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EDITORIAL

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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.

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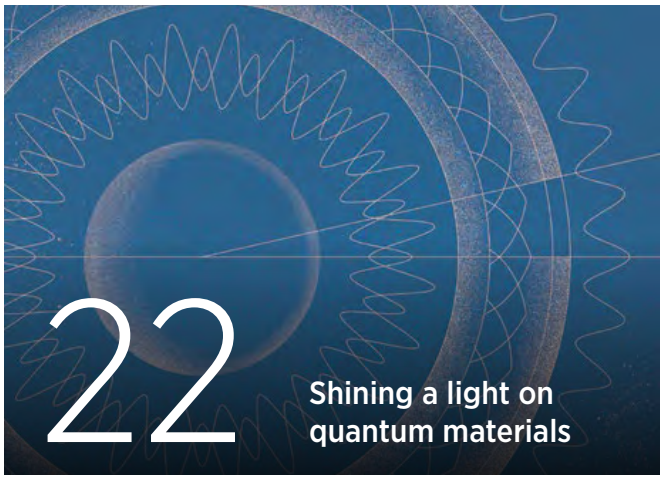

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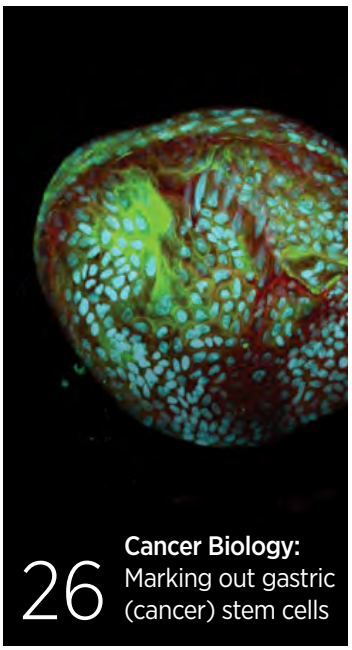

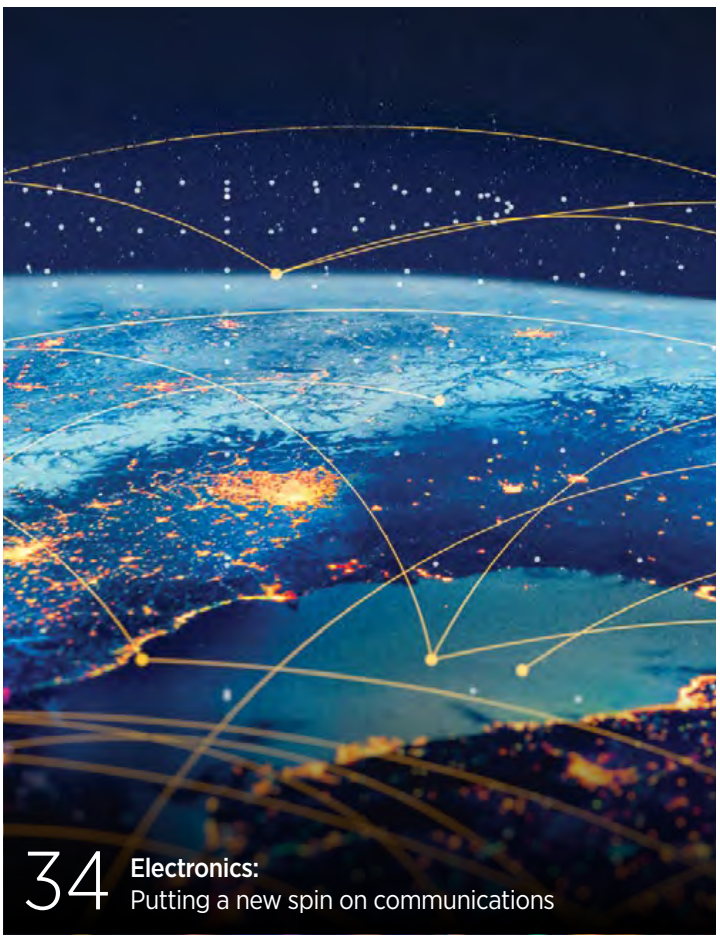

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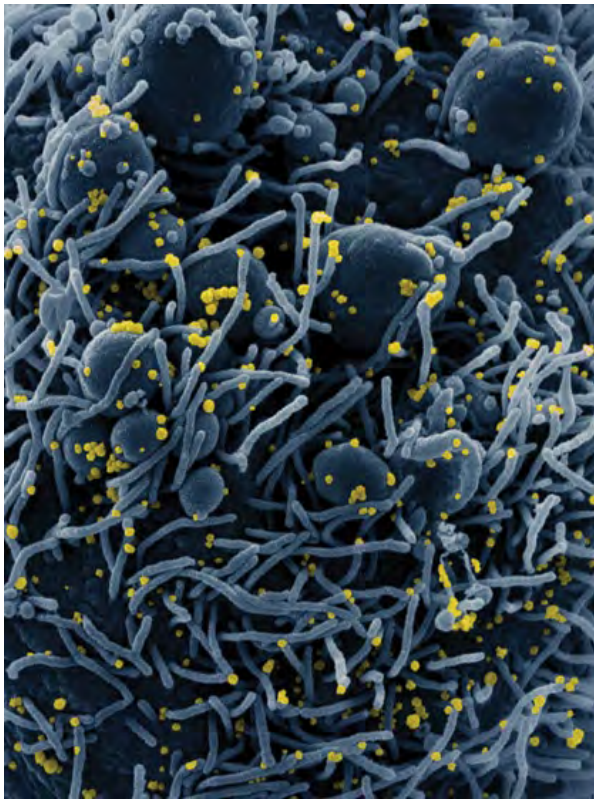


Credit: NIAID

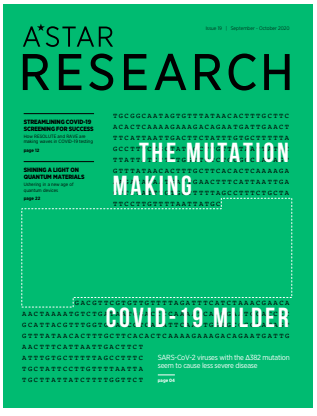
Having already infected 26 million people around the world and taken the lives of nearly 900,000, COVID-19 has plunged the world into turmoil. Yet amid the tragic loss of human life and untold economic impact, there is steady progress being made and even pockets of good news—all thanks to scientific research.

For one, the virus appears to be adapting to humans and becoming milder. In our cover story 'The mutation making COVID-19 milder (p.04),' find out how a mutation called Δ382 seems to result in a strain of SARS-CoV-2 that causes less severe symptoms. In a further positive development, A*STAR researchers have discovered that although antibodies against SARS-CoV-2 might not last as long as hoped, people might be able to fight off the virus using a different branch of the immune system: T cells. Read about how T cells are involved in COVID-19 immunity in 'The immune system remembers' on p.09.

While some researchers race to find out more about the virus and the immune response to it, others have poured their efforts into accelerating the technologies that could help us contain the outbreak. In our Industry Impact features, 'Streamlining COVID-19 screening for success (p.12)' and 'Assuring asymptomatic COVID-19 carriers are identified (p.14),' find out how A*STAR was involved in speeding up COVID-19 testing with automation and a new rapid antibody test, ASSURE®.

Beyond COVID-19, A*STAR research also touches everyday life in areas ranging from green chemistry with 'Piezoelectricity made simple (p.19);' cybersecurity with 'Leaving cyberattackers lost in the fog (p.35);' and electronics with 'Putting a new spin on communications (p.34).'

Whatever your interests, do visit our website: **research.a-star.edu.sg** and follow us on Twitter at **@astar_research** and LinkedIn at **A*STAR Research** for the latest updates on COVID-19 and much more.



On the cover
SARS-CoV-2 viruses missing a stretch of 382 nucleotides seem to cause less severe symptoms of COVID-19.

For the latest on A*STAR's COVID-19 research, please visit: https://research.a-star.edu.sg/tag/covid-19/

THE MUTATION MAKING COVID-19 MILDER

Scientists at A*STAR have found that a mutation in SARS-CoV-2 called Δ382 leads to milder clinical outcomes, with implications for COVID-19 treatments and vaccines.

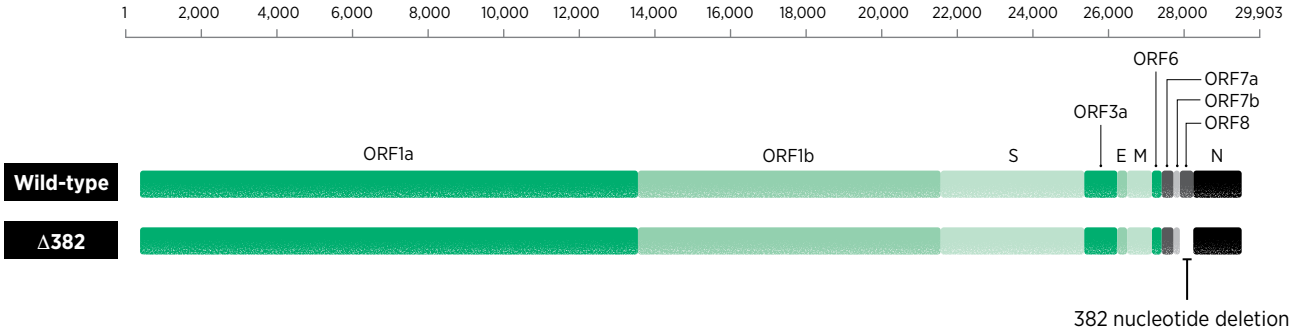
Like any other organism on the planet, viruses are prone to the natural genetic diversity that may arise from mutations. Since the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) hit the world, there have been fears that mutations could lead to more infectious or even more lethal strains of the coronavirus disease 2019 (COVID-19). Thankfully, the reverse may also be true.

With my colleagues at A*STAR's Singapore Immunology Network (SIgN) and collaborators from institutes around Singapore, I investigated a genetic variant of SARS-CoV-2 that resulted in a less severe form of the disease, with a muted immune response, milder infections and better clinical outcomes. I will discuss our findings, which we published in *The Lancet*, here.

GENETIC VARIATION IN SARS-COV-2

There have been many variants identified in the SARS-CoV-2 genome. Because such genetic variation can translate to different features that affect the virus in different ways, there is interest in identifying the variants and their effects. For example, variants in immune targets or in regions of the virus that are targeted by diagnostic tests could lead to serious implications in our fight against the virus. Genetic variations may also affect how transmissible and virulent the virus is, sparking fears of more dangerous strains.

We focused our study on a particular variant that was detected through the routine sequencing of the SARS-CoV-2 genome in a cluster of cases in Singapore that occurred between January and February of this year. The sequencing studies were carried out at Duke-NUS Medical School and also at the National Public Health Laboratory (NPHL), which is part of the National Centre for Infectious Diseases at Singapore's Ministry of Health.



The genome of wild-type SARS-CoV-2 (top) compared to its Δ382 variant (bottom). The 382 nucleotide deletion that gives Δ382 its name spans both ORF7b and ORF8.

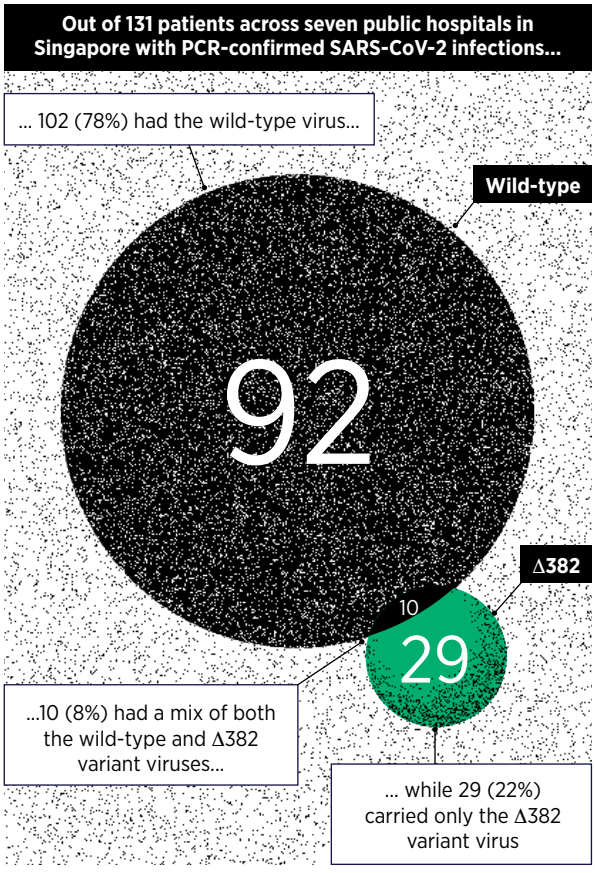
This variation is a deletion of 382 nucleotides, which is why we refer to it as the Δ382 variant. The deletion is located in a region of the genome called the open reading frame 8 (ORF8) region, a known hotspot for mutations and genetic variation in coronaviruses. In this case, the deletion has resulted in the removal of the ORF8 transcription regulatory sequence, meaning the ORF8 protein is not produced.

Back during the SARS epidemic in 2002-03, a deletion of 29 nucleotides in ORF8 resulted in a variant of the virus that was unable to replicate as efficiently as the wild-type virus. This observation led to some speculation that the mutation could have resulted in a milder illness as well, although it was not examined at the time.

We decided it was worth looking into the Δ382 variant further. My colleagues at NPHL and Duke-NUS first screened 131 patients across seven public hospitals in Singapore with PCR-confirmed SARS-CoV-2 infections and found that the variant was present in about 30% of the patients. Of those 131 patients, 29 (22%) carried only the Δ382 variant virus, while 10 (8%) had a mix of both the wild-type and Δ382 variant viruses. Similar variants with deletions of varying lengths in ORF8 have been observed in countries such as Bangladesh, Australia and Spain.

THE DELETION IN ACTION

Given what we know about the ORF8 region and from a similar deletion in the SARS-CoV genome, we wanted to determine if the Δ382 variant affected the severity of SARS-CoV-2 infection. The doctors on our team looked at the clinical features of COVID-19 patients, taking their need for supplemental oxygen as a measure of infection severity for patients infected with the variant or wild-type strain.



Interestingly, patients with the Δ382 variant were less likely to need supplemental oxygen. Although all patient groups developed pneumonia at a similar rate, no patients in the Δ382-variant-only group required supplemental oxygen. They were also less likely to develop hypoxia, a dangerous state of oxygen deprivation that arises in severe COVID-19 cases.

Not only was hypoxia less likely to occur, patients infected with the Δ382 variant also had lower concentrations of pro-inflammatory cytokines and chemokines that are strongly associated with severe COVID-19. Notably, they displayed lower levels of growth factors associated with lung injury and regeneration, suggesting that the infection was not severe enough to damage the lungs.

The patients with the Δ382 variant also showed a better immune response: further immunological analysis revealed that they were able to more effectively regulate their platelet and T cell responses in the early phase of infection, a process that is usually severely impaired in SARS-CoV-2 infection. Instead, patients with the variant showed a more robust production of a cytokine called IFN-γ, which could be the reason for the rapid and effective immune responses observed.

These observations held true even after we re-classified the patient group for age and the presence of comorbid conditions. Because of this, we suspect that this variant somehow triggers a reduced pro-inflammatory response and a lower, less-damaging cytokine storm that resulted in a milder form of the disease.

Our observations and findings support the suggestion that the Δ382 variant of SARS-CoV-2 is associated with a milder infection and better clinical outcomes. However, we do not yet know why this is so. Unlike the 29-nucleotide deletion in the SARS-CoV virus, tests have shown that the Δ382 variant does not alter how well the SARS-CoV-2 virus replicates, as evidenced by the similar viral loads observed in patients with and without the Δ382 variant.

