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The Way We Learn

VITAL SCIENCE

This e-communications update is produced by the Office of Communications, Development and Alumni Relations
Produced by: Janice Tan (Editor), Dharshini Subbiah and Sheralyn Tay

Our banner story: Duke-NUS' Class of 2014 Graduates. Read the story here.

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DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

New Horizons: Taking the CVMD Program Further

Professor Thomas Coffman, Program Director, Cardiovascular & Metabolic Disorders Program (CVMD) shares his thoughts on the Program and his new role as Duke-NUS' Executive Vice Dean

There are bright things on the horizon for Duke-NUS' Cardiovascular and Metabolic Disorders (CVMD) Program, a signature research program that has come into its own since its inception in 2005. Dr. Thomas (Tom) Coffman, Program Director, highlighted, "Since I came to Duke-NUS in 2010, the CVMD program has grown significantly, from three scientists to 10. We have in the last few years attracted a number of outstanding scientists to the program and published several important research studies." The faculty is comprised of leading scientists Stuart Cook, Karl Tryggvason, Paul Yen, Sujoy Ghosh, Scott Summers, David Silver, Shirish Shenolikar, Paul Yen, Lei Sun and Jean-Paul Kovalik. Dr. Coffman is himself a renowned researcher in the area of diabetic nephropathy (kidney damage caused by diabetes), and is concurrently Chief of the Division of Nephrology at Duke University Medical Center.

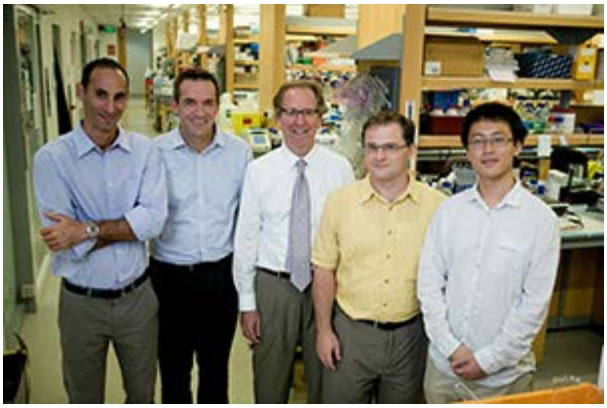
Prof. Tom Coffman, Executive Vice Dean, Duke-NUS

Since January, Dr. Coffman has been based primarily in Singapore and has high hopes that the CVMD program will go even further. "The CVMD program is focused on studying a range of very relevant, very significant diseases to Singapore and to the world in general," he said. Today, chronic kidney disease, a common but 'silent disease, is becoming an area of focus.

"Kidney disease also has a lot of intersection with other diseases such as diabetes and high blood pressure, even the risk of cardiovascular and heart disease," Dr. Coffman pointed out. "Many of the links are not well understood, despite the significance of the problem. This makes the area of kidney disease a very compelling field for research." Singapore, he added, is a great place to study the ethnic and genetic basis of the disease. The approach of the CVMD Program, which looks at all the related conditions in a holistic way and its links rather than as a single disease, is a novel and impactful way to address the multi-faceted problems.

Some areas he hopes the CVMD Program will tackle are to develop better animal models for diabetic nephropathy and study the genetic causes of diabetes. This will add to the significant body of work already being produced by CVMD researchers. One of these is a new drug developed by Professor Karl Tryggvason that will soon be tested in a phase 3 clinical trial. Another area that is moving towards the clinic is a research project by Professor Stuart Cook who is developing testing platforms to look at genetic markers for heart failure. "All this will play an important role to improve diagnosis, treatment and understanding of the disease," Dr. Coffman said.

As for his role as Executive Vice Dean of Duke-NUS, Dr. Coffman hopes to impact the programs and school in a broader way. His 'big job' over the next few years is two-fold: sustain the research and education programs that are ongoing; and help develop the Academic Medical Center. "The Academic Medical Center is really unique because we are building it from scratch and can take advantage of the blank slate to structure things in new and more effective ways," he said, adding, "Having spent my whole career in world-class institutions that have effectively combined research and clinical practice, I have seen how much added benefit academic medicine brings to patients, not just in day to day care, but also in improving the way their care is delivered." This push towards academic medicine has many benefits, he pointed out. "It retains the best doctors, keeps people sharp and focused on patient care and aware of not only new treatments but the ways to deliver these in the best way. It is a powerful combination that benefits both patients and public health."



Some of the researchers in the CVMD Program (L-R): Drs. David Silver, Stuart Cook, Tom Coffman, Jean-Paul Kovalik and Sun Lei

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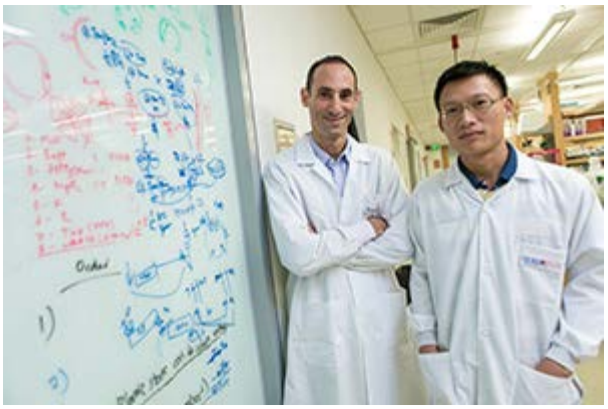
Getting to the Root of DHA and Making Better Nutrition for the Brain



Solving the DHA mystery: Assoc. Prof. David Silver and Dr. Long Nguyen

A Singapore-based research study has made a significant finding on how we can more effectively get an important brain-building nutrient to where it is needed. Associate Professor David Silver from the Cardiovascular and Metabolic Disorders (CVMD) Program at Duke-NUS and his team have identified an important transporter for DHA, a type of Omega-3 fatty acid that has long been thought to be essential for brain function (e.g. learning, memory).

"Though we know DHA is good for the brain, science has not found out how it gets there," said Dr. Silver, "The interesting fact is that while the brain and eyes are rich in DHA, these organs cannot actually make DHA. We have to ingest DHA or other lipids that can be synthesized by the liver before the brain can take it up. The question is: how does the body transport DHA into the brain through the blood-brain barrier?"

In a landmark piece of research, Dr. Silver's laboratory in Singapore identified the primary transporter for DHA into the brain - a protein called Mfsd2a. The team also made the significant discovery that DHA is actually transported into the brain not as DHA but in a different chemical form, a phospholipid called lysophosphatidylcholine (LPC). "We knew LPC is made in the liver and is found in our blood at high levels, but no one knew what it was for," Dr. Silver said, "Now we know the liver first has to convert DHA into LPC and that Mfsd2a only recognizes LPC and then transports it to the brain."

Remarkably, mice engineered to not have Mfsd2a have extremely small brains, indicating that LPC is critical for brain growth. "This has a direct impact on how we can make better nutritionals, to improve brain growth and function. It's especially important for pre-term babies who have not received sufficient DHA during fetal development," said Dr. Silver.

The discovery also traces a route through the highly selective blood-brain barrier which separates circulating blood from brain fluid in the nervous system. The barrier is there to protect the brain from foreign invaders but makes treatment of neurocognitive diseases extremely difficult. The Duke-NUS team is hopeful that the Mfsd2a pathway can be exploited for drug delivery to the brain and believes the findings have huge potential for commercial application.

The study was published in *Nature* in May and is supported by the Singapore National Research Foundation under its Cooperative Basic Research Grant (CBRG) and administered by the Singapore Ministry of Health's National Medical Research Council.

A spectrum of opportunities

Apart from his research work in lipid metabolism, Dr. Silver is also director of Graduate Studies, where he works with Associate Professor Silke Vogel, who is Assistant Dean of Graduate Studies and married to Dr. Silver. Dr. Vogel, who has a PhD in nutritional sciences, formerly ran a research lab at Columbia University that worked on vitamin A metabolism and identifying factors involved in the development of obesity and insulin resistance. Her scientific background has put her in good stead to develop a rigorous, supportive, and high quality PhD program here in Duke-NUS.

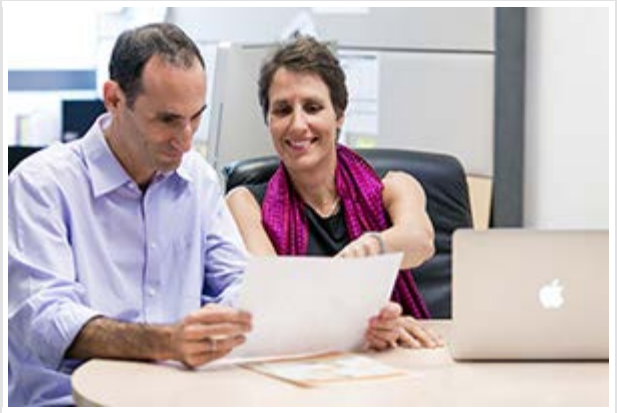
Their roles as scientists, educators and mentors form an effective synergy, said Dr. Vogel, “Because David is also faculty liaison, it helps a lot to bridge the communication between students, myself and the faculty. Conversely, being a researcher, David can help identify the courses that students can take up to improve various skillsets or knowledge. It’s a nice complementary role that benefits the students.”

She shared, “My long-term goal is to improve health through research and education. As Assistant Dean of Graduate Studies, I oversee all the administrative and educational activities. My role is to ensure that the guidelines and policies are in place to ensure our PhD students get the support they need. In addition, my role is to advise students and help them overcome their challenges.” She also identifies the areas in which students need more educational or research support and brings these ideas to Dr. Silver, who as the director raises these ideas with the executive committee. “Being content experts in science ourselves, with research backgrounds, we both understand what students need in their pursuit of a PhD,” Dr. Silver added.

