MediCine

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NIPPING CARDIOVASCULAR DISEASE IN THE BUD

Study identifies ways to predict and prevent cardiovascular-metabolic disease

Contents

MediCine

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Dean's Message

Dear Reader,

As the practice of Medicine pivots from the traditional treatment of diseases to incorporate their prevention, early detection and intervention, researchers around the world have identified five areas in the world where local populations comprise a very high number of centenarians.

In these so-called blue zones (a term expanded by Dan Buettner, a National Geographic Explorer and Fellow in 2004 for Ikaria in Greece, Okinawa in Japan, the Ogliastra region, Sardinia, Loma Linda, California and the Nicoya Peninsula in Costa Rica), the people live longer, enjoy a high quality of life and good health in their twilight years. The very healthy and active senior citizens in these five places shared common lifestyle traits: low-protein diets heavy in vegetables, fruits, nuts, fish, healthy fats and low in meat products; strong social networks, regular, low-intensity physical activity and strong life purpose or religious faith.

I believe Singapore could become a blue zone if we can increase the Healthy Life Expectancy or Healthspan of Singaporeans by five years by 2050 through modifications to our lifestyles and diet. Towards this end, NUS Medicine, together with the Ministry of Health, the Housing Development Board, and the National University Health System, has embarked on a first-of-its-kind multi stakeholder collaboration with the public, private and social sectors to form the Health District @ Queenstown.

Mirroring Singapore's projected demographics by the year 2030, the population of Queenstown, is expected to be 100,000 in 2026, with 21% of residents over the age of 65 years and 80% living in HDB apartments. As such, it is chosen as the pilot site for putting in place sustainable programmes to help residents lead healthier lives. The Health District @ Queenstown will provide a key platform for translating healthcare education, research, and innovation, into practical solutions to health-related issues, providing a supportive and conducive environment for residents to enjoy a good quality of life.

Aligning to this mission of increasing health span, the Healthy Longevity Translational Research Programme at NUS Medicine seeks to improve health by understanding the biology of ageing, as well as developing and testing interventions to prolong the healthy years of individuals in Singapore.

Hence, by investing and optimising health and human potential in early life, and encouraging healthier ageing across the life course, there will be a far-reaching impact on our nation's overall health, healthcare system and economy.

Another initiative that will also have a positive impact on Singaporeans' health and well-being was also launched in August, here at NUS. It brings together about 870 Medicine, Nursing, Pharmacy and Dentistry first-year students in five specially-designed courses as part of their learning journey.

A key content pillar in the Common Curriculum is the *Social and Behavioural Determinants of Health* pillar, which will educate healthcare students on the practical, social and emotional needs that affect individuals' health and well-being in communities.

Students will also participate in interdisciplinary experiential learning through the *Longitudinal Patient Experience*, where teams of students from various healthcare disciplines will visit patients in their homes and living environments continually for one year. This immersive learning journey provides students with opportunities to provide holistic care for their patients, while fostering empathy and resilience.

In conjunction with the new Common Curriculum for Healthcare Professional Education, NUS Medicine has also enhanced its curriculum for Medicine undergraduates by implementing a Minor that delves into Artificial Intelligence (AI) and Biomedical Informatics, to better prepare students for the new era of AI-driven digital medicine.

Students from other NUS faculties, schools and colleges will also have the opportunity to acquire knowledge about the workings of modern healthcare systems through a new Minor in Integrative Health.

Health and well-being are more than just caring for the sick. To help people stay healthy as long as they live, and better care for them when they are ill, we need to look beyond the traditional confines of medicine and science and tap on the experiences and knowledge of blue zone populations. Live to 100? That is already reality for an increasing number of Singaporeans. Our holy grail is to have a nation whose citizens age actively and healthily into their centenaries.

Yap Seng

Public Health Service 2023: An Enduring Mission to Help Improve the Lives of People

BY ELVIA NG CHIN BOON AND CHONG SHU TING, PHASE III MEDICINE STUDENTS, YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE (NUS MEDICINE)

Every year, we begin the academic season with the highly anticipated Public Health Service (PHS) annual health screening, one of the largest community service events undertaken by NUS Medicine students.

Now in its 20th year, PHS has evolved into much more than just a medical outreach programme. It is a cherished tradition and testament to the shared dedication of NUS Medicine students in desiring to empower communities and making a meaningful and sustained impact on both healthcare education and accessibility. This year's PHS took place at the Canopy @ J-Link, Jurong East, and was attended by 653 residents of the HDB blocks in the constituency.

PHS was initiated in 2004 by a small and enthusiastic group of medical students from NUS Medicine. From its beginnings as a simple screening event with only four modalities, PHS has grown tremendously. Today, it stands at the intersection of public health, community outreach and medical education.

Planning and preparations for the event

The PHS mission is to achieve a cumulative benefit in our community, and reintegrate those who have fallen through the cracks, back into the primary healthcare system. We aim to do so through a comprehensive health screening and concurrent health exhibition, focusing on not only secondary prevention, but also primary prevention via health education.

Our volunteers, supervisors and committee members during the PHS Public Health Screening event.

To realise these ambitions, the journey towards a successful health screening began months in advance. Our organising committee dove headfirst, and worked tirelessly through meticulous preparations—arranging logistics, contacting partners, and designing outreach strategies.

Reaching out to the community

One of the first steps in the planning process was identifying the communities that would benefit most from our services. PHS tirelessly reached out to local organisations, community leaders, and healthcare providers to establish partnerships. These collaborations enable us to tap into the local networks and engage with the community effectively.

Prior to the screening weekend, our committee also carried out several rounds of door-to-door and centralised publicity. Apart from spreading awareness about our screening, these publicity rounds allowed us to engage directly with residents in order to understand more of their needs, which serves to shape the future initiatives and direction of PHS.

The driving force: Volunteers and organisers

PHS is a long-standing project which owes its success to our volunteers. Some volunteers contribute their time and effort to the mission of PHS every year. The remarkable resilience and gratitude of the individuals served, and the fulfilment that comes with bearing witness to the transformation of residents' fears into relief, despair into hope and isolation into connection, fuels the volunteers' passion to return time and again.

For the students organising this monumental effort, it is a profound sense of responsibility and commitment to the principles of public health that keeps us going. We are driven by the belief that healthcare is a fundamental human right, and we are dedicated to making a difference.

Overcoming challenges

Of course, no endeavour is without its challenges. From funding constraints to unpredictable weather on screening days, PHS has faced its fair share of obstacles. But resilience and teamwork have been our greatest assets.

As one committee, we've learned that adversity only strengthens our resolve. Together, we've found creative solutions, sought support from our school and local organisations, and rallied community volunteers to ensure that the show goes on.

↑

Top: The organising committee of PHS carried out door-to-door publicity, engaging and finding out the needs of the residents.

Bottom: Meddy, the mascot of NUS Medicine, made his rounds around the neighbourhood during the screening event.

A platform for doctors-in-training

Participating in the annual health screening is an invaluable experience for medical students. It provides a hands-on opportunity to apply our medical knowledge in a real-world setting, to hone our clinical skills and enhance our ability to communicate effectively with patients. It is a reminder that medicine is more than just the science; it is about caring for people, understanding their needs, and fostering trust.

Furthermore, it exposes us to the multifaceted challenges of healthcare access and equity, lessons that will guide us throughout our medical careers. It instils in us the values of empathy, compassion, and humility—qualities that every physician should possess.

Reflections

As we look back over the years of PHS's annual health screening, we see not just a collection of medical check-ups, but a mosaic of human stories of resilience and transformation. It is a testament to what a group of dedicated individuals can achieve when driven by a shared purpose.

In closing, our annual health screening has transcended its status as a mere event—it is a tradition, a commitment, and a testament to the power of community-driven healthcare. We are excited about the years to come and the positive impact we will continue to make.

At the heart of this initiative, we find not only future doctors but also compassionate individuals committed to help heal the world, one screening at a time.

Top:
Our committee members at the PHS Public Health Screening event.

Bottom:
PHS student volunteers interacting and screening residents during the screening event.

Our annual health screening has transcended its status as a mere event—it is a tradition, a commitment, and a testament to the power of community-driven healthcare. We are excited about the years to come and the positive impact we will continue to make."

Helping Future Professionals Think Outside the Box:

NUS Enhances Undergraduate Healthcare Education

In light of evolving healthcare needs in Singapore, where creative problem-solving skills and technological capabilities are warranted for the provision of holistic and patient-centric care, three new curricula initiatives have been introduced by the National University of Singapore (NUS) to better prepare future doctors, nurses, dentists and pharmacists for the challenges that they will face.

Starting August 2023, the National University of Singapore (NUS) has implemented a new interdisciplinary common curriculum for undergraduates in Dentistry, Medicine, Nursing and Pharmacy. This timely repositioning of the University's healthcare education tailors the development of healthcare talents in response to Singapore's 'Healthier SG' vision, a new national initiative focusing on integrated and preventive care.

The 'Healthier SG' vision entails a major reform of the healthcare system to help Singaporeans age in place through the use of technology and analytics. This requires doctors, nurses, dentists and pharmacists to work together to support and holistically care for the community in all aspects of their healthcare needs. These professionals trained by NUS would need to be equipped with the knowledge, skills, and attitudes to help shape a resilient and responsive healthcare system in Singapore.

From left: Year 2 students Kanesananthan Yahrliny from NUS Department of Pharmacy, Faculty of Science, Yunn Honey Aye Kyaw from NUS Medicine, and Tan Wan Ru Deiondre and Muhammad Amir Bin Mohamed Imran from NUS Nursing attended the pilot courses under the NUS Common Curriculum for Healthcare Professional Education.

About 870 first-year students from Dentistry, Medicine, Nursing and Pharmacy would take five specially-designed courses together, and collaborate across the four healthcare disciplines as part of their learning journey. The common curriculum, which is to be completed in the first two years of their candidature, will complement the existing curriculum of the respective degree programmes.

In conjunction with the new Common Curriculum for Healthcare Professional Education, the NUS Yong Loo Lin School of Medicine (NUS Medicine) has also enhanced its curriculum for Medicine undergraduates by implementing a Minor that delves into Artificial Intelligence (AI) and Biomedical Informatics, to better prepare students for the new era of AI-driven digital medicine. Medical students will need to complete this Minor during their undergraduate candidature.

Students from other NUS faculties, schools and colleges would also have the opportunity to acquire knowledge about the workings of modern healthcare systems through a new Minor in Integrative Health.

"Health and well-being are more than just caring for the sick. To help people stay healthy as long as they live, and better care for them when they are ill, we need to look beyond the traditional confines of medicine and science, and draw upon other disciplines. Health sciences education should prepare tomorrow's doctors, nurses, dentists and pharmacists to harness the power of AI, computing, business analytics, even music and the arts, in the provision of holistic, patient-centric healthcare," said Professor Chong Yap Seng, Dean of NUS Medicine.

NUS Common Curriculum for Healthcare Professional Education

The specially curated two-year common curriculum draws on the academic content from Dentistry, Medicine, Nursing, and Pharmacy. It seeks to cultivate in students from Dentistry, Medicine, Nursing, and Pharmacy the awareness of social issues and their impact on health, teamwork, communication skills, professionalism, digital literacy, and interprofessional education.

A key content pillar in the common curriculum is the *Social and Behavioural Determinants of Health*, which educates healthcare students on the practical, social and emotional needs that affect individuals' health and well-being in communities. This pillar forms the foundation for the other four content pillars, which cover areas such as professionalism and ethical practice, teamwork and communication skills, as well as data and digital literacy.

Students also participate in interdisciplinary experiential learning through the *Longitudinal Patient Experience*, where teams of students from various healthcare disciplines will visit patients in their homes and living environments continually for one year. This immersive learning journey offers students opportunities to apply the concepts learnt in class to holistic care of their patients. At the same time, it fosters empathy and resilience in the students.

"Health sciences education should prepare tomorrow's doctors, nurses, dentists and pharmacists to harness the power of AI, computing, business analytics, even music and the arts, in the provision of holistic, patient-centric healthcare."

Professor Chong Yap Seng, Dean of NUS Medicine

"I attended the pilot session for the common healthcare curriculum in August 2022. It was eye-opening to learn that we should adopt a multifaceted approach to health, and not view health as merely a physical condition or illness. It was also interesting to understand how non-medical factors, such as social and environmental factors, play an important role in how doctors view and manage a patient's health. This will be an essential skill for me as a doctor in future," said Ms Yunn Honey Aye Kyaw, Phase II student at NUS Medicine.

She added, "Personally, the course, *Social and Behavioural Determinants on Health*, which delved into health in vulnerable groups, stood out for me. It highlighted the various barriers vulnerable patients face, such as the social, economic, environmental or political aspects of their lives, which affect how they receive care. These sessions have allowed me to reflect how I can be a better advocate for health, and reinforced the importance of being empathetic towards my future patients."

About
870
first-year students from Dentistry, Medicine, Nursing and Pharmacy would be taking the new common curriculum

It was also interesting to understand how non-medical factors, such as social and environmental factors, play an important role in how doctors view and manage a patient's health. This will be an essential skill for me as a doctor in future."

Yunn Honey Aye Kyaw, Phase II student at NUS Medicine

Minor in Biomedical Informatics

Harnessing data and technology to improve patient care, advance medical research, enhance population health management, Biomedical informatics holds tremendous potential in the healthcare system and can shape the future of healthcare delivery.

The Minor in Biomedical Informatics offered by NUS Medicine combines healthcare, data science, AI, and information technology to provide medical students with the necessary knowledge and skills to stay ahead of the healthcare curve.

Students develop skills in large language models, data management, health information systems, biomedical data analysis, and medical decision support systems. They also learn core skills such as evidence-based clinical decision-making, effective communication, strategic leadership, and entrepreneurship. All first-year medical students in the current Academic Year 2023/2024 are required to complete this Minor during their undergraduate candidature.

Minor in Integrative Health

A major aspect of integrative health involves the provision of optimal health and wellness, which will rely on advancements in areas such as healthcare technologies, environmental and building design, psychological care, data analytics, health economics, and healthcare innovations.

The new Minor in Integrative Health, which is open to first, second and third-year undergraduate students from non-healthcare disciplines from Academic Year 2023/2024, aims to educate and inspire students to lead, implement, and coordinate health-promoting research and development efforts using an interdisciplinary and cross-domain approach. Students will also cultivate an interdisciplinary mindset to solve complex health issues, and enhance individual and population health.

This Minor is offered by NUS Medicine, together with the Department of Information Systems and Analytics at the NUS School of Computing, as well as the Department of Architecture, Division of Industrial Design, and Department of The Built Environment at NUS College of Design and Engineering. It is also designed in consultation with the NUS Centre for Future-ready Graduates and industry partners from sectors such as healthcare, medical technology, pharmaceuticals, consulting, design, architecture, and facilities management.

Students will complete a total of five courses over two years or more. The inaugural cohort will comprise 50 students with the prospect of increasing the intake over the next three years.

From left: Year 2 students Moh Xin Qian Hilary from the NUS Faculty of Dentistry, Muhammad Amir Bin Mohamed Imran from NUS Nursing, Kanesananthan Yahrliny from the NUS Department of Pharmacy, Faculty of Science, and Yunn Honey Aye Kyaw from NUS Medicine.

The Future of Healthcare is Interdisciplinary

NUS Medicine Launches Programme for Students from Other Academic Disciplines

BY ASSOCIATE PROFESSOR CHEN ZHIXIONG, ASSISTANT DEAN (EDUCATION), DEPARTMENT OF PHYSIOLOGY AND NUS CENTRE FOR CANCER RESEARCH, YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE (NUS MEDICINE)

Among the lessons learned from the COVID-19 pandemic is one where we now know that a whole-of-society approach is required to overcome the next global health crisis. Healthcare and non-healthcare professionals will need to work collaboratively and synergistically together. Yet, non-healthcare professionals today who work in health-related areas mostly train and collaborate on the job, and the learning curve is steep.

At the same time, an increasing number of companies are incorporating health-related functions or interests into their businesses as societies move to deal with rapidly ageing populations and the uncertain evolution of diseases while capitalising on waves of technological advancement. There is a need to prepare the workforce for a health crisis-resilient nation and an ageing population, and provide ethical, thoughtful and sustainable healthcare solutions to the community. This is in line with the recently launched 'Healthier SG' initiative that necessitates the training of a workforce beyond healthcare workers that will take on roles to comprehensively improve population health outcomes.

Thus, an educational programme is needed to produce non-healthcare graduates who understand the health sector, and can contribute effectively with their expertise to improve individual and population health. They would need to possess the ability to:

- Be self-aware of the strengths and weaknesses that their expertise brings
- Receive new learning and form networks beyond their own professional disciplines
- Straddle fields, create new fields or pivot from one field to another

> **“An educational programme is needed to produce non-healthcare graduates who understand the health sector, and can contribute effectively with their expertise to improve individual and population health.”**

A programme like no other

In August 2023, the NUS Yong Loo Lin School of Medicine will launch the first-ever undergraduate programme called the Minor in Integrative Health (MIH) to train non-healthcare undergraduates on how to situate their disciplines in the context of others and adopt an interdisciplinary mindset towards identifying unmet needs and providing holistic healthcare solutions. They will learn alongside peers from non-healthcare disciplines across NUS through five courses conducted and developed by academic staff from NUS Medicine, College of Design and Engineering, School of Computing, and community and industry partners.

The four-unit courses (What Impacts Health?; Improving Health: Beyond Medicine; Barriers to Health; The Landscape of Health: Evolving Spaces and Technology Integrative Health Capstone) will cover 1) WHO health dimensions and bring 'Healthier SG' to the fore; 2) key conditions that affect Singapore and the region, and the medical sciences behind them; 3) barriers in accessing health with respect to demographic groups of interest in Singapore; 4) the future of health via system and user-centric design; and 5) the application of prior learning to solve real-world problems.

These courses will be coordinated by the Departments of Physiology (Dr Ivan Low and Dr Amanda Wong), Biochemistry (Dr Long Yun Chau), Pharmacology (Dr Inthrani Raja Indran and Dr Serena Seah), and Microbiology and Immunology (Dr Ch'ng Jun Hong and Dr Png Chin Wen) with strong support from the Departments of Anatomy and Pathology, and NUS Centre for Future-ready Graduates.

The Minor will equip students with basic health literacy and education as well as competencies such as interdisciplinary collaboration, ethics and humanism, and leadership and management. It will be offered to all NUS students (excluding Dentistry, Medicine, Nursing and Pharmacy) with an initial cohort of 50 students. Students who choose not to pursue the Minor may still read some of the courses as unrestricted electives.

Hands-on, immersion learning

Students will participate in interdisciplinary learning that focuses on various aspects of health. They will gain first-hand exposure to current industry trends, problem identification and solutioning in practice, thus, offering real-world learning beyond theoretical concepts of healthcare. The courses in the Minor are designed to guide students to contextualise and apply critical design, system and ethical thinking to make strategic decisions with consideration of physical, bio-psychosocial, environmental and technological factors to solve real-life health and wellness issues.

The Minor aims to produce graduates from various disciplines who can embrace the meaning of health through a medical science understanding of the human body and its limits, and the constraints that exist in accessing good health at the individual and population level, so that they can recognise, innovate and advocate solutions wherever they choose to be employed.

