VITAL SCIENCE

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Duke-NUS in Singapore's Translational Medicine Ecosystem

Assoc. Prof. Ooi Eng Eong

Ten years after Singapore announced the Biomedical Sciences Initiative and the vision of being a translational science hub, the term bench-to-bedside has become more than a catchphrase. It is now an expected key performance indicator for government, education, healthcare and research institutions.

Institutional targets and personal ambitions aside, translational medicine makes sense. It is based on the idea that research targeted at treating patients is worth funding because it ultimately makes a positive impact on healthcare delivery.

Four inspiring Duke-NUS trailblazers share the important collaborations that they have been working on at Duke-NUS and beyond – projects that have taken basic concepts to clinical implementation in a few short years.

A SMARTer Way to Fight Dengue

The Singapore-MIT Alliance for Research and Technology (SMART) is a major research enterprise set up in 2007 by the Massachusetts Institute of Technology (MIT) and the Singapore National Research Foundation (NRF). For Associate Professor Ooi Eng Eong, this alliance has led to collaborations, among which is one with MIT Professor Ram Sasisekharan and Dr. Jenny Low in Singapore General Hospital (SGH), for a new dengue therapeutic to start clinical trials late next year or early 2016.

When SMART was set up, dengue was not one of the areas of focus of the Infectious Disease Interdisciplinary Research Group (ID-IRG). However, it became clear very quickly that the technologies developed in the ID-IRG were able to address questions on dengue in unique ways. In 2009, the ID-IRG shifted its focus to include dengue. Assoc. Prof. Ooi jointly heads the dengue program at SMART with MIT Professor Jianzhu Chen.

Concurrently, as Deputy Director of the Emerging Infectious Disease Program (EID) at Duke-NUS, Assoc. Prof. Ooi and his team uncovered the mechanism that dengue uses to circumvent the immune system, causing a more serious infection when an individual is infected with a different strain of dengue. Separately in MIT, Prof. Sasisekharan examined dengue to see if it was possible to engineer an antibody that recognizes all four strains of dengue and thus be useful as a therapeutic.

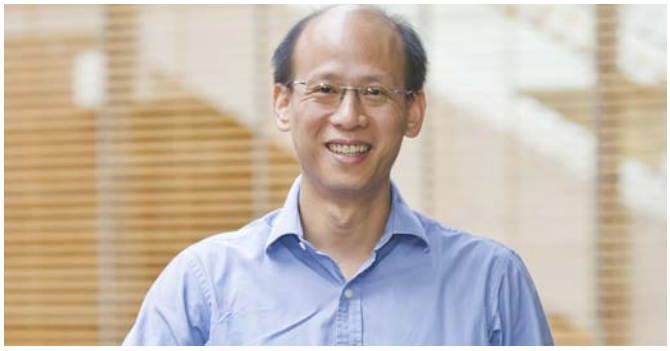
With SMART as 'matchmaker', Profs. Sasisekaran and Ooi found a perfect union in their respective research. To make the translation from laboratory to the clinics, Prof. Sasisekharan founded Visterra with a vision to bridge the MIT area ecosystem in Cambridge with that of Singapore. Visterra has since established Visterra Singapore International Pte Ltd, which will spearhead the development of this dengue therapeutic through clinical trials to eventual marketing. Singapore will be in the lead for all clinical development stages of this therapeutic.

Assoc. Prof. Ooi, who will extend his advisory role in the new collaboration with Visterra Singapore International, aims to chart a pathway for the development of other viral pathogen therapeutics in Singapore. He said, "It is exciting because it may help people who want to develop therapies to combat viruses and put in place the necessary infrastructure to make translational science possible. We can show people where to draw on the expertise they need, get appropriate funding and communicate with the public on such issues." In July 2014, Duke-NUS Dean, Professor Ranga Krishnan signed a Memorandum of Understanding between Duke-NUS and Visterra. This project will involve the initial evaluation, clinical evaluation and hopefully the approval of the drug within Singapore.

Making Experimental Therapeutics for Cancer a Reality

A*STAR's Experimental Therapeutics Centre (ETC) develops therapeutics based on novel biological hypotheses. However, it is not novelty that motivates ETC to start a new drug discovery effort; projects are pursued when strong

Prof. David Virshup



Assoc. Prof. Ong Sin Tiong

rationale supports the notion that a new experimental drug truly has the potential to significantly improve patient's lives. One of the first such translational projects taken on by ETC was proposed by Professor David Virshup, Director of the Program in Cancer and Stem Cell Biology (CSCB) at Duke-NUS. Since 2008, Prof. Virshup's lab has worked with a team at ETC to develop drugs to inhibit the Wnt signaling pathway to target cancer.

Wnt is a type of signaling protein that, when activated, plays an important role in normal growth and development. Excessive Wnt signaling can result in cancer. Important basic research into how Wnt is activated provided the foundation for developing targeted therapies to stop Wnt. Developing targeted therapies is a modern "paradigm shift" that many researchers now follow to discover more effective and less toxic treatments for cancer.

Taking the idea to ETC resulted in what Prof. Virshup refers to as a 50/50 partnership - with Duke-NUS contributing the domain expertise while drug development is carried out by ETC. By openly sharing information and experimental data, the collaboration has developed a promising drug that is in preclinical testing. Funding for this portion of the project came from ETC through A*STAR'S D3 platform.

"Singapore gave me the opportunity to turn this idea into a reality," said Prof. Virshup. "Because we have collaborators like ETC that consider investing in academic institutions, it is possible to do truly significant research here. I am honored and pleased to have had the Wnt project from our group at Duke-NUS chosen as one of ETC's first projects." Going forward, Prof. Virshup and his team are ready for the next stage; supporting clinical trials at the National Cancer Centre Singapore (NCCS) and the National University Hospital (NUHS).

Addressing Unmet Medical Needs with ETC

Six years ago, Associate Professor Ong Sin Tiong and Dr. Sharon Lim from the CSCB program at Duke-NUS identified the MNK protein as an important contributor to the aggressive behaviour of 'blast phase' (BP) cells in chronic myeloid leukaemia (CML).

CML is a blood cancer that has seen a great improvement in treatment outcomes following the introduction of tyrosine kinase inhibitor (TKI) drugs that specifically target the BCR-ABL gene, a genetic abnormality that is characteristic of CML. However, patients with BP CML, which consists of 5 to 10 percent of those with CML, invariably develop resistance to TKIs. Eventually, this resistance results in the death of almost all patients with BP within a year. Furthermore, since there are very few clinical trials that employ novel drugs against BP CML, BP therapy is a major unmet medical need.

When Assoc. Prof. Ong's team discovered the importance of the MNK kinase in BP CML, they proposed targeting MNK as a novel way to treat BP CML. Since ETC had the expertise to develop novel and potent MNK inhibitors, the team collaborated with the Centre to turn such treatment into reality. Together with a group led by Drs. Jeff Hill and Kassoum Nacro at ETC, Assoc. Prof. Ong and his team have now identified highly potent MNK inhibitors that are effective against BP cells in the test tube and in animal models of BP.

"Currently, we have identified several drug candidates with dual inhibitory activity against MNK and BCR-ABL," said Assoc. Prof. Ong. "Once this stage is complete, we will seek approval from regulatory agencies to begin clinical trials in humans. If all goes to plan, we estimate that such studies will begin in 2015 at the Singapore General Hospital." Assoc. Prof. Ong will undertake the next phase with Asst. Prof. Charles Chuah, a Senior Consultant in SGH's Department of Hematology. Dr. Chuah is also the lead clinician for CML at SGH, and holds an appointment at the CSCB program in Duke-NUS.

POLARIS: Making Clinical Implementation Possible

The idea that an individual's genetic makeup may hold the key to that person's health, and how one is treated, is becoming a reality. Professor Patrick Tan, recently appointed Associate Director of Genomic Medicine at the Genome Institute of Singapore (GIS) has said that, "Medicine is on the cusp of a revolution where genetic information is going to be a standard part of the patient's medical record in the near future."

For the past 10 years, Prof. Tan has held a joint appointment as a Professor in Duke-NUS' CSCB and at A*STAR's GIS. GIS focuses on the intersection of genomics, cell biology and medicine, taking advantage of the regional Asian population to achieve genomic discoveries.

Prof. Tan believes that his new role as Associate Director in GIS reflects the promise of genomic medicine as way to translate knowledge into clinical outcomes. Understanding a person's genomic code may make it possible to prescribe personalized treatments, test the likelihood of disease development, and ascertain familial risk of certain conditions so as to better prevent and treat disease. The work at GIS has the potential for improving outcomes for individual patients, both in terms of quality of life and financial cost.