Reflecting on the Graduate Program, both professors noted that it was making good strides since it started in August 2010. “We are very proud of the quality of work that is coming out of our PhD program.” Dr. Vogel said, “During our recent first annual Student Research Symposium, the faculty commended the students on the excellent science and outcomes. We have a good diversity of students; they come from a variety of backgrounds and with great credentials. The students are also bonding well and are benefiting from the mutual expertise from their peers and the faculty.”

Separately, Dr. Vogel is also involved in the Academic Medicine Research Institute (AMRI), where she leads the Voice Annotated presentations (VAPs) team. VAPs are Duke-NUS’ unique learning innovation, which have played a crucial role in delivering a comprehensive, up-to-date and accessible database of education materials for students and healthcare professionals.

The husband-and-wife team both agreed that the move to Singapore in 2012 has been a good one for them. “Singapore has extraordinary research opportunities; the infrastructure is also outstanding and makes for a world class research environment. Duke-NUS in particular is very unique in that enterprise,” said Dr. Silver. As for Dr. Vogel, “The chance to build and develop a novel education program at Duke-NUS was a big draw.”



Dynamic duo: Assoc. Prof. David Silver and Assoc. Prof. Silke Vogel discuss matters pertaining to the Graduate Studies program

Careers aside, Singapore has been good for them as a family too. The two are parents to two boys, aged 10 and 13, who have adjusted very well to life here. “Besides school, our older son is a competitive swimmer for a local club and our younger son is with the Singapore Lyric Opera Children’s Choir. Living and working in Singapore, we are able to spend a lot of quality time together.”

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Duke-NUS' Class of 2014 Graduates

Duke-NUS leaders and faculty were extremely proud to witness the graduation of the school's fourth M.D. (Doctor of Medicine) class on May 31, 2014. Graced by Guest-of-Honor Mr. S. Iswaran, Minister in the Prime Minister's Office and Second Minister for Home Affairs and Trade & Industry, 51 students from the Class of 2014 received their scrolls at a ceremony held at The Academia. This year, the keynote lecture was delivered by Duke University's Professor Robert Lefkowitz, who won the Nobel Prize in Chemistry in 2012.

In his address to the graduating class before he took up the post as president at the US National Academies' Institute of Medicine on July 1, Prof. Victor Dzau encouraged the Class of 2014 to serve with passion and purpose, to "commit to a career that is characterized by medical, scientific and research excellence, and service to [the] community".

Sharing the same sentiment in his keynote address, Professor Robert Lefkowitz reminded the graduating class to fulfill their calling to be doctors by always believing in what they are doing and to follow their own path while remaining enthusiastic and optimistic.

The Class of 2014 came from a myriad of academic backgrounds, ranging from the Sciences, Engineering, Humanities and Social Sciences. Some students entered with Masters Degrees or PhDs. They continued to excel over the four years, winning awards, securing patents, and balancing their studies while representing Singapore at international sports competitions.

Some student highlights:

• **Kavisha Singh:** Received the Duke-NUS Achievement Prize, SingHealth Top Student Gold Medal, SingHealth Prize in Family Medicine and Neurology.
• **Esther Low:** Received the Feng Pao Hsii Prize in Rheumatology award for the best research project in the field of rheumatology. She is also the outgoing Duke-NUS Student Council president.
• **Sophie Carrie Cai Shan**: A Ngee Ann Kongsi Distinguished Scholar, she won the Dermatology Best Research Studies Award and the SingHealth Seah Cheng Siang Gold Medal in Medicine.
• **Tay Yu Ling:** A former national fencer, Yu Ling was awarded the College of Family Physicians Singapore Prize in Family Medicine.
• **Toh Li Ying:** A national sailor who won the SingHealth Prize in Pediatrics.
• **Lai Hsuan & Darius Aw:** Both invented an integrated medical device that can be used to diagnose lumps on the neck.
• **Wijaya Martanto:** Co-founded the Duke-NUS Medtech student interest group. Wijaya was also the recipient of the SingHealth Prize in Obstetrics & Gynecology.

The auditorium was filled by parents, family and friends, faculty and leaders of Duke, NUS, Duke-NUS and SingHealth, who looked on in pride as the students walked across the stage to receive their hoods and scrolls.

The students began their residency in their assigned specialties in July.

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Surviving Residency: The Initial Years

Once, I was asked to recount the funniest moment from my Houseman year:

One morning during clinical rounds, a new patient stated quite seriously, "I can't take Panadol. I'm allergic to it."

The Registrar promptly asked, "So what do you take for a fever, sir?"

"Paracetamol," he replied.

There was a pause. The Registrar kept his cool and assured the patient that he would only be given Paracetamol in view of his Panadol allergy.

I could catalogue whole journals of every funny or heart-breaking moment in my short medical journey so far. But for now, here are four guiding principles to get through the terrors of starting out as a House Officer or Junior Resident:

1. Be prepared for anything

My first call happened on my second day of work. There were no tag-on calls or settling-down period. It was 5pm and the lives of several hundred patients weighed heavily on my inexperienced shoulders. Yet, I somehow survived the night, as did the patients. My Medical Officer (MO) tried to make a tutorial out of every new admission which was thoughtful but untimely especially at 3am. During a patient's MRI scan, my Registrar gave me advice and reassurances (I called him out on it. Before 5pm, he'd told me, "Anything, just call. Anything." Famous last words!). In the end, I managed to wrangled 50 minutes of sleep, survived post-call rounds with much yawning, before collapsing back home in my bed.

From sudden disappointments (your patient being unable to go home because he spiked a fever), to pleasant surprises (a nursing friend offering chocolate éclairs to eat during your call), and anything else (being scolded by seniors from other departments, patients' relatives or by nursing officers), the list goes on. Medicine is unpredictable because people are unpredictable. So be prepared for anything and everything to happen.

2. Diplomacy never fails. If it does, just bite your tongue

Much of the practice of medicine involves talking. If you are not spending time explaining things to patients or their relatives, then you are on the phone speaking to the lab, radiologist, surgeon, or the medical sub-specialist. Some days, it seems all I ever do was sit by a phone and make countless calls. Otherwise, I would be sitting by a phone waiting to make calls.

What I still dread is making urgent calls to surgeons or radiologists in the night; or having to beg the specialist to pretty-please-come-see-my-patient-because-my-consultant-said-so-and-I-don't-really-know-

why. I have since learned to start these tough conversations with the most humble and sincere apologies and prepare myself to be yelled at anyway simply because the person at the other end can, given that they are more senior than me. My job is to sweet-talk my target specialist into doing something for my patient. If this does not work, I simply move on to call the next unsuspecting specialist.

3. Do your best for your patients, even if it may not be enough

No matter how jaded or exhausted you feel, human lives are in your hands. An MO once told me: "We are Internal Medicine. We take care of everything. We coordinate everything" - from the specialist consult to the allied health referral. The moment that patient becomes yours, it is your job to sort out their medical problems, social issues and post-discharge plans.

Yet sometimes, no matter how hard you try, things just do not work out. Some patients die despite your valiant efforts. Some become worse after admission. Some never seem to leave the hospital because the nursing homes or community hospitals are choked to the brim. The blame does not rest with any one party, yet you somehow feel responsible. Do not despair, Junior Resident, because of number four.

4. No matter how hard it gets, eat well, have a good laugh, be thankful for the little things – and have a shower

Sleep will be elusive, especially when you are on call. But this does not mean you cannot do other things in life. All of us are called on to care for people who have entrusted their lives to us. It is an incredible responsibility. But I think what really gets us through the blood, sweat and tears are the things that make us human. Laugh over funny moments, discuss wedding plans, take on home renovations, talk about our kids' schools, compare car prices, argue over politics and bond over meals. Ordinary things can help us forget the difficulty of battling diseases, limited resources, and "the system". It reminds us why we have chosen this path in medicine. It makes us smile when we see the gratitude in our patients' eyes, or when the consultant compliments you, or when your colleagues tell you, "You'll be missed".

Dr. Tina Tan, Duke-NUS MD Graduate (2011)

I rounded off my housemanship with the horror of all postings: General Surgery. My personal experiences there warrant a whole article on its own. When that was finally over, I heaved a gigantic sigh of relief and started my Psychiatry postings proper. Amid studying for exams (and flying overseas to take them), running clinics, and learning new skills designed to help me in my chosen specialty, I've realized that the things I told myself about housemanship still apply as a Medical Officer /Resident and will continue to long after I've finished my training.

A consultant once told me that things do not get "easier" after housemanship. Sure, you have less scud work to do, you do not have to take that patient's GXM or give first-dose antibiotics anymore. But the responsibilities pile up as your knowledge and experience increase. Yet, some things do remain the same: anything can happen; diplomatic communication works (but not all the time), do your best for your patients, and please, do take a shower.

Dr. Tina Tan is a Psychiatry resident at the National Healthcare Group and a Duke-NUS MD Graduate (2011).

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Beyond the Hospital: One Program's Approach to Reducing Hospital Readmissions and Associated Costs

Qasim Hussaini, first-year Duke-NUS medical student

In a flat in Yishun, two nurses swiftly check Madam Lan's sugar levels and blood pressure. She reports she has been walking less in the past month and the nurse notes her sugar is high. After working on simple exercises, they discuss Madam Lan's health plan and medication changes are confirmed with the domestic helper.

This visit is not unlike others. 76-year-old Madam Lan was recently discharged from the hospital after suffering an upper respiratory tract infection. Currently on antibiotics, she is also prescribed medication for diabetes, high blood pressure, and the blood thinner warfarin to prevent stroke. She also happens to be under the Ageing-In-Place (AIP) program at Khoo Teck Puat Hospital (KTPH).