Evidence suggests that the ORF8 protein plays an important role, although the exact function of this protein in SARS-CoV-2 remains unclear. One study has suggested that it may help the virus evade immune detection, while another has indicated that ORF8 is frequently an early target for human antibodies during SARS-CoV-2 infection. Considering all this, we speculate that the Δ382 variant might be less effective at establishing infection in a new host because of the loss of immune evasion conferred by ORF8. Therefore, potential therapeutic strategies that inhibit ORF8 could be considered.

HOPE FOR THE FUTURE

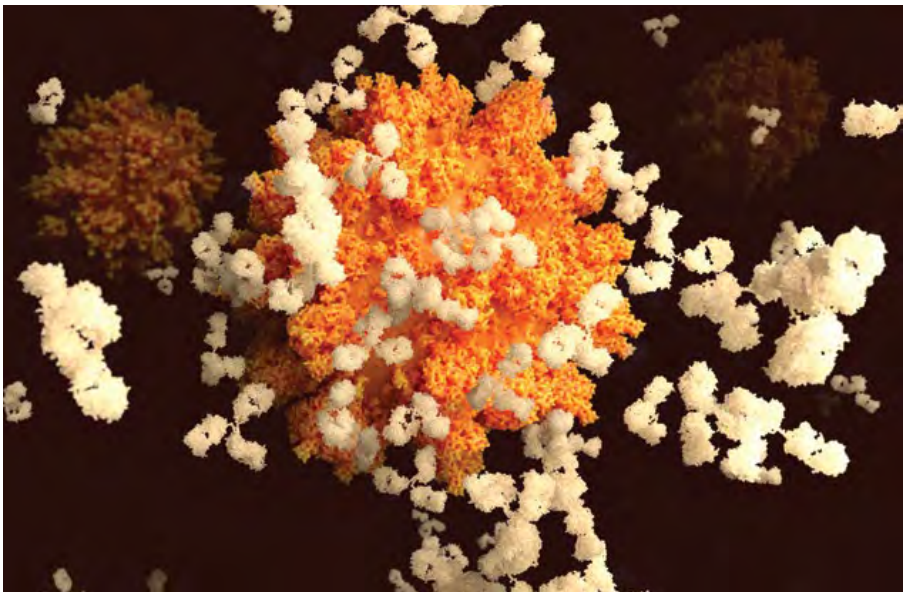
So what does it all mean? It is interesting to speculate how a deeper understanding of these genetic variants could lead to future treatments or vaccines that exploit them. If deletions in ORF8 translate to milder infection as they do in the Δ382 variant, it could have implications for the development of attenuated live vaccines, for instance.

In the future, my team and I would like to decipher the molecular mechanisms of the variants that drive their respective immune responses. For now, I want to credit my collaborators at the National Centre for Infectious Diseases, the Ministry of Health, Duke-NUS Medical School, and A*STAR's Infectious Disease Horizontal Technology Centre (ID HTC) and Bioinformatics Institute (BII) for their work on this paper, from collecting the clinical samples to conducting the experiments and analyzing the data. ★

ABOUT THE RESEARCHER:

Lisa F.P. Ng obtained her PhD in molecular virology in coronaviruses from the National University of Singapore (NUS) in 2002. After joining A*STAR's Genome Institute of Singapore (GIS) in 2002 as a Postdoctoral Fellow, she worked on viral diseases such as hepatitis, severe acute respiratory syndrome and influenza. Ng is currently the Executive Director (Talent and Strategic Initiatives) of A*STAR's Biomedical Research Council (BMRC), and holds a concurrent appointment as a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SIgN) where she focuses on the immune responses to arthritic arboviruses that are epidemic or highly endemic in the tropical region.

1. Young, B., Fong, S.W., Chan, Y.H., Mak, T.M., Ang, L.W., *et al*. Effects of a major deletion in the SARS-CoV-2 genome on the severity of infection and the inflammatory response: an observational cohort study. *The Lancet*. (2020).



IMMUNOLOGY

A spike of hope for COVID-19 detection

Antibodies that recognize the SARS-CoV-2 spike protein show potential for diagnosing COVID-19.

Though a recent entrant into our daily vocabulary, the word 'coronavirus' was first coined in 1968 to describe a family of viruses, so named because the viruses were surrounded by a 'crown' of spiky protein projections.

As it turns out, these spikes give coronaviruses more than just their crown-like shape and name: they are also the key to their infectious ability. Each coronavirus spike contains a receptor-binding domain which binds to a specific target protein on host cells so that the virus can enter and infect them.

Interestingly, the spike of SARS-CoV-1, the virus responsible for the severe acute respiratory syndrome (SARS) epidemic in 2003, has some similarity to the spike of SARS-CoV-2, the virus responsible for the current COVID-19 pandemic. They both also share the same target: a protein on host cells called angiotensin-converting enzyme 2.

"We are working with industry partners to see if mAb 1A9 can be incorporated into COVID-19 diagnostic kits."

With this knowledge, a team of researchers led by Yee-Joo Tan, a Principal Investigator at A*STAR's Institute of Molecular and Cell Biology (IMCB), decided to see if SARS-CoV-1 monoclonal antibodies (mAbs) could cross-react with SARS-CoV-2, in the hope that the same antibodies may be applied in COVID-19 research.

Using a range of immunological and bioinformatics analyses, they discovered that four monoclonal antibodies they previously generated and reported in a 2006 study to react to a section of the SARS-CoV-1 spike protein are able to recognize and cross-react with SARS-CoV-2 as well.

"SARS-CoV-1 and SARS-CoV-2 have a similar protein known as viral surface spike glycoprotein (S protein), which is responsible for binding to the host cell. 77.8 percent of the amino acid sequences in the S protein of these two viruses are identical," Tan explained. "These antibodies bind to a part of the spike that is the same in both viruses."

One of the antibodies, mAb 1A9, was shown to be able to detect purified S protein in a sandwich ELISA assay, as well as SARS-CoV-2-infected cells 24 hours after infection. The findings are an encouraging testament to the antibodies' potential as a diagnostic tool, but the team noted that there is still a need to determine if the antibodies are sensitive enough to detect SARS-CoV-2 in clinical settings.

"We are working with industry partners to see if mAb 1A9 can be incorporated into COVID-19 diagnostic kits," said Tan, adding that an antibody-based approach would complement existing PCR-based detection methods. ★

ABOVE
A*STAR researchers have identified antibodies against SARS-CoV-1 spike protein that could also bind to SARS-CoV-2.

1. Zheng, Z., Monteil, V.M., Maurer-Stroh, S., Chow, W.Y., Leong, C., *et al*. Monoclonal antibodies for the S2 subunit of spike of SARS-CoV cross-react with the newly-emerged SARS-CoV-2. *Eurosurveillance* **25**(28) (2020).

Photo credit: Juan Gaertner / Shutterstock

IMMUNOLOGY

The immune system remembers

The presence of memory T cells in COVID-19-recovered patients hints at their importance in COVID-19 immunity.

Antibodies—Y-shaped proteins that recognize and neutralize pathogens—have so far dominated discussions about how to beat COVID-19; however, there are signs that the antibody response may be short-lived. Meanwhile, increasing evidence is showing that a second branch of the immune system that uses T cells, a type of white blood cell that 'remembers' a pathogen for quick destruction, deserves a closer look.

"T cells, and not only antibodies, are an essential part of antiviral immunity," noted Antonio Bertoletti, a Professor at Duke-NUS Medical School's Emerging Infectious Diseases Program and an Adjunct Principal Investigator at A*STAR's Singapore Immunology Network (SIgN). "This concept has been present in the scientific community for over 50 years, but so far has been largely ignored in discussions related to COVID-19 immunity."

In a study published in *Nature*, Bertoletti and his collaborators in Singapore sought to introduce a more 'balanced' view of the conversation about COVID-19 immunity. They did so by characterizing the SARS-CoV-2-specific T cell response in patients who have recovered from the severe acute respiratory syndrome (SARS) and COVID-19, as compared to uninfected healthy individuals.

Because SARS-CoV-2 is made up of several different proteins, the researchers analyzed whether the patients' T cells recognize nucleocapsid (N) protein, an abundant structural protein, and NSP7 and NSP13, two non-structural proteins.

"It is important to understand whether it is the structural proteins or the non-structural proteins (proteins necessary for replication but not structure) of the virus that can elicit a T cell response," explained Yee-Joo Tan, a Principal Investigator at A*STAR's Institute of Molecular and Cell Biology (IMCB) who initiated this study with the Duke-NUS team.

Of the 36 COVID-19-recovered patients tested, all produced T cell responses against the N protein and less so against the non-structural proteins, as did all 23 SARS-recovered patients tested 17 years after infection. This result suggests long-lasting cross-reactivity between the T cells that recognize SARS-CoV-1 and SARS-CoV-2.

Surprisingly, half of the 37 uninfected individuals also showed a T cell response against SARS-CoV-2. Unlike SARS and COVID-19-recovered patients, who showed a dominant T cell response to the N protein, T cells from uninfected individuals recognized both structural and non-structural proteins. These cross-reactive T cells have likely been induced by contact or infection with other coronaviruses.

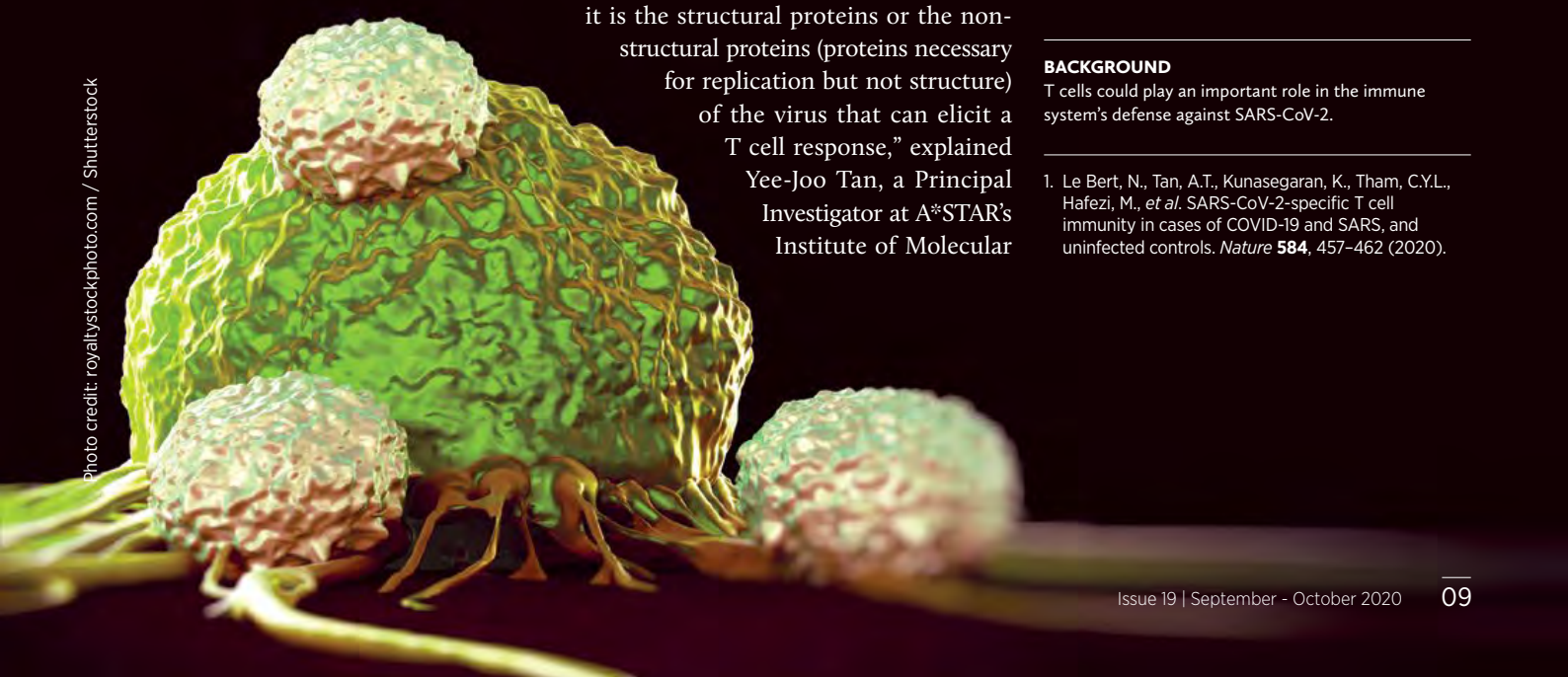
"There is this idea of the total absence of immunity against coronaviruses in the general population, which is clearly incorrect," said Bertoletti. "Other coronaviruses have always been circulating in humans."

The next step is to determine whether memory T cells can protect against or change the pathogenesis of COVID-19. This study will require a large sample of exposed uninfected individuals, Bertoletti said. ★

BACKGROUND

T cells could play an important role in the immune system's defense against SARS-CoV-2.

1. Le Bert, N., Tan, A.T., Kunasegaran, K., Tham, C.Y.L., Hafezi, M., *et al.* SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature* **584**, 457–462 (2020).



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WEARABLE TECHNOLOGY

Smarter than the average mask

An A*STAR-designed 'smart mask' may reduce the risk of infection in healthcare workers by enabling remote, real-time monitoring of patients' symptoms.

After some controversy early in the ongoing COVID-19 pandemic, face masks are now widely considered an effective means for preventing the spread of virus particles by forming a physical barrier between the wearer and others. But what if a mask could not only stop an infected person from passing on the virus, but also monitor their symptoms without burdening healthcare workers?

"A system that remotely monitors patients' vital parameters can help reduce face-to-face contact between healthcare workers and patients," noted Xian Jun Loh, Executive Director of A*STAR's Institute of Materials Research and Engineering (IMRE). "Such a remote system also benefits recovering patients by helping them track their progress, relieving the stress on overwhelmed healthcare systems during a pandemic."

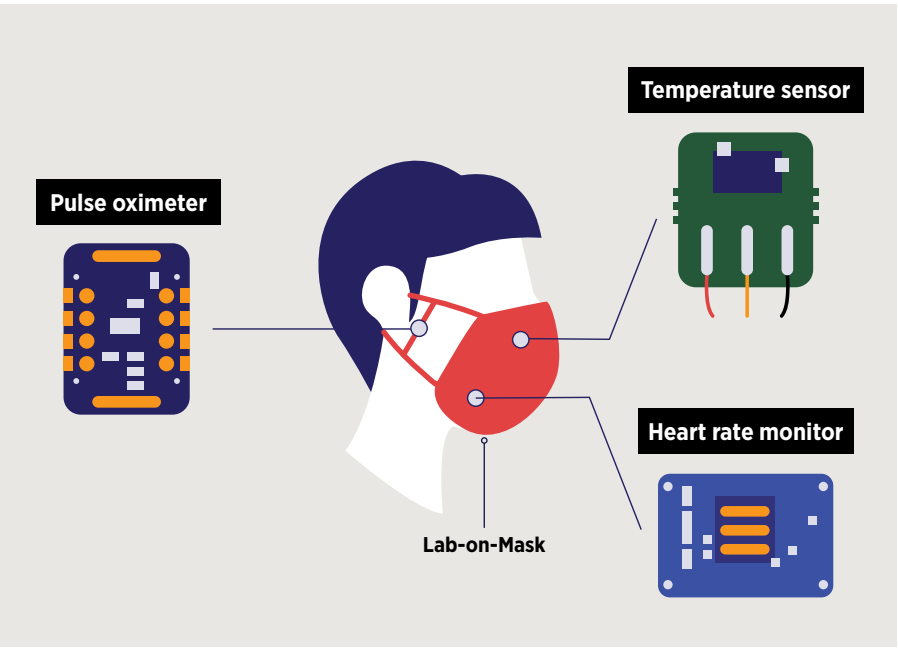
Loh and a team of researchers, in collaboration with Xiaodong Chen from Nanyang Technological University, Singapore, and Ban Hock Tan, a Senior Consultant from the Infectious Diseases Department, Singapore General Hospital, have developed a mask that can monitor pneumonia-related parameters. "We have monitored in real-time the heart rate, blood pressure, blood oxygen saturation and temperature of a person remotely over seven consecutive hours," said Loh.

