting to go to Rochester and as I was preparing all my winter clothing, Rafael emailed me a month before my departure. "Sorry, we have a change in plans. I am now

going to Arizona – Mayo Clinic still – because I've been asked to go there to head this new division of haematology and set up a genomics collaboration with a big genomics institute in Phoenix. Are you still coming?" I said yes, because I want to learn from him. I threw away all my winter clothes and bought shorts and t-shirts because I was now going to the sunny state where you see cactus and sand and mountains and there's hardly anything else. This was one major twist, but it turned out to be a great place because they were recruiting all these top scientists in myeloma and building a new institute and I got to be right in the middle of it all.

The second twist was that I was supposed to go there and learn about mutations in genes that control cell division. In myeloma there is a lot of abnormal DNA or chromosomal segregation. So the idea is, the genes that control mitosis are abnormal so that the separation of the chromosomes become abnormal. Within six weeks of getting to Mayo in Arizona, we did screening of these mutations using many patient samples and they were all negative. So it was back to the drawing board; it was not a programme that would work. Rafael quickly concluded that we should not waste time on this, and to start on a project with this genomic institute to look at microarray and gene expression in myeloma. One thing that the Mayo Clinic has a lot of is patient samples. So I went and learned different techniques to do microarray.

MAYO DAYS

I picked up different sets of techniques that were completely different from what I was initially intending to learn. They were very useful techniques to acquire and continue to help me throughout my research career, because these have become a core skill. Within the first year, I managed to complete one of these projects and submitted the manuscript to the journal, Blood. To a Singaporean haematologist, Blood is the 'holy grail', the top haematology journal we read for the latest advancements, what we should do for our patients and so on. At the Mayo Clinic, Blood is the basic – you must do enough quality work to submit to Blood first. I submitted my work and thought, fat chance this will get in. Funnily enough, they came back with only minor revisions in the first round. So I thought, "Research is not that difficult!" I was lucky enough to get my first paper in Blood. This was the only time that it was that easy!

My 2 - 3 years at Mayo were spent working really hard. I was alone; my wife and children were back home. So all I did was research every day and I also read a lot. I was picking up a lot of new things, like gene expression. This is one thing which I find many of our younger postdocs and graduate students do not do, with many preferring the shorter route – their source of reference is Google or Wikipedia.

In their presentations, some refer to Wikipedia and that is not a good thing. You really need to read and understand. So sometimes when I tell them to work on a newer area of research, I ask if they've read the key papers in this area and what are the essays that investigators use to look at this pathway (for example) and they look at me, in expectation that I would provide the answer. No, you must go and read and find out and enquire and plan and come back to me with a plan which we will then discuss. So I think the willingness to put in the hard preparation work is often not there nowadays.

MENTORS MATTER

Another thing that is important is the choice of mentors. I went to the right place at the right time; I didn't just get Rafael – I got Keith (Stewart) and Leif (Bergsagel). These are fantastic scientists. Leif was the one who cloned all the mutations that we know of today in myeloma. He taught me more about scientific thinking. Rafael turned out to be a very good administrator-scientist, while Keith is very translational, seeing the clinical potential of many things. He is the director driving the precision medicine initiative for the entire Mayo Clinic and will be visiting us sometime later this year. So I didn't get just one, but three mentors.

Mentors are important and you need to choose them carefully. It is not always the case that great scientists, very famous people, are good mentors. Not all leaders in their field make the best mentors. Neither do all senior people fit the bill. Instead, some of the junior and upcoming scientists are the ones who are very invested in people. For example, Rafael taught me that research is like an investment portfolio. You shouldn't place all your money on just one project. You should have your portfolio of low-risk, middle-risk and high-risk projects. The high-risk ones will get high impact publications but you are prepared to fail there because it's not always easy. The middle ones are the ones you get into Blood and so on and they are a bit harder but nonetheless do-able. Then the easy ones are maybe your impact factor 5 types, with a near certainty of getting published. And you want to make sure that you always have this so that at any one time, you're publishing something. So you don't have gaps in your publication history. I thought that's very sensible and that's essentially what I have done and still do.