It has been three years since the inception of the AIP program which was born out of an over-demand for subsidized beds at KTPH. This occurred almost immediately after the hospital first opened its doors in 2010. Patients with more than three hospital admissions over a six-month period are placed in the AIP program.

In setting up the AIP program, clinicians and administrators worked together to identify these patients and understand what services could be offered at home that would alleviate their need for hospitalization. What they found was eye-opening – bags of outdated and conflicting prescriptions, unsafe homes, and untrained, stressed caregivers. The AIP program was thus developed to serve its goal of delivering efficient patient-centered healthcare beyond the hospital.

Once a patient is identified and enrolled into the AIP program, a two-nurse team visits the patient's home within two weeks of discharge. During this first visit, a comprehensive medical history is taken and information on the primary caregiver and their ability to provide support is assessed. If required, the AIP team provides the necessary training and education. For instance, Madam Lan's domestic helper is now well-versed in monitoring her daily warfarin intake, and is trained to look out for simple signs like bruising, that would alert her to call a healthcare provider.

An assessment of the patient's home environment is also key. Reduced vision or mobility of the patient may necessitate arranging for installation of a non-slip floor or support bars in the washroom, or moving clutter and securing loose rugs. Following this first visit, a detailed care plan is written and short- and long-term goals are identified. Across subsequent visits, the care plan is then revisited to chart progress and assess health.

The AIP program has shown promising initial results since its inception almost three years ago. It has served close to 1073 patients, and the average number of readmissions has decreased from 3.5 to 1.2 over a six-month period. This impressive progress has earned the program a national award and a major grant from the government to expand its services. It is an exemplar of new efforts to address the care needs of the chronically ill in Singapore in a way that assures continuity and accountability.

In keeping with its culture of carefully charting its own progress, the AIP program is undergoing a rigorous evaluation by the Health Services & Systems Research Program at Duke-NUS. A quantitative assessment of the program currently includes measuring 30-, 90-, 180-day hospital admission rates, length of stay, and number of A&E visits post-discharge. To assess whether these outcomes are attributable to the AIP program, results for individuals eligible for the program will be compared to those in communities where the AIP program is not available.

A qualitative assessment of the AIP program, based on interviews with patients and caregivers, will help uncover factors that influence the success of the program. Currently, close to 20% of contacted patients decline enrollment into the program. The reasons behind this will be assessed. Finally, the AIP program will be evaluated on its cost-effectiveness, including the cost per prevented admission.

In the meantime, the AIP program is continually improving its service. Each time a patient is admitted, a text is sent to the respective nurse team. More than two admissions in a month - and the patient is "flagged" for discussion of care improvement at weekly meetings with geriatricians, nurses and hospital administrators. Further, readmissions rates for nurse teams are revisited every month for improvement. The ultimate goal is to improve the program's operational efficiency. The AIP program is also incorporating new technology to enhance the connection between providers and with patients; soon, all nurses will be equipped with an iPad synced to the electronic medical record system, linking AIP staff, clinics, and hospital.

For patients like Madam Lan, the AIP program has provided a powerful tool to keep tabs on their complex and changing health needs. There are great hopes that it will yield better use of healthcare resources and reduce unnecessary hospital stays. What is clear is the AIP program provides a friendly face and a visit they can look forward too, by skilled providers reaching out beyond the confines of a hospital to allow people to appreciate another day in good health, at home.

The writer of this article is Qasim Hussaini, a first-year medical student at Duke-NUS. He graduated from Johns Hopkins University with a Master of Science degree in Biotechnology. Qasim is working with Professor David Matchar, Program Director (Health Services & Systems Research) who is currently evaluating the AIP program.

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Learning to Serve in Batam

On April 25, 16 of us embarked on the annual two-day pediatric health-screening in Batam, Indonesia, organized by the Citramas Foundation and supported by Duke-NUS, KK Women's and Children's Hospital (KKH), Palang Merah Indonesia (Red Cross organization) and Rumah Sakit Budi Kemuliaan (a local affiliated hospital). In its eighth year now, this health-screening exercise aims to improve the community's health awareness and provide early interventions for underprivileged children in Batam.

Our group was made up of students from all four years and despite our diverse backgrounds, we all shared the common desire of wanting to serve the community through our clinical abilities and various language skills.

On the ferry en route to Batam

We were warmly welcomed by the local organizers after a 30-minute ferry ride to Batam. After settling down, we started preparations for the next day. Most of us had minimal knowledge of Bahasa Indonesia and had taken the time on the ferry to study the extremely useful notes prepared by native speakers – Jia Loon, Billy, Oka and Stella. Meanwhile, others had browsed *Baby Bear* books to read about common pediatric conditions and differential diagnoses of failure to thrive (delayed growth). Our team leader Sumitro, briefed us on how the health screening would run and our roles in triaging, plotting the children's growth charts and checking their immunization status. Over our welcome dinner later on, we gathered with the KKH volunteer doctors and nurses, as well as Dr. June Lou and Dr. Darryl Lim who have headed this project since its inception.

As we trooped to the screening site the next morning, we were joined by Indonesian doctors, local volunteers and another team of doctors and nurses that had arrived from Singapore. We set up the various stations for the health-screening, and watched as the first of many buses rolled into the parking lots. A stream of mothers and children trickled in and started registration for the health screening.

"Selamat pagi!" we greeted them, testing our command of the Indonesian language. Plotting the children's height and weight measurements revealed a harsh reality – a significant proportion of their vital statistics were below average. It made us realize the importance of regular charting of growth during early childhood – a critical period that would affect the rest of the child's life. It was heartening to think that we were making a difference by identifying these children and intervening at the right time. Charting their growth rates was just the beginning and the main "action" was in the screening area inside.

The screening room was buzzing as stations were set up around the room with doctors and nurses examining the children. This was one of the most exciting aspects as it offered the opportunity to learn important clinical signs and skills, and possibly coming across rare clinical cases. In one corner Chester and Natalie examined an infant with features of progeria, an extremely rare genetic condition that causes premature aging, while Anu, Zhou Yi and Dypti listened to the lungs of a little boy with a congenital chest abnormality.

Plotting growth charts

"Fever...cervical lymphadenopathy...strawberry tongue…" Marcus was teaching a group of first year students the symptoms of Kawasaki disease. One could not help but smile at the collegiality and camaraderie that was evident as they worked diligently. The mini teaching sessions came with its share of laughter. "No, that's not how we describe breath sounds! You would say it was an expiratory wheeze", one senior corrected a junior student who made gurgling noises when asked to describe the patient's breath sounds.

Making new friends

The Indonesian students amongst us had taken particularly active roles in patient education. Sitting beside the doctor, Freda explained a child's diagnosis and treatment to the concerned mother. Stella, Billy and Oka, accompanied by dietitians, carried out a workshop on healthy weaning.

As we rode the bus back to our rooms, we were invited by Dr. Darryl to join him and the other doctors for a drink by the jetty. As we stood by the water with our drinks, he shared with us his experiences over the past seven years, and how the project has evolved from where they were crammed in a small clinic seeing thousands of patients, to the space we now enjoy and the expansion of manpower. As we walked to the end of the jetty, one could not help but think about how fortunate we were to be a part of this experience, and how much more lies ahead in this incredible journey of becoming a physician with a heart.

Sitting in the ferry that evening, the atmosphere was one of calm and satisfaction. A group of first year students listened intently as Marcus continued to explain the signs of Kawasaki disease. Another group chatted animatedly, recounting memorable happenings from the past days. A few others dozed off, lulled by the sway of the ferry and tired from our busy weekend. Venturing onto the breezy upper deck, we caught our final glimpse of the picturesque island of Batam - that lush tropical haven to which we had arrived full of expectations and were now leaving with our hearts enlightened, friendships kindled and many a story to tell.

All smiles: the team of volunteers from Duke-NUS

Contributed by Shashendra Aponso, Anu Pandey, Zhou Yi & Sumitro Harjanto, third-year M.D. students.

Click here for more photos from the health screening.

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A Nobel Encounter: Professor Robert Lefkowitz Spends an Afternoon in Duke-NUS

Duke-NUS faculty and students were given a rare treat when they had the chance to attend a research seminar by Duke University's Professor Robert Lefkowitz, 2012 Nobel Prize winner in Chemistry on May 30. In town to deliver the keynote address at the 2014 Graduation and Hooding Ceremony, Prof. Lefkowitz also dropped by Duke-NUS to share his experience studying the seven transmembrane receptors for over 40 years and for which he won the Nobel Prize.

Hosted by Prof. Patrick Casey, the seminar was so well received that the amphitheater was packed to the brim. Some were even turned away due to the overflowing capacity. "It was terrific to see such an amazing turnout for Prof. Lefkowitz's seminar, which nicely captured the sense of excitement that can sustain one's enthusiasm for science across decades of effort," said Prof. Casey.

Following his seminar, things took a more relaxed turn as Prof. Lefkowitz held a lunch forum with post-doctoral research fellows and MD and PhD students. During the forum, he was introduced by his former trainee, Assistant Professor Mei Wang, who commented that "his enthusiasm for science has always been infectious, and draws in everyone who spends time in his lab." Prof. Lefkowitz shared how his interests shifted from being a physician to a scientist and the wisdom he gained over his illustrious career, such as research mentorships and how research allows one to be creative. Although Prof. Lefkowitz conceded that nothing is ever certain, he encouraged the research fellows and students to maintain a strong sense of optimism, faith and hunger in their own work. Prof. Lefkowitz also shared about his desire and experience of winning the Nobel Prize and life after that as a Nobel Laureate, humbly maintaining that nothing has changed despite winning the prestigious award. His passion for research still very much drives him to work every day.