The mask is made of a flexible skin-like material called polydimethylsiloxane, which has embedded within it a non-contact sensor system the researchers have named 'Lab-on-Mask.' Within the Lab-on-Mask system are various sensors that collect information from the wearer's face and convert them into electrical signals. The signals are sent to data-processing modules and delivered via a wireless Bluetooth system to an external device, such as a smartphone app, for real-time monitoring.

For example, to measure blood oxygen saturation, infrared light-emitting diodes (LEDs) in the Lab-on-Mask system shine light onto the blood vessels under the skin. A light detector and amplifier receive the reflected light and convert it into electrical signals that inform clinicians about the narrowing and expansion of the patient's blood vessels. Heart rate and blood pressure are measured in a similar manner using green LEDs.

The researchers confirmed that all measurements made with the smart mask were accurate by comparing them with those measured using standard methods. And as a bonus, the entire system conforms well with the wearer's face, making the mask comfortable to wear.

In the future, the researchers plan to collaborate with hospitals to promote the use of the smart mask for remote, real-time monitoring of infected patients. They are also considering ways to optimize the mask, such as by adding anti-viral chemical sensors and coatings that can monitor and deactivate viruses. ★



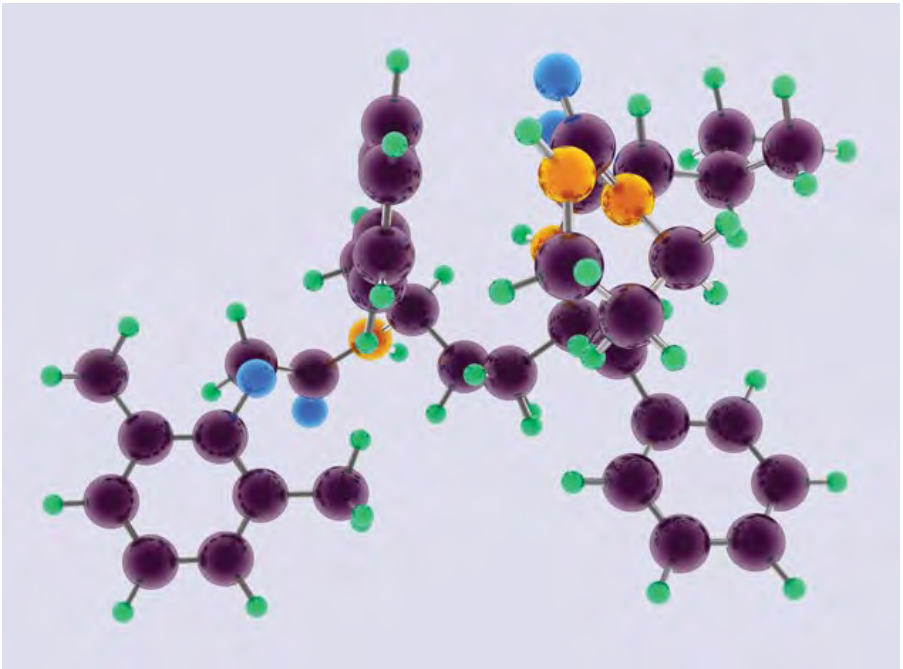
Different sensors like pulse oximeters, temperature sensors and heart rate or blood pressure monitors can be incorporated into the Lab-on-Mask, which is made of flexible polydimethlsiloxane.

1. Pan, L., Wang, C., Jin, H., Li, J., Yang, L., *et al*. Lab-on-Mask for Remote Respiratory Monitoring. *ACS Materials Letters* **2**, 1178–1181 (2020).

PHARMACOLOGY

Could an HIV drug treat COVID?

Digital drug simulations may help predict whether repurposed antivirals will work against COVID-19.



In the hunt for pharmaceuticals to combat COVID-19, repurposed antiviral drugs are low-hanging fruit; instead of starting drug discovery from scratch, it is much faster to use drugs that are already known to be safe and effective in treating viral infections. In particular, a drug used to treat HIV infections—lopinavir—is of particular interest to scientists. Not only had the antiviral shown clinical efficacy in HIV patients, but it also inhibited the growth of coronaviruses closely related to SARS-CoV-2 in prior outbreaks.

Given its successful track record, could lopinavir also be used to treat COVID-19 patients? To answer this question, a team of researchers led by James Chan of A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI) turned to a state-of-the-art computational tool, called the Simcyp® Simulator, to carry out physiologically-based pharmacokinetic (PBPK) modeling. In PBPK modeling, hundreds of differential equations are integrated to create a virtual human being that is then used to digitally map drug kinetics in the body.

When a patient takes a dose of lopinavir, most of the drug binds strongly to proteins in the bloodstream, with only the unbound drug remaining clinically active. Of this, only a fraction of the unbound drug then finds its way to the lungs. Even though lopinavir was found to inhibit SARS-CoV-2 in cell-based systems, its clinical efficacy is not guaranteed. "Being pharmacodynamically active is only half the story. We have to ensure that the drug reaches where it is needed, and at a high enough level to work," explained Chan.

The team deployed the PBPK model to estimate how lopinavir would be absorbed, distributed and metabolized by COVID-19 patients over time. "While it is reasonably easy to repeatedly measure the levels of a drug in the blood of a human subject, it is considerably harder and deeply invasive to do the same in tissues such as the lung," said Chan. "One major advantage of the virtual human model is the ability to accurately estimate drug levels within human organs using modeling and simulation."

Unfortunately, the simulations revealed that administering the standard twice-daily regimen of lopinavir would not give patients high enough drug concentrations in the lung to inhibit SARS-CoV-2. Ramping up the dose is also not an option, as it may result in serious side effects. Similar limitations have also caused other antivirals such as hydroxychloroquine to fall flat as COVID-19 countermeasures.

The researchers have not stopped searching, however, and are currently running PBPK as well as viral dynamics simulations on other promising antivirals for COVID-19. "Coupling both types of simulations will allow us to determine the effective window to initiate treatment and the appropriate duration of treatment. These considerations are important to optimize therapy and ensure the judicious use of antivirals," said Chan. ★

ABOVE
The molecular structure of lopinavir, an HIV medication that is being investigated for its potential to treat COVID-19.

1. Thakur, A., Tan, S.P.F., Chan, J.C.Y. Physiologically-Based Pharmacokinetic Modeling to Predict the Clinical Efficacy of the Coadministration of Lopinavir and Ritonavir against SARS-CoV-2. *Clinical Pharmacology and Therapeutics* (2020).

Photo credit: SenSeHi / Shutterstock

STREAMLINING COVID-19 SCREENING FOR SUCCESS

By eliminating bottlenecks and automating manual processes, the joint RESOLUTE and RAVE system co-developed by A*STAR scientists and their collaborators will help give COVID-19 testing a much-needed boost.

For all the advances of modern medicine, SARS-CoV-2—the new coronavirus behind the pandemic—is alarmingly successful. It is stealthy, with symptoms that only show up a week or two later, if at all. It spares no one, from seemingly healthy young adults to elderly patients who often bear the brunt of the disease. Above all, it has already infected millions—and those are just the cases that we know about.

Without a vaccine, the 'test, trace and isolate' trifecta appears to be the most practical way to quell any potential community outbreak. But as Singapore looks to safely restart leisure travel, it needs to significantly expand COVID-19 testing. Accordingly, the Republic aims to conduct up to 40,000 tests per day in the latter half of 2020.

It is an ambitious goal, but not impossible. By streamlining and automating key steps in the current testing protocol, an integrated COVID-19 testing system developed by A*STAR and its collaborators is set to help the country achieve this milestone.

THE NEED FOR SPEED

The most common COVID-19 testing method relies on a technique known as real-time reverse transcriptase polymerase chain reaction (RT-PCR). Though no single test is 100 percent accurate, RT-PCR hits close to the mark, boasting specificity rates of over 99 percent. For this reason, the technique is widely regarded as the gold standard for detecting and diagnosing viral infections.

RT-PCR derives its name from a key step in the process known as reverse transcription. While most people are familiar with DNA, SARS-CoV-2's genetic material takes the form of RNA. Hence, before any subsequent analyses like PCR can occur, the coronavirus' RNA must be converted to DNA by the reverse transcriptase enzyme. This process occurs after viral RNA has been successfully isolated from patient samples. If RNA isn't extracted and purified, contaminants in the sample may interfere with the PCR reaction and lead to inaccurate results.

Once the purified viral RNA has been converted into DNA, the PCR reaction finally takes place. Upon the addition of matching DNA sequences called primers, a series of heating and cooling cycles prompts the Taq polymerase to repeatedly synthesize multiple copies of viral DNA until it reaches a detectable threshold.

RT-PCR, however, has its drawbacks. First of all, it is a time-consuming process. The A*STAR-developed Fortitude test kit currently takes at least 90 minutes to run. Factor in the time required to collect patient swabs and extract RNA, as well as testing backlogs, and COVID-19 test results may

RESOLUTE 2.0 is a direct mulitplex RT-PCR COVID-19 diagnostic test that halves test delivery time compared to other approved RT-PCR tests.

Photo credit: A*STAR

very well take a day or longer to be released. In resource-strapped settings, this excruciating wait could even take up to a week.

To make things even more complicated, global shortages in RNA extraction kits have also slowed down RT-PCR testing everywhere from the US to India. As speed is essential in containing the virus, scientists worldwide have been searching for ways to make the testing process more efficient, as well as resilient to shocks in the supply chain.

MINIMUM EXPOSURE, MAXIMUM EFFICIENCY

The RESOLUTE test kit jointly developed by the DSO National Laboratories and A*STAR's Diagnostics Development (DxD) Hub is poised to halve testing times. The test achieves this through a breakthrough direct PCR method that skips the RNA extraction step entirely. Instead, the patient samples are placed in a universal transport medium, which can store viruses stably at room temperature. Samples are then placed in wells containing the pre-mixed RESOLUTE reagents, after which RT-PCR commences as usual.

To further accelerate the process, A*STAR is automating the RESOLUTE test with the help of the robotics system RAVE, which stands for Rapid Automated Volume Enhancer. The automated laboratory system was co-developed by A*STAR's Advanced Remanufacturing and Technology Centre (ARTC) and Singapore Institute of Manufacturing Technology (SIMTech) in around three months—a considerable achievement as such projects typically take at least a year to complete.

Their achievement is made even more impressive in light of the many setbacks the team encountered along the way. "There were tons of challenges in our journey from conceptualization to deployment," shared Rick Chua, Senior Business Development Manager at ARTC. "There was no opportunity to test our system with live samples. We tried to simulate mucus [from the swab] with shampoo, detergent, ladies' finger (okra), starch, glue and even grease."

RAVE automates the manual steps required for processing samples during RT-PCR, including moving and uncapping tubes, pipetting reagents and even scanning the barcodes on the tubes that distinguish individual samples from one another. In doing so, the system significantly speeds up the testing process from start to finish. Combined, the RESOLUTE test and RAVE system can process 96 samples in under an hour, resulting in a record-shattering output of 4,000 samples processed per day.

Beyond speed, the integrated RESOLUTE and RAVE system also delivers a host of other benefits. By eliminating the RNA extraction step, the RESOLUTE test simplifies sample processing and lessens the chance of human error. The test also removes the need to acquire RNA extraction kits, reducing costs and making the workflow less likely to be affected by supply chain shortages. Meanwhile, by automating various steps in the RT-PCR protocol, RAVE makes the technique more accessible even to entry-level technicians and minimizes the prolonged exposure of staff to the virus.

RACING TO THE FINISH LINE

The RESOLUTE test and RAVE system will be distributed by Advanced MedTech Holdings, which has also received provisional authorization from the Health Sciences Authority to manufacture RESOLUTE. The joint solution is already being used at three hospitals in Singapore, but may soon also be deployed overseas.

Neighboring countries like Indonesia and the Philippines as well as far-off nations like the US have expressed interest in acquiring the combined system. Given this, the teams at ARTC and SIMTech are looking into equipping the RAVE system with industrial Internet of Things (IIoT) capabilities. According to Chua, IIoT could allow the team to remotely monitor the health of various RAVE systems that could soon be installed all over the world.

As scientists scramble to develop vaccines in highly compressed timelines and deploy artificial intelligence to speed up drug discovery, it's clear that time is of the essence in the fight against the coronavirus. Testing is no exception. To safely navigate the world out of this crisis, widespread testing should immediately take place on a global scale. The joint RESOLUTE and RAVE system could be a shot in the arm that COVID-19 testing urgently needs. ★

"We tried to simulate mucus [from the swab] with shampoo, detergent, ladies' finger (okra), starch, glue and even grease."

ASSURING ASYMPTOMATIC COVID-19 CARRIERS ARE IDENTIFIED

A*STAR researchers have developed a point-of-care rapid antibody test kit that can detect antibodies produced in response to SARS-CoV-2 infection in just fifteen minutes.

We've all heard the saying that early detection saves lives. It is why traditional public health strategies have relied on the speedy and accurate detection of diseases to contain their spread. But what happens when the disease you're trying to control doesn't allow for that? This is exactly the challenge presented by the COVID-19 pandemic.

Unlike the 2002-03 SARS epidemic, where the spread of the disease was brought under control due to its easily identifiable symptoms, things are not as straightforward with COVID-19. Researchers have had to contend with complications such as presymptomatic transmission, where people may be infectious before symptoms develop, as well as asymptomatic transmission, where people may infect others without ever developing symptoms at all.

These covert coronavirus carriers are a considerable concern, but thanks to A*STAR and MP Biomedicals, a new rapid antibody test kit may offer a way to identify them.

THE CASE FOR ANTIBODY TESTING

The current gold standard for COVID-19 testing is the real-time reverse transcriptase polymerase chain reaction (RT-PCR) test, which screens for the presence of SARS-CoV-2 genetic material. Some RT-PCR test kits can take as little as 90 minutes to run, but the bottleneck for their overall speed and accuracy is their reliance on specialized resources such as equipment, reagents, trained personnel, and sample collection and preparation processes. In light of this, there is a demand for easy-to-use test kits and devices that would allow for testing outside of laboratory settings. One such proposed strategy is antibody testing.

Antibodies are proteins produced by immune cells in response to foreign invaders like the SARS-CoV-2 virus. Even after the infection is cleared, these antibodies remain in the body to respond quickly if reinfection occurs. Antibody tests search for antibodies in the blood or plasma, cutting down on the amount of time and work needed to amplify and detect viral genetic material that is the case in RT-PCR-based tests.

Furthermore, because they target antibodies that remain in the bloodstream long after recovery, antibody tests have proven valuable in contact tracing and retroactively discerning the links between cases in infection clusters, such as in the Grace Assembly of God cluster in Singapore. From this case, it is clear how a rapid antibody test kit can help identify those who have recovered from the virus but might still be contagious, even if they had been mildly symptomatic or completely asymptomatic.

Antibody tests also offer more information beyond past infections. They can assess the extent and length of COVID-19 infection in populations to provide valuable insight into viral epidemiology, or be used to screen donor blood for antibodies against SARS-CoV-2, and to identify those lacking antibodies as prime candidates for a potential vaccine.

RAPID RESULTS

A locally developed test kit by A*STAR and diagnostic company MP Biomedicals Asia Pacific offers a truly fast and easy form of rapid antibody testing. Known as ASSURE®, the test kit can tell if someone has been previously exposed to SARS-CoV-2 in just 15 minutes, and at a low cost. Moreover, ASSURE® is a point-of-care test kit, which means that the finger-prick samples do not have to be processed in a laboratory and patients can receive their results almost immediately following the test.

