A*STAR RESEARCH

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A*STAR Skin Research Labs (A*SRL)
Advanced Remanufacturing and Technology Centre (ARTC)
Bioinformatics Institute (BII)
Bioprocessing Technology Institute (BTI)
Experimental Drug Development Centre (EDDC)
Genome Institute of Singapore (GIS)
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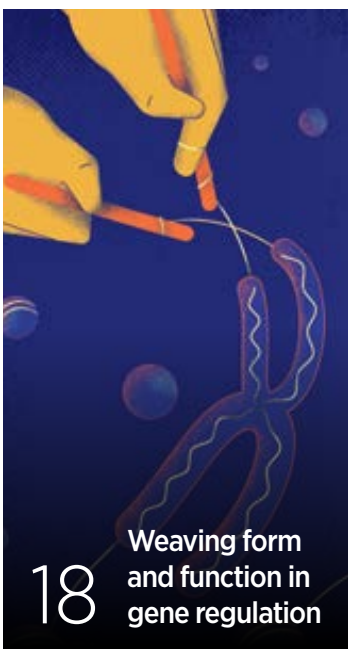

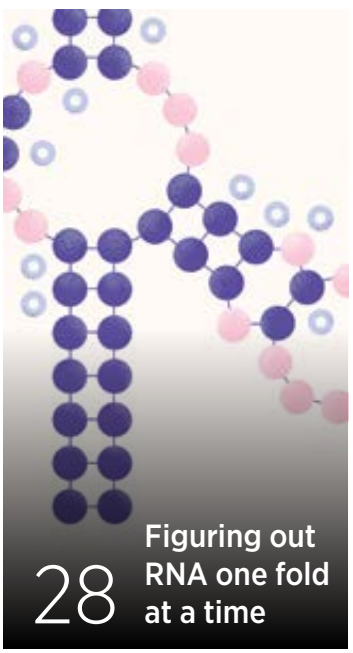

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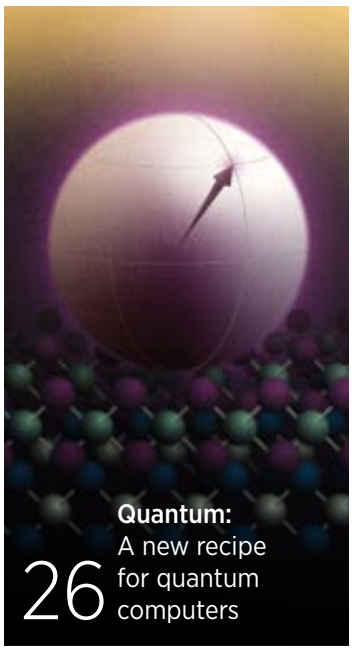
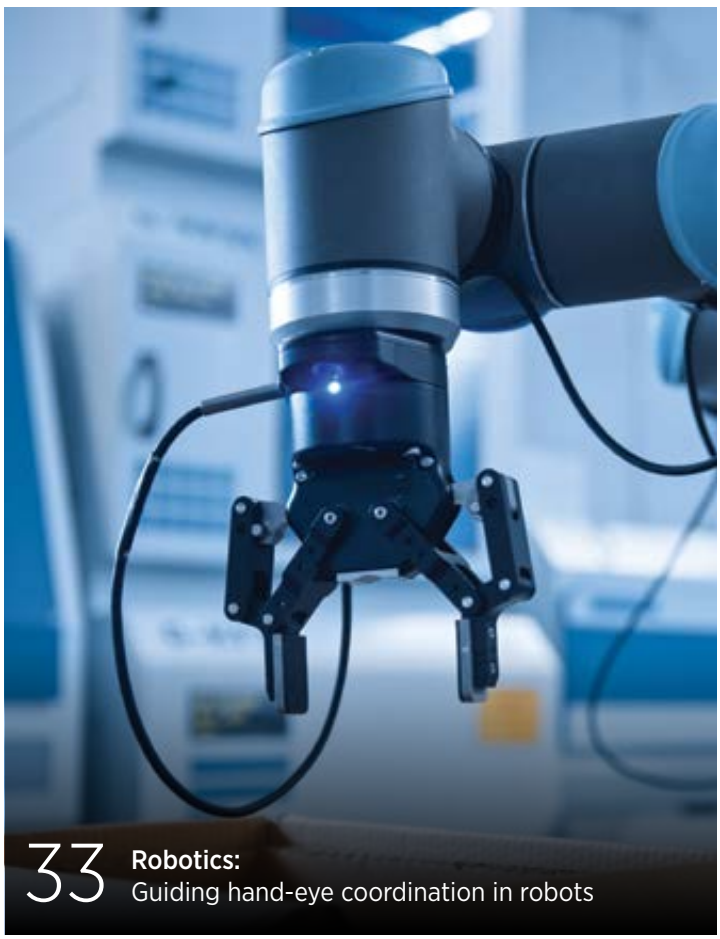




EDITORIAL NOTES

In the early 20th century, the concept of the 'magic bullet' was coined by Nobel laureate Paul Ehrlich to describe an ideal disease treatment that causes no collateral damage to the patient. The drive to unearth this magic bullet has since been the motivation behind the discovery of revolutionary therapies such as chemotherapy and antibiotics.

In the present day, with our deeper understanding of how diseases develop and progress at the molecular level, magic bullets are continually being studied and being developed—especially in the field of precision medicine. By taking a closer look at ribonucleic acid (RNA), a tiny and yet mighty building block of life, A*STAR researchers are pushing the frontiers of what RNA-based therapies can do.

From developing targeted treatments for cancer and eczema to creating nanoparticles for effective drug delivery, take a deep dive into the fascinating world of RNA-based therapies in our cover story 'Nucleic acid therapeutics: riding the wave of mRNA (p. 08)'.

Meanwhile, Mei Sheng Lau from the Institute of Molecular and Cell Biology (IMCB) is looking at intricate ways in which chromatin can fold to silence genes and affect their expression in the feature 'Weaving form and function in gene regulation (p. 18)'. By understanding the complex ways in which chromatin fold, Lau hopes to provide insights into disease development and support the discovery of new treatments.

At the Genome Institute of Singapore (GIS), Yue Wan and Ashley Aw are developing techniques for elucidating the structures and functions of RNA. Read about their work and the importance of mentorship in advancing science in 'Figuring out RNA one fold at a time (p. 28)'.

Beyond molecular biology, A*STAR researchers have also been making discoveries in materials science and robotics. Find out more about their achievements in these fields in 'A three-in-one sustainable, self-healing coating (p. 24)' and 'Guiding hand-eye coordination in robots (p. 33)'.

To learn more about the latest developments from A*STAR scientists, visit our website at **research.a-star.edu.sg**. Stay up-to-date by following us on Twitter at **@astar_research**, LinkedIn at **A*STAR Research** and Telegram at **A*STAR Research**.

On the cover
A*STAR researchers are unlocking the potential of messenger RNA to be used in drug development.

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

SUSTAINABILITY

Greener solutions to pandemic pollution

A*STAR scientists uncover surprising truths behind biodegradable face masks, prompting the need for greener alternatives.

Since the onset of the COVID-19 pandemic two years ago, the use of face masks has been a major protective measure in reducing the chance of getting infected. This practice, however, has now turned into an environmental catastrophe: disposable, single-use masks are ending up everywhere from street corners to coral reefs, worsening the already serious plastic pollution crisis.

Growing public concerns have inspired mask manufacturers to turn to eco-friendly materials such as polylactic acid (PLA)—a low-cost, water-resistant and antimicrobial polymer made from corn starch. However, while much is known about how pure PLA degrades over time, there is a need for more information on how PLA breaks down when woven into fabrics for face masks, especially when mixed with other fossil-based polymers.

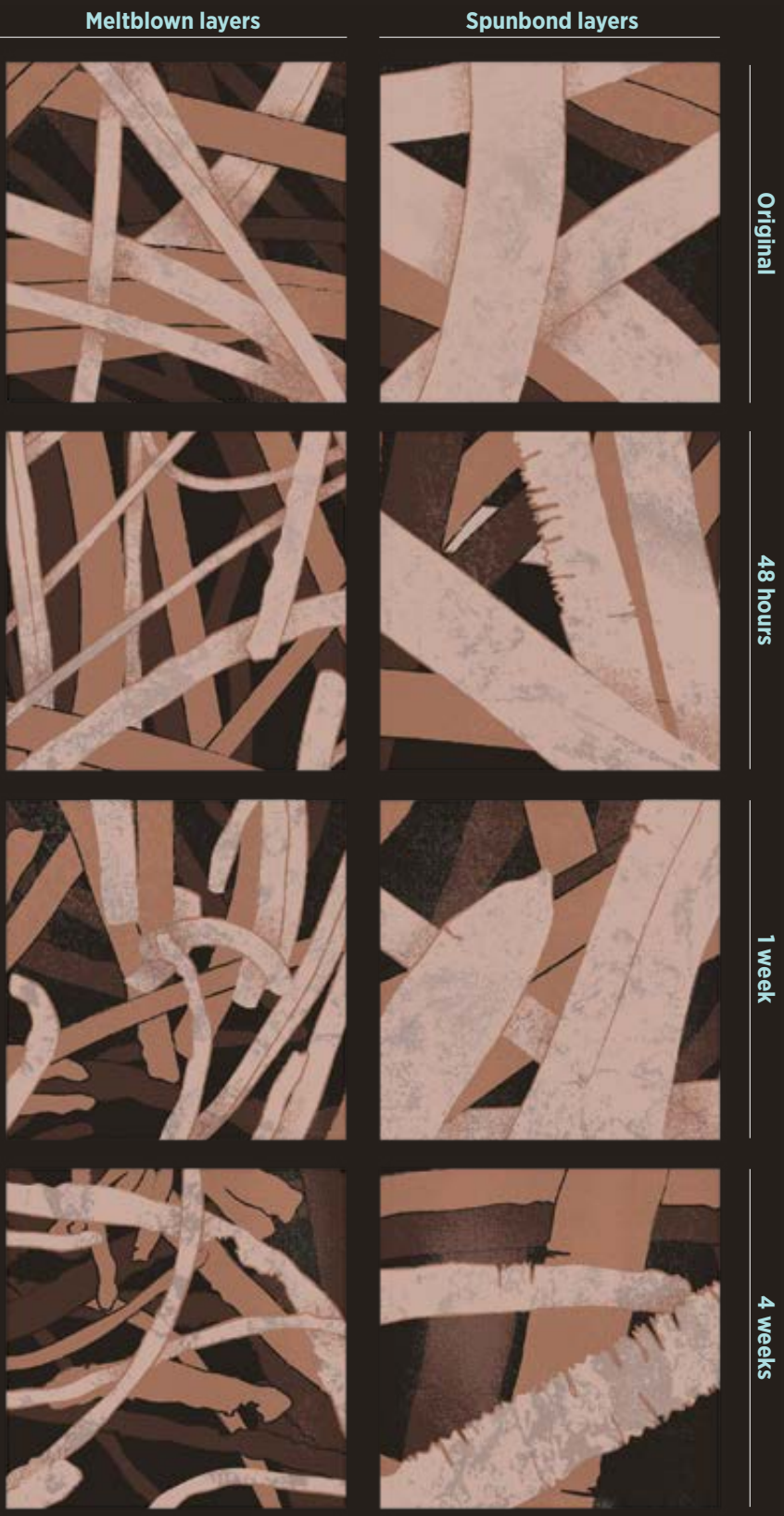
"We need to characterise its biodegradation so that we can optimise the rate, such that masks do not degrade during usage, but rapidly do so after being disposed of," said Xian Jun Loh, Executive Director at A*STAR's Institute of Materials Research and Engineering (IMRE).

To understand whether biodegradable PLA face masks are truly a greener alternative, Loh and his colleagues performed lab-based simulations to study how they degrade over time. This involved PLA face masks being soaked in a panel of acidic, basic and neutral solutions. Pieces from cut-up face masks were also mixed with sewage sludge to recreate how they might break down in the natural setting.

The experiments revealed that PLA did not degrade completely, despite the face masks being marked as eco-friendly. The masks in acid and neutral solutions remained relatively unchanged in terms of their weight. The ones submerged in basic solutions, however, did lose a quarter of their initial weight after a week.

Images captured using high-powered scanning electron microscopy showed that the thickness of the masks' PLA fibres influenced their ability to break down. Fibres under seven micrometres thick degraded the most, while thicker ones remained mostly intact.

Photo credit: Nana Bolivani / Shutterstock



Scanning electron microscopy images of the polylactic acid face mask's meltblown (thinner) and spunbond (thicker) layers degrading in a basic solution over the course of four weeks.

"We need to characterise its biodegradation so that we can optimise the rate, such that masks do not degrade during usage, but rapidly do so after being disposed of."

The samples kept in sewage sludge displayed a similar trend. Those with thinner PLA fibres showed extensive degradation, losing more than a quarter of their weight after a month, while thicker fibres disintegrated at half the rate.

"With this knowledge, future mask material should contain PLA material with thinner fibres to increase the biodegradation rate," said Loh, adding that his team has already begun exploring this avenue. "Hopefully, we will be able to find an optimum thickness that can easily be mass produced for future applications." ★

Researcher
Xian Jun Loh, IMRE

IN BRIEF
Despite being touted as an eco-friendly material, masks made of polylactic acid barely degrade in acidic and neutral environments.