Dr. Mei Wang congratulates Prof. Lefkowitz on his Nobel Prize in Duke University

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Precision Medicine Healthcare Joint Laboratory Launched

A new corporate laboratory was recently launched in Singapore by ImaginAb, Inc and Duke-NUS with the purpose of developing precision medicine strategies for healthcare. An initiative under the National Research Foundation (NRF) Corp Lab @ University scheme, the lab is accessible to both industry and academic collaborators.

Termed the “Imaging Biomarker Development Lab” (IBDL), the IBDL program represents a $15 million commitment between ImaginAb, Duke-NUS and the NRF. It will uniquely feature a state-of-the-art molecular imaging facility, operating within Duke-NUS Specific Pathogen Free (SPF) space. An invaluable resource for immunology-based research, the facility will explore new ways to study cancer biology and brain and immune function, with an Asian disease-centric focus.

Earlier this year, the establishment of protein engineering and molecular imaging capabilities designed to interface with Duke-NUS Signature Research Programs (SRPs) in cancer and stem cell biology, cardiovascular and metabolic diseases, neuroscience and immunology, were announced. These capabilities will also be used to support ImaginAb’s Research and Development.

“We are pleased to have this new capability on-line and to have recruited the initial team that will launch this exciting new translational research opportunity,” commented Professor Patrick Casey, Senior Vice Dean (Research) of Duke-NUS. It is particularly important that, in addition to our collaborations with ImaginAb and internal use of the facility, we send a message to our academic and industry collaborators that this capability is available.”

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Transforming Vision into Reality

Professor Lee Seng Teik, Emeritus Consultant of Singapore General Hospital’s (SGH) Department of Plastic, Reconstructive & Aesthetic Surgery said that his decision to establish the Chair, was in-part a “response” to Prof. Ivy Ng’s (SingHealth Group CEO) vision of establishing the SGH campus as a leading Academic Medical Center (AMC). It was a long-held belief in the importance of medical research that led Professor Lee Seng Teik to drive the Lee Seng Teik & Lee Hoo Leng Professorship in Plastic Surgery & Regenerative Medicine.

All along, he pointed out, the Department of Plastic Surgery has always had the tradition of requiring all its trainees to carry out research projects from beginning to end. Trainees are required to come up with an area of study and see it through to completion during their four-year advanced training program. “They need to engage in

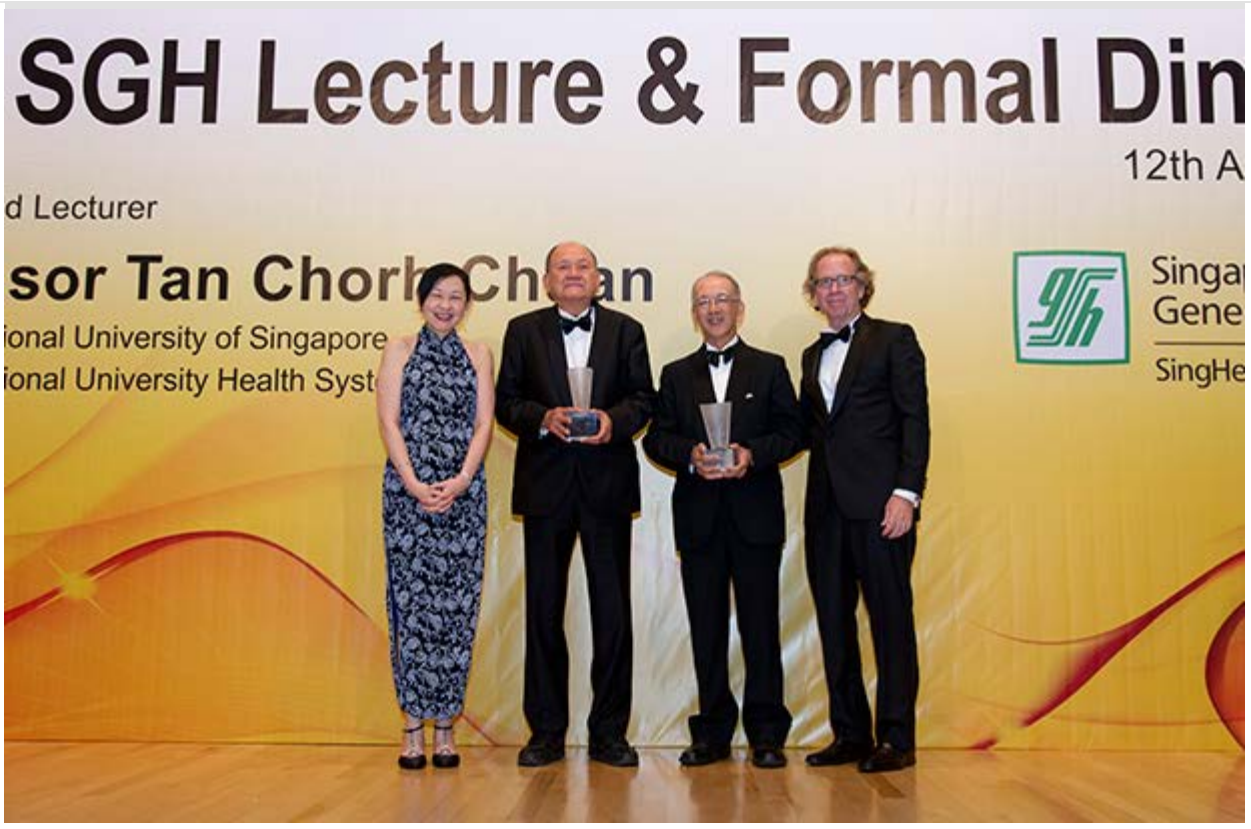
one basic research project – and this means getting it published at the end of the project," he said. Today, trainees do two research projects. Through the years, despite the small size of the Department, their doctors have made their mark by winning Young Investigator Awards at the Annual Scientific Meeting. "Research helps our trainees to think. The research mindset drives improvement, resolves problems and engenders innovation in a scientific manner," Prof. Lee emphasized.

This passion to drive a more research-focused approach forms the basis for this Professorship, Prof. Lee explained. He hopes that it will act as a "challenge" and a "catalyst" to other much bigger Clinical Departments to take on a bigger academic role. He said, "In our developing Academic Medicine Center, bigger Departments are in a better position to do the same and do even better than what we have done."

The Lee Seng Teik & Lee Hoo Leng Professorship in Plastic Surgery & Regenerative Medicine is established under the Surgery Academic Clinical Program. It is the first professorship in Singapore that recognizes and supports an individual's work in Plastic Surgery and Regenerative Medicine. According to Prof. Lee, this Chair is an advantageous confluence of Regenerative Medicine and Plastic Surgery that will transform advances in patient care. "It is the most relevant, to my mind, for our ageing population," he said. The idea of regeneration encompasses the breadth of many of the issues that plague us and Regenerative Medicine encompasses a variety of research areas such as cellular research, tissue engineering and biomaterials engineering. Many of these reconstructive techniques can repair, reconstruct and regenerate tissues or organ function that is lost due to age, disease, accident, or congenital defects. In the same vein, research in plastic surgery can address the restoration of form and function of the body. It includes many types of reconstructive surgery, hand surgery, microsurgery and the treatment of burns. These new insights into tissue and organ regeneration also dovetail with Duke-NUS' Cancer and Stem Cell Biology Signature Research Program and place the SingHealth-Duke-NUS partnership in a stronger position to make progress in regenerative medicine and plastic surgery.

Who are behind the establishment of the Lee Seng Teik & Lee Hoo Leng Professorship in Plastic Surgery & Regenerative Medicine

Prof. Lee is Emeritus Consultant of SGH's Department of Plastic, Reconstructive & Aesthetic Surgery. From 1985 to 1998, he was the Head of SGH's Department of Plastic Surgery and Burns and in 1990, he founded the National Burns Centre's skin culture lab at SGH. From 1994 to 2001, he was Founding Director of the SGH-Postgraduate Medical Institute (SGH-PGMI). Prof. Lee served as Chairman of Education and Training of the SingHealth cluster from 2001 to 2004 and was a Clinical Professor with the Faculty of Medicine at the National University Hospital from 2001 to 2006. He is currently holding the position of Adjunct Professor in Duke-NUS. He is also the Founding Director and Advisor for the SGH Museum. In his spare time, Prof. Lee continues to lead many humanitarian missions. Mr. Lee Hoo Leng is a close family friend of Prof. Lee.



(L-R): Prof. Ivy Ng, Group CEO, SingHealth & Chairman, Development Committee, Duke-NUS, Mr. Lee Hoo Leng, Prof. Lee Seng Teik and Prof. Thomas Coffman, Executive Vice Dean, Duke-NUS (SGH 21st Lecture & Formal Dinner, Apr 12, 2014)

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A Gift That Keeps On Giving

The generous gift of $80 million from the Estate of Tan Sri Khoo Teck Puat has enabled Duke-NUS to make bold strides in research and discovery. The gift, made in 2007 is the first and largest donation made to Duke-NUS by a single donor, and was matched dollar-for-dollar by the Singapore government. The Estate's generous gift has enabled Duke-NUS to substantially accelerate and strengthen its planned research programs to address medical and healthcare problems of significance to Singapore and Asia.

Over the last seven years, the Gift has supported ground-breaking research across Duke-NUS' four Signature Research Programs in infectious diseases, cancer and stem cell biology, neurobehavioral disorders, and cardiovascular and metabolic disorders. Most recently, it paved the way for an important finding that will help liver cancer patients make better treatment decisions (see box story).

The Gift has established the Khoo Discovery, Khoo Clinical Project Awards and Khoo Investigator Awards. To date, 12 individuals have benefited from these awards and 22 clinician researchers have graduated from the Khoo Scholars Program. 10 Khoo award recipients have also since gone on to win prestigious national research awards and six others have garnered industry grants and other sources of funding. For example, Dr. Andrea Low, who was selected for the Khoo Scholars Program and awarded the Khoo Pilot Award (previously known as Khoo Clinical Scholars Pilot Award) in 2011, went on to receive an NMRC Transition Award in 2013. The Khoo Pilot Award has also allowed 16 researchers to develop their careers as clinician-investigators and as future leaders in clinical research.

