Highlights

Diving Into 'Big Data'

Bioinformatics and computational biology – scientific disciplines that use computer science, statistics and applied mathematical techniques – are used to make sense of today's avalanche of big biological data.

Read More

Creativists in Our Midst

Duke-NUS' faculty have made contributions across a wide range of fields, from the areas of research and education to extending mentorship and leadership to others. Vital Science profiles two leading researchers who have inspired many through their creativity, curiosity and passion for their work.

Read More

Nurturing Leaders in Medicine

Associate Professor Arpana Vidyarthi, Director of Leadership Development at Duke-NUS explains how leadership development and change management play an important role in medicine.

Read More

Printable Version

News In Brief

- The Class of 2017 Makes Their Presence Felt
- Annual Giving Campaign Returns!

Research News

- Taking the Anxiety Out of Ageing
- Three Subtypes of Gastric Cancer Suggest Different Treatment Approaches
- Herbal Compound AA Found to be Carcinogenic; Implicated in Kidney and Liver Cancers
- Caffeine May Decrease Fatty Liver
- Potential Link Between Circadian Rhythms and Metabolic Disorders
- Decision-making May Be Predictable

Grants Awarded
Click here

The Way We Learn

Electing Uganda: Lessons From Across the World

Fourth-year student Eric Cher shares his clinical experience in Uganda.

Read More ▸

VITAL SCIENCE

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

Our banner story: The Class of 2017 Make Their Presence Felt. Read the story here.

Duke-NUS Graduate Medical School Singapore
8 College Road, Singapore 169857 | Tel: (65) 6516 7666 | Fax: (65) 6516 7396
Email: communications@duke-nus.edu.sg | Web: http://www.duke-nus.edu.sg

DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

VITAL SCIENCE

NOV 2013

Diving Into 'Big Data'

As research increasingly relies on high-throughput instrumentation and immense databases of biological information, the ability to collect, manage and interpret these vast quantities of data is key to turning it into usable, relevant and applicable knowledge. Helping researchers translate the tsunami of 'big data' into tangible medical reality is the Duke-NUS Centre for Computational Biology (CCB).

The team at the Center of Computational Biology

Bioinformatics and computational biology – scientific disciplines that use computer science, statistics and applied mathematical techniques – are used to make sense of today's avalanche of big biological data. For example, when scientists use a "DNA sequencer" to read the DNA sequence of a tumor, they need to use bioinformatics to find the mutations (DNA spelling errors) that occurred as the tumor developed. Bioinformatics is also necessary to help scientists understand which mutations caused the cancer, and which mutations are harmless.

Steve Rozen, Associate Professor and Director of the Duke-NUS Center of Computational Biology (CCB) explained, "The need for computational biology and bioinformatics is now pervasive in biomedical research. That means that access to CCB opens up entire new areas that were previously unavailable." He stated that bioinformatics and computational biology are essential for understanding DNA sequence, how cells react to drugs or genetic changes, and how cells control gene expression. Bioinformatics and

computational biology are also necessary to develop biomarkers that will indicate which treatments will be most effective in a particular patient – so called "precision medicine". Assoc. Prof. Rozen also noted that "CCB faculty and staff collaborate widely within Duke-NUS and SingHealth, and also pursue their own research projects.". He added that "CCB's members often form an integral part of scientific teams as co-investigators on grant applications, and CCB works closely with the Duke Genome Biology Facility, which generates a great deal of high-throughput data."

Assoc. Prof. Steve Rozen working with his team in the lab

According to Associate Professor Sujoy Ghosh, the important role of the CCB underscores one of the "major breakthroughs" in genetic research: the dramatic advance in technologies that has made the generation of big data both affordable and easy. "This is causing a fundamental paradigm shift in the nature and focus of biological research and eventually, the practice of medicine," he said. Research has moved on from a traditional model of focusing on a single or handful macromolecules (genes, protein, metabolites) and studying biological mechanisms and pathways in isolation to a more "data-driven, systems-based model".

This, he said is, "where a system is studied in the context of its complete (or near-complete) repertoire of macromolecules and the dynamic interactions among them. Such an approach increases the research reach of Duke-NUS investigators to the leading edge of transformative 'big science' to facilitate novel discoveries with strong potential for translation. Profiling the genome, he said, helps unravel important differences. "Genetic analysis leads to the identification of novel targets and mechanisms that can eventually lead to the development of novel therapeutics. This is particularly important for conditions that impose a major public health burden but currently lack adequate pharmaceutical options'" he said, such as for obesity and diabetic kidney disease.

Assoc. Prof. Ghosh, who also holds an appointment at the Cardiovascular & Metabolic Disorders (CVMD) Program, added that the best approach to maximize the return on investment from mega data are these partnerships and collaborative approaches that couple deep biological expertise with computational and bioinformatics know-how. For instance, in the last two years since it has been in operation, the CCB has been instrumental in aiding Duke-NUS researchers in various groundbreaking studies.