ASSURE® looks for the presence of Immunoglobulin G (IgG) and Immunoglobulin M (IgM) antibodies, which are produced by the immune system after viral exposure. To detect IgG and IgM, the kit development process was accelerated by using human monoclonal antibodies identified in March by a team of scientists from A*STAR's

Photo credit: A*STAR

Institute of Molecular and Cell Biology (IMCB), led by Associate Professor Yee-Joo Tan. Also, MP Biomedicals used proprietary synthetic SARS-CoV-2 proteins which could bind to the IgG and IgM antibodies if they are present in the sample and much like a pregnancy test, results are indicated by red lines in the result window of the test kit.

As a rapid antibody test, ASSURE® is not intended to accurately detect COVID-19 in the early acute phase of infection. Instead, by detecting the presence of the two different antibodies, ASSURE® can establish an estimated timeline of when the infection occurred. As IgG antibodies typically appear at later stages of infection, their presence in the test would indicate that the infection probably took place several weeks ago. In contrast, as IgM antibodies are produced by the body first, their presence could indicate a recent infection that most likely began less than 14 days ago. A repeat test can be done in the following week or two to confirm that IgM antibodies are no longer present.

"We brought in IMCB to produce antibodies to simulate the antibodies produced during COVID-19, which helped us to accelerate the optimization of the kit."

THE POWER OF COLLABORATION

Even more impressive than the speed and ease of how ASSURE® works is how fast it was assembled: the entire kit took MP Biomedicals about two months to develop from start to finish. Once the IMCB team identified the human monoclonal antibodies, MP Biomedicals then developed ASSURE® based on their lateral flow platform, while A*STAR's Diagnostics Development (DxD) Hub co-developed the validation protocols and quality controls.

"The development was fast because of the close collaboration and trust between the different parties involved," said Yongfeng Li, DxD Hub's Chief Development Officer.

MP Biomedicals has a long history of developing rapid antibody tests for other diseases such as dengue and HIV, explained Li. Recognizing this, A*STAR and the National University Hospital (NUH) were quick to offer them support to adapt their rapid test platform for the fight against COVID-19.

Even so, ASSURE's development wasn't without its challenges. Li said that the urgency to launch the test kit in time, compounded by the shortage of clinical samples to optimize its performance, were some of the stumbling blocks the teams had to overcome.

"As the project manager, DxD Hub had to pull together different component capabilities to assist in the development process," Li said. "For example, we brought in IMCB to simulate the antibodies produced during COVID-19, which helped us to accelerate the optimization of the kit. We also helped by providing market intelligence and advice regarding verification and validation protocols, bringing in NUH to facilitate the clinical validation, and having Temasek Foundation help with scaling up local production and piloting its use in our local community."

In evaluations by NUH's Department of Laboratory Medicine, ASSURE® was shown to perform well with both serum and whole blood samples, with performance comparable to commercial tests. Now registered, ASSURE® has since been granted Provisional Authorization by the Health Sciences Authority and has been distributed to regions such as Europe, Africa and South America.

Asymptomatic transmission has been dubbed the Achilles heel of current strategies for controlling the spread of COVID-19. But with the insights they offer, rapid antibody tests like ASSURE® will be on hand to inform future public health interventions in a more cost-effective and user-friendly way. ★

LEFT
The ASSURE® test kit detects antibodies produced by the human immune system in response to SARS-CoV-2 exposure in as little as 15 minutes.

MICROBIOLOGY

The hospital bugs that never get discharged

An extensive survey of pathogens in hospital environments finds distinct microbial communities enriched for multidrug resistance.

Healthcare crises like the ongoing COVID-19 pandemic are a reminder of just how easily infections can spread. Given that hospital environments are a central battleground for the rising threat of antibiotic resistance, characterizing the pathogens present in hospitals can provide crucial information for managing outbreaks.

To survey microbes in hospital environments, they are first isolated and cultured before the functional and genetic characteristics of individual strains can be identified. However, culturing is laborious, prone to isolation bias, and ineffective for isolating a large proportion of pathogens.

In collaboration with local and international partners, a Singapore-based research team turned to metagenomics, a scalable, high-throughput method that can be used to profile the overall community structure and characteristics of microbes, without the need for isolation.

"A large baseline survey such as the one conducted in this study provides vital information to hospitals for infection control, by highlighting high-risk areas and the opportunity to tailor cleaning practices," said study corresponding author Niranjan Nagarajan, Associate Director and Senior Group Leader at A*STAR's Genome Institute of Singapore (GIS).

Over 1.5 years, the researchers took swab samples from 179 sites within Tan Tock Seng Hospital, a major tertiary-care hospital in Singapore. By combining metagenomics with culturing in the presence of various antibiotics, they were able to enrich for antibiotic-resistant pathogens present at low levels and ultimately produce a database of genetic elements related to antibiotic resistance found in hospital environments.

"Our findings suggest that hospital environments harbor distinct microbial communities, such as biofilm-forming and human-skin-associated bacteria, which persist despite extensive cleaning, and appear to be enriched for multi-antibiotic resistance," said Nagarajan.

Phylogenetic analysis and comparisons with samples taken from patients more than eight years prior revealed just how persistent some microbial strains can be despite extensive cleaning. It highlights the possible existence of stable reservoirs in the hospital, such as plumbing, drainage and air-conditioning systems, which are not eliminated by standard cleaning protocols.

These reservoirs of microbiome diversity can be the origin of new opportunistic infections and serve as fertile ground for the evolution of multidrug-resistant superbugs, Nagarajan noted. "It raises a plausible concern that aggressive cleaning measures may be selecting for them, and suggests that alternative avenues to 'rebalance' environmental microflora with other species could be worth exploring."

The methods adopted in this study may also be useful for understanding how RNA viruses like SARS-CoV-2 can persist in hospital environments, Nagarajan suggested. "With the ongoing COVID-19 outbreak, it would be both interesting and relevant to utilize the technology and approach developed in this study to understand the distribution and persistence of SARS-CoV-2 in hospital environments." ★

Photo credit: hxdbzxy / Shutterstock

LEFT
Drug-resistant bacteria can persist in hospital environments such as air-conditioning systems despite extensive cleaning.

1. Nagarajan, N., Chng, K.R., Li, C., Bertrand, D., Ng, A.H.Q., *et al*. Cartography of opportunistic pathogens and antibiotic resistance genes in a tertiary hospital environment. *Nature Medicine* **26**, 941–951 (2020).

GENETICS

Hunting an East Asian killer cancer

A study implicates novel genetic risk factors in a rare and aggressive lymphoma affecting Asian populations.

While some diseases are universal, affecting people similarly no matter their genetic background, others are linked to certain ancestries. Take for example extranodal natural killer T cell lymphoma (NKTCL), an extremely aggressive cancer limited almost exclusively to East Asian and Latin American populations, and which seldom occurs in those of European ancestry.

NKTCL is a baffling disease that originates in the nasal cavity before quickly spreading to other tissues. Apart from its unique epidemiological distribution, Epstein-Barr virus (EBV) infection has also been flagged as a significant contributing factor.

Despite the disproportionate impact of NKTCL on Asian communities, people of Asian descent are considerably underrepresented in published genetic studies on the topic, making it difficult for experts to draw clear lines around the genes that contribute to an increased risk for NKTCL.

The many unanswered questions surrounding NKTCL's origins have spurred an in-depth genome-wide association study published in *The Lancet Oncology* that focused entirely on East Asian populations—the largest of its kind to date.

An international team of researchers and physicians from countries including China, Hong Kong, South Korea, Singapore and Malaysia came together to find novel distinguishing genetic patterns tied to NKTCL development. Over 1,400 NKTCL patients and 20,000 controls were recruited from 11 centers across East Asia.

Among the study's authors were Chiea Chuen Khor, a Senior Principal Investigator from A*STAR's Genome Institute of Singapore (GIS), and Soo-Yong Tan, a Senior Principal Investigator at A*STAR's Institute of Molecular and Cell Biology (IMCB).

"We know that cancers that associate with EBV may have a strong genetic predisposition," Khor said. "To be sure, we designed a well-powered initial genome-wide scan, followed by validation testing in three additional independent collections."

Using a suite of bioinformatics approaches, the research team identified two chromosomal regions called IL18RAP and HLA-DRB1 that control immune cell activation following infections and also play a part in the genesis of NKTCL.

"The findings tell us that NKTCL is a highly immune tumor," said Khor. "To treat it, we have to harness the immune response appropriately." With these new findings, cancer immunotherapies may someday replace the current gold standard of care for NKTCL, chemotherapy and radiotherapy, both of which are associated with a low five-year survival rate.

The study also highlights the importance of ethnic diversity in genetic studies, paving the way for more population-specific investigations into the relationships between our genes and cancer.

"It is critical that we conduct population-specific genetic analyses to delineate the genetic component of cancer development, as different cancers have different preponderances in different populations," Khor said. ★

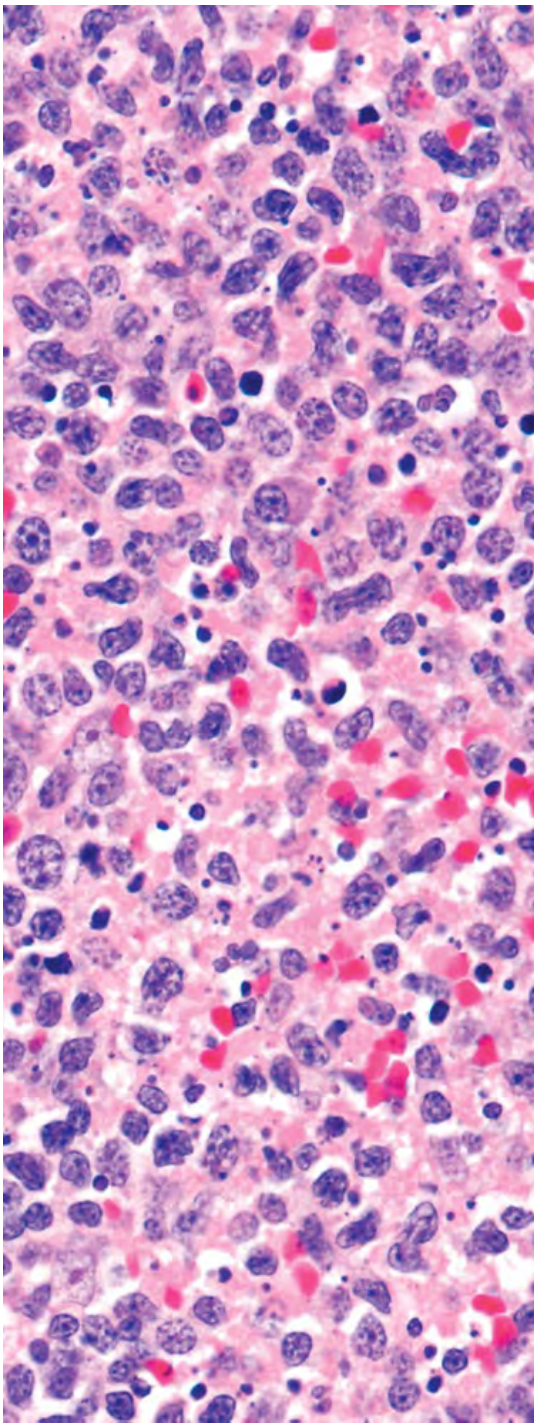


Photo credit: Webpathology / Science Photo Library

ABOVE
A light micrograph of natural killer T cell lymphoma, a disease that has unique risk factors in Asian populations.

1. Lin, G.W., Xu, C., Chen, K., Huang, H.Q., Chen, J., *et al*., Genetic risk of extranodal natural killer T-cell lymphoma: a genome-wide association study in multiple populations. *The Lancet Oncology* **21**(2), 306–316 (2020).

NANOTECHNOLOGY

Paving the way for infrared photodetectors

Faster temperature scanners may be on the way, thanks to an infrared photodetector that works at room temperature.

With the need to control the potential spread of COVID-19, thermometers and temperature scanners have become a common sight at the entrance points to nearly all public spaces. In areas of high foot traffic such as in airports, where many people need to be screened in a short amount of time, scanners that operate on an infrared photodetector can get the job done quickly.

However, there's a problem. While fast, most high-performance infrared photodetectors can only work at low temperatures, requiring bulky and expensive cryogenic cooling systems—not an ideal situation for temperature scanners in public spaces. A photodetector that could operate without the need for a cooling system would result in a cheaper and more compact scanner, which would help in its widespread market adoption.

A discovery by a team led by scientists from A*STAR's Institute of Materials Research and Engineering (IMRE) and Institute of High Performance Computing (IHPC) has now taken us a step closer to this ideal system. They demonstrate that infrared photodetection enabled by interlayer excitons (ILEs) generated between tungsten and hafnium disulfide (WS_2/HfS_2) can operate at and above room temperature, paving the way towards cheaper and more convenient infrared photodetectors.

"One of the bottlenecks for mid-far infrared technology is the lack of high-efficiency photodetectors operable at room temperature," said corresponding author Jinghua Teng, a Principal Scientist at IMRE. "We have been trying to solve this issue by using ILEs in 2D heterostructures. We chose WS_2/HfS_2 after carefully studying and screening various options."

According to Teng, the highly responsive photodetection that they observed is a result of the large oscillator strength of the ILEs in the WS_2/HfS_2 heterostructure, combined with its large exciton binding energy and unique band alignment.

"We postulate this is due to the sizable charge delocalization and ILE accumulation at the interface," said Teng. The team also showed that their WS_2/HfS_2-based photodetector is more responsive at long wavelength infrared than any other 2D material-based device.

"Our work points to a promising direction for the development of future mid-far infrared photodetectors and photoemitters," said Teng. Moving forward, he hopes to explore the potential of this technology and develop it for use in real-world applications such as photodetector arrays and infrared cameras.

"Extending the operation wavelength to the far-infrared and terahertz range would be another interesting and impactful work," he added. ★

ABOVE
In the future, thermal imaging cameras like those used at airports could be made of tungsten and hafnium disulfide, materials that enable them to function efficiently at room temperature or higher.

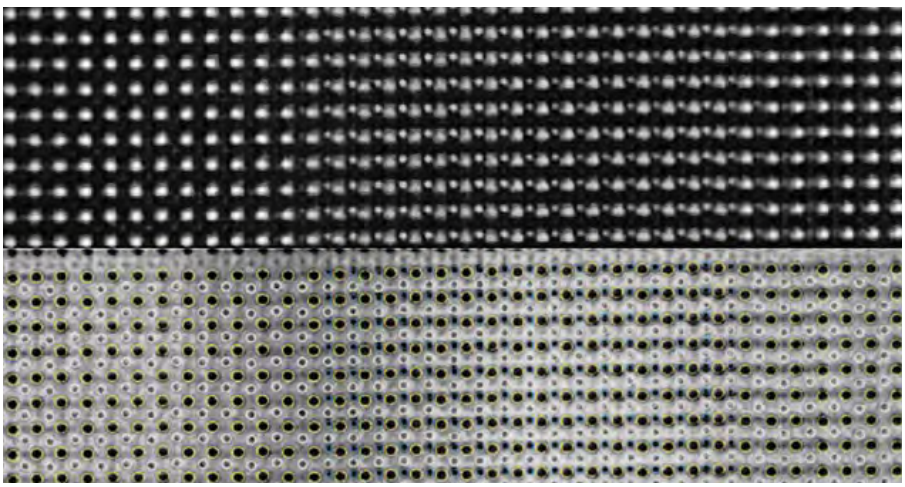
Photo credit: fmua / Shutterstock

1. Lukman, S., Ding, L., Xu, L., Tao, Y., Riis-Jensen, A.C., *et al*. High oscillator strength interlayer excitons in two-dimensional heterostructures for mid-infrared photodetection. *Nature Nanotechnology* **15**, 675–682 (2020).

MATERIALS ENGINEERING

Piezoelectricity made simple

A*STAR researchers have discovered a way to generate strong piezoelectricity with simpler and greener materials.