Through the Minor, students will have opportunities to build valuable connections with individuals and stakeholders from different backgrounds. It will help students understand the roles of different stakeholders and the value they bring to these organisations. The interdisciplinary nature of the programme also encourages students to develop a receptive mindset and agility to deal with ever-changing challenges to become future leaders in the health sector.

The programme also utilises a constructivist approach to deliver education, whereby students make judgments and interpretations of the content based on their prior knowledge and experience. It focuses on providing spaces to 'co-everything'—from co-conceptualisation to co-implementation. Students will participate in highly interactive dialogue sessions with local and global leaders in various fields. Peer learning, constructive collaboration and self-actualisation will be fostered in these students as they actively participate in team projects, real-life case studies and real-world tasks. Experiential learning through field trips will form part of the course curriculum to connect theories and knowledge learned in the classroom to real-world situations. Final evaluation of the students will be through a capstone project in which they will apply what they learned and work on real-world projects from industry partners or come up with projects themselves, guided by industry and faculty experts.

In all, the Minor aims to produce graduates from various disciplines who can embrace the meaning of health through a medical science understanding of the human body and its limits, and the constraints that exist in accessing good health at the individual and population level, so that they can recognise, innovate and advocate solutions wherever they choose to be employed. This aim is achieved by using computing technology, environmental design and medical sciences as sample disciplines to illustrate the power of interdisciplinary integration in safeguarding health.

Planting the seeds of tomorrow's healthcare workforce

Integrative health goes beyond disease diagnosis, prevention, and treatment. The provision of overall optimal health and wellness is a major aspect of integrative health. Improved healthcare technologies, environmental and building design, psychological care, data analytics, health economics and healthcare innovations are some key areas that have contributed to the development of integrative health globally.

Therefore, it is important to understand that different fields of expertise from many non-healthcare disciplines have become increasingly important for effective healthcare innovations and interventions. The responsibility of delivering '360' healthcare can no longer be restricted to just healthcare professionals, but must instead be extended to all professions including those in biotechnology, product design, supply chain, IT, finance, urban planning and more.

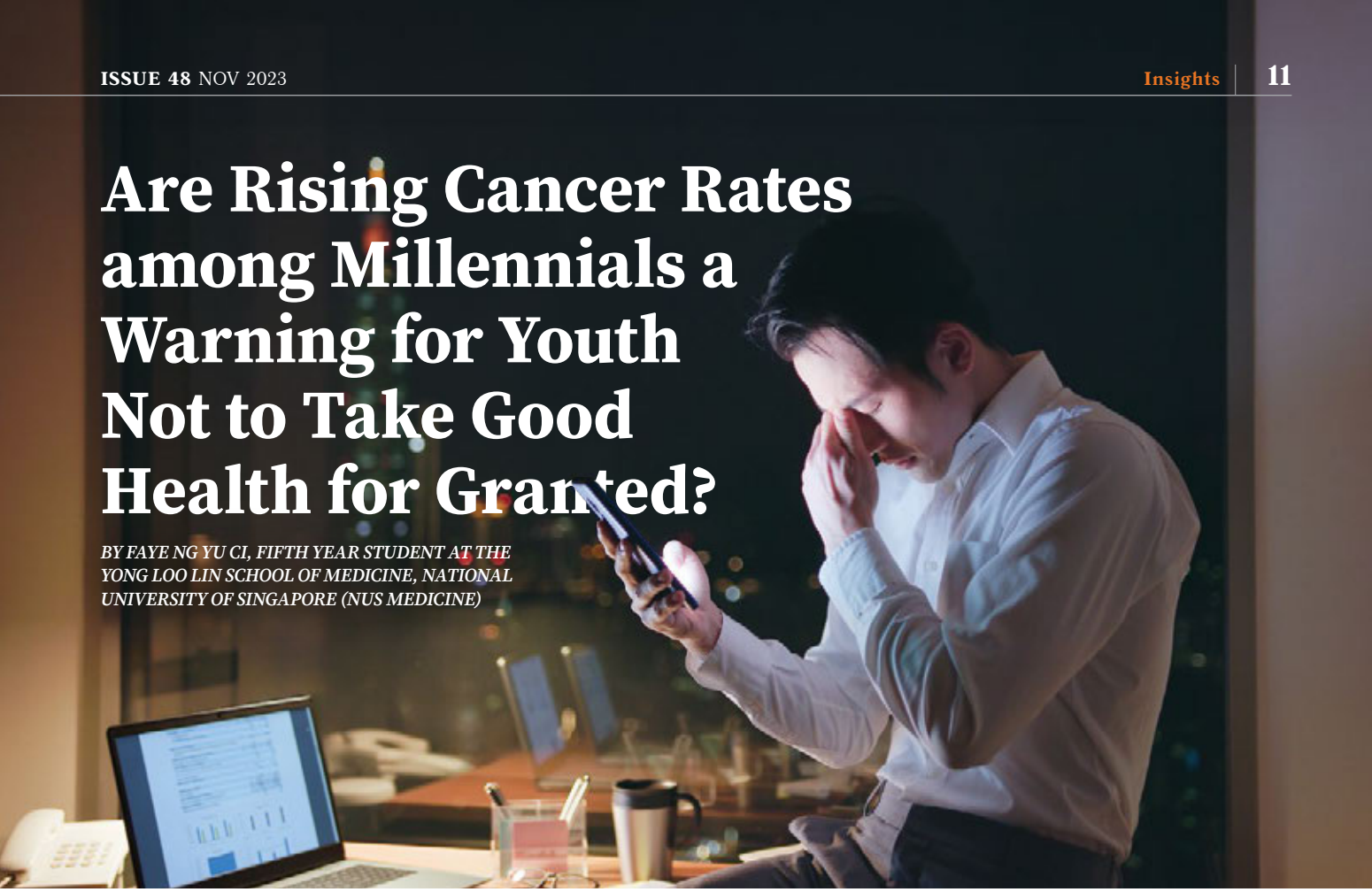
The MIH programme is designed to give non-healthcare students a head start in careers across a wide range of industries that contribute to health. MIH graduates will enjoy diverse job opportunities in industries ranging from public healthcare and pharmaceutical sector to MedTech and consulting. Indeed, industry leaders in healthcare, MedTech, design/architecture/facilities management, and healthcare consulting welcomed the Minor and unanimously agreed that students with knowledge and understanding of various disciplines would be highly valuable as they are able to coordinate various components of a complex healthcare solutioning system in an ever-interconnected global health market.

Nationally, graduates will be able to contribute to the 'Healthier SG' initiative through community partnerships and employment in relevant organisations. They will be able to provide the necessary support structures in manpower, finance, IT, data and public health education to drive the health reforms needed to provide affordable, seamless, integrated, preventive and targeted care to the community.

With competencies in applying interdisciplinary knowledge to close disciplinary skill gaps and improve interventions for health, MIH graduates will be able to navigate and contribute to the complex health sector with greater confidence.

Scan to read more information here:

Are Rising Cancer Rates among Millennials a Warning for Youth Not to Take Good Health for Granted?



BY FAYE NG YU CI, FIFTH YEAR STUDENT AT THE YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE (NUS MEDICINE)

As a medical student on my clinical rotations, the usual patient demographic I'm used to seeing in the wards for cancer-related cases are in their 70s and 80s, with some others in their late 50s and 60s.

However, that stereotypical profile of oncology patients might just become younger, according to data from the Institute for Health Metrics and Evaluation at the University of Washington School of Medicine.

According to an analysis by the Financial Times, cancer rates in the G20 group of industrialised nations have increased faster for 25- to 29-year-olds than any other age group in the past three decades. These rates jumped by a staggering 22% between 1990 and 2019.

In other words, rates of malignancy in millennials in these countries are now at their highest level in 30 years. On the other hand, the incidence of cancer in those over 75 has declined from its peak in 2005.

Researchers have no definitive answers explaining why young people in the prime of life seem to be more susceptible to disease than those of previous generations, but suspect it might have to do with nutrition and lifestyle changes that took hold in the middle of the last century.

Some have postulated that modern diets and the increasing consumption of saturated fat, oil and sugar, along with more sedentary lifestyles, disordered sleep patterns and nocturnal light exposure, may all have had a part to play in the pathogenesis of the disease.

These changes interact in complex ways with each other, and in turn, have wide-ranging effects on our gut microbiome composition, circadian rhythm, and metabolism.

Meanwhile, there is concern over whether the rise in cancer cases over the past few decades in the younger population represents only the tip of the epidemiological iceberg for other health conditions.

Cancer rates in the G20 group of industrialised nations jumped by a staggering

22%

between 1990 and 2019

As a young person graduating to join the medical profession, the article gave me pause to reflect. As a doctor-in-training, I felt pained and aghast for my future patients. As a millennial, I felt vulnerable.

From my Family Medicine posting as well as news reports and information from health authorities, I knew that chronic diseases such as diabetes and hypertension were on the rise in the younger generation.

But cancer? It seemed like something far away and foreign to people my age.

Being young makes it easy to feel invincible.

Many of us function on a cocktail of caffeine excess and adrenaline high, carrying a mountain of sleep debt on our tense and overloaded shoulders.

In university, students often have a habit of eating fast food for convenience and hanging out over midnight suppers with friends—with co-curricular activities, practices and committee meetings in school ending late.

During the finals season, undergraduates pack into the library, studying late into the night, coffee tumblers beside them.

Even after starting work, our propensity to push our bodies beyond their limits continues.

The long hours and late nights from school carry over into the workplace—this time, with the added pressure of actual stakes and real responsibilities.

Whatever industry and work one is engaged in, young people generally feel a need to prove themselves early in their careers.

When your body feeds on excess reserve, you just feel like you have so much to go on. Yet how long does it take before we start running on empty?

Ask any young person and they'll expound on how they're constantly squeezed for time—there's always more things to do, friends to hang out with, and milestones to reach.

It is such a cliched notion to "make the most" of youth, until it hits you with startling clarity how much youth has passed you by.

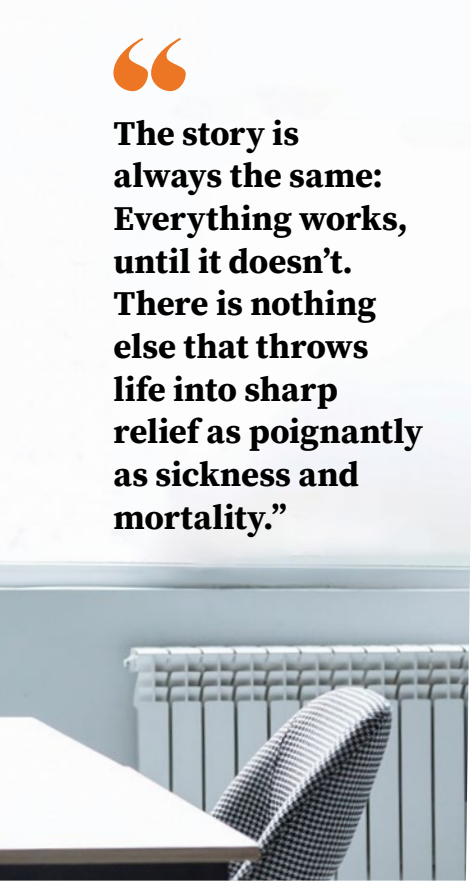
Nowadays when I am in MRT trains or buses looking at secondary and junior college students jabbering away in school uniforms, I contemplate how much time has elapsed since my "formative" schooling days—was that really just five to 10 years ago? Since then, how have I grown and changed?

Your 20s and 30s are a time when you supposedly flourish, the prime years of your life.

Yet paradoxically, being young, we rely on the illusion that time is always on our side; rest can wait, sleep can wait, self-care can wait. Sometimes, even our families and loved ones take the back seat, as we make a mental note to "make it up to them" in the future, thinking we'll have more time to spare.

Yet perhaps it is that earnestness and fervent insistence to live a full life, enthusiasm flaring and ambition radiant, that defines being young and wilful.

↑ Whatever one's industry, youths generally feel a need to prove themselves early in their careers. Yet how long does it take before we start running on empty?



“The story is always the same: Everything works, until it doesn’t. There is nothing else that throws life into sharp relief as poignantly as sickness and mortality.”

Nevertheless, the lifestyle choices we live by and everyday habits we cultivate in our youth do have consequences for the future.

If health is our most precious asset, why do we not seem to value it? Our daily acts of waking, commuting, and interacting with the world around us are things that we often take for granted.

The story is always the same: Everything works, until it doesn’t. There is nothing else that throws life into sharp relief as poignantly as sickness and mortality.

From multiple heart-to-heart conversations with young people from work and school, I realise that most of us have a concept of “healthy” versus “unhealthy” ways of living, and endeavour to make lifestyle choices that promote our well-being in the long run.

Innately, we are aware of what should be done and what matters, living right by the health-conscious standards and principles we have been taught. With this in mind, why do we find it so hard to enact these priorities in our daily lives?

In healthcare, we use the knowledge, attitude, and practice framework to evaluate behavioural change in public health interventions, for example, healthy eating campaigns or smoking cessation programmes.

To form an opinion or perspective about a subject, one must first acquire sufficient knowledge and information. Sometimes, knowledge is intuitive; sometimes, knowledge is gained through reading different resources and accumulating life experiences.

After an attitude is developed, practice then takes time, repetition, and positive environmental reinforcement to inculcate.

Both intrinsic and extrinsic motivation are crucial for sustained behavioural change.

Intrinsically, young people must learn to inherently enjoy making nourishing food choices and establishing a balanced work-life rhythm, reaching for more greens on their plates and turning in early to clock more than seven hours of sleep each night.

Extrinsically, young people must desire the benefits their lifestyle changes bring about, appreciating the worth of improved mood and energy levels, increased longevity, and weight control.

If either component is missing or inadequate, the knowledge-behaviour gap occurs and behavioural change becomes difficult to keep up.

The article about the rising incidence of cancer among young people might just seem like a blip on the radar, but in a way, it is communicating something serious and urgent to us, encouraging us millennials to make more intentional and conscious lifestyle choices.

Collectively, as a society, this may be a chance for us to pause and reflect. Perhaps this can serve as a reminder to slow down our pace of life at times, to re-centre what we value and cherish, as well as to extend more grace to ourselves and each other.

Perhaps not everything has to be done right here and right now. What is pressing might not necessarily be what is important, and what is precious might not always be what is most apparent.

After all, we have only one body. Our health is ours to take care of, our future is ours to protect.

This article was first published in TODAY and reproduced here with edits.

Scan to read the original article here:

Parasites of Viruses Drive Superbug Evolution

In a study led by Assistant Professor John Chen from the Department of Microbiology and Immunology and the Infectious Diseases Translational Research Programme at the NUS Yong Loo Lin School of Medicine (NUS Medicine), researchers have discovered a previously unknown mechanism by which bacteria share their genetic material through virus parasites. The insights could help scientists to better understand how bacteria rapidly adapt and evolve, and how they become more virulent and resistant to antibiotics.

In a study published recently in *Cell*, one of the most prominent peer-reviewed scientific journals in the field of Biochemistry & Molecular Biology, scientists from the National University of Singapore (NUS) and Imperial College London have discovered a new way by which bacteria transmit their genes, enabling them to evolve much faster than previously understood.

The ability to share genetic material is the major driver of microbial evolution because it can transform a benign bacterium into a deadly pathogen in an instant. Phages, the viruses of bacteria, can act as conduits that allow genes to transfer from one bacterium to another by a process known as genetic transduction. Currently, there are three known mechanisms of transduction: generalised, specialised, and lateral. Lateral transduction was also discovered by the same researchers in 2018, and it is at least one thousand times more efficient than the next most powerful mechanism, generalised transduction.

The new process discovered is termed lateral cotransduction, and the architects behind this new frequency and speed in bacterial evolution are the *Staphylococcus aureus* pathogenicity islands (SaPIs), which are selfish DNA elements that exploit and parasitise phages, and are commonly found integrated into the chromosomes of *S. aureus* isolates. *S. aureus* is a type of bacteria that can cause Staph infections in humans and animals. While it primarily manifests as skin infections, it can become life-threatening if it spreads to the bloodstream and infects organs, bones, or joints.

Professor José R. Penadés from the Department of Infectious Diseases, and Director for the Centre for Bacterial Resistance Biology at Imperial College London, said, “This breakthrough sheds light on a novel pathway through which bacteria evolve. Given the alarming surge of antibiotic-resistant superbugs, comprehending the mechanisms driving bacterial evolution becomes increasingly critical.”

This newly discovered process, lateral cotransduction, rivals lateral transduction in terms of efficiency but surpasses the latter in versatility and complexity. While lateral transduction is only known to occur when dormant phages within bacterial genomes

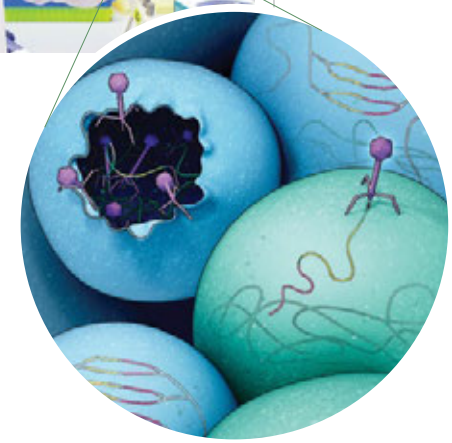
become reactivated and initiate reproduction in the lytic cycle, lateral cotransduction can occur during the reactivation process and the infection of new bacterial cells.

Additionally, unlike phages that sacrifice their genes to transmit bacterial host DNA, SaPIs can transfer themselves completely intact with bacterial DNA through lateral cotransduction. This remarkable capability enables them to perpetually repeat the process, making them significantly more potent and efficient in transmitting bacterial genes.

Asst Prof Chen said, "Through the study, we have demonstrated that bacteria can evolve much faster than we understood. While genetic transduction has always been the exclusive domain of phages, in an unexpected twist of irony, our research has shown that parasites of the most prolific parasites on the planet (the phages) are probably the most powerful and efficient transducing agents currently known."

From friend to foe: the unwitting accomplices of SaPIs

The rise of superbugs has called for new ways to treat antibiotic-resistant strains. One such method that has gained traction in recent years is phage therapy, which involves the use of phages to eliminate harmful bacteria in infections and diseases. However, instead of just fighting bacteria, some therapeutic phages could turn out to be the unwitting accomplices of SaPIs or other related elements capable of lateral cotransduction.



"They (phages) could be used to destroy bacteria in the short term but end up spreading harmful genes to other cells in the long term, which could prove to be disastrous. With this new way of understanding the evolutionary mechanisms of disease-causing organisms, it is important for therapeutic phages to be carefully vetted before they are used for therapy."

Asst Prof John Chen, Department of Microbiology and Immunology and the Infectious Diseases Translational Research Programme, NUS Medicine

In circle: An illustration of lateral cotransduction between *Staphylococcus aureus* pathogenicity islands (SaPIs).

According to Prof Penadés, "This process likely occurs in various other bacterial species as well. This groundbreaking finding marks a paradigm shift in our understanding of bacterial evolution and will immensely influence the ways we combat antibiotic resistance."