These include:

- Dr Rozen and Dr Patrick Tan's discovery of three subtypes of gastric cancer, the findings of which could lead to the development of a genetic test to classify tumors and match them to the therapies that offer the best outcomes
- The joint Singapore-Taiwan research on DNA mutations caused by the carcinogen Aristolochic Acid (AA) in a form of kidney cancer
- Dr Patrick Tan's identification of the critical genes mutated in stomach cancer, that paves the way for treatments tailored to the genetic make-up of individual stomach tumors

Beauty in the data

Assoc. Prof. Sujoy Gosh shares how he fell in love with 'big data' and his research interests

I got into data analysis by 'accident' in the 1990s. A colleague at GlaxoSmithKline, Greg Horesevsky, was conducting a gene expression study on the treatment of rats with parathyroid hormone. The data was presented in thousands of rows of gene expression signals and was hard to make sense of. At that time, I happened to be reading about (what was then) a very new technique known as 'microarrays' and a software for generating heatmaps from gene expression data made freely available by Mark Eisen.

When Greg mentioned his dilemma, I volunteered to run the data through the software. We were then able to demonstrate remarkably distinct patterns of gene expression changes in response to

the timing of parathyroid hormone injections. The beauty of the results got me hooked into microarray data and eventually onto big data. Today, my research interest is in applying big data centered methods to study the genetic architecture underlying complex diseases such as Type 2 diabetes, obesity and cardiovascular disease. This area of research is also known as 'systems biology' research, where a biological or disease process is studied in the context of a complete collection of biomolecules (nucleic acids, proteins, metabolites) instead of focusing on just a few of them.

Assoc. Prof. Sujoy Ghosh

Here at Duke-NUS, I have the fantastic opportunity to be involved with top-notch research activities across a broad spectrum of disciplines. My primary objective here is to help Duke-NUS investigators in their computational biology needs. This can take several forms such as pre-planning to address experimental design issues, analysis and interpretation of data, and cross-training of research scientists so they can better understand and prosecute the output from big data. Sometimes, an investigator may hesitate to embark on a complex study involving big data due to apprehensions about how to manage and interpret the results. My job is to remove such apprehension and encourage all PIs to fully consider such studies whenever appropriate. Having said that, there are some great studies already underway involving CCB-CVMD partnerships; these include next-generation sequencing projects to interrogate the browning of white fat cells to combat obesity (with Asst. Prof. Sun Lei) and studies on diabetic kidney disease (with Prof. Karl Tryggvason).

Back to top ▲

Duke-NUS Graduate Medical School Singapore
8 College Road, Singapore 169857 | Tel: (65) 6516 7666 | Fax: (65) 6516 7396
Email: communications@duke-nus.edu.sg | Web: http://www.duke-nus.edu.sg

DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

VITAL SCIENCE

NOV 2013

Creativists in Our Midst

Duke-NUS' faculty have made contributions across a wide range of fields, from the areas of research and education to extending mentorship and leadership to others. Vital Science profiles two leading researchers who have inspired many through their creativity, curiosity and passion for their work.

C. Frank Starmer: The value of curiosity
Associate Dean, Learning Technologies

It is a spirit of curiosity that drives Prof. Starmer in his work, life, research and even his passion for photography. Formally trained as an electrical engineer, Prof. Starmer was encouraged by the late Eugene Stead, renowned medical educator, researcher, and the founder of the Physician Assistant profession, into starting his career in the cardiology division of the Department of Medicine at Duke instead. His first project, exploring the nature of electrically induced ventricular fibrillation "ignited" his curiosity in the underlying nature of cellular communication. In four decades, Prof. Starmer has delved into understanding the way people learn and forget, solve problems and think critically.

Prof. C. Frank Starmer
Associate Dean, Learning Technologies

At Duke-NUS, Prof. Starmer has drawn from his understanding of these areas to help develop the way TeamLEAD lectures are delivered. The goal, he explained, was to nurture curiosity, exploration, flexible autonomous learning and collaboration. "Curiosity is something we are all born with, but it gets extinguished ... It's an important – if not essential – part of life and learning. My mentor Gene Stead has been a role model because of his insatiable curiosity about everything. He had broad curiosity and focused curiosity."

With TeamLEAD, to get rid of obstacles to curiosity, Duke-NUS chose to use open-source platforms and voice-annotated PowerPoint lectures, he said, giving students the flexibility to study in their own way. The collaborative discussion-based approach of TeamLEAD also helps overcome the "cultural resistance" to challenge authority. Prof. Starmer observed that the team approach nurtures the skill of discussion, challenge and analysis. "TeamLEAD is also internet-centric so students can combine the power of the internet to harvest resources and link these to what they are studying from the annotated lectures. These resources combine to help students learn, problem-solve and apply knowledge."

As for himself, Prof. Starmer nurtures his own curiosity through photography. Not only does it help him focus his curiosity, the act of reviewing and reflecting on his

photos motivates learning, discovery of new patterns and generating questions arising from curiosity-driven why. "It gives me the opportunity to see things everyone else sees without really seeing."

Read Prof. Frank Starmer's thought-leadership articles in TODAY here:

- **How to exceed expectations**
- **Curiosity, the best motivator**
- **Learning languages for (and through) life**
- **Dad's wisdom made learning part of life**

Nephila pilipes. The larger spider is the female and the smaller orange spider near a front leg is the male. Nephila weave a web of golden silk, the strongest known fiber - stronger than Kevlar

Gasteracantha cancriformis, Spiny orb weaver. They decorate their web with patches of silk - called stabilimenta.

