A*STAR
RESEARCH

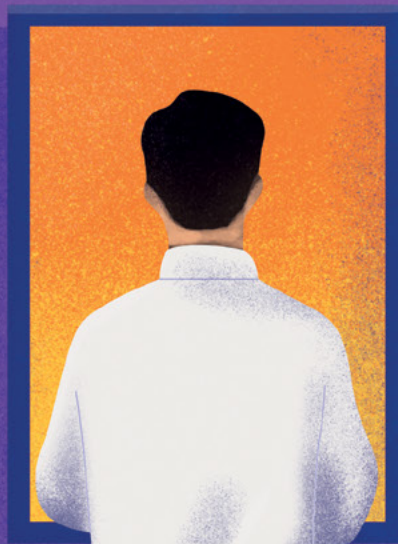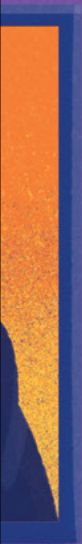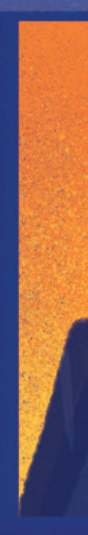## MAPPING COUGH DROPLETS IN FLIGHT

How computer simulations are shedding light on COVID-19 transmission

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COMMEMORATING OUTSTANDING SCIENCE AND EXCELLENT SCIENTISTS

Winners of the President's Science and Technology Awards 2020

page 24

MEET THE CLASS OF 2021

Three young A*STAR researchers have received the prestigious National Research Foundation Fellowship

page 08

The Agency for Science, Technology and Research (A*STAR) is Singapore's lead government agency dedicated to fostering world-class scientific research and talent for a vibrant knowledge-based economy.

A*STAR actively nurtures public-sector research and development in biomedical sciences, physical sciences and engineering, and spurs growth in Singapore's key economic clusters by providing human, intellectual and industrial capital to our partners in industry and the healthcare sector.

A*STAR currently oversees the following research institutes, consortia and horizontal technology centers, and supports extramural research with universities, hospital research centers, and other local and international partners:

Advanced Remanufacturing and Technology Centre (ARTC)
Bioinformatics Institute (BII)
Bioprocessing Technology Institute (BTI)
Experimental Drug Development Centre (EDDC)
Genome Institute of Singapore (GIS)
Horizontal Technology Centres (HTC):
　AgriTech and Aquaculture
　Artificial Intelligence, Analytics and Informatics
　Infectious Disease
　Integrative Social Sciences
　Health and MedTech
　Robotics
　Urban and Green Tech
Institute of Bioengineering and Nanotechnology (IBN)
Institute of Chemical and Engineering Sciences (ICES)
Institute of High Performance Computing (IHPC)
Institute for Infocomm Research (I²R)
Institute of Medical Biology (IMB)
Institute of Molecular and Cell Biology (IMCB)
Institute of Microelectronics (IME)
Institute of Materials Research and Engineering (IMRE)
National Metrology Centre (NMC)
Singapore Bioimaging Consortium (SBIC)
Singapore Immunology Network (SIgN)
Singapore Institute for Clinical Sciences (SICS)
Singapore Institute of Manufacturing Technology (SIMTech)
Singapore Institute of Food and Biotechnology Innovation (SIFBI)
Skin Research Institute of Singapore (SRIS)

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EDITORIAL NOTES

With vaccines on the horizon and the gradual reopening of borders, 2021 represents a new opportunity to start afresh after the chaos brought about by COVID-19.

Standing on the cusp of their scientific journeys are A*STAR scholars Sarah Luo, Caroline Wee and Kaicheng Liang—all of whom have been awarded the prestigious National Research Foundation Singapore (NRF) Fellowship. From mapping the mechanisms of metabolism to harnessing artificial intelligence for high-resolution medical imaging, find out how the newly-minted NRF Fellows are blazing the trail in their respective fields in our cover story on p. 08.

Also upholding A*STAR's tradition of excellence are our scientists advancing research on multiple fronts behind the scenes. Consider Jianjun Liu, who has made it his life's mission to place long-overlooked Asian genomes under the spotlight. His pioneering efforts have led to advances in the treatment of leprosy and nose cancer—as well as the 2020 President's Science Award, the highest national honor that scientists in Singapore can receive. Read about his contributions to research, as well as those of Young Scientist Award winners Wei Leong Chew and Si Hui Tan in our feature 'Commemorating outstanding scientists and excellent scientists (p. 24).'

Beyond the life sciences, this issue of *A*STAR Research* also covers fluid dynamics with 'Mapping cough droplets in flight (p. 04);' optics with 'Seeing (infra)red more clearly (p. 22);' and cybersecurity with 'An ultrathin shield defends against cyberattacks (p. 33).'

For more inspiring stories of innovation from A*STAR scientists, do visit our website at **research.a-star.edu.sg** or follow us on Twitter at **@astar_research** and LinkedIn at **A*STAR Research**. We'd love to hear what you'd like to see in this magazine for the rest of the year!

On the cover
Sarah Luo, Caroline Wee and Kaicheng Liang have been awarded the 2021 National Research Foundation Fellowship.

FLUID DYNAMICS

Mapping cough droplets in flight

Computational models show that there's much more to COVID-19 transmission than the airborne-or-droplet binary.

Is COVID-19 airborne? As with almost everything in science, the answer may not be that straightforward. Instead of trying to classify COVID-19 as airborne or not, new research suggests it may be more helpful to understand what exactly happens to a droplet once it exits the body.

"There is a prevailing, but somewhat misguided view that airborne droplet transmission can be cleanly segregated into two modes," said Fong Yew Leong, a Scientist at A*STAR's Institute of High Performance Computing (IHPC).

According to this view, large droplets are heavy and succumb easily to the pull of gravity. Smaller ones, typically under 5–10 μm in diameter, are much lighter in comparison and can ride the wind, bringing their viral motherlode to distant areas. In this depiction, droplets are simplified as either airborne or not. Diseases, in turn, are transmitted either one way or the other.

To clear the air, Leong and the IHPC team used their computational modeling prowess and the National Supercomputing Centre (NSCC)'s facility to recreate a spray of droplets from a cough. In contrast to the prevailing theory, they found that a droplet's fate is not only determined by its size. As it soars through the air, the droplet loses much of its water to evaporation and shrinks. The smaller it becomes, the lighter it gets, and the longer it can stay airborne.

Their simulations have shown, for instance, that a large droplet 100 μm in diameter could remain in flight for around eight seconds and reach a distance of over six meters away. Alarmingly, even a mammoth droplet spanning 1,000 μm can travel up to 1.3 meters.

Clearly, such figures have implications for the design of safe management measures to contain the COVID-19 outbreak. The findings demonstrate that it is still important to wear a mask, observe social distancing, and be mindful of personal hygiene so that droplets that settle on the clothes have no chance of making it inside the body, said study first author Hongying Li, a scientist on the IHPC team.

> **"A droplet's fate is not determined by its size. As it soars through the air, the droplet loses much of its water to evaporation and shrinks. The smaller it becomes, the lighter it gets, and the longer it can stay airborne."**

"These findings are greatly dependent on the environmental conditions," Leong added. On a particularly arid day, for example, evaporation ramps up, prolonging a droplet's hang time. Variables such as the speed and direction of the wind can also greatly affect a droplet's ultimate fate.

"Since these variables can fluctuate throughout the day, we aim to undertake more studies under different environmental conditions," Li said. Together with A*STAR's Institute of Materials Research and Engineering (IMRE), the team has been working with partners to study different sites and environmental settings. ★

Photo credit QUT media / Flickr

BELOW

How droplets of various sizes move from a person who coughs to another person standing one meter away. Large droplets tend to fall to the ground or on the lower part of the second person's body, while smaller droplets are buoyed by the hot air from the mouth and transported over a longer distance.

Droplet size

2 μm .... 100 μm

0.5s

1s

3s

5s
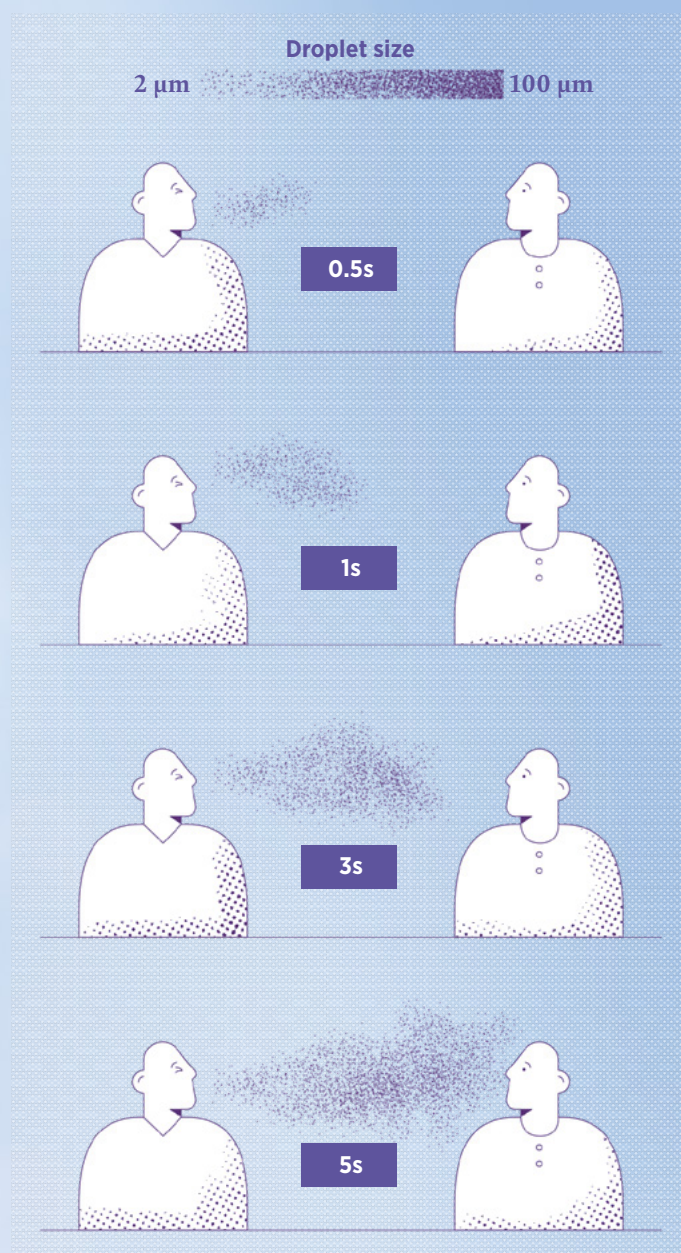
1. Li, H., Leong, F.Y., Xu, G., Ge, Z., Kang, C.W., Lim, K.H. Dispersion of evaporating cough droplets in tropical outdoor environment. *Physics of Fluids* **32**, 113301 (2020).

Reducing uncertainty about COVID-19

A multifaceted study by the Singapore 2019 Novel Coronavirus Outbreak Research team is filling in some of the gaps left in the urgent quest to understand COVID-19 infection.

When COVID-19 first emerged, the mystery surrounding what was causing the disease and how it was being transmitted incited fear and confusion around the world. An unprecedented global research effort has since provided clarity on these matters, but important questions like how long the virus remains infectious and what causes severe disease remain.

"A clearer understanding of disease pathogenesis is necessary to support the development of risk stratification tools, improve limited medical resource allocation and develop novel or re-purpose existing therapeutics which target critical pathways in the COVID-19 inflammatory cascade," said Lisa Ng, a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SIgN) and Executive Director of the A*STAR Biomedical Research Council (BMRC).

With other members of the Singapore 2019 Novel Coronavirus Outbreak Research team, an interdisciplinary group of researchers from various institutions across the country, Ng and Executive Director of A*STAR's Infectious Diseases Laboratories Laurent Renia conducted a comprehensive study to better understand COVID-19 and improve management of the disease. "Our findings on the virus have implications on identification, patient triage and transmission control measures," he said.

To design effective transmission control measures, it is important to know how long the virus remains infectious. While most studies have looked at the number of days the virus remains viable after infection, Ng and her team found that a proxy value called the cycle threshold, or C_t value, may also be useful.

The C_t value describes the number of cycles needed to detect the virus in a polymerase chain reaction test, the gold standard test used to detect SARS-CoV-2. Viable virus was only detected at a C_t value of less than 30, or in samples collected less than 14 days after symptoms first emerged. However, Ng cautioned that additional studies are needed in more patients—including asymptomatic cases—before the C_t value can be widely used as an indicator.

The study also looked at the link between disease severity and the appearance of antibodies and inflammatory signals across time. The researchers found that patients with severe symptoms develop antibodies earlier and at higher concentrations than those with mild symptoms, knowledge that can be used to predict which patients may develop severe disease.

What's more, severe cases had higher levels of several proinflammatory signals and growth factors. This implies that already available drugs that target and inhibit these signals could be repurposed to treat patients with severe COVID-19, Ng said.

The team is now monitoring patients throughout both disease and recovery to better understand changes in the immune response with time. ★
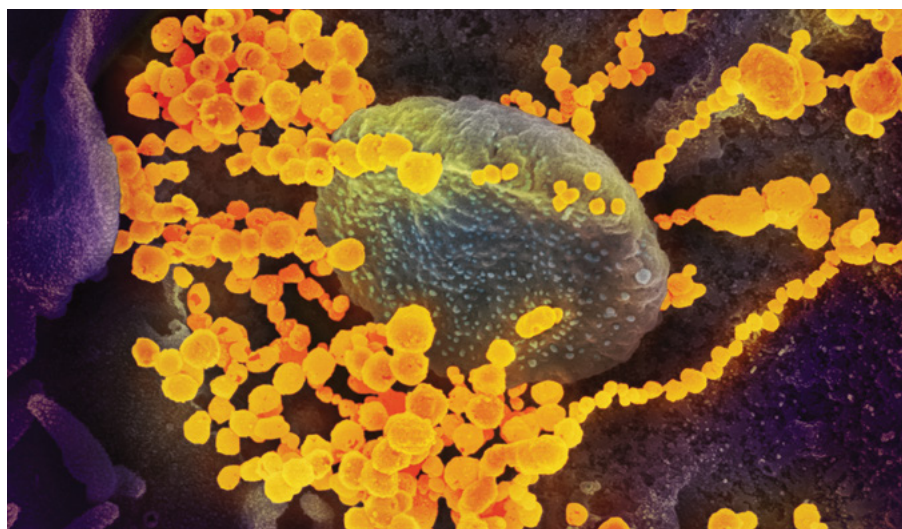
A scanning electron microscopy image of SARS-CoV-2 virus particles emerging from the surface of cells cultured in the lab. The number of cycles it takes to amplify SARS-CoV-2 genetic material could indicate if the patient the sample was taken from is still infectious or not.