High-angle annular dark-field (top) and bright-field images (bottom) of a cross-section of the nanopillar material, showing structural distortions that enhance the material's piezoelectric performance.

Photo credit: © A*STAR's Institute of Materials Research and Engineering (IMRE) and Institute of High Performance Computing (IHPC)

You may not think it, but there's a good chance that there's electricity running through your wristwatch. Quartz watches run on piezoelectricity—the electric charges that accumulate in solid materials when mechanical stress or pressure is applied to them—hence its name, which stems from the Greek word to squeeze or press.

Whether it is the tiny quartz crystal helping your watch keep time or the precision actuator controlling the deposit of ink in a printer, piezoelectric devices are highly dependent on the materials used to make them. For over 60 years, the main way to boost the performance of piezoelectric materials has been to construct multiphase boundaries by tuning their chemical composition. However, this strategy usually involves complex chemical compositions and results in materials that are not stable at high temperatures.

Now, an international team of researchers, including scientists and engineers from A*STAR's Institute of Materials Research and Engineering (IMRE) and Institute of High Performance Computing (IHPC), has found a simpler way to induce a piezoelectric response.

"With just three elements—sodium, niobium and oxygen—we obtained a much larger effective piezoelectric response compared to the complex compositions designed using conventional strategy," said Kui Yao, the study corresponding author and a Principal Scientist at IMRE.

The secret to their success was the nanopillar structures that spontaneously formed in the material during the deposition process. Structural distortions in these nanopillar regions lowered the symmetry of the resulting crystal, significantly enhancing the material's piezoelectric performance.

"Using our new films, we observed a giant effective piezoelectric coefficient which is more than twice that of the market-dominant lead zirconate titanate (PZT) films, with an applied electric field of 125 kV/cm at 1 kHz," said Yao, adding that the material had the additional benefit of being more environmentally friendly since it does not contain toxic lead unlike PZT.

"We observed a giant effective piezoelectric coefficient which is more than twice that of the market-dominant lead zirconate titanate films."

Furthermore, the results showed that the material remained piezoelectric even at temperatures of up to 450°C, making it suitable for electromechanical devices that are required to operate at a wider range of temperatures. Yao suggests that the material, which IMRE has filed a provisional patent for, could be used to create micro-actuators that have lowered driving voltage and micro-sensors that have improved sensitivity.

According to Yao, this strategy of modifying a material's properties through self-assembling nanopillars could also be used to design and optimize other functional materials. ★

1. Liu, H., Wu, H., Ong, K.P., Yang, T., Yang, P., *et al.* Giant piezoelectricity in oxide thin films with nanopillar structure. *Science*. **369** (6501):292-297 (2020).

PHOTONICS

Silicon nanochains that 'sing' with light

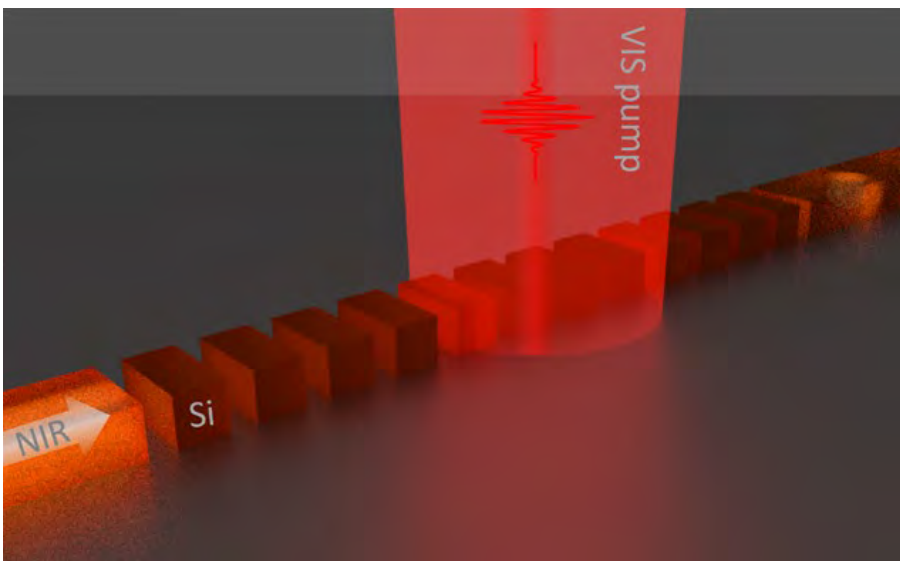
A nanoparticle chain that resonates with light is opening up new possibilities in nanophotonics and optoelectronics.

Running your finger along the rim of a wineglass produces a haunting, clear tone—a beautiful demonstration of resonance, as mechanical energy excites the glass to 'sing' at its natural frequency. A wineglass 'orchestra' can even be made by filling the glasses with different amounts of water to modify their frequencies and produce different notes.

Instead of resonating with sound, scientists are designing materials at the nanoscale that resonate with light, also known as optical resonators. Current optical resonators such as gratings or photonic crystals use regular spacings between nanostructures to resonate with the desired wavelength of light.

"Optical resonators can trap large amounts of light energy in a very small volume, allowing us to build compact devices that manipulate light on the nanoscale—nanophotonics—or even replace electrical signals with light—optoelectronics," said Arseniy Kuznetsov, a Principal Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE) who led the study.

To build a more sensitive and effective optical resonator, Kuznetsov's team turned to silicon, which changes its refractive index when pumped with visible light energy. The goal? To develop a compact optical resonator that can be switched on and off quickly and efficiently using light input alone.



Together with colleagues from A*STAR's Institute of Microelectronics (IME), Kuznetsov's team designed and fabricated a chain of silicon nanoblocks, with both the dimensions of the blocks and the spacing between blocks optimized for infrared resonance.

"Our one-dimensional nanoparticle chain resonator is composed of a series of silicon nanoantennas (resonant nanoparticles) embedded in silicon dioxide cladding," he explained. "Under optical excitation, the silicon nanoantenna absorbs light and the refractive index of silicon is modified by the photo-generated free carriers."

Their experiments confirmed that the nanochain resonated with the correct wavelength of infrared light, and that a short visible laser pulse could indeed shift the resonance enough to prevent the original infrared wavelength from resonating inside the nanochain.

"The collective nature of the nanochain resonance makes it extremely sensitive to any induced changes, which allowed us to switch the device on and off by light alone, using far less laser power compared to competing designs," Kuznetsov said. "The low power also prevented the device from accumulating heat, allowing it to be switched on and off within nanoseconds."

The researchers are now investigating if their highly sensitive silicon nanochain resonator can be used to sense biological molecules such as DNA or proteins. "We are also hoping to develop compact modulator devices based on the nanochain for use in optical communications and optoelectronics," he added. ★

LEFT
An illustration of a chain of silicon nanoblocks optimized for infrared resonance. The IMRE team used silicon to build an optical resonator that can be switched on or off using visible light.

1. Ding, L., Morits, D., Bakker, R., Li, S., Eschimese, D., *et al*. All-Optical Modulation in Chains of Silicon Nanoantennas. *ACS Photonics* **7** (4): 1001-1008. (2020).

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

PHOTONICS

Shaping LED light with metasurfaces

A compact LED device with complete light control may someday replace lasers in various applications.

Since they were invented in the early years of the 20th century, light-emitting diodes (LEDs) have ushered in a new era in optical technology. LEDs are cheap, bright and efficient light sources. However, due to the incoherent and non-directional nature of the light they emit, LEDs are thought to be inferior to lasers. Powerful laser beams have applications ranging from communication to medicine and sophisticated optical manipulation.

Now, scientists at A*STAR's Institute of Materials Research and Engineering (IMRE) and Institute of High Performance Computing (IHPC), in collaboration with Nanyang Technological University, have demonstrated that the humble LED can be transformed to obtain laser-like directional light and be manipulated in similar ways to create any desired light output.

"LEDs typically emit light in all directions, but we wondered if we could concentrate LED light into a more directional, laser-like beam," said first author Egor Khaidarov, a Scientist from IMRE. "Such a collimated light beam could then be shaped using metasurfaces, which manipulate light at the nanoscale using sub-wavelength structures, making the overall size of the device highly compact," explained Zhengtong Liu, a Scientist from IHPC involved in the study.

"This work shows how a metasurface, resonant cavity and LED can be integrated to produce compact, self-contained and power-efficient devices with special functionalities."

To concentrate the LED light, the researchers decided to use a Fabry-Perot resonant cavity, which is a pair of parallel mirrors that can amplify a source of light. They first fabricated a micrometer-thick resonant cavity LED by using a commercial LED wafer on a gold base. Gold functions as the first mirror; on top of the LED they deposited several dielectric layers which act as the second mirror. As expected, they found that the optical cavity successfully concentrated the LED light into a narrow-angle, directional beam.

Khaidarov further fabricated two different metasurfaces on top of the resonant cavity LED—one designed to deflect light at an angle and another designed to twist light into an 'optical vortex,' with the intensity profile resembling a donut. In both cases, the experimental results matched Liu's simulations, showing that the resonant cavity LED light was compatible with the metasurfaces.

"This work shows how a metasurface, resonant cavity and LED can be integrated to produce compact, self-contained and power-efficient devices with special functionalities," Liu said.

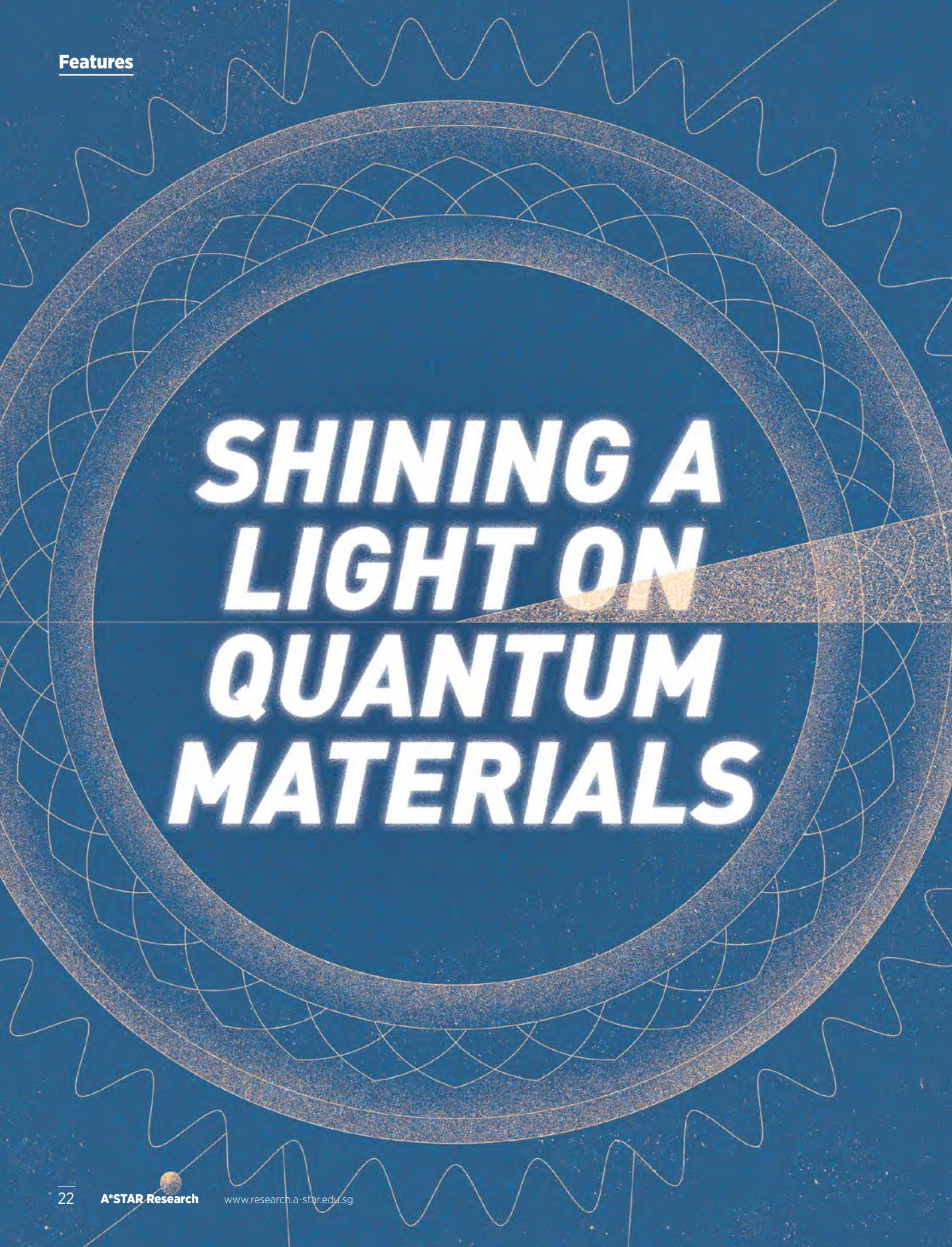
These devices could have a wide range of applications, such as in optical telecommunications, smart lighting, display screens and projectors. "They could even replace lasers in some applications, with their lower power consumption and relaxed safety regulations," Khaidarov added.

Moving forward, the team hopes to expand this technology to industrial-level light sources and electrically driven devices, as well as experiment with broadband collimators that can concentrate and amplify a wider range of wavelengths. ★

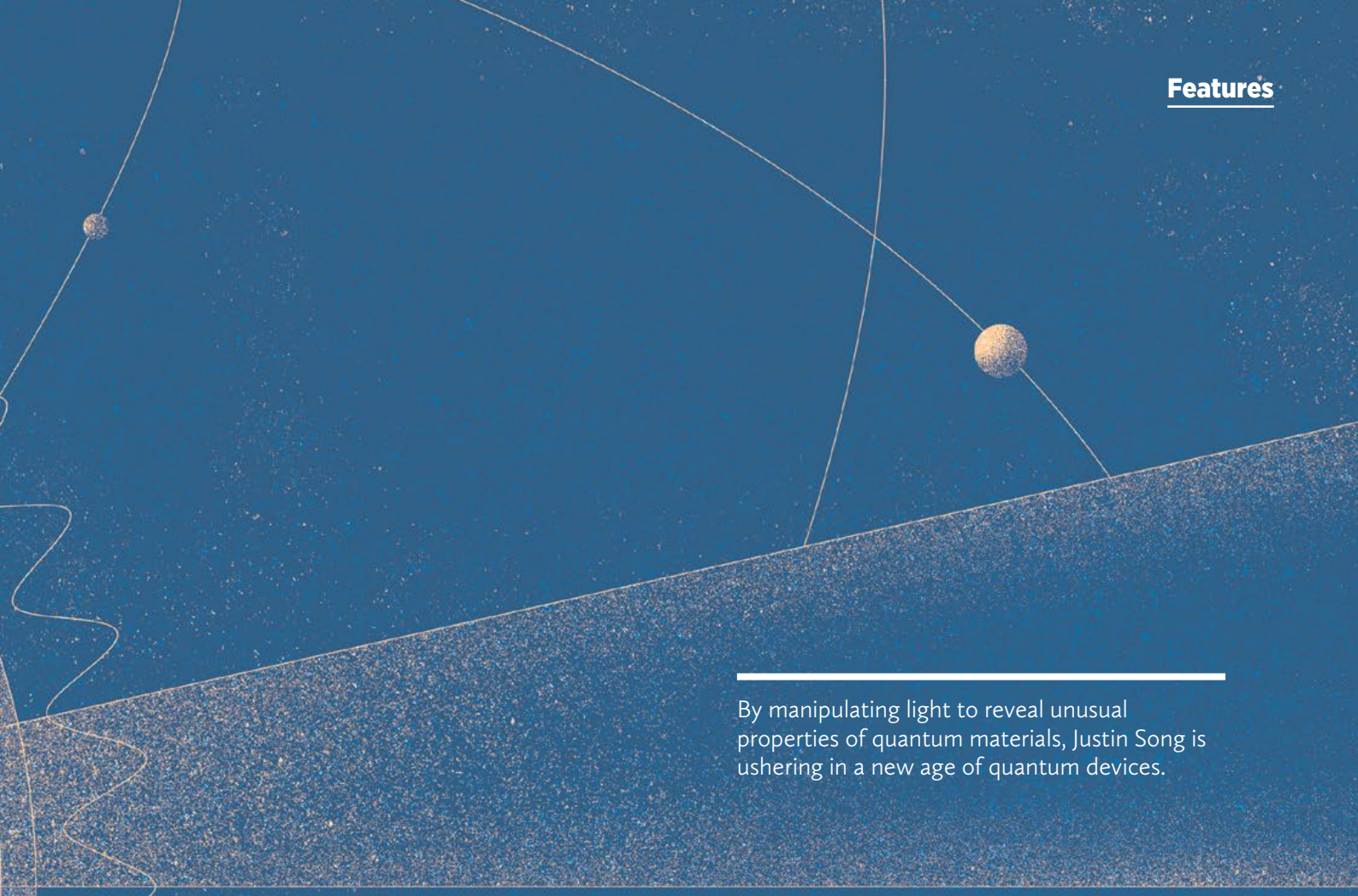
ABOVE
LEDs can be turned into laser-like directional light with the help of metamaterials.