A Huntsman Spider hiding on a leaf

Lens effect of drops on a frangipani blossom

Red ant with well-defined mandible and an unpleasant bite

A praying mantis cleaning one of her legs, sitting on a heliconia

Dale Purves: Vision and Audition

Director, Neuroscience & Behavioral Disorders Program, Professor of Psychology and Neuroscience, Duke University, Professor of Philosophy, Duke University

Trained as a medical doctor with the intention of pursuing psychiatry as his specialty, Prof. Purves – after four years of medical practice – sought to explore the merits of basic science. After getting a taste of research doing a postdoctoral fellowship at Harvard Medical School, he fell in love with research and made a wholehearted commitment to neuroscience. Following a second postdoc in the 1970s working in the Department of Biophysics headed by Sir Bernard Katz, the pioneer in understanding synaptic transmission, he joined the faculty at Washington University School of Medicine as an assistant professor.

After nearly 20 years studying the development of the peripheral nervous system at Washington University, Prof. Purves joined Duke University in 1990 as the founding Chairman of the Department of Neurobiology.

"Moving to Duke then was a chance for me to take look at a very different issue, vision and the way visual perception works," he shared. Purves and his students study how people perceive brightness, color, motion, and depth, pursuing a radically different hypothesis about how the visual brain operates. The laboratory also works on the perception of music as a means of understanding auditory aesthetics.

Prof. Dale Purves
Director, Neuroscience & Behavioral Disorders Program

In a third major transition, Prof. Purves moved to Singapore's Duke-NUS in 2009 where he has pursued his research on visual and auditory perception.
Looking back on his four years in Singapore, he reflected, "It has been a great opportunity in every respect. To have the chance to see another country and participate in a unique medical school with wonderful leadership that is doing things in a different way. I am especially grateful for the support of my research during this period."

Back to top ▲

Duke-NUS Graduate Medical School Singapore
8 College Road, Singapore 169857 | Tel: (65) 6516 7666 | Fax: (65) 6516 7396
Email: communications@duke-nus.edu.sg | Web: http://www.duke-nus.edu.sg

Nurturing Leaders in Medicine

Associate Professor Arpana Vidyarthi, Director of Leadership Development at Duke-NUS, explained that leadership development and change management play an important role in medicine. Leadership is the language with which change, innovation and knowledge is disseminated; such as how teamwork is necessary in the first-year curriculum with TeamLEAD.

As medicine and medical systems get more complex and diverse, the practice of effective medicine is no longer based on just physician competency, but also on communication, teamwork and personal leadership. At Duke-NUS, leadership-building pedagogies are instilling the leadership ethos and developing these crucial skills. Dr. Vidyarthi, whose background was in the medical quality and safety field, shared, "I started out at the University of California, San Francisco where part of the focus was learning about ways to support and improve performance in the field when I realized that within every system, checklist and process, that the 'people factor' played an important role. So I started to look at people, leadership development and change management."

"True and effective leadership - contrary to common perception - is not just an inherent trait but must be taught, nurtured and developed. Even natural leaders may not be outstanding leaders. Leadership is a deliberate practice that comprises various elements."

Assoc. Prof. Arpana Vidyarthi
Director, Leadership Development

She found that leadership is a skill like any other, requiring foundational knowledge, practice and reflection. "Let's say one is learning to do a suture," Dr. Vidyarthi illustrated, "It requires a basic understanding of how it works; practice to refine the skill and reflection on how to do it better the next time. Leadership is the same."

In the day-to-day practice of medicine, aspects of leadership (see box story) such as communication, resilience and teamwork, make a large impact. In an emergency situation for example, a doctor who is a good leader with keen observation and sharp communication skills has to assess the situation and relay instructions to a large team in a matter of seconds. It is through leadership that book knowledge can be translated to action in a real situation. "A good leader may notice a junior nurse or doctor is nervous because it's his or her first experience with a trauma case and be able to offer the reassurance and confidence that brings the team together to save lives."

In fact, leadership in the wider context of medical education is a necessity. This is made very clear, in the Singaporean context, by various accreditation schemes such as ACGME-I of which medical knowledge and patient care are only two out of the six of competency criteria. "The other competencies including interpersonal skills/communication, system-based practice, and professionalism are foundational to leadership development," underscoring the importance of these skills in the practice of medicine," pointed out Dr. Vidyarthi.

At Duke-NUS, leadership is a core aspect of the curriculum and its practice is threaded through all four

years of study, so that students eventually embody the various skills and competencies required of a leader.

Physician Leadership Competencies (Consists of seven characteristics) - A Framework Developed by Dr. Vidyarthi and Dr. Anda Kuo (Department of Pediatrics, University of California, San Francisco)

- Change creation: Proactively and reactively creating and managing change
- Working with others: Creating relationships that bring others to work in a unified manner to accomplish desired outcomes
- Communication: Exchanging information effectively and creating shared meaning
- Contextualized thinking and knowledge: Incorporating the knowledge of one's environment into decision making and strategic thinking
- Management skills: Planning and organizing structures and people to produce predictable results
- Leadership attributes: Espousing personal qualities of effective leadership
- Resilience: The ability to thrive in times of conflict and change

Can you teach someone to be a leader? (Duke Today, October 21, 2013)

Duke-NUS integrates real-world experiences into the curriculum, thus helping our students to develop leadership attributes.