ABOUT MENTORSHIP

And what is mentorship? They also taught me that it's not knowing everything under the sun, but knowing where to get the information. Mentors know how to facilitate things; they know how to guide you when you're unsure of how to do certain things, and they don't control exactly what you do. The micro-managing type of mentorship really doesn't work. Good mentors allow you creativity, freedom, they give you broad strokes – this is what they think conceptually you should think about. They offer you career advice.

When I was asked to be director of the National University Cancer Institute, Singapore, I went back to my mentors and asked, "What do you think?" I didn't just ask our own guys. I consulted my mentors because they've been through it, are directors of institutes and they know whether it's possible to continue to manage their research portfolio and all these things. So my mentors have become friends, which I think is a relationship that is worthy to establish and think about. We don't always have very good mentors available in Singapore because the pool is small, though it is growing. There is no better time than now to be a clinician-scientist, but you need to be aware of all these things and plan carefully.

WHAT IT TAKES

Recently there was an NMRC Symposium and many like Goh Boon Cher, Khoo Chin Meng and Tai E Shyong shared their experiences as clinician-scientists. As I sat there listening, I thought, "This is quite amazing because all of them mentioned very similar things – the need to handle rejection well and possessing tenacity, amongst others – which highlights to me that there are some qualities that are innate to all good clinician-scientists. That brings me to this question that I ask myself: now that we have funding for clinician-scientists and we have a mandate that we need to train 80 by 2020; can we really do that? Can we turn someone into a clinician-scientist? They must be born

with certain qualities. And I think that is an interesting conundrum. But I truly feel that you must have some passion and interest because it is a very harsh environment; a very tough journey; you take a longer time than your colleagues – you must really want it. If not then, even if we give you money to help you with the first few steps, you ain't going to continue on the rest of the journey because the money may run out. It's not going to always be there. You have to fight for the money eventually.

CULTURE AND ENVIRONMENT

A culture of research is very important. I was lucky to be in a department where there are clear role models. Boon Cher and many of us had understanding Heads who recognised even at that time, the importance of academic excellence and research. And I was given protected time as a junior faculty member and encouraged to do what I wanted to do. For Heads who want to build up departments with more clinician-scientists, some flexibility is very important. And of course, funding is important, though this should not be an issue in Singapore now.

RECRUIT AND BUILD THE POOL OF CLINICIAN-SCIENTISTS

Overall in the world, there is a fear that this group of people is diminishing. In America and Canada, part of this is due to poor funding. One important way to develop more clinician-scientists is to recruit the right people from medical school. The way we structure our interviews of students seeking admission to medical school here – do we consider the elements that will make good CSs or are we just recruiting pure clinician types? This is important to consider because whoever you recruit will determine the kind of output you most likely will get.

GETTING STARTED

Once I graduated, I had to shift my focus to how could I be successful when I came back to Singapore. I would no longer be in the cradle that is the Mayo Clinic, with all the resources that they have, and this is where planning and strategy is important. You need to play to your strengths. I asked myself these questions:

- ***What is your strength?***
- ***What do you need?***
- ***What is available?***
- ***What is important?***

I did that thinking and realised that I would be in trouble if I wanted to do my own research alone. I have about 30 new cases of myeloma in NUH per year. They (Mayo Clinic) have a few hundred each year. There was no way I could compete with these guys. Even if I want to build up a bank or a prospective cohort, it will take some time. So I needed to look at other potentials. During my time at Mayo, I made trips back home, talked to people here and understood who the people doing research in haematology were and what they were interested in.

At that time we had a new pathologist, Ng Siok-Bian, who was interested in a rare type of lymphoma called NK/T cell lymphoma. She was collecting samples. I thought that this was useful for Singapore as it is common, a very deadly disease that we know nothing about and I have the skill (in microarray gene expression) with which I could interrogate this kind of disease. So I worked with Siok-Bian and within two to three years, we submitted a paper. The collaboration has continued and we have become one of the known centres in the world that is studying the biology of this disease. So, you need to be strategic; you need to know your needs, your strengths, who you can collaborate with, and start to form some collaborations. This is the part that will bridge my gap and build my research in myeloma, and it is something which will take time.

BUILD THE RESEARCH

Those who are interested in doing translational type research should build their infrastructure. You need your clinical database – you need this to be linked into a cell bank. If you need to do genomics, a bioinformatics framework or some ability to analyse that data is required. For those who want to do drug testing, you need to build the model, i.e. in vitro and in vivo drug testing platform. Do you fulfil them all in one day? No. It takes time, but you need to start with the first two i.e. a clinical database and cell bank – they are the easiest and they are your 'currency', because they are the resources your basic scientist researcher will come to you for. And this is where you will get your initial collaboration.