"They (phages) could be used to destroy bacteria in the short term but end up spreading harmful genes to other cells in the long term, which could prove to be disastrous. With this new way of understanding the evolutionary mechanisms of disease-causing organisms, it is important for therapeutic phages to be carefully vetted before they are used for therapy," said Asst Prof Chen.

Scan to read the journal article here:

New Treatment Method Reduces Size of Atherosclerotic Plaque on Arterial Walls, Preventing Heart Diseases

While Docosahexaenoic acid (DHA), an omega-3 fatty acid, could help to prevent the build-up of fatty deposits in arteries, traditional treatment methods such as oral consumption of DHA is often ineffective in treating atherosclerosis.

Atherosclerosis is a disease in which fat, cholesterol, and other substances build up inside artery walls. This can lead to plaque formation, which can block arteries and cause heart attacks and strokes. It is the leading cause of coronary heart disease, and is responsible for an estimated 17.9 million deaths in 2020.

In Singapore, 21 people die from heart disease and stroke every day, accounting for 32% of all deaths in 2021, making it the top disease burden in Singapore.

Atherosclerosis: A silent killer, years in the making

Atherosclerosis is a chronic disease which takes years to develop, with no clinical symptoms manifested in the early stages. However, risk factors such as high blood cholesterol, high blood pressure and obesity can accelerate the progression of the disease. In patients with advanced-stage atherosclerosis, symptoms such as chest pain and breathlessness may be exhibited, indicating severe artery blockage.

Coronary heart disease caused around **17.9 MILLION** deaths in 2020

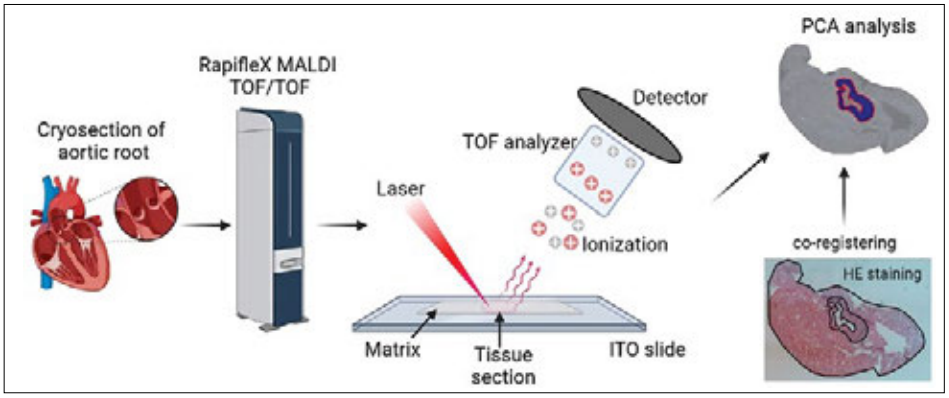
In Singapore, **21** people die from heart disease and stroke every day

Early interventions such as lifestyle modifications and medications to lower blood cholesterol are desirable and effective for most patients. DHA has been shown to have anti-inflammatory and antioxidant properties, which could help to prevent the build-up of fatty deposits in arteries—a major cause of heart attacks and strokes. DHA supplements are often consumed orally, but most are poorly absorbed by the gut.

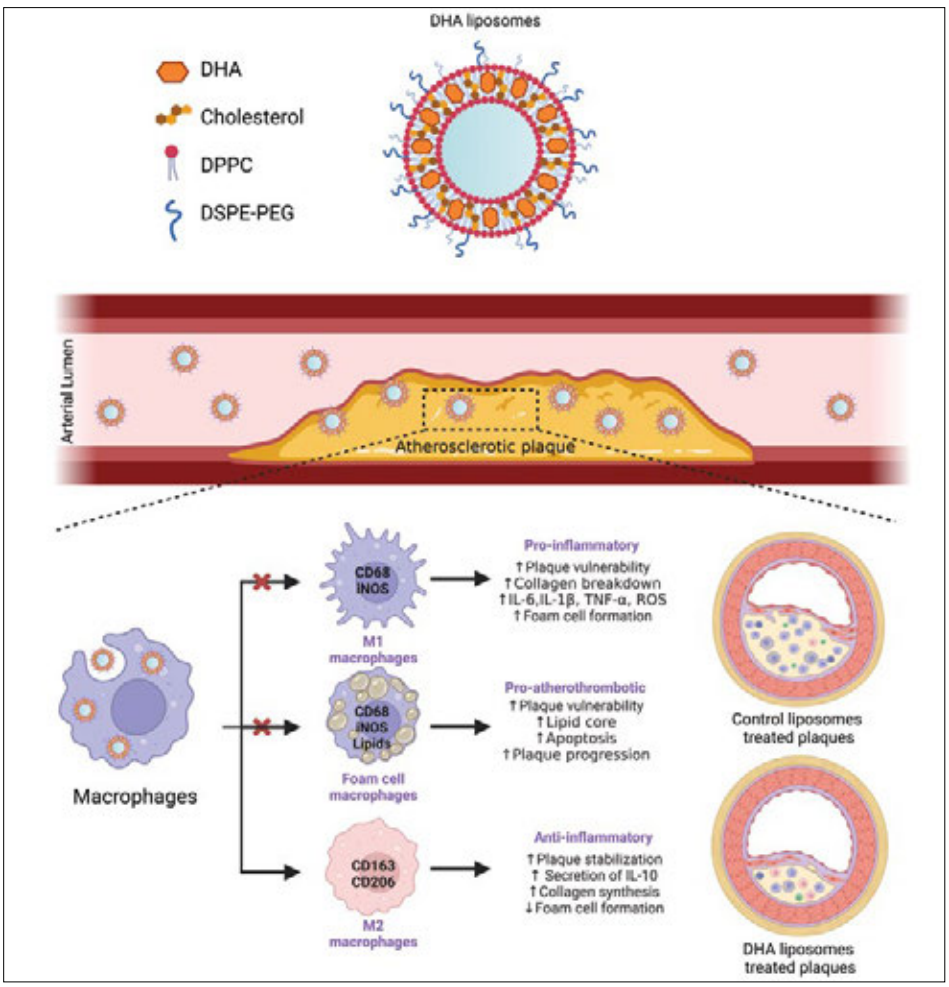
Nanomedicine as a useful treatment tool

To improve the availability of DHA in the bloodstream, a research team led by Assistant Professor Wang Jiong-Wei from the Department of Surgery, the Nanomedicine Translational Research Programme, Centre for NanoMedicine and Cardiovascular Research Institute, at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), and Professor Gerrit Storm from the Department of Surgery and Nanomedicine Translational Research Programme at NUS Medicine, worked on laboratory models to deliver DHA to the bloodstream that could be more effective than oral consumption—via DHA liposomes, a form of nanomedicine. This study is published in the *Journal of Controlled Release*.

DHA liposomes are small vesicles made up of phospholipids, a major membrane lipid which acts as a barrier to protect the cell against various adverse environmental conditions. The liposomes can help to reduce the size of plaques and the amount of inflammation in arteries. When delivered into the blood stream, DHA liposomes accumulate in the plaques on the arterial walls.



An illustration of mass spectrometry imaging (MSI) on atherosclerotic plaques.



Graphical representation of the treatment process.

The liposomes can help to reduce the size of plaques and the amount of inflammation in arteries. When delivered into the blood stream, DHA liposomes accumulate in the plaques on the arterial walls.

The research team found that macrophages, a type of white blood cell, absorb the DHA liposomes, resulting in reduced inflammation and increased healing of the atherosclerotic plaques. These liposomes also help reduce the amount of lipids in the build-up and prevent its rupture.

In collaboration with Associate Professor Glenn Bonney, Senior Consultant, Division of Hepatobiliary & Pancreatic Surgery, and Director of Research, Department of Surgery, National University Hospital, the researchers employed a state-of-the-art mass spectrometry imaging technology termed rapifleX, to analyse the plaque. It revealed that DHA liposomes can restore the lipid balance in the artery to that of healthy arteries in which less harmful lipids are present. These results suggest that DHA liposomes could be a promising new treatment for atherosclerosis.

"This is the first study to demonstrate that an injectable nanoformulation can remarkably improve the therapeutic effects of DHA against atherosclerosis at a dose of 40,000 to 400,000 times lower than reported usage of oral DHA. We are optimistic about the clinical benefits it may bring to our patients, and are exploring clinical trials on patients in the near future," said Asst Prof Wang.

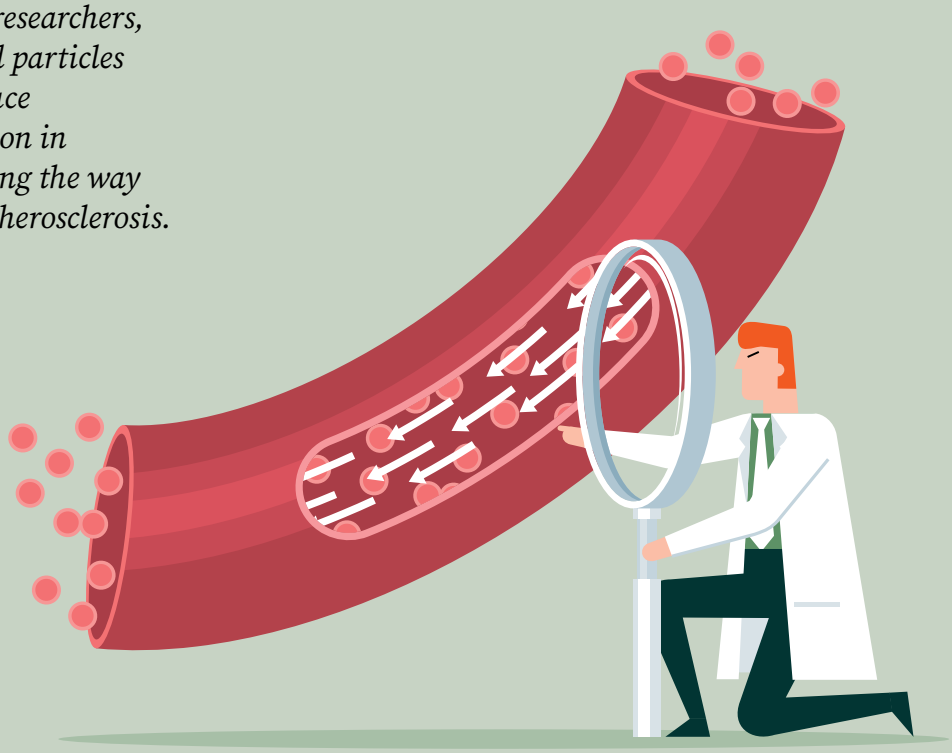
Scan to read the journal article here:

From left:
The research team, comprising Assistant Professor Wang Jiong-Wei from the Department of Surgery, the Nanomedicine Translational Research Programme, Centre for NanoMedicine and Cardiovascular Research Institute at NUS Medicine; Associate Professor Glenn Kunnath Bonney from the Department of Surgery at the National University Hospital and the Director & Principal Investigator of SurgiCAL ProtEomics Laboratory (SCALPEL), iHealthtech, NUS; Professor Gerrit Storm from the Department of Surgery and Nanomedicine Translational Research Programme at NUS Medicine; Ms Chong Suet Yen, PhD student at the Department of Surgery and Cardiovascular Research Institute at NUS Medicine; and Dr Looi Wen Donq, Application Specialist at Bruker Daltonics.

Behind:
rapifleX, the technology which performs mass spectrometry imaging (MSI) on atherosclerosis plaques, allowing for the visualization of different types of lipids on the plaques.

Red Blood Cell Particles Reduce Fat Deposition in Arteries, Potentially Treating Atherosclerosis

In a study conducted by NUS researchers, they found that the nano-sized particles released by red blood cells reduce inflammation and fat deposition in immune cells, potentially paving the way for new methods of treating atherosclerosis.



Atherosclerosis is a disease in which fat, cholesterol, and other substances build up inside artery walls. This can lead to plaque formation, which can block arteries and cause heart attacks and strokes. Immune cells play a key role in cleaning the blood, by interacting with red blood cell extracellular vesicles (RBCEVs), which are nano-sized particles released by red blood cells.

Commonly referred to as "first responders" to infections, macrophages are immune cells which detect and clear pathogens and dead cells, and secrete molecules to activate other immune cells.

To understand what happens to macrophages that are exposed to a high amount of RBCEVs and whether they prove to be beneficial in treating atherosclerosis, a multi-institutional team examined the mechanisms of how RBCEVs are internalised by macrophages and analysed the consequent changes.

Led by Assistant Professor Minh Le from the Department of Pharmacology and the Institute for Digital Medicine (WisDM), Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), the study demonstrated that the uptake of RBCEVs by macrophages was highly efficient, as the particles induced multiple changes in the macrophages.

Following exposure to RBCEVs, the macrophages had decreased levels of proteins that promote inflammation, suggesting the potential use of RBCEVs to alleviate conditions associated with excessive inflammation. The macrophages also produced higher levels of an enzyme which protects cells against oxidative damage—commonly observed in inflammatory and cardiovascular diseases. In addition, the RBCEVs led to higher resistance to lipid uptake in the macrophages, reducing fat deposition—which characterises the condition of atherosclerosis.

Published in the *Journal of Extracellular Vesicles*, one of the top Cell Biology journals, the study was conducted in collaboration with the Department of Surgery, Department of Physiology, Nanomedicine Translational Research Programme, and Cardiovascular Research Institute at NUS Medicine; the School of Mechanical and Aerospace Engineering and Lee Kong Chian School of Medicine, Nanyang Technological University (NTU); and the Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR).

Asst Prof Minh Le said, "We have known for a while that RBCEVs tend to go to macrophages when they enter the body, but we did not realise some of the implications until now. The properties of RBCEVs that we have uncovered here are desirable for treating atherosclerosis and possibly other inflammatory diseases."

The team hopes to leverage their improved understanding to manipulate RBCEV uptake by macrophages and thus adjust the distribution of RBCEVs to different tissues in the body. The team also plans to further explore the therapeutic potential of RBCEVs by combining their natural beneficial properties with exogenously loaded drugs designed to treat inflammatory conditions. These plans are part of the expansion of their ongoing work on developing the RBCEV platform for the treatment of various diseases including cancer, cancer-associated muscle loss, and COVID-19.

"Atherosclerosis causes heart disease and stroke, affecting millions of people. This discovery by the team is paving the way towards exciting new therapeutic strategies that can have a real impact on healthcare. We can now start looking into the use of very tiny particles made from our own red blood cells to treat atherosclerosis and potentially other diseases."

Prof Lee Chuen Neng from the Department of Surgery, and Nanomedicine Translational Research Programme at NUS Medicine

"Atherosclerosis causes heart disease and stroke, affecting millions of people. This discovery by the team is paving the way towards exciting new therapeutic strategies that can have a real impact on healthcare. We can now start looking into the use of very tiny particles made from our own red blood cells to treat atherosclerosis and potentially other diseases," said Professor Lee Chuen Neng from the

Department of Surgery, and Nanomedicine Translational Research Programme at NUS Medicine. He is also Clinical Director, Institute for Health Innovation & Technology, NUS.

Scan to read the journal article here:

Large Language Models:

Praise, Blame, Personalisation and Co-Creation

BY DR SEBASTIAN PORSDAM MANN, UNIVERSITY OF OXFORD AND PROFESSOR JULIAN SAVULESCU, DIRECTOR, CENTRE FOR BIOMEDICAL ETHICS, YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE (NUS MEDICINE)

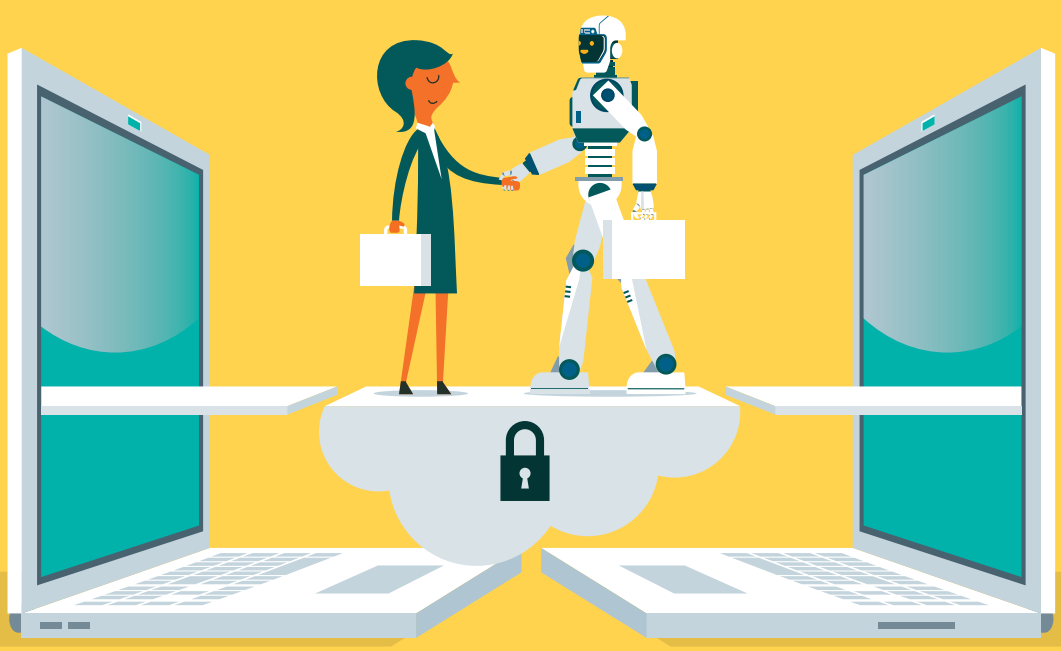
In Goethe's "The Sorcerer's Apprentice," an eager apprentice, left alone, uses magic to avoid chores by making a broom fetch water for him. The unintended results—multiplication of brooms, rampant flooding, desperate attempts to stop the mad magic—are familiar to most of us, thanks to Disney's beautiful rendition of this cautionary tale (Fantasia).

In an age where the powers of Artificial Intelligence (AI) models have advanced to a point comparable to the apprentice's magic, the story offers a poignant warning of what can happen when we set in motion powerful forces without sufficient skill or foresight.

One means and source of such foresight is ethical analysis of AI uses. Like many other academic areas, practical ethics has been galvanised by the release of generative AI models such as ChatGPT (a large language model or 'LLM') or MidJourney (a text-to-image generator), which allow users to generate words, sounds, or images in near-real time from natural language descriptions. These instructions, were they not written down, would seem to resemble nothing so much as spells and incantations. Yet in real life, we do not have the luxury of waiting for the return of the sorcerer to undo our mistakes and mop up the mess. It is therefore even more important for us than for the sorcerer's apprentice to foresee and forestall potential problems and pitfalls before releasing our brooms into the wild.

Ethics and LLMs

LLMs are machine learning programs that have learned patterns and associations in huge amounts of natural language sourced from the internet. They work by predicting the statistically most likely next word (or fragment of a word),



based on all the preceding text. Although undoubtedly very powerful and useful, these models have also resulted in numerous warnings being sounded. These include concerns based on the (lack of) equal representation in the text used as training data—which comes disproportionately from young, English- and Chinese-speaking men. Among other well-known concerns are the fact that these models cannot yet distinguish reliably between falsehood and truth in all cases and therefore often make up ('hallucinate') information. Another concern is the environmental impact of massive amounts of computation expended to train and operate these models.