Click here to read more.

Back to top ▲

Duke-NUS Graduate Medical School Singapore
8 College Road, Singapore 169857 | Tel: (65) 6516 7666 | Fax: (65) 6516 7396
Email: communications@duke-nus.edu.sg | Web: http://www.duke-nus.edu.sg

DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

Electing Uganda: Lessons From Across the World

In Uganda, traffic accidents account for more than 49 per cent of the total injuries seen at the casualty unit. With less than 30 orthopedic surgeons serving the country, most of the musculoskeletal conditions are handled by trainee residents and orthopedics officers. I had the privilege of completing my elective in Orthopedics Trauma at Mulago Hospital, the nation's referral and teaching hospital. Unlike the Singapore General Hospital, which deals with a range of orthopedic concerns, Mulago Hospital sees primarily orthopedics trauma and spine patients, something I was keenly interested in.

Mulago Hospital

During my month-long elective, I rotated through two of the primary orthopedics trauma wards; the casualty department where most of the trauma cases were seen as well as outpatient consults including general orthopedics and clubfoot clinic, where patients suffer from foot abnormalities since birth.

As a medical student, I was given ample opportunities to participate in all aspects of patient care, ranging from ward work, to being a primary assistant during surgeries and triaging patients as they arrive at the casualty department. Due to the shortage of healthcare professionals, students play a significant role in patient care. The doctors and nurses at Mulago Hospital were incredibly helpful when it comes to teaching students and have no qualms about letting us perform procedures under supervision. Very quickly, I got used to the work rhythm and was able to independently handle simple conditions such as cleaning and suturing large lacerated wounds, abscess drainage and preliminary management of both close and open fractures.

Eric with the interns at the Casualty Department

It was here at Mulago Hospital where I had the opportunity to do my very first manipulation of a dislocated shoulder and performed my first external fixation as the first assistant surgeon. Being the first assistant surgeon was particularly significant, since we hardly get the chance as medical students. Usually, we would either be observing or helping minimally with the surgeries. With this level of responsibility, it very quickly dawned upon me the importance of being proficient and confident in my work. As a student, we need to be mindful of our limitations, and to become a doctor, we must be aware of our professional boundaries.

While the hospital has limited resources and lacks medical technology compared to those I have worked in before, the experience I gained is something words cannot quantify. There were countless learning opportunities and hands-on experiences, as well as the tremendous sense of satisfaction I felt to be working in such a challenging environment. While I derived great joy from tending to patients in roles normally reserved for junior residents, I was also deeply humbled by the healthcare system and the people I worked and interacted with. When it comes to research, there is no other place that is in need of more creativity and innovation to solve the nation's long-term healthcare problems. Rather than spearheading cutting-edge technological and medical advances, some of the simplest engineering designs and clever use of local resources are what are most needed here.

I had the opportunity to live and learn alongside both medical and nursing students from all over the world. Educated through different healthcare systems and having gone through various volunteering experiences, our passion for helping people served as a common denominator, creating the perfect environment for ideas to propagate.

Being in Uganda was not without its share of fun. Although safari visits and sightseeing were not part of my primary agenda, I did visit a nearby island (Banda Island) with a group of international friends. Located four hours away from the city by boat, the beauty of the crystal clear blue water, together with the rustic campsite right next to the beach painted a calming and mesmerizing view and a good respite for the mind and body.

Eric interacting with the neighborhood children during an outreach program

The international exposure gained from being in Kampala has made obvious the different spectrum of healthcare challenges faced by many developing nations. There are multiple avenues available to help these communities, but at the same, one has to think beyond satisfying one's passion and look at problems and solutions from a macro view. The amazing cross cultural experience of interacting and working with the local community has given me a small glimpse into a different realm of medicine, providing new insights and perspectives into how I want my personal and professional life to be as a doctor.

I had the privilege of being the first Duke-NUS student to complete an overseas elective in Uganda, thanks to the tremendous support from the school. Duke-NUS supported my request for an overseas elective and enabled me to embark on this memorable experience. I hope that through this experience, more students are encouraged to partake in overseas clinical electives during their medical education, and subsequently, as a physician.

Back to top ▲

Duke-NUS Graduate Medical School Singapore
8 College Road, Singapore 169857 | Tel: (65) 6516 7666 | Fax: (65) 6516 7396
Email: communications@duke-nus.edu.sg | Web: http://www.duke-nus.edu.sg

DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

The Class of 2017 Make Their Presence Felt

The Class of 2017 is a unique one. First of all, it is Duke-NUS' largest MD intake to date with an impressive enrolment of 59 students. Amongst them are scholars, athletes, martial artists, and Masters and PhD holders. Students come from a variety of academic backgrounds, such as the biological sciences, engineering, business and the arts.

Their medical school journey started with a flurry of activities, commencing with a two-week orientation program which consisted of ice-breaker games, talks, seminars and leadership and team-building workshops conducted by Duke Corporate Education. The workshops were particularly significant as it prepares the students for TeamLEAD, where students are expected to work in teams throughout their first year and beyond. It culminated with the White Coat Ceremony held on August 16 at the College of Medicine Building Auditorium, where the class recited the Hippocratic Oath as they were welcomed into portals of Medicine. Joining their seniors, medical graduates and mentors, the Class dedicated themselves to upholding the core values of Medicine.