According to Prof. Tan, a new effort will take genomic research further into the clinic for the benefit of Singapore's patients. Prof. Tan is Program Director of POLARIS (Personalized OMIC Lattice for Advanced Research and Improving Stratification), a consortium focused on diagnostics and the genomic stratification

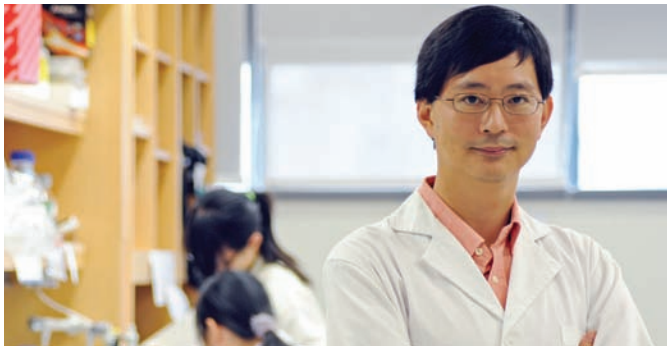
of patients so as to develop more effective development of targeted therapeutics. POLARIS will leverage exisiting omic (genomics, proteomics, and metabolomics) information and research infrastructure already present in Singapore to consolidate expertise and solve problems. It brings together research giants such as A*STAR's GIS and Bioprocessing Technology Institute and SGH Pathology, NUHS, NCCS and the Singapore National Eye Centre (SNEC).

POLARIS is in the midst of taking techniques and tools beyond the laboratory into the clinical realm by setting up the POLARIS @ GIS and POLARIS @ SingHealth labs, and aims to apply for the labs' College of American Pathologist's (CAP) accreditation by next year. CAP accreditation will ensure that a standard of excellence while running parallel activities and sharing processes.

POLARIS has already recorded three successful clinical implementation projects:

- The development and introduction of the POLARIS™ TGFBI (Transforming Growth Factor beta-Induced) test. This aids in the diagnosis and management of Stromal Corneal Dystrophies (CDs) by measuring the gene in patients. Contributing parties to the POLARISTMTGFBI genetic test include SNEC, Singapore Eye Research Institute (SERI), SGH, NUHS and GIS.

- Assessing a test that identifies variations in the BIM gene to pick out people who cannot respond to TKI treatments. This will enable better outcomes for clinical trials and add to the body of knowledge surrounding Asian genetic variations. The test is based on work by Assoc. Prof. Ong Sin Tiong from Duke-NUS and SGH is a contributing party to this research.



Prof. Patrick Tan

- A Cancer Gene Panel that builds on the work of Prof. Tan, as well as Professors Teh Bin Tean and Steve Rozen from NCCS and Duke-NUS respectively, along with other NCCS collaborators. They are working on discovering gene mutations present in gastric, bile duct, breast cancers and more. The studies done at the institutions will be used to aid in the diagnosis of these cancers.

Collaboration Empowers Clinical Solutions

The value of collaboration is clearly evident as a critical factor in shaping the future of clinical research. It is often stated that collaboration in science is essential, and it certainly appears all the more relevant in Singapore as its biomedical ecosystem continues to thrive on it. Clearly, this synergy is enabled not only through close geographic proximity but also through an abiding willingness by researchers and their respective institutions to bring multiple disciplines together in order to answer some of society's most pertinent clinical problems. ■

Nurturing Next-Gen Scientists

Assoc. Prof. Silke Vogel

Just four years old, Duke-NUS' signature PhD program has graduated its first students and to date, students have authored a total of 30 research publications. Associate Dean Silke Vogel, shares the challenges and successes faced thus far.

First launched in 2010 with 11 students in its inaugural class, the Duke-NUS PhD program in Integrated Biology and Medicine (IBM) now counts 58 students in its ranks, including 39 PhD and 19 MD/PhD students. Associate Professor Silke Vogel, Associate Dean, Graduate Studies, said, "The program has made great progress and has become highly sought-after and competitive. Each year, only about 12 to 15 students enter the program out of a pool of around 100 applicants." With eight of its inaugural cohort expected to graduate by January 2015, the program will have an average of 10 to 12 students graduating annually in the coming years.

Making an Impact Through Science

According to Assoc. Prof. Vogel, the program has compared well to other similar programs elsewhere. "Our students come from diverse backgrounds in science and professional experiences, enriching our classrooms and laboratories. Importantly, our students are publishing their work in internationally reputable journals," she said.

Assoc. Prof. Vogel noted that, unlike more traditional programs, the IBM program is centered on research in disease areas with less coursework. In the initial phase of the program, students complete three research rotations to identify their thesis mentor. "The first-year foundation class, 'Molecules to Medicines'- provides the incoming students with a primer in biochemistry and an overview of the research themes found in our Signature Research Programs (SRPs)," she explained. "Once students select their research setting, they take two additional classes specific to their SRP. A key to the success of our students is that they are self-motivated, and immerse themselves completely in their research projects."

Neo Shu Hui (left) and Asst. Prof. Itahana Koji (right) doing a forest adventure activity (Ziptrek) at Whistler, in Canada, after attending a conference in March 2014

Prof. Shirish Shenolikar

Prof. Patrick Casey

It was this unique program structure that appealed to Neo Shu Hui, a recent graduate from the program. She said, "I was drawn to the core curriculum, Molecules to Medicines, which encourages collaborative group learning and is different from the usual lectures and tutorials held in other schools." She also found that the lab rotations offered important exposure. "I think lab rotations are essential to make sure that we choose the most ideal field to study and allow us to explore areas that we may never have thought of having interest in."

A Focus on Translational Science

The Duke-NUS PhD program offers five signature research areas: Cancer and Stem Cell Biology, Emerging Infectious Diseases, Cardiovascular and Metabolic Disorders, Neuroscience and Behavioral Disorders and Health Services and Systems Research. It takes an average of four to five years to complete the degree and culminates with the development of a written thesis and a successful oral dissertation defense. One distinctive feature of the program is that it emphasizes training in translational bioscience and prepares researchers to take their research findings from bench to bedside. This is reflected in both the name of the PhD program 'Integrated Biology and Medicine' as well as the foundational 'Molecules to Medicines' course.

"Another key feature is the larger proportion of MD/PhDs", said Prof. Shirish Shenolikar, who co-developed the Duke-NUS PhD program with Prof. Patrick Casey, Senior Vice Dean for Research. "Our mandate in developing the IBM training program was to focus a little more on developing MD/PhDs so that we could build more bench-to-bedside partnerships in the future and ensure that PhDs mingled with MD/PhDs to acquire a translational perspective that would be critical to drive biomedical research in Singapore in 21st century." Prof. Shenolikar noted that typically, MD/PhDs form a very small proportion of the PhD pool (at around six to eight per cent in the best US-based programs).

"We wanted to train more clinician scientists but we also wanted a different training experience. So we aimed at doing something that no other US medical school has done, which was to increase the ratio of MD/PhDs to 25 per cent of each class. And we achieved this in the very first year." Having more MD/PhDs in a PhD class "changes the conversation", he said, from one that is more academic to one that is more medicine-centric. "Together with the team-based learning approach that is another unique feature of Duke-NUS medical education, the Duke-NUS PhD program is truly unique," said Prof. Shenolikar. "It forges the connections that will promote better communications across the research community when our students become principal investigators and clinician scientists."

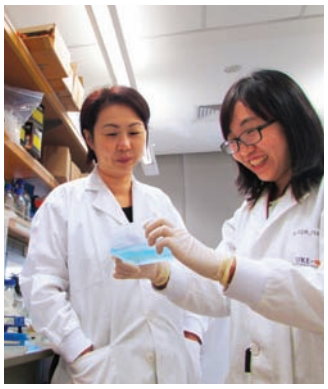
"This culture of collaborations is already seeing good outcomes," said Prof. Casey, who noted that it was also encouraging to see Duke-NUS PhD students taking ownership and being the intellectual driving force for projects, research and papers. "Though they still require a level of mentorship, the students in the program are making contributions in their own right and we are seeing discoveries emerging from our labs that would not have been possible without the work of our PhD students."

"Partly, this is driven by the ethos of mentorship and the culture of support that is a particular feature of Duke-NUS academic life," said Prof. Casey. "We are a community that prizes collaborations, and it is heartening to see the PhD students coming up with the collaborations and embarking on these research projects together."

