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Pioneering Team-Based Learning Model Spurs Advances in Education

For six years now, TeamLEAD, Duke-NUS' unique medical education pedagogy built upon a team-based learning framework, has been instrumental in developing a proactive, and dynamic learning environment for students.

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The Long Road to a Patent

Thanks to the guidance of their mentors and the opportunity to take their ideas further, several Duke-NUS students have secured patents – a commendable milestone in their academic journey.

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The Class of 2013 Graduates

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In the world of academia, research is often confined within the hallowed walls of the respective institutions.

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This e-communications update is produced by the Office of Communications, Development and Alumni Relations
Editorial team: Janice Tan, Dharshini Subbiah, Wee Lai Ming (Duke-NUS) and Sheralyn Tay

Our banner story: Pioneering Team-Based Learning Model Spurs Advances in Education. Read the story here.

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DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

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Pioneering Team-Based Learning Model Spurs Advances in Education

For six years now, TeamLEAD, Duke-NUS' unique medical education pedagogy built upon a team-based learning framework, has been instrumental in developing a proactive, and dynamic learning environment for students.

In recent years, the success of Duke-NUS' team-based learning model has been validated in numerous ways (see box story) - and attracted the interest of over 170 educators in Singapore and abroad. Visitors have come from Yale-NUS College, A*STAR, National University Health System, Tan Tock Seng Hospital, Ministry of Education, Ministry of Health, Flinders University, Guangzhou Medical University, the Imperial College (London) as well as Lee Kong Chian School of Medicine and many more.

"Since its launch in 2006, TeamLEAD has been a powerful innovation that has allowed us to deliver quality learning to students," affirmed Professor Bob Kamei, Vice Dean, Education, and Director, Academic Medicine Education Institute. "Our exchange and visitor program has been a hallmark of the school - we've held workshops and talks aimed at sharing our experience of implementing team-based learning. It is not an easy strategy to implement, so we hope others can learn from us."

Prof. Bob Kamei

Assoc. Prof. Sandy Cook

In order to better serve the academic tenet of knowledge sharing, Duke-NUS has launched a **Fellowship in Team-Based Learning (FTBL)**. According to Associate Professor Sandy Cook, Senior Associate Dean, Curriculum, "The FTBL offers a structured program and allows participants to learn the full range of skills in developing and running TBL modules." Instead of hosting one-off visits here or conducting workshops around the world, Duke-NUS can now accommodate more requests from institutions keen on understanding more about team-based learning in an organized and systematic manner. Prof. Kamei added, "Many universities are coming here to learn different ways to teach and Duke-NUS has been happy to share its various novel teaching methods in the spirit of improving medical education both for learning institutions overseas as well as in Singapore."

The TeamLEAD fellowship is a 1.5-year program that includes three visits and on-going support from Duke-NUS. Apart from core skills, the program will help Fellows design and develop their own team-based learning modules, practice effective facilitation and create evaluation strategies. Fellows will not only experience the TeamLEAD process, but design their own approach, test it and tweak it so as to better shape it for their context and individual needs. The fellowship has already attracted 38 participants from countries such as Japan, Brunei, Philippines, Tanzania, Saudi Arabia China, Vietnam and Sweden.

Taking the (Team)LEAD

Duke-NUS has not only been the first medical school in Singapore to use team-based learning, but is among the first in the world to do so.

Team-based learning – a concept which has been around for 40-years – focuses on peer teaching,

Students learning together through discussions

collaboration and self-directed learning. While business schools have tried implementing team-based learning in their curriculum since the 1960s, the idea has never been successfully applied and sustained so comprehensively in medicine until its inception in Duke-NUS.

Prof. Kamei attests that the proactive e-learning elements and interactive educational innovations developed with input from the faculty have led to the success of team-based learning, as demonstrated in a paper published in *21st Century Learning in Medicine: Traditional Teaching versus Team-based Learning, in the Medical Science Educator* in 2012. The paper demonstrated that Singapore's Duke-NUS medical students not only learnt as well as their US counterparts, as reflected in test scores, but could do it in half the time.

Furthermore, the Duke-NUS model has become an AAMC (Association of Medical Colleges) case study: AAMC Readiness for Reform

"This validates the success of our approach and belief that team-based learning can be done on a wide-scale basis in a medical school," added Prof. Kamei. Assoc. Prof. Cook also observed that more than ten new medical schools in the US are now using TBL, in one way or another.

Video: Learn more about TeamLEAD

Blazing the Trail

Apart from successfully applying team-based learning in an effective and sustainable way, Duke-NUS' other educational approaches have added value and innovation to how medicine is taught, assessed and practiced.

The standardized patient program:

Under this program, individuals are trained to portray themselves as patients with specific histories, personalities, attitudes and physical findings to run simulated doctor-patient encounters. This allows Duke-NUS students to conduct realistic consultations for learning and assessment while also being monitored by the faculty who can pause the simulation at any time to give feedback and make teaching points.

A MD student examines a standardized patient as part of his first-year study

The method is also useful to conduct objective assessments because the 'patients' are trained to play a consistent role for each student. Apart from learning basic physical examination skills and building confidence in this area, the program also enhances communication skills – particularly in relaying news to patients about their conditions and improving doctor-patient relationships. A relatively new concept to Singapore when it was introduced to Duke-NUS' inaugural class in 2007, Duke-NUS has shown that it is possible to have valuable interactions with standardized patients.

Research experience:

Students dedicate ten months towards research in clinical, translational or services research together with a research mentor. The challenging but intensive experience exposes students to meaningful lab work and significant research projects, during which they benefit from the experience of renowned senior doctors. The goal is not only to build quantitative competency as well as deeper appreciation and understanding of scientific study, but also underscore the meaning of translational medicine.

Third-year students are mentored during their research year. This file photo shows Syeda Kashfi Qadri with Assoc. Prof. Ooi Eng Eong (left) and Prof. Duane Gubler (right)

During their third year, students get the chance to bridge the gap between research in the lab and the implications for patients. One significant outcome of this research year is that some students get the exciting opportunity to see their name in print, and publish their work. By having students spend a focused time on research, it is also hoped that they will gain the skills to think critically about statistical data and its clinical significance in the light of the statistical outcomes. The value of this experience was explored in a paper published in a special edition of the *Medical Science Educator*, Volume 23 (1S) 2013, which found that 49 per cent of students rated their third-year research experience as “excellent” and 40 per cent as "good".

Teamwork & leadership training:

Before Duke-NUS freshmen tackle biology, anatomy and physiology, they experience education of another kind – how to work in teams, resolve conflicts, build networks and negotiate in a group. This unique exposure is aimed at developing doctors that can work in multidisciplinary teams. Duke Corporate Education, a leader in its field having topped the *Financial Times'* Business Education Ranks for the past decade, exposes students to managerial and teamwork skills and effective strategies to communicate. This builds the foundations for developing critical and creative thinking skills and the facility to work with others. Cultivating these skills early on also enables our students to constantly apply them as they navigate through TeamLEAD with their teammates and beyond when they work with their colleagues in the hospitals.

However, beyond just helping students to cope with the rigors of learning in teams, teamwork training is also an integral element of patient safety. Effective teamwork can have immediate and positive impact on patients in healthcare delivery and this importance is growing due to the increase in complexity and specialization of care, co-morbidities, chronic disease, global workforce shortages and safe working hours initiatives. As Dr. Paul Schyve, Senior Advisor, Healthcare Improvement, The Joint Commission, observed, “Our challenge… is not whether we will deliver care in teams but rather how well we will deliver care in teams”.