Photo credit: NIAID / Flickr

1. Young, B.E., Ong, S.W.X., Ng, L.F.P., Anderson, D.E., Chia W.N., *et al*. Viral dynamics and immune correlates of coronavirus disease 2019 (COVID-19) severity. *Clinical Infectious Diseases*, ciaa1280 (2020).

IMMUNOLOGY

Predicting severe cases of COVID-19

A*STAR researchers identify new, specific markers of severe COVID-19 that may improve the management and treatment of patients.

One of the most intriguing features of COVID-19 infection is the wide range of outcomes the disease is capable of causing—from no symptoms at all to severe pneumonia and acute respiratory distress syndrome, which can ultimately lead to death. The fast and furious COVID-19 research being performed around the world is revealing that an individual's outcome is highly dependent on their immune system.

"As it is often the case for pathogenic infections, the host immune system is a key player in viral clearance and resolution of disease," explained Lisa Ng, a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SIgN), and Infectious Diseases Laboratories (ID Labs). "In this case, an imbalance between inflammation and protection leads to the progression to more severe disease."

The problem is we still don't know exactly which immune cells drive this progression. In early March 2020, Ng and a team of researchers, in collaboration with clinicians at the National Centre for Infectious Diseases in Singapore, began a search to find a marker of disease severity. Their study pointed to changes in specific subtypes of lymphocytes and neutrophils—two types of white blood cells.

Using a technique called high-dimensional flow cytometry, the researchers were able to efficiently study more than 50 types of immune cells in COVID-19 patients with varying symptoms in the early stages of the disease. They found that COVID-19 infection reduced the number of T cells expressing CD8 and VD2 proteins. Conversely, it increased the number of immature neutrophils, rather than total neutrophils as shown by other studies.

Noting that these patterns were more pronounced in severe cases, the researchers looked at the link between disease severity and the ratio of immature neutrophils to T cells expressing CD8 or VD2. They found that these ratios were both strong indicators and predictors of severe respiratory symptoms, with the ratio of immature neutrophils to VD2 T cells outperforming the ratio of total neutrophils to lymphocytes or CD8 T cells proposed by other studies.

"We hope that our findings will allow for rapid triage possibilities in heavily burdened hospitals," said Ng, adding that the ratios can be used to predict whether a patient will develop severe COVID-19 symptoms, allowing them to receive early pre-emptive treatment if needed.

Ng and her team are now studying the immune systems of symptomatic and asymptomatic patients to identify potential differences. "Hopefully, this can help guide therapies and inform vaccine or treatment design," she said. ★

> "We hope that our findings will allow for rapid triage possibilities in heavily burdened hospitals. Hopefully, this can help guide therapies and inform vaccine or treatment design."

Photo credit: Dlumen / Shutterstock

ABOVE
An electron micrograph of immune cells known as neutrophils. The level of immature neutrophils in the blood can predict the severity of COVID-19, researchers say.

1. Carissimo, G., Xu, W., Kwok, I., Abdad, M.Y., Chan, Y.H., *et al*. Whole blood immunophenotyping uncovers immature neutrophil-to-VD2 T-cell ratio as an early marker for severe COVID-19. *Nature Communications* **11**, 5243 (2020).

MEET THE CLASS OF 2021

Three A*STAR scholars—Sarah Luo, Caroline Wee, and Kaicheng Liang—have been selected for the highly competitive National Research Foundation Fellowship out of over 134 applicants worldwide.

With their enthusiasm, creativity and fresh perspective, young researchers are often drivers of innovation. Early-career scientists are more likely to study 'hot and novel' topics compared with their older counterparts, according to a text analysis of more than 20 million biomedical papers in the last 70 years, published in the US National Bureau of Economic Research.

At the same time, the odds can sometimes be stacked against young scientists, who face a host of challenges their veteran colleagues may not: establishing credibility, building prestige, and gaining access to grants and other resources. To give the most promising ones a leg up, the National Research Foundation Singapore (NRF) launched the eponymous NRF Fellowship in 2008. Since then, more than 100 early-career researchers from all over the world, in fields ranging from infectious diseases to microelectronics, have been awarded fellowships.

In 2020, three A*STAR scholars continued to uphold that tradition of excellence. Sarah Luo, Caroline Wee and Kaicheng Liang were each awarded a S$3 million grant to respectively carry out ground-breaking research in metabolic circuits, gene-diet interactions affecting food choice, and tissue pathology. The powerhouse trio will conduct their research in Singapore at an A*STAR host institution of their choice over the next five years. In this feature, we delve into the impact and inspiration behind their work.

MAPPING THE MECHANISMS OF METABOLISM

As anyone who's ever tried to stuff themselves during a buffet will know, we can tire of the same food rather quickly, no matter how good it tastes. But is there some internal mechanism beyond our conscious taste system that tells the brain we've had too much of a particular kind of food?

This mechanism, and how it occasionally malfunctions and leads to disordered eating behaviors and metabolic diseases, is what Sarah Luo, a Senior Research Fellow at A*STAR's Singapore Bioimaging Consortium (SBIC), intends to explore. Her research will define the neural circuits between the brain and the different organs involved in metabolic regulation, with a particular emphasis on the liver. Following this, Luo will investigate how dysregulation in such circuits can lead to health conditions like obesity and diabetes.

"Our brains act as master regulators of metabolism," Luo said. "But how does the brain get information from the body to coordinate its regulatory function?" Studies on metabolic neural circuits have so far emphasized communication between the brain and the gut, with its associated microbiome, but Luo chose to focus on a nearby, lesser-spotlighted neighbor.

"The liver is a major metabolic organ; it receives digested nutrients from the stomach and intestines and processes these in response to the body's changing needs. So it's in a prime location to sense incoming metabolic substrates," Luo explained. "I am investigating how the liver acts as a nutrient sensor and feeds metabolic information back to the brain, as well as how the brain, in turn, regulates liver function through neural circuits."

Mapping body-brain circuits may be basic science, but the techniques required are far from fundamental.

Luo will be studying peripheral neural circuits in mice from the molecular and cellular to system-wide levels. She intends to conduct single-cell analysis of the neurons connecting the liver and brain to identify unique gene signatures, and use a new tissue-clearing technology that will render the brain and liver transparent for clearer circuit imaging. She will also use single-cell imaging of neural activity to identify neurons that respond to infused nutrients such as sugars or fats.

"Evidence has accumulated that dysregulated neural circuits can contribute to metabolic diseases," Luo said. "If your nutrient sensors are desensitized, you could end up in a vicious cycle where your brain acts in a nutritionally deprived state even though you are already consuming a lot of fatty and sugary food." By mapping these circuits, Luo hopes to contribute to emerging therapies for metabolic diseases, such as developing neural devices that can stimulate relevant peripheral nerves in patients.

> *I am investigating how the liver acts as a nutrient sensor and feeds metabolic information back to the brain, as well as how the brain, in turn, regulates liver function through neural circuits.*
>
> **Sarah Luo**
> Senior Research Fellow
> Singapore Bioimaging Consortium (SBIC)

FISH ARE FRIENDS IN UNDERSTANDING FOOD

In science, inspiration can come from anywhere. In Caroline Wee's case, it was from briefly experimenting with the trendy ketogenic diet. This low-carbohydrate, high-fat diet many swear by forces the body to burn a different type of fuel—fat, instead of the usual sugar—which has been said to promote weight loss and other health benefits. Trying out these 'keto' meals, Wee observed changes in her appetite and cravings. However, she was surprised at the lack of understanding of underlying mechanisms. Such observations sparked her interest in dissecting how our genes and diet interact to affect our appetite and food decisions.

Key to Wee's project is the diminutive zebrafish, a tropical freshwater fish with a genetic and anatomical structure surprisingly similar to humans. Wee, who is a Research Fellow at A*STAR's Institute of Molecular and Cell Biology (IMCB), has worked extensively with zebrafish, having chosen them for their simplicity and capacity for high-throughput experimentation. The fish is also transparent at their larval stages, allowing her to comprehensively examine whole-brain and body mechanisms controlling feeding behavior.

"There's evidence that both an animal's nutritional needs and the nutrient cues it's exposed to can change the amount and type of food it chooses to eat. But as we all know, biology is complex; for example, a high-fat diet could enhance or suppress appetite depending on the context," Wee said. "One such important context is our genetic makeup," she continued, noting that many human studies have identified genes correlating with dietary preferences and effects, but have yet to successfully establish causality. Furthermore, the microbes in our guts, as well as environmental factors such as stress, are also important players in these decisions.

A neuroscientist by training, Wee plans to use optical, molecular and circuit dissection techniques to explore the underlying gut-brain signaling mechanisms. Then, by selectively mutating genes associated with, say, fat preference or obesity in humans, Wee hopes to draw causal links between genetic makeup, metabolism and eating behaviors. "This will really open the door towards precision medicine and nutrition, where the fish can then be used to screen for therapeutics that target specific genetic predispositions," she added.

Apart from identifying potential therapies and interventions for humans, Wee hopes her research will also benefit her aquatic subjects. With food security concerns at the fore and Singapore aiming to produce 30 percent of its nutritional needs by 2030, Wee intends to apply her work directly in aquaculture, particularly fish farming. "Fish feeding and growth optimization is a big bottleneck in food production," she explained. "If we can figure out when, what and how best to feed these fish, we could expect to see huge gains in aquaculture health and productivity, directly benefiting local industries and society."

> ### Fish feeding and growth optimization is a big bottleneck in food production.
>
> **Caroline Wee**
> Research Fellow
> Institute of Molecular
> and Cell Biology (IMCB)
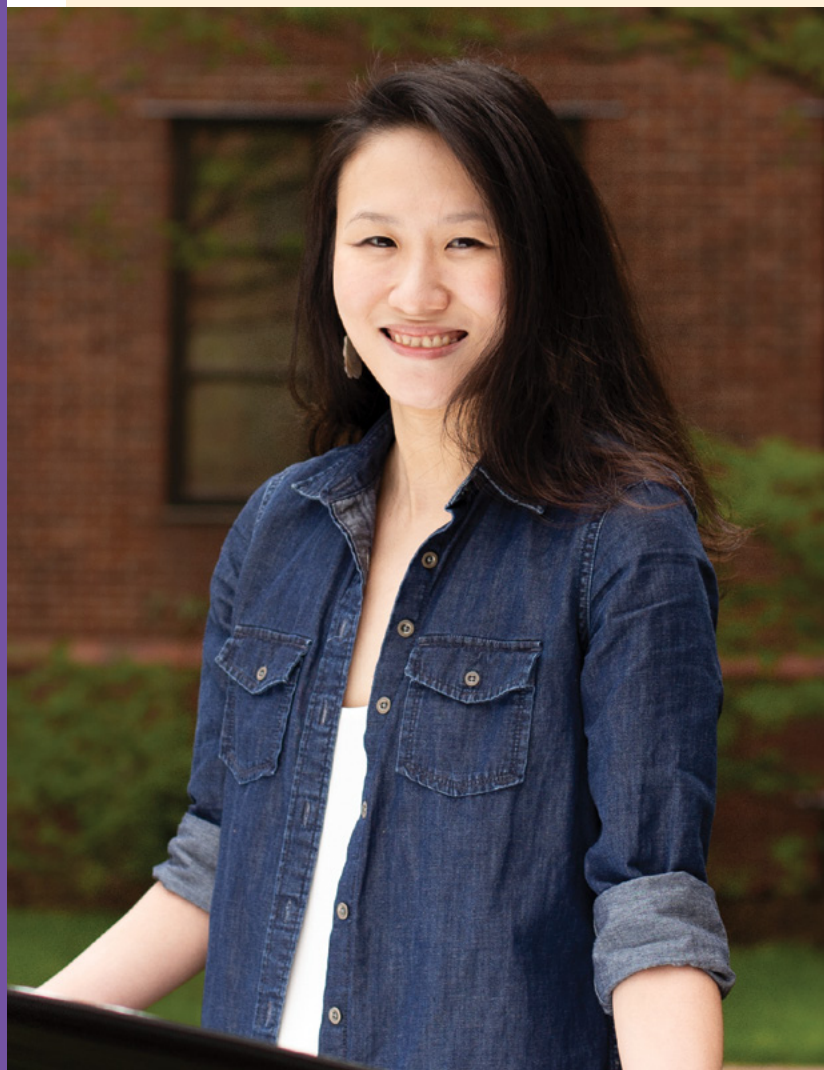
> *With this real-time information, doctors can get faster feedback during surgery and make better decisions, which hopefully will lead to better outcomes for patients.*
>
> **Kaicheng Liang**
> Research Scientist
> Institute of Bioengineering and
> Nanotechnology (IBN)

USING AI FOR AN EXTRA PAIR OF EYES

When cancer patients undergo surgery, doctors try as much as possible to remove all traces of cancerous tissue. Their margin of error is literally microscopic—any malignant cells unwittingly left behind will result in the disease's recurrence. To reliably check for cancerous tissue, pathologists sometimes carry out microscopic analysis during surgery, a time-consuming process in an event where every minute counts.

Speeding up this process is what Kaicheng Liang, a Team Leader and Research Scientist at A*STAR's Institute of Bioengineering and Nanotechnology (IBN), aims to do. His research looks into developing tiny endoscopic devices for high-resolution optical imaging, which will facilitate the instantaneous diagnosis of cancerous tissue among other applications in tissue pathology. "I want to put these devices inside the body and get pictures of tissue that are so detailed, it's almost like real microscopy," Liang explained. "With this real-time information, doctors can get faster feedback during surgery and make better decisions, which hopefully will lead to better outcomes for patients."