Over half of the multilingual and multiethnic class comprise of Singaporeans while the rest come from countries across Asia, the United States, Canada, and the UK. Nicholas Brian Shannon, PhD, explained that Duke-NUS was ultimately his choice because of its focus on academic medicine which he saw as necessary to improve healthcare and benefit patients. This will enable Nicholas, who did his doctoral studies in molecular oncology at the University of Cambridge, to fulfill his career goal of "…bringing the ability to care for people on a personal level into [his] day-to-day job."

The Class of 2017

Nicholas Shannon (3rd from right) with his classmates after the White Coat Ceremony

Back to top ▲

Annual Giving Campaign Returns!

Early this year, Duke-NUS celebrated the success of its inaugural Annual Giving Campaign on March 8. It was heartening to see many donors, faculty, staff and students coming together to challenge themselves for their chosen causes. Planning for our second Annual Giving Campaign is underway. We are incorporating ideas and feedback from previous participants to make our next Annual Giving Campaign even better and bigger! More information on this soon, and we promise more excitement and meaningful fun, so look out for it!

Read more about our inaugural Annual Giving Campaign here.

Back to top ▲

Duke-NUS Graduate Medical School Singapore
8 College Road, Singapore 169857 | Tel: (65) 6516 7666 | Fax: (65) 6516 7396
Email: communications@duke-nus.edu.sg | Web: http://www.duke-nus.edu.sg

DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

Taking the Anxiety Out of Ageing

Watch video at www.youtube.com/embed/ctFdr_Ym8FA?rel=0

The research highlighted in the video involved a series of projects supported by the Tsao Foundation Ageing Research Initiative, Ministry of Social and Family Development (MSF), Ministry Of Education (MOE) and the Agency for Integrated Care (AIC). The projects involved national surveys and a randomized control trial. The goal of the work is to produce evidence for policy making and services that actually change the lives of older persons in Singapore.

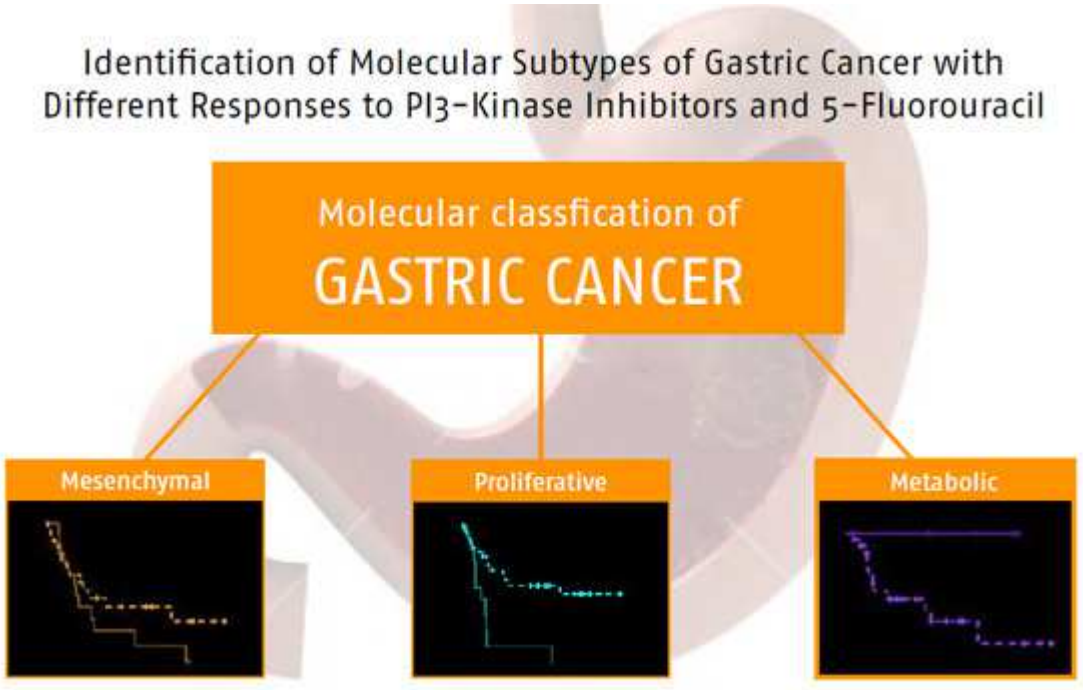
Video courtesy of the NUS Development Office. For more information, and to view further videos, visit www.giving.nus.edu.sg

Back to top ▲

Three Subtypes of Gastric Cancer Suggest Different Treatment Approaches

According to researchers at Duke-NUS, stomach cancer falls into three broad subtypes that respond differently to currently available therapies. Stomach cancer is one of the leading causes of cancer death worldwide. Despite differences in the way that stomach cancer tumors respond to treatments, patients often receive a "one-size-fits-all" treatment approach. The finding could greatly improve patient care, as it makes possible the development of a genetic test to classify tumors and match them to the therapies that offer the best outcomes.

"One of the features that makes gastric cancer so lethal is that it arises from many genetic alterations, creating differences in how the tumors respond to therapies," said Associate Professor Steve Rozen, senior author and Director of Duke-NUS' Center for Computational Biology. "There has been an urgent need for an improved classification of gastric cancer that provides insight into the biology of the tumors and that might help predict treatment response," added co-senior author Professor Patrick Tan of Duke-NUS' Cancer and Stem Cell Biology Program.