> “Students not only graduate as exemplary clinicians and clinician scientists, but also with the skills to lead in these fields throughout their career.”
>
> Assoc. Prof. Arpana R. Vidyarthi,
> Director of Leadership Development

Besides teamwork, Duke-NUS also believes in molding tomorrow's medical leaders. Assoc. Prof. Arpana R. Vidyarthi, Director of Leadership Development at Duke-NUS, illustrates how students undergo training to help them understand themselves, others, and various communication styles through the Myers-Briggs Type Indicator. Leadership skills training is then thread throughout their four years into the existing curriculum. This involves a deliberate process building competencies which include leadership attributes, resilience, systems, communication, self-awareness, change creation, and management. In this way, these students not only graduate as exemplary clinicians

and clinician scientists, but also with the skills to lead in these fields throughout their career.

Duke-NUS Colleges:

Students from the Benjamin Sheares College spearhead the annual World Autism Awareness Day

Extending its ethos of providing a strong network of support, Duke-NUS introduced the college system to provide a community of mutual peer support and advising system for students. The Duke-NUS Advisory Colleges are a local adaptation of the Advisory Dean System instituted by Duke University's Dr. Doyle Graham in 1987. At the colleges, students meet weekly, building meaningful friendships not only with the students in their year but in other years as well. The College system also build students' professional and personal development by providing support, advice, and mentoring that helps overcome the stresses and challenges of medical education, under the guidance of their respective college masters. Social, recreational and community service projects are a hallmark of the colleges and activities that nurture friendships, idealism, empathy, and compassion help students to become better medical professionals overall. The four Colleges are named after legendary figures in medicine: Gordon Arthur Ransome College, Seah Cheng Siang College, Benjamin Sheares College and Eugene Stead College.

National Board of Medical Examiner (NBME) assessments:

Duke-NUS uses the NBME assessments to ensure the quality of graduating students. These exams are also used in the US as the United States Medical Licensing Exam (USMLE) and are well-researched and rigorous assessments of a physician's ability to apply their medical skills and concepts safely and effectively before they are allowed to enter residency. The Ministry of Health (MOH) and the Singapore Medical Council require Duke-NUS students to pass these exams, which also helps in reassuring patients that Duke-NUS students are well-prepared at the highest standards. Two of the three "steps" must be completed before graduation and cover basic science principles, clinical application and reasoning. These exams assess physicians' competency, knowledge, expertise and abilities. The third step, developed with NBME specifically for Singapore, is taken after first year of residency and required for final licensure in Singapore.

Related story: Nurturing the Next Generation of Doctors and Interview: Professor Ranga Krishnan, Dean, Duke-NUS Graduate Medical School (Singapore Medical Association, SMA News, July 2013)

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The Long Road to a Patent

Thanks to the guidance of their mentors and the opportunity to take their ideas further, several Duke-NUS students have secured patents – a commendable milestone in their academic journey. We feature three of Duke-NUS' intrepid inventors.

The difference mentors make

Lai Hsuan & Darius Aw

Patent: A Cervical Collar with Mounted Robotic Biopsy Subunit Containing Inbuilt Ultrasound Scanner and Robotic Needle for Biopsy of Neck Lump

The invention is an integrated medical device that can be used to diagnose lumps on the neck. The design enhances precision and efficiency during localization and collection of samples, making it easier for physicians to perform the procedure.

For Lai Hsuan and Darius Aw, the road to securing a patent was a meaningful and challenging learning experience. Not only did it appeal to their passion for bioengineering, for which they both hold a degree in from Johns Hopkins University and Nanyang Technological University respectively – but widened their perspectives as well. “The more we delved into it, the more we realized it wasn’t that easy to put something on the market,” Hsuan reflected, “There are so many things involved, from the medical to the technological, legal and business. It was a great learning experience and an exciting journey for me.” Her co-inventor Darius agreed, adding that it was unexpected but rewarding to secure the patent in the first place, despite there being a long way to go.

Co-inventing classmates: Lai Hsuan and Darius Aw

Darius and Hsuan’s research mentors: Assoc. Profs. Paul Yen and Marcus Ong

Both highlighted the importance of their mentors. “I was fortunate to have a mentor who is a thyroid specialist. Assoc. Prof. Paul Yen from the Cardiovascular & Metabolic Disorders Program played an instrumental role in helping us to look through the grant, give advice, connect us with the right people, including senior medical professionals from SGH and NUHS so that we had an impressive medical team behind us,” said Darius.

Hsuan, whose mentor Assoc. Prof. Marcus Ong is himself a prolific clinician-scientist in Singapore with several patents to his name and a Senior Consultant, Department of Emergency Medicine at SGH, also played a very supportive role and was happy to share his own experience in securing a patent with her.

Above all, the experience for the two third-year students has reinforced their passion for medicine. “Duke-NUS has helped us strive for our dreams and empowered us to pursue our interests beyond just studying medicine,” said Darius.

Building a community of medtechies

Wijaya Martanto
Patent: Optimizing micro infusion into skin using micro needles

Use: Improving the painless delivery of drugs through micro needles to allow capillary uptake but minimize pain.

Pursuing a medical degree at Duke-NUS, on top of a PhD from Georgia Institute of Technology in chemical engineering, has allowed Wijaya to pursue his passion – medtech.

At Duke-NUS, he has found the perfect environment to explore the application of engineering technology in medicine. Wijaya said the “excellent medical education” and the supportive culture of the school has provided him with many opportunities, particularly in supporting the MedTech student interest group that he co-founded.

Duke-NUS' Deans and Dr. Tan Sze Wee from A*STAR, together with the Singapore Stanford Biodesign fellows, have also played a strong role to support and grow the medtech interest group. “I am able to interact with my colleagues at Duke-NUS and SingHealth's physicians and surgeons who share a similar

interest in applying technological advancement for medical/healthcare field," he said. The diversity of Duke-NUS students – with engineering and non-engineering backgrounds – has also helped grow the interest group and offer different complementary perspectives, he added.

Passion for MedTech: Wijaya Martanto

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The Class of 2013 Graduates

The Class of 2013 celebrated the milestone achievement of completing their four-year medical training on June 1.

This year's Graduation Celebration & Hooding Ceremony at the Yong Siew Toh Music Conservatory was graced by Guest-of-Honor Health Minister Gan Kim Yong, together with NUS President Prof. Tan Chorh Chuan, Dr. Victor Dzau, Duke University's Chancellor for Health Affairs and Prof. Tan Eng Chye, Deputy Chairman, Duke-NUS Governing Board & Provost, NUS. This event preceded the official graduation ceremony that was held during the NUS Commencements in July.

The Class of 2013

In his message to the graduating class, Dean Ranga Krishnan shared words of wisdom and encouragement: "You now stand at the threshold of an exciting new chapter of your professional life. To ensure continued success, do make learning an integral part of your medical journey. Always strive to be courageous, curious as well as compassionate. While there may be tough lessons and choices ahead, uphold your moral compass and do not shy away from doing the right and humane thing."

The keynote speech was delivered by Prof. Peter Agre, 2003 Nobel Laureate in Chemistry, and former Chair of Duke-NUS' scientific advisory board. Following the speeches, the Class recited the Hippocratic Oath together with all physicians present before receiving their hoods from the student-nominated Ceremonial Hooders, Assoc. Prof. Simon Ong and Assoc. Prof. Lai Siang Hui, as family and friends looked on with pride. The ceremony ended with a class video presentation and speech by nominated class speaker, Dr. Szymon Mikulski.