1. Soo, X.Y.D., Wang, S., Yeo, C.C.J., Li, J., Ni, X.P., *et al*. Polylactic acid face masks: Are these the sustainable solutions in times of COVID-19 pandemic? *Science of the Total Environment* **807** (3), 151084 (2022).

IMMUNOLOGY

Immune secrets of the symptom-free

Unique immune responses shield some COVID-19 patients from the disease's worst effects.

Not all SARS-CoV-2 infections are created equal. Some infected individuals bounce back quickly after mild symptoms subside, while others bear severe, life-threatening symptoms and long recovery times. Curiously, yet another group gets off completely scot-free. Though these asymptomatic individuals test positive, they are spared from the fever, cough and fatigue commonly associated with the disease.

While research on symptomatic patients have provided valuable insights into COVID-19's inner workings, studying their asymptomatic counterparts could support the development of better therapies. "Aside from identifying the mechanisms underlying disease progression during SARS-CoV-2 infection, it is also important to elucidate the ones underlying disease tolerance," said Lisa Ng, Executive Director at A*STAR Infectious Diseases Labs (ID Labs).

Unfortunately, existing studies on asymptomatic COVID-19 cases have not yielded any clear answers. Until now, scientists continue to debate whether this ability to fend off the coronavirus can be attributed to the body's first line of defense known as the innate immune system or the adaptive arm responsible for immune memory.

In search of more conclusive answers, Ng and colleagues analysed a cohort of 263 Singaporean COVID-19 patients, 48 of whom were asymptomatic. The team looked for clues from multiple angles, tracking gene signatures, characterising immune cells as well as measuring antibody and cytokine levels in samples obtained from the participants.

Crucially, the researchers identified an immunological tipping point that could be responsible for triggering the onset of COVID-19 symptoms. "We found that excessive pro-inflammatory responses and the regulation of T cell responses in COVID-19 patients are important factors that can influence symptom development in COVID-19," explained Ng.

The team also uncovered unique protective immune responses in asymptomatic patients that set them apart from their symptomatic equivalents: lower levels of inflammation, more active T cells and elevated tissue healing factors.

According to Ng, these findings set the stage for novel therapeutics that mirror the immune responses of asymptomatic patients by dampening pro-inflammatory immune pathways, while boosting levels of protective growth factors.

For now, the team will continue to track health outcomes in the asymptomatic group. "We are monitoring the asymptomatic patients longitudinally to study the longevity of the immunity raised from the primary SARS-CoV-2 infection," explained Ng. "We are also evaluating the efficacy of that immunity in long-term protection against subsequent exposures to SARS-CoV-2." ★

"Aside from identifying the mechanisms underlying disease progression during SARS-CoV-2 infection, it is also important to elucidate the ones underlying disease tolerance."

Researcher
Lisa Ng,
ID Labs

Photo credit: GoodStudio / Shutterstock

IN BRIEF
Asymptomatic COVID-19 patients have unique protective immune responses not seen in symptomatic patients, such as more active T cells and elevated tissue healing factors.

1. Chan, Y.H., Fong, S.W., Poh, C.M., Carissimo, G., Yeo, N.K.W., *et al.* Asymptomatic COVID-19: disease tolerance with efficient anti-viral immunity against SARS-CoV-2. *EMBO Molecular Medicine* **13** (6), e14045 (2021).

COVID-19

COVID-19's far-reaching effects from lung to liver

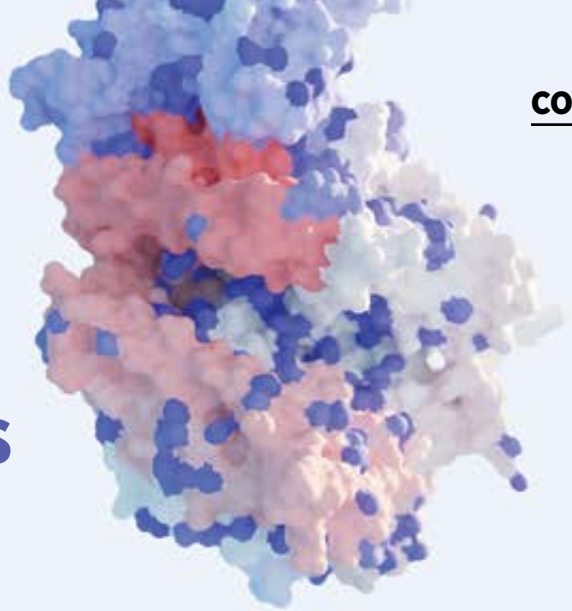


Photo credit: wimagine / Shutterstock

Using single-cell sequencing technology, A*STAR scientists have identified a rare population of liver cells susceptible to damage from SARS-CoV-2 infections.

By now, many people are familiar with COVID-19's respiratory symptoms: dry cough and shortness of breath, for instance, are among the most well-known early warning signs of infection. However, a significant number of COVID-19 patients with severe infection also go on to develop serious liver-related symptoms. Until now, the underlying mechanisms driving this process have remained elusive, making the clinical management of these patients particularly challenging.

In search of answers, Ramanuj DasGupta and a team of scientists from A*STAR's Genome Institute of Singapore (GIS) and Singapore Immunology Network (SIgN) turned to a comprehensive technology known as single-cell RNA sequencing to study SARS-CoV-2's impact on the liver.

"Single-cell RNA sequencing allows high-throughput gene expression profiling of thousands of individual cells," explained DasGupta, a Senior Group Leader at GIS. "The throughput and scale of this technology enable us to understand at single-cell resolution what genes are expressed, in what quantities and how they differ across thousands of cells within a heterogeneous tissue type."

The researchers profiled around 300,000 individual liver cells, looking for cell populations that express both the *ACE2* and *TMPRSS2* genes. In the respiratory system, these genes are known to be abundantly expressed, with the TMPRSS2 enzyme priming SARS-CoV-2's spike protein to latch on to the ACE2 protein receptor on host cells—two critical steps in the infection process.

"Our study paves the way for querying single-cell atlases for identifying cell types involved in viral entry and the impact of the virus on these cells."

From their analyses, the team found that these two genes are co-expressed in TROP2$^+$ progenitor cells, a distinct subset of cells lining the bile duct that facilitate liver regeneration in response to damage. Interestingly, the scientists also observed that patients with liver cirrhosis had more of these *ACE2* and *TMPRSS2*-expressing progenitor cells, suggesting that COVID-19 patients with existing liver damage may require more careful attention.

"Overall, our study suggests that COVID-19-associated liver dysfunction and co-morbidities may be associated with infection of the liver progenitors that could impair their regenerative capacity in patients exhibiting liver damage," explained DasGupta.

Going forward, the researchers intend to use single-cell RNA sequencing to study progenitor cells from other organs that may be susceptible to SARS-CoV-2 infection, especially considering the systemic internal damage often observed in fatal cases of COVID-19.

"Our study paves the way for querying single-cell atlases for identifying cell types involved in viral entry and the impact of the virus on these cells," added DasGupta. "The next line of investigation may lead to identifying novel ways of blocking viral entry in human tissue for better disease management." ★

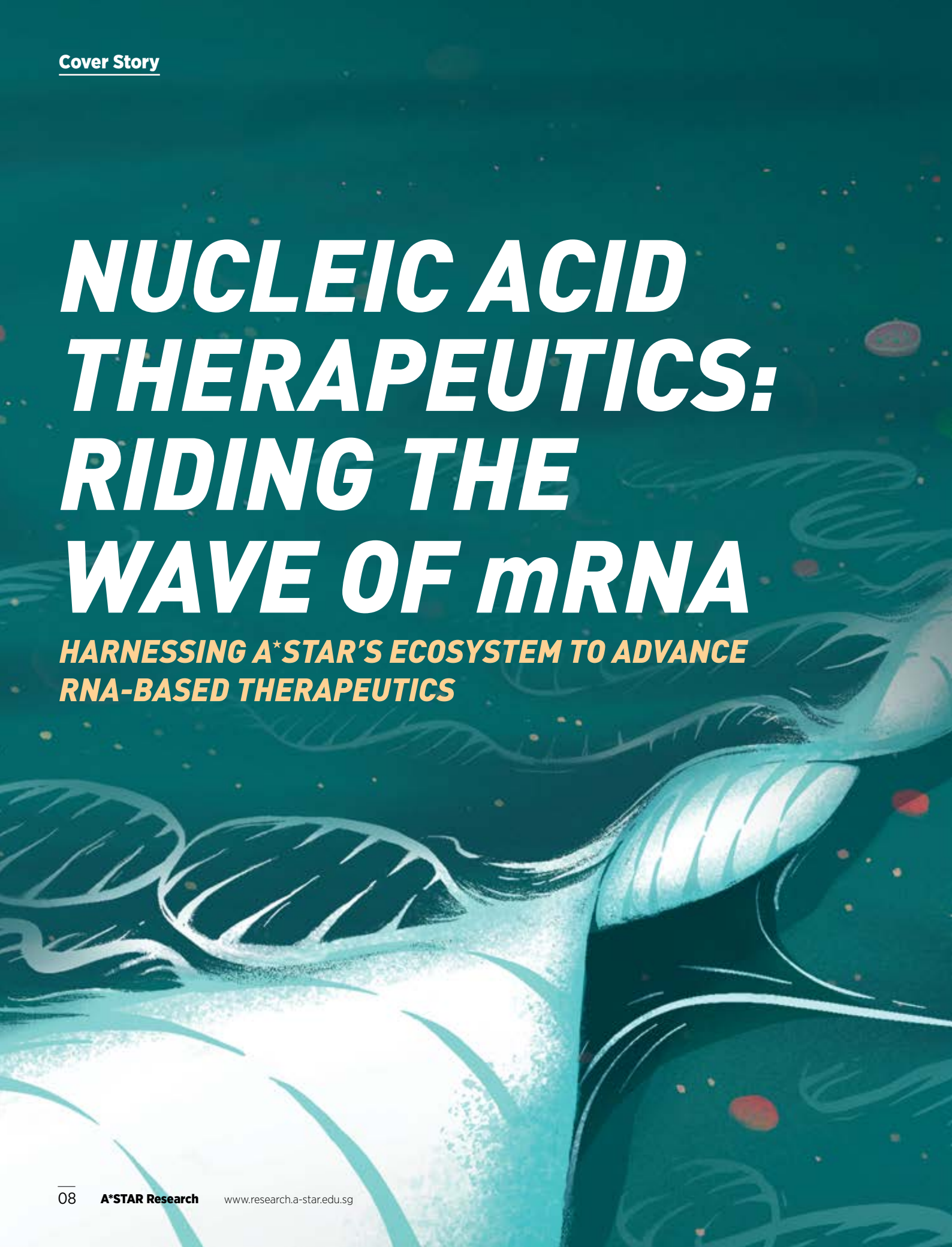
Researcher
Ramanuj DasGupta, GIS

IN BRIEF
Cell types involved in viral infection of the liver are elevated in liver cirrhosis patients, highlighting the potential dangers of SARS-CoV-2 infection on top of existing liver damage.

1. Seow, J.J.W., Pai, R., Mishra, A., Shepherdson, E., Lim, T.K.H., *et al*. Single-cell RNA-seq reveals angiotensin-converting enzyme 2 and transmembrane serine protease 2 expression in TROP2$^+$ liver progenitor cells: Implications in coronavirus disease 2019-associated liver dysfunction. *Frontiers in Medicine* **8**, 603374 (2021).

NUCLEIC ACID THERAPEUTICS: RIDING THE WAVE OF mRNA

HARNESSING A*STAR'S ECOSYSTEM TO ADVANCE RNA-BASED THERAPEUTICS



Ushering in an era of targeted precision medicine, scientists across A*STAR are propelling the research, commercialisation and implementation of RNA-based therapeutics.

In just over a year, the urgent administration of over a billion doses of mRNA-based COVID-19 vaccines worldwide has placed RNA therapeutics fresh in the minds of communities around the world.

RNA therapeutics and other nucleic acid therapeutics (NATs) which operate using engineered nucleotide sequences have proven to be quick and effective alternative candidates to traditional therapies—from slowing the spread of cancers to speeding up wound healing.

Because just a few thousand of these synthetic nucleotide sequences need to be screened, as opposed to the millions of molecules in typical drug discovery processes, the speedy turnaround of RNA-based therapies narrows the gap between bench and bedside. This is particularly crucial when it comes to global emergencies like the COVID-19 pandemic.

Fresh off the crest of the world's largest vaccine and therapeutics rollout in history, find out how A*STAR continues to ride the wave of burgeoning RNA technologies to develop novel solutions beyond battling COVID-19.

BUILDING ON THE BUILDING BLOCKS OF LIFE

Far from being a rushed development, the journey to understanding RNA and its applications began more than a century ago with the discovery and isolation of DNA in 1869 by Swiss physician Friedrich Miescher.

In 1961, Nobel laureate Sydney Brenner, who later helped place Singapore on biotech world stage, and eight other pioneering researchers detailed how cells use RNA[1,2] to translate and transport information from DNA to ribosomes that synthesise proteins. It wasn't until a decade later that scientists began to consider the possibility of harnessing one particular form of RNA—messenger RNA, or mRNA, as a tool to fight disease.

One of three types of RNA involved in protein synthesis, mRNA plays the role of messenger, as the name implies, by transcribing information from DNA and translating it into proteins by attaching to a ribosome.