In our work as practical ethicists focused on biomedical issues—bioethicists—these are familiar concerns whenever a novel, powerful technology comes around. However, there are also fascinating ethical issues unique to generative AI programs such as LLMs which have no parallels to other technologies. Convinced of the importance of understanding issues unique to this powerful technology, we set out to investigate these in a series of papers co-authored with colleagues from across the physical and academic world.

Credit and blame

One set of issues concerns who can take credit and who must shoulder blame for harms and benefits arising from LLM use. Like the sorcerer's apprentice, a LLM user attempts to formulate a set of instructions which sets in motion an autonomous process, the results of which will affect the interests and well-being of others. Intuitively, we know who is to blame in Goethe's story: the apprentice is reckless or at least negligent with respect to the risks and bites off a larger piece of magical pie than can be digested. Similarly, we hypothesised that users of LLMs are also fully responsible for harms resulting from their use of these programs, even where these were not intended.

In a recent paper in Nature Machine Intelligence,[1] we argued that the reverse situation does not hold: where LLM use results in benefits, users cannot take full credit for these. Had the sorcerer's apprentice been lucky and cast a spell better fit for purpose, they would not deserve as much credit for cleaning up the sorcerer's lair as they would had they done so on their own. This is because, as colleagues and one of us has previously argued,[2] to deserve credit one must have made sacrifices, used skills, or at least employed effort—elements which are notably missing in cases where LLMs (or, for that matter, other humans) are instructed to carry out one's work.

Based on this insight, we argued that LLM use entails a credit-blame asymmetry: "the use of generative AI elevates the bar for earning credit, but standards for assigning blame remain the same." If this is the case, this insight has numerous implications for how we should approach the ethical evaluation of LLM use in contexts such as work and education. One important consequence may be what we call the achievement gap: "good, useful outcomes will be produced, but many of them will not be achievements for which human workers and professionals can claim credit."

Empirical work confirms the existence of a credit-blame asymmetry

In as-of-yet unpublished experimental work, we surveyed samples in the UK, US, Singapore, and China, and found that respondents do indeed assign similar levels of blame, but much reduced amounts of credit for LLM users, as compared to completing the same work without help from an LLM. Interestingly, however, we found no differences across surveys between credit given for text written without LLMs and text written using *personalised* LLMs. A personalised LLM, as we use the concept, is a language model adapted to information pertaining to a specific individual.

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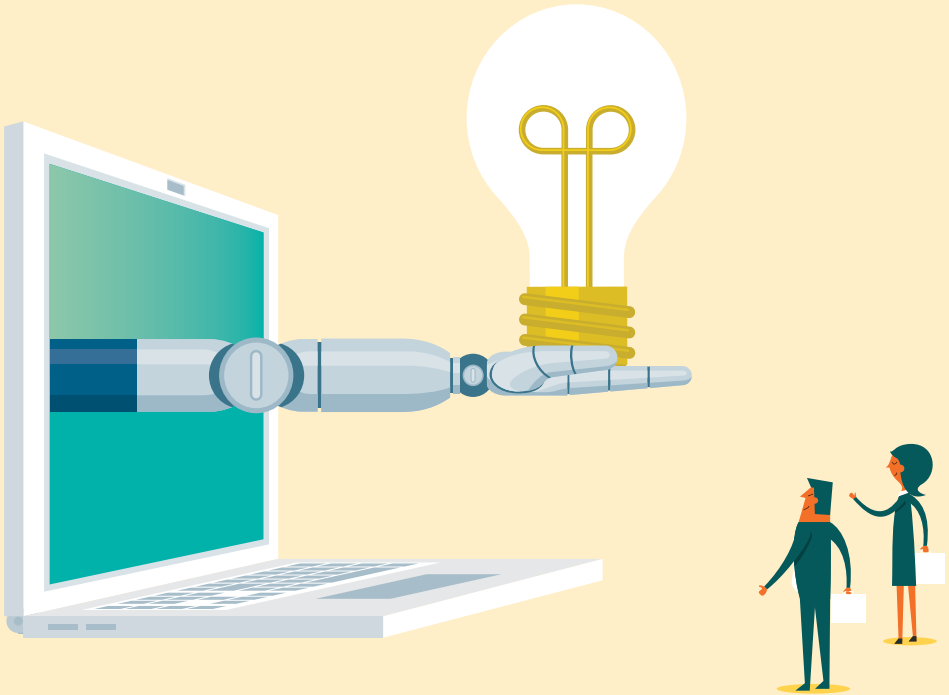
Personalising LLMs

We first introduced the concept of personalised LLMs in the specific context of academic prose generation.[3] As noted above, LLMs in general are trained on a vast trove of mostly indiscriminately collated internet text. For this reason, LLMs are jacks-of-all-trades, yet master of none: models trained on more specific, specialised datasets outperform, as a rule, more general models. One way to combine elements of both general and special-purpose models is known as *fine-tuning* and involves exposing an existing, general LLM (such as GPT-3, the precursor to ChatGPT) to a more specialised dataset. The result is a model based on a general purpose LLM, but adapted to a more specific context: a jack-of-all-trades with further training in one of those trades.

One way to personalise an LLM is thus to fine-tune it on material relevant to or produced by an individual. To try this out, we created a custom dataset consisting of the previously published academic articles of ourselves and another of our collaborators (Brian Earp) and fine-tuned GPT-3 on this custom dataset. The result was striking: the fine-tuned model appeared to adapt to our style of argumentation, producing much more coherent and detailed responses to our queries in the style of an academic paper.

The ethical implications of this are numerous: on the positive side, increased productivity and potential for generating new ideas which can stimulate scientific progress; on the negative side, style theft and impersonation as well as multiple other potential misuses. To take just one example, we used for our training data only articles on which we were first authors and which we had thus largely written ourselves—but nothing prevents others from including whatever articles they want, whether written by themselves or not, in their custom dataset.

In another recent paper, we extended this idea of personalisation to a rather different arena: that of preference predictions for incapacitated patients.[4] When individuals are not medically competent to make treatment decisions for themselves—for example, because they are in a coma—others must make these decisions for them, ideally in the same way that the incapacitated person would have made them had they been able to. Unfortunately, it turns out that such 'surrogate' decision-makers are little more accurate than chance in these predictions. Moreover, they suffer significant distress and anxiety due to having the burden of decision-making placed squarely on their shoulders.



The ethical implications of this are numerous: on the positive side, increased productivity and potential for generating new ideas which can stimulate scientific progress; on the negative side, style theft and impersonation as well as multiple other potential misuses.

To counter these problems, ethicists have previously suggested the use of a patient preference predictor: a statistical model which, based on large-scale survey responses by representative samples, could be used to suggest, based on a patient's demographics, what "others like them" would choose. This information could then be used by a surrogate decision-maker to make their task less burdensome. However, critics have contended that such an algorithm would not, in the relevant ways, respect the incapacitated person's autonomy, because it would be based on group- and demographic-level data.

In response, we have proposed a *personalised* patient preference predictor ('P4'): an LLM fine-tuned, with actual or proxy consent, on an individual's writings and other information about them (e.g. social media posts, electronic health record information, data from medical interviews and fitness trackers, etc.). We argue that such a P4 would likely be more accurate than both surrogates and the demographic-level algorithm, since it takes into account more relevant information and does so in a more technically rigorous way. But crucially, the P4 would also base its predictions on individual-level information, thus aligning much more closely with the incapacitated individual's actual desires and preferences (and therefore better respecting their autonomy).

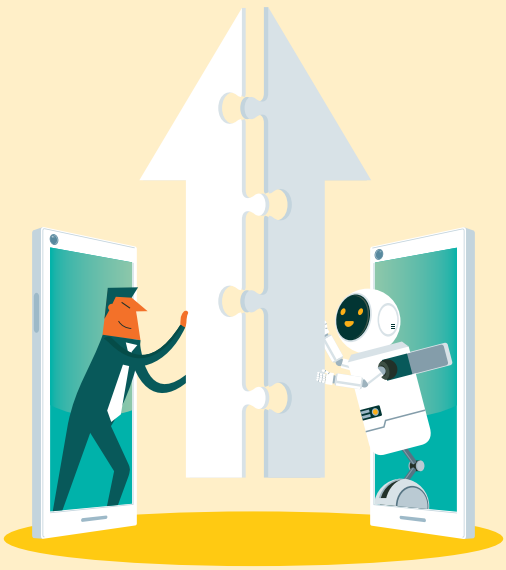
Co-Creation

What should we think of such uses of generative AI—personalised or otherwise? In the scientific arena, the logic of the process implies two different answers: on the one hand, anything that facilitates scientific progress is to be applauded and used, as we need more of this vital substance. This refers to what we might call the *outcome goals* of science and academia more broadly:[5] new knowledge, new cures, new technologies. But academia is also a human battleground in which opposing forces vie for limited positions, funding, and accolades. Seen from this perspective, questions of fairness, disparities, and advantages loom much larger: even if, for the purposes of argument, we assume that personalised (and general) LLMs can facilitate the progress of science, we might also want the *process* by which these outcomes are realised to be fair, out of respect for the many individuals engaged in these endeavours.

In ongoing work, we sketch a response to these concerns based on the concept of *co-creation*: while uncritical use (e.g. simple copy-pasting) of LLMs is problematic from the view of both outcome and process, involving essentially an instrumentalisation and servitude on behalf of the human user of LLMs, a more critical and involved process of co-creation is preferable on both counts. In this process, the LLM user does not simply uncritically accept and feed forward the results of an interaction with a language model, but rather serves as a discriminating senior co-author or editor. Under co-creation, the results of an LLM query are meticulously scrutinised for accuracy and fit and are iteratively refined in a process to which both human and machine contribute their special capacities in greatest feasible measure. This idea is aimed at harvesting the potential benefits of LLMs while reducing or avoiding their pitfalls, all the while maintaining, as much as possible, traditional standards for credit and blame attribution.

Conclusion

LLMs are a scientific advance, a general-purpose technology, of the first order. They have the potential to undermine society through misinformation and unintended consequences. But they also have tremendous potential to facilitate science and academia as well as many other areas of life. To maximise their benefits and minimise their harms, difficult conversations need to be had about acceptable uses of these technologies. Our work as described here represent some first tentative steps in that direction.



GPT-4 was used to suggest analogies between the sorcerer's apprentice and ethical issues in large language models. All text was written by the authors.

1 Porsdam Mann, S., Earp, B.D., Nyholm, S … Savulescu, J. Generative AI entails a credit–blame asymmetry. *Nat Mach Intell* 5, 472–475 (2023). https://doi.org/10.1038/s42256-023-00653-1.

2 Maslen, H., Savulescu, J. & Hunt, C. *Australas. J. Philos*. 98, 304–318 (2019).

3 Sebastian Porsdam Mann, Brian D. Earp, Nikolaj Møller, Suren Vynn & Julian Savulescu (2023) AUTOGEN: A Personalized Large Language Model for Academic Enhancement—Ethics and Proof of Principle, The American Journal of Bioethics, DOI: 10.1080/15265161.2023.2233356.

4 Brian D Earp, Sebastian Porsdam Mann, Jemima Allen, … Julian Savulescu. A Personalized Patient Preference Predictor for Substituted Judgments in Healthcare: Technically Feasible and Ethically Desirable. Pre-print, available at: https://www.researchgate.net/profile/Brian-Earp-2/publication/372986750_A_Personalized_Patient_Preference_Predictor_for_Substituted_Judgments_in_Healthcare_Technically_Feasible_and_Ethically_Desirable/links/64d33687b684851d3d92e5ba/A-Personalized-Patient-Preference-Predictor-for-Substituted-Judgments-in-Healthcare-Technically-Feasible-and-Ethically-Desirable.pdf.

5 Sebastian Porsdam Mann, Pablo de Lora Deltoro, Thomas Cochrane & Christine Mitchell (2018) Is the use of modafinil, a pharmacological cognitive enhancer, cheating?, Ethics and Education,13:2, 251-267, DOI: 10.1080/17449642.2018.1443050.

Five Takeaways from the Pandemic

BY NEAL RYAN RUI YANG FRIETS, FIRST-YEAR PHD STUDENT AT THE YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE (NUS MEDICINE)

Professor Peter Singer, Ira W. DeCamp Professor of Bioethics at the University Center for Human Values at Princeton University, delivered the second Global Ethics Lecture organised by the NUS Centre for Biomedical Ethics recently, on 24 August 2023. He highlighted five lessons to be taken away from the COVID-19 pandemic, in the areas of: (i) Allocating ICU beds, (ii) Using human volunteers for challenge trials, (iii) Lockdowns, (iv) Vaccine mandates and distribution, and (v) Preventing future pandemics.

Prioritise fitter, younger patients for ICU admission

Prof Singer advocated that ICU admissions should be based on maximising utility, as some countries did at the height of the pandemic when faced with bed shortages. Those who would be likely to survive if given treatment, and have more years ahead of them, should be prioritised, rather than the first-come-first-served system. Prof Singer rebutted claims of ageism, stating it is merely a fact that older persons will live less long if their life is saved, and quality of life starts to decline after a certain age. Thus, the utility of saving a much older person over a younger one is difficult to justify.

A reasonable and less objectionable alternative Prof Singer raised was also prioritarianism, where ICUs prioritise those who are more likely to die. This would still be better than the current lottery system, and lead to greater benefit for society overall.

Use of volunteers in human challenge trials

Moving on to human challenge trials, Prof Singer proposed applying the principle of risk parity to human research on vaccines. Society viewed it as permissible to expose some members of society (such as healthcare workers) to a given level of risk because the cost of not doing so would have been too great for others. Therefore, Prof Singer asserted that it would also be permissible to expose fully informed volunteers to a comparable level of risk in the context of promising research into a given pandemic disease.

As each day delaying a vaccine during the COVID-19 pandemic cost thousands of lives, the risk parity principle should have been applied to research in the same way it was for the healthcare industry and other frontline sectors.

Professor Peter Singer, Ira W. DeCamp Professor of Bioethics in the University Center for Human Values at Princeton University, shared his views on the need to strike a balance in global distribution of vaccine, at the second Global Ethics Lecture organised by the NUS Centre for Biomedical Ethics.

Vaccines

The third lesson Prof Singer identified as a takeaway from the pandemic was regarding vaccine mandates and distribution. He posited the justification of mandating vaccination as a case of soft paternalism, where a large portion of the population was opposed to vaccination based on misinformation or false beliefs, and where it would be therefore justifiable to ensure they are correctly informed before allowing them to not be vaccinated. Another stronger justification was Mill's harm principle, as Prof Singer cited evidence that not being vaccinated increased the risk of harm to others, especially in vulnerable settings such as hospitals and care homes.

Regarding vaccine distribution, he took a utilitarian view that it should be done to maximise benefit to society as a whole. For example, healthcare workers should be given the highest priority since they are integral to saving lives. Additionally, those at greatest risk of dying should get priority despite having fewer years left to live on average. Since younger people had a lower risk of death, vaccinating them first would be less beneficial overall.

Addressing objections about racial bias in vaccine distribution, Prof Singer replied that race should only be considered where it indicates higher medical risk.

Furthermore, he highlighted that it is crucial to strike a balance in global distribution, where the priority should be on maximising life-years globally, and not focused on a single country. Despite 72% of the world having received at least one dose of a vaccine, a majority of the remaining 28% comprised members of low-income countries. While the age distribution in these countries is much lower, and therefore prioritising vaccines to them may have saved fewer life-years overall compared to higher-income countries, there is an element of distributive justice that demands attention beyond mere objective calculation of life years saved.

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Lockdowns

Briefly addressing the permissibility of lockdowns early in the pandemic, he felt that a better means of assessing and comparing different harms and benefits is necessary to making more informed decisions regarding such drastic measures.

Future prevention

Concluding his lecture, Prof Singer discussed the prevention of future pandemics. He highlighted that a majority of new diseases originate from animals, and modern farming practices have only increased the chance for such diseases to mutate and transmit across species. Factory farming involves cramped conditions and greatly stresses animals, creating an ideal home for viruses to mutate.

Concluding thoughts

Prof Singer's lecture was a good reminder of the necessity to draw lessons from the pandemic and the ethical issues faced. Even as the world continues to recover from its effects, we must look ahead and think of solutions to such problems that are justifiable and practical to implement, so as to reduce the tangible human costs in the next pandemic.

↑ Prof Singer interacting with students from NUS Medicine, who attended the lecture.

72% of the world population received at least one dose of a vaccine with a majority of the unvaccinated coming from low-income countries

The Patient as Safety Partner

BY PROFESSOR JOSE M VALDERAS, HEAD, DEPARTMENT OF FAMILY MEDICINE, YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE (NUS MEDICINE)

The World Health Organization (WHO) has instituted September 17 as World Patient Safety Day. Every year, a different theme is selected to gather momentum on a particular aspect of patient safety. This year, the focus is on patient and family engagement for patient safety.

The WHO has made patient safety a priority, as evidence of the harm that is associated with the delivery of care has progressively accumulated. We do not refer to just unavoidable harm, such as when an individual suffers a reaction to a medication he or she has not been previously exposed to, or from undesirable effects of a surgical intervention. The real problem is harm which is preventable and that is unfortunately part of the everyday experience of patients and professionals alike.

A number of approaches are being used simultaneously to reduce patient safety events and limit their impact when they happened. One strategy that is crucial and which is currently underutilised is to engage patients and their families in patient safety. This implies making patients active partners in our efforts to reduce harm and its impact.

This is not necessarily straightforward. People are particularly vulnerable when they need healthcare. Asymmetry in the amount of and familiarity with the relevant health and healthcare information between health professionals and patients is a gulf that is difficult to cross for many patients, unless proactive efforts are made and appropriate systems are put in place to support patients and their families. One place where this is potentially easier is in the interactions between patients and their family physicians.

There are very good reasons why patients and their families should have a significant role in patient safety. Firstly, they are free of competing incentives that may affect professionals in their professional environment. Secondly, they have a comprehensive perspective that is not limited to a particular professional, service or setting. And lastly, interactions with health professionals are but a small part of all the healthcare that patients receive, which mostly take place in their homes and are delivered by themselves and their families. Helping patients be active partners in these efforts can unleash a huge potential that presently remains largely untapped.

The Department of Family Medicine is also making patient safety a priority and contributing to this year´s Patient Safety Day, the first of many to come. We want to ensure that we make patient safety one of the core values of Family Medicine practice. To realise this, we are synthesising the best available evidence on the interventions that have been proven to be effective in improving patient safety in Family Medicine through patient and family engagement. We will be promoting and disseminating best practices in a webinar celebrating patient safety day together with our own academics, clinicians and patients as well as with international experts.

I am honoured to represent all family doctors—GPs and family physicians—at the World Organization of Family Doctors (WONCA) Global Conference themed “Elevate the voice of patients!” in Geneva on 12 – 13 September 2023 to celebrate Patient Safety Day. We will also lead the development and presentation of a training workshop for family physicians at the WONCA world meeting in Sydney on 25 October 2023. If you are a family medicine and primary care professional, a patient or simply somebody with an interest in supporting patients and contribute to patient safety, do get in touch and join us!