Prof. Doyle Graham

The Class of 2013 has certainly left a deep impression on the faculty and their juniors during their time at Duke-NUS. In their yearbook messages, Prof. Doyle Graham revealed: "Over time, you garnered our sincere affection. We found you to be serious students of medicine, who worked hard, took risks to participate in team and class discussions, and consistently displayed an excellent attitude toward learning… I hope that your career in medicine stimulates your brain, warms your heart, and feeds your soul."

Petty Chen, from the Class of 2014, also reveals the lighter side of the graduating class, recounting fond memories - "If you gaze up to the third floor library during lunchtime, you are bound to find a few of our beloved seniors there. I know that sounds vague, but the Class of 2013 does not really have a "class" character. They are creatures of diverse personalities,

unique in their own rights. They are lively. They know exactly what they want and will go for it."

Drs. Christopher Schlieve and Maryanne Chew Romero

Class Speaker Szymon Mikulski (center) with Mr. Tony Chew, Ms. Karen Chang, Prof. Peter Agre and Dr. Victor Dzau

Pavaani D/O Thiagayson from the Class of 2013 reflected, "As we stand on the threshold of our careers as doctors, I think that some of our medical student angst has been tempered by our sense of purpose and accomplishment. Our achievements would not have been possible without our families, friends and mentors."

Video: Graduation Celebration & Hooding Ceremony

Photos from the 2013 Graduation Celebration & Hooding Ceremony

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New Center for Technology and Development Launched

In the world of academia, research is often confined within the hallowed walls of its respective institutions.

While this does not render the studies or work done less important than those with commercial application, it does mean that sometimes discoveries that could change patients' lives are not developed further. With the new Center for Technology and Development (CTeD) – Duke-NUS hopes to change this.

Since its inception in 2006, numerous innovations have come about from the research activities of Duke-NUS' prolific faculty and students, bringing to reality the goal of bench-to-bedside treatment that improves patient outcomes. To date, 37 patent applications have been filed for research and technological innovations conceived from work at Duke-NUS. In addition, over 50 invention disclosures have been filed. Thus far, Duke-NUS and its partners have completed the out-licensing of five technologies. As more such scientific endeavors begin to also reach commercial potential, more support is needed to help investigators achieve that goal.

Assoc. Prof. David Epstein

According to Associate Dean David M. Epstein, who heads the Center, "The aim is to facilitate translation of research arising from the activities of Duke-NUS, SingHealth and its partners into commercial application. As Duke-NUS' research activities come to fruition, Duke-NUS investigators and research personnel will require more support to facilitate commercial development by establishing sustainable, long-term relationships with external private and public partners."

Assoc. Prof. Epstein, previously Senior Vice President Oncology, Chief Scientific Officer, and Site-Head at OSI Pharmaceuticals in New York, is a leading scientist in cancer drug discovery and translational sciences. His work in targeting drivers of cancer development and epithelial-mesenchymal transition has led to the discovery and development of four agents able to target cancers of the lung, ovary and prostate.

Under his leadership, Assoc. Prof. Epstein aims for CTeD to provide long-term value to biomedical research at Duke-NUS by helping its innovative translational programs realize commercial potential. The Center will also contribute to Duke-NUS' training of biomedical scientists, particularly in technology development and applications, so as to facilitate manpower development for the Singapore biomedical industry.

CTeD is part of the Duke-NUS Office of Research. Added Prof. Patrick Casey, Senior Vice Dean, Research: "The Center will further develop Duke-NUS technologies and provide entrepreneurial training to interested scientists and staff with the goal of enhancing the commercialization of our technologies and to demonstrate a positive return on the investment that our stakeholders have made in Duke-NUS."

Key activities of CTeD:

- Development of a strategic plan aligning intellectual property with internal research and commercial opportunity assessment
- Advancement of selected programs with commercial potential to value inflection points
- Provide consultation and training to investigators, as well as Duke-NUS MD and PhD students, in developing translational programs and seeking funding from commercial enterprises to support these programs

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Celebrating Eight Successful Years with Inaugural Gala

More than 900 guests attended Duke-NUS' inaugural Gala Dinner on May 30, at The Ritz-Carlton, Millennia Singapore. Singapore's President Tony Tan Keng Yam graced the occasion as the Guest-of-Honor. It was especially meaningful since he was the architect behind the vision of Duke-NUS as Singapore's second medical school, and the Patron of the Duke-NUS Development Committee.

By the time the dinner had ended, the School had received gifts totaling more than $17 million pledged from foundations, doctors, students and alumni.

Donations play a critical role in the growth and progress of Duke-NUS. Besides providing for student financial aid, they also help fund research and education programs enabling researchers to carry out

studies that become the basis for future patient treatments and enhancement of care. Besides making many key research breakthroughs over the past eight years, the School has also managed to attract outstanding faculty, develop a highly successful teaching method called TeamLEAD that is being adopted and implemented in two undergraduate medical courses in Duke University, and achieved 52 invention disclosures and licenses, and over 1,000 publications.

"We are exceedingly grateful to individuals, their families, organizations and foundations, as well as Duke-NUS students, staff, faculty and alumni, who have demonstrated faith, commitment and effort to achieve our common goal to improve patients' lives." said Prof. Soo Khee Chee, Senior Vice Dean (Clinical and Academic Faculty Affairs), Deputy Group Chief Executive Officer of SingHealth and Chairman of the Gala Dinner's organizing committee.

One such example is the gift from the late Sister Tan Sew Kee, a senior staff nurse with the Singapore General Hospital for over 30 years. She bequeathed the entire sales proceeds of $321,000 from the sale of her apartment to the Neuroscience Academic Clinical Program to advance research on motor-neuron disease (MND), an incurable disease which claimed her life in August 2011. She hoped that her Gift will help push the boundaries of MND research and that one day, advancement in MND treatments and care will help improve the lifespan and quality of MND sufferers.

The desire to give was palpable, with guests giving generously during an auction held that night. A total of $73,500 was raised that night from the sale of two vintage wines, a four-night stay at a private five-bedroom pool villa in Phuket and the "8 Fables" - a set of eight paintings done by Singapore's renowned artist Mr. Tan Swie Hian.

Dean Ranga Krishnan was heartened to see the rousing support for the school. "The persistent and sustained effort of many individuals, stakeholders, students, faculty and our donors is testimony that the Duke-NUS model shapes the future of medicine, research and patient care". He also thanked all donors for their faith in the School.

Held in conjunction with celebrating the achievements of the graduating Class of 2013, the Gala also saw a slew of awards being given out. Comprising three Gold Medal Awards and four Prizes, the 2013 SingHealth Graduation Awards were given out by Prof. Ivy Ng, SingHealth Group CEO, to Szymon Mikulski (SingHealth Top Student Gold Medal), Zhang Zewen (Top Student in Internal Medicine and Neurology), Ku Chee Wai (Top Student in Surgery and Obstetrics & Gynecology), Michael Ku-Hung Hsieh (SingHealth Prize in Family Medicine) and Law Shipei (SingHealth Prize in Pediatrics). These awards recognize academic excellence and high standards shown at clerkship postings within SingHealth institutions.