The first step, transcription, is the process of creating a single-stranded copy of the target gene—smaller than a DNA strand and just the right size to slip through nuclear pores and exit the nucleus into the cytoplasm of the cell.

Like an instruction manual, the mRNA is then 'read' in the next major step—translation, where ribosomes in the cytoplasm use mRNA as a template to assemble specific chains of amino acids which form proteins. Here, mRNA can be synthesised to hijack the body's natural processes and essentially 'tell' cells what proteins to make.

Aside from making new proteins, NATs also inhibit the creation of harmful proteins. Many currently approved NATs rely on antisense oligonucleotides (ASO), explained Prabha Sampath, a Senior Principal Investigator at the A*STAR Skin Research Labs (A*SRL). Essentially, ASOs are complementary to the relevant mRNA strand in the body and bond with it to inhibit the translation process.

"These synthetic nucleic acids modify the functions of endogenous cellular RNAs by interacting with them through Watson-Crick base pairing," Sampath said. "All current ASO therapeutics target protein-coding RNAs and exert their effects by altering protein synthesis."

SAYING NAY TO CANCER WITH NATS

One major application for NATs is using it as a tailored cancer therapy. Because cancer is a result of genetic mutation—where either tumour suppressor genes, oncogenes or DNA repair genes do not function as they should, genetic therapies like NAT have the potential to effectively target and suppress the effects of these mutations.

"Depending on how they are designed and engineered, NATs can virtually abolish or titrate the expression of a gene, edit an aberrant genetic variant or increase expression of a gene," explained Si Hui Tan, a Senior Director at Cargene Therapeutics and a former A*STAR researcher, who received the Young Scientist Award in 2020.

"The beauty of NAT lies in its simplicity," said Tan. "Genetic information suffices for effective drug design."

Theoretically, once the patient's specific mutation is discovered the relevant NAT can be deployed to combat it. Such targeted cancer therapies have been the goal of Tan from her time as an A*STAR researcher at Nick Barker's laboratory to her current role at Cargene Therapeutics.

Tan's previous work saw the discovery of aquaporin-5 (AQP5) as a marker for gastric cancer stem cells[3]. By isolating these stem cells and growing organoids to study their behaviour, researchers could potentially modify the organoids and transplant them back into the patient to repair the damaged stomach lining.

Since then, Tan has pivoted her efforts to focus on oligonucleotide therapy at Cargene Therapeutics. In particular, the biopharmaceutical company develops siRNA-based therapies—one of the frontrunners for NAT therapies next to ASOs. Small interfering RNA, or siRNA, is a double-stranded non-coding structure capable of degrading target mRNA and inducing gene silencing. Cargene's technologies, originating from A*STAR, allow researchers to discover the relevant target mRNA, generate siRNA sequences, design stable siRNAs and effectively deliver them to target organs.

At the Genome Institute of Singapore (GIS), Group Leader Jay Shin and his team also work to uncover the therapeutic potential behind non-coding DNA and RNA through new technologies and large-scale assays. One such molecule, long non-coding RNA, or lncRNA, shows promise as a tissue-specific regulator of gene expression.

Recently, Shin's lab mapped out lineage-specific lncRNAs in human dermal lymphatic and blood vascular endothelial cells, known as LECs and BECs, to discover their potential role in cancer progression, chronic inflammatory diseases and diseases that lead to blindness.

Interestingly, the team was able to identify LETR1 as a modulator of essential genes and gatekeeper of the LEC transcriptome—indicating that every cell type could express precise lncRNA signatures to control lineage-specific regulatory programmes[4].

However, even with an in-depth understanding of various non-coding RNAs, targeted cancer therapies are easier said than done. According to Tan, NAT-based cancer therapies face three major challenges—recurrence, delivery and cancer with epigenetic or post-translational causes. The first, recurrence, happens when the bulk of a tumour is eliminated but a minor population harbouring its own set of mutations remains resistant. This minor population eventually grows to form a new tumour.

"This is where tumour sequencing and NAT can synergise to deliver precision medicine," explained Tan. "Based on the patient's tumour genetic profile, effective NATs could be prescribed or designed when needed."

Similarly, precise NATs tailored to individuals can also tackle cancers with epigenetic or post-translational causes.

Despite having a less direct effect, as researchers gain a deeper understanding of the pathways in which affected genes act, the relevant molecular interactors can be identified and targeted with NAT.

Finally, to send such therapies to tumour cells, specific and efficient delivery agents must be developed—a field that A*STAR's bioengineers are extensively looking into.

"NAT is a very promising class of drugs with a great deal of global momentum across academia, start-ups and pharmaceutical companies," said Tan. "I foresee NAT benefitting cancer patients on a large scale in the next decade."

A MICRO MOLECULE WITH MASSIVE IMPACT

Another class of non-coding RNA, microRNA (miRNA), has a major role to play in the NAT landscape. These short, single-stranded molecules can be harnessed to bind to the relevant mRNA sections of harmful genes and inhibit protein synthesis.

At A*SRL, Sampath and her team investigate miRNA's role in skin cancer, inflammation and wound healing. In particular, the researchers analysed the difference in miRNA and mRNA expression between individuals with and without atopic dermatitis, commonly known as eczema. Their study not only reaffirmed the role of miRNA in eczema but also identified several specific miRNA involved[5].

Building on their discovery, Sampath's team sought to identify the underlying mechanisms behind skin barrier defects that contribute to the disease's development. They found miR-335 to be the most consistently downregulated miRNA in patients with eczema. Responsible for keratinocyte differentiation and cornification, miR-335 represses SOX6 and is essential for proper skin barrier maturation[6].

"We are looking for small molecules that restore miRNA expression in the epidermis, the outermost layer of skin on the body," explained Sampath. "Compound effects are assayed by imaging skin cells expressing a fluorescence-based biosensor we developed in-house. Candidate substances identified through screening will be subjected to *in vitro*, *ex vivo* and *in vivo* testing to validate their effects on skin maturation."

One such candidate drug Sampath's team has identified is belinostat, which was found to consistently induce miR-335 expression to repair barrier defects in the epidermis[7]. With further investigation into its applications and delivery, belinostat has the potential to be a frontrunner in alleviating the uncomfortable effects of eczema, according to Sampath.

"We are looking for small molecules that restore miRNA expression in the epidermis, the outermost layer of skin on the body."

— Prabha Sampath, Senior Principal Investigator at the A*STAR Skin Research Labs (A*SRL)

When it comes to wound healing, miRNA research holds similar promise but runs into unique challenges. "Resolving wound healing defects often involves a fine balancing act," explained Sampath. "Many of the cellular and molecular pathways that encourage wound healing can potentially trigger malignant pathways if inappropriately activated."

Sampath's team is particularly familiar with the intricate relationship between wound healing and epithelial cancers that attack the exterior surfaces of skin and internal organs[8]. Beneficial processes like keratinocyte migration, upregulation of cell proliferation and neo-angiogenesis can encourage wound healing, but with the risk of being hijacked by tumour cells for cancer progression.

Similar to their work with eczema, Sampath's team has identified a potentially relevant miRNA, miR-198, for its role in encouraging safe wound healing[9].

miRNA also has applications in potentially treating neurodegeneration and movement disorders—a field Sherry Aw, a Principal Investigator at the Institute of Molecular and Cell Biology (IMCB), has been involved in extensively.

Along with her team, Aw works closely with computer scientists, chemists and engineers within the A*STAR ecosystem to study how defects in miRNA biology can lead to neurodegeneration, tremor and movement disorders.

One significant achievement from the lab was the development of the RNA biosensor Pandan[10]. It builds on a fluorescent RNA known as Spinach by altering

> ***"Our contributions will be towards improving manufacturing processes, removing existing operations bottlenecks, improving quality and reducing the cost of drugs."***
>
> — Boon Tong Koh, Executive Director at A*STAR's Bioprocessing Technology Institute (BTI)

the ends of the structure and including an additional stem loop. The new structure allows for a switch-on in fluorescent signal intensity when the biosensor binds to target miRNA, allowing direct miRNA detection within complex RNA mixtures. Currently, Aw's lab is working to develop additional RNA sensors that can function as new diagnostic and therapeutic modalities.

DETERMINING THE RIGHT DELIVERY

After understanding mRNA's role and developing the right RNA solution, the NATs need to be sent to where they can make an impact—in the bodies of patients. Yi Yan Yang, covering Executive Director of the Institute of Bioengineering and Bioimaging (IBB), explains that in addition to using viral vectors to deliver genetic material to target cells, there are two main types of nanoparticles used to transport NATs—biopolymer-based nanoparticles and lipid nanoparticles.

Biopolymers include synthetic biodegradable polymers, which have been used to formulate nanoparticles for the delivery of various NATs[11, 12, 13]. Meanwhile, lipid nanoparticles, perhaps most notably utilised in COVID-19 vaccines, can be used to encapsulate mRNA to protect it against degradation and to deliver it to a desired cell type[14].

In their study, Yang and her team condense NATs into various nanoparticle types to be taken up by cells. They also develop nanocarriers to deliver NATs to the right tissues or cells. To date, in this field, Yang's lab holds the highest number of polymer-based NAT delivery patents in Singapore.

One particularly interesting project Yang's team is currently working on is a patch that functions as a potential replacement for injections. "NATs-loaded nanoparticles are contained within microneedles in the patch. Once it is applied to the skin, the nanoparticles will be released under the skin and travel to a target site like the lymph nodes—it's a painless application," Yang shared.

Yang was recently awarded a contract as a Co-principal Investigator from the prestigious Wellcome Leap R3 funding programme with GIS Principal Investigator, Yue Wan, to further accelerate the development and accessibility of mRNA technology.

Wan's lab primarily explores the complex secondary and tertiary structures of RNA after it folds to further understand its function in the human body.

Notably, RNA structures are notoriously difficult to crystallise and visualise. To that end, Wan's team developed a strategy called parallel analysis of RNA structures (PARS)[15] to examine thousands of RNA structures. PARS has been applied to study the transcriptomes of yeast[16] and humans[17] as well as the impact of temperature and mutations on RNA structure.

As part of the Wellcome Leap R3 programme, the team intends to develop circular RNA designs for mRNA vaccines which would increase and stabilise the amount of protein created—resulting in smaller doses and lower vaccine costs.

"It is a huge privilege to be able to be part of the programme," said Wan. "As different teams are working on a range of problems such as RNA manufacturing, design and downstream applications, we get to interact and plug into many of the newer technologies."

ENTERING A SEA OF OPPORTUNITY

In the wake of the rapid progress being made, A*STAR has shown a concerted effort to advance the implementation of RNA-based medicine in Singapore with the launch of an official NAT Programme, led by Senior Group Leader Kevin White, who is also a professor of precision medicine and biochemistry at the Yong Loo Lin School of Medicine, National University of Singapore.

Arriving with an extensive background in precision medicine, White was formerly the President and Chief Scientific Officer of Tempus, a prominent precision medicine company based in the United States. Before launching and helping to build Tempus into a multibillion-dollar company, he was a professor of human genetics

at the University of Chicago and the Founding Director of the Institute for Genomics and Systems Biology, which he led for a decade.

White will lead the NAT Programme alongside Boon Tong Koh, Executive Director of the Bioprocessing Technology Institute (BTI) at A*STAR. "BTI's programme is focused on the biomanufacturing aspects of mRNA," said Koh. "Our contributions will be towards improving manufacturing processes, removing existing operations bottlenecks, improving quality and reducing the cost of drugs."

While White believes that implementing NAT research in clinics and hospitals will generally face the same obstacles as most other drugs and vaccines—namely delivery, toxicity and efficacy—as an emerging field, NAT developers must also address regulatory uncertainty.

"As a relatively new set of modalities, there is a steep learning curve for most regulatory agencies," explained White. "It is especially crucial for NAT developers to have clear and frequent lines of communication with regulators."

Nonetheless, as the field continues to grow, A*STAR is in a strong position to ride the wave of mRNA therapeutics. According to Andre Choo, Executive Director of the Biomedical Research Council at A*STAR, this potential can be attributed to the diverse expertise of A*STAR's scientists that spans RNA design, protein engineering, process manufacturing and more. "This collaborative effort across the institutes gives us both breadth and depth to make a lasting impact in this new space," said Choo. "At the same time, the entire ecosystem is ripe for progress with the inclusion of A*STAR start-ups, industry partnerships and academic collaborations."