↑ Embodying patient safety is one of the core values of Family Medicine practice. World Patient Safety Day is held on 17 September every year, with this year’s theme hinging on patient and family engagement for patient safety.

“We want to ensure that we make patient safety one of the core values of Family Medicine practice. To realise this, we are synthesising the best available evidence on the interventions that have been proven to be effective in improving patient safety in Family Medicine through patient and family engagement.”

Repositioning the Lower Jaw for Improved Sleep and Better Blood Pressure

Trial Underway to Assess Efficacy of Mandibular Advancement Devices to Help Patients Suffering from Obstructive Sleep Apnea

BY PROFESSOR RONALD LEE CHI HANG, DEPARTMENT OF MEDICINE, YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE AND SENIOR CONSULTANT, DEPARTMENT OF CARDIOLOGY, NATIONAL UNIVERSITY HEART CENTRE, SINGAPORE

Obstructive Sleep Apnea (OSA) is a persistent sleep disorder marked by recurrent instances of either partial or complete collapse of the upper airway during sleep. This disruption in normal breathing leads to fragmented sleep patterns, fluctuations in intrathoracic pressure, reduced oxygen levels (hypoxemia), and heightened sympathetic activity.

It's estimated that a staggering one billion adults are affected by OSA, with a substantial proportion experiencing moderate-to-severe forms of the condition.

Notably, OSA often intersects with hypertension, as around half of OSA patients simultaneously battle this cardiovascular concern. In fact, the 2017 Hypertension Guidelines jointly issued by the American College of Cardiology and American Heart Association indicate that OSA contributes to 25 – 50% of cases of secondary hypertension.

Although OSA is prevalent in individuals with obesity, its reach extends even further due to distinct craniofacial traits among the Asian population. This specific anatomical characteristic renders them particularly vulnerable to OSA. Strikingly, a significant number of Asian patients with OSA exhibit lower body mass indices compared to their Caucasian counterparts, highlighting the nuanced nature of the disorder across different ethnic groups.

25 – 50%
of OSA cases contribute to secondary hypertension

1 BILLION
adults are affected by obstructive sleep apnea

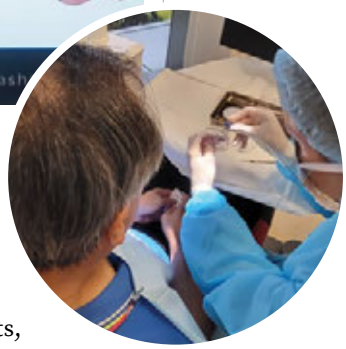
The utilisation of continuous positive airway pressure (CPAP) to manage OSA does exhibit a modest reduction in blood pressure (BP). However, the challenge lies in the suboptimal acceptance and tolerance of CPAP treatment among OSA patients. As an alternative therapeutic avenue, mandibular advancement devices (MADs) have garnered endorsement as per guidelines. MADs are particularly recommended for OSA patients who cannot or do not tolerate CPAP.

Nonetheless, the existing body of evidence regarding the comparative efficacy of MADs versus CPAP in terms of blood pressure reduction is somewhat constrained. Current data primarily stem from short-term studies, and although randomised trials have undertaken a comparison between MADs and CPAP, their findings have suggested comparable effects on lowering blood pressure. It's worth noting, however, that these trials grapple with certain limitations, such as relatively small sample sizes, the inclusion of patients lacking hypertension, the exclusion of severe OSA cases, and a relatively brief intervention period spanning one to three months.

We hypothesise that by repositioning the lower jaw to enhance upper airway openness during sleep, the mandibular advancement device (MAD) could offer heightened effectiveness, especially among Asian patients whose OSA stems primarily from a restrictive craniofacial structure. In the CRESCENT study (Cardiosleep Research Program on Obstructive Sleep Apnoea, Blood Pressure Control, and Maladaptive Myocardial Remodelling – Non-inferiority Trial, registered at clinicaltrial.gov under NCT04119999), our objective is to assess whether the treatment of moderate-to-severe OSA through the application of MAD yields improvements in BP and other pertinent health-related outcomes in comparison to CPAP.

MADs are recommended as an alternative treatment tool for patients with OSA that cannot tolerate CPAP.

In circle: Participants of the CRESCENT trial were subjected to a rigorous treatment regimen, administered by specialised practitioners in the form of either MAD or CPAP interventions.



With the marked prevalence of OSA in the Asian population and the considerable advantages associated with significant BP reduction, including pertinent data from Chinese cohorts, the findings of the CRESCENT trial will play a pivotal role in shaping healthcare recommendations.
The CRESCENT study, initiated by the National University Heart Centre Singapore with funding from the National Medical Research Council of Singapore in March 2019, underwent a meticulous evaluation process involving both international and Singaporean peer reviews.
Our investigation concentrated on Chinese participants, identified with a documented history of physician-diagnosed hypertension and elevated cardiovascular risk. These individuals underwent comprehensive polysomnography screening overnight.

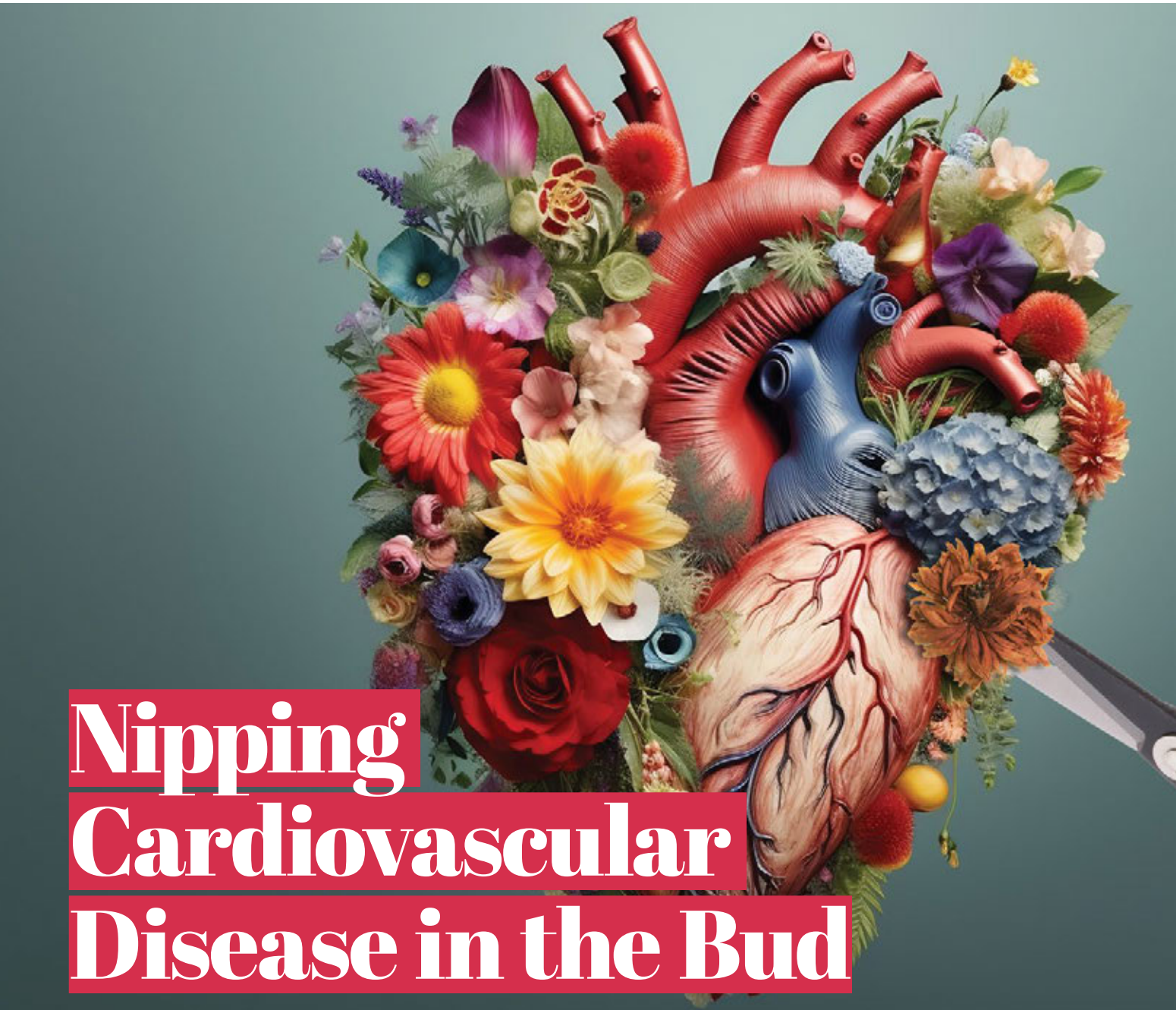
Subsequent to diagnosis, participants exhibiting OSA were subjected to a rigorous treatment regimen, administered by specialised practitioners in the form of either MAD or CPAP interventions, as per the stipulated study protocol, spanning a duration of 12 months. The operational backbone of this initiative is reinforced by a team of adept clinical research coordinators, ensuring smooth coordination and providing indispensable administrative support.

The observation window extends over a period of 12 months, with the primary focal point being the alteration in mean arterial blood pressure over a 24-hour cycle, juxtaposing baseline metrics against those obtained at the six-month juncture. Complementary to this pivotal metric, an array of secondary endpoints is assessed, encompassing systolic and diastolic BP measurements across a 24-hour spectrum, inclusive of daytime and nocturnal phases. Pulse pressure, nocturnal blood pressure dip (characterised by a nocturnal decrease of over 10% in BP), percentage of participants achieving systolic blood pressure levels below 130 mmHg and 120 mmHg at follow-up instances, arrhythmia evaluation through four-day electrocardiographic monitoring, meticulous biomarker and proteomic analysis, assessment of cardiovascular magnetic resonance-derived myocardial fibrosis and remodeling, in addition to comprehensive quality-of-life questionnaires, collectively contribute to the holistic evaluation of outcomes.

Subsequent to diagnosis, participants exhibiting OSA were subjected to a rigorous treatment regimen, administered by specialised practitioners in the form of either MAD or CPAP interventions, as per the stipulated study protocol, spanning a duration of 12 months.

Inception of participant recruitment took place on 1 October 2019, culminating on 5 December 2022, thereby encapsulating a comprehensive recruitment phase spanning 38 months. The primary outcome of the CRESCENT trial will be available in the first quarter of 2024.

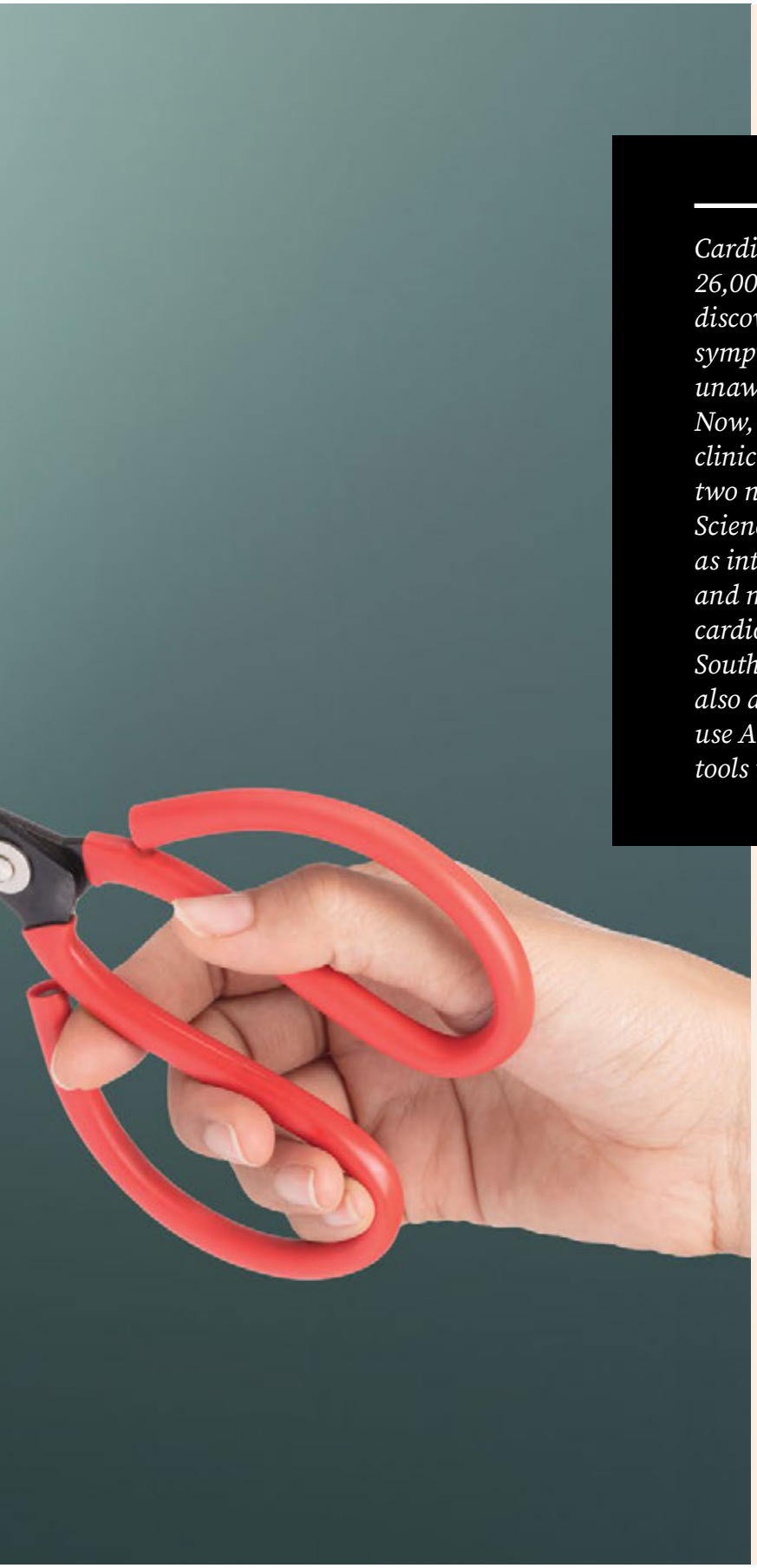
The research team behind the CRESCENT trial.



Nipping Cardiovascular Disease in the Bud

Study Aims to Identify Ways of Predicting and Preventing Cardiovascular-Metabolic Disease

BY DR HAYANG YANG, RESEARCH FELLOW, CARDIOVASCULAR METABOLIC DISEASE TRANSLATIONAL RESEARCH PROGRAMME, NUS YONG LOO LIN SCHOOL OF MEDICINE (NUS MEDICINE), MR SHAUN LOONG, FINAL YEAR MEDICAL STUDENT, NUS MEDICINE, DR PL SOONG, SENIOR RESEARCH FELLOW, CARDIOVASCULAR METABOLIC DISEASE TRANSLATIONAL RESEARCH PROGRAMME, NUS MEDICINE, DR MAYANK DALAKOTI, ASSOCIATE CONSULTANT CARDIOLOGIST, NG TENG FONG HOSPITAL, CLINICAL LEAD, CARDIOVASCULAR METABOLIC DISEASE TRANSLATIONAL RESEARCH PROGRAMME, NUS MEDICINE, PROFESSOR JOSIP CAR, HEAD OF SCHOOL OF LIFE COURSE AND POPULATION SCIENCES, KING'S COLLEGE LONDON, VISITING PROFESSOR OF MEDICINE, CARDIOVASCULAR METABOLIC DISEASE TRANSLATIONAL RESEARCH PROGRAMME, NUS MEDICINE, PROFESSOR WANG WENRU, PROFESSOR OF MEDICINE, ALICE LEE CENTRE FOR NURSING STUDIES AND CARDIOVASCULAR METABOLIC DISEASE TRANSLATIONAL RESEARCH PROGRAMME, NUS MEDICINE, AND PROFESSOR ROGER FOO, ZAYED BIN SULTAN AL-NAHYAN PROFESSOR OF MEDICINE AND DIRECTOR, CARDIOVASCULAR METABOLIC DISEASE TRANSLATIONAL RESEARCH PROGRAMME, NUS MEDICINE



Cardiovascular disease (CVD) killed over 26,000 Singaporeans in 2022[1]. Most people discover they have the disease only when symptoms present. Many others remain unaware, their latent illness undetected. Now, a nation-wide study involving clinicians and scientists from Singapore's two national heart centres, the Agency for Science, Technology and Research as well as international partners aims to track and map the causes, scale and extent of cardiovascular ill health in Singapore and Southeast Asia. The research team will also aim to identify disease markers and use Artificial Intelligence (AI) to develop tools that can detect and prevent CVD.

Cardiovascular disease (CVD) is the leading cause of death and illness worldwide. Its prevalence is surging, largely fuelled by a rise in obesity and other heart-related risk factors[2,3]. Large resources, spanning across decades, have been invested in the research of established CVDs (heart failure, myocardial infarction and stroke). However, in the current age of personalised preventive medicine, the more ambitious challenge will be to identify and tackle early drivers of CVDs, with the aim of arresting CVD development or progression before the manifestation of any symptoms.

Launched by Minister of Health Ong Ye Kung on 27 September 2023, Project RESET ("Redirecting immune, lipid and metabolic drivers of early cardiovascular disease") is a recently awarded Singapore National Medical Research Council (NMRC) Large Collaborative Grant (LCG). This project brings together our nationwide community of cardiovascular, metabolic, data science and digital health researchers, as well as clinicians across primary and tertiary care to study the immune, lifestyle and metabolic underpinnings of early CVD[4].

The Multi-Ethnic Study in Atherosclerosis (MESA) in USA[5], and the Progression of Early Atherosclerosis (PESA) study in Spain[6], have paved the way for the characterisation and assessment of CVDs among predominantly European descent (white) populations. Beyond doubt, they have now confirmed that subclinical atherosclerosis progression is a key risk factor of CVD, which means that anyone who has atherosclerotic plaques is worth paying closer attention to, even if they may not yet have clinical symptoms.

In other words, we need to screen healthy people for subclinical atherosclerosis. This has resulted in the development and adoption of a holistic assessment strategy for CVD prevention, which considers regular screening for atherosclerosis such as with coronary artery calcium scoring (CACS), in addition to demographic and medium-term modifiable risk factors in quantitative, multivariate Atherosclerotic Cardiovascular Disease (ASCVD) risk scores[7].

A much-needed study

However, in Asian populations such as Singapore's, many patients with CVD have normal cholesterol levels, and many with elevated cholesterol do not develop CVD. The extent of subclinical atherosclerosis in our population is also uncharted. Hence, we need to improve risk assessment, especially for the under-studied 0.6 billion population in Southeast Asia. Moreover, studies here show that a heavy burden of metabolic risk factors contribute towards CVD among Southeast Asian populations, and more so than is in the West[8,9,10]. Hence, subclinical CVD itself needs clearer study in our region.