Other prize winners included the following:

Institute of Mental Health Prize in Psychiatry	Pavaani D/O Thiagayson
Singapore Medical Association-Lee Foundation Achievement Prize	Qian Qi
Singapore Medical Association-Lee Foundation Teamsmanship Award	1. Koh Huilin 2. Jason Lam Shang Leen 3. Ting Boon Ping 4. Felix Maverick Rubillar Uy 5. Zhang Zewen
College of Family Physicians Singapore Prize in Family Medicine	Koh Huilin
Duke-NUS Achievement Prize	Law Shipei

Duke-NUS Humanism Award	Zhang Zewen
NUSS Medal for Outstanding Achievement	Tan Shuhui, Sara

The faculty was also recognized for their hard work and dedication in guiding and mentoring the students during their journey through medical school. Winners were nominated by students and this year, fifteen faculty members were recognized. They are:

1. Assoc. Prof. Lai Siang Hui
2. Assoc. Prof. Simon Ong
3. Prof. Lim Shih Hui
4. Dr. Chong Shu Ling
5. Asst. Prof. Phua Ghee Chee
6. Assoc. Prof. Koong Heng Nung
7. Assoc. Prof. Thirumoorthy
8. Assoc. Prof. Koo Wen Hsin
9. Assoc. Prof. Loo Chian Min
10. Prof. Julian Thumboo
11. Prof. Soo Khee Chee
12. Prof. Pierce Chow
13. Asst. Prof. Tan Tong Khee
14. Asst. Prof. John Allen
15. Assoc. Prof. Thng Choon Hua

Click here for more photos of the inaugural Duke-NUS Gala Dinner

View gallery:

Welcoming the Guest-of-Honor, President Tony Tan Keng Yam and Mrs. Mary Tan

Dean Ranga gives the Opening Presentation

Prof. Ivy Ng presents Szymon Mikulski with the SingHealth Top Student Gold Medal Award

President Tony Tan, Duke-NUS Development Committee Patron receiving a donation from the Estate of Madam Tan Sew Kee on behalf of the School

Duke-NUS Gala Dinner

Mr. & Mrs. Tanoto with Prof. Ivy Ng (center) and Mrs. Melanie Chew and Mr. Tony Chew

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Charting New Ground: Duke-NUS Medical Alumni Association is Launched

A new milestone was reached as alumni from the MD Class of 2011 and 2012 came together to form the pro tem committee to get the new Duke-NUS Medical Alumni (DNMA) off to a strong start. Registered on April 15 this year with the Singapore Registry of Societies, DNMA was officially launched at the inaugural Duke-NUS Fundraising and Graduation Gala Dinner on May 30, 2013. His Excellency President Tony Tan Keng Yam, together with 900 distinguished guests, faculty, staff, graduates and parents marked Duke-NUS' first eight successful years and welcomed its vision for the next lap.

DNMA President (Pro Tem) Dr. Chia Ghim Song congratulated the Class of 2013 on their graduation and immense achievements in surmounting the rigorous four-year curriculum. "This is only the beginning of your journey as the study and practice of medicine is life-long," he said. "To quote Hippocrates, 'Ars longa, vita brevis': the art is long, life is short. Even as you graduate from Duke-NUS, I hope that you will, as I did, bring with you many fond memories marked by enduring friendships and inspiring mentorships by our dedicated faculty. We warmly welcome you as you join our ranks as the Alumni of Duke-NUS, and we look forward to working closely with you as colleagues in the wards."

Besides welcoming the Class of 2013 to the alumni fold, Dr. Chia also recognized the association's first Honorary Member, Mr. Tony Chew, former chairman of the Duke-NUS Governing Board. Mr. Chew was

given this honor in recognition of his extraordinary service to the School and the wider community. As founding chairman from 2005 to 2012, Mr. Chew's strong leadership and vision was instrumental to the School's remarkable growth and accomplishments as well as Duke-NUS' strong reputation as an internationally-acclaimed center for medical education and research.

With goals to facilitate interaction and strengthen ties between the School and its alumni, the association intends to promote the interests of the School and help its members stay connected through various professional, social and community service activities.

President Dr. Chia Ghim Song presents Mr. Tony Chew, the first Honorary Member of DNMA, with a framed stethoscope

Drs. Chia Ghim Song (L) and Bianca Chan (R) from the Class of 2011 flank Vice Dean for Education Prof. Bob Kamei at the 2013 Graduation Celebration and Hooding Ceremony

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Self-Perpetuating Signaling Circuit in Cells May Drive Cancer Spread

A team of international researchers led by Dr. Marc Fivaz from Duke-NUS and Dr. Takanari Inoue from the Johns Hopkins University School of Medicine in the United States has shed some light on the extraordinarily complex process of cell migration.

They showed that cells use a self-perpetuating signaling circuit that allows them to form a front and a back and propel themselves in a particular direction.

The self-perpetuating circuit is analogous to a bank run, which occurs when a large number of customers withdraw their money from a bank due to concerns about the bank's solvency. As more people withdraw their funds, the probability of default increases, prompting more people to withdraw their money, in a kind of positive feedback loop.

This propulsion is the same movement that tumor cells use to invade healthy tissue, so learning more about this signalling network may lead to new therapeutic strategies against cancer and other devastating diseases.

This study, published online in *Molecular Biology for the Cell* on July 15, also highlighted that two important protein components of this signaling circuit, called Ras and PI3K, are often mutated in cancer. This suggests that misregulation of this circuit may increase the invasiveness of cancer cells.

Dr. Marc Fivaz

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Identification of Key Protein Leads to New Leukemia Treatment Testing

A Duke-NUS study led by Associate Professor Ong Sin Tiong has identified ways to inhibit the function of a key protein linked to stem cell-like behavior in terminal-stage chronic myeloid leukemia (CML). This may lead the way to develop drugs to extend the survival of patients.

Previously, tyrosine kinase inhibitor (TKI) drugs revolutionized the treatment of CML as these specifically targeted the abnormal BCR-ABL fusion gene that is characteristic of this blood cancer. However, when CML progresses to its terminal stage, TKIs become ineffective as patients develop drug resistance.

Dr. Sharon Lim and Assoc. Prof. Ong Sin Tiong

Assoc. Prof. Ong, who is a medical oncologist and clinician scientist explains, "TKI therapy is highly effective in chronic phase CML, and enables most patients to survive many years. In contrast, patients with blast crisis CML usually succumb to their disease within one year."

The team recognized that the cluster of cells associated with TKI drug resistance exhibit characteristics of self-renewing stem cells. Subsequently it was proposed that targeting this particular malignant cell population would be effective in treating blast crisis CML. After testing a panel of drugs that inhibit MNK kinase activity, it was found that these inhibitors were effective in preventing blast crisis cells from behaving like cancer stem cells in both in vitro laboratory tests and animal studies.

Assoc. Prof. Ong hopes that the findings from this study will open new research directions in the treatment of blast crisis CML. The study was published in *Proceedings of the National Academy of Science* (PNAS) on June 3rd 2013, with Dr. Sharon Lim, a research fellow at Duke-NUS, as its first author.

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Better Quality of Life for Families Who Rely on Foreign Domestic Workers

A study led by Prof. Truls Ostbye at the Duke Global Health Institute and Asst. Prof. Rahul Malhotra at

Duke-NUS, has found that family caregivers who receive support from a foreign domestic worker report more control over their daily schedule, better health, a stronger financial situation and more family support.

Currently over 50 percent of disabled elderly in Singapore receive some level of support and caregiving from live-in foreign domestic workers. Given Singapore's rapidly aging population and limited use of institutional long term care facilities, the number of live-in foreign domestic workers is likely to increase as families try to cope with caregiving for their older members.