"I hope to see a strong integration between local SMEs, investors and the academic sector in Singapore in the area of NATs," White added. "I believe it could be a model to demonstrate how innovations funded by the public sector can be rapidly developed into useful products for humanity." ★

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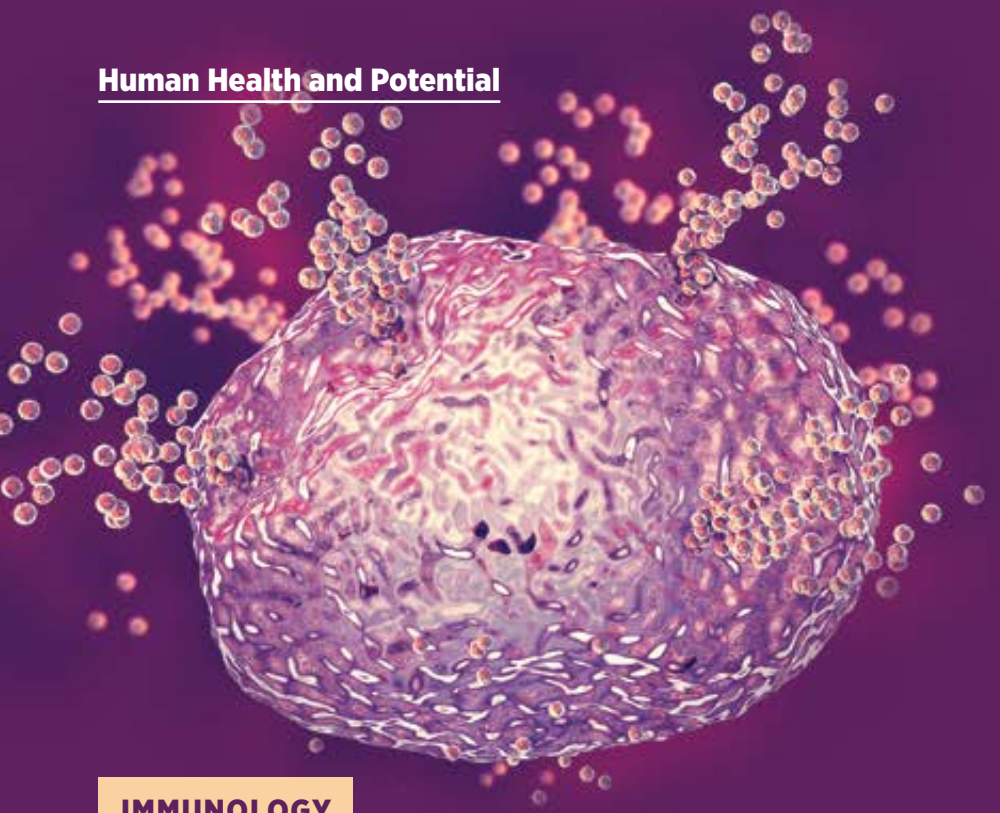

IMMUNOLOGY

When allergies pass from mother to child

Maternal antibodies can cross the placenta and pass a mother's allergies to her child in the womb.

Pregnant mothers provide their growing babies with everything they need to thrive: oxygen, nutrients and immune factors to protect the vulnerable fetus. As it turns out, mothers could also be unsuspectingly passing on other 'unwanted' attributes, like allergies.

Previously, scientists had found traces of immune cells known as mast cells as well as antibodies called immunoglobulin E (IgE) in mouse fetal tissues, both of which play key roles in allergic reactions. When exposed to an allergen, the body produces IgE, activating mast cells that release inflammatory molecules. However, little is known about the origins of fetal IgE and how exactly its presence influences the onset of allergies in infants.

To address these questions, Florent Ginhoux, a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SIgN), along with collaborators Ashley St. John from Duke-NUS Medical School and Jerry Chan from KK Women's and Children's Hospital, used cellular and imaging techniques to characterise mast cells in fetal tissues and investigate their interactions with maternal IgE in mice.

They observed that maternal IgE produced in response to specific allergens could transfer from pregnant mothers across the placenta and into the womb with the help of a protein receptor called FcRN.

Once bound to fetal mast cells, IgE triggered the immune cells to release their characteristic cocktail of chemicals that activate the allergic response. Further studies revealed that maternal IgE also binds to human fetal mast cells, suggesting they can cross the placenta in humans in a similar manner.

Fascinatingly, they found that mouse pups born to mothers with specific allergies inherited these maternal sensitivities—resulting in constricted airways after a single exposure to the allergen. In contrast, adult mice typically require two allergen exposures before displaying a reaction.

"These pups had never seen the allergen in their life, but once exposed to pollen, they react immediately," said Ginhoux. "The capacity to respond to the allergen was transferred from their mothers."

Crucially, the developed sensitivities in the newborn mice were allergen-specific. While the pups whose mothers were allergic to pollen also reacted to ragweed, no adverse reactions were reported with dust mites, another common allergen.

For now, the team can only speculate what evolutionary advantage passing allergies on from mother to child could have. In follow-up studies, Ginhoux and the team plan to explore fundamental unknowns about the role of mast cells during embryonic development. "We want to understand how mast cells modulate the physiology of fetal organs and the long-term consequences of their activation by maternal IgE," he concluded. ★

Researcher
Florent Ginhoux, SIgN

IN BRIEF
In mice, allergic reactions can be inherited when a mother's antibodies cross the placenta and enter the womb, causing their offspring to react immediately once exposed to an allergen.

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VACCINOLOGY

Smoothing out the kinks in vaccine production

A new streamlined method for purifying lab-grown viruses could accelerate vaccine production, allowing manufacturers to respond rapidly to emerging viral threats.

When a viral outbreak strikes, vaccines are our best hope of stopping its spread and saving lives. The expedited global rollout of COVID-19 vaccines, for example, has saved countless lives and continues to protect vulnerable populations from potentially life-threatening infections.

Despite the progress made so far, viruses can sometimes stay one step ahead of our ability to respond to them. Pathogens such as the influenza virus mutate rapidly, creating the need for new vaccine formulations that 'retrain' our immune systems to recognise and eliminate emergent viral strains.

The pressure to keep up with these elevated vaccine demands can be challenging for manufacturers. After all, commercial vaccine production is often a lengthy, multi-step process where viruses grown in cell culture systems must first be harvested and purified.

"We need to develop efficient and simplified purification workflows to accelerate viral vaccine development and production," said Wei Zhang, Group Leader of the Downstream Processing Group (DSP) at A*STAR's Bioprocessing Technology Institute (BTI).

Presently, sluggish viral purification methods are a critical bottleneck in vaccine manufacturing. In fact, even the gold standard flow-through anion exchange chromatography method requires multiple clean-up steps.

"We need to develop efficient and simplified purification workflows to accelerate viral vaccine development and production."

To rise above these barriers, Zhang and colleagues tested a newly-developed anion exchange platform, the Nuvia™ HP-Q. Previously, this technology was found to enhance the purification of relatively larger proteins like antibodies; however, adopting the HP-Q for viral purification applications had never been explored.

Using H1N1—the virus responsible for seasonal flu outbreaks—as a model pathogen, the team created an optimised HP-Q protocol for viral purification. Promisingly, they found that the HP-Q resin displayed an excellent binding capacity for H1N1, capturing a high proportion of viral particles and effectively separating them from unwanted cell culture impurities.

Moreover, Zhang and colleagues found that they could eliminate steps upstream and downstream of HP-Q runs with no loss of efficiency. A single HP-Q chromatographic run could recover 70 to 80 percent of H1N1 proteins while simultaneously removing over 95 percent of residual host cell protein, without comprehensive prior-purification sample preparation and post-purification clean-ups.

According to Zhang, these exciting results could pave the way for faster, simpler and more cost-effective vaccine development and production, allowing manufacturers to be more agile and responsive in the event of an emerging viral threat. Ultimately, the team is confident that the benefits of the HP-Q can extend beyond the creation of flu vaccines.

"Although we used the H1N1 virus as the model product to establish the simplified HP-Q process for virus purification, this process could be adapted to the purification of other types of viruses, including the coronavirus," remarked Zhang. ★

Researcher
Wei Zhang, BTI

IN BRIEF
To speed up flu vaccine development, A*STAR researchers have adapted HP-Q to purify viral particles.

1. Ta, D.T., Chu, K.L., Soonaan, N.I., Chin, C., Ng, S.K., *et al*. A new and simplified anion exchange chromatographic process for the purification of cell-grown influenza A H1N1 virus. *Separation and Purification Technology* **263**, 118412 (2021).

Photo credit: Golden Shrimp / Shutterstock

GENOMICS

Mapping modified RNA with xPore

A new computational method called xPore identifies and estimates the number of specific RNA modifications in biological samples.

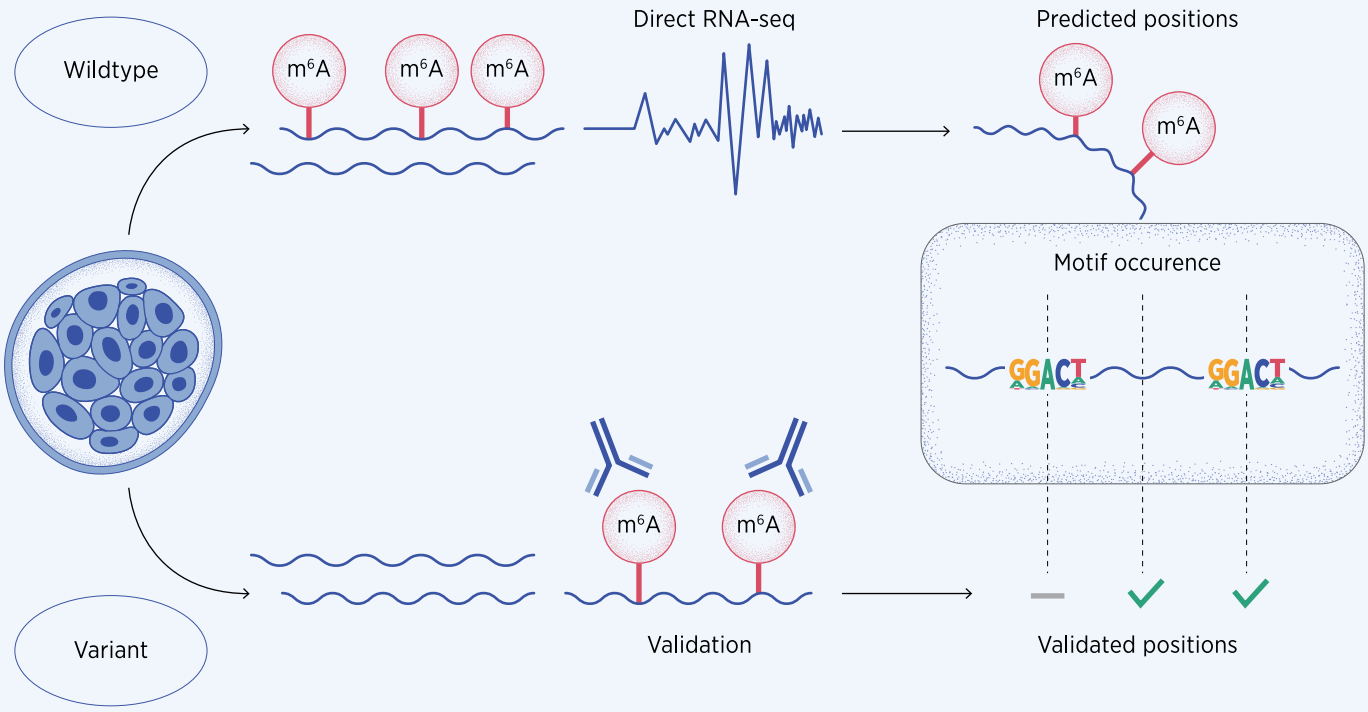
Cells behave like little factories, copying information encoded in DNA to RNA molecules to create a never-ending stream of proteins that translate the assembly line. However, just as factories occasionally encounter bumps in their conveyer systems, aberrant RNA modifications may also affect protein production with potential impacts on cellular function.

Accordingly, the ability to detect and profile these naturally occurring changes to RNA molecules during gene expression has enormous research and clinical value, given that these changes have been linked to conditions like cancer and heart disease. Existing approaches to track modified RNA bases, however, are too complicated to be performed routinely.

"Current methods to profile RNA modifications often involve highly specialised protocols, so only a few teams can perform these experiments," explained Jonathan Göke, a Principal Investigator at A*STAR's Genome Institute of Singapore (GIS).

To analyse RNA modifications in a simpler and more accessible manner, Göke and his team developed a novel computational technique called xPore, which leverages data from direct RNA-sequencing. By comparing statistically significant differences between multiple samples, xPore can make accurate inferences on where and how many RNA were modified, even without a control sample.

The researchers validated their method in six different cell lines as well as in multiple myeloma patient samples in search of one of the most common RNA tweaks known as the N6-methyladenosine (m^6A) modification. Indeed, in one cell line, xPore correctly identified over 90 percent of m^6A modifications from the top 1,000 positions in RNA, outperforming current methods in both accuracy and efficiency.



Using the xPore technique, scientists estimated m⁶A modification rates in sequenced wildtype and variant cell types. Next, they validated their results in six different cell lines by testing for the occurrence of the m⁶A motif.

"Current methods to profile RNA modifications often involve highly specialised protocols, so only a few teams can perform these experiments."

The beauty of xPore lies in its simplicity. xPore can be fed direct RNA-sequencing data for analysis without the need for matched sample controls, therefore producing results in much fewer steps compared with current methods. This allows xPore to detect genes that are rarely turned on in the cell by pooling samples to create more opportunities to identify novel RNA modification sites usually missed by approaches requiring a matched control.

Additionally, the computational tool can be extended to extract other genomic insights, which points to xPore's immense flexibility and potential. "It's even possible to artificially introduce modifications that approximate other biological aspects of interest like RNA structure. xPore could be used in similar scenarios as well," said Göke.

Going further, the team is developing additional machine learning-based methods capable of identifying RNA modifications using only a single sample. This feature would complement xPore's current capabilities to unlock novel diagnostic biomarkers of clinical importance. ★

Researcher
Jonathan Göke, GIS

IN BRIEF
Unlike current methods for profiling RNA modifications, the computational technique xPore does not require matched control samples, producing accurate results in fewer steps.