To ensure the pictures of tissue are not just taken but also examined in real time for instantaneous diagnoses, Liang will combine machine learning with endoscopic microscopy. For example, the technology can rank pictures by severity so surgeons know which areas to first prioritize. Artificial intelligence (AI) can also help doctors to overcome another key challenge: that of high-speed imaging during surgery leading to lower resolutions. Machine learning can be used to enhance these images, though care must be taken to ensure the AI makes responsible inferences for accurate cancer diagnoses, Liang said.

Another hurdle lies in making the devices small enough for different types of surgery, including keyhole surgery. To meet this size requirement without compromising too much on image quality, Liang intends to incorporate micro-sized motors and use their mechanical motion to improve imaging performance. To this end, working with doctors, engineers and other researchers will be crucial and Liang has already begun building a network of collaborators within IBN and A*STAR as well as the broader Singapore-based biomedical ecosystem. "I've been pleasantly surprised by how easy it is to form collaborations, with IBN and A*STAR being such interdisciplinary places," he said.

Lasting collaborations will be essential as Liang's project, a type of use-inspired basic research, could take up to a decade—from working prototypes in limited patient trials within five years to eventual approval by the US Food and Drug Administration. "I'll still be alive then," he said, unfazed. "I've got easily 30 years of this work to go. I can definitely see this happening within my lifetime." ★

ABOVE
Mouse microglial cells as captured by a scanning electron microscope. Microglia are immune cells that are found in the brain.

1. Geirsdottir, L., David, E., Hadas, K., Weiner, A., Bohlen, S.C., *et al.* Cross-species single-cell analysis reveals divergence of the primate microglia program. *Cell* **179**, 1609–1622 (2019).

IMMUNOLOGY

Mapping 450 million years of microglial evolution

Single-cell genomic technology is providing fresh perspectives on the origins of microglia, ancient immune sentinels found in the brain.

Microglia are the brain's resident immune sentinels and account for around ten percent of all brain cells. These dynamic, highly specialized cells control a plethora of neurobiological functions, from scavenging pathogens and damaged brain cells to orchestrating inflammation and promoting repair.

Despite being the subject of intense research, much of microglia's origin story remains shrouded in mystery. A*STAR researchers, with international collaborators, thus turned to a genomic technique called single-cell sequencing to chart the spectrum of microglia biology over 450 million evolutionary years.

The study was led by Ido Amit's laboratory at the Weizmann Institute of Science in Israel, with contributions from the laboratory of Florent Ginhoux, a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SIgN).

The researchers' deep dive into microglial biology spanned 18 species—including humans, whales, marmosets, snakes and macaques—and showed that these cells have been around for a long time. "We found that microglia exist in multiple species, including old ones! It is a macrophage population that has been conserved for millions of years," said Ginhoux.

Take, for example, the differences between human and mouse microglia, which have an evolutionary distance of about 96 million years. The researchers found that humans have signature genetic patterns relating to Alzheimer's and Parkinson's disease susceptibility that mice lack. Longer-living species such as humans also have a higher degree of diversity and heterogeneity among their microglia.

By examining the genetic information of individual cells with next-generation sequencing, the researchers were able to amplify subtle differences between microglia subpopulations in the context of its microenvironment, revealing never-before-seen layers of complexity in the cellular and genetic makeup of the brain.

"Single-cell analysis allows us to map every cell, group them by their expression profile, and appreciate the level of heterogeneity within a cell population like never before," explained Ginhoux.

Such investigations are integral to advancing our understanding of brain aging and neuropathology—areas of research that have been limited due to the lack of robust experimental models. It will also support neurobiologists seeking novel targets for clinical interventions against Alzheimer's disease and other neurodegenerative conditions, Ginhoux said.

"We are trying to find new [microglia] sub-populations, better separate them and study them at single-cell resolution. When you know what molecules and proteins are involved in cellular pathways, you can then design better treatments," he said. ★

An indelible memory of dengue

New clues into how the immune system remembers a dengue infection may lead to a better vaccine.

Anti-dengue efforts ranging from awareness campaigns to fogging may be commonplace in tropical countries, but did you know that there is a vaccine against dengue? If you didn't, there's probably a simple reason why: it isn't perfect.

Although effective on people who have contracted dengue before, the vaccine increases the risk of severe dengue and hospitalization in people who have never had the disease. This unfortunate reaction is most likely due to complications with immune system memory and multiple dengue serotypes.

Now, a team of researchers led by Laura Rivino at Duke-NUS Medical School and the University of Bristol, and Evan Newell at the A*STAR Singapore Immunology Network (SIgN) and Fred Hutchinson Cancer Research Center, are taking a computational immunology approach to studying T cells, which are central to the immune response against dengue infection.

Using mass cytometry and a peptide-human leukocyte antigen tetramer staining strategy, the researchers isolated T cells from dengue patients at different time points of the disease, and probed the T cells with 430 dengue and control candidate epitopes. They tracked a large number of activation, tracking and differentiation markers in the T cells, painting a comprehensive picture of the T cells' response to dengue infection.

In their study, they found that dengue-specific T cells differentiated into two major cell fates: CD57$^+$ CD127$^-$ cells, which resemble memory cells that are terminally differentiated, and CD127$^+$ CD57$^-$ cells, which resemble memory cells capable of proliferating. These cells continue to exist at elevated frequencies in the body for up to a year after infection.

"I used a tool called Cytofkit, which we developed in-house to analyze the data," said Jinmiao Chen, a Principal Investigator at SIgN and a co-author of the study. "This tool was specifically designed and developed for analyzing mass cytometry data. It is a one-stop toolbox that allowed us to visualize and interpret the analysis results effectively."

Although their observational study could not confirm the function

of these two classes of memory cells, the team hypothesizes, based on existing research, that the CD57$^+$ CD127$^-$ cells can kill rapidly once activated because they express granzyme B, a serine protease commonly found in natural killer cells, while the CD127$^+$ CD57$^-$ cells can persist for a long time as memory cells and proliferate to make more memory cells.

The researchers plan on performing functional studies on both groups of dengue-specific T cells to confirm their hypothesis. Beyond dengue, Chen hopes to use similar methods to study human gastric cancer, to reveal how cancer cells escape immune surveillance. ★

"The Cytofkit is a one-stop toolbox that allowed us to visualize and interpret the analysis results effectively."

BOTTOM
A new tool for tracking T cells has helped clarify how the immune system responds to dengue infection.

1. Chng, M.H.Y., Lim, M.Q., Rouers, A., Becht, E., Lee, B., *et al.* Large-scale HLA tetramer tracking of T cells during dengue infection reveals broad acute activation and differentiation into two memory cell fates. *Immunity* **51** (6), 1119-1135 (2019).
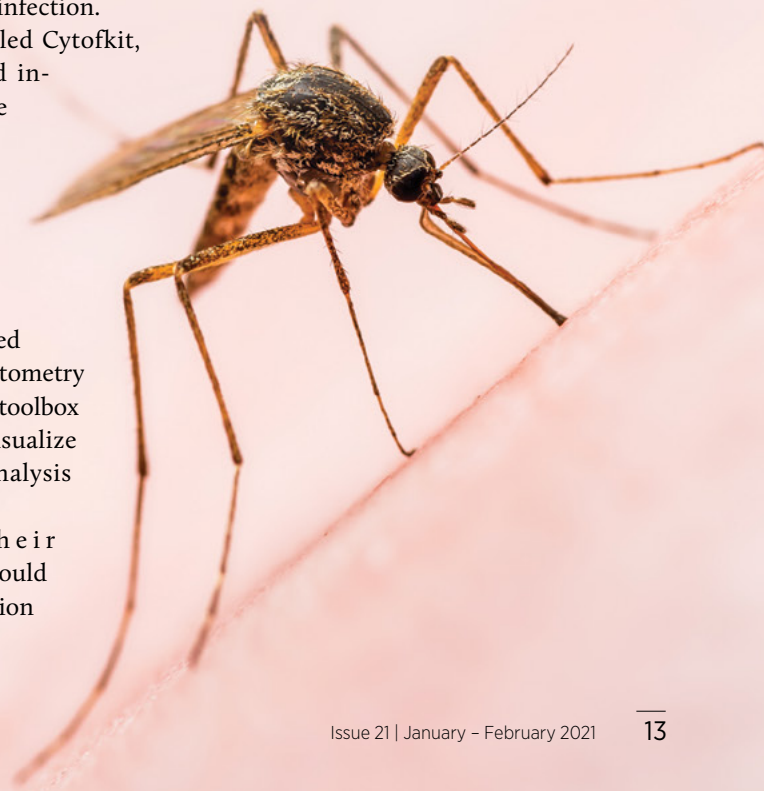
Tiny but full of energy

Researchers at A*STAR have discovered how a class of small proteins is essential for metabolism.

The largest protein in the human body, titin, has a molecular weight of three million Daltons and is composed of 27,000 amino acids. But in biology, the smallest things can often have the biggest impact, as a new discovery proves.

With lengths of less than 100 amino acids, small open reading frame-encoded peptides (SEPs) are tiny in comparison. Their small size also makes them hard to detect with conventional methods and few studies have attempted to validate their functionality and biological relevance in a systematic manner.

In particular, nuclear-encoded SEPs that are localized to the mitochondria, called mitochondria-targeted SEPs (mito-SEPs), represent an unexplored repository of new gene functions and therapeutic targets.

"The major challenge is that there is no definitive way of predicting if a protein is part of the mitochondrial proteome, which consists of about 1,500 proteins," said

> **"The major challenge is that there is no definitive way of predicting if a protein is part of the mitochondrial proteome, which consists of about 1,500 proteins."**

study corresponding author Lena Ho, an Assistant Professor at Duke-NUS Medical School and a Joint Principal Investigator at the A*STAR Institute of Medical Biology (IMB). The study also included A*STAR-affiliated researchers from the Institute of Molecular and Cell Biology (IMCB) and the Skin Research Institute of Singapore (SRIS).

"To come up with a plausible candidate list, we decided to combine independent methods of proteomic and transcriptomic-based analyses to search for these proteins and tailor our approach to small proteins."

Through a combination of proteomics, metabolomics and metabolic flux modeling, the researchers screened the SEP peptidome, which led them to identify 16 mito-SEPs, including one with significant implications in energy metabolism: BRAWNIN.

In knockout studies, zebrafish lacking BRAWNIN were growth-stunted and displayed a range of features characteristic of mitochondrial diseases in humans—a dangerous build-up of lactic acid and early death. BRAWNIN was shown to be a central regulator for the assembly of vertebrate respiratory complex III (CIII), which is crucial for survival.

"CIII is essential for life, thus humans with mutations in components of CIII are rare," explained Ho. "Figuring out the assembly of mammalian CIII and how to manipulate the process to exert metabolic control are very fundamental questions."

"In parallel, we are also trying to understand how the electron transport chain—the machinery that produces ATP—responds to external metabolic cues," she added. According to Ho, this is an important question because the failure of the electron transport chain to keep up with cellular energetic demands is a feature of most degenerative diseases, including aging. Small proteins like BRAWNIN could be a link in this mechanism, she said.

"The progressive failure caused by mitochondrial decline and dysfunction underlies all degenerative diseases, and has also been widely implicated in cancer," said Ho. "The proteins we've discovered, including BRAWNIN, represent potential targets in reversing this." ★

LEFT
Targeting small peptides found in the mitochondria could help to prevent degenerative diseases.

1. Zhang, S., Reljić, B., Liang, C., Kerouanton, B., Francisco, J.C., *et al*. Mitochondrial peptide BRAWNIN is essential for vertebrate respiratory complex III assembly. *Nature Communications* **11**, 1312 (2020).
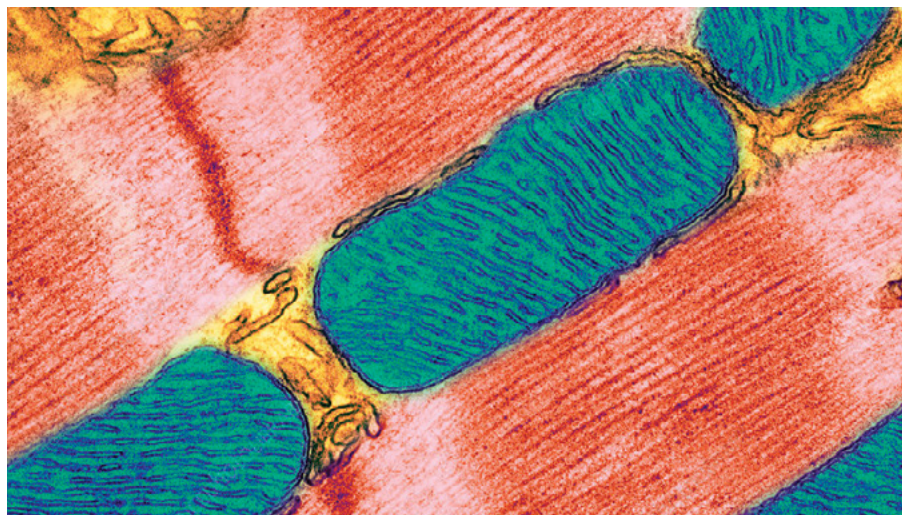
Genetic clues lead to the identification of Jamuar Syndrome

An international consortium gives a debilitating childhood disorder a name and a genetic cause.

3D model of UDP-glucose 6-dehydrogenase, a protein newly found to be involved in a developmental disorder known as epileptic encephalopathy.

Photo credit: Pleiotrope / Wikimedia Commons

Imagine a disease that strikes in childhood, leaving children with frequent epileptic seizures, delayed intellectual development and movement that sometimes worsens to the point they are unable to walk and eat. These devastating disorders—known as developmental epileptic encephalopathies—are unfortunately real.

Researchers have long believed that developmental epileptic encephalopathies have a genetic basis, but their genetic underpinnings have not been fully elucidated until now. An international team of researchers has found one underlying genetic cause for this disease: recessive mutations in the gene UDP-glucose 6-dehydrogenase (*UGDH*).