Prof. Truls Ostbye

Asst. Prof. Rahul Malhotra

Study findings highlight the need for more affordable long-term care options for elderly persons in Singapore; the need for more health and safety training for foreign domestic workers; and the need for immigration policies to accommodate the increasing number of foreign elder caregivers in Singapore.

The research, based on data from a survey commissioned by the Ministry of Social and Family Development, Singapore, was funded by an A*STAR infrastructure grant to the Duke-NUS Program in Health Services and Systems Research, and a grant from the Tsao Foundation, Singapore. The study was published in *The Journals of Gerontology* is the first of its kind to document the role and impact of foreign domestic workers in the caregiving of the elderly in Singapore.

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Cardiovascular Risk for Patients with Chronic Kidney Disease

A recent study by a team of international researchers, including Duke-NUS Professor Tazeen Jafar, has explored the link between individuals with chronic kidney disease and how it increases the risk of cardiovascular complications. They recommend changes in the prevention and diagnosis for such individuals and also offer guidance for future research.

Since the association between chronic kidney disease and cardiovascular abnormalities were first discovered in 1836, many subsequent studies have confirmed and extended this finding. As chronic kidney disease progresses, kidney-specific risk factors for cardiovascular events and disease come into play. Yet cardiovascular disease is often underdiagnosed and undertreated in this group of patients, despite treatments of proven usefulness being available.

The researchers recommend that patients with chronic kidney disease should be acknowledged as a group at high risk of cardiovascular events and disease that requires special attention. This should be taken into account when guidelines are developed and research priorities are defined. Trials dedicated to prevention of cardiovascular disease in patients with chronic kidney disease are also urgently needed. They specially advise investigation of preventive strategies in early-stage chronic kidney disease and multifactorial interventions in late-stage chronic kidney disease.

Commenting on the work Prof. Jafar added, “The strong relationship between small reduction in kidney function and high normal levels of urine albumin with cardiovascular disease means that even small changes in these parameters cannot be neglected and warrant prompt recognition and immediate initiation of multifactorial intervention including lifestyle (smoking cessation, increased physical activity and healthy diet) and glucose management (in diabetics), statins, ACE inhibitors, other antihypertensive agents, and aspirin.”

The study was published on May 31 in *A Lancet Series on Global Kidney Disease.*

Prof. Tazeen Jafar

Preventable ‘Lifestyle Diseases’ Costs Pakistan a Hefty Sum

Pakistan’s health systems are unprepared to address the country’s rising rates of non-communicable diseases (NCDs) which are predicted to cost the country almost $296 million annually by 2025. Current trends estimate NCDs may lead to nearly 4 million (3.87 million) people aged 30 – 69 dying prematurely in Pakistan by the same year.

A study led by Professor Tazeen Jafar of Duke-NUS and published in *The Lancet* calls for action to counter this and recommends increasing healthcare spending per head, earmarking funds specifically for preventative policies and services for NCDs (such as increasing tax on sales of cigarettes, and programs promoting healthy eating and exercise), better enforcement and structuring of road safety laws, and improving health workers’ training in delivering care to people with NCDs.

“The burden of non-communicable diseases is very high in Pakistan, and is projected to increase. Immediate interventions are needed urgently, not only from the new government of Pakistan, but also from international donor agencies, who need to reprioritize their portfolios to fund non-communicable diseases and injuries in Pakistan,” emphasized Prof. Jafar.

With interventions in place, a 20% reduction in the number of deaths from NCDs could be possible by 2025. Implementing them would cost only $2 per person per year, a very small amount compared to the estimated costs to Pakistan’s productivity and economy if the NCD epidemic is allowed to continue unchecked.

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DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

VITAL SCIENCE

AUG 2013

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GRANTS AWARDED
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Details of projects awarded to Duke-NUS researchers from April-June 2013

No.	PI	Dept	Project Title (Please click titles for details)	Grant Call	Duration (Months)
1.	Shirish Shenolikar	CVMD	Molecular and genetic dissection of the role of BAG3 and the BAG3 interactome in cardiomyopathy	A*STAR - TCRP 2012	36
2.	Karl Tryggavason	CVMD	Relationship of CTNNB1 and early cardiac progenitors in cardiac fate determination of human pluripotent stem cells	A*STAR - TCRP 2012	36
3.	Goh Liang Kee	CSCB	miRNAs and small RNAs as Potential Biomarkers for the Identification of Cirrhosis and Hepatocellular Carcinoma	A*STAR - TCRP 2012	36
4.	David Virshup	CSCB	Pharmacological manipulation of intestinal stem cells to protect from inflammation and infection	A*STAR - TCRP 2012	36
5.	Helen Zhou Juan	NBD	Multimodal connectome analysis for differentiating subtypes within early-stage dementia and mild cognitive impairment	A*STAR - TCRP 2012	36
6.	Shirish Shenolikar	NBD	Targeting the role of LRRK2 in mitochondrial and protein homeostasis for the development of novel Parkinson's disease therapeutics	A*STAR - TCRP 2012	36
7.	Paul Yen	CVMD	Reverse epigenetics of hyperhomocysteinemia-induced gene expression and cytokine profiles in stroke patients, rodents and human peripheral blood mononuclear cells	A*STAR - TCRP 2012	36

8.	Hyunsoo Shawn Je	NBD	Linking Human and Experimental Genetics to Pinpoint Causes of Autism	A*STAR - TCRP 2012	36
9.	Benjamin Haaland	OCS	Identification of Genetic biomarkers for disease progression in Angle Closure	A*STAR - TCRP 2012	36
10.	Ooi Eng Eong	EID	The role of pre-existing cross-reactive antibodies in determining the efficacy of vaccination in humans	A*STAR - TCRP 2012	36
11.	David Virshup	CSCB	Drug repurposing for the treatment of aggressive myeloid leukaemia	A*STAR - TCRP 2012	36
12.	Steven Rozen	CSCB	Developing a clinically testable biomarker-based predictor for early stage colorectal cancer likely to metastasize	A*STAR - TCRP 2012	36
13.	Antonio Bertoletti	EID	T Cell receptor mediated immune therapy in chronic hepatitis B and hepatocellularcarcinoma	NMRC STaR 2012	60
14.	Chetna Malhotra	HSSR	Impact of advance care planning on end-of-life care for patients with advanced cancer and heart failure : A randomized controlled trial	NMRC TA Nov 2012 Grant Call	36
15.	Paul Yen	CVMD	Hormonal regulation of hepatic lipophagy, beta-oxidation, and gluconeogenesis	NMRC CSA Nov 2012 Grant Call	60
16.	Ong Sin Tiong	CSCB	Overcoming Resistance to Targeted Therapies in Blast Phase Chronic Myelogenous Leukaemia	NMRC CSA Nov 2012 Grant Call	60

Total Amount of Funding Received: $43,496,674.00

Synopsis

1. Molecular and genetic dissection of the role of BAG3 and the BAG3 interactome in cardiomyopathy

Shirish Shenolikar, Cardiovascular & Metabolic Disorders

Heart failure (HF) is a worldwide epidemic with HF hospitalizations increasing 2-fold in the last decade and HF treatments costing tens of billions of dollars every year. Despite considerable investment in HF treatments, one in five HF patients die within a year of diagnosis. Recent genetic studies have robustly identified a new gene, called BAG3, that when mutated causes HF.