The Khoo Gift also allowed Duke-NUS to introduce two new award categories in 2013 to improve the breadth and depth of quality research projects: the Khoo Mentored Research Award (KMRA) and the Khoo Student Research Award. The KMRA engages experienced clinician researchers and scientists to mentor and develop the careers of younger clinician investigators and clinician scientists; while the Khoo Student Research Award aims to facilitate

greater scientific engagement and learning for third-year Duke-NUS medical students engaged in basic, clinical and translational research projects in Singapore.

Making a decision for treating liver cancer

Prof. Pierce Chow, Khoo Clinical Discovery Project Award recipient

Making a decision about the 'right' way to treat liver cancer has long been a medical and emotional challenge. In the important group of patients with early liver cancer and good liver function it has been unclear if the choice should be liver resection or transplantation. In liver resection, the cancerous portion of the liver is removed, leaving the remaining healthy liver to regenerate. A liver transplant is another option where a healthy donor liver is grafted to take the place of the diseased liver. If the cancer is in its early stages, both treatments offer a good chance of survival over five years.

Despite the large burden of liver cancer – the third leading cause of cancer deaths in the world affecting up to a million new patients a year, predominantly in Asia which carries 70 to 80 per cent of the cases– there has been no definitive study that determines which procedure is more effective – medically and from a cost-utility point of view.

A landmark study by Professor Pierce Chow from the Dept. of HPB Surgery and Liver Transplantation at SGH, a Khoo Clinical Discovery Project Award recipient, has weighed the outcomes of both treatment modalities to develop an Outcomes Decision Model that will help doctors, patients and family members make better decisions.

"It is difficult for individual doctors and patients to access recent data and to conduct a rigorous analysis of the data on their own. Decisions on this issue have thus been frequently made on the basis of outdated reports and analyses or even on opinions expressed in the lay media," Prof. Chow explained.

"Our study rigorously analyzed recent data and makes this available to everyone. While our study used data from three countries namely the USA, Switzerland and Singapore, the approach we adopted can be applied to any country as long as outcomes data and costs of that country are available. Using this approach one can determine which of the two treatment modalities is more cost effective in his or her country."

The Model found that liver resection is a more cost-effective option as both modalities of treatment have similar survival outcomes but liver transplantation is almost ten times the cost of liver resection and is associated with higher operative risks.

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Victor Dzau Honored for Outstanding Service

For his numerous contributions to shaping medical education, healthcare policy and scientific research, Professor Victor J. Dzau, MD, has been awarded the NUS Outstanding Service Award. The National University of Singapore (NUS) Awards recognize and honor individuals who have left an indelible mark through their exceptional achievements in education, research, and service to Singapore and the community.

Outstanding Service Award recipient, Professor Victor J. Dzau

Dr. Dzau, a member of the Duke-NUS Governing Board until July 1, 2014, was instrumental in the creation of Duke-NUS in April 2005 and was the school's initial proponent and driving force. Apart from being signatory to the historic agreement between Duke and NUS, he has also played a critical role in shaping the academic medicine partnership between Duke-NUS and the Singapore Health Services. Dr. Dzau was also Chancellor for Health Affairs at Duke University and President and CEO of the Duke University Health System. Starting July, Dr. Dzau officially assumed his new role as the President of the US National Academies' Institute of Medicine.

Dr. Dzau has served as an advisor to universities, corporations and governments, sharing his expertise and leadership on academic health systems, global health and healthcare innovation. The Shanghai-born cardiologist also specializes in cardiovascular translational research and has earned numerous awards and recognition for his work throughout his career.

"I am deeply honored to be recognized with this award as I consider the successful collaboration between Duke and NUS that created the Duke-NUS Graduate Medical School one of the most significant achievements of my time at Duke," Dr. Dzau said.

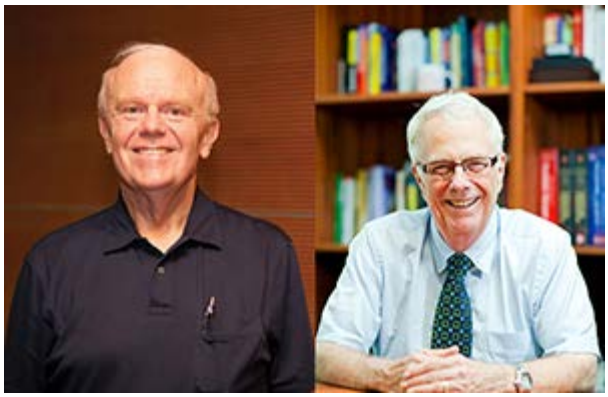
Dr. Dzau also sits on the Board of SingHealth, the academic medicine partner of Duke-NUS.

Emeritus Professor

Besides, Dr. Dzau, NUS has also conferred the title of Emeritus Professor on two Duke-NUS faculty members in recognition of their distinguished scholarship and outstanding service to medical education and research. Prof. Doyle Graham's advocacy of Duke-NUS and TeamLEAD, and his passion for medicine and education made him an outstanding senior role model for our students. He contributed to the foundations of Duke-NUS' innovative and internationally-renowned TeamLEAD self-directed learning methodology developed by the Education Deans.

Prof. Augustus John Rush was also honored as Emeritus Professor for pioneering and developing programs for clinician-scientists in Duke-NUS. In his role as Vice Dean of Clinical Sciences, he also established the Academic Medicine Research Institute in 2012 and served as its inaugural Executive Director. This institute has successfully developed education, training and career development programs to mentor and groom emerging clinician-scientists.

NUS President Professor Tan Chorh Chuan said the recipients stand out as role models of excellence who have made outstanding contributions and served the university and society with passion, energy, and creativity in their respective fields of expertise.



Emeritus Professors Doyle Graham and Augustus John Rush

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A Better Understanding of Cell Fate

Prof. David Virshup

A Duke-NUS study has broadened the understanding of cell development and the mechanisms involved in cell defects and mutations. Professor David Virshup, Director of the Cancer and Stem Cell Biology Program, led the team that identified how a vitally important signaling protein called Wnt moves out of the cell and goes on to affect cell development and cancer proliferation.

Dr. Virshup explained, “Wnt is a family of signaling proteins that are very important in the development processes. It was originally identified in wingless flies. Wnt determines whether a fly will develop wings or whether a mouse will develop a brain.” Past research has shown that a defect in Wnt (either too much or too little) results in developmental defects and cancer. However, not much was known about how Wnt is secreted.

Research findings showed that in order for Wnt to be secreted, another protein called Wntless (Wls) is needed. “Understanding the mechanism of how Wnt moves out of the cell, gives us a better picture of how to identify what can go wrong and cause mutations,” said Dr. Virshup. This study adds to his previous research on a signaling protein called Porcupine (porcn), which is the carrier that ‘loads’ Wnt into the Wls before the latter is secreted.

These findings, published in *Developmental Cell* in April, fill an important knowledge gap in the field of cell biology and contribute to cancer research. Dr. Virshup added, “Studying these cell pathway studies is important in better understanding both cancer and its development and ultimately helps in the development of better diagnoses, treatments and drugs.”

The study was funded by the Singapore National Research Foundation under its STaR Investigator Award (STaR/0002/2008) administered by the Singapore Ministry of Health’s National Medical Research Council.

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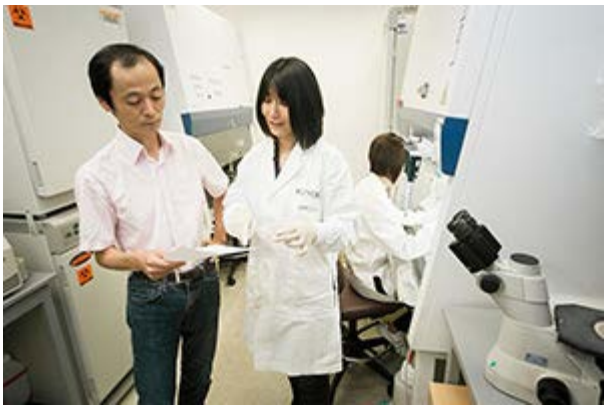
A Novel Disease-Preventing Antioxidant Pathway

Recent research, led by Assistant Professor Koji Itahana of Duke-NUS, has showed that uric acid is a major intracellular antioxidant, possibly even more important than the antioxidants we try to eat. The study also discovered how uric acid helps to prevent aging and disease and in the treatment of cancer. Traditionally, uric acid has a bad reputation because high levels of the compound are associated with gout and other medical conditions. However, these findings revealed that uric acid also has important antioxidant properties.

The team from the Cancer and Stem Cell Biology Program at Duke-NUS also demonstrated how uric acid gets into cells to protect them in the event of stress. It goes through a transporter called SLC2A9 which itself is regulated by the protein p53, one of the most important tumor suppressors that mutated in about a half of cancers worldwide and has been implicated in other diseases. These findings provide new evidence as to how oxidative stress impacts aging, cancer, cardiovascular and neurodegenerative diseases.



Asst. Prof. Koji Itahana and Dr. Yoko Itahana

Understanding this antioxidant pathway will enable researchers and clinicians to better understand how to prevent aging and other such diseases. Interestingly, Dr. Itahana also showed that shutting down the SLC2A9 antioxidant pathway in cancer may be an unorthodox way to target cancer once the patient already has the disease.

Published in *Oncogene* in May, the study was supported by the Singapore Ministry of Education Academic Research Fund Tier 2 (MOE2013-T2-1-123) and the Duke-NUS Signature Research Program, with funding from the Ministry of Health.