1. Khaidarov, E., Liu, Z., Paniagua-Domínguez, R., Ha, S.T., Valuckas, V., *et al.* Control of LED Emission with Functional Dielectric Metasurfaces. *Laser and Photonics Reviews* **14**, 1 (2019): 1900235.

Photo credit: Racool studio / Freepik



SHINING A LIGHT ON QUANTUM MATERIALS



By manipulating light to reveal unusual properties of quantum materials, Justin Song is ushering in a new age of quantum devices.

Over the years, the dizzying pace of scientific research has brought many technologies out of the realm of science fiction and into reality. These days, we barely bat an eye at the prospect of driverless cars or cutting and pasting DNA. Still, there's one field with discoveries that routinely sound straight out of science fiction—quantum physics.

What, then, makes quantum physics seem so bizarre? For starters, many of its basic principles appear to defy our everyday instincts of how the world should work. Consider quantum entanglement, where quantum particles can become 'entangled' such that any action on one of the particles instantly affects the other, even at great distances.

But by exploiting these principles, researchers can unlock a vast world of possibilities, with far-reaching implications beyond the quantum realm. Justin Song, a Senior Scientist at A*STAR's Institute of High Performance Computing (IHPC) and Nanyang Assistant Professor at Nanyang Technological University, is one such researcher exploring how quantum effects manifest in different materials.

Specifically, Song's theoretical work tackles the use of light in altering the properties of materials, like potentially turning a non-magnetic metal into a magnet. For unveiling the novel properties of quantum materials, Song was conferred the prestigious Young Scientist Award in 2017. In this conversation with *A*STAR Research*, Song walks us through the weird, wonderful world of quantum materials and shares his take on the wider relevance of his research.

Q: HOW DID YOU BECOME INTERESTED IN YOUR FIELD OF RESEARCH?

I think it was largely by accident. While I've always been interested in science in general, I would say I stumbled into my area—condensed matter physics and quantum materials—by chance.

Q: TELL US ABOUT THE KEY PROBLEM YOU ARE TRYING TO SOLVE WITH YOUR RESEARCH.

It is a little hard to pinpoint a specific key problem that we're trying to solve since we're actively pushing on multiple fronts. But broadly speaking, we're trying to come up with new 'out-of-equilibrium' strategies for designing quantum material behavior. Typically, quantum devices work at or close to thermodynamic equilibrium, where energy is uniformly distributed among all components in a system. Many thermodynamic factors restrict material performance and behavior at equilibrium, but these constraints quickly fall away when materials are pushed far out-of-equilibrium. Therefore, one of our research directions is formulating new means for manipulating energy, charge or spin when a material is excited out-of-equilibrium.

A concrete example of the importance of investigating systems that are out-of-equilibrium involves spintronics devices. In spintronics, an electron's spin is used to carry information, instead of its electrical charge. Compared to conventional electronics, spintronics is a promising alternative that enables the faster processing of information despite using less energy.

To create a spintronics device, spin currents must be injected into semiconductor materials from magnetized metal cheaply and efficiently. However, transferring these spin currents is a challenging process that requires conditions close to equilibrium. In a recent study published in *Nature Physics*, we showed that heating a cobalt ferromagnet using laser pulses generates spin-carrying electrons unevenly distributed in energy—in other words, 'out-of-equilibrium'—that then selectively diffuse into the semiconductor. So far, our technique has proven to be much simpler and more efficient compared to other methods.

"Our work will benefit the scientists and quantum engineers looking to building new types of quantum devices and sensors that rely on the delicate quantum properties that can be sustained in materials."

Q: WHAT ARE SOME RECENT DEVELOPMENTS IN YOUR FIELD THAT YOU INTEND TO BUILD UPON?

There are lots of developments that we're building on in our field. One particularly striking recent finding is that of 'twistronics,' the study of emergent behavior (e.g., superconductivity) that occurs when two seemingly ordinary layers of graphene are twisted together at a special 'magic' angle. This means that while electrons in a single layer behave like a normal metal, the electrons in twisted graphene bilayers move in a way that exhibits zero resistance. In other words, electrons can travel without dissipating energy, turning the bilayer into a superconductor with a simple twist. This very unusual behavior is not understood, and we intend to find out what components go into supporting this behavior.

Q: COULD YOU PLEASE DESCRIBE ONE OF THE MOST EXCITING PROJECTS YOU ARE WORKING ON RIGHT NOW?

One thing we're most excited about now concerns sustaining topological, or deformed, states out-of-equilibrium. There is a class of materials called topological materials with useful properties like one-way electronic channels that possess very low resistance. These materials are hard to synthesize, often require exotic configurations, and/or manifest at super low temperatures.

One idea that has been gaining traction recently is using laser light to warp the structure of a material so that it exhibits topological properties (e.g., one-way electronic channels) while the light is turned on. These are called Floquet topological insulators. However, Floquet topological insulator states require tremendous light power to induce and they vanish rapidly once the light is turned off. We are currently working on a protocol that can 'freeze' some of the properties of these topological states for long periods of time even when the light is off.

Q: WHAT ARE SOME OF THE IMPLICATIONS OF YOUR RESEARCH? WHO WILL BENEFIT FROM THE FINDINGS?

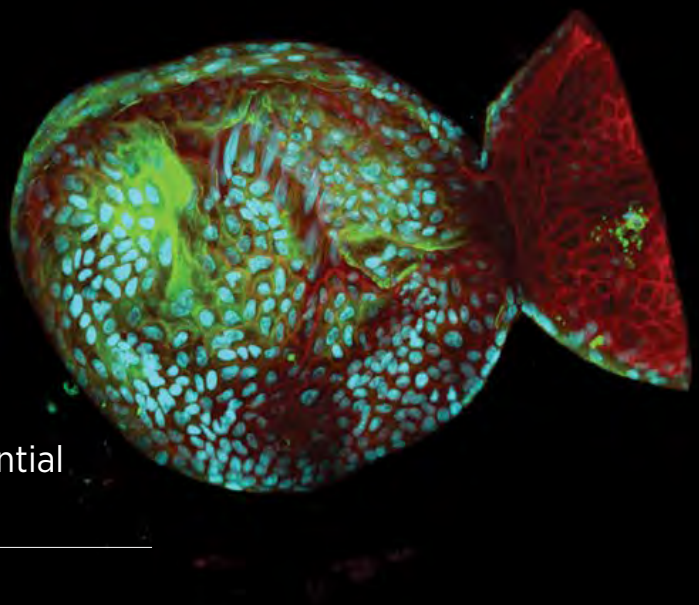
It is very difficult to predict who will directly benefit from our findings since our work is largely theoretical. What we mainly do is chart out the possibilities and strategies that engineers and experimentalists can undertake to realize completely new behavior. We're like cartographers mapping out the routes forward. I anticipate that our work will benefit the scientists and quantum engineers looking to building new types of quantum devices and sensors that rely on the delicate quantum properties that can be sustained in materials. ★

ABOUT THE RESEARCHER:

Justin Song received his PhD degree from Harvard University in 2014 and joined A*STAR's Institute of High Performance Computing (IHPC) in 2016 after spending two years at Caltech as a Burke Fellow and Sherman Fairchild Scholar in Physics. His research interests cover a broad range of key themes in theoretical condensed matter physics and emergent phenomena in quantum materials. Some current projects his lab is working on include novel charge/valley/spin/energy transport, topological materials, and 2D layered heterostructures. Song has received a number of awards for his research, including a National Research Foundation fellowship, a Caltech prize fellowship in physics, and an A*STAR National Science Scholarship. He also holds the appointment of Nanyang Assistant Professor at Nanyang Technological University's School of Physical and Mathematical Sciences.

CANCER BIOLOGY

Marking out gastric (cancer) stem cells



A novel surface marker may help identify potential cancer stem cells in the distal stomach.

Finding Waldo in a puzzle book filled with look-alike cartoon figures is no easy task at first glance. But if you keep your eyes peeled for his unique outfit, you'll be able to find him reliably on every page. In the same way, researchers looking for a specific subpopulation of cells first need to know what makes them distinct from all the other cells in the body.

Epithelial stem cells are specialist tissue populations that usually ensure the daily renewal of the linings of many organs. However, they also serve as key sources of many cancers following mutation. The resulting tumors themselves contain similar populations called cancer stem cells, which are responsible for cancer growth, dissemination and resistance to clinical therapies. Lgr5 is used to identify many epithelial stem cells, including those in the mouse distal stomach, but the equivalent population in the human stomach remains undiscovered.

"Furthermore, because of its expression on multiple stem cell populations throughout the gastrointestinal tract like the small intestine and colon, as well as the lack of available anti-LGR5 antibodies facilitating the isolation of both mouse and human stomach stem cells, we sought to identify a more highly expressed surface marker that is specific for stomach stem cells," said Nick Barker, a Research Director at A*STAR's Institute of Medical Biology (IMB).

By comparing the genes in LGR5-expressing stem cells present in the small and large intestines as well as different parts of the stomach, the team first shortlisted six genes found primarily in the pylorus. Of these, AQP5 emerged as a promising candidate due to its robust, yet highly selective expression on the surface of pyloric stem cells, as well as the commercial availability of good anti-AQP5 antibodies.

"This is the first demonstration of stomach stem cells being important sources of Wnt-driven gastric cancer following mutation."

Using these antibodies, the team isolated AQP5-positive cells from a healthy human stomach for the first time, and showed these to be stem-cell-like by virtue of their ability to grow organoids—3D cellular structures resembling cells lining the stomach wall—*in vitro*.

Delving deeper into the molecular mechanisms driving oncogenesis in humans, the team employed quantum computing to identify key signaling pathways—including the Wnt pathway—that are commonly dysregulated in human gastric cancer. Using this knowledge, they targeted pathway mutations found in mouse gastric stem cells *in vivo*, resulting in the rapid generation of invasive cancers in the distal stomach.

"This is the first demonstration of stomach stem cells being important sources of Wnt-driven gastric cancer following mutation," said Barker.

The resulting mouse gastric cancers contained an AQP5-expressing subpopulation, which behaved as cancer stem cells in organoid assays. Similarly, most human gastric cancers were found to harbor similar subsets of AQP5-expressing cells, suggesting the clinical relevance of the team's findings.

"If human AQP5-expressing gastric cancer cells are indeed cancer stem cells, it will be an important therapeutic target for the future development of more effective treatments in the clinic," said Barker.

Moving forward, the team plans to further evaluate human AQP5-expressing cells as potential gastric cancer stem cells through *in vivo* transplantation experiments and explore whether AQP5 itself influences tumor migration, invasion and survival. They hope to eventually establish AQP5 as a novel therapeutic target to improve gastric cancer diagnosis and treatment in the clinic. ★

ABOVE
A mouse stomach organoid grown from a single AQP5-expressing stem cell (AQP5 stained green).

1. Tan, S.H., Swathi, Y., Tan, S., Goh, J., Seishima, R., *et al.* AQP5 enriches for stem cells and cancer origins in the distal stomach. *Nature* **578**, 437–443 (2020).

CANCER BIOLOGY

Targeting triple-negative breast cancer

A*STAR scientists have identified a microRNA that can potentially be targeted for the treatment of triple-negative breast cancer.

With advances in medicine, a cancer diagnosis is no longer regarded as a death sentence, especially if the disease is caught early. Yet, a one-size-fits-all treatment for cancer remains elusive because no two cancers are the same.

For instance, breast cancer alone has many subtypes. Hormone-sensitive breast tumors express estrogen and progesterone receptors which can be targeted by drugs mimicking the molecular shape of the two natural hormones. Another class of breast tumors with the HER2 protein on their surface can be treated with an antibody drug, Herceptin.

Meanwhile, some breast tumors express neither hormone receptors nor HER2. These tumors come under the category of triple-negative breast cancer (TNBC), and the prognosis for patients with TNBC tends to be poor due to the lack of available treatment options.

Instead of searching for druggable receptors on TNBC, researchers led by Prabha Sampath at A*STAR's Skin Research Institute of Singapore (SRIS) screened triple-negative breast tumors for microRNAs, which are short sequences of nucleotides that regulate gene expression by binding to and destroying messenger RNA.

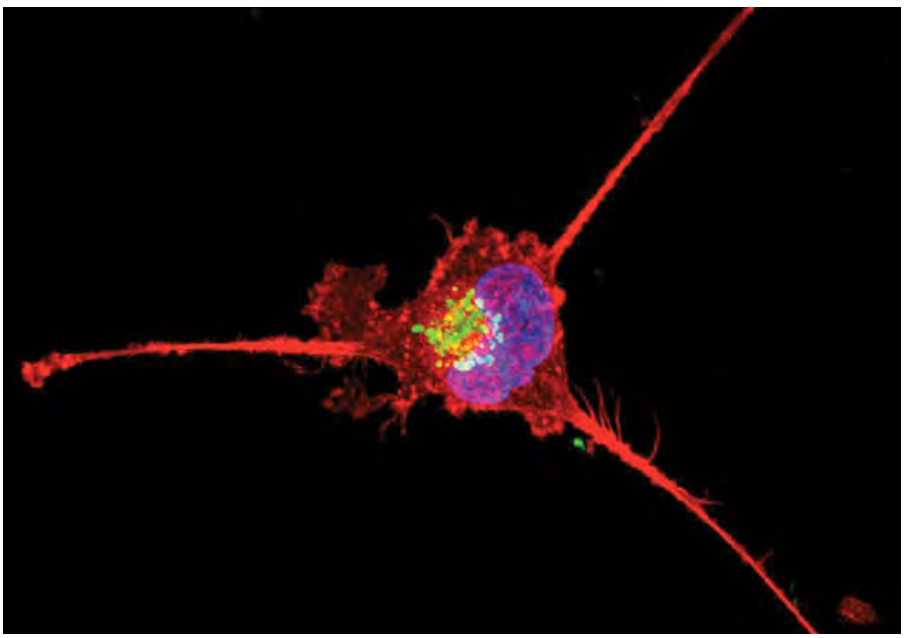


Photo credit: National Cancer Institute / Science Photo Library

"We discovered that a microRNA species called miR-138 is expressed in TNBC but absent in healthy breast tissue and other types of breast tumors," Sampath explained, adding that "the greater the abundance of miR-138, the lower are the chances of patient survival."

Further experiments revealed that miR-138 blocks the production of the tumor suppressor protein TUSC2. Hence, when miR-138 expression is elevated, TUSC2 levels drop and TNBC cells divide more rapidly.

On the other hand, by blocking the activity of miR-138 in TNBC cells with an oligonucleotide (a short nucleotide strand that binds to and neutralizes miR-138), the researchers were able to inhibit cell division and induce programmed cell death. In mice, breast tumors depleted of miR-138 were also significantly smaller than breast tumors that expressed miR-138.