A Community of Support

"To support the students in the challenging journey towards a PhD, the program offers a supportive and communal environment", said Assoc. Prof. Vogel. "We believe providing students with a supportive community really helps." While each student is expected to be self-motivated to go through the program and commit to the work, each student has not only a thesis mentor but also an advisory committee that supports the students. The journey is not easy, acknowledged Assoc. Prof. Vogel. "Students need to handle failure well, because research is not always a straight path from A to B. Students have to constantly solve problems, roll with failure or success and keep thinking about and revising their hypotheses. The mentor is there to guide and offer support." A mandatory weekly student research seminar is also held so that students can share ideas, ask for help and connect with other students. "Seeing they are not alone in their struggle will help them all get through it," said Prof. Vogel.

Melissa Wirawan from the Emerging Infectious Diseases Program, Emerging Infectious Diseases, whose mentor Associate Professor Lok Sheemei is a recipient of the prestigious National Research Foundation Fellowship, said she joined the program to 'do good science' – solve puzzles, troubleshoot, and make new discoveries. "I was impressed by how enthusiastic all the principal investigators are about their research and on training students to carry on their work in the field," she said. And though the learning curve has been steep, help and support has always been close at hand. "Prof. Lok is always full of new ideas on what other questions we can try to answer and at the same time supportive and patient enough to guide me in designing experiments to answer them."



Melissa Wirawan (right) showing Dr. Lok Shee Mei (left) her findings

Catherine Goh (left) and Prof. Shirish Shenolikar (right)

Success from failure

Other students highlighted that peer support and the challenging process of discovery and learning, as well as the rewarding journey, were key features of their years in the program. “The most challenging part of a PhD is probably figuring out how science works,” said Catherine Goh, a recent graduate from the program. “Figuring out the science entails asking the right questions, designing experiments, interpreting results, and doing the actual experiments. “In time, you learn, from talking to others, from reading papers, even from student seminars,” she shared. Catherine, whose previous work experience was centered on the development of drugs for neurodegenerative disorders, joined the Neuroscience and Behavioral Disorders program under the guidance of Prof. Shenolikar with the goal to make a difference.

Vera Goh, who is in the Cardiovascular and Metabolic Disorders program, cites perseverance and learning from failure as important in her own PhD pursuit. “I've hit many dead ends, but each one has given me new insights into how to further disentangle a difficult question.” Her peer, Benjamin Farah, who is in the same signature research program, said of facing each obstacle: “I remember that a PhD is a marathon, not a sprint. If something is important, there's always time to do it.” ■

Vera Goh and Assoc. Prof. David Silver

Benjamin Farah (left) and Assoc. Prof. Paul Yen (right)

Rubbing shoulders with scientific giants

By Sheila Soh

Sheila Soh and her mentor Assoc. Prof. Ong Sin Tiong

Sheila and Prof. Elizabeth Blackburn (right) at one of the dinners during the meeting

PhD student Sheila Soh had the chance of a lifetime to attend the 64th Lindau Nobel Laureate Meeting earlier this year, where she was immersed in a world of learning, science and passion for research. She shares her experience with Vital Science.

From 29 June to 4 July this year, I had the honor of attending the 64th Lindau Nobel Laureate Meeting with 600 other young scientists. This year’s theme was Physiology and Medicine. The week-long program included a daily panel discussion with topics ranging from women in science to challenges for the clinician scientist. These were followed by a series of plenary lectures given the Nobel laureates. I got to hear German virologist, Harald zur Hausen talk about his ongoing project of uncovering oncogenic viruses in meat as well as American cell biologist, Randy Schekman who spoke out against the tyranny of the editorial process and overemphasis on impact factor in a scientific career. The lecture series concluded with a speech from American geneticist, Oliver Smithies who shared humorous anecdotes about his journey in science in his talk, ‘Where Do Ideas Come From?’. We spent the afternoons in smaller groups to attend discussions conducted by the laureates.

I am deeply grateful for the opportunity to attend such a unique meeting where I got to meet many other young scientists from all over the world. I could feel the passion that the laureates had for their research and the curiosity with which they approached the world. Their talks were peppered with pieces of advice on our scientific career. For example, the importance of finding a good mentor, of working on a problem that was important and that you were interested in, and of not giving up if you believe your data. To prove his point, Australian physician, Barry Marshall showed us rejection letters from conferences to which he first submitted abstracts on data showing the link between H.pylori (Helicobacter pylori) infections to ulcers.

I am indebted to Assoc. Prof. Silke Vogel, for encouraging us PhD students to apply for the meeting, my mentor Assoc. Prof. Ong Sin Tiong for writing a recommendation letter for me at short notice, as well as Duke-NUS and the National Research Foundation for sponsoring my trip.

About the Lindau Noel Laureate Meetings

The Lindau Nobel Laureate meeting began in 1951 under the patronage of the Bernadotte family (members of Swedish royalty) as an initiative to foster interactions between German students and Nobel laureates. The annual scientific conference held in Lindau, Germany, has since expanded to include young scientists from more than 70 countries to promote scientific exchange and inspiration; with the yearly meetings rotating between the three Nobel science prizes - chemistry, physics, and physiology/medicine.

Regulatory Leadership and Excellence Gets a Boost

The "CoRE" members at the launch of Centre of Regulatory Excellence (CoRE). (L-R) Executive Director of CoRE, Assoc. Prof. John Lim, Dean Ranga Krishnan, Advisory Board Chairman Prof. Sir Alasdair Breckenridge and Deputy Director Silke Vogel

This November, a new Centre of Regulatory Excellence (CoRE) to promote regulatory leadership, policy innovation in regulatory science and scientific excellence has been set up at the Duke-NUS Graduate Medical School Singapore. The Centre will support the fast growing biomedical sciences industry in Asia and the wider Asia-Pacific.

Enhancing Biomedical Regulatory Expertise

The biomedical and life sciences sectors have been rapidly developing across Asia, both in terms of clinical trials as well as biomedical research. While this presents opportunities, there continues to be a shortage of regulatory expertise and supporting systems to facilitate regulatory policy innovation addressing regional issues and diverse regulatory requirements. These challenges may compromise the development of and timely access to quality therapeutic products for patients.

Singapore aims to address these issues by establishing a Centre in an academic setting to develop strong regulatory capabilities and advance thinking and practice in regulatory capabilities and regulatory innovation. Through enabling and promoting discussion around regulatory processes, a better environment can be created for the development, commercialization and accessibility of new healthcare products to meet the needs of Asian populations.

"The Centre is the first dedicated pan-Asian Centre for regulatory excellence targeted at the needs of both national health regulators and the biomedical industry, including pharmaceutical and medical device companies," said Duke-NUS Dean, Professor Ranga Krishnan.

Leveraging on the Duke-NUS e-learning platforms and infrastructure, the Centre will develop programs with a focus on establishing competencies and building leadership capacity amongst senior staff and executives, across the biopharmaceuticals, medical devices and consumer healthcare industries. This is part of a multi-pronged strategy to promote regulatory excellence on a regional level.

The Centre will also organize executive workshops and scientific seminars to stimulate ideas and discussion on key issues and topics across the regulatory landscape in Asia. These include the regulation of mobile health applications, adaptive licensing for expedited approvals, and personalised medicines.

CoRE is supported by Singapore's Ministry of Health (MOH), Health Sciences Authority (HSA) and the Economic Development Board (EDB).

It is led by Executive Director, Associate Professor John Lim, concurrently MOH's Deputy Director of Medical Services for Industry & Research Matters and the former CEO of HSA. An Advisory Board comprising key leaders with experience in regulatory agencies, industry and academia has been assembled to provide longer term strategic guidance for the Centre.

"Regulation must follow science and where science proceeds apace, regulation may find it difficult to keep up. Thus, the creation of the CoRE in Singapore is both timely and opportune. It will offer a facility where the benefits of modern regulatory science can be debated and applied regionally. It is a great privilege to be part of this ground breaking venture whose real beneficiaries will be patients and the public health," said Advisory Board Chairman, Professor Sir Alasdair Breckenridge.

Said Assoc. Prof. John Lim, "CoRE will take on the broader role and responsibility to develop regulatory leaders and promote regulatory innovation in Singapore and across Asia. This will help to consolidate and advance the region's significant biomedical and life-sciences initiatives."

Kevin Lai, Executive Director of Biomedical Sciences, Singapore Economic Development Board (EDB) said, "CoRE is a strategic platform where industry and regulators will be brought together to enhance regulatory know-how and promote best practices in the region. With the increasing interest among global biomedical companies in Singapore as their regional headquarters in Asia, CoRE will help to build a pipeline of regulatory talent to support the growth of industry and Asia's healthcare needs."

Forging Greater Collaboration

The new Centre will also link Duke-NUS initiatives in Singapore back to Duke University's Translational Medicine Institute (DTMI) in USA – a centre where the clinical and translational research community comes together.