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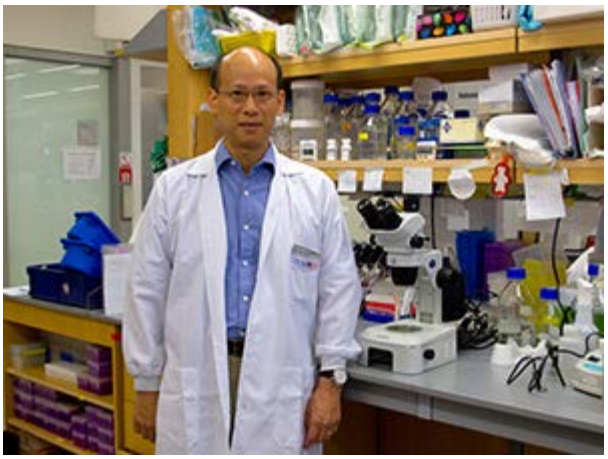
Cancer Stem Cell-Protecting Switch Uncovered

A Duke-NUS led research team has identified a molecular switch used by chronic myeloid leukaemia (CML) stem cells to resist standard therapy. The study, led by Associate Professor Ong Sin Tiong from the Cancer and Stem Cell Biology Program, revealed that the low oxygen concentrations (physiologic hypoxia) normally found in human bone marrow is a critical factor enabling leukaemia stem cells (LSCs) to evade therapy with tyrosine kinase inhibitor drugs (TKI), as well as maintain their stem cell characteristics. This discovery explains in part why patients with CML have to remain on life-long TKI therapy, since cessation of treatment results in recurrent disease in over 90% of patients. This is financially draining as TKI treatment in Singapore can cost more than $4000 a month.

While TKIs are effective in killing most of the CML cells in patients and provide effective disease control, CML LSCs are resistant to TKIs and persist in the bone marrow of patients even during TKI therapy. When TKI therapy is stopped, the small population of LSCs in the bone marrow starts proliferating again and causes the CML to recur. This is very troubling both from a disease and financial perspective.

Dr. Ong's team grew CML LSCs in low (physiologic hypoxia) and atmospheric oxygen concentrations, and showed the hypoxia both enhances the ability of CML LSC to survive in the presence of TKIs, as well as maintains their ability to function as LCSs. They were then able to identify a molecular switch, the HIF1α protein, which is turned on by physiologic hypoxia, and



Assoc. Prof. Ong Sin Tiong

which facilitates the protective effects of hypoxia on CML LSCs.

The findings suggest that drugs which interfere with either HIF1α expression or function might be helpful in eradicating CML LSCs in patients. If successful, such an approach might enable patients with CML to be cured, and remove the need for life-long TKI therapy. Given the financial costs and side-effects of long-term TKI therapy, such a scenario would both improve the management of patients with CML, and result in significant cost-savings for patients and healthcare systems caring for them.

In addition to Dr. Ong, study authors include post-doctoral researcher Dr. Ng King Pan, Duke-NUS MD/PhD student Ms. Aditi Manjeri, Assistant Professor Charles Chuah from the Singapore General Hospital and Duke-NUS, and Dr. Lee Kian Leong and Professor Lorenz Poellinger from the Cancer Science Institute of Singapore, National University of Singapore. Published in April, in the journal *Blood*, this research is supported by the Duke-NUS Signature Research Program, with funding from the Ministry of Health.

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Collaborative Neuroscience Research Institute Launched

The National Neuroscience Research Institute Singapore (NNRIS) was recently launched to enhance treatment of cognitive disorders and steer the course of neurological research in Singapore. A joint collaboration by Duke-NUS and the National Neuroscience Institute (NNI), NNRIS will bring together more than 200 neurologists, neuroscientists and researchers from the two institutions.

Professor Lee Wei Ling, Director of NNI, elaborated on the prudence of this collaboration. “NNRIS, which will be Singapore’s largest institute specializing in neuroscience, represents Singapore’s first concerted step to tackle neurological problems and to look for practical solutions for our patients in the face of our ageing population and the rising incidence of neurological diseases.”

NNRIS aims to combine the expertise from Duke-NUS and NNI’s neuroscience research programs, consolidate research resources and develop a research facility. The institute’s vision is set to benefit Singapore, whose demographics - especially with regard to its ageing population - currently steers public policy.

Professor Ranga Krishnan, Dean of Duke-NUS, also weighed in, “Doctors and researchers across the neuroscience field can now collaborate easily to turn pertinent clinical observations into research that leads to practical solutions for patients.”

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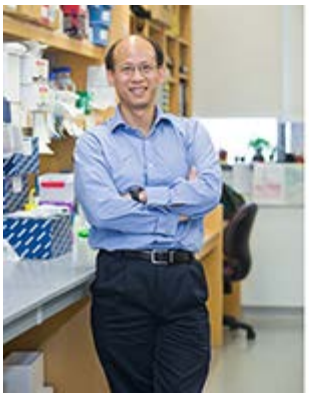
Duke-NUS Professors Elected to the American Society for Clinical Investigation

The American Society for Clinical Investigation

(ASCI) has welcomed 76 new members to their ranks this year, which include two members of the Duke-NUS Faculty. Associate Professor Ong Sin Tiong and Professor Teh Bin Tean from the Cancer and Stem Cell Biology Program were among the inductees of 2014.

Established in 1908, the ASCI has over 3,000 members from all medical specialties with outstanding achievements in biomedical research. Members submit nominations of physician-scientists aged 50 years or younger; the ASCI then elects up to 80 new members each year based on their significant research accomplishments.



Assoc. Prof. Ong Sin Tiong and Prof. Teh Bin Tean (credit: NCCS)

A clinician-scientist and medical oncologist, Assoc. Prof. Ong Sin Tiong's research is directed toward understanding the mechanisms underlying drug-resistance in human cancers, and in devising clinical trials to overcome drug resistance in patients. Dr. Ong is also a Visiting Consultant at the Singapore General Hospital and the National Cancer Centre Singapore.

Professor Teh Bin Tean is an international leader in kidney cancer (renal cell carcinoma) and Asian cancer genomics. In addition to his appointment at Duke-NUS, Dr. Teh is Principal Investigator for the Laboratory of Cancer Epigenome at the National Cancer Centre Singapore and Senior Principal Investigator at the Cancer Science Institute of Singapore, National University of Singapore.

They join their colleagues Professor Thomas Coffman, Professor David Virshup and Professor Patrick Tan who were elected to the ASCI as members in 1996, 2000, and 2013, respectively.

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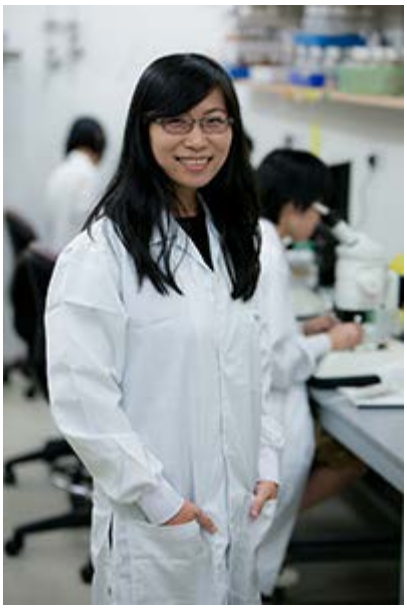
Protein Discoveries Have Implications For Brain Tumor Treatments



Assoc. Prof. Hongyan Wang

Two studies, led by Associate Professor Hongyan Wang from the Neuroscience and Behavioral Disorders Program at Duke-NUS, have found protein complexes that may have implications on how brain tumors are treated in the future. In both instances, the fruit fly (*Drosophila melanogaster*) model was used to conduct the research.

The first study, published in *EMBO Reports* in January, discovered the protein complex, SCFSlimb E3 ubiquitin ligase, which regulates asymmetric division of neuroblasts. Fruit fly larval brain neuroblasts divide asymmetrically to balance between self-renewal and differentiation. This process is an important part of healthy brain function and when a neuroblast divides symmetrically, which is irregular in this case, it can cause the formation of tumors.

In the same study, Dr. Carol Tang and Associate Professor Christopher Ang Beng Ti from the National Neuroscience Institute collaborated with Dr. Wang's team and showed that the human counterpart of Slimb was lost in most of glioma patients. The findings could improve prognostic tests and prediction of patient survival for human patients with brain tumors.

The second study, published in *eLIFE* in March, identified that a protein complex, composed of Brahma, HDAC3 and Earmuff, plays an important role in preventing dedifferentiation. Dedifferentiation (reversion) of neural progeny leads progenitor or mature cells to become 'ectopic neural stem cells' which can cause tumors.

By detecting this protein complex, Duke-NUS researchers shed light on a process that inhibits tumor development and gives hope for the discovery of therapies and treatments that target tumor prevention through this pathway.

Both studies are supported by the National Research Foundation, Prime Minister's Office, Singapore under its Research Fellowship (NRF-RF2009-02) and the Duke-NUS Signature Research Program, with funding from the Ministry of Health.

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Separation Anxiety - Keeping Cell Division Stable

A recent study, led by Assistant Professor Lee Sang Hyun from the Cancer and Stem Cell Biology Program at Duke-NUS, has discovered one of the key mechanisms involved in coordinating chromosome segregation during cell division (a process called cytokinesis). In order for cytokinesis to occur, the chromosome passenger complex (CPC) and the protein Aurora B kinase must relocate to the cell equator. This is where a checkpoint process ensures that the cell replication will be stable and prevents genomic instability

Asst. Prof. Lee Sang Hyun and his research team

Carried out by Dr. Mayumi Kitagawa and Ms. Sarah Fung in Dr. Lee's laboratory, the research shows that the mitotic checkpoint regulation by Cdk1/cyclin B1 kinase is essential in coordinating the relocation of CPC and the protein Aurora B kinase. This finding provides a deeper understanding of the key mechanics involved in the landmark events of chromosome segregation and cytokinesis.