Four thematic studies of the heart

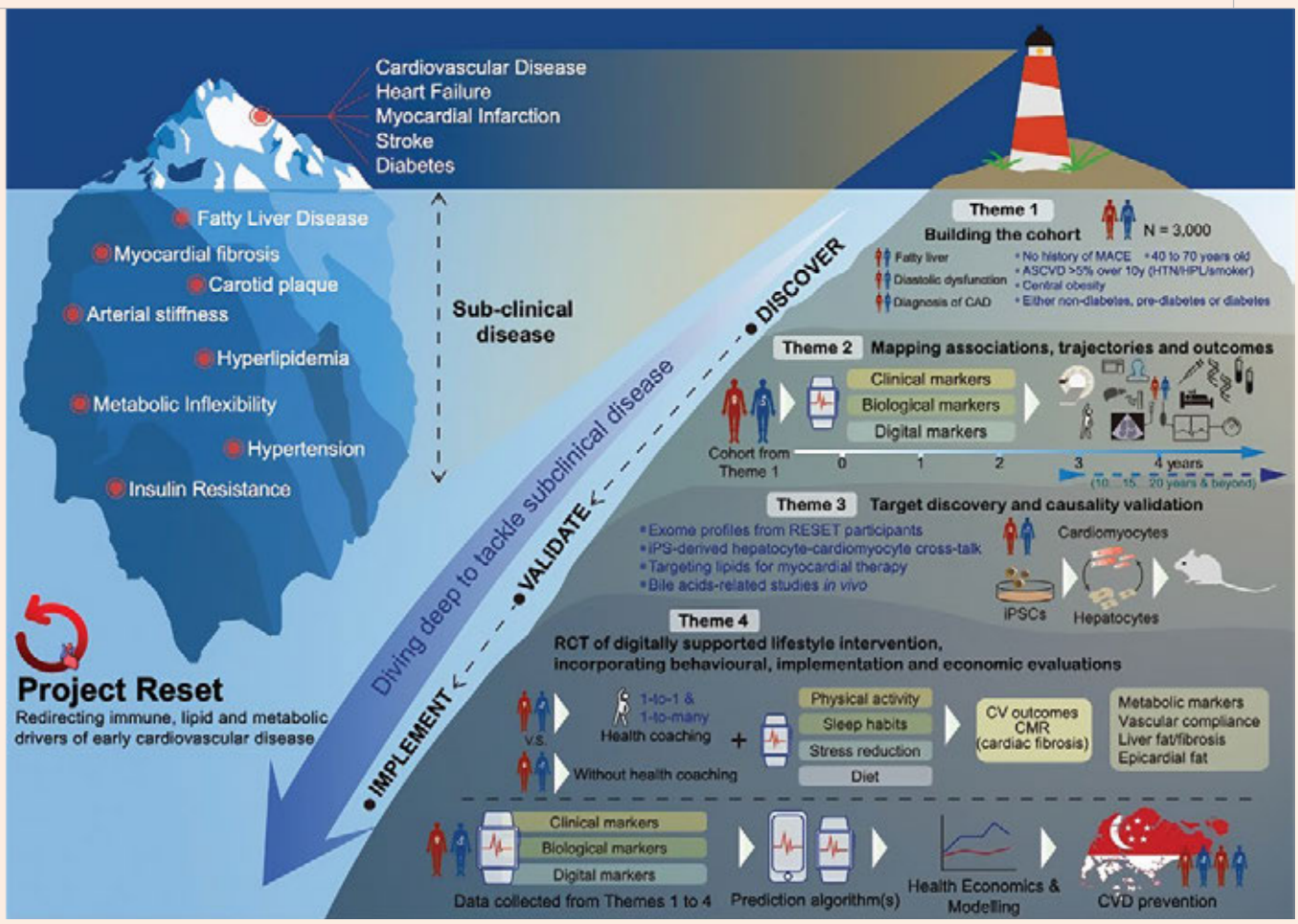
First, RESET will compile and study dynamic lifestyle and physiological variables, all of which are not yet included in current risk prediction algorithms. We believe that these represent a promising but unexploited dimension of personalisable modifiable risk factors. Moreover, while lifestyle factors such as diet, physical activity and sleep patterns have all been shown individually to play important roles in CVD development, none have been studied in a deeply characterised cohort, nor have all the lifestyle variables been integratively analysed.

Second, we will establish a selection of molecular markers comprising metabolites, cytokines, RNA and DNA, either free in plasma or packaged within exosomes, and have them systematically characterised for subclinical disease.

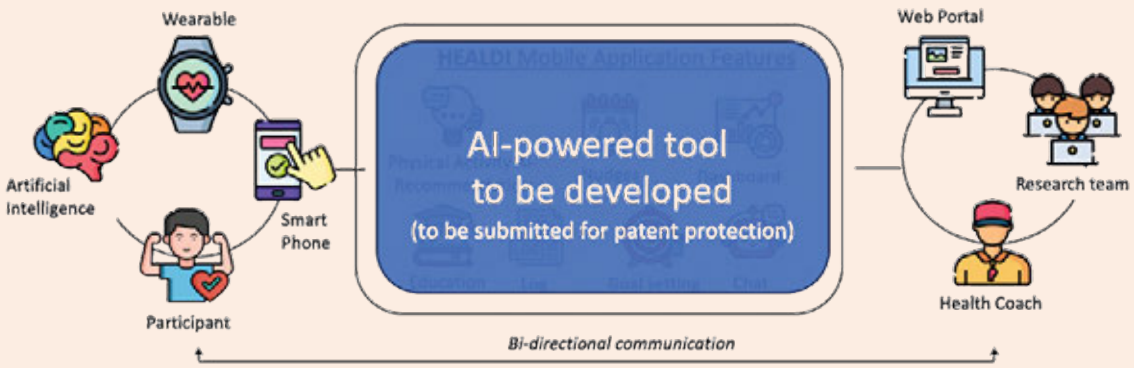
Third, with rapidly advancing tools for big data and AI, we will generate data-driven and AI-powered algorithms for the prediction and prevention of subclinical CVD. We hypothesise that future prediction tools will rely on an individual's billion-point database, rather than conventional singular predictive assays, enabling personalised management and tracking of disease progression or regression.

Finally, we will assess subclinical markers in the heart muscle itself, such as left ventricular (LV) fibrosis, which may uncover especially relevant early disease trajectories in Asia, where heart failure frequently progresses independently of blocked arteries, and where up to 60% of heart failure patients never had a history of ischemia[11,12].

"This project brings together our nationwide community of cardiovascular, metabolic, data science and digital health researchers, as well as clinicians across primary and tertiary care to study the immune, lifestyle and metabolic underpinnings of early CVD."



The RESET cohort will be followed longitudinally for five years, and beyond. Annual interval assessments will be carried out for RESET participants, comprising cardiac, liver, and metabolic tests.

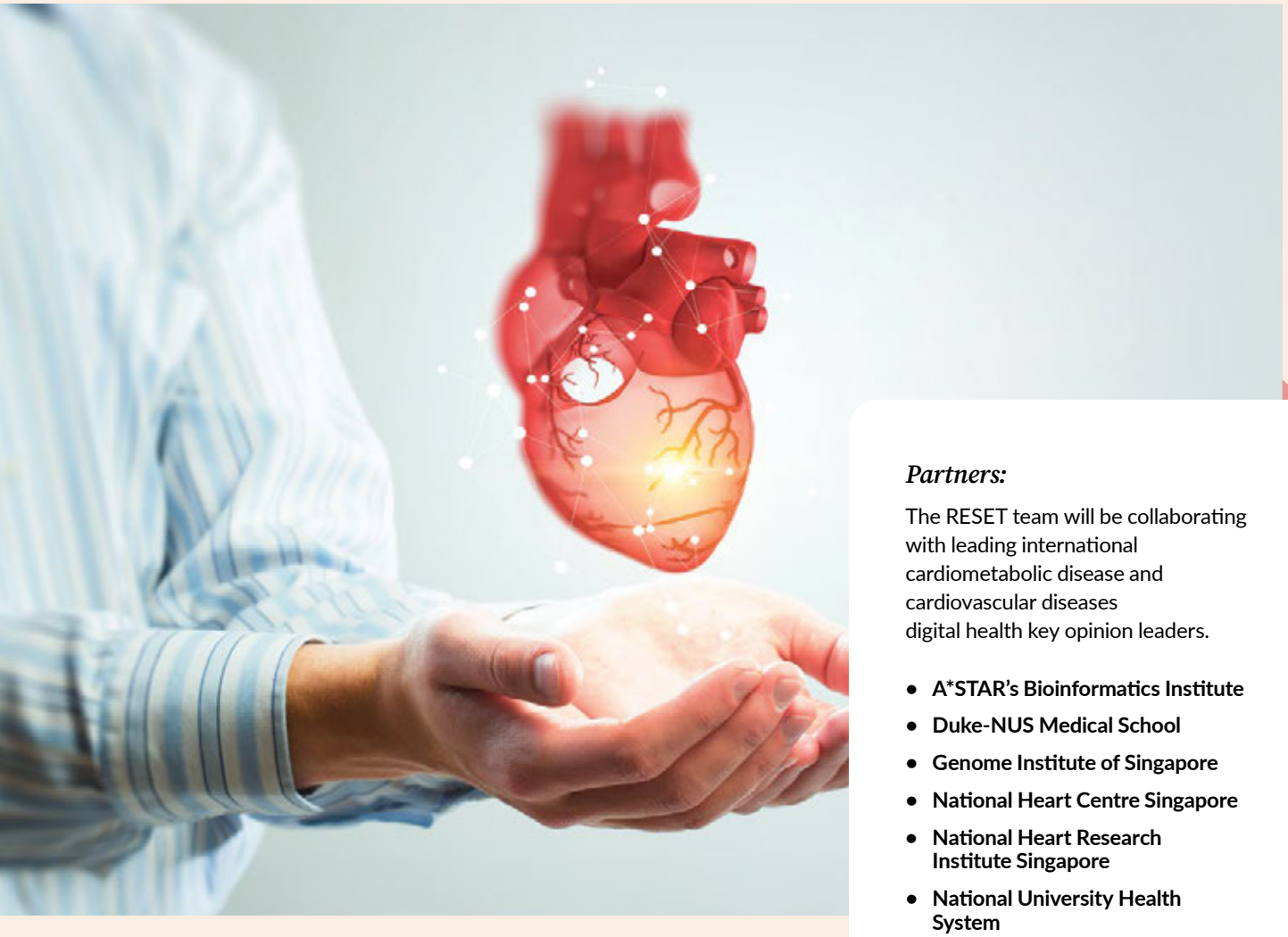


A sub-group of 200 participants with LV fibrosis on cardiac MRI will be invited to join an intervention study to test the efficacy of a one-year long digitally-enhanced lifestyle intervention, incorporating behavioural, economic and implementation evaluations.

Five years to analyse, understand workings of the cardiometabolic system

The RESET cohort will be followed longitudinally for five years, and beyond. Annual interval assessments will be carried out for RESET participants, comprising cardiac, liver, and metabolic tests. Samples will be biobanked for molecular profiling and dynamic lifestyle data collected by a study app and smartwatch, which will be given to each RESET participant for five years.

A sub-group of 200 participants with LV fibrosis on cardiac MRI will be invited to join an intervention study to test the efficacy of a one-year long digitally-enhanced lifestyle intervention, incorporating behavioural, economic and implementation evaluations. The primary outcome of the trial will be LV fibrosis, and secondary outcomes will be vascular, metabolic, and molecular phenotypes.



A national study with global implications

The RESET team will also be collaborating with leading international cardiometabolic disease and CVD digital health key opinion leaders. They will form a RESET advisory panel. Finally, reflecting the timeliness of increasing attention on cardiometabolic disease, early disease detection, and global prevention, exciting plans are also underway for parallel RESET cohort studies in the United Kingdom and Southeast Asia.

Amidst huge strides made towards developing precision medicine in Singapore, RESET will push the envelope of precision medicine towards heart disease prevention. Leveraging the most up to date deep learning and AI methods, we are now more than equipped for the deep dive into the vast ocean of data that will be generated in Project RESET.

Scan the QR code to find out more about Project RESET here:

Partners:

The RESET team will be collaborating with leading international cardiometabolic disease and cardiovascular diseases digital health key opinion leaders.

- **A*STAR's Bioinformatics Institute**
- **Duke-NUS Medical School**
- **Genome Institute of Singapore**
- **National Heart Centre Singapore**
- **National Heart Research Institute Singapore**
- **National University Health System**
- **National University Heart Centre, Singapore**
- **Nanyang Technological University, Singapore**
- **Ng Teng Fong General Hospital**
- **Singapore Institute for Clinical Sciences**

1 https://www.myheart.org.sg/.
2 doi:10.1016/j.eclinm.2023.101850.
3 doi:10.1161/CIR.0b013e31820a55f5.
4 doi:10.1093/eurheartj/ehad543.
5 doi:10.1093/aje/kwf113.
6 doi:10.1016/j.ahj.2013.08.024.
7 doi:10.1161/01.cir.0000437741.48606.98.
8 doi:10.1016/j.ajpc.2020.100096.
9 doi:10.1016/j.jacc.2022.11.005.
10 doi:10.1016/j.jacasi.2021.04.007.
11 doi:10.1016/j.jchf.2020.12.015.
12 doi:10.1161/JAHA.119.012199

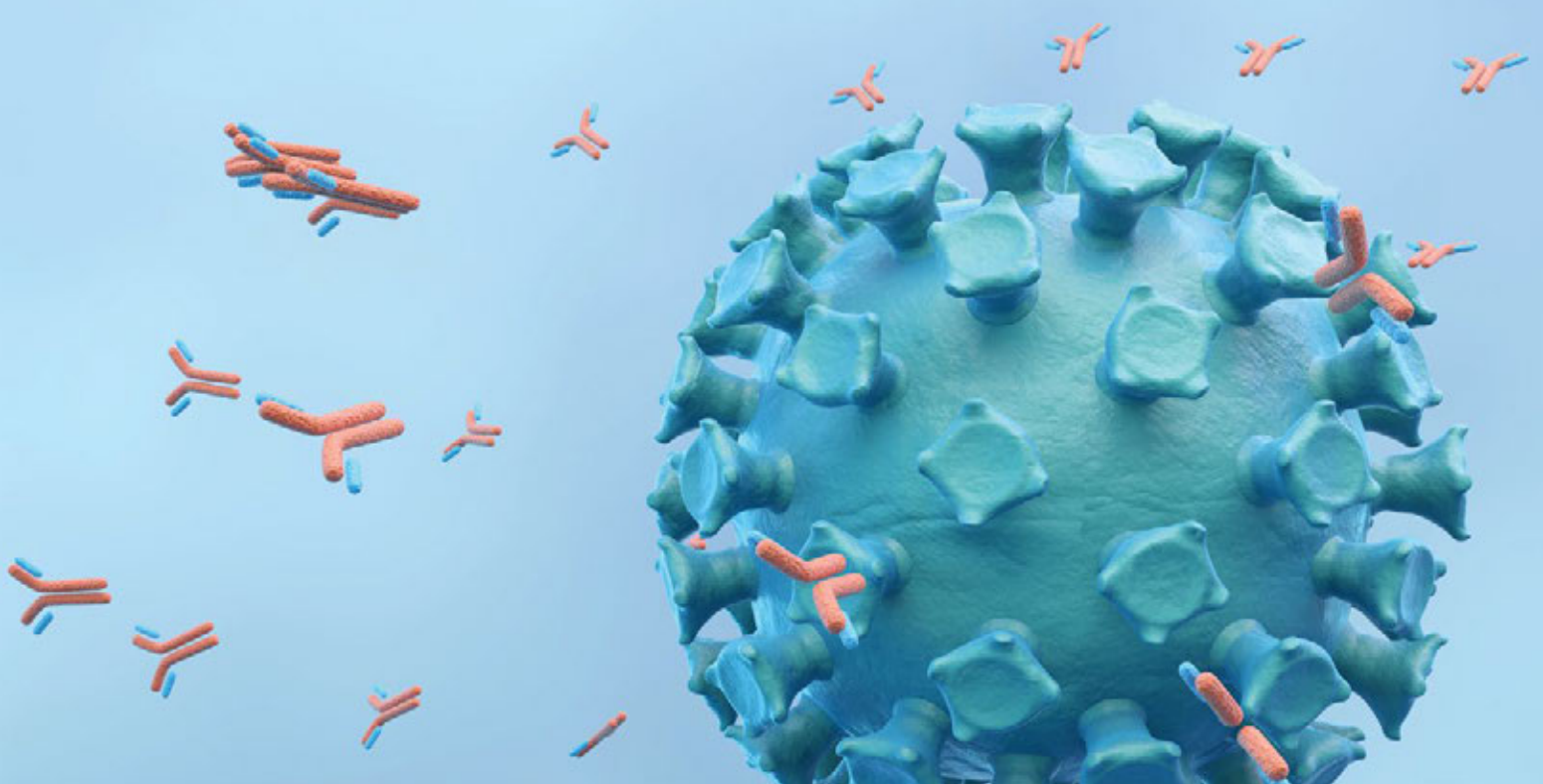
Antibodies, The Magic Bullets (Zauberkugel) in Medicine

BY ASSOCIATE PROFESSOR PAUL A. MACARY, DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY, YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE (NUS MEDICINE), AND DIRECTOR, LIFE SCIENCES INSTITUTE

One of the key foundational principles of drug development in modern medicine is Zauberkugel, a German translation for magic bullets. This defines the ability of a medicine to target and treat disease-causing microbes and/or mechanisms without harming the human host.

In the late 1800s, Louis Pasteur's epoch-making research established the 'Germ Theory' of disease. As a result of Pasteur's observations, the prevalent dogma amongst physicians at the time was that *all human disease* could be linked directly to 'toxins' released by microbial pathogens that infect the blood and organs. At this time, human populations were afflicted by recurrent outbreaks of deadly infectious diseases such as diphtheria (caused by the Gram-positive bacilli *Corynebacterium diphtheriae*) and tetanus (caused by the Gram-positive anaerobe *Clostridium Tetani*), where secreted exotoxins drive the underlying pathology. This was at a time before the advent of toxoid vaccines or the discovery of Penicillin in the 1920s, and thus, there were no prophylactic or therapeutic interventions that could be used for these diseases.

In the 1890s, contemporaries of Pasteur, Emil Von Behring, a German physician, and Shibasaburo Kitasato, his Japanese student, published their discovery that graduated doses of heat-killed diphtheria bacilli derived from the cadavers of German children who died of this lung infection, could be injected into rabbits. These rabbits produced substances in their blood (antitoxins) that neutralised the toxins produced by *Corynebacterium diphtheriae*. As part of the same experiment, they also showed that the antitoxins produced by one animal could be passively transferred in serum to protect another animal showing early symptoms of diphtheria infection.



This great discovery was subsequently confirmed by peers like Robert Koch (the 'grandfather' of Microbiology). Von Behring concluded that this anti-toxin effect was mediated by undetermined substances that he called 'immuno-bodies'. He combined the two words (Immuno-body and anti-toxin) to give us 'Antibody', which represents one of the earliest descriptions of *immunisation*.

Following experimentation in animals, Von Behring treated diphtheria infections in a group of German school children using 50ml of serum derived from immunised rabbits and showed that he could effect a reduction in their mortality. He then established a collaboration with the German bacteriologist Paul Erlich, a Nobel Laureate in 1908, who developed methods to enrich and quantify the anti-toxin effects in animal serum. Erlich described these antibodies as '*Zauberkugel*' or Magic Bullets, because they target and treat the microbial pathogen without harming the human host.