Duke-NUS Dean Ranga Krishnan explained: "DTMI has established a long-standing relationship amongst regulators, academics, industry, patients and agencies, and offers educational, research and training opportunities and programs for larger policy-making. This will be the start of a strong and productive partnership." ■

Keeping SCORE: Anatomy of a Right-Siting Program

By Qasim Hussaini

Qasim Hussaini, second-year Duke-NUS medical student

The first time I heard the word right-siting, I acknowledged it with a knowing nod, scribbled it in my notebook and continued with our conversation on reducing post-cardiac mortality. It was only a few seconds later I realized I actually had no idea what it meant. "Excuse me Professor…uhh….*right-siting* you said?"

And so I learned. The term literally meant channeling a patient's care in the right direction. It has been increasingly used in Singapore in the past decade to describe efforts to transfer the management of care from a specialist to a primary care setting for patients with chronic disease. More recently, it has been piloted by the National Heart Centre Singapore (NHCS) to provide a more streamlined continuum of care to its patients.

With the primary objective of promoting faster right-siting of stable patients and empowering them with tools that make them less reliant on acute hospital care, NHCS initiated the *Standardized Care for Optimal Outcomes, Right-Siting and rapid Re-Evaluation* program, or SCORE in short, in September 2011. The need for SCORE arose due to an over-burdening of the system by patients that could potentially be discharged to make way for others.

Initially begun as a quality improvement program at NHCS, the SCORE program offers a helpful peek inside a right-siting program and its preliminary success so far in achieving its goals.

In designing the program, NHCS aimed to improve the quality of care offered to patients yet have measurable outcomes to study the impact of their intervention. Initially, this translated into targeting a small subset of low-risk patients that underwent the percutaneous coronary intervention (PCI), a non-surgical procedure that treats narrowed arteries of the heart. As more funding became available, the study group was expanded to include patients with acute coronary syndrome (ACS) that covers a range of heart-related clinical presentations.

In SCORE, early engagement with the identified patient is accomplished on the ward floors itself. A nurse coordinator will meet to reinforce compliance to medication, discuss lifestyle changes, educate on symptoms, and refer to cardiac rehabilitation if needed. Over the following year of attachment to a primary care physician, the same nurse coordinator will make regular phone calls to reinforce education, titrate statins or stop dual anti-platelet medication (total 3 phone calls over a year). Specialist Outpatient Clinic (SOC) visits are scheduled at 3 and 6 months following which the patient is discharged into primary care for lipid, blood pressure or sugar control. Test results from regular visits are automatically uploaded to the SCORE server. In the unfortunate event that symptoms recur, the patient may be scheduled in for an early SOC visit or Accident and Emergency (A&E) if need be.

During my time meeting with the SCORE team and nurse coordinators, one thought echoed almost unanimously were the benefits of having a helpful IT system for identifying patients, planning management and measuring outcomes over time. Potential patients that may benefit from the program are seamlessly identified using a database that accounts for the patient's left ventricular ejection fraction, or a previous history of a PCI, acute myocardial infarction (AMI) or coronary artery bypass graft. Current exclusion criteria include a prior history of AMI or any further scheduled PCI. Information gained during active follow-up with patients are directly entered into the computer including blood results, LDL (Low-density lipoprotein) or HbA1c (glycated hemoglobin) from the respective primary care providers.

Currently in its third year, preliminary results from SCORE have been promising. "Right-siting" appears much more effective under SCORE and there is evidence of an encouraging reduction in LDL levels. As more data is analyzed and interpreted, the SCORE team is hopeful the numbers hold. As it continues to grow and right-site patients, the team is hopeful the program could also be expanded to Malay-speaking populations. On this front, obtaining additional manpower and nurse training is a current constraint to the program. Convincing physicians to discharge patients into the program is the other.

The SCORE team has emphasized that their results would not be possible without the strong support of the SingHealth Delivering-On-Target (DOT) program. An already established right-siting program, DOT has been instrumental to SCORE in successfully building their program and working with patients. At Duke-NUS, the Health Services & Systems Research (HSSR) program is working with SCORE on proposal development, follow-up surveys, and data analysis.

If the success of SCORE continues to hold in its measurable outcomes and possibly a more efficient allocation of finite services and resources, it provides a model of care and follow-up that could be studied and replicated elsewhere within Singapore and its network of healthcare providers.

Qasim Hussaini is a graduate of Johns Hopkins University with a Master's degree in Biotechnology/Regulatory Affairs. He completed his graduate work in neuroscience at the Johns Hopkins School of Medicine and the Mayo Clinic. Presently a second-year Duke-NUS M.D. student from the Class of 2017, he is mentored by Professor David Matchar, Director of the Health Services and Systems Research Program at Duke-NUS. ■

Looking Back on My Three Years

By Edwin Yang

Third-year MD student and second-time Class President, Edwin reflects on his journey through medical school, from being lost at "sea", finding his stride and being buoyed by the joys, challenges and rewards of learning and doing medicine.

MD Program Year 1 – TeamLEADs and the Never Ending Tests

I last recalled writing an article at the end of my first semester at Duke-NUS about life as a first-year medical student and here I am, in my third year, penning down my thoughts again. I can't help but be amazed at the journey that I've survived and how much I have learnt since joining medical school. Truly, the metaphor, drinking from a fire hydrant, has been apt since – that feeling of being overwhelmed and lost in the sea of information. My advice to my juniors: don't give up even on the bad days because all of us will have them (and many of them in fact). What matters is that you pick yourself up and learn from your mistakes and deficiencies. Also learn from your team members because that's what Duke-NUS is all about – team-based learning. You'll find this useful in real life and when you do your ward rotations.

MS 2 – "The Clinical Year" Sink or Swim

Year Two is perhaps the best time to be a medical student because you get to apply the material taught in first year. Unlike Year One when most of the information is already included in patient scenarios, you have to skillfully navigate past language barriers and simultaneously build rapport with patients in the clinics and wards, so as to obtain the information needed to aid in diagnosis and management plans. The more engaged you are, the more fulfilling a time you will have and the more you can glean from the clinical experience. Being able to function as part of the medical team and affect patient care, even as a medical student is definitely something that lifts me up and gives me energy even after a tiring day.

MS 3 - A Year of Independence

Having just completed my USMLE (United States Medical Licensing Examination) Step 1 examinations, I urge my juniors to pursue research topics for which they are passionate about. Use the first two years to discover what ignites your excitement. Being able to do research in your area of interest and future choice of residency is a bonus and I think that your passion and research interests should be the guiding principle in choosing a research topic. Try speaking to potential research mentors early and decide if their projects are of interest to you.

As our class embarks on advanced clinical rotations early, prior to our research (the first class to do so!), I become even more aware that being in third year is indeed a different experience. The expectations in the wards have shifted from simple history taking and physical examinations and we now essentially function as doctors: talking about how to care for patients; developing clinical diagnostic criterion and presenting these cases on morning rounds like the junior medical staff.

Having the privileged to be elected again as the Class President, I hope that I can make a difference and champion causes that matter, and give Duke-NUS – still a 'young' medical school – a voice. In the same way, I hope that you, my fellow medical students, can be the change you wish to see. What better way is there than to step forward, suggest solutions to problems and propose new ideas to make the school a better learning environment?

Despite the rigors of medical training, remember to have hobbies (and a life) outside of medicine. And beyond seeing one another in white coats every day, talking about our individual experiences, it is nice to know the more personal side of a fellow "Dukie" for a change. I also look forward to a more cohesive Duke-NUS community where we can all take pride in the Duke-NUS identity. I am definitely looking forward to the challenges in the final year and I hope I can learn as much as I can, to be the best doctor I can be for my future patients.

Edwin Yang is an MS3 student and has been twice elected President of the Class of 2015. ■

Edwin's first dive in Phuket. "Diving in low visibility and strong currents, much like one's journey in medicine."

Edwin's first clinical rotation at Paediatrics, with Dr Gan Bin Kee (center)

Edwin with fellow Duke-NUS riders at the end of 2014's Ride for a Tobacco Free Generation event.

Donald Tan Awarded Arthur Lim Professorship

Arthur Lim Professor in Ophthalmology, Prof. Donald Tan (photo credit: SNEC)

Leading Ophthalmologist, Professor Donald Tan, Chair of the Ophthalmology & Visual Sciences Academic Clinical Program at Duke-NUS, has been conferred the prestigious Arthur Lim Professorship in Ophthalmology.

The professorship, awarded by Duke-NUS and the Singapore National Eye Centre (SNEC), honors the late medical luminary Professor Arthur Lim and acknowledges Prof. Tan as an outstanding clinician, researcher and educator who has advanced the frontiers of medicine.