"Germline mutations of the enzyme *UGDH* are a common cause of epileptic encephalopathies in children," said study corresponding author Bruno Reversade, a Research Director at A*STAR's Institute of Medical Biology (IMB) and Institute of Molecular and Cell Biology (IMCB). "This is evidenced by a large number of subjects found all over the world."
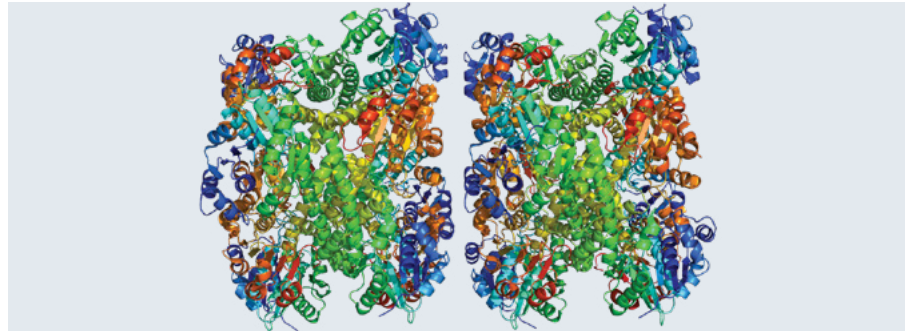
In a collaborative effort co-led by Ludger Schöls at the University of Tübingen, the researchers arrived at their answer through a process of genetic detective work. The first clue was the knowledge that defects in glycosylation, the process of adding sugar chains to proteins and lipids in the body, can result in symptoms similar to that of developmental epileptic encephalopathies.

With this in mind, the team proposed that *UGDH* might play a role in the disease. Under normal conditions, the *UGDH* gene codes for an oxidoreductase enzyme that is involved in the glycosylation process. To confirm these suspicions, the team first looked at a pair of Singaporean siblings with developmental epileptic encephalopathy. Exome sequencing of the siblings revealed they both carried a rare recessive loss-of-function variant of the *UGDH* gene, stemming from a single missense mutation.

They then searched for more individuals with similar mutations in *UGDH*, discovering 27 other cases from 24 unrelated families across the world. Using the patients' primary fibroblasts and biochemical assays, they confirmed that the mutations impair *UGDH* stability, oligomerization or enzymatic activity and established the role of *UGDH* in the production of extracellular matrix components that are essential for human brain development.

After ten weeks of differentiation, cerebral organoids created from patients' neural progenitor cells showed marked underdevelopment compared to wildtype or carrier organoids. Not only did this study confirm that *UGDH* mutations behave as loss-of-function alleles, it also demonstrated that cerebral organoids can serve as a 'disease-in-a-dish' model.

The team proposed to name the disease Jamuar Syndrome after Saumya Jamuar, a clinical geneticist at the KK Women's and Children's Hospital in Singapore, who cared for the Singaporean family that was the starting point in this discovery.

"Understanding the genetic etiology of human disease is a stepping stone towards thinking about possible therapeutic interventions," said Reversade. "Being able to pinpoint the genetic origin for an orphan disease allows for families of affected children to end a diagnostic odyssey and reach psychological comfort that a definitive cause has been unveiled." ★

1. Hengel, H., Bosso-Lefèvre, C., Grady, G., Szenker-Ravi, E., Li, H., *et al*. Loss-of-function mutations in *UDP-Glucose 6-Dehydrogenase* cause recessive developmental epileptic encephalopathy. *Nature Communications* **11**, 595 (2020).
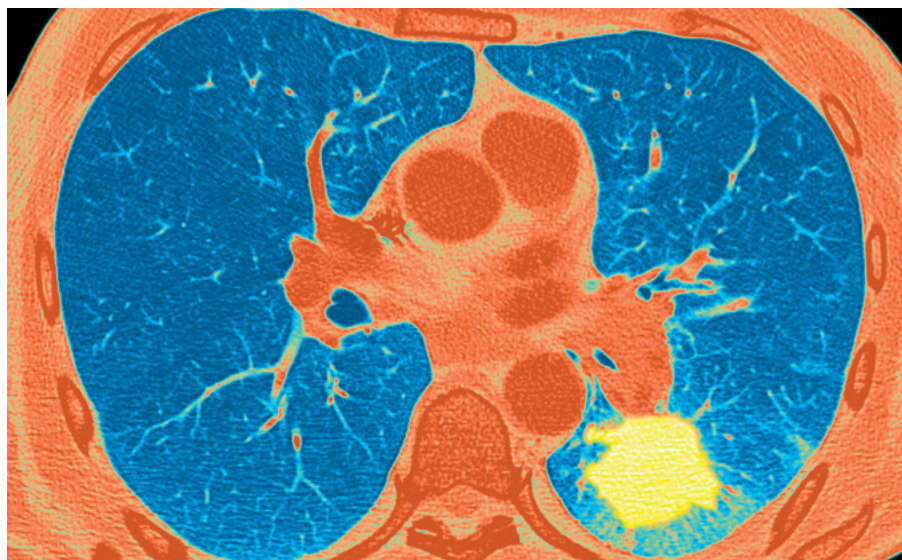
CANCER BIOLOGY

Catering to the quirks of lung cancer in East Asians

A large genetic study has identified distinct features of lung cancer in East Asians, which could improve prediction and treatment outcomes.

The 'one-size-fits-all' approach in medicine is slowly giving way to personalized treatment strategies as scientists continue to learn how and why individuals with the same disease can have very different outcomes and response to treatment. Understanding the characteristics of patients down to the gene level can make diagnosis more accurate and treatments more effective.

For example, ethnicity appears to play a major role in the prevalence of lung adenocarcinoma (LUAD), the most common type of lung cancer in the world. "In Asians, we commonly see the never-smoker phenotype associated with the EGFR mutation," explained Daniel Tan, a Senior Clinician Scientist at A*STAR's Genome Institute of Singapore (GIS). This is in contrast to LUAD in Europeans, which tends to occur in male smokers without the EGFR mutation.

However, because previous studies only examined small populations, they were unable to comprehensively characterize the unique features of East Asian LUAD patients. A study published in *Nature Genetics* led by study first author Jianbin Chen, a Research Associate at GIS, has overcome this issue by combining new data from Chinese patients from Singapore with existing data from other Chinese patients.

The researchers conducted whole-exome and transcriptome sequencing—techniques that look at regions of the DNA that encode proteins—in their large group of LUAD samples from East Asian patients and compared these results to available data from patients of European ancestry.

They found that East Asian patients had more stable genomes, a trait that may influence cancer progression and the development of resistance, said Tan. This genome stability may explain why survival predictions were more accurate for East Asian patients over European patients.

By using an unsupervised algorithm—which searches for previously unknown patterns with minimum input from humans—to cluster their sequencing data, the researchers identified a unique subgroup of tumors in the East Asian population with high levels of inflammation-related genes and immune cells.

"This may represent a unique feature of the tumor microenvironment in lung cancer in Asians," said Tan. "With the burgeoning pipeline of new immune targets, our analysis could shed light on novel immunotherapy strategies."

The study highlights the usefulness of genetic features for predicting patient prognosis. The researchers are now exploring the deeper clinical relevance in relation to other features, including pathology reports, immune markers and clinical outcomes including response to therapy. "In the near future we hope to deploy these selection features in the clinic prospectively," Tan said. ★

ABOVE
Researchers have identified the genetic reasons why lung adenocarcinoma affects Asians differently from Europeans.

1. Chen, J., Yang, H., Teo, A.S.M., Amer, L.B., Sherbaf, F.G., *et al.* Genomic landscape of lung adenocarcinoma in East Asians. *Nature Genetics* **52**, 177–186 (2020).

Finding the perfect fit

A*STAR scientists aim to design better immunotherapies by simulating the binding of antibodies to their targets.

When a spacecraft docks at the International Space Station, it must ensure a perfect fit to prevent malfunction. Although on a much smaller scale, antibodies produced by our bodies against a foreign invader must also 'dock' perfectly on their target to elicit an effective immune response.

In recent years, scientists have co-opted the body's natural defenses to fight cancer. Called immunotherapy, one example of it uses therapeutic monoclonal antibodies to find and destroy cancer cells.

"Monoclonal antibodies like pertuzumab and trastuzumab are widely used in targeted therapies against HER2-overexpressing breast cancer," said co-corresponding author Peter Bond, a Senior Principal Investigator at A*STAR's Bioinformatics Institute (BII).

> **"There is a need for guidance to ensure maximum success in the rational design of IgM therapeutics."**

Both pertuzumab and trastuzumab inhibit cellular signaling by targeting HER2, a cell-surface receptor upregulated in about 20 percent of breast cancers. Co-corresponding author Samuel Gan, a Principal Investigator at BII, also of the Experimental Drug Development Centre (EDDC) and p53 Lab, previously showed that although the trastuzumab IgG subtype bound to HER2 with higher affinity as compared to pertuzumab IgG, pertuzumab IgM conversely showed stronger binding as compared to trastuzumab IgM.

To explain their antibody binding data, the collaborative team used a combination of structural data and modeling to derive complete models of trastuzumab IgM and pertuzumab IgM. They also conducted multiscale modeling and simulations to predict molecular interactions with HER2.

Based on this work, they discovered a protruding surface of the HER2 protein that causes 'steric clashes,' or poor binding, with trastuzumab IgM. In contrast, pertuzumab IgM utilized all of its antigen-binding sites with HER2, which resulted in stronger binding.

In laboratory studies, the researchers validated their simulation data by showing that pertuzumab IgM inhibited the proliferation of HER2-positive breast cancer cells more effectively than trastuzumab IgM and pertuzumab IgG.

"There is a need for guidance to ensure maximum success in the rational design of IgM therapeutics," explained Bond. "Our findings highlight the importance of studying complete antibody-antigen interactions at the molecular level for the evaluation of 'designer antibody therapies' that would deliver the most effective and cost-effective outcomes for patients."

Moving forward, the team envisions that modeling and simulation will be incorporated into the design and selection of immunotherapies against metastatic cancer. ★

Photo credit: © Bioinformatics Institute (BII)

LEFT
Pertuzumab IgM (blue; shown as a monomer) can simultaneously bind to multiple extracellular domains of HER2 (represented in green and orange).
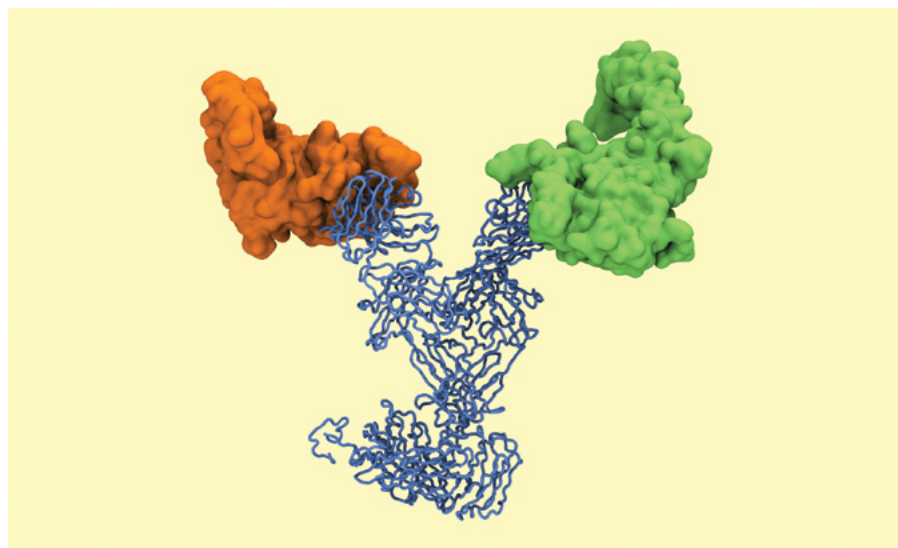
1. Samsudin, F., Yeo, J.Y., Gan, S.K., Bond, P.J. Not all therapeutic antibody isotypes are equal: the case of IgM versus IgG in Pertuzumab and Trastuzumab. *Chemical Science* **11** (10), 2843-2854 (2020).
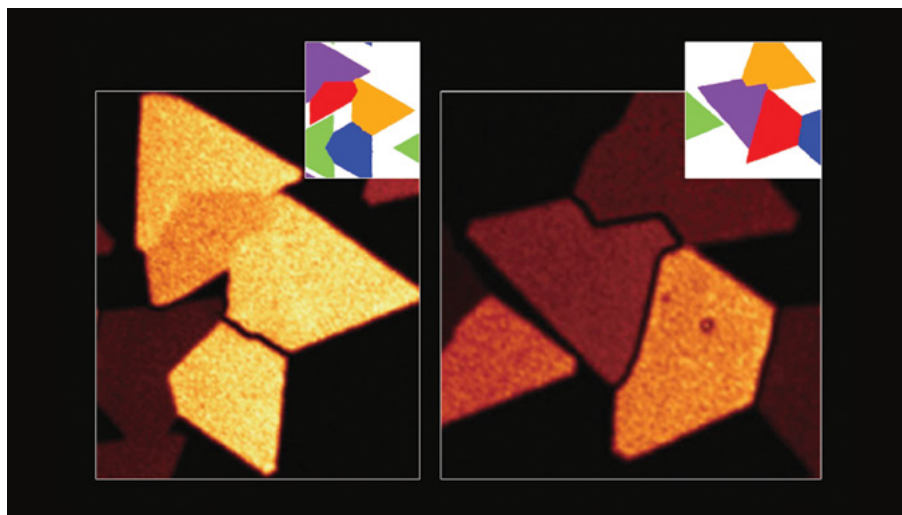
COMPUTATIONAL PHYSICS

Simulating the shapes of nanoflakes

New computer models show how semiconductor flakes with fancy shapes grow from simple starting points and rules.

Have you ever been told that every snowflake is unique? By the tiniest of degrees perhaps, but within each snowflake lies a universal six-sided symmetry that emerges from the orderly pattern of water molecules as they crystallize.