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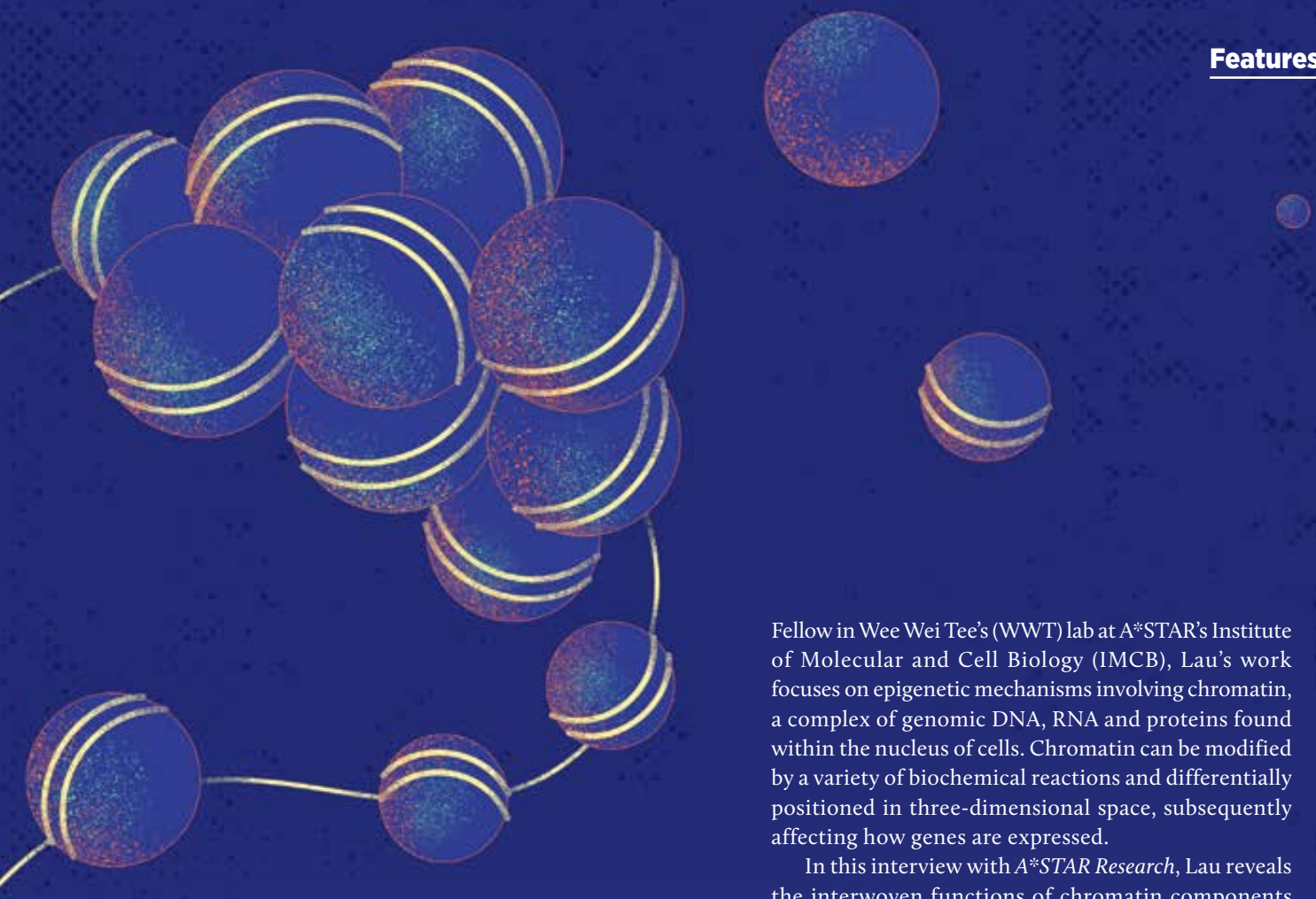
WEAVING FORM AND FUNCTION IN GENE REGULATION

Delving deep into the fundamentals of development and the frontiers of disease therapeutics, Mei Sheng Lau unravels the roles chromatin plays in gene regulation.



When we first learn about genes, we tend to be taught only a simplified picture of what takes place in nature. Like the blueprints of a house, genes contain instructions for producing the RNA and proteins that govern every aspect of life, with variations in this genetic blueprint resulting in a myriad of differences, or phenotypes. In reality, however, the path from gene to phenotype is not as straightforward as it seems.

Phenotypes are not only affected by the genetic code and gene mutations, but also by the factors that determine when and where those genes are expressed. For instance, the phenotypic consequence of switching off or silencing an otherwise functional gene is almost equivalent to that of a mutation rendering a gene non-functional.

This modulation of gene expression that is independent of changes in the genetic code, or epigenetics, is a burgeoning field that Mei Sheng Lau has spent years exploring. As a Postdoctoral Research Fellow in Wee Wei Tee's (WWT) lab at A*STAR's Institute of Molecular and Cell Biology (IMCB), Lau's work focuses on epigenetic mechanisms involving chromatin, a complex of genomic DNA, RNA and proteins found within the nucleus of cells. Chromatin can be modified by a variety of biochemical reactions and differentially positioned in three-dimensional space, subsequently affecting how genes are expressed.

In this interview with *A*STAR Research*, Lau reveals the interwoven functions of chromatin components and gene expression outcomes and explains how the regulation of gene expression plays a critical role in development and disease.

Q: WHAT SPARKED YOUR INTEREST IN BIOCHEMISTRY AND EPIGENETICS?

I am fascinated by the fact that the form and function of biological molecules are so elegantly connected. It is not always easy to understand how a biological molecule works. But when we eventually do, we tend to realise in hindsight how obvious it should have been based on how the molecule looks.

Chromatin is a fine example of this concept. It simultaneously enables very long DNA strands to be packaged in the confined spaces of a cell while determining which genes should be active or silenced according to different cell states.

I first learned about chromatin biology during my undergraduate studies at the University of Cambridge in the UK. I was immediately captivated by it, which spurred my desire to venture into epigenetics—a field of study where chromatin plays a prominent role.

Q: WHY IS IT IMPORTANT TO STUDY GENE REGULATION AT THE CHROMATIN LEVEL?

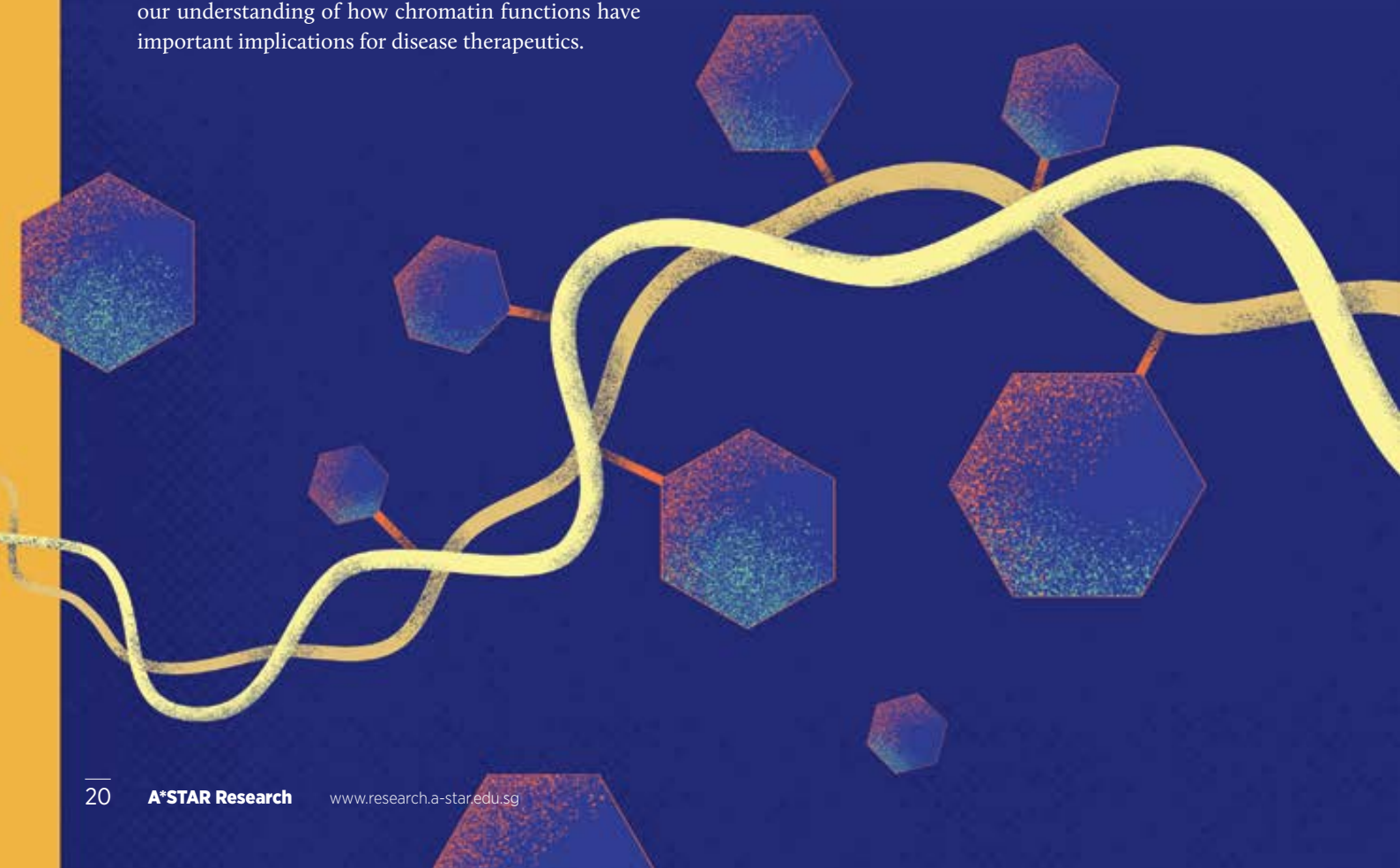
Chromatin directly influences gene regulation in many ways. For example, whether the chromatin packaging is 'loose' or 'tight' has direct implications on cell function. An illustration of this is in stem cells which generally contain more loosely packaged chromatin. This structure allows a stem cell to have a higher degree of plasticity and to retain its ability to develop into other specialised cell types. As a stem cell differentiates and specialises, the chromatin within it becomes increasingly 'tight' and permanently represses the genes associated with other now-irrelevant cell lineages. In this way, chromatin locks in the cell's identity at each developmental stage. Another example is chromatin folding in three-dimensional space, which physically brings together related genes so that they can be regulated in close coordination.

Chromatin's critical role is made clear by the large number of disease-associated mutations in genes that code for chromatin components. Some of these genes, like *EZH2* and *BRD4*, are now important drug targets in cancer therapeutics. As such, they advance our understanding of how chromatin functions have important implications for disease therapeutics.

Q: HOW HAS YOUR RESEARCH DIRECTION EVOLVED SINCE COMPLETING YOUR PHD DEGREE?

In my PhD research project, I mainly investigated the role of chromatin components called Polycomb group proteins in transcriptional regulation—how they normally work and the corresponding consequences on development and disease when their function is disrupted.

While I still study chromatin function, the scope of my research has broadened. One of my current projects involves investigating the influence of DNA in the chromatin complex, which is the lesser-studied component in chromatin, and epigenetic silencing. I am also exploring how we can use information in chromatin for predictive and engineering purposes. For example, chromatin status can be used to predict whether a particular cell source would be suitable for cell-based therapy. With that knowledge, we can also alter other cell sources to improve their suitability for therapeutic applications.



Q: HOW HAVE A*STAR AND THE WWT LAB SUPPORTED YOUR GROWTH AS A YOUNG SCIENTIST?

A*STAR's National Science Scholarship made it possible for me to pursue a world-class education without the financial burden. As a scholar, I had the opportunity to be involved in other aspects of science, like recruiting young talent through A*STAR's scholarship programmes, participating in public outreach initiatives and being a part of policymaking and event planning. These experiences gave me a more holistic view of the scientific ecosystem.

As a Research Fellow now, I appreciate the support IMCB offers to relatively new labs like ours. The WWT lab was just established when I joined, so I experienced the challenges faced by a small lab trying to make a name for itself. I am thankful to my supervisor Wee Wei Tee, who worked relentlessly to ensure that my colleagues and I had the right environment and resources we needed to carry out our research.

Q: WHAT RESEARCH PROBLEMS DO YOU HOPE TO ADDRESS IN THE NEXT DECADE?

I want to apply my knowledge in chromatin biology to study heterogeneous and complex neurodevelopmental disorders like autism spectrum disorder (ASD). Among the many risk genes identified for ASD, more than half of them surprisingly code for chromatin factors and gene expression regulators. This suggests that chromatin plays a significant role in the mechanisms underlying ASD. I welcome potential research partners with complementary domain knowledge and the relevant skills to join me in my quest to uncover more answers. ★

MEI SHENG LAU

Postdoctoral Research Fellow
Institute of Molecular and Cell Biology (IMCB)

"I want to apply my knowledge in chromatin biology to study heterogeneous and complex neurodevelopmental disorders like autism spectrum disorder (ASD)."