Prof. Tan is also Senior Consultant Ophthalmologist, Corneal and External Eye Disease Department, SNEC and Senior Principal Clinician Scientist of the Singapore Eye Research Institute (SERI). He has made significant contributions to the field of ophthalmology and is a renowned research pioneer for innovations in corneal and stem cell transplantation, refractive surgery, myopia treatments and patented surgical devices. He has pioneered various corneal and stem cell transplantations, patented numerous surgical devices, published more than 300 scientific papers and conducted numerous local and international teaching courses.

Prof. Tan is also credited with being the architect of SERI and was instrumental in introducing the SingHealth Duke-NUS Ophthalmology & Visual Sciences Academic Clinical Program, of which he was also the founding Chair.

Speaking in support of Prof. Tan's Professorship, the current Medical Director of SNEC and Vice Dean of Duke-NUS' Office of Clinical Sciences, Professor Wong Tien Yin said, "Prof. Tan's contributions are far-ranging and include clinical service in cornea and refractive surgery, outstanding research work, and mentorship of a generation of young ophthalmologists. His work extends beyond the region and he has substantially enhanced the reputation of Asia Pacific ophthalmology in the global arena."

Professor Ranga Krishnan, Dean of Duke-NUS and Chairman of the selection committee for the professorship said, "Prof. Tan exemplifies the sterling qualities for which the Arthur Lim Professorship stands. As the highest recognition and honor that can be bestowed upon a faculty member in ophthalmology, we are confident Prof. Tan will scale new heights in teaching, mentoring and generating new knowledge."

Established with initial seed funding of S$2.5million from the SNEC Health Research Endowment fund and matched dollar-for-dollar by the Singapore Government, the combined endowed gift of S$5 million will provide Prof. Tan with sustainable resources for his work. "We hope this Professorship will enable him to continue to lead in research, mentor and inspire the next generation of ophthalmologists, just as did his distinguished predecessor, the late Professor Arthur Lim.", said Professor Ivy Ng, Group Chief Executive Officer SingHealth and a member of the selection committee for the professorship. ■

The Future of Heart Disease Research in Singapore

Tanoto Foundation Professor of Cardiovascular Medicine, Prof. Stuart Cook

Cardiology researcher Professor Stuart Cook speaks to Vital Science about the promising future of heart disease research, strong medical partnerships and better diagnostic tests.

Professor Stuart Cook is optimistic about the future of research into heart disease. The Deputy Director of the Cardiovascular and Metabolic Disorders (CVMD) Signature Research Program (SRP) at Duke-NUS, who also helms the new National Heart Research Institute Singapore (NHRIS), sees huge potential in the strengthened partnerships that will arise from the NHRIS.

Prof. Cook, who was recently named the Tanoto Foundation Professor of Cardiovascular Medicine, said the NHRIS will focus on key research focus areas such as heart function and genetics, regenerative medicine and metabolic heart disease and cardiac imaging. "The NHRIS will be the umbrella under which Duke-NUS and the National Heart Centre Singapore (NHCS) can collaborate. It will be both a real and virtual environment for the basic science of Duke-NUS to come together with the patient-facing translational work done at NHCS." The vision, he said, is for NHRIS is to be a premier regional centre for cardiovascular research to drive excellence in patient care and to better understand cardiovascular disease manifestation in the Asian population so that treatment and prevention can be improved. The recently awarded Tanoto Foundation gift of S$3 million (see box story) will allow his research team to take what has been done so far in genetics and translate the findings into patient care.

A Focus on Diagnosis and Prevention

Cardiovascular disease – such as stroke and heart disease – is the leading cause of death worldwide. Alarmingly, the incidence of the disease is on the rise due to an increase of individuals with metabolic syndromes and also because of rapidly ageing populations in a number of countries. While science and research has gone a long way to treat the condition, much of the focus has been on the 'end result' – and those therapies

tend to be increasingly expensive. “Instead, we (as researchers) should look at cheaper approaches, such as moving towards prevention. Genetics is one way to do this,” said Prof. Cook. “We need to focus on diagnosis and prevention so people can live longer healthier lives rather than longer but sicker ones.”

Genetic studies – a key focus area for the NHRIS – can identify markers that can play an important role in stemming future complications, he added. One example is a simple diagnostic array that has been developed to identify the people with an inherited condition called familial hypercholesterolemia. This disease causes people to develop high cholesterol levels from a young age, thereby dramatically increasing their risk of stroke or heart attack. “It affects 1 in 500 people – so it’s not that rare and this means some 15,000 people in Singapore suffer from this; we just don’t know who they are,” explained Prof. Cook.

Prof. Cook is currently developing a test that will be able to diagnose the illness early so that treatment can be administered before it manifests into a serious condition. “If we know the condition is there, we can give a tablet to the affected person and this will stop them from getting a heart attack or stroke when they are 20 or 30.”

This is just one example of the vast potential in the area of genetics that can lead to a better understanding of the variations for improved diagnostics and more targeted treatments. Having an Asian-based research population also helps to build a better understanding of how treatments vary based on ethnic differences. “It helps doctors make more informed decisions, understand disease processes in a local context and improves healthcare,” Prof. Cook said. ■

About Professor Stuart Cook, Tanoto Foundation’s Professor in Cardiovascular Medicine

Professor Stuart Cook, a leading cardiovascular research expert with extensive work in human genetics, heart muscle disease and cardiac imaging, has explored both the clinical and academic facets of the field in prestigious institutions such as St Bartholomew’s Hospital, the National Heart and Lung Institute, Harvard and the Imperial College London. In 2012, he was conferred a Singapore Translational Research (STaR) Investigator Award by Singapore Ministry of Health’s National Medical Research Council (NMRC), and appointed as Professor of Clinical and Molecular Cardiology at Duke-NUS and senior consultant at the NHCS. Prof. Cook became Deputy Director of the CVMD SRP at Duke-NUS in 2013 and was appointed as founding Director of the NHRIS in 2014.

The Tanoto Foundation’s Professorship in Cardiovascular Medicine

The gift of S$3 million is awarded to an outstanding clinician researcher who demonstrates the ability to advance cardiovascular medicine through academic leadership, medical education and innovation. S$2.5 million of the grant will be used to set up the Professorship in Cardiovascular Medicine and the remaining S$500,000 will go to the Tanoto Foundation Initiative for Genetics and Stem Cell Research at NHRIS to identify new ways of diagnosing, stratifying and testing patients with cardiovascular diseases, so as to drive early prevention for those who are genetically predisposed.

His Excellency, President Dr. Tony Tan Keng Yam receiving the S$3 million Tanoto Foundation’s gift cheque from Mr Sukanto Tanoto, Founder and Chairman of the Tanoto Foundation Board of Trustees, during the SingHealth Duke-NUS Scientific congress held on September 5, 2014. (photo credit: SingHealth)

Tanoto Foundation’s gift check was presented by Mr Sukanto Tanoto, Founder and Chairman of the Tanoto Foundation Board of Trustees, to Singapore President Tony Tan Keng Yam, who received it in his capacity as Patron for the Duke-NUS Development Committee at the SingHealth Duke-NUS Scientific Congress held on September 5, 2014.

Bey Soo Khiang, Chairman of the Tanoto Foundation Board of Governance, highlighted the Foundation’s goals in improving the quality of people’s lives. He said, “Tanoto Foundation has, over the years, been a strong supporter of medical research that has the potential to bring about transformative impact to society. We are particularly delighted today to contribute to the advancement of research in cardiovascular medicine for the Asian community, as we believe the breakthrough results will enable healthcare practitioners to address the region’s medical needs more effectively, in relation to heart diseases. To this end, Tanoto Foundation hopes to continue to play a positive role in helping to improve the quality of people’s lives.”

Professor Ranga Krishnan, Dean of Duke-NUS stressed that the gift would be instrumental in catalysing a stronger collaboration, “We are deeply grateful to the Tanoto Foundation for establishing the Professorship in Cardiovascular Medicine and the Initiative in Genetics and Stem Cell Research. The gift will strengthen Duke-NUS’ and SingHealth’s joint push in improving clinical care and translational research for better patient outcomes.”

Protein Folding Mechanism Discovery Paves the Way for Better Understanding of Human Disease

(L - R), Dr. David Reid, researcher Angeline Tay and Prof. Shirish Shenolikar (photo credit: Don Heng)

Duke-NUS Research Fellow David Reid, graduate student, Angeline Tay and their current mentor Professor Shirish Shenolikar as well as David's graduate advisor Professor Christopher Nicchita, Associate Dean for Research Training at Duke University School of Medicine, published a landmark study in *Cell* identifying an entirely new mechanism of how the cell responds to stress – paving the way for a better understanding of how chronic diseases develop.