Over the last few years since I built up those databases, we've had engagement from NUS, from industry, from A*STAR

to academic institutes to run different drug screening programmes for them. It's produced more than 60 since 2009, just using these resources that we have built up.

BUILD THE TEAM

"If you only do what you can do, you will never be better than what you are."

I picked up this quote when I went to watch Kung Fu Panda with my kids. It shows that you can learn from everywhere. I think this is a very profound statement. What it says is that we shouldn't limit ourselves to our own comfort zones.

This is how I view building my team:

Complementary expertise. It could be easy for a PI to employ only those who know less than the boss. In this way you will never be able to go beyond your own comfort zone and grow. In fact, if I know that the project requires a lot of protein-based knowledge that I don't really have, I get a good postdoc in that area to come and I build this team.

Keep good people and allow them to blossom. Some of my team have been with me for more than 10 years, getting long service awards. Tae Hoon, who is my bio-informatician, was working with me when I was in Arizona. When I came back to Singapore, he asked if I had a job for him – he wanted to be nearer to his home in South Korea. He's been working with me for more than 10 years. The understanding we have is highly valuable.

BUILD THE PROGRAMME

Over time, we have pieced things together and have a clear idea of the research we want to do, the disease models that we want. It an integrative approach, not haphazard, not piecemeal. I know that if I want to make a real impact on patients' lives, I also need to improve the clinical trials capability in haematology. I was in a department that already had a very nice group of clinical trial coordinators and setup, so I was fortunate to be able to tap into that. But it requires energy. Before I came back in 2008/9, there was very little haematology research activity and Boon Cher will tell you that. Since then, we have built our recruitment so that over a period of 6 - 7 years, we have five times the number of patients recruited. Last year, we were involved in a trial where we were one of the top recruiters in the world as a single centre here at the NUH for a global study in a disease like myeloma and which resulted in senior authorship in a paper that resulted in the approval of a drug. Again, small size doesn't mean you cannot succeed. With organization, some energy and effort, you can also make an impact in the global setting.

BUILD THE NETWORK

It's also important to build your network because if you're alone, in this day and age, it is very hard to do good and impactful research. Collaboration is key. Sometimes I hear others say that it's hard to work with colleagues from other hospitals. Well, in haematology we have managed to set up a national consortium. Each party has ownership of different programmes that makes research very effective. Sometimes we also find it hard to collaborate with our friends in Hong Kong, Korea etc. – we view them as our competitors. But again, we have managed to set up an international consortium that has been very successful.

GIVING BACK

We need to contribute to our institutions at some point in our careers and there is no better way to do so, than to be in a position to change policy so that we help to make things better.

My plate is full these days and they keep me going, because if there is only one thing and that thing is not really working well, you will actually become very frustrated. But here sometimes I'm frustrated in some areas but in others, I'm getting joy. So overall, it keeps me going.

MAINTAIN WORK-LIFE BALANCE

The other important thing is family. Have some interests outside of work. Spend time with your family. My family gives me the energy to do what I do: I am blessed to have an understanding wife. And because I have to be away from home sometimes, I am also thankful for the support of my staff.

A WORTHWHILE JOURNEY

Apart from some personal accolades, the important thing is to be a good CS, to make impact for our patients. Through the work, I have seen the survival rate of myeloma patients almost double since the time that I began working on myeloma.

We have managed to implement new models of care that actually help our patients, such as the outpatient transplant, which reduces the length of hospital stay for the patient. There is no increase in mortality or complications, but it saves the patient about 30% of the cost of the transplant. And it frees up hospital beds for other patients.

Through our clinical trials, we've also seen patients who have benefitted from access to new drugs. A patient of mine was dying of a disease that was at end-stage. He participated in a clinical trial, had another two years of good quality of life, saw his daughter graduate from Pharmacy studies and his older daughter get married. This is a meaningful outcome for patients.