— Mei Sheng Lau, Postdoctoral Research Fellow at A*STAR's Institute of Molecular and Cell Biology (IMCB)

CARBON CAPTURE

Carbon-capturing minerals promise a greener tomorrow

Life cycle assessments show that a technology that captures waste carbon dioxide and turns it into sand may help Singapore reduce its carbon emissions.

From extreme flooding to blazing wildfires, communities around the world continue to be impacted by the snowballing effects of climate change. Taking a stand against the escalating environmental crisis, Singapore has pledged to halve carbon dioxide (CO_2) emissions by 2050 as part of the Paris Agreement under the United Nations Framework Convention on Climate Change. But what will it take to meet this ambitious target?

One way to reduce carbon emissions is a process called carbon capture and utlisation (CCU). CO_2 captured from power plants or factories is collected and funnelled into other manufacturing processes.

At A*STAR's Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2), researchers have patented a CCU technology that makes use of the magnesium-rich mineral serpentine. Once heat-activated, serpentine captures CO_2 emitted by waste incineration plants. The end product of this chemical reaction, known as CO_2 mineralisation, is carbonate, which can be used in construction as a sand alternative.

Given the promise of CO_2 mineralisation technology, Zi-Yu Khoo from A*STAR's Singapore Institute of Manufacturing Technology (SIMTech), together with colleagues from the Institute of Materials Research and Engineering (IMRE) and ISCE^2 set out to investigate the feasibility of using this CCU approach to help Singapore curtail its carbon emissions.

The team performed a life cycle assessment of CO_2 mineralisation starting from the mining and transport of serpentine to the end-stage production of the sand alternative. "Carbon emissions along the entire life cycle or supply chain were scrutinised to evaluate net carbon abatement of the technology," explained Khoo.

The researchers' analyses revealed that CO_2 mineralisation indeed offers Singapore the ability to effectively capture and repurpose waste CO_2 from incineration plants, enabling net carbon abatement. "Additionally, the technology also produces an alternative sand, which could supplement Singapore's need to import the compound for national development," said Khoo.

However, the researchers note that a few tweaks and optimisations could elevate the potential of this carbon capture technology even further. For example, Khoo recommends that serpentine be sourced from countries close to Singapore to limit long transport distances. She also recommends using heat emitted from other industrial processes to power the thermal activation of serpentine.

Ultimately, the team sees these and other carbon abatement methodologies as a path towards a cleaner, greener Singapore with dramatically reduced emissions. "CO_2 mineralisation as a CCU technology could be considered as a part of a suite of technologies for Singapore to achieve this goal, while contributing to national sustainability and development targets," said Khoo.

Moving forward, Khoo calls for similar life cycle assessments to be performed for other decarbonisation strategies to assess, rank and identify the most effective solutions for Singapore. ★

Photo credit: Anatoliy Berislavskiy / Shutterstock

Researcher
Zi-Yu Khoo,
SIMTech

IN BRIEF
A mineral called serpentine is able to capture carbon dioxide emitted by waste incineration plants and turn it into carbonate.

1. Khoo, Z.Y., Ho, E.H.Z., Li, Y., Yeo, Z., Low, J.S.C., *et al.* Life cycle assessment of a CO_2 mineralisation technology for carbon capture and utilisation in Singapore. *Journal of CO_2 Utilization* **44**, 101378 (2021).
2. Bu, J., Yeo, T.Y. Method and System for Converting Carbon Dioxide into Solid Carbonates, WO/2018/182506 (2019).

FOOD SCIENCE

Getting plant proteins to take root

New technologies that turn plant proteins into better ingredients and food items could help feed the growing human population with less impact on natural resources.

How do you feed over nine billion people? According to a population projection by the United Nations, we will need an answer to this question by 2050—most likely even sooner. With estimates that the demand for food in 2050 will be 60 percent higher than it is today, the problem of food security becomes even more complicated when we consider the environmental cost of conventional protein production methods like fishing and raising livestock.

One promising solution to the protein problem is to source it from crops. Because plants require less land, water and other resources than livestock, plant proteins may be a promising sustainable food source. However, plant protein technology is still in development and further research is needed before crops can replace animals as a reliable source of protein.

"Most importantly, these novel plant-based foods must be safe for consumption and provide adequate nutrition to support growth and health," explained Christiani Jeyakumar Henry, Deputy Executive Director at A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI) and Director at the Clinical Nutrition Research Centre (CNRC).

In that vein, Henry and his colleagues reviewed the pressing problems and the most promising developments in plant protein research, with a focus on innovative technologies that can be easily adopted.

"To ensure plant proteins provide optimal functionality and nutrition, we must understand the current gaps in plant protein ingredient development. Only then can we bridge the gaps with existing technologies or new solutions," added lead author Shaun Sim, a Senior Research Fellow at SIFBI.

One crucial roadblock is that plant proteins are much harder to extract, often requiring harsh processing techniques that may damage the extracted proteins. In their review, the authors highlighted in-house solutions that can solve this dilemma by modifying the structures of these damaged proteins to improve their functionality.

One such solution aims to make better yoghurt from plant proteins. Unlike dairy, plant-based milks don't ferment well due to their lower sugar and protein content. As a result, most plant-based yoghurts are too starchy or watery, lacking the more desirable smooth and creamy texture of dairy yoghurts.

As an alternative to fermentation, the authors described the use of high-pressure processing, which enables controlled protein unfolding and aggregation for better gel formation. The amount and duration of pressure applied can also be fine-tuned to tailor the consistency of the final product. Such emerging technologies not only turn plant proteins into better ingredients, but also better food items with more appealing taste, texture and nutrient profiles.

"To ensure plant proteins provide optimal functionality and nutrition, we must understand the current gaps in plant protein ingredient development."

"With increasing consumer demands for other food formats like meat cuts and fish fillets, we hope to produce the next generation of healthier alternative protein foods," the study authors wrote. ★

Researcher
Christiani Jeyakumar Henry and Shaun Sim, SIFBI

IN BRIEF
Plant protein production is held back by harsh processing techniques and less desirable material properties, but developments in food technology aim to boost the way plant-based ingredients are created and consumed.

1. Sim, S.Y.J., SRV, A., Chiang, J.H., Henry, C.J. Plant proteins for future foods: A roadmap. *Foods* **10** (8), 1967 (2021).

MATERIALS ENGINEERING

A three-in-one sustainable, self-healing coating

Next-generation self-healing polymers use eco-friendly building blocks and manufacturing processes, providing superior durability and longevity to the materials they coat.

When we get a scratch or cut, our skin's healing mechanisms repair the damage, quickly restoring the barrier against environmental threats. Wouldn't it be fantastic if everyday objects had the same restorative capabilities? From a sustainability perspective, such self-healing materials would be transformative—not only would objects last longer, but they would also not need to be replaced so frequently.

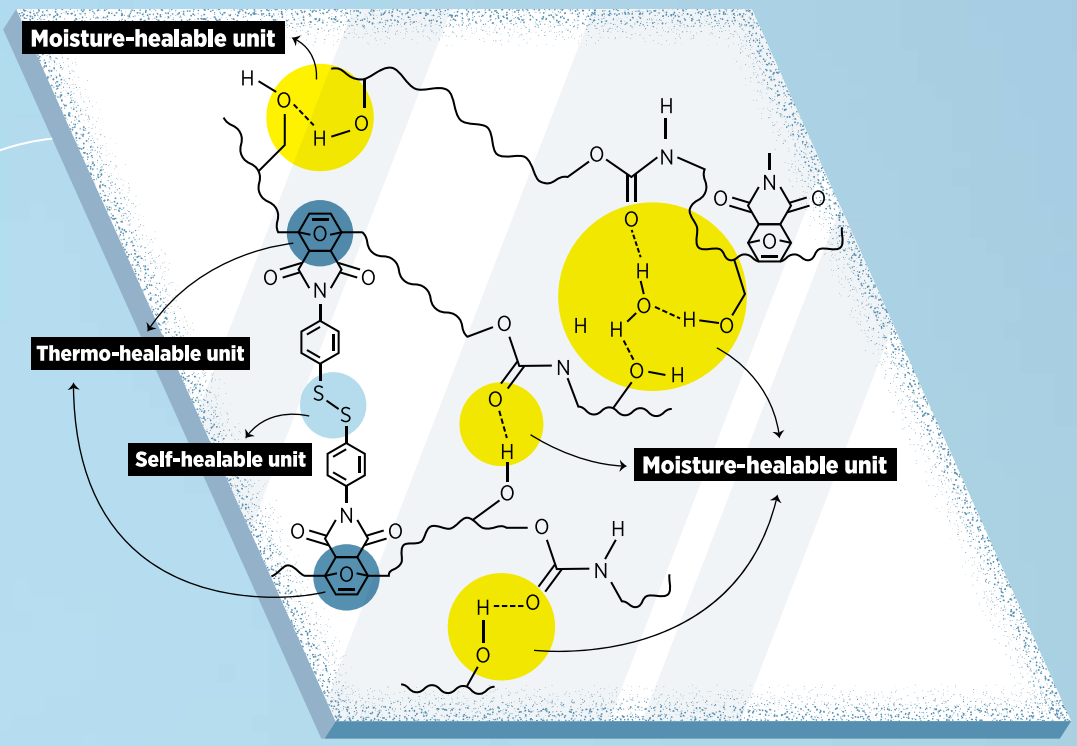
Thanks to innovations in materials science, this is already a possibility. Scientists have designed an array of polymer-based surface coatings with molecular properties that enable them to repair themselves after wear and tear. However, a major drawback is that the process of creating such self-healing surfaces is far from eco-friendly. These coatings use fossil fuels as raw materials and require the use of toxic chemicals during production.

In search of greener surface coating alternatives, a team of researchers led by Satyasankar Jana and Jayasree Seayad at A*STAR's Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2) explored the possibility of using an emerging class of polymers called non-isocyanate polyurethanes, or NIPUs. Unlike traditional polyurethane coatings, NIPUs are made from sustainable, bio-derived building blocks and can be manufactured efficiently using non-toxic chemicals, explained Jana.

In their study, the team investigated the self-healing properties of four novel NIPU formulations that they created. These NIPUs contain furan rings in their main polymer chain, which allows them to crosslink to compounds called bismalemides, a reaction that gives them their intrinsic healing capabilities.

"We will also investigate the self-healing property of NIPU-based pigmented coatings as the pigments and other coating additives may influence their healing performance."

Photo credit: nevodka / Shutterstock



A unique cross-linked structure between furan rings and bismalemides gives NIPU coatings their intrinsic healing capabilities.

A closer look at the regenerative capacity of these NIPU-based surface coatings revealed a remarkable discovery. Existing self-healing surfaces modifications typically display a single mechanism of action, with their healing properties triggered by exposure to either heat or moisture—a feature that has limited the widespread application of these coatings. The next-generation NIPU coatings developed by the researchers, however, possess not one but three different healing sites, giving them the unprecedented potential to self-repair even at room temperature.

"Coatings with multiple healing mechanisms, especially room-temperature healing, are really interesting as they will not require the inspection of healing sites or the application of special treatments like heat or moisture," commented Jana, who added that this would substantially extend the service life of the coated substrates.

The team sees a niche for NIPU-based coatings in several commercial settings, including the automotive industry. As the next steps, there are plans to develop colourless NIPUs that can be used as clear glass coatings, given that current iterations of NIPU formulations are lightly coloured. "We will also investigate the self-healing property of NIPU-based pigmented coatings as the pigments and other coating additives may influence their healing performance," added Jana. ★

Researcher
Satyasankar Jana and Jayasree Seayad, ISCE²

IN BRIEF
A*STAR researchers have developed sturdier and longer-lasting coatings with not one, not two, but three different healing mechanisms.

1. Choong, P.S., Chong, N.X., Tam, E.K.W., Seayad, A.M., Seayad, J., *et al*. Biobased nonisocyanate polyurethanes as recyclable and intrinsic self-healing coating with triple healing sites. *ACS Macro Letters* **10** (5), 635–641 (2021).

QUANTUM

A new recipe for quantum computers

In developing a new process to synthesise stable qubits, A*STAR researchers are paving the way towards scalable and practical quantum devices.

In the realm of computing, bigger is better: scalability allows computers to perform increasingly demanding tasks using fewer resources. From the first vacuum-tube computers to pushing the limits of today's silicon chips, boosts in computing power are often attributed to breakthroughs in material synthesis.

Quantum computers, which are governed by the laws of quantum physics as opposed to classical physics, also depend on material development. Scaled-up quantum computers require an increasing number of qubits, their basic building blocks, but supporting this number of qubits is no easy feat. While qubits are highly sensitive to changes in the environment, quantum computers that are too protected from these external factors risk leaving their qubits inaccessible, which in turn renders the system impractical to perform real calculations.

In the search for a material that strikes a balance between stability and accessibility, Kuan Eng Johnson Goh, a Principal Investigator at A*STAR's Institute of Materials Research and Engineering (IMRE), turned to making qubits out of a two-dimensional transitional dichalcogenide (TMDC) semiconductor material called tungsten disulfide (WS_2).

Characterised by a crystal structure made up of two different metal atoms, WS_2 exhibits unique properties that can give quantum devices optimal characteristics such as higher carrier mobility. However, conventional methods used to synthesise WS_2, such as mechanical exfoliation, are inconsistent and prone to contamination.

"This study marks the first time this property called 'interface roughness' has been systematically measured and quantified."