Cells are responsible for the production of more than 25,000 different proteins with specific shapes and functions. When cells get stressed due to overheating or starvation, the proteins that they produce no longer fold properly. Some of these unfolded proteins accumulate in the endoplasmic reticulum (ER), a network of tubules and sacs that transport proteins to the surface of cells. When unfolded proteins accumulate, the stress which results is known to contribute to the development of many diseases including cancer, diabetes, autoimmune disorders, obesity and neurodegenerative disorders.

The Duke-NUS and Duke collaborative study found that when a cell is stressed, it activates the unfolded protein response, or UPR, which slows down the assembly of new proteins, gaining itself time to clean up the existing improperly folded products.

The discovery highlights previously unknown processes of UPR and provides new insight into diseases that result from the accumulation of unfolded proteins. It is hoped that this knowledge will ultimately lead to the development of novel therapies to target chronic diseases.

Currently Dr. Reid is based in Prof. Shenolikar's laboratory in the Cardiovascular and Metabolic Disorders Program. Together they are working on follow-up research to determine the mechanisms that cells employ to execute the stress response.

The study was published in September 2014 and was supported by the National Institutes of Health (GM101533) and the Singapore Ministry of Health (Duke/Duke-NUS Research Collaboration Award).

Translating Basic Science into Tangible Outcomes

The 2014 Albert Lasker Basic Medical Research Award honored science that led to the discovery of the unfolded protein response, highlighting that UPR research is currently a highly valued and visible area in biomedical research.

At Duke-NUS, UPR research is also underway. Taking the lead is Prof. Shirish Shenolikar, who is the interim Director of the Signature Research Program in Neuroscience and Behavioural Disorders and a Professor in the Cardiovascular and Metabolic Disorders Program. His research is focused on understanding how unfolded proteins arise and exploring small molecules that might guide the development of new treatments for diseases that stem from accumulated protein deposits.

One area of the work is to discern why in some people, cells are better at clearing away the faulty proteins, while this function is not as efficient in individuals who develop disease. The research concentrates on neurodegenerative diseases and how one might keep cells alive for longer to prevent or delay the devastating symptoms of these aging-related diseases.

The research has been made possible with the Duke and Duke-NUS collaborative grant laying the profiling groundwork, research collaborations with the National Neuroscience Institute contributing to the disease expertise and Glaxo Smith Kline (GSK) providing the compounds to test their effects on cell stress.

"We have industry, clinical and basic science collaborations," said Prof. Shenolikar. "Together we hope to identify the fingerprint of Parkinson's disease is and assess what it tells us about the onset or progression of this disease."

Prof. Shenolikar believes that the goal of pushing back Parkinson's disease can be achieved in his lifetime and hopes that drug development spawning from his current research could be possible in three to five years. Though a relatively short timeline for developing treatments for Parkinson's, his commitment to collaboration and belief in Duke-NUS's focus on translational research is the catalyst for the multi-institution research inspiration pushes him forward. When asked how he hopes to execute his current protein related Parkinson's research as well as manage the bevy of grants he was just awarded, Prof. Shenolikar is clear. "Plan ahead, think ahead." ■

Collaborations For Better Patient Outcomes

This work is made possible by the Duke/Duke-NUS Research Collaboration Award, a joint US and Singapore grant, which was awarded with the assumption that grant holders will move their research towards human applications. Prof. Shenolikar had identified GSK as the intended industry partner prior to the initiation of this grant enabling him to receive full funding under the terms of this research.

Students Hold Event for Pediatric Brain Tumour Patients

Duke-NUS student volunteers along with "Spidey" and the Princess playing their part at the event

A day of fun filled activities!

An inspirational talk by Prof. David Virshup at the event

On November 1, 2014, the first-ever Brain Tumour Awareness Day was held in Singapore by the Brain Tumour Society (Singapore) or BTSS to draw attention to the disease. The highlight of the event was the Brainy Car Rally that saw about 40 Lamborghini and Ferrari car owners rallying behind the cause. Half of these cars drove patients, survivors and caregivers from Kallang Leisure Park to various locations in Singapore – AMK Hub, Junction 8 and Toa Payoh HDB Hub – where they distributed BTSS grey balloons and information materials on the disease.

The remaining cars travelled to KK Women's and Children's Hospital (KKWCH), where Duke-NUS medical students held the first Pediatric Brain Tumour Awareness Day (PBTA). The cars ferried about 20 paediatric brain tumour patients on a Brainy Car Joyride from KKWCH to Kallang Leisure Park, where the rally ended. Organised by the Duke-NUS students in collaboration with BTSS, this event also featured a public exhibition, seminars, and interactive game booths contributed by Science Centre Singapore.

There are more than 120 types of primary brain tumours, which are tumours that originate or arise from the brain. In Singapore, about 40 children and about 100 adults are diagnosed with malignant brain tumours every year.

Car rides involving Lamborghinis and Ferarris were flagged off by Mrs Jennifer Yeo, Guest-of-Honor, PBTA

"I am pleased that our medical students are leading an initiative that would make a difference to the lives of patients, so early on in their training. They have put in many hours despite their heavy schedules. I am proud of their efforts," said Professor Thomas Coffman, Executive Vice Dean of Duke-NUS. ■

**Photos courtesy of Dr. Joshua Chua and Nicholas Shannon*

Two Awards for Professor Tom Coffman

Executive Vice Dean, Prof. Tom Coffman

Duke-NUS Executive Vice Dean, Professor Thomas Coffman was named co-recipient of the 2014 Excellence Award for Hypertension Research from the Council on Hypertension, American Heart Association (AHA).

Professor Coffman was presented the Excellence Award at the High Blood Pressure Research 2014 Scientific Sessions in San Francisco in September 2014. Supported by a grant from Novartis Pharmaceuticals Corporation, the Award recognizes researchers who have made a major impact in the field of hypertension and whose research has contributed to improving treatment and understanding of high blood pressure.

"I am very honoured and humbled to have received the Excellence Award for Hypertension research," said Prof. Coffman, who holds the title of James R. Clapp Professor of Medicine, Chief of the Division of Nephrology and Senior Vice Chair in the Department of Medicine at Duke University Medical Center. "Over time we think our work will help researchers understand better how the current approaches for treating hypertension work and also help identify new targets for this disease that affects millions of people."

In October 2014 Prof. Coffman also received the 2014 Distinguished Faculty Award from the Duke Medical Alumni Association. He is among seven distinguished individuals recognized by the Duke Medical Alumni Association for their sterling contributions to medicine.

Prof. Coffman was a resident and fellow at Duke University from 1980 to 1985 and it is where he began his career as a clinician and researcher. Having spent his entire career at Duke and now Duke-NUS, one of his many notable contributions was being the founding director of the Duke Cardiovascular Research Center in 2010 and being named the Director of the Cardiovascular and Metabolic Disorders Program at Duke-NUS in the same year. ■

Vitamin D Associated with Cognitive Impairment in the Elderly

Prof. David Matchar

A recent study led by Professor David Matchar, Director of the Program in Health Services and Systems Research at Duke-NUS has found an association between low vitamin D levels and cognitive impairment in the elderly population in China. The study sought to close the gap in knowledge about the impact of low vitamin D levels on cognitive function in Chinese populations. Thus far, research conducted in the United States and Europe suggests that low levels of vitamin D are linked to cognitive impairment, which can manifest as dementia. Compared to the rest of the world, Asia has lower levels of vitamin D, but little research has been done in this area.

Prof. Matchar and his team measured the vitamin D levels and cognitive abilities of participants in the Chinese Longitudinal Healthy Longevity Survey (CLHLS). The study, which was undertaken in 2012, was based on an analysis of the data of 2004 Chinese (936 men and 1,068 women) in China with an average age of 84.9 years.

Typically, the level of vitamin D should be about 50 nanomoles (nmol) per Litre(L) of blood, whereas some researchers suggested that a range of 75 - 100 nmol/L is the appropriate range for optimal health. In this study, participants had a mean vitamin D level of 43.1 nmol/L which is lower than the minimum advised level.

After adjusting for age, gender, chronic conditions, smoking and drinking habits, outdoor activities, depression, and mobility limitations, results found that those with decreased vitamin D levels were 2.15 times more likely to be associated with cognitive impairment than participants with higher levels of vitamin D. Currently, Prof. Matchar and his team are in the process of doing a follow up study of this group, spurred on by these results, to examine whether a vitamin D deficiency causes cognitive impairment.