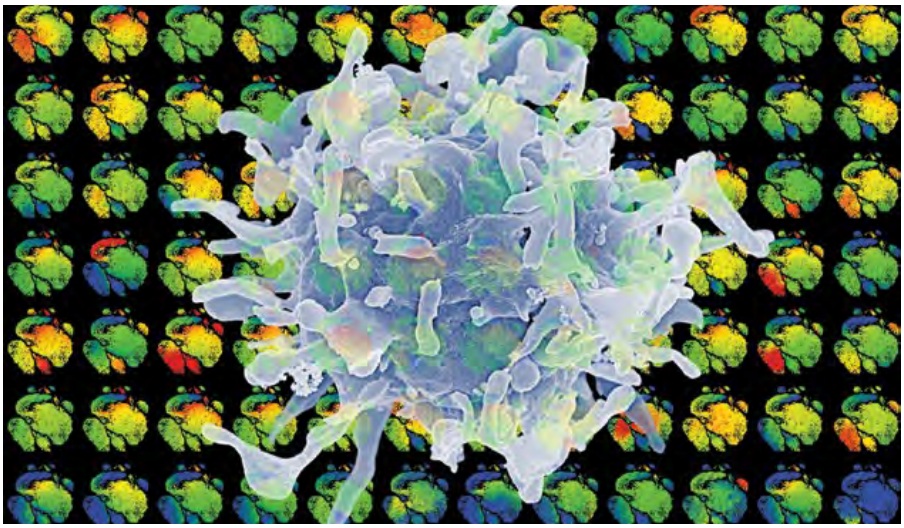
"The current mainstay for TNBC treatment is chemotherapy. As a critical microRNA required for cancer cell survival and growth, miR-138 is an attractive therapeutic target for combating TNBC," Sampath said.

However, she noted that therapeutic oligonucleotides targeting microRNAs such as miR-138 must first withstand degradation, be delivered precisely to the tumor tissue, then be taken up efficiently by cancer cells. These are hurdles that Sampath and her team are looking to overcome.

"We have a patent application on the anti-miR-138 oligonucleotides, which we are developing for therapeutic use in TNBC and glioblastoma, an aggressive brain cancer," she said. ★

LEFT
Triple-negative breast cancers, which are traditionally difficult to treat, might be susceptible to therapies targeting cancer-specific microRNA.

1. Nama, S., Muhuri, M., Di Pascale, F., Quah, S., Aswad, L., *et al*. MicroRNA-138 is a Prognostic Biomarker for Triple-Negative Breast Cancer and Promotes Tumorigenesis via TUSC2 repression. *Scientific Reports* **9**, 12718 (2019).



IMMUNOLOGY

Sorting cells in the blink of an AI

A*STAR scientists can now classify immune cell populations with greater precision thanks to a machine-learning algorithm.

To the untrained eye, a blood smear under the microscope reveals two types of immune cells: red blood cells and white blood cells. But immunologists know that white blood cells can be further categorized into a staggering array of subpopulations, distinguished by the genes, or markers, they express.

Over the years, scientists have found specific sets of markers that identify different immune cell populations. But as the library of markers grows, so does the complexity of correctly assigning markers to a particular immune cell subtype, especially when those subtypes overlap in function and location in the body.

Florent Ginhoux, a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SIgN), views this complexity as a classification problem that machine learning is well suited to solve. In a study published in the journal *Immunity*, his team devised a method called InfinityFlow, which leverages machine learning to characterize immune cell populations based on 332 markers. Collaborators from Greece, the Netherlands and the US were involved in the study.

"The innovativeness of our approach lies in integrating the data on all 332 markers and analyzing them using a machine-learning algorithm," Ginhoux explained. "This allowed us to predict which sets of markers best defined which immune subtypes."

The researchers used their technique to clarify the identities, functions and lineages of two types of immune cells: conventional dendritic cells and classical monocytes. Previously, a marker called CD14 was thought to be a positive and definitive identifier of classical monocytes. However, the analysis by Ginhoux's team revealed that a subset of cells expressing CD14 were not monocytes, but belonged to the dendritic cell family—they were in fact a population of cells called DC3, which are known to promote inflammation.

Hence, instead of using CD14 as a marker for monocytes, the researchers recommended two alternative markers, CD88 and CD89, instead. On the other hand, they found that DC3 cells could be identified based on their expression of CD5, CD14 and CD163 markers.

Further analysis showed that DC3 cells play a significant role in systemic lupus erythematosus, an autoimmune disease more commonly diagnosed in women and characterized by a butterfly shaped rash on the face. DC3 cells secreted several pro-inflammatory molecules such as IL-1α and CXCL1, which are known to contribute to lupus onset and progression.

Ginhoux noted that the InfinityFlow method used in this study will be useful for identifying immune cell types involved in other diseases such as cancer and atopic dermatitis. "From a clinical perspective, we may get to a point where we can pinpoint which immune cell is the 'bad guy' and develop drugs to kill or remove it," Ginhoux said.

"We're also preparing to release a paper detailing how to use InfinityFlow for profiling immune cells so that the technique is more accessible to the wider research community," he concluded. ★

ABOVE
A machine-learning algorithm called InfinityFlow is helping scientists rapidly classify diverse immune cell populations.

1. Dutertre, C.A., Becht, E., Irac, S.E., Khalilnezhad, A., Narang, V., *et al*. Single-Cell Analysis of Human Mononuclear Phagocytes Reveals Subset-Defining Markers and Identifies Circulating Inflammatory Dendritic Cells. *Immunity* **51**(3), 573-589.e8 (2019).

Photo credit: © Singapore Immunology Network (SIgN)

STEM CELLS

Unlocking the full potential of stem cells

Modifying how embryonic stem cells use sugar can switch them into a totipotent state, A*STAR researchers say.

The 2012 Nobel Prize in Physiology and Medicine was jointly awarded to Shinya Yamanaka and John Gurdon for their discovery that mature cells can be reprogrammed to take on a stem-cell-like state. These reprogrammed cells, known as induced pluripotent stem cells (iPSCs), regain the ability to differentiate into a range of cell types in the body.

However, these iPSCs are not totipotent—they are unable to form the placenta. By this definition, even embryonic stem cells (ESCs) are not totipotent. The classification of totipotency is therefore reserved strictly for cells formed during the earliest stages of embryonic development (the zygote and two- to four-cell stages).

"Totipotent stem cells are the most versatile of the stem cell types," said Wee-Wei Tee, a Principal Investigator at A*STAR's Institute of Molecular and Cell Biology (IMCB). "In this study, we found that we can activate the totipotent state simply by tweaking the gene expression and metabolic programs of ESCs."

Tee's team first analyzed the complete gene expression profiles, or transcriptomes, of pre-implantation mouse embryos at various development stages. Using a hierarchical clustering algorithm, the researchers were able to identify stage-specific gene signatures, allowing them to focus their attention on genes expressed at the two-cell stage of embryonic development.

"This unbiased approach led us to uncover, for the first time, a maternal factor called negative elongation factor A (NELFA) that is involved in totipotent gene expression," Tee explained.

The researchers then overexpressed NELFA in mouse ESCs and observed that genes associated with totipotency were upregulated. They found that the NELFA protein interacted with another protein, Top2a, to activate the transcription factor Dux, which is responsible for increasing the expression of the totipotency gene set.

Further delving into the biological processes altered by NELFA in mouse ESCs, the researchers noticed that glycolysis—the pathway by which cells break down sugar—was suppressed during the two-cell stage of embryonic development. Suspecting that this was a characteristic of totipotent cells, the researchers decided to inhibit glycolysis in ESCs using a chemical that mimics glucose.

They found that the inhibition of glycolysis indeed caused ESCs to revert to a totipotent-like state. Concordantly, NELFA expression was increased in glycolysis-inhibited ESCs. These findings suggest that NELFA is a master regulator of totipotency.

"Discovering this method of inducing totipotency in cells allows us to engineer cells with maximum cell plasticity, thus increasing the potential applications of regenerative medicine," said Tee.

Moving forward, Tee and colleagues intend to identify non-genetic means, such as the use of small molecules and specific culture conditions, to induce and stably propagate totipotent cells from a variety of cell types.

"Non-transgene approaches are important for cell replacement therapies," Tee noted. ★

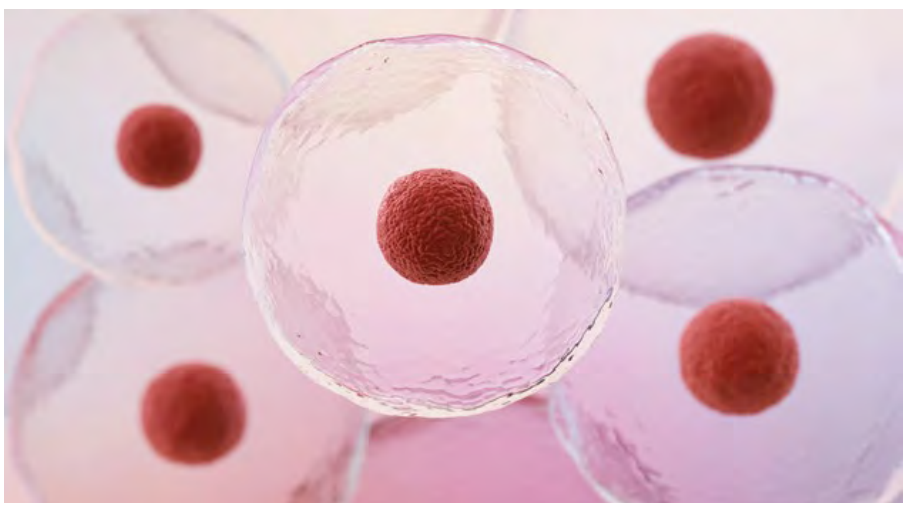


Photo credit: Anusorn Nakdee / Shutterstock

LEFT
Inhibiting the breakdown of glucose in embryonic stem cells can make them totipotent, researchers say.

1. Hu, Z., Tan, D.E.K., Chia, G., Tan, H., Leong, H.F., *et al*. Maternal factor NELFA drives a 2C-like state in mouse embryonic stem cells. *Nature Cell Biology* **22(2)**, 175-186 (2020).

REGENERATIVE MEDICINE

Why stress makes muscles grow

A protein called SUN1 enables muscle cells to respond to mechanical forces by modifying microRNA levels.

In the context of bodybuilding, the aphorism 'no pain, no gain' has literal meaning—when a weightlifter works out, he or she is causing muscle fibers to tear and regenerate, which increases the number and size of those fibers. Underlying these changes are molecular switches that instruct a muscle cell to divide, grow and replace its worn-out counterparts.

Probing the fundamental biology of muscle cells in mice, Tsui Han Loo, a Scientist at A*STAR's Institute of Medical Biology (IMB), and Colin Stewart, the Deputy Executive Director of IMB, have identified a key pathway regulating muscle regeneration. The research, performed in collaboration with colleagues in the UK and France, reveals the pivotal role of a protein called SUN1.

SUN1 is a component of a larger protein complex that connects the nucleus to the cytoskeleton in cells. The existence of such a protein complex suggests that mechanical forces, such as those exerted by and on muscle cells, can be sensed by the nucleus to elicit an appropriate cellular response.

"RTL1, or the biochemical pathways it regulates, could be a therapeutic target for muscular dystrophies."

Using a technique known as a yeast two-hybrid screen, Stewart's team first identified other proteins that interact with SUN1. Among the interacting proteins, the researchers found a protein complex involved in the processing of microRNAs (miRNAs)—short sequences of nucleotides which silence specific instructions from the cell's nucleus. Further experiments showed that SUN1 impaired miRNA processing in muscle cells.

Notably, when the scientists deleted the SUN1 gene in muscle cells, they observed that the levels of four miRNAs—miR-127, miR-431, miR-433 and miR-434-3p—were increased. These four miRNAs prevented the production of a protein named RTL1, the loss of which was associated with delayed muscle regeneration in a mouse model.

Conversely, RTL1 overexpression results in increased muscle growth, a feature first noted in callipyge sheep, named for their 'beautiful buttocks.' The results indicate that SUN1 maintains RTL1 expression in muscle cells at the right levels and is critical for efficient muscle regeneration.

"RTL1, or the biochemical pathways it regulates, could be a therapeutic target for muscular dystrophies," said Stewart. He added that since RTL1 expression levels are high in the growing muscles of young mice but decline with entry into adulthood, it will be interesting to establish what happens to the expression of RTL1 when muscles start to age.

"Can the activation or re-expression of RTL1 in old muscle defer muscle breakdown and contribute to better muscle health? This is a question that we want to pursue the answers to in the future," he concluded. ★

BACKGROUND

After a hard workout, muscle fibers need to be regenerated. Researchers now have a better understanding of the molecular processes involved.

1. Loo, T.H., Ye, X., Chai, R.J., Ito, M., Bonne, G., *et al.* The mammalian LINC complex component SUN1 regulates muscle regeneration by modulating drosha activity. *eLIFE* **8**, e49485 (2019).

Photo credit: WhiteDragon / Shutterstock

BIOTECHNOLOGY

Aid for chronic wounds

A new generation of smart dressings could help to guard against the danger of wounds that do not heal.

A simple cut or burn may barely register as a concern for most people, but what if that wound never healed? Without the proper healing processes, even the smallest of wounds may take months to heal or turn into potentially fatal infections.

For the elderly and diabetic patients, impaired acute wound healing is a very real fear. Compromised blood vessels as a result of age or diabetes lead to poor blood, oxygen and nutrient supply—all of which impair normal healing processes and lead to chronic wounds.

Besides that, the chronic inflammation in wounds can stimulate the release of leukocytes and reactive oxygen species that impede healing and prematurely age cells. Higher pH and proteolytic enzyme activity levels at the wound site can also prevent a wound from healing the way it is supposed to.

However, not all of these factors are necessarily present in every chronic wound. As a result, it can be hard for a healthcare worker to decide on a suitable course for treatment.

To assist with the diagnosis and treatment of chronic wounds, researchers from A*STAR's Skin Research Institute of Singapore (SRIS) and Nanyang Technological University, Singapore (NTU) discussed a range of smart dressings that can react to and treat the different features of chronic wounds through novel drug combinations and delivery mechanisms.

"As there are often many things going wrong in a chronic wound, it is unlikely that a single treatment can fix all of them. Combinatorial treatments are thus most likely to help in the future," said David Becker, the corresponding author of this review article in *Advanced Drug Delivery Reviews*.

Futuristic smart dressings can be integrated into the wound bed to replace lost tissue and stimulate cell growth, Becker said. The dressings act as a reservoir for the sustained release of drugs to the wound site for as long as needed, or even change their delivery profile throughout the healing process.

"Current treatments deal with recognized problems as and when they occur in a wound, but different stages of the healing process might need different treatments."

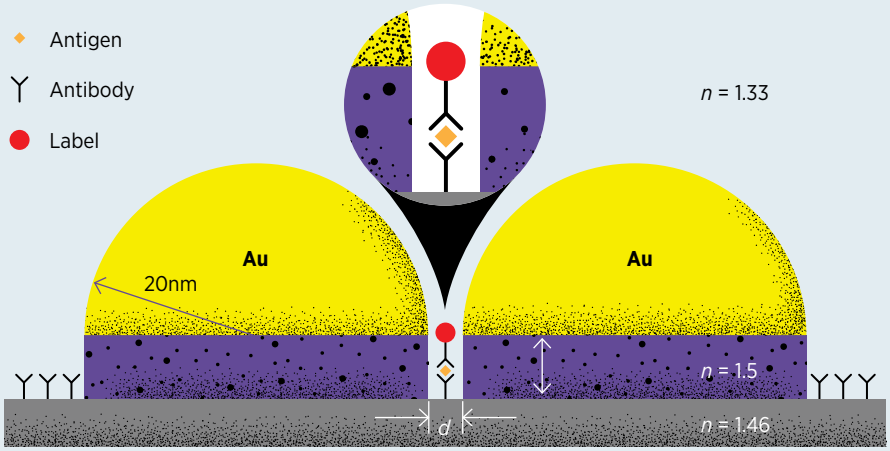
"For instance, a high pH could trigger the release of a buffer that can bring the pH back to normal," he explained. "Current treatments deal with recognized problems as and when they occur in a wound, but different stages of the healing process might need different treatments."