At the nanoscale, we can also find three-sided symmetry in the shapes of nanometer-sized flakes of molybdenum disulfide (MoS_2), a promising semiconductor material for the next generation of lighter and faster electronic devices. These 'nanoflakes' merge with nearby neighbors as they grow, forming complex clusters of multiple 'grains' with different crystal orientations.

To predict how grain boundaries form and spread as nanoflakes grow, researchers led by Yong-Wei Zhang at A*STAR's Institute of High Performance Computing (IHPC) developed computer simulations providing molecule-by-molecule replays of nanoflake growth.

Shuai Chen, a Scientist at IHPC, and colleagues accomplished this by using

> **"The grain boundaries where these different orientations meet are useful in some semiconductor devices and harmful in others."**

a probabilistic 'kinetic Monte Carlo' technique, which starts with multiple initial MoS_2 'seeds,' or nuclei, and then randomly adds atoms to available edges at rates consistent with experiments.

"Unlike in other models, we gave each nucleus its own lattice, letting each grain preserve its initial orientation as it grows. While this increases the computational cost greatly with each additional nucleus, it allows us to accurately predict the behavior of multi-grain growth and grain boundary formation," Chen said.

From different starting configurations, the researchers were able to grow complicated shapes like bowties, hexagons and six-pointed stars, and even merge two triangular crystals to resemble the 'fast-forward' icon. These shapes matched observations from various MoS_2-growing experiments—including those seen by collaborator Dongzhi Chi at A*STAR's Institute of Materials Research and Engineering (IMRE).

"We also showed that crystals meeting head-on had straight, smooth grain boundaries, while crystals growing at a glancing angle developed jagged grain boundaries instead," Chen said, noting that the grain boundaries where these different orientations meet are useful in some semiconductor devices and harmful in others.

The researchers have also simulated the effects of changing the molybdenum-to-sulfur input ratio or growing large single-grain flakes on terraced substrates. They ultimately hope to extend this method to both multi-layered structures and etching processes, creating a truly versatile toolkit for modeling semiconductor crystal flake growth. ★

ABOVE
Nanometer-sized flakes of molybdenum disulfide compared to grain boundaries predicted by simulation (insert).

1. Chen, S., Gao, J., Srinivasan, B.M., Zhang, G., Yang, M., *et al*. Revealing the grain boundary formation mechanism and kinetics during polycrystalline MoS_2 growth. *ACS Applied Materials & Interfaces* **11** (49), 46090-46100 (2019).

ADDITIVE MANUFACTURING

Smoothing the way for 3D-printed metal parts

A*STAR researchers have discovered that thin-walled metallic parts built via additive manufacturing are weaker than expected, initiating a search for solutions.

In science-fiction movies, advanced robots make copies of themselves by building complex objects of any shape and design from scratch. This is approaching reality with the rapid development of additive manufacturing, or 3D printing, where powders or filaments of input material are melted and converted into computer-aided designs.

Additive manufacturing allows thinner metal structures to be mass-produced with ease, inspiring manufacturers to replace solid metal components with thinner struts or lattices. Computer models can simulate the performances of lattices using standard material properties, and ensure that they can withstand the same mechanical load while using less material—or so the theory goes.

However, new research from A*STAR suggests that surface roughness can unexpectedly weaken 3D-printed metal parts, suggesting the need for caution. According to Pan Wang, a Scientist in the Metal and Ceramic Forming Group at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech), few researchers have studied the mechanical properties of additively-manufactured metal products.

Wang and his team have been studying a technique called electron beam melting (EBM), where a high-power electron beam is used to build an object layer by layer, by melting selected spots on a bed of metal powder. "While the hot process produces parts with no residual stress, and the vacuum environment remains clean and highly controlled, we wanted to know if and how the process of EBM can jeopardize the strength of the final product," Wang said.

To address these concerns, the researchers used the EBM technique to manufacture two car suspension wishbones, one using a conventional design and the other with thinner, computer-optimized walls. Mechanical testing revealed that the computer-optimized design was less stiff than the conventional design—and while the conventional design was strong enough to withstand a weight of over ten tons, the computer-optimized design was only able to bear 73 percent of the maximum load.

Further tests revealed that EBM samples of two millimeters or less in thickness had lower per-area stiffness and strength than thicker EBM samples under as-built conditions. This differs markedly from standard computer models, which assume that such material properties remain constant regardless of thickness. "Under the microscope, we found that although thinner EBM samples had finer microstructure, which implies a high strength, the rougher surfaces led to local flaws that weakened the metal overall," Wang said.

As Wang explained, these findings indicate that any new EBM designs need careful attention and testing before mass production, especially for the design of thin walls and struts. "We are preparing new databases for thickness-dependent mechanical properties, and updating simulation software to take these limitations into account," Wang said. Improving the surface finishing of 3D-printed metal can help to reduce local flaws and make full use of high strength microstructure of thin walls and struts, ultimately smoothing the path to end-user adoption. ★

Photo credit: Foundry / Pixabay

LEFT
Surface roughness can compromise the strength of 3D-printed metal parts.

1. Wang, P., Song, J., Nai, M.L.S., Wei, J. Experimental analysis of additively manufactured component and design guidelines for lightweight structures: A case study using electron beam melting. *Additive Manufacturing* **33**, 101088 (2020).

The defects that spark joy

Natural imperfections trigger a Kondo effect in 2D materials that bring their thermoelectric performance to new heights.

Electrical measurements

You're probably thinking of the wrong Kondo. Unlike how TV personality and author Marie Kondo keeps closets spotless and tidy, new research suggests that in thermoelectric materials, embracing and taking advantage of impurities—the Kondo effect—could show the way forward.

The thermoelectric caliber of any given material—that is, how well it can convert a temperature difference into electric power—often depends on three factors: the Seebeck coefficient, which is a measure of the temperature-induced voltage build-up, and its electrical and thermal conductivities. Ideal thermoelectric materials need to exhibit a high Seebeck coefficient and electrical conductivity, while simultaneously having low thermal conductivity.

The problem is that the Seebeck coefficient and electrical conductivity sit on opposite ends of a see-saw—when one rises, the other drops. Such an interdependency puts a cap on thermoelectric performance, as too much heat is needed to generate an underwhelming amount of power.

To break through this anti-correlation ceiling, a team including first author Wu Jing and co-corresponding author Kedar Hippalgaonkar, both Research Scientists at A*STAR's Institute of Materials Research and Engineering (IMRE), looked at naturally occurring defects in a two-dimensional stack of n-type molybdenum disulfide (MoS_2)

supported on a hexagonal boron nitride (h-BN) substrate.

These defects, which are caused by missing sulfur atoms within the MoS_2/h-BN lattice, could be observed using a technique called low temperature-scanning tunneling microscopy. "Thanks to our colleagues Yanpeng Liu and Kian Ping Low at the National University of Singapore, we were able to obtain high-resolution images of the defects, which helped to isolate the cause of our surprising results," Hippalgaonkar said.

The researchers propose that these sulfur vacancies could act like magnetic impurities and, at relatively low temperatures, trigger a Kondo effect in the MoS_2 flakes—scattering its conduction electrons, altering its band structure, and amplifying its thermoelectric properties.

> **"Our MoS₂/h-BN sample can exhibit both negative Seeback values due to its n-type nature, and positive Seebeck values by inducing band hybridization."**
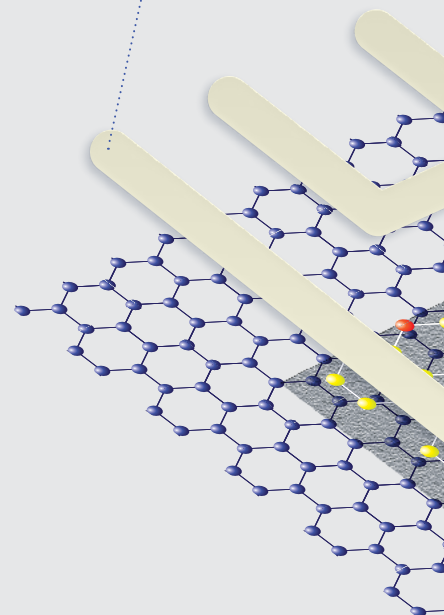
Indeed, when warmed to only around 60 K, Kondo scattering started to dominate the thermoelectric transport in the flakes. In turn, this drove the Seebeck coefficient up to an extremely large peak value of ~2 mV/K. At the same time, interactions between the electrons and impurities gave rise to a Kondo resonance effect, leading to an anomalous reversal in the Seebeck coefficient's sign, from negative to positive.

"Our MoS₂/h-BN sample can exhibit both negative Seeback values due to its n-type nature, and positive Seebeck values by inducing band hybridization," Jing said. "These results suggest that a singly doped material could be used to fabricate thermoelectric devices such as nanoscale cooling devices." ★

Heater

Thermometers

Titanium / gold

MoS₂

h-BN
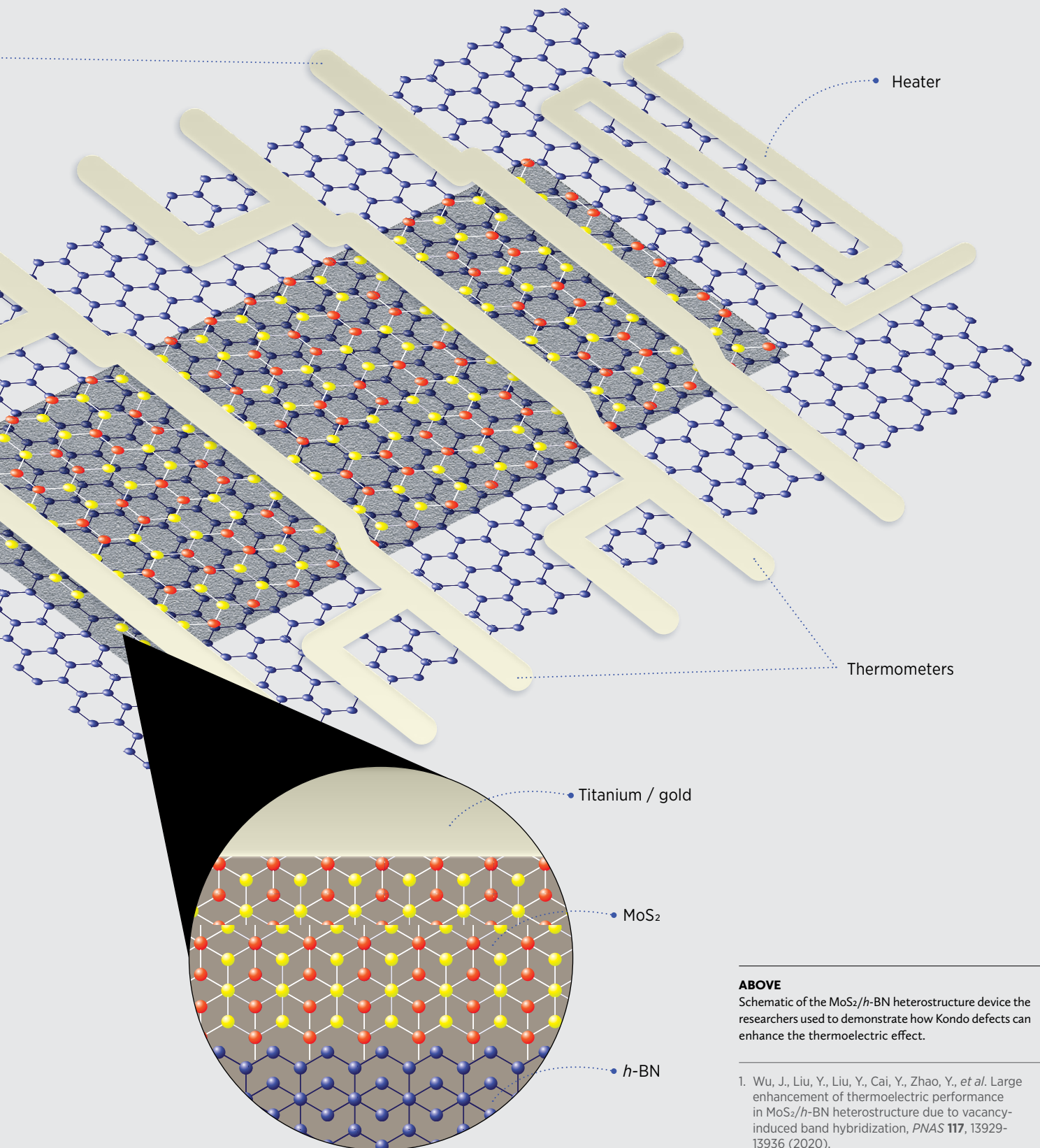
ABOVE
Schematic of the MoS₂/*h*-BN heterostructure device the researchers used to demonstrate how Kondo defects can enhance the thermoelectric effect.

1. Wu, J., Liu, Y., Liu, Y., Cai, Y., Zhao, Y., *et al*. Large enhancement of thermoelectric performance in MoS₂/*h*-BN heterostructure due to vacancy-induced band hybridization, *PNAS* **117**, 13929-13936 (2020).

Seeing (infra)red more clearly

Adding more crystals to a quantum optical infrared sensor improves its sensitivity and opens the door to broader use.

Thin films on water display a mesmerizing array of colors as beams of light bounce off the water surface and 'interfere' with each other—a brilliant demonstration of a physical phenomenon called interference.

In the lab, devices for precise measurement based on interference patterns—called interferometers—are used in applications ranging from analyzing biological samples to measuring time. Major advancements in the burgeoning field of quantum optics have led to the development of nonlinear interferometers, which enable the characterization of a sample's infrared properties using inexpensive components designed for visible light.

Nearly five years ago, Leonid Krivitsky, a Senior Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE), and colleagues were among the first to pioneer a low-cost, compact nonlinear interferometer that can detect infrared by measuring only visible light. However, the device used just two nonlinear crystals, placing a limit on its sensitivity.

"Conventional (linear) interferometers with N-elements are well known," Krivitsky said. "The most common configuration is a Fabri-Pérot interferometer, which consists of two opposing mirrors with the light 'bouncing' between them. We found that if we substitute standard mirrors with nonlinear crystals, the working principle remains the same."