What Erlich had in mind was a scene from his favourite opera *Der Freischütz*. In this opera, Max, a useless huntsman, forms a pact with the devil, who gives him magic bullets that will always hit their mark. Thus, this concept of *Zauberkugel* is one of the foundational principles that underlies all drug discovery in modern Medicine.

With Erlich's help, the production of animal anti-serum was scaled up from rabbits to horses, and from the end of the 1890s to the 1930s, it became the principal treatment provided to patients with diseases like diphtheria and tetanus.

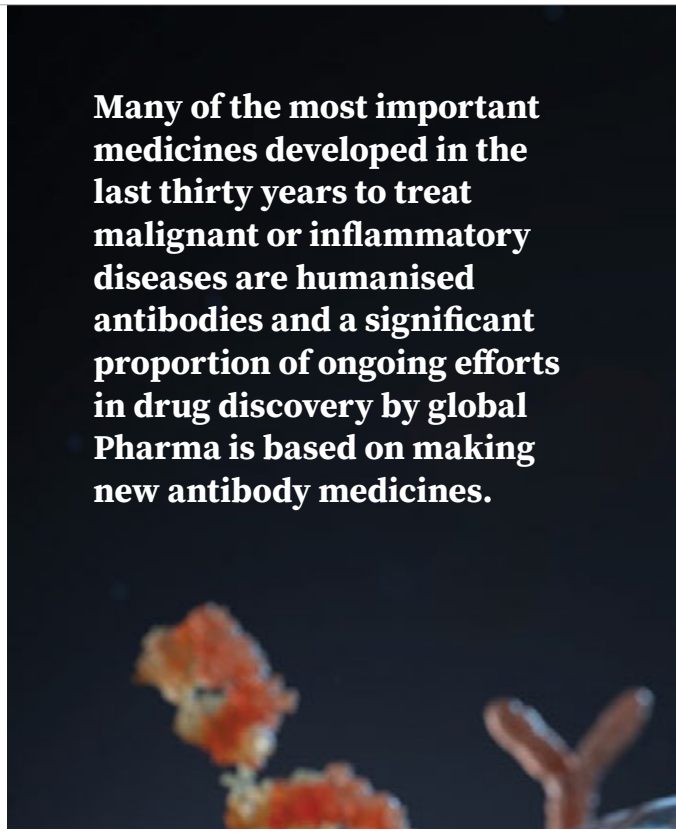
Building upon Erlich and Von Behring's observations for infectious diseases, a French Physician, Charles Richet, removed tumour cells from a group of patients with sarcoma, and injected these cells into dogs to raise anti-serum, then treated the patients with the dog anti-serum. He observed that while several of the treated patients showed a transient improvement in their symptoms, none were cured. These findings were reported in a manuscript entitled *"'Physiologie Pathologique'- de la serotherapie dans la traitment du cancer"* Published in 1895 in *Comptes Rendus Hebd Seane Acad Sci*, this represents the first documented example of using immunotherapy to treat cancer.

Richet was treated with derision by the French medical establishment who either dismissed or caricatured his research. However, Richet's efforts paid off and he had the last laugh when he was awarded the Nobel Prize for Medicine and Physiology in 1913, based on his description of anaphylaxis. He then went on to become one of Europe's most respected physicians.

The magic bullet – Too good to be true?

While serum therapy proved efficacious for treating infections, it also came with significant risks. The horse serum used to treat infected patients was full of complement, stress factors, serum albumins and other contaminating proteins derived from the horse. These could cause severe rheumatic-like reactions in treated patients. Termed 'serum sickness', many of them suffered joint and renal inflammation. Thus, when alternative approaches for prophylaxis (Toxoid vaccines) or therapy (Penicillin) became widely available, serum therapy was dropped as a frontline treatment, and antibody-based magic bullets were largely shunned in Medicine for the next 60 years.

Many of the most important medicines developed in the last thirty years to treat malignant or inflammatory diseases are humanised antibodies and a significant proportion of ongoing efforts in drug discovery by global Pharma is based on making new antibody medicines.



Development of antibodies into modern medicines

The development of antibodies into modern medicines required a number of new discoveries. The first of these was made in the 1950s, when a veterinarian from Ohio State University called Bruce Glick identified the cells that are the source of antibodies. Glick was interested in analysing the physiological role of an organ in the chicken that looks like a human appendix. This organ is termed the Bursa of Fabricus, which is named after an Italian anatomist, Hyronimus Fabricus (1533-1619), who produced volumes of illustrations of birds.

The Bursa of Fabricus was described as a sac connected to the dorsal part of the cloaca. To define the role of this organ, Glick developed a surgical procedure termed a bursectomy, to excise the organ, and submitted these chickens to a battery of physiological tests. His key finding was that bursectomised chickens cannot make antibody responses, regardless of how strongly they are immunised. The cells that are prevalent in the Bursa of Fabricus, known as B cells, were identified and defined as the cells that make antibodies.

Glick's attempts to have these findings published in top scientific journals were rejected and this pivotal discovery for Immunology ended up in 'Poultry Science' (published in 1954). The mammalian equivalent of the Bursa of Fabricus Cells were subsequently identified in the bone marrow and spleen of rodents and humans.

Twenty years after the discovery of B cells, Caesar Milstein and Jorges Köhler (Nobel Prize winners for Physiology and Medicine in 1984) invented a new method to immortalise B cells, through fusing them with tumor cell lines to form Hybridomas[1]. The resulting hybridoma cells can be diluted into single-cell cultures and expanded *in vitro*. The net result is a culture of immortalised cells derived from single-cell clones that produce an antibody of a single specificity, and this is termed as a monoclonal antibody.

The capacity to create antibodies of a single specificity that can be produced in large quantities *in vitro* created an explosion of interest in exploiting these molecules for human therapy. However, the method developed by Milstein and Kohler only worked for mice and rats. Thus, from 1975 through to the mid-1990s, mouse or rat monoclonal antibodies were raised against human disease markers by immunising them with the relevant human markers and proteins. This included receptors that can be targeted on human tumor cells or factors (such as cytokines) that drive inflammatory disease.

A further refinement that improved the safety and efficacy of antibody-based medicines was the development of methods to make rodent antibodies more suitable for humans. These methods involve exploiting principles of molecular engineering, where the small regions of rodent antibody proteins that provide the specificity for the therapeutic target are pasted onto human antibody scaffolds. The resulting proteins are 90 – 95% humanised with a small number of components retained from the original rodent antibody to ensure the required specificity[2].

Many of the most important medicines developed in the last 30 years to treat malignant or inflammatory diseases are humanised antibodies (Humira, Remacade, Retuxan, Herceptin, Keytruda and Avastin as examples) and a significant proportion of ongoing efforts in drug discovery by global Pharma is based on making new antibody medicines. Thus, while it has taken over 100 years, the *Zauberkugel* has finally fulfilled the promise envisioned by Von Behring and Erlich.

[1] Continuous cultures of fused cells secreting antibody of predefined specificity. Köhler G, Milstein C. Nature. 1975 Aug 7;256(5517):495-7. doi: 10.1038/256495a0.
[2] Reshaping human antibodies for therapy. Riechmann L, Clark M, Waldmann H, Winter G (1988). Nature. 332 (6162): 323–7.

Gen Y Speaks:

I Aspired to be a Radio DJ, but My Grandfathers' Deaths Led Me to Nursing

BY KIMBERLEY-ANN TAN ZI YING, ALUMNA OF THE ALICE LEE CENTRE FOR NURSING STUDIES (NUS NURSING) AT THE YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE, AND SENIOR STAFF NURSE AT TAN TOCK SENG HOSPITAL

Growing up obsessed with pop culture, I was certain that my goal in life was to become a radio deejay. I was passionate about the music scene and was the programme director of my polytechnic's very own radio station.

Convinced that this was my road to success, I sought to turn my passion and craft into a professional career in media and entertainment.

So, as a 17-year-old, I embarked on my diploma in mass communications at Ngee Ann Polytechnic with a clear vision of what I wanted to do in the future.

But as they say, life is what happens to you while you're making other plans.

During the final year of my diploma studies, both my grandfathers had to go in and out of the hospital for various reasons.

My maternal grandfather had Alzheimer's disease, which eventually led to him struggling with severe dementia.

He started losing his memory and his ability to independently carry out his daily activities, and my grandmother had to take up the role of being his primary caregiver.

I remember offering to stay over to watch my grandfather overnight so that my grandmother could rest and take a break from her caregiving responsibilities.

I spent the entire night watching him abruptly wake up from his sleep, watching him while his eyes stayed open, talking to the ceiling over and over again while trying to take off his mittens that we had to put on to protect him from involuntarily scratching his fragile skin.

Kimberley-Ann Tan Zi Ying decided to enrol in nursing school at the National University of Singapore despite having no medical knowledge at all.

"I was certain that my goal in life was to become a radio deejay. I was passionate about the music scene and was the programme director of my polytechnic's very own radio station."

This gave me my first glimpse of what it was like to be a caregiver and having to bear the physical, emotional and mental load of someone who could not do it for themselves any longer.

But being only 19 and having zero medical knowledge at the time, all I knew was that my grandpa was slowly slipping away, and my time left with him was limited.

Over the next few months, my grandfather's condition deteriorated and he had to be admitted to Tan Tock Seng Hospital (TTSH).

This was my first ever memory of being in a hospital setting. He was admitted to a geriatric ward but was only there for a short period of time before he passed on.

I remember being the one to realise that he had stopped breathing, and alerted my family members who then informed the nurse in charge.

I was impressed with how calm and collected the nurses were, and how they exercised compassion towards us and treated my grandfather with dignity in his final moments.

Sadly, less than a year later, my paternal grandfather unexpectedly passed away as well.

Their deaths struck me deeply, because they were the first closest relatives of mine that I had lost. I was experiencing and understanding grief for the first time in my life.

It was also at this point in time that I was in the last few months of my diploma studies and had to start my university applications.

Although I had really wanted to further my studies in communications, my grades were not adequate enough to enrol into the course that I had wanted.

So, I stopped to rethink what I wanted my future to look like.

Nursing as a career

My father suggested trying out nursing because I always had a soft spot for the elderly and loved taking care of people.

I was unsure at first, and started to ask around to see what people thought of me joining the profession.

Although many said that they couldn't imagine me being anyone other than "Kim the DJ", some said otherwise and easily pictured me becoming a nurse.

I then learnt that growing up, the women who I looked up to as role models also happened to be nurses. My paternal grandmother worked as a senior assistant nurse. The captain of my Girls' Brigade co-curricular activity in Presbyterian High School at the time is currently an advanced practice nurse.

In that sense, I felt an affinity with the industry even though it was not something that I had considered before.

Another big motivator was the fact that I wanted to study something that would give me more practical skills, after the helplessness I felt during my two grandfathers' final months.

I wanted to be able to take care of my parents and family in the future, and not feel as clueless as I previously did.

So, I decided to enrol in nursing school at the National University of Singapore with no medical knowledge at all.

"Another big motivator was the fact that I wanted to study something that would give me more practical skills, after the helplessness I felt during my two grandfathers' final months. I wanted to be able to take care of my parents and family in the future, and not feel as clueless as I previously did."

The first few months were an uphill battle, and I remember constantly reflecting on whether I made the right choice.

But thankfully, I managed to find my footing one step at a time, and fell in love with the exciting new journey I was on.

Eventually, I graduated with a Bachelor's degree in nursing in 2020.

But my final year was the hardest hurdle to cross, as the COVID-19 pandemic had thrown the world of healthcare into a tizzy.

Braving the pandemic

I was attached to TTSH as part of my final hospital attachment before I graduated. That was in April 2020, when the first circuit-breaker was implemented in Singapore.

I admit I was very scared to leave the safety of my home to head to the hospital at a time when not much was known about the virus. It was a strange sensation to head to work when everyone was forced to stay home.

But the work needed to be done and lives needed to be saved.

A few months later, I officially started work as a staff nurse in TTSH. Due to the strict safe distancing measures back then, many of our orientation programmes were delayed, cancelled, or conducted online instead.

This meant that we had to adapt and learn many things on-the-job.

As much as I would've liked to say that I coped with the transition well, the truth is that I had never experienced this much stress and anxiety before.

Nothing could have prepared me fully for how mentally, physically, and emotionally demanding nursing was.

From having to increase my knowledge through learning about different diseases, care plans and medications, and keeping up with the ever-changing protocols; to becoming competent and efficient in my nursing care, I was forced to absorb everything and learn from my seniors as quickly as possible.

Due to the heavy workload, I lost a lot of weight. This definitely made work even more draining: Imagine a 42kg 24-year-old trying to carry patients double or triple her size.

Truth be told, there were more lows than highs in my first year of nursing.

But the one thing that always rekindled my sense of purpose was reminding myself that although I wasn't able to take care of my grandfathers anymore, I was entrusted with the duty of looking after someone else's life while they are at their most vulnerable state.

Having that perspective really kept me grounded and motivated me to continue to be the best nurse I could be for my patients.

A fulfilling journey

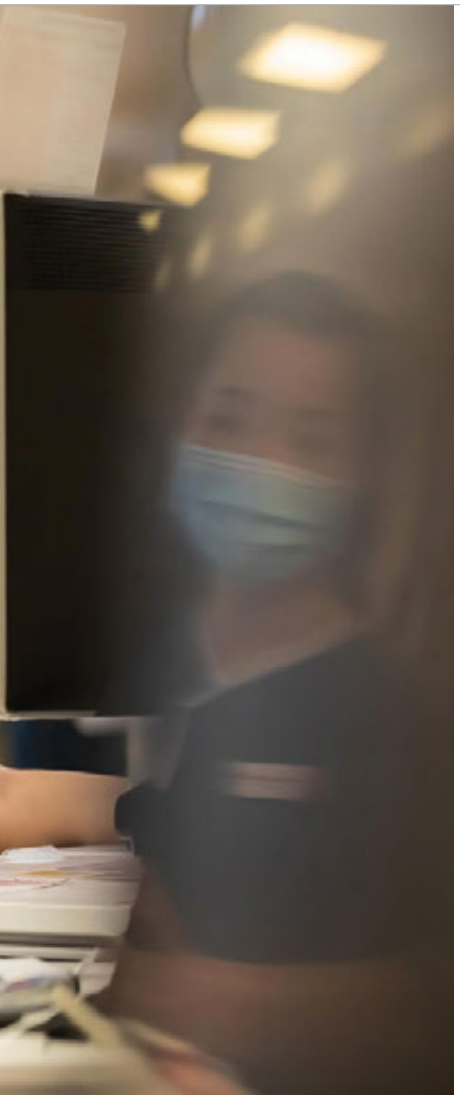
Three fulfilling years later, I'm currently a senior staff nurse in an acute internal medicine unit at TTSH.

I'm also currently a preceptor to students and new nurses who are at the start of their nursing journey. I do my best to support them just like how my seniors supported me at the beginning of my career.

I frequently reflect on my journey and think about how differently I deal with similar situations now, thanks to the experience I've gained over the past few years.

I know that three years ago, I would not have had the confidence I currently possess to handle demanding patients and their family members, while being efficient and effective in the coordination of my patients' care.

↑ Kimberley-Ann Tan Zi Ying (right) speaking to her colleague in one of the wards at Tan Tock Seng Hospital on July 28, 2023.



But it was thanks to hard work and the support of my seniors that showed me how it is done.

I'm also proud of how the role of nurses has evolved over the years, as well as the opportunities given to us to specialise in our areas of interest such as research, education, management, or clinicals.

Nursing is hardly a stagnant role, and there are schemes to encourage innovation among us too. For example, TTSH's Nursing Innovation Bunch has a S$1,000 funding scheme for new nurses to trial their innovative ideas in their first and second year of employment.

I'm able to do less repetitive and strenuous tasks thanks to robotics and automation, which frees up my energy to focus on building trust and strong relationships with my patients and their families.

This allows me to provide more holistic patient care and attend to their emotional needs, a vital aspect of a patient's recovery journey that is often overlooked.

I decided to write this article because my career in TTSH nursing has been nothing short of fulfilling and exciting, despite all the challenges that come along with it.

Every shift is completely different, and you learn and experience something new every single day. It's one of the professions that changes your life for the better while you do the same for others.

Despite mostly being in clinical nursing, I've also embarked on many creative projects along the way in TTSH, tapping into my past as a mass communications student.

From creating nursing content for our social media, to writing articles and hosting events, I've been given many opportunities to keep my creative side alive.

My advice to anyone who might be at the crossroads of deciding what career path to head down, would be to take a chance at something new.

After all, my experience taught me that we don't just have one passion in life to pursue.

Work hard and learn as much as you can no matter which stage of life you're in. You'll pick up things that'll help you wherever you're going next, even though they may seem completely irrelevant at that point in time.

After all, my experience taught me that we don't just have one passion in life to pursue. Work hard and learn as much as you can no matter which stage of life you're in. You'll pick up things that'll help you wherever you're going next, even though they may seem completely irrelevant at that point in time."

This article was originally published in TODAY.

Scan to read the article here:

Discovering Coding's Joys on an Internship

Phase V NUS Medicine student Elgene Yeo Zhen Hao seized the opportunity to intern with a Toronto firm specialising in crafting tech solutions for healthcare and manufacturing industries. He shares about how seemingly disparate opportunities converged to open the door to an interesting three months as a participant in the NUS Overseas Colleges (NOC) programme.

Finding a job as a medical student brims with unique challenges. Unlike our peers mastering marketable domains like Marketing, Coding, Business Management, or Communications, medical students often find their skill set seemingly non-transferable. The question looms—would anyone enlist a medical student for roles beyond their niche? Yet, a silver lining emerged. It was woven into to my coding hobby, the unexpected source of marketable skills. If any laurels grace my NOC journey, they are owed to my younger self for dedicating time to nurturing a passion that ultimately paved the way.

Venturing into coding during my third year was such an unexpected development. Prior to that, life was a delicate balance between academia, friends, and family, much like any university student's. However, I yearned for a break from monotony, from the set routines of non-stop lectures and study sessions, from a life that seemed to have more to offer than what I had glimpsed. While I stayed at Tembusu Residential College, a Telegram chatbot that enabled users to chat anonymously in an Angels & Mortals game sparked my curiosity about coding. It was a skill, using knowledge that could create a realm of possibilities previously unattainable.

Learning coding was a chance to break the cycle, to embrace novelty. Yet, having to divide my time between my non-productive coding hobby and keeping pace with the competitive culture in university academics presented a challenge. Moreover, the steep learning curve of the coding language I needed (JavaScript) to create a Telegram bot really put a lot of doubt into whether I could create anything of value.