Assoc. Prof. Rozen and colleagues analyzed 248 gastric tumors, then further grouped them according to the genes that were expressed in the tumors. The gene expression analysis broadly sorted the tumors into three subtypes: proliferative, metabolic and mesenchymal. These subtypes also differed in their genomic and epigenomic properties.

"If confirmed in future studies, the classification of gastric cancers reported here could guide development of therapies tailored to the molecular subtypes," said lead author and Duke-NUS Research Fellow Dr. Zhengdeng Lei.

The study was published in the September issue of the journal *Gastroenterology*. It was supported by the Duke-NUS Signature Research Programs, with funding from the Singapore Agency for Science, Technology, and Research and the Singapore Ministry of Health; the Singapore National Medical Research Council; the Singapore National Research Foundation and Ministry of Education; and the Singapore Biomedical Research Council.

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

Herbal Compound AA Found to be Carcinogenic; Implicated in Kidney and Liver Cancers

A joint study conducted by researchers from Duke-NUS, the National Cancer Centre Singapore (NCCS) and Taiwan's Chang Gung Memorial Hospital, LinKou, has found that Aristolochic Acid (AA) - a natural compound found in *Aristolochia* plants - is a carcinogen that causes abundant DNA mutations that can lead to kidney and liver cancers. Traditionally, *Aristolochia* plants are used in herbal remedies for weight loss and other purposes. While AA has been banned in Europe and North America since 2001 and in Asia since 2003, certain AA-containing products are still permitted under supervision and are easily available worldwide, including over the internet.

The team, led by Professors Teh Bin Tean, See-Tong Pang, Patrick Tan and Steve Rozen used advanced DNA sequencing technologies to determine that AA is the most potent carcinogen identified to date. It actually causes more DNA mutations than cigarette smoke or ultraviolent light.

"AA's contributions to kidney failure and cancer have been documented, but AA's possible role in other cancer types was unknown. In this study, we found that the AA-related DNA fingerprint could be used to screen for the potential involvement of AA exposure in other cancers, such as liver cancer," said first author Dr. Poon Song Ling, a research fellow from NCCS. The findings of the Singapore-Taiwan study, published on August 7, 2013 in *Science Translational Medicine* , could lead to a new wave of DNA-based detection systems for monitoring carcinogen exposures in humans and the environment.

The research was supported by grants from the Singapore National Medical Research Council, the Singapore Millennium Foundation, the Lee Foundation, the National Cancer Centre Research Fund, The Verdant Foundation, Duke-NUS, the Cancer Science Institute of Singapore, the Chang Gung Memorial Hospital, LinKou, the Taiwan National Science Council, and the Wellcome Trust.

Back to top ▲

Caffeine May Decrease Fatty Liver

Using cell culture and mouse models, a team of researchers from Duke-NUS and the Duke University School of Medicine suggest that increased caffeine intake may reduce fatty liver in people with non-alcoholic fatty liver disease (NAFLD). Worldwide, 70 percent of people diagnosed with diabetes and obesity have NAFLD, the major cause of fatty liver not attributed to excessive alcohol consumption.

How caffeine helps reduce fatty liver

Lead authors Associate Professor Paul Yen and Research Fellow Dr. Rohit Sinha from Duke-NUS' Cardiovascular and Metabolic Disorders Program observed that caffeine stimulated the metabolism of lipids stored in liver cells and decreased the amount of fat in the livers of mice that were fed a high fat diet.

These findings suggested that coffee and tea consumption (equivalent to the caffeine intake of four cups a day) may be beneficial in the prevention and protection against the progression of NAFLD in humans.

This research could lead to the development of caffeine-like drugs that do not have the usual side effects related to caffeine but retain its therapeutic effects on the liver. It could also be starting point for studies on the additional benefits of caffeine and related therapeutics in humans.

Assoc. Prof. Paul Yen

Collaborators also included Professor Christopher Newgard, Director of the Sarah W. Stedman Nutrition and Metabolism Center at Duke University School of Medicine, where the metabolomics analysis of the data was conducted. The study, published in the September issue of *Hepatology*, was supported by funding from Singapore's Agency for Science, Technology, and Research; the Ministry of Health; and the Ministry of Education.

Back to top ▲

Potential Link Between Circadian Rhythms and Metabolic Disorders

Researchers at Duke-NUS, the National University of Singapore (NUS) and the National Neuroscience Institute (NNI) have found that the lipids (fat-storing molecules) in the bloodstream are regulated by the body's circadian clock. The study also showed that people can be classified as "morning types" or "evening types" based on differences in the timing of lipid rhythms.

Asst. Prof. Joshua Gooley

"Our research demonstrates that there are morning and evening types based on variation in levels of glucose (sugar) and lipids in their blood, and this may explain why some people are better suited to shift work than others," said senior author Assistant Professor Joshua Gooley, from the Neuroscience and Behavioral Disorders Program. This may also explain why some shift workers gain weight, and could lead to a better understanding of who may be at greater risk of developing metabolic disorders such as diabetes.