And while theoretical studies on nonlinear interferometers have hinted that increasing the number of nonlinear elements can enhance their sensitivity, no such device existed until Krivitsky and his IMRE colleague, Anna Paterova, decided to build one—a stable and versatile nonlinear interferometer with up to five nonlinear crystals.

The researchers first performed a theoretical study to calculate ideal values for parameters including the wavelengths of the two quantum-linked beams and the orientation of each crystal. They confirmed that increasing the number of nonlinear crystals from two to five caused a narrowing of bright interference fringes or bands, improving the accuracy and precision of their device.

"The width of the interference fringes determines how accurately we can measure the phase shifts in the interferometer caused by the analyte," explained Krivitsky. "Thus, by increasing the number of nonlinear elements, we improve the sensitivity of the interferometer."

The researchers confirmed their theoretical findings by building and testing a nonlinear interferometer with two to five crystals. Importantly, they discovered that parameter setting, particularly the angle of each crystal, becomes increasingly important with the addition of more nonlinear crystals.

To show real-life applicability, the researchers confirmed experimentally that the five-crystal configuration had greater accuracy for detecting carbon dioxide gas over the two-crystal configuration.

"We are now working on realizing such interferometers using integrated optical chips," concluded Krivitsky. "By developing interferometers on a chip, it will allow us to achieve an increase in sensitivity down to the molecular level on a compact and robust platform." ★

ABOVE
By using five crystals instead of just two, scientists have improved the sensitivity of interferometers for sensing or quantum engineering.

1. Paterova, A.V. and Krivitsky, L.A. Nonlinear interference in crystal superlattices. *Light: Science & Applications* **9**, 82 (2020).

One Organisation, Multiple Careers

A*STAR is Singapore's lead public sector science and technology agency. A*STAR has a strategic R&D agenda, driving use-inspired basic research, advancing translational programmes, spearheading economic growth and advancing social well-being through scientific discovery, technological innovation and talent development.

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Agency for Science, Technology and Research
SINGAPORE

COMMEMORATING OUTSTANDING SCIENCE AND EXCELLENT SCIENTISTS

From genomics to gene editing and cancer research, the A*STAR winners of the 2020 President's Science and Technology Awards and Young Scientist Awards are blazing the trail in biological research.

For much of modern medicine's history, the 'one-size-fits-all' approach reigned supreme—with drugs and treatments broadly prescribed to large groups of patients. Thanks to advances in genomics and gene editing—along with increasingly sophisticated molecular biology techniques—we now know that a more tailored approach is key to treatment success.

Promising to advance personalized medicine in Singapore and beyond, three researchers from A*STAR—Jianjun Liu, Wei Leong Chew and Si Hui Tan—were recognized at the 2020 President's Science and Technology Awards (PSTA) and Young Scientist Awards (YSA) for their outstanding achievements in developing more effective treatments for various diseases.

Awarded annually since 2009, the PSTA represents the highest national honors that researchers in Singapore can receive. The awards are meant to recognize individuals or teams who have made invaluable contributions to the country's vibrant research and development landscape.

Carefully chosen by key representatives from industry, academia and research, the 2020 PSTA winners epitomize the best scientific talent Singapore has to offer.

The Young Scientist Awards (YSA), organized by the Singapore National Academy of Science and supported by A*STAR, recognize the accomplishments of researchers under 35, who have shown the potential to be world-class experts in their chosen fields.

CAPTURING ASIA'S GENETIC DIVERSITY

Despite accounting for over half of the world's inhabitants—a whopping 4.4 billion—Asian populations remain underrepresented in genetic studies. A 2019 analysis published in *Cell* revealed that of all the individuals included in genetic studies of disease to date, only 10 percent were Asian.

Seeking to address genetic research's glaring diversity gap, Jianjun Liu—Deputy Executive Director of A*STAR's Genome Institute of Singapore (GIS)—has made it his life's mission to place Asian genomes under the spotlight and herald a revolution in precision medicine.

Take the ancient disease leprosy, a disfiguring infection caused by *Mycobacterium leprae* that causes skin lesions and sensory loss. While no longer an epidemic of biblical proportions, over 200,000 new leprosy cases are still diagnosed each year. One effective treatment for leprosy is the antibiotic, dapsone. However, the drug can provoke a potentially fatal reaction in hypersensitive patients.

Through genome-wide association studies, Liu and his team discovered an Asian-specific biomarker called HLA-B*1301 was associated with the onset of dapsone hypersensitivity syndrome (DHS). According to their analysis, individuals with one copy of the biomarker are 34 times more likely to develop DHS, while those with two copies are 101 times more susceptible to the syndrome than those without. Thanks to Liu's pioneering work, leprosy patients are now screened for the presence of HLA-B*1301 before receiving dapsone.

Liu also helped identify specific strains of the Epstein-Barr virus (EBV) associated with nasopharyngeal carcinoma (NPC)—a nose cancer so common in South China that it is informally known as the 'Cantonese cancer.' By sequencing the genome of EBV isolates from patients and healthy people living in NPC-endemic regions, Liu and his team discovered two EBV variants that account for 83 percent of the risk of developing NPC. Similar to his leprosy research, these findings could be used to screen individuals and identify those who are at high risk for the cancer.

In his most ambitious project to date, Liu and his collaborators from the National University of Singapore, Duke-NUS Medical School and local public hospitals recently sequenced the genome of nearly 5,000 Singaporeans hailing from Chinese, Malay and Indian

Jianjun Liu
Deputy Executive Director
Genome Institute of Singapore (GIS)

ethnic groups. Their findings represent the world's largest genetic databank of Asian populations to date, capturing 80 percent of the region's genetic diversity in the process.

For his pioneering contributions to the genetic studies of Asian populations, Liu was awarded the 2020 President's Science Award (PSA). "This award is a recognition of the importance of studying Asian genetics," he said. "The award also recognizes the great research environment at GIS and A*STAR."

Even after winning the PSA, Liu has no plans of resting on his laurels. After all, there's still much work left to do. As of writing, around half of the 10,000 individuals targeted by his team's genome sequencing initiative have had their genomes sequenced. "Our study is just the beginning for the National Precision Medicine program," said Liu. "A much bigger study will be launched soon."

Liu also intends to intensify his efforts to sniff out the genetic roots of nose cancer. "We are working to discover additional EBV risk variants or strains in Southeast Asia, as well as develop biomarkers and diagnostic assays for population screening." Indeed, by shining a much-needed light on Asia's unique genetic heritage, Liu has cemented a legacy of his own.

→

Wei Leong Chew
Senior Research Scientist
Genome Institute of Singapore (GIS)

GEARING UP FOR GENE EDITING

Less than a decade after CRISPR burst into the public imagination, the gene-editing technology had already garnered its pioneers Emmanuelle Charpentier and Jennifer Doudna the Nobel Prize. Considering that scientists often wait around 20 years or more for the coveted award, CRISPR's fast-tracked recognition is a testament to its sheer impact on biological research.

Today, CRISPR has become a mainstay in molecular biology laboratories worldwide. As a Senior Research Scientist at GIS, Wei Leong Chew is rewriting the code of life by enhancing gene editing and gene therapy delivery techniques. For instance, Chew was one of the first to successfully achieve gene editing across multiple organs of live mammals—opening up possibilities for the correction of various genetic diseases. Previously, CRISPR had only been applied in cell culture.

Chew also provided early proof that CRISPR delivery with an adeno-associated virus (AAV) vector triggered an immune response in mice—providing an initial glimpse into the safety of CRISPR-based therapeutics. Accordingly, to safely bring these therapeutics from bench to bedside, his team is now working to predict and minimize the adverse immune reactions to gene editing.

In light of his seminal efforts to advance gene-editing therapy, Chew was recognized with the 2020 Young Scientist Award under the Biological & Biomedical Sciences category. "I am tremendously honored and humbled to be awarded," he said. "This a strong testament to the excellent science that our team is doing. This also emphasizes the fantastic environment at A*STAR, where we can come together as one team to solve pressing issues in Singapore and globally."

Much like Liu, Chew has no plans of resting anytime soon. "Our research is moving faster than ever before," he shared. "We have recently developed a new class of precision gene editing technology, called C-to-G base editors, that changes a single letter within the human genome in unprecedented ways." His team is also currently working on novel molecular assays, as well as therapeutics for diseases long considered incurable. By reassembling life's building blocks, Chew is paving the way for better, safer and more effective medicines.

STAMPING OUT CANCER STEM CELLS

Since their discovery in mice in 1981, stem cells have been widely touted as a panacea for diseases ranging from leukemia to vision loss. Despite their status as a miracle treatment, stem cells also have a sinister counterpart: cancer stem cells.

As indicated by their name, cancer stem cells possess characteristics associated with regular stem cells. That is, they can self-renew and give rise to the various cell types found in tumors. These cancer stem cells, therefore, act as a reservoir that can result in relapses. Unless these cancer stem cells are unequivocally eliminated, the tumor will continue to grow back—similar to how weeds repeatedly return time and time again.

Si Hui Tan, formerly a Research Scientist in Nick Barker's laboratory at A*STAR's Institute of Medical Biology (IMB), has devoted her career to weeding out these cancer stem cells. "My interest in stem cells came to the fore because of the discovery of cancer stem cells when I was about to embark on my PhD," she shared.

Focusing on gastric or stomach cancer, which is especially common in Asia, Tan identified aquaporin-5 (AQP5) as a new marker that can be used to isolate human stomach cells. Notably, AQP5 may also be a marker for gastric cancer stem cells—and an intriguing new target for drugs in development.

For her contributions to cancer stem cell research, Tan received the 2020 Young Scientist Award under the Biological & Biomedical Sciences category. "It is heartening to see that purposeful and rigorous basic science is valued by our society," said Tan. "Basic science is the key foundation for future translational discoveries."

After making waves in cancer research at A*STAR, Tan is now leading a research team at local start-up Cargene Therapeutics. "We have a multidisciplinary team working on oligonucleotide therapy for various indications," she explained. In oligonucleotide therapy, chemically synthesized nucleic acids silence gene expression by binding to a target nucleic acid.

Along with local quantum computing start-up Entropica Labs, Tan is also harnessing artificial intelligence to dole out personalized cancer diagnoses based on signaling pathways. With her innovative approach and drive for excellence, Tan will surely thrive in whatever field she chooses to explore. ★
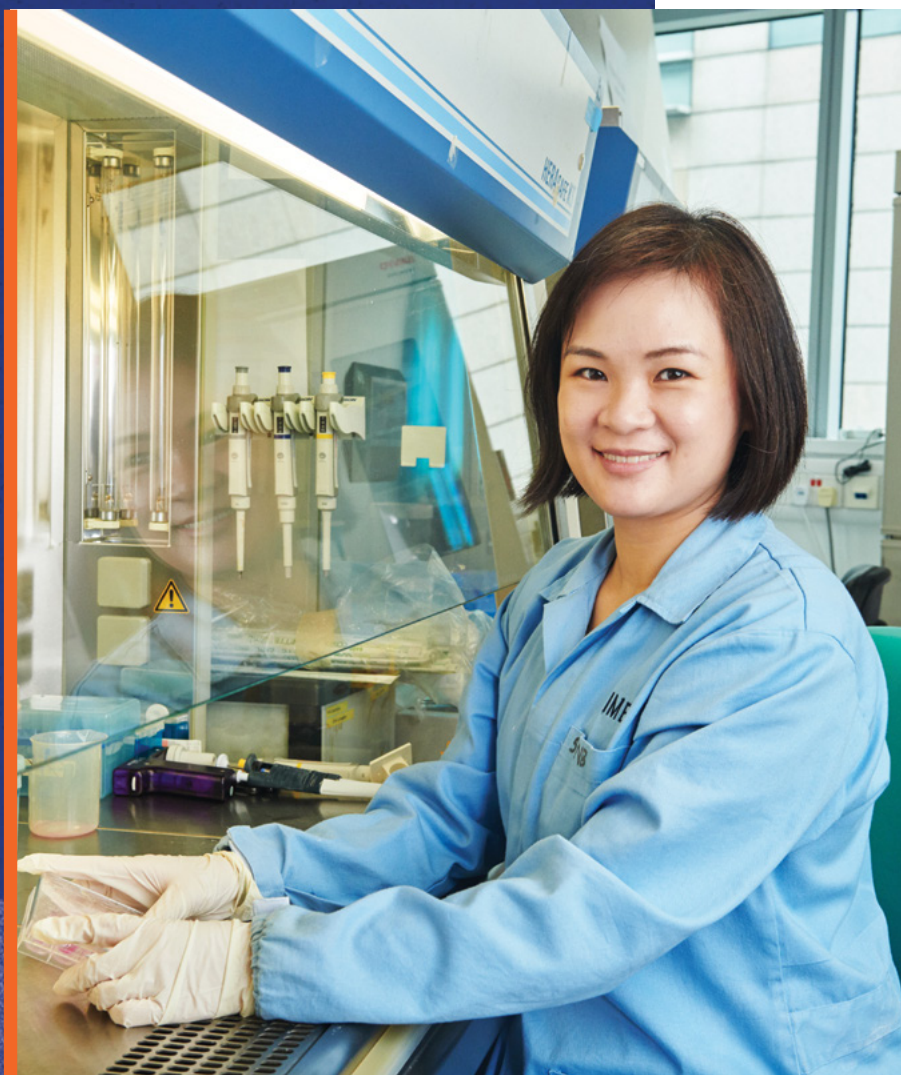
Si Hui Tan
Associate Director
Biology Cargene Therapeutics

POLYMER SCIENCE

Transforming common plastics into powerful antimicrobials

Researchers are upcycling plastic waste into antimicrobial products to fight some of the most challenging bacterial infections.

Much of the achievements of modern medicine can be attributed to antibiotics, without which even routine surgery can quickly turn into a life-threatening infection. However, drug-resistant bacteria are beginning to evolve, threatening to undo decades of progress in global health, particularly for diseases like tuberculosis.