I've managed to be involved with and form the Asian Myeloma Network. I have helped start clinical trials in Asia so that we can push the agenda for our Asian patients. This has helped to elevate our institution's international standing and drive some initiatives through the international myeloma working group, while also writing consensus statements. All these came about because I was able to stand on the shoulders of many giants. They have helped, supported, encouraged and nurtured me over these many years of my journey. That's why it's important for me to make it happen for my younger colleagues as well. Mentoring medical undergraduate and graduate students and our other doctors in the department and creating an environment and a legacy that can last for generations is what I want to do. It's important to ensure that we make it happen for others as well.

SCHEDULER

MAY – JULY

Date	Event & Venue
May 10 – 13 May 17 – 20	**Simulation as a Teaching Tool: Instructor Course** Centre for Healthcare Simulation, Level 3, Centre for Translational Medicine (CeTM), MD6, NUS
May 28	**Alumni Wine Series 2016: Italy's Greatest Hits*** Pepenero
July 3	**Medical Dinner 2016** Padang & Collyer Ballrooms, Level 4, Raffles City Convention Centre
July 9 – 10	**RadioPath 2016** T06-03, NUHS Tower Block
July 10	**Commencement Ceremony** University Cultural Centre, NUS

Details may be subject to change at the discretion of the respective departments without prior notice.

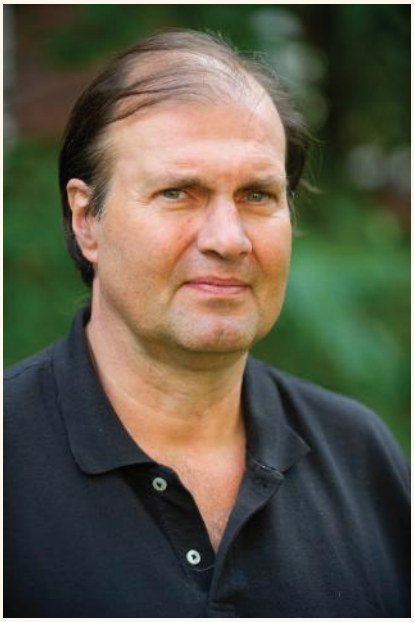
Pre-event registration is compulsory. Email **alumni.med@nus.edu.sg to register*

Congratulations

Congratulations to the Division of Graduate Medical Studies (DGMS) for being awarded the NUS HR Learning Award.

The HR Learning Award is organised by the NUS Office of Human Resources and recognises best practices in talent and leadership development in NUS. It aspires to create a platform for staff to engage in self-directed learning, to achieve department goals and by extension, the University's mission and goals.

IN MEMORY OF PROFESSOR LORENZ POELLINGER



Lorenz Poellinger obtained an MD and a PhD from Karolinska Institutet. His doctoral thesis elucidated important details of cellular signaling by dioxin. He pursued post-doctoral training in the laboratory of Robert Roeder at the Rockefeller University, where he made groundbreaking discoveries on promoter/enhancer binding. In 1996, Lorenz Poellinger was appointed Professor of Molecular Biology at Karolinska Institutet. He continued his research on dioxin-mediated cellular signaling but also extended his research into a related field, that of HIF transcription factors and became a leading scientist in mechanisms of hypoxia-driven transcription.

In 2008, Lorenz Poellinger joined the Cancer Science Institute (CSI), National University of Singapore (NUS). He was one of the original founding members of CSI and was a Senior Principal Investigator with the Cancer Stem Cells and Biology Program and Professor at the Department of Medicine, Yong Loo Lin School of Medicine, NUS. He was instrumental in many of the CSI management committees, in which his experience, scientific excellence and willingness to contribute were deeply appreciated. With his enthusiastic support, the Institute has grown from strength to strength.

Many are the students, postdocs and scientists Lorenz Poellinger trained and mentored and many are those who could have benefitted from his training.

We will remember Lorenz as a brilliant, creative, and generous scientist, colleague and friend who left us at too early an age.

Karin Dahlman-Wright
Acting Vice-Chancellor
Karolinska Institutet

Daniel G. Tenen
Director
Cancer Science Institute of Singapore

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Celebrating Our Medical Education Community

Join us for a joyful evening of camaraderie,
good food and drink!

Reconnect with old friends as we toast to celebrate
the graduation of the Class of 2016.

Sunday, 3 July 2016
Raffles City Convention Centre
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Dress Code: Smart Casual

For enquiries, please contact Ms Justine Teo at 6772 3764 or email medjtx@nus.edu.sg

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