To overcome these limitations, the research team married two different industrial processes to make WS_2 semiconductor crystals. In this novel two-step process, the research team first enabled the formation of a thin layer of WS_2 through chemical vapour deposition (CVD). Compared to conventional methods, CVD allows the synthesis of WS_2 on a large, scalable area. The second step entailed the uniform encapsulation of the WS_2 crystals with a protective dielectric layer made of hafnium oxide (HfO_2).

Through this technique, the team managed to synthesise stable WS_2 crystals over an area hundreds of times larger than that of mechanical exfoliation. "This provides enough real-estate to fabricate many tens of quantum devices so that we can effectively test them to further enhance the synthesis process," said Goh.

The researchers also discovered that imperfections between the WS_2 and HfO_2 layers are detrimental to the working efficiency of the quantum devices. "This study marks the first time this property called 'interface roughness' has been systematically measured and quantified," Goh said.

The research team plans to reduce and eliminate interface roughness that affects the performance of quantum devices. "Further optimisation of the qubit design will allow us to synthesise high-quality single- and double-qubit gates," Goh said. ★

Researcher
Kuan Eng Johnson Goh, IMRE

IN BRIEF
By combining two industrial processes, the researchers' novel method can overcome the challenges in synthesising the tungsten disulfide crystals needed to make scalable qubits.

1. Lau, C.S., Chee, J.Y., Cao, L., Ooi, Z.E., Tong, S.W., *et al*. Gate-defined quantum confinement in CVD 2D WS_2. *Advanced Materials*, 2103907 (2021).

MATERIALS SCIENCE

Giving neural networks a power boost

A new method to create artificial synapses could make neural networks more efficient and less energy-intensive.

From recognising friends in your photos to plastering an Instagram filter over your face in real-time, you don't have to look far to see that computers are now capable of performing complex image processing. These impressive feats are possible largely due to the development of artificial neural networks, a circuit of components that mimic the behaviour of neurons and synapses in the brain. Just like their biological counterparts, however, artificial neural networks do have their shortcomings—they consume a lot of energy.

Memristors, a type of electrical component, might just be the solution to less energy-intensive artificial synapses for neural networks. Memristors arranged in a grid, forming what is known as a crossbar array (CBA), hold promise for building scalable neural networks with high-performance computing capacities.

This is particularly true for memristors made from two-dimensional (2D) materials which possess unique properties and superior device performance compared to their transition metal oxide-based counterparts. But due to limitations in fabrication methods, 2D material-based memristors aren't as easy to make and integrate into devices.

Now, a team of researchers led by Dongzhi Chi and Kah-Wee Ang, both Principal Scientists at A*STAR's Institute of Materials Research and Engineering (IMRE), has demonstrated a novel way to create and integrate a 2D memristor CBA into neural network hardware—without the drawbacks.

"Previous research focused mainly on single device characteristics, which is far from array-level applications," said Chi and Ang. "Here, we fabricated memristor CBAs and demonstrated their capacities at an array level."

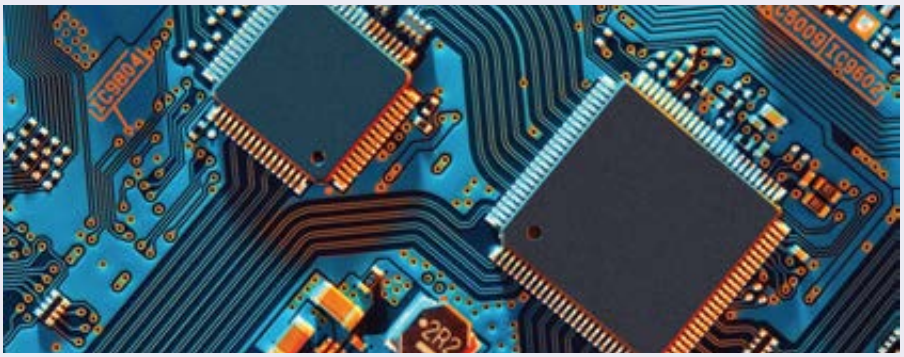


Photo credit: raigvi / Shutterstock

The researchers used a process called molecular beam epitaxy to create wafer-scale 2D hafnium diselenide ($HfSe_2$) films, the material for their memristors. Unlike the inconsistent mechanical exfoliation process commonly used to fabricate 2D materials, the researchers were able to achieve controllable and uniform growth of the films.

Furthermore, the use of ultra-thin $HfSe_2$ films allowed filaments to form within the memristors in the CBA at a low voltage, a key feature for facilitating signal processing with low switching energy.

"We leveraged the intrinsic defects that exist in the polycrystalline $HfSe_2$ film to facilitate the formation of filament for switching," explained the researchers. "The result was a memristive CBA with a low switching voltage and thus lower energy consumption."

When the researchers tested their creation on the multiply-and-accumulate (MAC) operations widely used in image processing, they found it performed with a high level of efficiency and accuracy.

"The CBA can also perform multiple MAC operations simultaneously, thereby enabling parallel computing," added Chi and Ang.

The team hopes to integrate their CBAs with access devices such as selector diodes that will allow precise control of individual memristors. They also plan to build a complete image processing hardware by connecting their CBAs with custom-designed circuits. ★

Researcher
Kah-Wee Ang and Dongzhi Chi, IMRE

IN BRIEF
Two-dimensional material-based memristor crossbar arrays are ideal for making powerful and energy-efficient neural network hardware.

1. Li, S., Pam, M.E., Li, Y., Chen, L., Chien, Y.C., *et al.* Wafer-scale 2D hafnium diselenide based memristor crossbar array for energy-efficient neural network hardware. *Advanced Materials,* 2103376 (2021).

FIGURING OUT RNA ONE FOLD AT A TIME

YUE WAN

Principal Investigator
Genome Institute of Singapore, A*STAR

Understanding the mechanisms behind RNA structure and folding could pave the way for more effective medical treatments, say Yue Wan and Ashley Aw.

If you're reading this, there's a good chance you have been on the receiving end of a product that is the culmination of decades of research: an RNA therapeutic. Having recently entered popular knowledge thanks to the mRNA COVID-19 vaccine, the earliest research into the use of RNA as a way to deliver medical treatments can be traced back to the 1960s.

However, while technological advancements and research breakthroughs have since made mRNA vaccines possible, there remains much more to discover about RNA and its other potential therapeutic uses.

RNA is a uniquely fascinating molecule. If the double-stranded DNA helix serves as the genetic blueprint that outlines the protein to be made, then the single-stranded RNA can be thought of as the construction crew needed to build that protein from the blueprint. RNA can fold into different forms which allow it to carry out a vast array of functions, ranging from reading the DNA blueprint to transporting and assembling the amino acids needed to make up a particular protein.

At A*STAR's Genome Institute of Singapore (GIS), Yue Wan is the Principal Investigator of a laboratory that focuses on developing technologies to capture accurate snapshots of RNA's many forms and structures. Wan and her team also aim to better understand the mechanism behind RNA folding and how RNA structure affects health and disease, to harness its potential as a targeted therapy against disease.

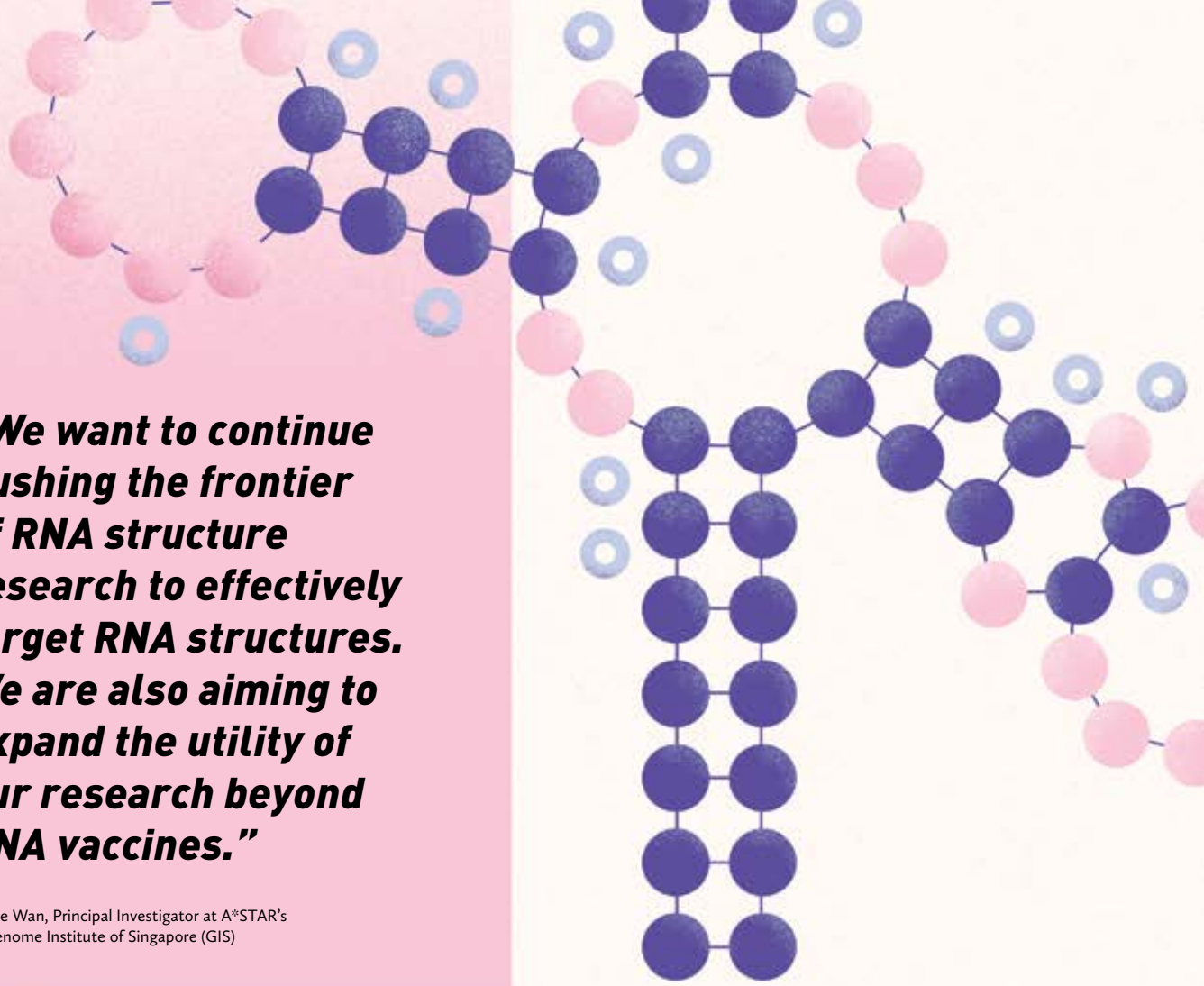
In this interview with *A*STAR Research*, Wan and her graduate student Ashley Aw talk about their research on RNA and its therapeutic potential, along with the importance of mentorship in advancing science.

Q: WHAT MADE YOU FOCUS ON RNA STRUCTURE?

The past decades have been dedicated to understanding protein structures and how they can be targeted by small-molecule drugs. However, it has become clearer in recent years that only a small fraction of these proteins can be targeted. As such, we need to identify new drug targets in different diseases. RNA makes for a good candidate here because it can fold into complex secondary and tertiary structures.

That said, we must acknowledge that the field of RNA structure is about 20 years behind that of protein structure. Much remains to be learnt about the structure and function of RNAs in diseases.

The COVID-19 pandemic has further highlighted how important it is for us to understand RNA structure and folding. Like all viruses, SARS-CoV-2 uses RNA as its genetic material. We already know that some structures along the SARS-CoV-2 genome are important for virus translation, but much of it is still unexplored. The more we know about this viral genome, how it folds and what it interacts with, the better we can disrupt these interactions to prevent its spread and infection.



"We want to continue pushing the frontier of RNA structure research to effectively target RNA structures. We are also aiming to expand the utility of our research beyond RNA vaccines."

— Yue Wan, Principal Investigator at A*STAR's Genome Institute of Singapore (GIS)

Q: WHAT MAKES RNA-BASED THERAPIES SO PROMISING?

The world got a glimpse of RNA's therapeutic potential with the mRNA COVID-19 vaccines. We can now quickly order genes of interest, make RNA out of them and deliver it into the body to generate vaccines. This system is highly flexible, allowing us to change sequences to quickly adapt to variants and respond rapidly to new infectious agents. Nonetheless, we are barely scratching the surface of this intriguing RNA realm—I believe we can take RNA therapeutics to new heights.