In this project we will test the specific hypothesis that that impaired processing of cardiac proteins is mechanistically important in the development of human HF and that the BAG3 protein, which functions as a co-chaperone, which enhances the folding of proteins into the native state and also eliminates mis-folded proteins through a process known as autophagy, is central to this process. We take full advantage of the distinct and complimentary skills of the research team to investigate this hypothesis.

First, we will examine whether BAG3 can modify HF symptoms in a newly developed animal model of HF. Next, we will identify the network of genes that transduce BAG3's functions in the human heart and explore their contributions to HF in a well-studied cohort of patients. Furthermore, we will undertake molecular and cellular studies to establish how BAG3 regulates the cell's physiology.. Finally, we will establish how thyroid hormone, which improves heart function and may prevent HF in some individuals, impacts these cellular processes. Overall this proposal will identify new HF susceptibility genes, which in turn may help to create new medicines for a disease that currently shortens the lives of millions around the world.

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2. Relationship of CTNNB1 and early cardiac progenitors in cardiac fate determination of human pluripotent stem cells

Karl Tryggavason, Cardiovascular & Metabolic Disorders

Pluripotent stem cells (PSCs) are cells capable of differentiating into any tissue cell type in the human body. The ability tocoax human pluripotent stem cells (hPSCs) towards specific cell types is essential for the development of cell therapy of various tissue injuries. One such area is heart disease such as myocardial infarction caused by heart muscle damage. Pluripotent stem cells are known to express high levels of pluripotency-associated genes, but their ability to consistently differentiate into heart muscle cells differs greatly. This has obstructed efforts to generate large amounts of heart muscle cells for clinical use and such uncertainty has become the foremost rate-limiting step in personalized medicine. In this project, the groups of Drs Winston Shim at the National Heart Center and Karl Tryggvason at Duke-NUS plan to investigate the possibility to direct pluripotent stem cells into in cardiac muscle cells that then can beused to repair heart muscle injury.

Patient-derived so-called induced PSC lines are cultured on unique embryonic and heart muscle proteins called laminins, that can support the development of heart muscle cells that, in turn, may be applicable for treatment of heart injury. Of particular interest is to explore the role of CTNNB1, a pluripotency factor, in the differentiation process. The investigators will study DNA and RNA sequencing data obtained from human induced PSC lines with high and low cardiac differentiation efficiency. This work can provide a new understanding of mechanisms that direct pluripotent stem cells towards cardiac differentiation, as well as possibility to develop a method for large-scale production of cardiomyocytes that can be used to treat individuals afflicted with cardiac diseases.

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3. miRNAs and small RNAs as Potential Biomarkers for the Identification of Cirrhosis and Hepatocellular Carcinoma

Goh Liang Kee, Cancer & Stem Cell Biology

Liver cancer or hepatocellular carcinoma (HCC) is amongst the top 5 cancers in Singapore with poor five-year survival of only ~5%. Although there are a lot of research on HCC, translating our knowledge into the clinic as diagnostic kits or therapeutic options remains elusive.

The poor prognosis for HCC patients is mainly due to the late diagnosis of the disease. Current methods to diagnose HCC relies on routine screening of at-risk patients, including those with cirrhosis due to viral hepatitis, by screening serum alpha-fetoprotein (sAFP) levels as well as performing ultrasound of the liver but this combination has limitations as these are not very sensitive since not all tumors produce sAFP. Moreover, these methods usually only identify tumors at advanced stage. Hence, there is an urgent need to identify better, more reliable non-invasive biomarkers with higher sensitivity and specificity for early detection of HCC.

In this proposal, we would like to investigate if a novel class of molecules, namely microRNAs (miRNAs), can serve as useful novel biomarkers to detect HCC at an earlier stage and even to detect individuals with liver cirrhosis. miRNAs are small RNA molecules that can regulate different messenger RNA (mRNAs) so that the levels proteins produced from these mRNAs will be altered. We will employ the current state-of-the-art next-generation sequencing technology to determine the identity and measure the expression of these miRNAs in normal healthy individuals, cirrhotic individuals, HBV chronic carriers, and individuals with HCC. Samples from the same individuals collected longitudinally will be compared to evaluate the robustness of the miRNA biomarker(s) either by themselves or in combination with current biomarkers.

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4. Pharmacological manipulation of intestinal stem cells to protect from inflammation and infection

David Virshup, Cancer & Stem Cell Biology

The human small intestine functions both as an absorptive organ and as an interface with a rich community of commensal flora.The intestinal epithelium is capable of renewing itself every 4-5 days. This incredible state of proliferation is maintained by a population of stem cells that while proliferating differentiate into specialized epithelial cell lineages. One lineage of those differentiated cells, known as Paneth cells, produces antibacterial peptides regulating survival of intestinal microorganisms.

Interestingly, recent studies reveal that Paneth cells are not essential for normal homeostasis of the intestine. This study will investigate how Wnts and intestinal cells interact in response to normal colonization and pathological inflammation. We believe that better understanding of pathways that control epithelial growth and regeneration allows to facilitate healing after gastrointestinal infections and minimize post-infection complications that may include irritable bowel syndrome and cancer.

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5. Multimodal connectome analysis for differentiating subtypes within early-stage dementia and mild cognitive impairment

Helen Zhou Juan, Neuroscience & Behavioral Disorders

The prevalence of dementia is predicted to increase rapidly in Singapore and around the world. While strong effort is in place to identify pharmacological treatment to slow the disease progression, numerous studies have demonstrated that the key to successful treatment of dementia lies in early diagnosis before irreversible brain damage occurs. However, it is difficult to develop clinically and scientifically useful noninvasive neuroimaging biomarkers for early diagnosis and accurate prognosis. Recent work from our group and others has demonstrated that multimodal connectome analysis provides a noninvasive neuroimaging method for detecting specific early network-based neurodegeneration. The connectome is a comprehensive map of neural connections in the brain. The functional connectome, derived from task-free functional magnetic resonance imaging, maps activity synchronization between different neural assemblies. The anatomical connectome, derived from diffusion tensor imaging, measures white matter pathways connecting brain regions within networks.

In this proposal, using neuroimaging and genetic approaches, we aim to study three common types of dementia, including Alzheimer's disease (AD), behavioral variant frontotemporal dementia (bvFTD), and subcortical vascular dementia (SVD). We hypothesize that integrated anatomical and functional connectome assays will prove sensitive to (1) differentiate between early-stage AD, bvFTD, and SVD; and (2) identify amnestic and non-amnestic mild cognitive impairment (MCI) subjects who are at high risk for conversion to dementia. Moreover, we will investigate the relationships between genetic risk factors and connectome assays in AD and amnestic MCI. The proposed studies are the first step toward multimodal neuroimaging assays, seeking knowledge that will translate into clinical and scientifically useful biomarkers for early diagnosis and treatment of dementia.

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6. Targeting the role of LRRK2 in mitochondrial and protein homeostasis for the development of novel Parkinson's disease therapeutics

Shirish Shenolikar, Neuroscience & Behavioral Disorders

Parkinson's disease (PD) is the most common neurodegenerative brain disorder seen at the National Neuroscience Institute (NNI). The gene encoding the Leucine-rich repeat kinase 2 (LRRK2) represents the most prevalent genetic contributor to sporadic and inherited forms of PD.

We are pursuing the hypothesis that abnormal LRRK2 resulting from gene mutations negatively impact the functions of two important cellular organelles, mitochondria and endoplasmic reticulum (ER) in the brain cells. In the long term, we anticipate that this research will greatly aid the development of new and more effective treatments for PD.