Dr. Lee explained, "The mitotic checkpoint ensures chromosome alignment before separation starts. Anything that goes wrong in this process leads to unbalanced chromosome segregation, resulting in aneuploidy, a condition found in over 90% of human solid cancers. This new understanding of orchestrating the mitotic process helps scientists better understand the cause of genomic instability in human cancers and may be developed to target cancer therapy."

This finding was published in *Cell Reports* in April and is supported by the National Research Foundation, Prime Minister's Office, Singapore under its National Research Foundation Fellowship (NRF RF Award No. NRF-RF2010-02).

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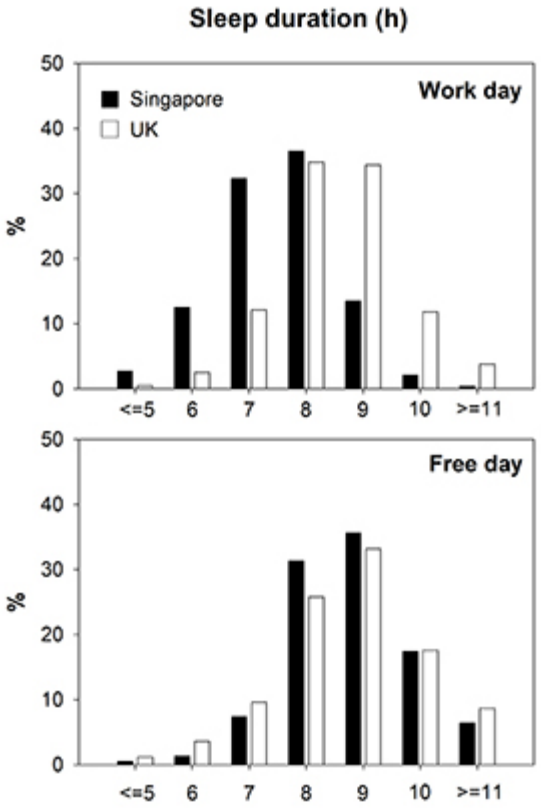
Singapore Young Adults Sleep Less Than UK Counterparts

A sleep survey, jointly conducted by Duke-NUS and the University of Surrey, on more than 2,700 young adults in Singapore and the United Kingdom has shown that on working days, young people in Singapore slept about one hour less than their counterparts in the UK. These findings shed light on the issue of sleep deficiency in Singapore.

The research, led by first author Dr. June Lo, Duke-NUS Research Fellow, and senior author



Distribution of sleep duration on working and free days in Singapore and the United Kingdom.

Professor Michael Chee, compared the sleep duration and timing of young adults aged 18 to 35 from Singapore (1898 people) and the United Kingdom (837 people). On working days, young adults in these two countries woke up at similar times but the Singapore cohort charted later bedtimes – which meant that they had shorter sleep duration.

Surprisingly, on free days, the Singapore participants did not clear their additional sleep debt by sleeping more than participants in the UK. The findings suggested that the Singapore cohort was more sleep-deprived, and this could reflect greater demands from work and study in Singapore.

The study was published in *Frontiers in Neurology* in May. Data collection in Singapore was supported by the Singapore National Research Foundation under its STaR Investigator Award (STaR/0004/2008) administered by the Singapore Ministry of Health's National Medical Research Council, and in the UK by the Air Force Office of Scientific Research (FA-9550-08-1-0080) and the Biotechnology and Biological Sciences Research Council (BB/F022883/1 and BSS/B/08523).

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Study Addresses Cost of Childhood Obesity

A recent Duke-NUS and Duke Global Health Institute study shows that childhood obesity is not just a health burden – it is also a substantial financial one. Referring to the findings, lead author Professor Eric A. Finkelstein from the Health Services and Systems Research Program at Duke-NUS confirmed, "Reducing childhood obesity is a public health priority that has substantial health and economic benefits."

The research team examined the lifetime medical cost estimates for obese and normal weight children over a 15 year period. Based on this evidence, US$19,000 is the estimated lifetime medical cost of an obese child compared with a child of normal weight who maintains a normal weight throughout adult life. On the other hand, the estimated lifetime medical cost of an obese child is US $12,900 when taking into account the possibility of normal weight children becoming overweight or obese in adulthood.

In addition to Dr. Finkelstein, study authors included Assistant Professor Rahul Malhotra and Wan Chen Kang Graham of Duke-

NUS. Published online in *Pediatrics* in April, the study was funded by the Robert Wood Johnson Foundation.

Prof. Eric Finkelstein

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The Singapore Chinese Health Study - Three Significant Findings

Assoc. Prof. Koh Woon Puay

Associate Professor Woon-Puay Koh from Duke-NUS and the Saw Swee Hock School of Public Health (SSHSPH), National University of Singapore (NUS), is the site-principal investigator of the Singapore Chinese Health Study (SCHS), a population-based long-term prospective cohort study in Singapore.

The SCHS was established by the recruitment of 63,257 middle-aged and elderly of Chinese residents living in Singapore between 1993 and 1998. This cohort has been followed-up actively through interviews and also via linkage with nationwide disease and death registries.

The SCHS is funded by grants from the U.S. National Institutes of Health, and receives active collaboration and support from The Ministry of Health in Singapore. Being the largest study of its kind in Southeast Asia, it represents a unique constellation of strengths highlighting the importance of Singapore as a hub for biomedical research: a well-defined motivated study population with nearly complete follow-up, strong expertise in epidemiology and biochemical measurements, and an Asian setting that importantly complements studies conducted in western countries.

Late last year, using data from the SCHS, Dr. Koh, Assistant Professor Pan An from the SSHSPH and Dr. Angela Koh from the National Heart Centre Singapore showed that both omega-3 fatty acids derived from seafood and plant sources, such as nuts and seeds, are good for the heart. Participants who were in the top 25% intake of omega-3 fatty acid in this cohort were 17% less likely to die of cardiovascular disease compared to the lowest 25% intake.

While previous studies have linked omega-3 fatty acid intake with a lower risk of death from cardiovascular complications, most of these studies have been conducted in Western populations and do not differentiate between seafood and plant sources. Published in the *European Journal for Preventive Cardiology*, this study among Chinese examined omega-3 fatty acids from seafood and plant sources separately, and found independent reduction in cardiovascular disease mortality risk with each source.

A second study, helmed by Dr. Koh and with authors Dr. George Boon-Bee Goh and Associate Professor Wan-Cheng Chow from Singapore General Hospital, found that drinking two or more cups of coffee daily decreased the risk of death from non-viral hepatitis liver cirrhosis by 66% compared to those who did not drink coffee daily.

Published in *Hepatology* and reported in over 50 media outlets worldwide, this research is novel in differentiating the effects of coffee on non-viral hepatitis and viral hepatitis-B related cirrhosis mortality, the latter being prevalent in this part of the world. Dr. Koh and her team speculate that coffee contains several active ingredients that can potentially reduce the process of inflammation leading to cirrhosis caused by alcohol abuse or fatty liver deposition in the liver.

Finally, Dr. Koh and PhD student Zhaoli Dai from NUS, in collaboration with the Ministry of Health in Singapore and US-based collaborators, found that a healthy diet rich in plant-based food such as vegetables, fruit and soy foods could reduce the risk of osteoporotic hip fractures.

Published in the *Journal of Nutrition,* the study compared two distinct Chinese dietary patterns, the vegetable-fruit-soy pattern and the meat dim-sum pattern unique to this cohort, and found that participants who were in the top 20% for consuming the most amount of food in the vegetable-fruit-soy pattern had 34% reduction in risk of hip fracture compared to those whose consumption was in the

lowest 20%. Conversely, the meat dim-sum pattern did not have any apparent effect on the risk of hip fracture. With the incidence of osteoporotic hip fracture rising rapidly in Asia, and Singapore, in particular, the findings encourage middle aged to elderly individuals to consume a healthy plant-based diet to strengthen their bones for fracture protection, in addition to maintaining a healthy body weight and exercising.

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GRANTS AWARDED

CONTENT

No.	PI	Dept	Project Title (Please click titles for details)	Grant Call	Duration (Months)
1.	Patrick Casey	CSCB	ImaginAb@DUKE-NUS Corporate Lab	Corporate Lab@Singapore, Duke-NUS ImaginAb partnership	60
2.	Lim Kah Leong	NBD	Adult and Induced Pluripotent Stem Cells for Neurological Disorders and CNS Repair	NTU Collaborations 2013	12
3.	Eyleen Goh	NBD	Adult and Induced Pluripotent Stem Cells for Neurological Disorders and CNS Repair	NTU Collaborations 2013	12
4.	Gavin Smith	EID	Genetic diversity of human influenza viruses from a community cohort versus sentinel and hospital-based surveillance in Singapore	MOH CDPHRG	36
5.	Marc Fivaz	NBD	Targeting the CA2+ sensor STIM2 for improved synapse therapeutics	A*STAR - JJSI	18
6.	David Virshup	CSCB	Regulation of Wnt Secretion	NMRC STaR	60
7.	Adam Claridge-Chang	NBD	The roles of context and arousal in Drosophila olfactory learning and memory	MOE Tier 2	36
Total Amount of Funding Received: $23.6 million					

Synopsis

1. ImaginAb@DUKE-NUS Corporate Lab

Patrick Casey, Cancer & Stem Cell Biology

Duke-NUS and ImaginAb Inc., a clinical-stage biotechnology company headquartered in Los Angeles, have partnered to establish a joint laboratory. Established under the Corp Lab@University scheme of the NRF, the laboratory represents a combined $15m commitment from ImaginAb, the National Research Foundation and Duke-NUS.