Instead of targeting specific bacterial proteins, antimicrobial peptides kill bacteria by targeting their negatively charged cell membrane. Scientists have mimicked this effect using positively charged polymers called polyionenes, which insert themselves into the bacteria membrane. "Polyionenes destabilize the phospholipid bilayer so that the bacteria have no chance to develop resistance," explained Yi Yan Yang, Covering Executive Director of A*STAR's Institute of Bioengineering and Nanotechnology (IBN).

In a finding that addresses the challenge of antibiotic resistance while recycling plastic waste at the same time, Yang and her team have developed a simple chemical process to turn one of the most common plastics into bacteria-killing polyionenes.

The team first broke polyethylene terephthalate (PET) down into three different monomers, using an inexpensive process that did not require catalysts or solvents. They then built up a library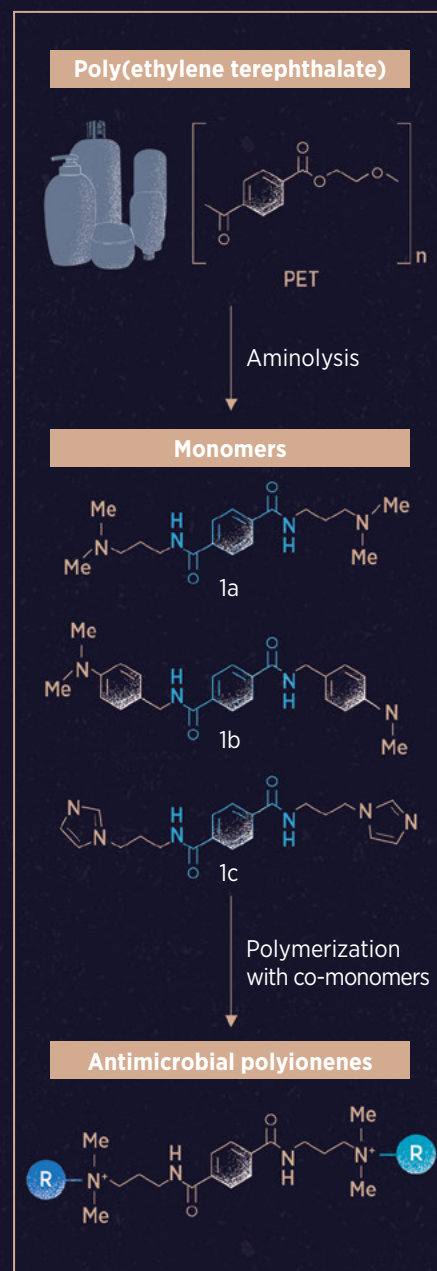 of potential polyionenes synthesized using different combinations of monomers, selecting those that were able to kill bacteria cells while leaving human red blood cells intact.

"We found that the hydrophobic-hydrophilic balance of the polymers ensures that we have the best in terms of antimicrobial activity and selectivity towards microbes over mammalian cells," Yang said.

One of the resulting polyionenes was even able to kill *Mycobacterium avium*, which, like the closely related *M. tuberculosis* bacteria, is difficult to treat because it resides inside the host cell. "The polyionenes might enter the mammalian cell by diffusion before eliminating the intracellular microorganisms based on the membrane-disruption mechanism," Yang said.

"From our studies, repeated treatment of bacteria over many passages using the polyionenes at sub-lethal doses did not increase the effective concentration of the polyionenes. In contrast, multiple treatments with antibiotics significantly increased their effective concentration," Yang said.

The researchers have filed for a patent on their process, which effectively turns plastic waste into a potent antimicrobial. This study is part of an ongoing collaboration with James Hedrick from the IBM Almaden Research Center.

"We are not only recycling the PETs, but upcycling them into antimicrobial products," added Yang. "In the future, we hope they can be used as disinfectants for the prevention of bacterial infections." ★

Poly(ethylene terephthalate)

PET

Aminolysis

Monomers

1a

1b

1c

Polymerization with co-monomers

Antimicrobial polyionenes

1. Tan, J.P.K., Tan, J., Park, N., Xu, K., Yang, Y.Y., *et al*. Upcycling poly(ethylene terephthalate) refuse to advanced therapeutics for the treatment of nosocomial and mycobacterial infections. *Macromolecules* **52**, 7878-7885 (2019).

POLYMER SCIENCE

Making plastic easier to recycle

A semi-batch approach to making acrylics could bring us one step closer to more planet-friendly plastics.

Acrylics, like their other plastic cousins, have always posed a tricky cost-benefit question. Seen in everything from paints to personal care products, acrylate-based polymers are incredibly useful, but are also tough on the planet. Most are non-biodegradable, and often end up in landfills or the open environment, making the end-of-life fate of acrylics a major dilemma for manufacturers and consumers alike.

An approach that is being studied is to copolymerize the acrylate building blocks with cyclic monomers that ring-open during manufacturing. The result is a large molecule chain with weak ester links that help with its degradability and could make those polymers more easily recyclable. This process, though, is inefficient and wasteful, often yielding heterogeneous products and leaving a lot of the monomers unreacted.

Led by Alexander van Herk and Praveen Thoniyot, Principal Scientist and Senior Scientist at A*STAR's Institute of Chemical and Engineering Sciences (ICES), a team of A*STAR researchers

> **"A very exciting step is that we are now also looking at polyethylene (LDPE), an important polymer for packaging."**

turned to semi-batch polymerization in hopes of optimizing this process.

Rather than having both reactants be completely present right from the start, the team gradually added the acrylate units to the cyclic monomers as the reaction progressed. To figure out the rate at which acrylate should be fed into the reaction, they used a predictive software called Monomer Addition Profiles (MAP), which takes into account the tendency of either monomer to attach to the growing end of the polymer chain.

The idea was that because acrylate units are much more reactive than cyclic monomers, controlling its entry into the reaction would prevent it from getting used up all at once, and instead allow both reactants to incorporate and intersperse evenly throughout the polymer.

The team saw that when they broke down the semi-batch polymers through alkaline hydrolysis, the pieces were roughly of the same size, suggesting that the weak links had indeed been integrated homogeneously. On the other hand, fragment sizes from the degradation of batch-processed polymers were much more varied, evidence of a haphazard assembly of the monomers.

According to van Herk, this homogeneity comes with many benefits. Small fragment sizes, for instance, are much more readily biodegradable, and having oligomers of roughly the same size makes it easier to repurpose and recycle them into other polymers.

Moving forward, the team wants to see how their approach could help solve the plastic crisis. "For some specific copolymers such as polyacrylates, we are also looking at biodegradability; for others like polystyrene we are looking at recyclability. A very exciting step is that we are now also looking at polyethylene (LDPE), an important polymer for packaging," said van Herk. ★

ABOVE
Acrylics—plastics found in everything from fish tanks to clothes—have now been made easier to recycle.

1. Lena, J., Jackson, A.W., Chennamaneni, L.R., Wong, C.T., Lim, F., *et al*. Degradable poly(alkyl acrylates) with uniform insertion of ester bonds, comparing batch and semibatch copolymerizations. *Macromolecules* **53**, 3994-4011 (2020).

Ultrasound imaging, the green way

Lead-free piezoceramics sacrifice performance for lower toxicity, but A*STAR researchers have developed a method to overcome that.

From the insides of your body to the deepest foundations of a building, ultrasound is an important way to visualize what the human eye can't. The key to each of these ultrasound imaging devices is a little component—called an ultrasonic transducer—that generates ultrasound waves with electrical signals and also converts the mechanical pressure exerted by ultrasound waves into electrical signals that the imaging devices can read.

For this reason, ultrasonic transducers must be made of special materials, such as piezoceramics, which can change their shape when an electric field is applied. However, commercial piezoceramics can contain more than half their weight in lead, such as in the form of the widely used lead zirconate titanate (PZT).

"Commercial piezoelectric ceramics contain a large amount of toxic lead, typically more than 50 percent by weight," explained study co-corresponding author Kui Yao, a Principal Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE).

"For environmental concerns starting from material manufacturing to waste disposal, it is desirable to be able to obtain lead-free alternatives to replace existing lead-based materials in devices."

Concerns over lead toxicity have driven the need to find lead-free piezoelectric materials and transducers, but current lead-free alternatives are both unstable at high temperatures and perform poorly. Yao and colleagues in Singapore and China have now discovered a new lead-free piezoceramic material that is suitable for practical use in devices, made from potassium sodium niobate (KNN).

"KNN-BNZ-AS-Fe is a ceramic with a complex lead-free composition that can achieve coexistence of multiple crystalline phases," Yao said. "This is an important structural feature for a piezoelectric material to have because it makes the material highly responsive to external stimuli, including ultrasound waves or electric fields."

On top of that, the engineered piezoceramic performed well, displaying both a strong piezoelectric response and stability under high temperature. These results indicate that the strategy of appropriately engineering the piezoceramic's structure to allow for multiple-phase coexistence can improve its piezoelectric performance and stability, the team noted.

Thanks to its stability and impressive piezoelectric properties even at high temperatures, an ultrasonic transducer using this new KNN-BNZ-AS-Fe ceramic could be a promising lead-free alternative to be used in piezoelectric-dependent devices such as ultrasonic transducers.

"We have demonstrated that the KNN-BNZ-AS-Fe ceramic has excellent and stable piezoelectric properties, and its performance as an ultrasonic transducer is competitive to those of PZT–based transducers," Yao shared. ★

LEFT
Lead-free piezoceramic materials could help usher in safer and more environmentally friendly ultrasonic sensors.

1. Zheng, T., Zhang, Y., Ke, Q., Wu, H., Liew, W.H., *et al*. High-performance potassium sodium niobate piezoceramics for ultrasonic transducer. *Nano Energy* **70** (2020).

Photo credit: Funtay / Shutterstock

MATERIALS SCIENCE

Two catalysts are better than one

A composite from two molybdenum-based catalysts could boost the efficiency and lower the cost of ammonia production.

Over 100 years after Fritz Haber won the Nobel Prize for the synthesis of ammonia from its elements nitrogen and hydrogen, the process he pioneered remains the main industrial method for making the foundational compound found in nitrogen-based fertilizers. More recently, a newer method—called the nitrogen reduction reaction (NRR)—is being touted as a more cost-effective and sustainable alternative.

In NRR, ammonia can be produced at standard conditions using electricity and two of the world's most abundant compounds: nitrogen and water. But limiting factors are the sluggish adsorption of N_2 and the high cleavage energy of the N-N triple bond. Another is the attendant hydrogen evolution reaction (HER), which occurs in competition with NRR.

> **"Molybdenum-based materials are regarded as one of the most promising catalysts for the nitrogen reduction reaction."**

In the past few years, the search for better catalysts has revealed that the element molybdenum—chemical symbol Mo—and Mo-based compounds like Mo_2C have the ideal configuration of electrons needed to weaken the bond in N_2. On their own, however, Mo and Mo_2C catalysts have different selectivity and are suboptimal for NRR.

A team of researchers from Singapore and China, including co-corresponding author Xu Li, a Senior Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE), predicted that combining Mo and Mo_2C into a composite catalyst could have a synergizing effect and ultimately boost ammonia production. Their new study provides evidence for this theory.

"Molybdenum-based materials are regarded as one of the most promising catalysts for NRR. In our catalyst system, the two active parts with different selectivity—Mo single atoms and Mo_2C nanoparticles—are mutually compensated through a synergistic interaction," explained Li.

Using theoretical calculations, the researchers first showed that Mo_2C is more selective for NRR, while Mo single atoms are more selective for HER. They then

went on to create and test three catalysts: Mo single atoms, Mo_2C nanoparticles, and a composite catalyst called MoSAs-Mo_2C/NCNT.

Performing NRR at room temperature and atmospheric pressure, the researchers found that MoSAs-Mo_2C/NCNT boosted the reaction speed by up to 4.5 times and efficiency by up to seven times, compared to Mo single atoms. The composite catalyst was incredibly stable, maintaining the same level of activity for over ten hours.

Next, the researchers plan to test their catalyst in larger-scale reactions. However, they caution that more research is needed before these composite-type catalysts can be relevant in industrial applications.

"A substantial challenge for composite-type nanomaterials is to control the ratio and distribution of the two or more different phases," Li said. "A deeper understanding of the mechanism in each case is urgently needed." ★

ABOVE
Catalysts made out of molybdenum could make the production of ammonia greener and more energy efficient.

1. Ma, Y., Yang, T., Zou, H., Zang, W., Kou, Z., *et al*. Synergizing Mo single atoms and Mo_2C nanoparticles on CNTs synchronizes selectivity and activity of electrocatalytic N_2 reduction to ammonia. *Advanced Materials* **32**, e2002177 (2020).

Single-layer

Bilayer

Metalized
indium / WS₂

Semiconducting WS₂
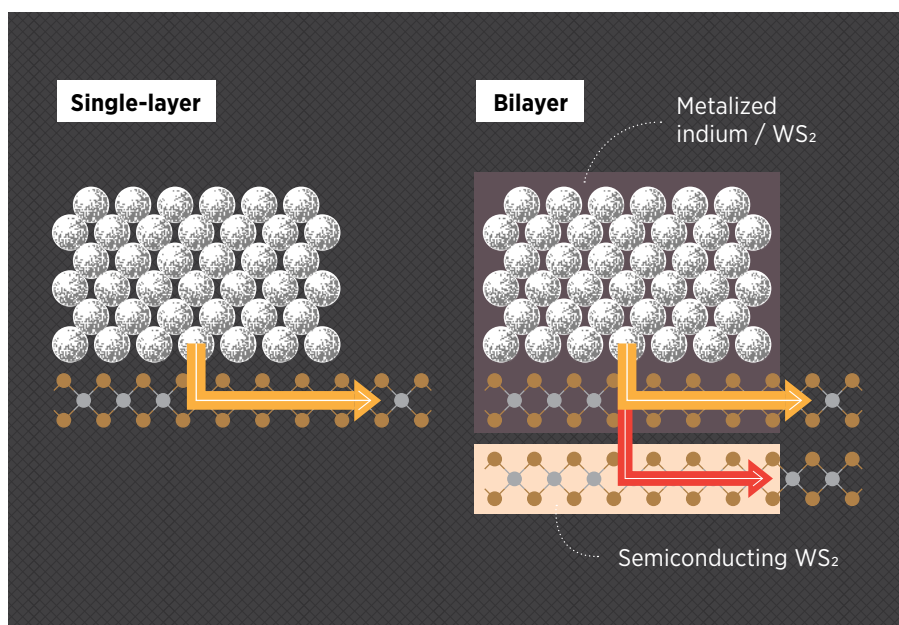
QUANTUM COMPUTING

Frozen: The quantum edition

To unlock the potential of quantum computers, researchers must find semiconductor materials and metal contacts that work well at sub-zero temperatures.