Using several different cellular and animal models, our experiments will address how and why mutant

LRRK2 causes mitochondrial and ER malfunction. By studying the molecular processes and pathways in these organelles, we hope identify new therapeutic targets whose pharmacological modulation can protect neurons that die in the PD brain and delay the onset or reduce severity of PD symptoms in patients. As a first step, we will conduct analyses of candidate drugs for their ability reverse or improve the damage to organelles caused by the LRRK2 mutations.

In addition to unraveling important pathophysiologic clues to PD, our proposal can have a major impact on the future development of novel therapeutics against PD based on the enhancement of mitochondrial and ER functions. By bringing together an experienced team of clinical and basic science researchers, this research projects aims to reduce the economic burden of PD in Singapore through development of novel therapies and more cost effective healthcare delivery

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7. Reverse epigenetics of hyperhomocysteinemia-induced gene expression and cytokine profiles in stroke patients, rodents and human peripheral blood mononuclear cells

Paul Yen, Cardiovascular & Metabolic Disorders

Stroke is a common medical condition in Singapore that can have serious consequences in patients. Homocysteine, is an altered form of the amino acid cysteine that is one of the building blocks for proteins. Elevated homocysteine blood levels increase the risk for stroke; moreover, homocysteine levels in the blood are modulated by hereditary and dietary factors. A variant of the methylenetetrahydrofolate reductase (MTHFR) gene is most commonly associated with high homocysteine in the blood. Vitamin supplementation reduces blood homocysteine levels.

Homocysteine, can alter gene activity but little is known about how this occurs. As a team from Duke-NUS and SingHealth, we plan to investigate whether vitamin supplementation affects the changes in gene structure and expression and to understand the underlying reasons for this. We will conduct studies in patients, animal models and in cell cultures. In particular, we plan to examine the effects of high homocysteine, variants of MTHFR, and vitamin supplementation on structural gene changes, gene activities and protein patterns in stroke patients with high homocysteine levels in their blood, mice with high homocysteine levels induced by genetic and dietary effects, and in human cell culture models.. These studies will employ experimental strategies to study gene activity changes due to high homocysteine and reversal of these changes in patients with high homocysteine levels, animal models and cells. These findings will provide evidence on whether it would be beneficial to correct homocysteine levels in patients with high risk of stroke and high homocysteine blood levels due to genetic or dietary causes.

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8. Linking Human and Experimental Genetics to Pinpoint Causes of Autism

Hyunsoo Shawn Je, Neuroscience & Behavioral Disorders

Autism spectrum disorders (ASDs) are a prevalent group of behavioral disorders that pose a major public health burden and that are highly heritable. We sequenced 695 genes in each of 500 ASD patients to identify novel genetic variants that may cause ASDs. We found that the genes that most frequently harbor novel variants in ASDs are disproportionately involved in the processes of neuronal migration and differentiation of neural progenitor cells. We are experimentally investigating one of these identified genes, PCM1 (pericentriolar material 1), using mouse as a model system. We postulate that dysfunction of PCM1 may underlie pathophysiology of ASDs and the loss of PCM1 during early neural development disrupts neural circuit formation and animal behavior. Positive findings would provide strong evidence that PCM1 disruption during early brain development indeed lead to the development of ASDs.

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9. Identification of Genetic biomarkers for disease progression in Angle Closure

Benjamin Haaland, Office of Clinical Sciences

Glaucoma is the leading cause of irreversible blindness worldwide, with primary angle closure glaucoma (PACG) a major form of glaucoma in Singapore and Asia. The disease is classified into three stages: primary angle closure suspects (PACS), primary angle closure (PAC) and PACG. Longitudinal observational studies report progression rates of angle closure from PACS to PAC and/or PACG ranging from 19.4% in 5 years to as high as 33% in 3 years. It is still not known why certain individuals with the disease progress from the early stages to blindness. As laser treatment may prevent PACG from developing, it is important to know which PACS subjects are at greatest risk of progressing to the severe stage of disease. Performing laser in all PACS eyes may not be cost effective as many eyes would probably never develop progressive disease.

Studies have shown that there is a genetic predisposition to developing PACG. Recently, we identified three genes that give risk of having PACG. In this study we plan to test whether these recently identified PACG genes are also involved in progression of disease. Using these genetic biomarkers we may be able to identify subjects at risk for disease and/or progression, and thereby aid in addressing treatment to this group of especially at-risk patients. Furthermore our discoveries on novel genetic risk factors will have potential to influence clinical guidelines for screening and diagnosis of angle closure disease and have a broad impact on public health and health economic.

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10. The role of pre-existing cross-reactive antibodies in determining the efficacy of vaccination in humans

Ooi Eng Eong, Emerging Infectious Diseases

Epidemics of emerging or previously neglected viral diseases are common. Preventing such epidemics would reduce unnecessary illness or death and also the high cost to society, as exemplified by severe acute respiratory syndrome outbreak in 2003. Among the preventive measures, vaccination is perhaps the most cost-effective. However, many people have already exposed to multiple previous vaccinations or natural infections. Antibodies developed following these exposures may, similar to what happens in dengue, cross-react with vaccines to alter their effectiveness. Indeed, at the vaccination site and the lymph nodes that drain the vaccination site are where cells that regulate the immune response aggregate.

These cells are known to express receptors that enable them to engulf antibody-bound vaccines or viruses. The uptake of vaccines by these cells may thus be either inhibited or enhanced when vaccines are bound with cross-reactive antibodies. In view of the limited knowledge on how immune response to vaccination is influenced by cross-reactive antibodies, we propose here a study that exploits the known cross reactivity between antibodies to Japanese encephalitis (JE) virus and yellow fever (YF) vaccine. We hypothesize that cross-reactive JE antibodies impacts antibody response to YF at the point vaccination by altering both uptake of vaccines by the cells of the immune system and their subsequent signaling for antibody production. We will conduct an open label clinical trial on serial vaccination with JE and YF vaccines.

The clinical materials obtained in the trial will drive basic laboratory investigations that determine molecularly how cross-reactive antibody affect vaccination. This proposed study represents one of the first clinical studies examining the role of cross-reactive antibodies in modulating immune responses to vaccines. The findings made in this study could potentially re-shape vaccination strategy where vaccine dosage is tailored to the background heterologous antibody titer of the vaccine for maximal cost-effectiveness.

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11. Drug repurposing for the treatment of aggressive myeloid leukaemia

David Virshup, Cancer & Stem Cell Biology

Since the introduction of targeted drug therapy, the treatment of many leukaemias, such as chronic myeloid leukaemia (CML), has improved tremendously. However these ‘magic bullets’ are not effective in eliminating leukaemia stem cells, especially in the more aggressive myeloid leukaemias. The majority

of CML patients with advanced blast phase disease are resistant to treatment or relapse after an initial response. There are many ongoing research efforts to discover drugs to eradicate these leukaemia stem cells. One strategy is to look for approved drugs that are effective against pathways required for the survival of the leukaemia stem cells and this is the premise of our research. We have identified a FDA-approved drug as a promising compound that can be used to target blast phase-CML stem cells. We will use in vitro and in vivo methods to demonstrate the drug's effect on the leukaemia stem cell. In addition, we will use innovative techniques to understand how the drug works in CML. We hope to translate our research findings into new treatment strategies for CML that will be moved to the clinics. The knowledge gained from our research will also be applied to other forms of leukaemias.