The first author of the study is Dr. Chern-Pin Chua, senior research fellow at Duke-NUS. The work was performed in collaboration with Associate Professor Markus Wenk from NUS and Principal Investigator Associate Professor Kathiravelu Puvanendran, previously from NNI.

Published in *Proceedings of the National Academy of Sciences USA (PNAS)* on August 12, 2013, the study is the largest of its kind to date. It was made possible by funding from the Duke-NUS Signature Research Programs, from Singapore's Agency for Science, Technology, and Research; Ministry of Health; the National Medical Research Council; and the SingHealth Foundation.

Back to top ▲

Decision-making May Be Predictable

Asst. Prof. Hsieh Po-Jang

A joint study conducted by Duke-NUS and Caltech has shown that it may be possible to predict decisions a person will make simply through a scan of their resting brain. A group of participants were shown a series of pictures of abstract art (acting as the stimulus) and were asked whether they "liked" or "disliked" them. Brain scans with fMRI showed that there was a difference in the way the brain looked in the instances before they saw the pictures they liked and the ones that they disliked. In essence, the participants' evaluation of the art could be predicted even before they had seen it.

"Previously it was believed that the qualities of the stimulus and the person's preferences are what determined their decision-making. These findings take us out of that mindset," explained lead author Assistant Professor Po-Jang (Brown) Hsieh in the Neuroscience and Behavioral Disorders Program.

Published in *Human and Brain Mapping* , the research demonstrates that there are parts of the brain that are causing people to make decisions even before they are conscious that there is a decision to be made. Identifying the essential brain areas of decision-making may be the first step to medical treatments of neurodegenerative diseases in which impaired-decision making is a common feature, such as Alzheimer's, Dementia, Parkinson's and Huntington's.

Further exploration may reveal the specific "neural causes" of decision-making, and be able to predict and treat addictive, gambling and irrational behaviors. This study, supported by the National Medical Research Council CBRG-NIG grant, may open the door toward future scientific discovery about decision making as a whole.

Back to top ▲

Duke-NUS Graduate Medical School Singapore
8 College Road, Singapore 169857 | Tel: (65) 6516 7666 | Fax: (65) 6516 7396
Email: communications@duke-nus.edu.sg | Web: http://www.duke-nus.edu.sg

DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

Details of projects awarded to Duke-NUS researchers from July-October 2013

No.	PI	Dept	Project Title (Please click titles for details)	Grant Call	Duration (Months)
1.	Mathijs Voorhoeve	CSCB	Yap-ping At The Achilles Heel Of Cancer: Genetically Defined Models Of Oncogenic Transformation In Fly And Man Uncover Collaborations Between Ras And Hippo/YAP Pathways	NMRC CBRG Nov 2013	36
2.	Scott Summers	CVMD	The Role Of Sphingolipids In the Pancreatic Beta-Cell	NMRC CBRG Nov 2013	36
3.	Patrick Casey	CSCB	G Protein Signalling In Oncogenesis & Metastasis	NMRC CBRG Nov 2013	36
4.	Ian Mendenhall	EID	Developing tools for risk assessment of bat-borne viruses in bats in Singapore	NMRC CBRG NIG Nov 2013	24
5.	Yvonne Su	EID	Antigenic Characterization Of Pandemic H1N1/2009 influenza Viruses Using Novel Monoclonal Antibodies: Insights into Influenza Antigenic Drift In Tropical Countries	NMRC CBRG NIG Nov 2013	24
6.	Sharon Cohan Sung	OCS	Tools to improve panic screening in the Emergency Department (TIPS-ED)	MOH HSR NIG Nov 2013	24
7.	Marcel Bilger	HSSR	"A Randomized Controlled Trial to Increase Glaucoma Medication Adherence using Value Pricing	MOH HSR NIG Nov 2013	24

Total Amount of Funding Received: S$ 5,222,910

Synopsis

1. Yap-ping At The Achilles Heel Of Cancer: Genetically Defined Models Of Oncogenic Transformation In Fly And Man Uncover Collaborations Between Ras And Hippo/YAP Pathways

Mathijs Voorhoeve, Cancer & Stem Cell Biology

Cancer is caused by mutations that change important regulatory mechanisms of the cell, e.g. those that make sure cells do not grow unasked or unaided, or in places where they do not belong. Modern sequencing technology allows us to read the mutations that occur in tumours. Before this can lead to better and more targeted therapies, we need to be able to interpret the consequences of these mutations. However, there are hundreds of genes that can possibly be mutated in various combinations in each individual tumour. It is known that tumours can form due to changes in only five central regulatory mechanisms. To understand how particular mutations in an individual tumour can affect these five mechanisms is a task that has no simple shortcuts or quick solutions, but requires long term research into the basic mechanisms that govern cell behaviour in the light of tumour progression.

Together with the Cohen lab at IMCB we have employed genetic models (in human cells and in fruitflies) in which we can mimick the changes that allow a tumour to form, as one way to study the possible mutations that make a tumour. Gratifyingly, we have been able to identify the final regulatory mechanism that needs to be disrupted, specifically to allow tumour cells to grow where they do not belong. We will use these models to uncover which mutations can work together to affect this mechanism, and thus help shed some light on the enormous amount of genomic data that is becoming available.