Imagine a computer so blazingly fast and impenetrable that no hacker can crack it. This is not science fiction: this is a real-world application of quantum computing, an emerging field that exploits the specific energy states of semiconductor materials to create devices with incredible processing power.

Now imagine having to operate this quantum computer at temperatures as low as 4 Kelvin, or -270 degrees Celcius. These sub-zero conditions are necessary as the fragile quantum state of these devices are susceptible to a physical phenomenon—heat.

In search of novel semiconductor materials that can withstand cryogenic temperatures, a team led by Kuan Eng Johnson Goh, a Principal Investigator at A*STAR's Institute of Materials Research and Engineering (IMRE), focused on tungsten disulfide (WS₂), a two-dimensional transitional dichalcogenide (TMDC) semiconductor material.

Unlike molybdenum disulfide (MoS₂), its well-studied TDMC counterpart, WS₂ is expected to have higher carrier mobility due to its lower effective mass compared to MoS₂. However, WS₂ remains poorly understood due to the low quality of materials available

and the lack of a robust contact strategy needed to probe its electronic quality. "Forming reliable contacts is the first step towards building quantum devices," said Chit Siong Lau, the lead author of the study.

Goh and colleagues selected an indium alloy for the metal contacts in their devices, based on a technique pioneered by co-author Manish Chhowalla at the University of Cambridge. Indium alloy contacts help to improve electron transport performance in quantum devices by overcoming contact resistance.

They built two WS₂ devices: single-layer and bilayer devices, and showed that both devices fared excellently down to 3 Kelvin, thanks to the high quality of the indium alloy contacts at these chilly conditions. The bilayer device, however, had one advantage: because electrons tend to travel in the top layer, the bottom layer acted as a protective layer, shielding electrons from defects in either the metal substrate or along the WS₂–indium interface.

These experimental findings were supported by density-functional theory simulation studies, which provided insights into quantum transport and the properties of the WS₂–indium interface.

Beyond the bilayer device, Goh's team is now looking to design a trilayer device—a 'sandwich' device that will shield the WS₂ layer from defects in the substrate and contaminants in the environment. "Our research unlocks the commercial potential of WS₂ for diverse applications such as transistors, optoelectronics, flexible electronics, photodetectors and sensors, as well as in low-temperature quantum devices for quantum information processing," Goh said. ★

ABOVE
While both single-layer and bilayer WS₂ devices functioned well at low temperatures, the bottom layer of the bilayer device shielded electrons from defects both within the metal substrate and along the WS₂–indium interface.

1. Lau, C.S., Chee, J.Y., Ang, Y.S., Tong, S.W., Cao, L., *et al.* Quantum transport in two-dimensional WS₂ with high-efficiency carrier injection through indium alloy contacts. *ACS Nano* **14** (10), 13700-13708 (2020).

An ultrathin shield defends against cyberattacks

Instead of software, hardware that can generate true random numbers could be the key to ensuring cybersecurity.

It's all online: from shopping and banking to work meetings and social networking, the internet is an indispensable part of our daily lives. Being connected, however, can be a risky business. Our devices are vulnerable to cyberattacks—increasingly sophisticated attempts by hackers to maliciously disable computers or steal data.

One way to protect sensitive data is to use encryption, a process of scrambling the information using random numbers that are known only to the sender and receiver of the message. Currently, these random numbers are approximated by software, which could be hacked. "True random numbers are preferred but also more challenging to achieve as they should follow certain statistical rules to ensure the

> **"Our method of generating multiple random states within a single cell helps to reduce the amount of hardware used."**

integrity of the randomness," explained Dongzhi Chi, a Principal Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE).

Instead of software, Chi and his team turned to hardware to generate true random numbers, exploiting the intrinsic randomness in the physical properties of a resistive random-access memory (ReRAM) device.

Although ReRAMs have been proposed as true random number generators in the past, they tend to degrade over time, ultimately leaving weak spots in the computer's cybersecurity armor. To improve the stability of their ReRAM device, the researchers used repeated ultrathin layers of a semiconductor called MoS_2, sandwiching them between insulating polymers. "This structure allowed us to keep the thickness of the active layer to a few nanometers without sacrificing the electrical properties," added study co-corresponding author Henry Medina, a Research Scientist at IMRE.

The new and improved ReRAMs were put to the test in a single cell which displayed ten random states—five times more than the typical binary random states. "Normally, random numbers are generated in a binary way, providing '1' or '0' states," Chi explained. "Our method of generating multiple random states within a single cell helps to reduce the amount of hardware used."

Now that they have applied for a patent on their invention, the team is looking to transition this technology to an industrial setting. Tackling the efficient production scale-up and reducing mechanical damage during manufacturing are among their primary concerns.

"After achieving these goals, we should be in a good position to engage industry partners for possible technology transfer, licensing or a potential start-up," said Chi. ★
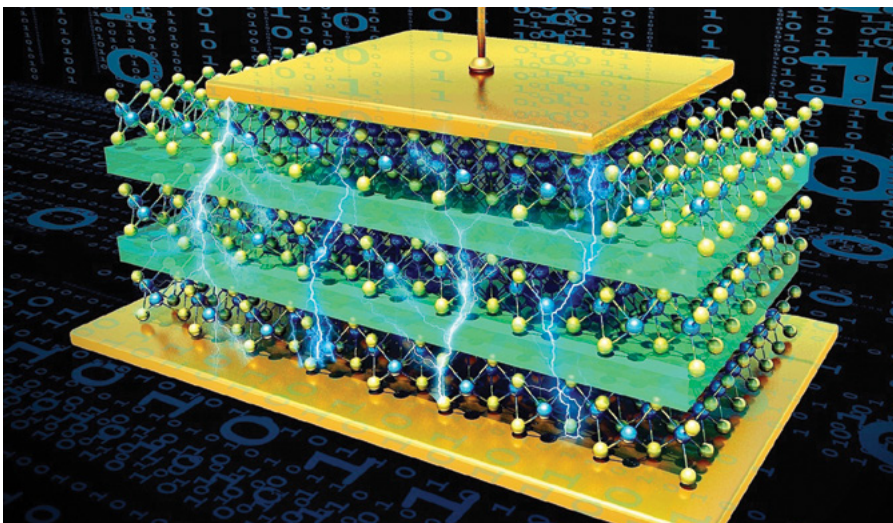
Researchers have made use of the inherent randomness in a resistive random-access memory device to generate true random numbers for cybersecurity.

Photo credit: © Institute of Materials Research and Engineering (IMRE)

1. Chai, J., Tong, S., Li, C., Manzano, C., Li, B., *et al*. MoS_2/Polymer heterostructures enabling stable resistive switching and multistate randomness. *Advanced Materials*, 2002704 (2020).

Seeing clearly through the haze

A promising new computational model can recreate clean images out of hazy ones.

If you've ever spent a day out in the haze, you might have noticed how difficult it is to see anything. But your human eyes aren't the only ones that struggle in such conditions—digital vision sensors and computer vision algorithms take a hit too, with potentially serious implications for systems that rely on a clear vision, such as video surveillance cameras or autonomous vehicles.

Because the smoke or dust particles that make up haze create a kind of non-additive noise, hazy images can't be resolved with just simple contrast enhancement methods. Instead, haze removal relies on the accurate estimation of two factors: global atmospheric light and the transmission map, which is the path of light that is not scattered.

Unlike most existing methods that estimate these two parameters separately, which reduces efficiency and accuracy,

researchers led by Hongyuan Zhu, a Research Scientist at the A*STAR Institute for Infocomm Research (I²R) on secondment to the Institute of High Performance Computing (IHPC), have created a new model that applies a generative adversarial network (GAN) to single-image dehazing for the first time.

With their two-network architecture, GANs can be used to produce high-quality images in tasks such as image generation

> **"The resulting model, aptly named DehazeGAN, has been shown to reliably recover clean images from hazy ones and outperform state-of-the-art methods."**

and object detection. The resulting model, aptly named DehazeGAN, has been shown to reliably recover clean images from hazy ones and outperform state-of-the-art methods.

"The noise created by haze is material and distance-dependent, according to the atmospheric scattering model. DehazeGAN is the first end-to-end method that solves the image 'dehazing' problem by embracing this model," Zhu said.

DehazeGAN's success lies in its two components: a novel compositional generator, which enables DehazeGAN to directly learn the physical parameters from data, and a novel deeply supervised discriminator, which ensures clean image output.

"Our method achieves superior performance in all metrics thanks to physical modeling and adversarial learning," he shared. "Moreover, it models the recovery process as a highly efficient, fully convolutional neural network with real-time performance."

According to the Zhu, DehazeGAN can be used to enhance the quality of vision sensors in autonomous vehicles or mobile phones, as well as the robustness and accuracy of existing computer vision systems under adverse weather conditions.

To test DehazeGAN's performance, the researchers created the HazeCOCO dataset of synthesized haze images, which they have shared for use in other single-image 'dehazing' efforts.

"HazeCOCO is currently the largest haze dataset with various diverse visual patterns for learning discriminative 'dehazing' features, which can benefit further research in this field," said Zhu. ★

BACKGROUND
The DehazeGAN model is a generative adversarial network that can recover clean images from hazy ones.

1. Zhu, H., Cheng, Y., Peng, X., Zhou, J.T., Kang, Z., *et al.* Single-image dehazing via compositional adversarial network. *IEEE Transactions on Cybernetics* **10**, 1109 (2019).

MACHINE LEARNING

Machine learning gets a new syllabus

A new deep learning method increases the accuracy and range of applications for computer vision platforms.

A new computer vision training regime called Deep Negative Correlation Learning could help machines become better at counting people in a crowd.

It takes just a split second for you to count how many people are in the elevator because human neural networks make the process of recognizing, processing and interpreting information based on visual cues seem effortless. Unsurprisingly, it is much more tedious for computers to do the same, and the science of computer vision is so much more than simply plugging a camera into a computer.

Take, for example, the task of counting the number of people at a park, based on live-streamed video footage. Computational models serve as the analytical powerhouse, allowing the computer to make predictions based on the relationship between dependent variables (in this case, the number of people) and independent variables (images of the park). While current computer vision platforms can accurately count how many joggers there are on a track, problems creep up when it has to count people sitting close together, or when some are closer to the camera than others.

"Crowd counting and age estimation are challenging because they need the machine to have a high-level global understanding of the input images," said study first author Le Zhang, a Scientist at A*STAR's Institute for Infocomm Research (I²R). "For crowd counting, significant hurdles occur due to occlusions, scale variations and diverse crowd distributions. As for age

estimation, one major difficulty is that different people age in different ways."

To better 'teach' computers to accurately identify and classify objects from input images, Zhang and an international team of researchers have come up with a new computer vision training regime called Deep Negative Correlation Learning, or DNCL. This method first divides large training tasks into bite-sized sub-problems. Then, unlike former platform iterations, DNCL trains the system to recognize large pools of regression relationships at a time.

The researchers validated the system in a range of diverse and challenging real-world

"We report four real-world applications in the paper: crowd counting, age estimation, image super-resolution and apparent personality analysis."

applications with exciting results. "We report four real-world applications in the paper: crowd counting, age estimation, image super-resolution and apparent personality analysis," said Zhang. "Our method also inspires some interesting follow-up studies for low-level computer vision tasks."

As the authors describe it, their 'divide and conquer' approach is a huge advancement in terms of efficiency, as it mimics an ensemble-learning system without increasing the number of parameters, and yields superior results such as super-resolution images with sharper edges.

"We are now generalizing this work to the classification scenario where the output targets the discrete category labels," added Zhang, with future work set to tackle even more challenging computer vision applications. ★

1. Zhang, L., Shi, Z., Cheng, M.M., Liu, Y., Bian, J.W., *et al.* Nonlinear regression via deep negative correlation learning. *IEEE Transactions on Pattern Analysis and Machine Intelligence* (2019).

NEXT ISSUE

Here's a sneak peek of the material covered in the next issue of *A*STAR Research*

MACHINE LEARNING
TAKING FASHION FROM STREETS TO SHOPS

Researchers have created a new computational framework that is set to transform the online shopping experience.

ARTIFICIAL INTELLIGENCE
A MAN-MACHINE WINNING TEAM

Leveraging both artificial intelligence and field knowledge may prove to be a superior strategy for predicting machine health.
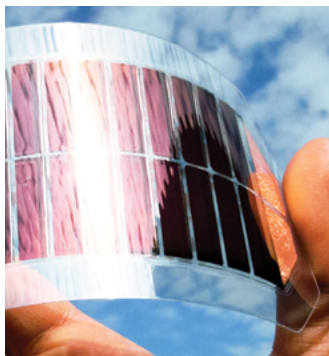
MATERIALS SCIENCE
SPINNING A WAY TO FLEXIBLE ENERGY HARVESTERS

Flexible polymers capable of turning physical movement into electricity will soon power the future of wearable devices.
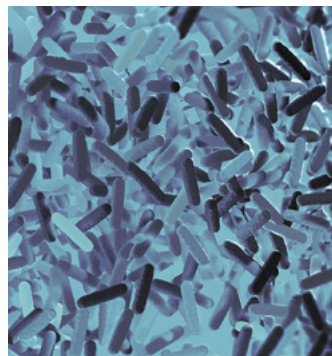
EPIDEMIOLOGY
CLUES TO CHILDHOOD OBESITY LIE IN OUR GUT

Early exposure to antibiotics can disrupt an infant's gut microbiota and predispose them to childhood obesity, finds an observational study.

A*STAR
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