Termed the “Imaging Biomarker Development Lab”, this academic/industry partnership combines Duke-NUS’ extensive research platform with ImaginAb’s antibody engineering technology and expertise in biomarker development for diagnostic imaging. As part of the collaboration, ImaginAb’s growing portfolio of in vivo diagnostic imaging agents for oncology and immunology will be made available and complement the research activities of Duke-NUS’ Signature Research Programs, as well as potentially create new precision medicine strategies in partnership with Duke-NUS PIs.

The laboratory is intended to serve as an accessible core facility for Duke-NUS research programs to support drug discovery and development. The lab’s capabilities are also available to industry and academia more broadly, and IBDL and welcomes proposals for collaboration. The laboratory will also support ImaginAb’s activities in the development of new in vivo imaging diagnostic agents and serve as a focal point for key collaborations in cancer and immunology with global biopharmaceutical companies.

The laboratory provides preclinical Positron Emission Tomography (PET), as well as gamma counting and radiometabolite analysis capabilities. Support and expertise includes applying applications of molecular imaging, preclinical model development, radiopharmaceuticals and image acquisition and analysis. These capabilities enable the evaluation of biodistribution, specificity, clearance and metabolic profiles of new in vivo imaging diagnostic agents. The capabilities can also be used for the characterization of disease models in vivo, and the establishment of imaging capabilities within the specific pathogen free (SPF) barrier facility will particularly enable longitudinal studies in immune compromised models.

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2. Adult and Induced Pluripotent Stem Cells for Neurological Disorders and CNS Repair

Lim Kah Leong, Neuroscience & Behavioral Disorders

This is a collaboration between Professor George Augustine (NTU) and Assistant Professor Eyleen Goh (Duke-NUS). One of the main objectives of our CRP subaward is to explore the potential of cell-based transplantation for treatment of Parkinson’s disease (PD) via induced pluripotent stem cells (iPSCs). Towards achieving this endeavour, we have successfully developed an optimized protocol for the efficient generation of iPSCs from adult PD patient and healthy donor skin fibroblasts in a viral and feeder-free manner. Recently, in partnership with scientists at the A*STAR Institute of Bioengineering and nanotechnology, we have also reported a xeno-free method in the generation of these pluripotent cells (Lu et al., 2014 Biomaterials). Prospectively, our combined viral, feeder and xeno-free procedure should pave the way for these cells to be used in the clinic. Using this approach, we have successfully derived iPSCs from 5 local patients and 4 healthy controls through our collaboration with Professor Tan Eng King from the National Neuroscience Institute. We have also generated 16 lines of iPSCs from commercially-available skin fibroblasts derived from Caucasian populations. These include 4 sporadic PD, 5 familial PD and 7 age- and sex- matched healthy controls. Together, we now have 25 iPSC lines. We have conducted a battery of standard assays to ensure that our human iPSC lines meet the most stringent criteria for pluripotent stem cells, including their ability to form teratoma in vivo. Transplantation of dopaminergic progenitors generated from these cells into our PD mouse model is currently underway to evaluate their efficacy in promoting functional recovery of the lesioned mouse. In parallel, we have also optimized the protocol for deriving dopaminergic neurons (up to 80% or more efficiency) from control and PD iPSCs to be used as an in vitro model for mechanistic studies and drug discovery. We anticipate that the outcomes of our project would guide us towards developing rational neuroprotective and neurorestorative strategies for PD.

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3. Adult and Induced Pluripotent Stem Cells for Neurological Disorders and CNS Repair

Eyleen Goh, Neuroscience & Behavioral Disorders

My lab is interested in understanding neurogenesis in the developing and adult brains and how this process can be manipulated and explored for enhancing brain functions or therapeutic purposes. For example, it is known that neurogenesis in hippocampus is important for learning and memory. Altered neurogenesis (including wiring of the brain) has been found in various neurological disorders such as autism spectrum disorders, schizophrenia, Alzheimer's disease and Parkinson's disease. Thus, manipulating neurogenesis process can potentially enhance normal brain functions or reverse defects in brains with neurological/pathological conditions.

In order for a resident newborn neurons or implanted cells to function in the brain, appropriate synaptic connections must be established between the new and pre-existing neurons. Therefore, we proposed to use optogenetic and cellular imaging approaches to define the ability of resident newborn neurons or implanted human patient-derived neurons to integrate functionally into the existing adult CNS circuitry. This study uses transgenic mouse lines that express the light-activate channel, channelrhodopsin-2 (ChR2) in genetically-defined populations of neurons in the adult brains (from Prof George Augustine's lab). These mice allow us to study and map the circuitry in specific brain regions of interest. With these tools on hand, we then are able to examine how factors known to affect endogenous neurogenesis can affect the functional incorporation of resident newborn neurons and implanted neurons. In this last phase of the funded period, we are focusing on studying the influence of nutrition and non-neuronal cells (microglia) on the functional integration of resident or implanted newborn neurons into the existing circuitry at the hippocampus. Our studies will provide basic understanding on resident newborn neurons and implanted neurons in adult brains and also shed light on potential therapeutic strategies for neurological disorders affecting neuronal development and circuitry.

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4. Genetic diversity of human influenza viruses from a community cohort versus sentinel and hospital-based surveillance in Singapore

Gavin Smith, Emerging Infectious Diseases

During March and early April 2009, an H1N1 virus lineage previously undetected in humans emerged in Mexico and the United States spreading rapidly via human-to-human transmission to develop into the first influenza pandemic, highlighting the importance of surveillance for infectious diseases. The World Health Organization influenza surveillance program relies heavily on samples and information from hospital laboratories, and is therefore biased towards more severe infections when compared to a community cohort. While the difficulties of accurately estimating epidemiological parameters such as incidence and severity from passive surveillance of influenza in hospitals are well recognized, a comparison of virus diversity captured from different surveillance systems has not been conducted. In this study we will quantify the relative genetic diversity of influenza A and B viruses collected in Singapore from hospital inpatients and outpatients, a sentinel surveillance system involving general practitioner clinics and a community-based, observational cohort. Analysis of associated epidemiological data will also allow us to identify potential viral genetic markers of disease severity. The information generated from this study on the effectiveness of different surveillance systems in capturing virus genetic diversity will contribute directly to enhancing influenza control and in global efforts for influenza pandemic preparedness.

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5. Targeting the CA2+ sensor STIM2 for improved synapse therapeutics

Marc Fivaz, Neuroscience & Behavioral Disorders

AMPA receptors (AMPARs) are the main mediators of excitatory neurotransmission in the brain and

their function is altered in a diverse array or neurological disorders, thus making AMPARs a prominent target for clinical intervention. Previous attempts to target AMPARs with small molecules were often associated with debilitating side effects, suggesting that indirect approaches to modulate AMPAR function might have therapeutic potential.

Our laboratory has uncovered a signaling pathway in excitatory neurons that promotes synapse formation and synaptic insertion of the AMPAR. This pathway is mediated by the Ca2+ sensor STIM2, a protein that resides in the endoplasmic reticulum (ER), and couples ER Ca2+ homeostasis to synaptic function. In this proposal, we will test the hypothesis that modulating (i.e. enhancing or inhibiting) STIM2 activity will restore AMPAR and synaptic function in disease states and provide an alternative therapeutic solution for neurological diseases associated with hypo- or hyper-function of the AMPAR.

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6. Regulation of Wnt Secretion

David Virshup, Cancer & Stem Cell Biology

Pathologic expression of Wnts occurs in cancers and other diseases. Targeting the production and secretion of Wnts may have therapeutic benefit. Funded by the first STaR Award, we identified new mechanisms in Wnt secretion, and in collaboration with the A*STAR Experimental Therapeutics Centre in Singapore, we developed new drugs (PORCN inhibitors) to block the secretion of all Wnts. These drugs can block Wnt-dependent pathology. Here we extend these studies by asking the next round of questions. How do we prospectively identify Wnt-dependent cancers? What cell types are making the Wnts? What signals turn on Wnt expression, and how are Wnts released from cells? This proposal builds on our recent advances to fill these gaps in knowledge with an integrated program with collaborators at Singapore General Hospital, National University of Singapore and Biopolis to study Wnt production, secretion and targets. Over the past grant period we found that all human Wnts require palmitoleation by the ER-resident O-acyl-transferase PORCN, and that this palmitoleation is required for all Wnts to be transported to the cell surface by the carrier protein WLS. We identified a key mechanism required for the release of Wnts from cells. In collaboration with Alex Matter and the Experimental Therapeutics Center, we developed and are patenting novel pharmacologically optimized nanomolar inhibitors of Wnt secretion that can be used in both discovery and potentially, in the treatment of Wnt-high disorders. Major insights into the source of Wnts in the stem cell niche came from our study of intestinal epithelium and bone marrow of mice homeostasis using mice with a floxed allele of PORCN. This current proposal builds on the collaborations and tools generated over the past grant period to translate new knowledge on Wnt secretion into therapeutic advances

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7. The roles of context and arousal in Drosophila olfactory learning and memorys

Adam Claridge-Chang, Neuroscience & Behavioral Disorders

Learning and memory are fundamental brain functions that are conserved from fly to human. In both animals, evolutionarily related parts of the brain are responsible for associative learning as well as high-level cognitive functions. In olfactory learning studies in the fly Drosophila, scientists have largely used a single apparatus, the classic T-maze assay in which around 80 flies are conditioned with odor-shock pairing before being transferred into a testing chamber. We previously developed a variant assay that uses single flies in a unchanged context, unlike the T-maze which changes context between training and testing. While using this new assay, we discovered two striking inconsistencies that suggest new roles for context and arousal state in olfactory learning.

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