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12. Developing a clinically testable biomarker-based predictor for early stage colorectal cancer likely to metastasize

Steven Rozen, Cancer & Stem Cell Biology

Colorectal Cancer (CRC) is one of the most frequent cancers in the developed world. In Singapore, it is the highest incidence cancer and the second leading cause of cancer death. Early-stage CRC is often curable by surgery alone. Nevertheless, ~25% of early-stage patients succumb to metastasis. Accurate prediction of early-stage CRCs likely to metastasize will identify patients who require chemotherapy to improve odds of long-term disease-free survival. Conversely, patients predicted to remain disease-free will be spared unnecessary costs and serious side-effects. Previously developed predictors for Caucasian populations are not effective for Singaporean patients. We previously published a preliminary gene-expression signature to predict metastasis-prone early-stage CRCs in Singapore Chinese patients. In the study proposed here, we will confirm the validity of this signature by studying gene expression in additional frozen tumor samples; we will also gather targeted genetic data to determine if this improves the predictor.

Frozen tissue samples are not widely used in clinical practice. Consequently, translation to routinely-used formalin-fixed, paraffin-embedded (FFPE) samples is crucial for eventual widespread clinical use of the predictor. Therefore, we will test the biomarker-based predictor on FFPE samples from the tumors that were the sources of the initially studied frozen samples. Finally, we will validate the predictor and biomarker-detection technologies in an additional independent group of 300 FFPE samples, half from early-stage tumors that eventually metastasized and half from tumors that did not. The ultimate goal is development of a biomarker-based predictor that can subsequently be made widely available to improve clinical outcomes

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13. T Cell receptor mediated immune therapy in chronic hepatitis B and hepatocellularcarcinoma

Antonio Bertoletti, Emerging Infectious Diseases

Immunotherapies are increasingly becoming a key component of mainstream clinical practice. In order to reconstitute the defective hepatitis B virus (HBV)-specific T cell immunity characteristic of patients with chronic hepatitis B (CHB), we generated a unique library of T-cell receptors (TCRs) that allow the engineering of TCR-redirected T cells with the capacity to recognize and kill HBV-expressing hepatocytes. We also produced antibodies with specificity identical to the anti-HBV-specific TCRs. We propose to use these novel and promising molecular tools to establish novel therapeutic platforms for personalized immune-based treatment of CHB infection, and of its neoplastic consequence, hepatocellular carcinoma(HCC).

We hypothesize that the efficacy of TCR-mediated therapy is modulated by the quantity and distribution of HBV-expressing normal and transformed hepatocytes and by the state of intrahepatic immunity. Thus, we plan to quantitatively define the expression of HBV antigens in normal and transformed hepatocytes using TCR-like antibodies and to characterize the profile of the intrahepatic immune system in different clinical situations (Aim 1). Based on encouraging preliminary results, we will test the efficacy of new methods to produce TCR-expressing lymphocytes, thus improving the clinical feasibility of TCR-mediated therapy (Aim 2). We have also already initiated a clinical trial of adoptively transferred TCR-redirected T cells in liver transplant patients with HCC metastasis. In this context, we intend to

build an experimental platform to optimize the therapeutic potential of different TCR-mediated therapies (TCR-modified T cells and TCR-like antibodies) (Aim 3). Theoretical and practical knowledge derived from these interconnected aims should significantly move the field of CHB immunotherapy forward and also extend to other areas of infectious diseases and oncology.

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14. Impact of advance care planning on end-of-life care for patients with advanced cancer and heart failure : A randomized controlled trial

Chetna Malhotra, Health Services & Systems Research

Advance care planning (ACP) is considered to be one of the most promising interventions to enable patients with life limiting illnesses to receive treatment at the end of life (EOL) according to their own preferences and to promote EOL conversations between patients and their health care providers. Through a 2-arm randomized controlled trial (RCT) of patients with stage IV cancer and advanced heart failure, we propose to assess (a) Whether patients in the ACP arm have a greater likelihood of receiving EOL care consistent with their preferences as stated in the last ACP document or the last patient interview, compared to patients in the control arm; (b) Heath care costs during study duration between patients in ACP and control arms; (c) Patient's understanding of own illness and their participation in decision making between the ACP and control arms; and (d) Patient's quality of life, anxiety and depression between ACP and control arms. Patients will be randomized to receive intervention (ACP arm; N=127) or usual care (control arm; N=127). Patients in both arms will be followed for one year or till death, whichever is earlier, and interviewed every 4 months during this duration. If benefits of ACP are confirmed through this trial, then it will help to promote acceptance of ACP among patients and health care providers across Singapore and elsewhere.

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15. Hormonal regulation of hepatic lipophagy, beta-oxidation, and gluconeogenesis

Paul Yen, Cardiovascular & Metabolic Disorders

Non-alcoholic fatty liver disease (NAFLD) frequently occurs in obesity and diabetes, and its incidence has been rapidly increasing throughout the world, including Singapore. NAFLD represents a grouop of liver diseases that initially starts with fat accumulation in the liver that can progress to fibrosis and liver failure. Moreover, NAFLD is commonly accompanied by abnormal liver glucose production. Currently, little is known about how these processes occur and they are regulated by various hormones in NAFLD.

Recently, we found that thyroid hormone (TH), epinephrine, and caffeine stimulate hepatic autophagy, a process by which intracellular substrates are engulfed by autophagosomes and are digested in autolysosomes after their fusion with lysosomes.. We observed that lipids from fat droplets are incorporated into autophagomes that later fuse with lysosomes (lipophagy). Triglycerides are broken down into fatty acids that are metabolized in the mitochondria. Lipophagy is important for fatty acid metabolism since defects in autophagy defects lead to fat accumulation in the liver and NAFLD. TH also stimulates transcription of the two key gluconeogenic genes involved in liver glucose production from proteins We recently found that TH surprisingly increases SIRT1 enzyme expression resulting in the removal of a carbon group from a gene regulator, FOX01 leading to its activation. In this proposal, we will study the effects of different hormones on fatty acid metabolism and liver glucose production under normal as well as diabetic/obese conditions. These studies will look at molecular and physiological changes in liver cells and animal models.

We expect that better understanding of hormone regulation of lipophagy/fatty acid metabolism and glucose production in the liver will help identify novel drug and hormone targets for the treatment of NAFLD, a condition for which there currently is no proven effective drug therapy. Furthermore, detailed understanding of these processes in NAFLD will improve early detection and management of NAFLD.

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16. Overcoming Resistance to Targeted Therapies in Blast Phase Chronic Myelogenous Leukaemia

Ong Sin Tiong, Cancer & Stem Cell Biology

Early stage chronic myelogenous leukemia (CML) responds well to tyrosine kinase inhibitors (TKI) targeting the oncogenic BCR-ABL kinase, while TKI resistance causes late stage blast crisis (BC) CML to be uniformly fatal. The long-term goal of this project is to develop new drugs that prolong the survival of patients with BC CML. BC is characterized by elevated b-catenin signaling in granulocyte macrophage progenitors, which enables this population to self-renew and function as leukaemia stem cells (LSC), and act as a reservoir for resistance. Specifically, we recently identified a MNK-eIF4E axis that activates the b-catenin-driven self-renewal program in BC LSCs but not normal haematopoietic stem cells. Importantly, we find that small molecule MNK kinase inhibitors can overcome TKI resistance and extinguish the self-renewal capacity of BC LSCs. In collaboration with the Experimental Therapeutics Centre, we will develop novel MNK inhibitors to target BC CML in patients.

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