Yet, the remote possibility of creating something meaningful was enough to drive me to embark on my first coding project. Challenges arose, and weeks dissolved into a blur of multifaceted problem-solving and creative activities. Persistence paid off, resulting in a Telegram bot[1] that defied conventional hosting costs. Running 24/7 for free on just a Google Sheet filled with jokes curated from Reddit and a Google Drive folder full of medical memes sourced from popular Instagram pages, it is the result of my passion and the remarkable journey of self-improvement. Empowered by this, I ventured into grander coding endeavours with greater potential for substantial social impact, such as a Telegram matchmaking event for all Singaporean university students.[2]

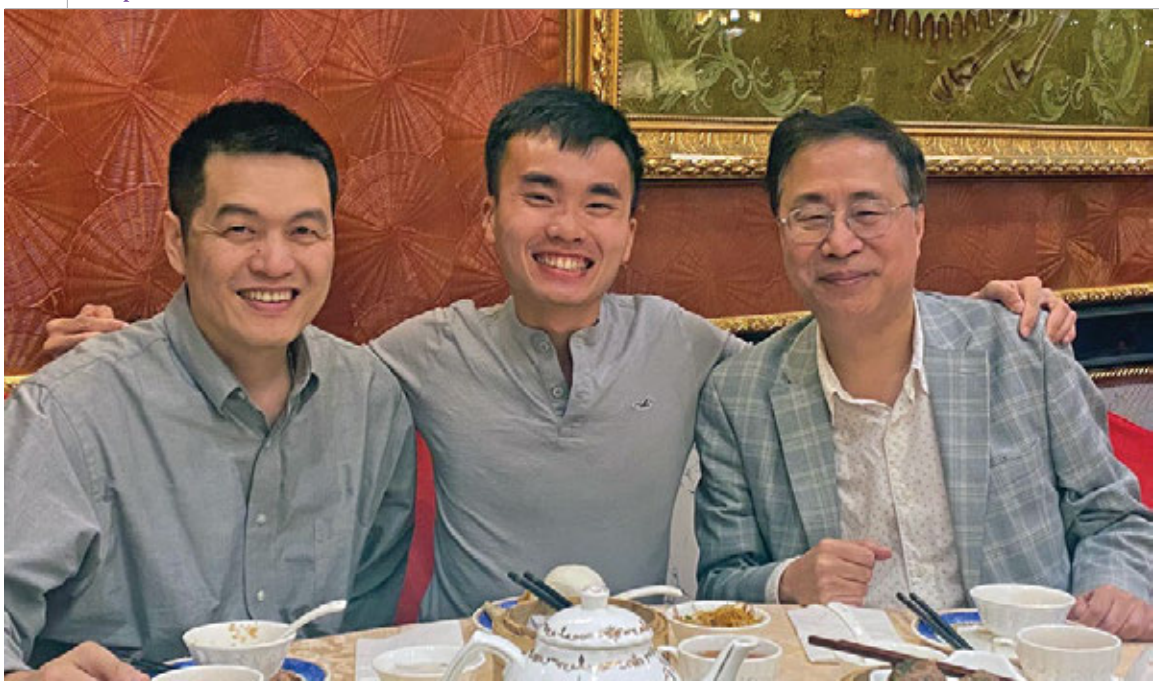
“Whilst learning about entrepreneurship, I also wanted to gauge the practicality of my coding skills, a challenge best undertaken in the furnace of a real-world software engineering job. Joining a startup, I braced for the rigours of the journey ahead—expecting minimal supervision and feedback, along with the weight of multidisciplinary challenges to be tackled solo.”

↑ Elgene at the well-known Distillery district in Toronto, as a participant in the NOC programme.

Louis Pasteur famously said, "In the fields of observation, chance favours only the prepared mind." This quote resonates deeply as my coding journey perfectly prepared me for my application to NOC. In the middle of my coding journey, a profound realisation emerged—I yearned to elevate my best ideas through entrepreneurship. Then, a stroke of serendipity unfolded: NOC opened sign-ups to Year 4 medical students, coinciding perfectly with my desire to plunge into entrepreneurship. I signed up without a moment's doubt, recognising it as the only gateway to entrepreneurship experiences I had been waiting for.

Fortuitously, I secured a position for a three-month internship under Stephen Chan, a successful entrepreneur in Toronto specialising in crafting tech solutions for healthcare and manufacturing industries. This was made possible through the efforts of Harpreet Singh and Gean Chu from NUS Enterprise, along with an unforeseen recommendation by NUS Medicine alumnus Dr Shoo Lee. Another fortuitous development boosted my internship experience: instead of being tasked with the tedious user interface enhancements or code refactoring as expected of a software engineering intern, I was tasked with learning to leverage on ChatGPT application programming interface (API) when it was just released on 6 March 2023 —illuminating my internship journey with the promise of mastering something entirely new.

As Aristotle aptly said, "Real skill is forged in the crucible of practical application." Whilst learning about entrepreneurship, I also wanted to gauge the practicality of my coding skills, a challenge best undertaken in the furnace of a real-world software engineering job. Joining a startup, I braced for the rigours of the journey ahead—expecting minimal supervision and feedback, along with the weight of multidisciplinary challenges to be tackled solo. Before my first line of code, I spent two weeks immersing myself in ChatGPT API documentation, online tutorials, and a series of trial-and-error experiments to gain a deeper understanding of how ChatGPT processes human input. The vast array of approaches to creating such a chatbot seemed daunting, yet I knew from past coding experiences that uncertainty is best tamed by leaping into action with the best approach, while embracing failure as the gateway to true learning.



Elgene (middle) with his manager, Simon (left), and his boss, Stephen Chan, Chief Executive Officer of VISFUTURE (right).

Through three months of coding of chatbot components, rigorous user testing and bug-fixing, I finally unveiled an operational ChatGPT chatbot tailored for a dental surgery company. This remarkable creation possesses the unique ability to provide comprehensive documentation-based responses in both English and French, catering to the diverse needs of native French-Canadians. The chatbot's responses are designed to be delivered with the poise and elan of a Singapore Airlines cabin crew member, the numerical precision of an accountant, and the intellect of someone well-versed in our documentation from which it derives its answers. Built with fail-safe measures, it even gracefully navigates nonsensical queries with the elegance of its standard greeting.

I owe a debt of gratitude to my NOC and startup supervisors, who, with their modest expectations of a medical student's coding abilities, unwittingly fostered a stress-free environment for my creative liberation, unburdened by the lack of weekly deadlines or progress reports. It was within this nurturing environment that I was able to hatch an innovative solution not taught by conventional ChatGPT chatbot tutorials.

In the initial half of my internship, I embarked on numerous daring experiments, some leading to amusing dead ends, yet each deepening my grasp of artificial intelligence (AI) intricacies. For instance, in my quest to mould ChatGPT as the ultimate human assistant, I endeavoured to infuse it with meticulousness by telling ChatGPT to be “the most helpful assistant”. However, this ambition led to an unintended cascade of unnecessary queries. For instance, a simple request like "I wish to book an appointment at ABC Dental Clinic" resulted in a string of additional questions like “Please tell me where you stay so I can book it at the clinic closest to you”, rather than a straightforward booking. Yet, this period of experimentation was the crucible for my growth, culminating in flourishing progress in the latter half of the internship. Looking back, the discouraging results of the first half of the internship illuminated the path towards progress that shone brighter with each passing day.

Navigating uncharted waters, I forged a path of creativity and perseverance. From coding curiosity to entrepreneurship aspirations, every endeavour illuminated the enigmatic journey.
If there’s anything I had learned in the three months in Toronto, it is that a life of dedication, innovation, and unwavering pursuit brings the power of ideas to life.

“I owe a debt of gratitude to my NOC and startup supervisors, who, with their modest expectations of a medical student's coding abilities, unwittingly fostered a stress-free environment for my creative liberation, unburdened by the lack of weekly deadlines or progress reports.”

[1] https://t.me/mednurseclubbot.
[2] https://t.me/delicaciesmatchmaking.

Remembrances

BY DR NOREEN CHAN, HEAD AND SENIOR CONSULTANT, DIVISION OF PALLIATIVE MEDICINE, NATIONAL UNIVERSITY CANCER INSTITUTE, SINGAPORE

At first glance he seemed like just another elderly man in hospital pyjamas, rendered thin and frail by age and illness (in his case, Parkinson's Disease), now dealing with another bout of pneumonia. But what caught my eye was a large framed black and white photograph on his bedside table, showing a bodybuilder striking a victory pose next to an enormous trophy. I looked at the muscular young man in the photo—which was clearly from the 1960's—and at the patient, and had to ask "Is this you?".

His daughter at the bedside immediately replied "yes, he was Mister Singapore you know!" and told me about how her father had to pursue his bodybuilding hobby as an amateur, how he was chased by girls but only had eyes for the woman who would eventually become her mother. This story was so embedded in the shared family history, that even the grandchildren knew it. Soon everyone was chatting excitedly and nostalgically, and the patient was so delighted that he allowed me to take a photograph of him beaming next to the photo.

Soon after that, I saw another man, this time suffering from cancer. He too shared memories of himself before his illness, when he was an all-round athlete who ran, played rugby and swam. Now bald, more than 10kg lighter and just about able to walk across the room, those memories were not comforting in the least, but bitter reminders of what he had lost, and would never get back. He did not want his old friends to visit him at the hospital, because "I do not want them to see me like this". It was interesting how recollections of the past could have such different effects on different people.

Lest we forget

Memory is the process of taking information from the world around us, processing (or encoding) it, storing and later retrieving or recalling it (even years later). Memory scientists describe different kinds of memory, for example implicit versus explicit memory. The latter involves conscious recall e.g. of a phone number or address, whereas implicit memory is unconscious recall, like riding a bicycle after not doing so for a long time.

We are storing memories all the time, often without realising it. While effort, practise and repetition can help us to remember what we need, sometimes it comes down to the immediate and personal impact of an experience that cements a memory. For example, I can still remember where I was when I learned about the terrorist attack on the World Trade Center towers in New York on 11 September 2001; I was with my sister and her friend, in a small restaurant somewhere in the outer districts of Bangkok. I cannot remember what we ate (I suspect no one was very hungry), but I do remember the grainy footage of the first plane flying into the first tower, on a small boxy television at the back of the shop, as our friend translated the Thai commentary. And I remember the feeling of disbelief and the chilling realisation that this was not some special effects; it was real.

Remembering has many benefits, not least because it allows us to learn, reason and develop higher thinking skills. It also contributes to our sense of personhood and self-identity. Reminiscence Therapy is used in conditions of severe memory loss—whether from dementia or brain injury—to try to stimulate and preserve long-term memory. For older dementia sufferers, this is done through old photographs, music or keepsakes, or even creating a setting like a typical living room from 50 years ago. As portrayed in Royston Tan's poignant short film "Ah Kong", sometimes this "version" of the person is what is left, when everything more recent has been lost.

Pain and tenderness

But memories are not always benign as sufferers of PTSD or Post-Traumatic Stress Disorder can attest. This is because memories are not just facts or the passive act of watching events play out on a screen; memories are deeply intertwined with emotions. The reason for this is that the part of the brain that processes emotions, the amygdala, is also involved in memory processing. The amygdala is part of the limbic system, which in turn is anatomically close to the region of the brain that handles olfaction or smells. Which explains why certain smells can evoke emotions and memories, like how the scent of Imperial Leather soap always reminds me of my father.

Human beings can be unreliable in their memories, and it is unpredictable what some people remember. Individuals involved in the same experience can recall it quite differently from their own perspective. People are also able to suppress memories as a form of self-protection, especially after a traumatic experience. But sometimes, these long buried recollections can resurface.

Some years ago, we were holding an examination at our hospital, and one of the stations involved the candidate assessing a patient. Suddenly an administrative staff member who was keeping time broke down. She had to leave the room and could not continue with the examination. During the debrief, it transpired that the scenario reminded her of her brother who had died from leukaemia. The session had triggered all her memories and pent-up emotions. Up until that point, she had felt fine, and from the outside, there was no hint that she had suffered such a devastating loss.

Memories are made of these

In Palliative Care, we do spend time with patients and families recalling memories, which could involve them sharing their illness journey (either as a patient or caregiver), or through a more guided process such as a Life Review. This aims to help people make meaning of their experiences. We also look for opportunities to *make memories*, through activities like granting wishes and legacy work. It could be something as simple as a family photo, or something more complicated like a solo exhibition of photographs or paintings. And it is as much for loved ones, as it is for the patient.

Patients and families living through terminal illness will face pain and struggle, but also fulfilment and joy and it is important that all those experiences are embraced. We live from moment to moment and those moments become memories, not only for patients, but also for those who will be left behind. Memories, like physical mementos, can be shared, treasured and passed down. How and where they find their place in our hearts and minds, how their personal meaning changes over time, is our choice.

The Way We Were

Songwriters: Marvin Hamlisch / Marilyn Bergman / Alan Bergman
Performed by Barbra Streisand

Memories
Light the corners of my mind
Misty watercolor memories
Of the way we were
Scattered pictures
Of the smiles we left behind
Smiles we gave to one another
For the way we were
Can it be that it was all so simple then?
Or has time re-written every line?
If we had the chance to do it all again
Tell me, would we?
Could we?
Memories
May be beautiful and yet
What's too painful to remember
We simply to choose to forget
So it's the laughter
We will remember
Whenever we remember
The way we were
The way we were

Scan to watch the short film "Ah Kong" here:

The Science (and Art) of Doing in Health

THE BANYAN TREE

This column is dedicated to the pursuit of continuous learning and development and takes its name from the banyan tree. It has roots that grow deep, anchoring it firmly in the soil. The tree spreads its shade wide and far and provides space for reflection and discussion. We invite you to come and take a seat under its shade.

Bridging the gap between research and practice in healthcare, the Centre for Behavioural and Implementation Science Interventions (BISI) at NUS Medicine aims to conduct research and educate on behavioural and implementation sciences, to more fully realise the benefits of evidence-based care.

Simply knowing is not enough—knowledge in and of itself does not necessarily lead to action for the better. Similarly, research or innovation, even when rigorous and relevant, does not automatically result in improved care or health. In fact, it is estimated that globally, 85% of the billions of dollars spent on health research are wasted because the research is not sufficiently usable or not put into practice.

Hence, BISI is established to bridge the know-do gap through world-class research and education on behavioural and implementation sciences, thereby more fully realising the benefits of evidence-based care for individuals, organisations and systems. BISI's education efforts begin with those who are already working in health and social care sectors, supporting them to translate research into practice and policy more effectively and sustainably.

BISI offers a continuing education and training (CET) course over two half-days, on the fundamentals of behavioural and implementation sciences for healthcare. Behavioural science is about understanding, predicting and influencing human behaviour. Implementation science is the systematic study of methods and strategies that facilitate the uptake and integration of research findings and evidence-based practice into routine use by practitioners and policymakers, whether in clinical or public health settings. BISI is unique in bringing together the two sciences for synergistic impact, while looking after the 'art' side of doing, ensuring that the desired outcomes are brought about in ways that are culturally fitting to this part of the world.

The lead trainer of the CET course is Associate Professor Robyn Mildon, Visiting Associate Professor at NUS Medicine, who is an internationally recognised figure in implementation science, evidence synthesis, knowledge translation, and programme and policy evaluations in health, education and human services. Her work spans multiple countries, including Singapore, helping to advance the implementation of better evidence in policy and practice settings.

Briefly, the course covers the following content:

- The role of behavioural and implementation sciences in healthcare
- Core scientific principles and investigative methodologies of behavioural and implementation sciences
- Core theories, frameworks and tools for the planning, development, implementation and evaluation of health interventions
- Assessment of different implementation approaches and strategies for behaviour change in healthcare-relevant contexts

Participants have ample opportunities to ask questions and take part in group discussions, applying the learnings using real-life case studies.Building on the fundamental-level CET course, BISI plans to commence an intermediate-level CET course on behavioural and implementation sciences for healthcare in 2024, along with other education offerings.

All courses by BISI are highly interactive. Classes are mainly held in person, to take full advantage of opportunities to engage, network and collaborate with trainers and peers, with some online sessions still available to better meet the needs of students.

To date, the course has run **twice**. An upcoming session is happening on **29 and 30 November 2023**. Scan to register here:

Past participants are mostly **frontline healthcare professionals**—doctors, nurses, pharmacists, healthcare researchers and administrators, and entrepreneurs.

100% of past participants who provided feedback on the course
- state that concepts and skills gained from the course are useful for their jobs.
- would recommend the course to others.

“The trainers are clearly experts in their field.”

“They emphasised that the whole business of behavioural and implementation sciences, while multi-factorial and very dynamic, there is a structure and a system to it.”

Take 5:
Q&A with Professor Nick Sevdalis

Q: What are some key principles and concepts of behavioural and implementation sciences that can be applied to improve health outcomes?
A: Human behaviour is not formed in isolation—it is shaped by various factors that are internal and external to the individual, which need to be addressed as a whole in order to be effective at changing behaviour and ultimately, improving outcomes. There are many theories, models and frameworks in behavioural and implementation sciences suitable for healthcare contexts (some are specific to healthcare). They are meant to enable behaviour change or evidence implementation efforts to be more systematic and therefore more likely to succeed, and to facilitate a better understanding of how and why such efforts are (or are not) successful.

Professor Nick Sevdalis, Academic Director of the Centre for Behavioural and Implementation Science Interventions (BISI), NUS Yong Loo Lin School of Medicine

Q: What are the common barriers or challenges encountered when integrating behavioural and implementation sciences into healthcare settings, and how can healthcare practitioners and organisations address these challenges to ensure successful implementation and achieve better health outcomes?
A: The first challenge lies in healthcare practitioners and organisations recognising the role of behavioural and implementation sciences. Implementation science is a young field born out of the evidence-based medicine movement in the last few decades, and there is room for more widespread awareness among healthcare professionals regarding the existence of implementation science and its value in improving care and outcomes. Related to this, there needs to be a sufficient workforce adequately trained in behavioural and implementation science methods and skills. It also makes a tremendous difference that healthcare practitioners and organisational leaders champion and support behaviour change and evidence implementation efforts.

Q: In your view, what are the emerging trends or future directions in behavioural and implementation sciences? How do you foresee these trends shaping the future of healthcare delivery and improving health outcomes?
A: It is known that it takes an average of 17 years to turn 14% of original clinical research into benefit for patients—too long and too little! Implementation science is aimed at closing this gap.

The substantial time lag between research discovery and uptake into routine practice is partly due to the conventional stepwise translational research pathway: from basic, pre-clinical research to clinical efficacy and effectiveness research, then finally implementation research. A recent development in implementation science is the emergence of hybrid effectiveness-implementation research designs blending the clinical effectiveness and implementation components—studying clinical effectiveness and implementation simultaneously to speed up the translational process (and there are other advantages too). Looking ahead, there is potential for such hybrid studies to be adopted more and become more integrated into health services.

Q: How do behavioural and implementation sciences work with other disciplines, such as medicine, public health, psychology and sociology, to achieve better health outcomes?
A: Behavioural and implementation sciences are inherently interdisciplinary, in the sense that they are rooted in, built on or overlap with many social science disciplines including behavioural economics, psychology, sociology and organisation studies. Essentially, they draw from social science methodologies for the specific purpose of understanding and influencing human behaviour and use of evidence-based practice and research findings. They can be applied to any pertinent topic area under any health discipline, such as adherence to a treatment by patients, use of a health technology or clinical innovation by clinicians, or uptake of a public health intervention by the general population. Behavioural and implementation sciences do not and cannot work in isolation—collaboration with other disciplines is crucial!

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