Back to top ▲

2. The Role Of Sphingolipids In the Pancreatic Beta-Cell

Scott Summers, Cardiovascular & Metabolic Disorders

Following consumption of a meal, increasing levels of glucose in the bloodstream trigger the release of insulin from the pancreas. This hormone is promotes the storage of nutrients into inert depots that can be rapidly accessed when energy is needed. In diabetes, the body produces inadequate amounts of insulin, and thus has difficulty storing nutritional fuels. This has disastrous consequences on health. The dysregulated metabolism that ensues puts people at risk for heart disease, blindness, limb amputations, etc. We are able to prevent the destruction of the cells that produce insulin in mice, and thus prevent the development of diabetes in this animal model. We achieve this by blocking the production of ceramides, which are toxic molecules that accumulate during times of stress. In this proposal we will evaluate the mechanisms through which ceramides modulate insulin synthesis and secretion, with hope that it will give us new insights about therapeutic strategies for combating the diabetes.

Back to top ▲

3. G Protein Signalling In Oncogenesis & Metastasis

Patrick Casey, Cancer & Stem Cell Biology

Although survival of patients with cancer that has not spread has improved in recent years, the outcome is still very poor for those in which the cancer has spread. The spread of cancer is termed metastasis, and understanding just how metastasis occurs could provide critical information needed to develop new treatments for patients with advanced cancer. We have found cancers that spread rapidly have high levels of molecules known as G12 proteins, and that activation of the G12 proteins in cancers that have not spread cause them to do so more quickly. Moreover, blocking G12 signaling inhibits the spread of cancer in laboratory experiments; this has been found for breast, prostate and nasopharyngeal cancer. Our current efforts are aimed at determining just how G12 proteins promote the spread of cancer in order to evaluate the effectiveness of blocking these proteins as a therapeutic strategy to treat cancer that has spread. The cellular regulatory pathways controlled by G12 proteins are complex, and we will determine which branches of these pathway are important for cancer metastasis. Successful completion of this project should provide experimental systems useful for discovery of new drugs that block the spread of cancer.

Back to top ▲

4. Developing tools for risk assessment of bat-borne viruses in bats in Singapore

Ian Mendenhall, Emerging Infectious Diseases

A majority of outbreak responses to emerging infectious diseases are reactionary, which tend to be costlier than proactive responses. Until we understand how pathogens emerge and spread, our approaches will always be trailing the outbreak. Rapid detection of circulating viruses and exposure greatly facilitates surveillance and prevention programs.

Bats are involved in the maintenance and transmission of several medically important viruses and now more than ever their interactions with humans are increasing. Developing diagnostic tests to detect and understand these emerging viruses is a prudent approach to pathogen surveillance.

The characterization of genetic information from multiple virus families detected with these tests will help fill the gaps in their evolutionary history, which in turn will assist in understanding virus natural ecology and the potential for cross-species transmission. Furthermore, these findings could also improve our ability to identify animal viruses by targeted surveillance, and better frame future questions regarding the role of specific bat species as virus reservoirs.

This project will aid in protecting human health through active surveillance, outbreak detection, and molecular epidemiology by providing a robust diagnostic panel for bat-borne viruses.

Back to top ▲

5. Antigenic Characterization Of Pandemic H1N1/2009 influenza Viruses Using Novel Monoclonal Antibodies: Insights into Influenza Antigenic Drift In Tropical Countries

Yvonne Su, Emerging Infectious Diseases

Human influenza viruses are responsible for annual seasonal epidemics that cause significant sickness and death worldwide. In March 2009, a new influenza virus that had previously not been detected in humans began infecting people in Mexico and the USA, eventually causing up to 500,000 deaths worldwide. Many international influenza researchers have collected thousands of virus isolates from humans and used virus genetic data to investigate how influenza viruses transmit around the world. However, influenza genes can also undergo mutations in their amino acids (known as "antigenic drift"), and these mutations allow influenza viruses to keep one step ahead of human immunity and influenza vaccines. However, there are fewer studies that investigate the antigenic changes of influenza viruses that result from these amino acid mutations, which is mainly because the correct tools are not available – in this case monoclonal antibodies. The aim of our project is to generate new monoclonal antibodies to investigate the antigenic evolution of influenza viruses to test specific questions about the global circulation of influenza virus in humans that have important consequences for how we try to control the virus, particularly through vaccination.

Back to top ▲

6. Tools to improve panic screening in the Emergency Department (TIPS-ED)

Sharon Cohan Sung, Office of Clinical Sciences

Panic disorder is a severe anxiety-related condition that is characterized by symptoms like shortness of breath, chest pain, and dizziness. In North America, about 25% of chest pain patients in the A&E are actually suffering from panic disorder. Unfortunately, only about 1-2% of these patients are diagnosed by the doctor during routine care. It is important to identify and treat these patients because untreated panic disorder is related to high unnecessary medical costs and poor outcomes, such as suicide. We aim to develop a brief screening method for detecting panic disorder in A&E patients. To do this, we will evaluate 309 adults who come to the Singapore General Hospital A&E with panic-like physical complaints. We will have them complete a short interview and fill out two questionnaires about their symptoms. We will compare the two questionnaires to see which is best able to detect panic disorder. We will also determine the rates of panic disorder in the local A&E setting and how often these cases are detected by the A&E doctors. This project will be the first in a series of studies evaluating how best to identify and treat A&E patients with panic disorder.