These findings were published in the November 2014 edition of the *Journal of American Geriatrics Society* and is supported by the Singapore National Research Foundation under its STaR Investigator Award (NMRC/STaR/0005/2009) administered by the Singapore Ministry of Health's National Medical Research Council. The research is also supported by the National Institute on Aging, National Institute of Health (RO1AG023627), and the National Natural Science Foundation of China (81273160). ■

Shorter Sleep Could Lead to Faster Brain Aging

Prof. Michael Chee

Professor Michael Chee and Research Fellow Dr. June Lo from the Neuroscience and Behavioral Disorders Program at Duke-NUS have found evidence that the less sleep older adults get, the faster their brains age. Their work paves the way for studies on sleep loss and its contribution to brain aging and cognitive decline, including dementia.

In the Singapore-Longitudinal Aging Brain Study that started in 2005 – one of the few Asian studies of its kind – Prof. Chee and Dr. Lo monitored brain and cognitive changes in a cohort of healthy adults of Chinese ethnicity aged 55 and above. Every two years, participants underwent structural MRI brain scans measuring brain volume and neuropsychological assessments testing cognitive functions. Their sleep duration was also measured with a questionnaire.

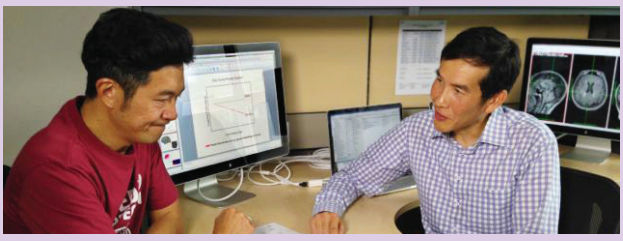
The results revealed that those who slept fewer hours showed evidence of faster ventricle enlargement and a decline in cognitive performance. While past research has examined the impact of sleep duration on cognitive functions in older adults, this study adds to the literature by showing that in addition to age-related cognitive changes, brain aging is also escalated by insufficient sleep.

"Work done elsewhere suggests that seven hours a day for adults seems to be the sweet spot for optimal performance on computer based cognitive tests. In coming years we hope to determine what's good for cardio-metabolic and long term brain health too," added Prof. Michael Chee, senior author and Director of the Centre for Cognitive Neuroscience at Duke-NUS.

Published in July 2014 in the journal *Sleep*, the study is supported by funding from the Biomedical Research Council, Agency for Science Technology and Research Singapore (BMRC 04/1/36/19/372) and the Singapore National Research Foundation under its STaR Investigator Award (NMRC/STaR/0004/2008) administered by the Singapore Ministry of Health's National Medical Research Council. ■

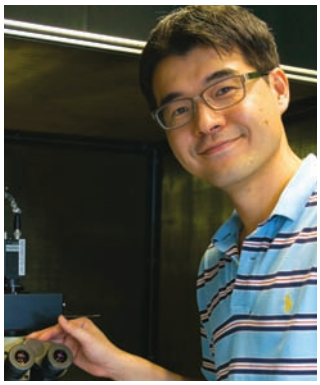
Chasing Longevity: Train your Brain

Earlier this year, Prof. Michael Chee's prolific research in the area of sleep was featured along with the work of Assoc Prof. Lee Tih-Shih, in Channel NewsAsia's documentary *Chasing Longevity*. Both were interviewed by host, Adrian Pang, who tapped their insights in order to address the mystery of how one can live better and longer.



Television host, Adrian Pang (left) and Prof. Michael Chee (right) filming "Chasing Longevity" (photo credit: June Lo)

Researchers Better Understand Links Between Mutated Protein and Brain Disease



Asst. Prof. Shawn Je

A research team led by co-first author Assistant Professor Shawn Je, from the Neuroscience and Behavioral Disorders Program at Duke-NUS, has discovered how the protein, Triad3A, regulates synaptic plasticity – a function that underlies learning and memory.

Synaptic plasticity is the ability of synapses (the structure that allows neurons to communicate) to strengthen or weaken in response to brain activity. Importantly, this synaptic plasticity is thought to be impaired in people with intellectual disabilities as well as with neuropsychiatric disorders, such as autism and schizophrenia. The balance, or homeostasis, of this change in neuronal connection is the key to what people associate with "normal behavior".

Synaptic plasticity is regulated by cytoskeletal protein (Arc), a protein synthesized in large quantities when neurons are active. Arc also degrades quickly in response to an unknown mechanism. In their study, Asst. Prof. Je and his colleagues identified the cause of this degradation: the Triad3A protein, which recognizes and degrades Arc thereby controlling the levels of Arc and synaptic plasticity.

With studies revealing that patients with autism and intellectual disability have multiple mutations within the gene encoding this Triad3A protein, Asst. Prof. Je believes his team's findings point to the misregulation of the Triad3A protein in the brain could contribute to the pathogenesis of brain disorders. Now, he and his colleagues at Duke-NUS aim to investigate whether the misregulation of Triad3A in animal models result in abnormal animal behaviors similar to those observed in people with brain disorders.

This study was published in June 2014 in the journal *Neuron* and is supported by funding from the Singapore Ministry of Education Academic Research Fund Tier 2 (MOE2012-T2-1-021). In addition to Asst. Prof. Je, study authors include Drs. Angela Mabb and Michael Ehlers from Duke University Medical Center. ■

Dengue Drug Trial Shows Treatment Promise

A trial to test the effectiveness of Celgosivir, a plant-derived drug for dengue, has shown some promise in its first stages and has demonstrated that Singapore is a viable site for dengue therapeutic trials. The trial was part of CELADEN (CELgosivir as a treatment Against DENgue), a collaborative study by Dr. Jenny Low from Singapore General Hospital (SGH) and Professor Subhash Vasudevan from Duke-NUS.

As a part of the study, 50 subjects with dengue were treated with Celgosivir or a placebo and monitored as inpatients for five days until they recovered. They were subsequently followed up with in outpatient clinics for two more visits on day seven and day 15, where medical histories, blood tests and physical examinations were performed. Though the administration of Celgovisir did not show a faster resolution of fever or a reduction in blood viral levels, the study's authors were pleased that the drug did not cause ill-effects.

"While the dosage prescribed in the trial may not have had the intended results, prior work conducted at Duke-NUS has demonstrated that dose regimen is an important factor in mediating the antiviral effects of Celgosivir," explained co-author Prof. Vasudevan from the Emerging Infectious Diseases Program at Duke-NUS.

"It is important that we have found that the drug regimen in CELADEN was well-tolerated and safe, so we can move on to the next phase," added Principal Investigator Dr. Low from SGH's Department of Infectious Diseases. "A regimen with more frequent dosing will be tested in the next phase of our trial to see its therapeutic effect."

Dr. Jenny Low with Prof. Subhash Vasudevan

Moving forward, SingHealth and Duke-NUS have signed an exclusive licensing agreement with 60 Pharmaceuticals (60P) to evaluate the efficacy and safety of an alternate dosing regimen as well as combination drug treatments in dengue patients.

The study was published in the journal *Lancet Infectious Diseases*, in May 2014, and is supported by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Programme (NMRC/TCR/005-GMS/2008) administered by the Singapore Ministry of Health's National Medical Research Council. ■

How Dengue Evades Our Immune Responses

Understanding a virus's biology enables researchers to better pinpoint how a virus functions and ultimately to better target therapeutics. Professor Mariano Garcia-Blanco has spent many years studying dengue from an RNA standpoint, and his new study in the journal *PLOS Pathogens*, has given us fresh insight into the virus.

Typically, when a virus enters the body and infects cells, it induces the production and release of interferons (IFNs), proteins, which raise the bodies' anti-viral defence mechanisms. When the dengue virus enters the cell, it produces large quantities of a non-coding, highly-structured viral RNA termed sfRNA, which is part of the genetic material of the dengue virus.

Prof. Mariano Garcia-Blanco

Prof. Garcia-Blanco's team found that sfRNA attaches itself to proteins in the cell (G3BP1, G3BP2 and CAPRIN1) that typically help in producing antiviral proteins in response to IFNs. Because of this interaction, the cell is unable to mount its antiviral defences and protect itself against virus replication.

The team essentially discovered a new way that dengue virus-2 (DENV-2) uses to evade the human defence system. These findings highlight new steps that regulate our immune response and the differences between the four dengue strains. Their work also demonstrates the need for more work to understand this high complex virus.

The study's authors also include Dr. Katell Bidet (NUS Graduate School for Integrative Sciences and Engineering, National University of Singapore and Duke-NUS) and Dhivya Dadlani (Duke-NUS). This research was published online in July 2014 and is supported by the Singapore Ministry of Health's National Medical Research Council under its Individual Research Grant (NMRC/1267/2010). ■

New Insights on an Ancient Plague Could Improve Treatments for Infections

A Duke-NUS and Duke Medicine research team has illuminated a pathway that shows how the human body responds to infections from bacteria that causes the bubonic plague. The insight provides a new avenue to develop therapies that block this host immune function. Incidentally, this approach is more effective than targeting the pathogens themselves which, though effective at first, often leads to antibiotic resistance.