At the moment, Becker is collaborating with clinicians at Tan Tock Seng Hospital and engineers and chemists at NTU to develop an antisense-based drug that promotes chronic-wound healing. "This system is currently in clinical trials for the treatment of chronic corneal wounds," he said. ★

ABOVE
Smart dressings that respond to changes such as pH could help chronic wounds heal better.

1. Chin, J.S., Madden, L., Chew, S.Y., Becker, D. Drug therapies and delivery mechanisms to treat perturbed skin wound healing. *Advanced Drug Delivery Reviews* **149**, 2–18 (2019).

Photo credit: Pao Laroid / Shutterstock



QUANTUM MECHANICS

A quantum leap for biosensors

A biosensor designed with quantum properties is 15 times more sensitive than classical sensors.

Easing COVID-19 lockdown restrictions and returning to a semblance of normal life will require numerous safety precautions to be put in place. Antigen testing, in particular, has been touted as a key measure for easing lockdowns, with businesses and governments even mulling over the use of 'immunity certificates.'

Quantifying the levels of antigens in a sample is currently carried out using a method called an immunoassay, where a target molecule is captured by an antibody specific for it. One variant of this method, plasmonic immunoassay, detects altered plasmon oscillation and changes in reflected light when a target molecule is captured onto a metal surface.

At infinitesimal quantities of a target molecule approaching the detection limit, however, frequency shifts become subtler and harder to detect. Now, scientists led by Lin Wu from A*STAR's Institute of High Performance Computing (IHPC) and Ortwin Hess from Imperial College London have found a way to enhance the sensitivity of classical plasmonic immunoassays by applying principles based on quantum mechanics.

In their simulation of a quantum plasmonic immunoassay, a metal surface displays a pair of gold nanohemispheres.

"To the best of our knowledge, our paper describes the first proposal of a quantum plasmonic biosensor that is sensitive enough to detect single molecules."

Each pair—or nanodimer—is separated by a one-nanometer space where target molecule binding occurs. This space functions as a nanoscopic lens that focuses light on a nano-hotspot.

"At such a hotspot, light-matter interaction is enhanced so drastically that the system enters the strong-coupling regime, where the coupling exceeds dissipative rates," explained Wu.

Detection in their assay relies on a phenomenon called Rabi splitting, which is much more sensitive than classical sensing and no longer dependent on the concentration of the captured target molecule, Wu said. Through computational experiments, the researchers found a massive sensitivity boost of nearly 15 times compared to conventional plasmonic sensors.

"To the best of our knowledge, our paper describes the first proposal of a quantum plasmonic biosensor that is sensitive enough to detect single molecules," Wu said.

This method of strong coupling could also be used in applications such as monitoring air quality and food safety, as it would be possible to detect single molecules and conduct quantum sensing at room temperature. Wu acknowledged that their assay design remains difficult to achieve in reality at this point, but she hoped that their work would inspire advances in plasmonic immunoassay sensors.

"Moving forward, our research team at IHPC will continue collaborating with our colleagues at A*STAR and at the local universities to find innovative solutions for plasmonic applications, such as next-generation electronics and ultra-high sensitivity biosensors," she said. ★

ABOVE
By placing the antibody-antigen-antibody complex between two gold hemispheres on top of a dielectric spacer, the signal from the label becomes strongly coupled with plasmonic resonance, amplifying the signal such that even single molecules can be detected.

1. Kongsuwan, N., Xiong, X., Bai, P., You, J., Png, C.E., Wu, L., Hess, O. Quantum Plasmonic Immunoassay Sensing. *Nano Letters* **19**: 5853-5861 (2019).

NANOTECHNOLOGY

With plasmonic color, less is more

A new technique for harnessing surface plasmon resonance may allow brilliant colors to be captured more easily and cheaply.

Unlike pigment-based color, plasmonic color is created when light reflects and interferes with fine arrays of metallic nanostructures, which confine electrons and force them to resonate at frequencies specific to the desired color. It can be found in the security holograms we routinely see behind our credit cards, where a chaotic pattern of tiny dots under a microscope produces a floating image with faint colors. While plasmonic holograms avoid problems such as toxicity and fading associated with physical dyes, the limited range and low vibrancy of plasmonic color have prevented widespread adoption.

But new research at A*STAR could one day make those colors more vivid and bright, thanks to the research conducted by Jinghua Teng, a Principal Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE), in collaboration with Cheng-Wei Qiu and Aaron Danner from the National University of Singapore, and Joel Yang from the Singapore University of Technology and Design. Together, they have created shallow silver nano-disks for plasmonic color with fewer manufacturing steps.

"Usually, there are several steps involved in producing these disks. We first cover the silver with a protective photoresist pattern, and then etch away the uncovered silver, before finally removing the photoresist to give the desired disks," Teng explained.

However, when Menghua Jiang, a PhD student in Teng's lab, inspected the photoresist-patterned silver under cross-polarized light, he found that it reflected vivid colors—even before etching had been performed. Further experiments and computer modeling verified that stopping halfway had created photoresist-on-silver surface plasmon resonances, with less than a five percent spread in the wavelengths of light reflected.

Varying the size and spacing of the photoresist ellipses allowed the researchers to produce a wide range of colors, with enough brightness to replicate the entire color output of a standard RGB monitor and 98 percent of all colors produced by the latest ultra-high-definition TVs.

"Our results have shown, for the first time, that plasmonic coloration offers a range and depth of color matching—and even outclassing—competing nanotechnology based designs," Teng said. "Furthermore, our simple design and unique etch-free technique allow for much easier and cheaper manufacturing."

Teng envisions that this technology could see a variety of applications, such as anti-counterfeiting tags in bank notes and luxury goods, plasmon-based biosensors and high-resolution displays. His team will continue to develop tunable plasmonic colors for use in dynamic displays, as well as explore other design structures for color encryption. ★

Photo credit: rihaij / Pixabay

BOTTOM
Researchers have devised a way to produce a wider range of plasmonic colors that are brighter and more vivid.

1. Jiang, M., Siew, S.Y., Chan, J.Y.E., Deng, J., Wu, Q.Y.S., *et al*. Patterned resist on flat silver achieving saturated plasmonic colors with sub-20-nm spectral linewidth. *Materials Today* **35**, 99–105 (2019).

ELECTRONICS

Putting a new spin on communications

Magnetic nanostructures known as magnonic crystals could give long-distance communications a speed boost.

'To boldly go where no man has gone before' is the famous mission of the starship Enterprise in the 1960s television series *Star Trek*. However, in reality, our ambition to explore uncharted regions in space is hampered by many obstacles, such as our communication capabilities, which still suffer from delays when transmitting and receiving information over great distances. For example, a message sent from Mars would take about 13 minutes to reach Earth, hardly an ideal situation in emergencies.

In the quest to improve ultrafast communications, researchers at A*STAR's Institute of Materials Research and Engineering (IMRE), who were previously working at A*STAR's Data Storage Institute (DSI), are tapping on spin-wave-mediated communication based on ultrathin magnets.

"Studying artificial spin ice dynamics reveals their prospects for ultrafast communications."

Using sophisticated lithography processes, the researchers previously created a specific class of metamaterials called magnonic crystals. In the present study, the researchers used a unique type of magnonic crystal that possesses magnetic monopole-like behavior, a property that does not exist in nature. The resulting structures are known as artificial spin ice (ASI) systems, named after the distinctive arrangement of water molecules in ice, where each oxygen atom is surrounded by four neighboring hydrogen atoms in space.

"ASI systems are attractive due to their unique static and dynamic features. For application purposes, control and tuning their characteristics will be essential," said Abhijit Ghosh, a Scientist at IMRE. "Our study of the high-frequency dynamics in ASI systems and other types of magnonic crystals are aimed at unveiling the prospects of such structures for ultrafast futuristic communications."

Using experimental techniques such as high-frequency ferromagnetic resonance spectroscopy in combination with micromagnetic simulations and semi-analytical techniques, Ghosh and his team found that the geometrical parameters of the nanostructured magnets strongly influence their high-frequency (microwave) characteristics.

The team then explored how introducing different geometrical parameters—generated through nanofabrication—influenced the magnetic properties of their ASI system. They showed that manipulating the dimensions of the magnonic crystals and the thickness of the magnetic layers could enable scientists to design ASI systems for specific functions.

In the future, ASI systems could be useful in diverse and intriguing applications beyond communications, such as neuromorphic computing for developing artificial intelligence and enhancing our data storage capabilities, added Ghosh. ★

BACKGROUND

Communication over long distances can be made faster with artificial spin ice systems.

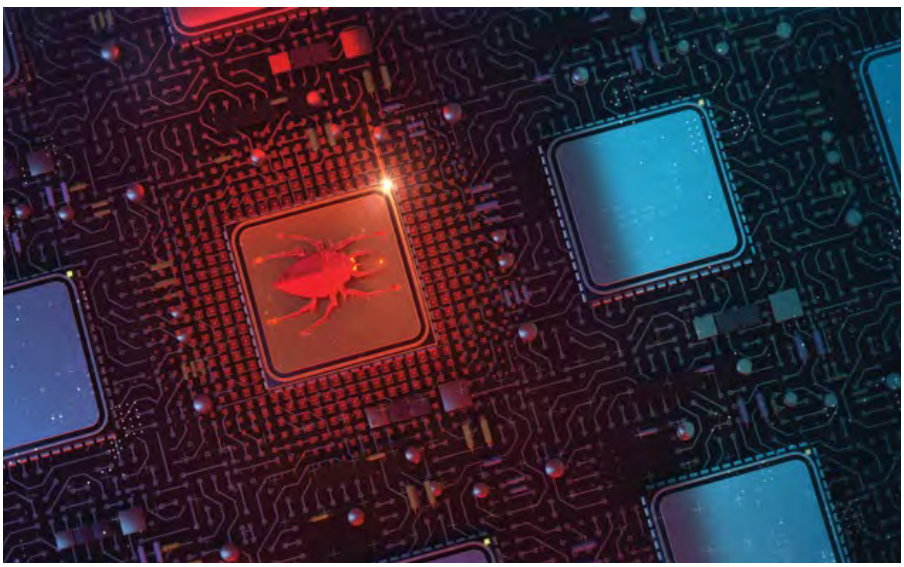
1. Ghosh, A., Ma, F., Lourembam, J., Jin, X., Maddu, R., *et al.* Emergent Dynamics of Artificial Spin-Ice Lattice Based on an Ultrathin Ferromagnet. *Nano Letters* **20**: 109-115. (2020).

Photo credit: greenbutterfly / Shutterstock

CYBERSECURITY

Leaving cyberattackers lost in the fog

Arresting cybersecurity attacks close to their source can help secure the industrial Internet of Things.



As wireless communication becomes cheaper and faster, more and more devices are being hooked up to the Internet of Things (IoT), promising real-time communication and control across a variety of sensors and devices. Applied in an industrial context—in what is known as industrial IoT (IIoT)—these technologies pave the way for predictive maintenance of machinery and remote monitoring of processes, among other useful functions.

However, with increased connectivity comes greater exposure to cyberattacks. "IIoT systems involve many devices distributed across locations with weak security protection, making them vulnerable to compromise," said Luying Zhou, a Research Scientist at A*STAR's Institute for Infocomm Research (I^2R).

"They are particularly prone to a distributed-denial-of-service, or DDoS, attack, in which compromised devices swamp the IIoT system in large volumes of communication traffic that consume the system or network resources, leaving the system unavailable for normal operation," he explained.

A DDoS attack can be defeated by detecting the compromised device and filtering out its suspicious communication. However, peripheral devices may not be able to detect if their fellow devices have been compromised, while the centralized cloud server may only detect an attack too late, after the increased traffic has already knocked out parts of the network.

As such, Zhou and his team devised a 'fog-computing' approach with a three-level architecture—field, local and cloud levels—that allows IIoT system operators to carry out in-depth investigation and analysis of malicious network behaviors.

In their scheme, firewalls and station servers at the field and local levels are configured to monitor and control traffic on nearby devices. Meanwhile cloud computing services allow traffic data analyses and time-sensitive tasks to be executed close to the system's end users. "Our method protects the whole IIoT system while reducing unnecessary data transfers," Zhou said.

Simulating an IIoT system under DDoS attack, the researchers showed that the fog-computing approach achieves faster detection and mitigation of malicious network behaviors. In their experiments, normal connectivity was restored in milliseconds when fog-computing was applied.

"Since attack traffic could be blocked near the attacking sources, we were able to achieve a faster detection time via cloud server coordination, a higher detection rate, and savings in bandwidth resources," Zhou said.

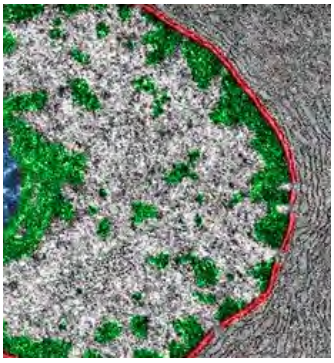
"We are confident that our approach will be a valuable resource for effectively detecting and stopping DDoS and other attacks," he concluded. ★

ABOVE
Preventing distributed-denial-of-service attacks is a crucial part of securing the Internet of Things.

1. Zhou, L., Guo, H., and Deng, G. A fog computing based approach to DDoS mitigation in IIoT systems. *Computers & Security* **85**, 51-62 (2019).

NEXT ISSUE

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



AGING

STOPPING PREMATURE AGING IN ITS TRACKS

DNA damage associated with premature aging in Hutchinson-Gilford Progeria Syndrome can be prevented if the abnormal protein progerin is removed before DNA replication.

REGENERATIVE MEDICINE

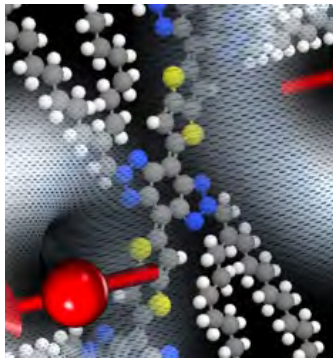
SCALING UP STEM CELL PRODUCTION

By enhancing stem cell proliferation, this newly developed heparan sulphate glycosaminoglycan bio-additive lowers the barriers to regenerative medicine.

IMMUNOLOGY

WHERE IMMUNE CELL REINFORCEMENTS COME FROM

A*STAR scientists have identified a molecular marker for tracing the origins of immune cells that reside within tissues and organs.



POLYMER SCIENCE

SMOOTHING THE PATH FOR CONDUCTIVE POLYMERS

Polymers with a special property called proquinoidal character can be used to make organic conductors a thousand to a billion times more conductive.

Agency for Science, Technology and Research
SINGAPORE

RE-ENVISION THE FUTURE

At A*STAR, you will be part of a vibrant and innovative team that advances science and develops innovative technologies to further economic growth and improve lives.

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- **Be an entrepreneur and create your own start-up**

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I enjoy sharing knowledge as well as conducting my own research.

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- **Be involved in academia and science education**
- **Conduct scientific research at A*STAR**

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I have a curious mind and enjoy teamwork and communication.

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- **Lead a team of researchers to conduct research and collaborations**

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- **Develop scientific expertise**

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- National Science Scholarship (NSS PhD)
- A*STAR Graduate Scholarship (AGS)
- A*STAR Computing and Information Science (ACIS) Scholarship
- A*STAR – University of Warwick (AWP) EngD Partnership
- A*STAR International Fellowship (AIF)

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