In a study published in *Immunity*, authors Assistant Professor Ashley L. St. John, from the Program in Emerging Infectious Diseases (EID) at Duke-NUS and Professor Soman Abraham, who holds appointments at both Duke-NUS and Duke Medicine, contributed to the understanding of how the human body responds to infections from bacteria that causes the bubonic plague. They found that the Yersinia pestis bacteria, which causes the bubonic plague, attaches to immune cells in the lymph nodes and eventually goes into the lungs and the blood stream where the infection is easily transmitted.

"The bacteria actually turn the immune cells against the body," said Dr. Soman Abraham. "The bacteria enter the draining lymph node and hide undetected in immune cells where they multiply. Meanwhile, the immune cells send signals to bring in even more recruits, causing the lymph nodes to grow massively and provide a safe haven for multiplication. Once the bacteria infiltrate the blood and lungs, the infection can easily be transmitted through body fluids, or via biting insects such as fleas."

Dr. St. John notes that there are several potential drug candidates that are able to target the trafficking pathways that the bubonic plague bacteria use. In animal models, the researchers successfully used some of these therapies to prevent the bacteria from reaching systemic infection, markedly improving survival and recovery.

"This work demonstrates that it may be possible to target the trafficking of host immune cells and not the pathogens themselves to effectively treat infection and reduce mortality," said Dr. St. John. "In view of the growing emergency of multi-resistant bacteria, this strategy could become very attractive."

The study was published online in September 2014 and was supported by funding from the National Institutes of Health. ■

A Way to Target Cancer Metabolism

Asst. Prof. Mei-Wang Casey (in beige) and her lab members

A recent study led by Dr. Mei Wang, a clinician scientist from the Cancer and Stem Cell Biology (CSCB) Program at Duke-NUS, has found that the enzyme Isoprenylcysteine carboxylmethyltransferase (Icmt) regulates mitochondrial respiration and cancer cell metabolism. This discovery adds to the understanding of how cancer cells differ from other cells and may contribute to the development of cancer treatments.

Dr. Wang's lab discovered that targeting an enzyme called Icmt can be useful in slowing and stopping cancer cell growth, eventually causing them to die. Icmt is an enzyme that modifies a group of proteins. Without the modifications, these proteins, many of which drive cancer development and cancer maintenance, lose their ability to function. For example, the infamous Ras onco-proteins that drives one third of all human cancers, is functionally modified by Icmt.

In their recent study published in the journal of *Oncogene*, Dr. Wang and her colleagues found that by suppressing Icmt, cancer cell mitochondrial respiration, or "breathing" function is significantly reduced. Mitochondrion, the "engine" of a cell, produces ATP and regulates a cancer cell's metabolism. Consistently, the team found that suppressing Icmt function led to a decrease in ATP and a depleted pool of important metabolites for cancer cell growth, preventing these malignant cells from forming tumors.

This discovery brings to light that cancer cells are more sensitive to mitochondrial inhibition than normal cells. The finding is doubly important because controlling mitochondria function is a previously unappreciated function of the enzyme Icmt. The team believes that Icmt, which modifies many tumor driving proteins, can be a drug target for cancer treatment.

"Our research is both basic and translational. In this study we identified an important function of an enzyme, which will provide us more information on the potential clinical application in cancer therapy," explained Dr. Wang, who both teaches at the Medical School and runs a busy lab.

This study was published in August 2014 and is supported by funding from the Singapore Ministry of Education Academic Research Fund Tier 2 (MOE2013-T2-2-170) and the Singapore National Research Foundation under its Clinician Scientist Award (NMRC/CSA/018/2010) administered by the Singapore Ministry of Health's National Medical Research Council and the Duke-NUS Signature Research Program, with funding from the Ministry of Health. ■

Team Makes Breakthrough in Fibroadenoma Research

(L-R) Prof. Patrick Tan, Assoc. Prof. Steve Rozen and Prof. Teh Bin Tean

A breakthrough in the understanding of the molecular basis of fibroadenoma may improve diagnostic tools to differentiate benign breast tumors from breast cancers. Fibroadenomas are the most commonly found benign breast cancer tumors in women of reproductive age. These benign tumors are usually discovered in clinical workups for breast cancer diagnosis and during breast cancer screening; but it is often difficult for clinicians to distinguish them from breast cancer tumors.

The team consisting of Professors Teh Bin Tean, Patrick Tan, Steve Rozen and Tan Puay Hoon from the National Cancer Centre Singapore (NCCS), Duke-NUS, and Singapore General Hospital, used their collective strengths to explore ways to identify genetic abnormalities in fibroadenomas that may be used to differentiate them. Using DNA sequencing technologies they were able to identify frequent mutations in a gene called MED12 in 60 per cent of fibroadenomas.

The findings were published in *Nature Genetics* in March 2014 and have numerous applications. For one, measuring the MED12 gene in breast lumps may help clinicians to distinguish fibroadenomas from other types of breast cancer. In the future, drugs that target the MED12 pathway or stromal cells, which is where the team found the basis of the MED 12 mutations, could be used to help patients with recurrent fibroadenomas to help them avoid surgery.

The multi-institution team, called BRGO (Breast Research Group at Outram), also observed that women with uterine fibroids have similar MED12 mutations which suggesting that these tumors may arise from cells abnormally responding to female hormones due to MED12 mutations. Moving forward, further studies are planned to investigate the role of MED12 in other categories of breast tumors.

Study authors include first author, Dr. Lim Weng Khong from NCCS and Duke-NUS. The research was supported by the the Singapore National Research Foundation under its STaR Investigator Award (NMRC/STAR/0006/2009) administered by the Singapore Ministry of Health's National Medical Research Council, the Singapore Millennium Foundation, the Lee Foundation, the Tanoto Foundation, the National Cancer Centre Singapore's NCC Research Fund, the Duke-NUS Graduate Medical School, the Cancer Science Institute, Singapore and the Verdant Foundation, Hong Kong.

Home Incense Use Associated with Cardiovascular Mortality

Assoc. Prof. Koh Woon Puay

A recent study conducted by Duke-NUS Associate Professor Koh Woon Puay and Assistant Professor Pan An from the Saw Swee Hock School of Public Health, National University of Singapore has found that long-term exposure to incense burning in the home could be associated with an increased risk of cardiovascular mortality.

Incense burning at home for ritual or religious purpose is a common practice among Chinese populations in China, Taiwan and Southeast Asia, including Singapore, as well as in populations of India and Arabian Gulf countries. Being a relatively unpolluted country, Singapore is an appropriate site to study the effects of indoor incense use on cardiovascular disease risk without the confounding effects from other sources of environmental pollutants.

This is the second study on incense and health risk from The Singapore Chinese Health Study (SCHS), a population-based cohort study which recruited 63,257 middle-aged to elderly Chinese residents in Singapore between 1993 and 1998. Previously, in 2008, Assoc. Prof. Koh and her team published findings in the journal *Cancer* that those exposed to indoor incense for a long duration had increased risk of developing cancers in the upper respiratory tract such as larynx and pharynx (windpipe).

The SCHS cohort was followed up for an average of 15 years per person and the risk of deaths from heart disease or stroke was compared among participants with different exposure to incense in the home. Compared to people who did not report using incense at the time of interview, those who said that they were using incense at home subsequently had increased risk of death from cardiovascular disease. This relative increase in risk was 12% for all cardiovascular deaths, 10% for coronary heart disease mortality and 19% for stroke mortality.

The study is the first to provide epidemiologic evidence that long-term exposure to indoor air pollution from incense burning can increase risk of death from cardiovascular disease. The results are not unexpected, given what scientists have shown from studies in the laboratory and in animal studies that long-term exposure to incense can cause metabolic changes in the animals that may increase inflammation in blood vessels and affect blood flow.

According to a recently published article in the Taiwanese paper, *Apple Daily*, a temple in Taipei has advised their worshippers to reduce the burning of incense and to just pray with their hands folded and heads bowed based on the results of this study published in the journal *Environmental Health Perspectives* in August 2014.

Heartened by the immediate impact of the research, senior author Assoc. Prof. Koh weighed in on the results, "This study is not intended to discourage burning incense at home, but to emphasize the importance of providing public health education to the users on positioning of altars and improvement of ventilation in order to reduce exposure. Future studies should be undertaken to identify the least harmful types of incense on health and also strategies that can be taken to reduce the exposure and improve indoor air quality when using incense."

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