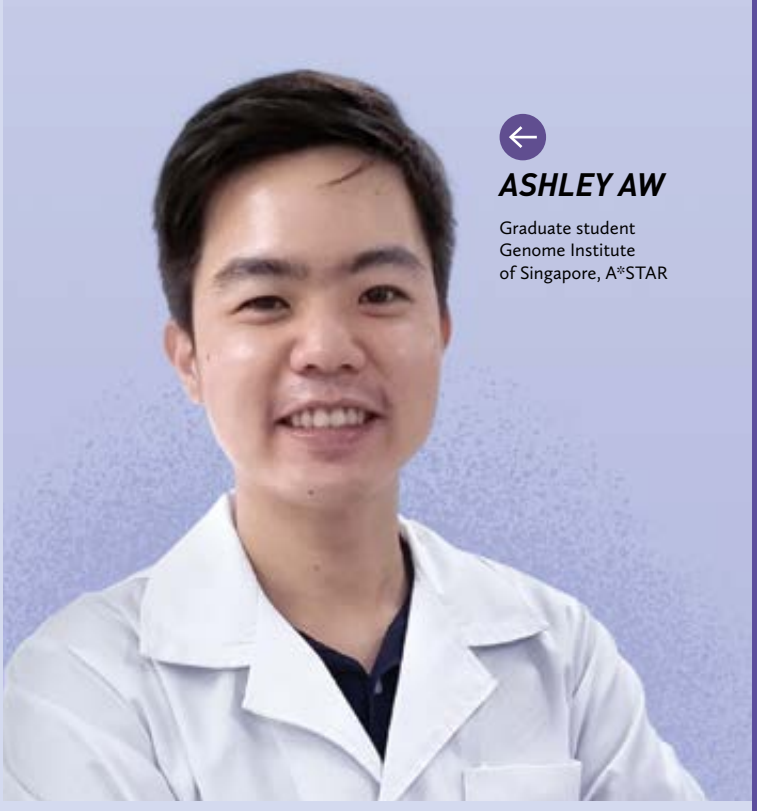
Q: WHAT IS NEXT FOR YOUR RESEARCH?

We want to continue pushing the frontier of RNA structure research to effectively target RNA structures. We are also aiming to expand the utility of our research beyond RNA vaccines.

Q: AS A GROUP LEADER, HOW DO YOU BALANCE MENTORING YOUNG SCIENTISTS WITH SELF-DEVELOPMENT?

I established my lab straight out of my PhD. I didn't have a lot of experience mentoring students to start with. However, two things have worked for me. First, I always try to solve my students' problems before working on things such as grants, because this helps guide them in the right direction as early career scientists.

Second, as a best friend of mine once advised me, a defining feature of a great leader is how they keep their supervisees' best interests at the forefront rather than their own. I believe that this sense of magnanimity is very important. These two beliefs have helped me to become not only a better mentor but also a better researcher.



ASHLEY AW
Graduate student
Genome Institute
of Singapore, A*STAR

Q: WHAT INSPIRED YOU TO PURSUE A CAREER IN SCIENCE?

At a young age, I was curious about how things worked. It was sometime during secondary school when I became entranced by how cells function, which led to my interest in the greater world of biological sciences.

After completing my undergraduate studies, I accepted the position of Research Officer at A*STAR and worked on projects involving viruses. This experience cemented my desire to pursue a career in scientific research. I was also certain that I wanted to pursue my PhD studies locally. The A*STAR Graduate Scholarship appealed to me the most as it allowed me to continue my passion for research without leaving Singapore or A*STAR.

Q: CAN YOU TELL US ABOUT YOUR PHD PROJECT AND WHY YOU CHOSE TO FOCUS ON RNA?

The focus of my project is to develop a method that uses direct RNA sequencing to look at the many different structures of RNA—the Wan Lab of RNA Structuromics led by Yue Wan allows me to do just that.

Before the development of our method, which we have named PORE-cupine, there was no easy way to determine the RNA structures of isoforms extracted from cells. Existing methods largely use short-read sequencing, which requires the amplification of RNA for reading and detection. This may, however, increase the complexity of the analysis.

In contrast, PORE-cupine can directly probe for RNA structural information without the need for any amplification, which simplifies the process.

RNA is a valuable biomolecule to study as it is versatile in its functions, ranging from being a bridge between DNA and proteins to having catalytic or recognition functions. By using PORE-cupine, we hope to identify the structures that are important for RNA's many functions.

Q: WHAT KEY PROBLEMS DO YOU HOPE TO ADDRESS WITH YOUR RESEARCH?

If we can identify the RNA structures that are important for the replication of RNA viruses, we might be able to develop anti-viral drugs that eliminate a particular virus from its host. Although the development of drugs that target RNA structures is still in its early stages, we are well aware of its vast potential.

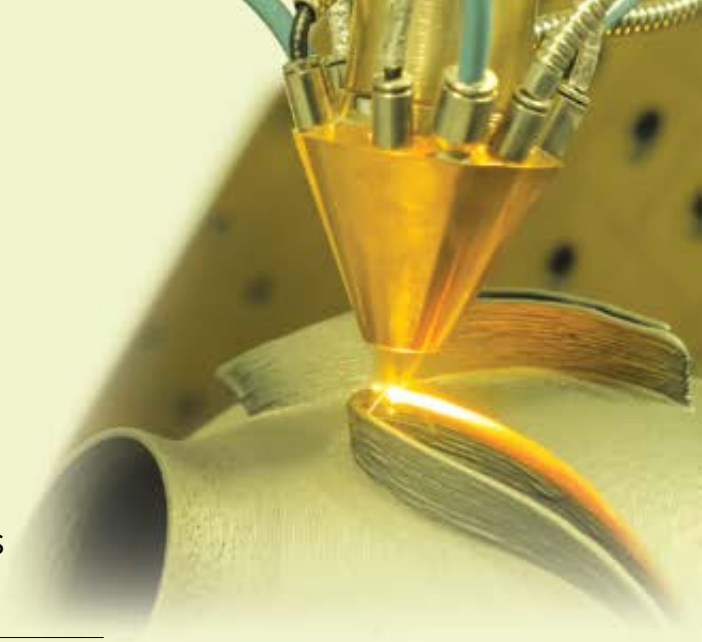
Q: HOW HAS YOUR TIME AS A GRADUATE STUDENT IN THE WAN LAB SHAPED YOUR CAREER?

My time in this lab has been really fulfilling. I was given the rare opportunity to develop my skills in both molecular biology and bioinformatics. My colleagues have also been very supportive and generous in sharing their knowledge. Above all, under the guidance and mentorship of Yue Wan, I have developed a solid mindset and am now more confident in every aspect of my work. ★

MATERIALS SCIENCE

Helping metals survive the cold

Materials scientists unlock novel chemical processes for manufacturing durable cold-resistant alloys.



If you've ever baked a cake, you would know how the careful combination of distinct ingredients like eggs, butter, sugar and flour can result in something more delicious than the sum of their parts. In a somewhat similar fashion, metal alloys combine two or more elements with distinct physical properties in exact ratios to enhance the end product's performance. For example, stainless steel, derived from the addition of chromium to steel, boasts improved properties like heat and corrosion-resistance and is used in everything from surgical tools and cutlery to trains and airplanes.

Nonetheless, one environment that alloys still struggle in is the cold. In chilly regions, metal components for constructing spacecraft or processing plants are typically subjected to extreme mechanical stress. For such applications, the cobalt-chromium-nickel (CoCrNi) alloy is presently an attractive choice as it has high printability and durability even under ultra-cold conditions. Another unique and intriguing characteristic of CoCrNi is that it comprises an equal proportion of each of the three elements—a trait that is not commonly seen in other alloys.

While more studies are performed to elucidate the properties and applications of laser aided additive manufactured (LAAMed) CoCrNi, materials scientists have revealed that chromium oxidation can limit the alloy's strength.

"Oxidation is almost inevitable during the LAAM process," said study first author Fei Weng, a Research Scientist at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech). "However, the effect of oxides on the mechanical properties of CoCrNi, especially in a cryogenic environment, remains unknown."

To create stronger CoCrNi alloys that can withstand cold conditions, Weng and his team set out to tweak established LAAM processes to optimise CoCrNi's oxide content. The team, led by SIMTech's Youxiang Chew and Guijun Bi, first investigated how the amounts of inert gas—used in LAAM to minimise alloy oxidation—influenced CoCrNi's mechanical properties. In the process, the team generated two distinct classes of CoCrNi alloys with either low or high oxide content.

Next, the team analysed how oxide content affected the strength of the alloy. To do so, the group performed a test that stretched and pulled the alloys under cold and ambient temperatures to measure how much force had to be applied before they deformed.

CoCrNi with higher amounts of oxide was found to be weaker, stretching apart under lower stress levels and elongation at room temperature. During tensile deformation, tiny structural gaps called microvoids form between the alloy matrix and oxides.

"With a higher oxide content, microvoids easily form and coalesce at the oxide matrix interface during deformation, resulting in premature fracture and lower elongation. Interestingly, the highly oxidised CoCrNi alloy showed comparable elongation at room temperature and -130 °C, which is attributed to the compensated effect from more deformation twinning at -130 °C," explained Weng.

Their discovery illustrates how LAAM can be modified to create alloys with specific properties, such as corrosion resistance and resilience against stretching forces at low temperatures. "By adjusting the process parameters, we can tune the microstructure and oxide levels of CoCrNi alloys to improve their mechanical properties at room or low temperatures," Weng said.

Moving forward, the team plans to perform more studies to enhance the mechanical properties of the CoCrNi alloy fabricated using the LAAM technique. This work would pave the way for new opportunities in the energy, aerospace and manufacturing industries and beyond. ★

Researcher
Fei Weng,
SIMTech

IN BRIEF
The discovery that alloys with higher oxide amounts are weaker highlights a factor that can be modified in additive manufacturing for improved mechanical properties.

1. Weng, F., Chew, Y., Zhu, Z., Sui, S., Tan, C., *et al.* Influence of oxides on the cryogenic tensile properties of the laser aided additive manufactured CoCrNi medium entropy alloy. *Composites Part B: Engineering* **216**, 108837 (2021).

ROBOTICS

Guiding hand-eye coordination in robots

A novel machine learning framework makes it faster and easier to train robots that can perform tasks with unprecedented precision.

In the first Industrial Revolution, many wondered if machines would replace humans in manufacturing jobs—a concern that is now echoed with today's developments in robotics and automation. But even if that scenario were to come to pass, humans are unlikely to be written out of the picture entirely. While robots can automatically perform repetitive tasks, they still rely heavily on human input for more precise pick-and-place operations.

Such robot-human teamwork is exemplified by a vision-based control method called 'visual servoing', where a user guides a robot's limb and gripper in performing delicate manipulation tasks. Traditional visual servoing techniques require humans to manually select features to use as feedback for the movement, making the process labour-intensive and limiting the robots to operate only in environments they have been pre-programmed to perform in.

Fortunately, algorithms called deep neural networks could eliminate human input, enabling robots to programme themselves. However, such algorithms require vast amounts of real-life training data and only work on limited functions, making them unprepared to fully take over from human controllers.

To address the functional and data limitations of current systems, En Yen Puang, a Research Engineer at A*STAR's Institute for Infocomm Research (I²R), together with colleagues Keng Peng Tee and Wei Jing, developed a novel keypoint-based visual servoing framework called KOVIS.

"KOVIS stands out from other visual servoing frameworks because of how easy, fast and labour-free it is when deployed on new tasks," explained Puang. Compared to its predecessors, KOVIS boasts a higher efficiency, using a deep auto-encoder algorithm to learn and encode visual features without any human input.

Uniquely, the system represents objects as keypoints based only on essential geometric information. This feature makes KOVIS quicker and easier to be used in new environments as it eliminates the appearance variations of an object in different settings. Consequently, KOVIS can quickly pick up the simple 'peg-and-hole' relationship between the robot's gripper and the target object.

Another major benefit of KOVIS is how little real-life training data the system needs to perform these tasks, with the framework trained entirely using synthetic images captured in simulated conditions. While these objects may appear different in reality, KOVIS works around this by generalising what it learns so that it can recognise the same objects in different environments.

When put to the test, KOVIS rose to the challenge. Despite being trained on only synthetic data, the system successfully performed real-world manipulation tasks like gripping a mug by its handle and inserting a peg and screw into a designated hole with a remarkable 90 percent success rate.

"Currently, KOVIS is being used in Collab-AI, a research project that aims to advance developments for safer and more efficient human-robot collaboration in production and manufacturing settings," Puang said.

The researchers plan to expand the applications of KOVIS from simple manipulation tasks to precise routine manoeuvres such as the docking and landing of mobile robots. ★

Photo credit: Gorodenkoff / Shutterstock

Researcher
En Yen Puang, I²R

IN BRIEF
The KOVIS framework can generalise what it learns from simulated conditions, minimising the need for real-life training data.

1. Puang, E.Y., Tee, K.P., Jing, W. KOVIS: Keypoint-based visual servoing with zero-shot sim-to-real transfer for robotics manipulation. *2020 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS)*, 7527-7533 (2020).

MATERIALS SCIENCE

Sluggish battery reactions get a boost

Insights into the intricate chemical reactions of lithium-sulfur batteries could pave the way for lighter, more powerful prototypes.

Batteries are the key to powering almost everything, from laptops and mobile devices to electric vehicles and even space missions. However, despite being hailed as a solution to fossil fuel dependence, today's lithium-ion batteries are not quite ready to fuel tomorrow's technologies for one sole reason: they are too heavy.

Take the electric vehicle Tesla Model S, for example, which uses a lithium-ion battery that measures a whopping 2,200 kg, about a quarter of the car's total weight.

To lessen the load, a team led by Zhaolin Liu, a Senior Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE), is developing a new wave of high energy density batteries. These lithium-sulfur (Li-S) cells are much lighter than their predecessors, have superior specific energy and are less prone to overheating during use. These properties make them ideal for transportation and aviation applications.

Photo credit: Sergii Chernov / Shutterstock

However, Li-S batteries still have their limitations, including low rate capability (the maximum charge/discharge rate of a battery) and low volumetric energy density (the amount of energy a system contains in comparison to its volume)—all of which hinder their commercial adoption.

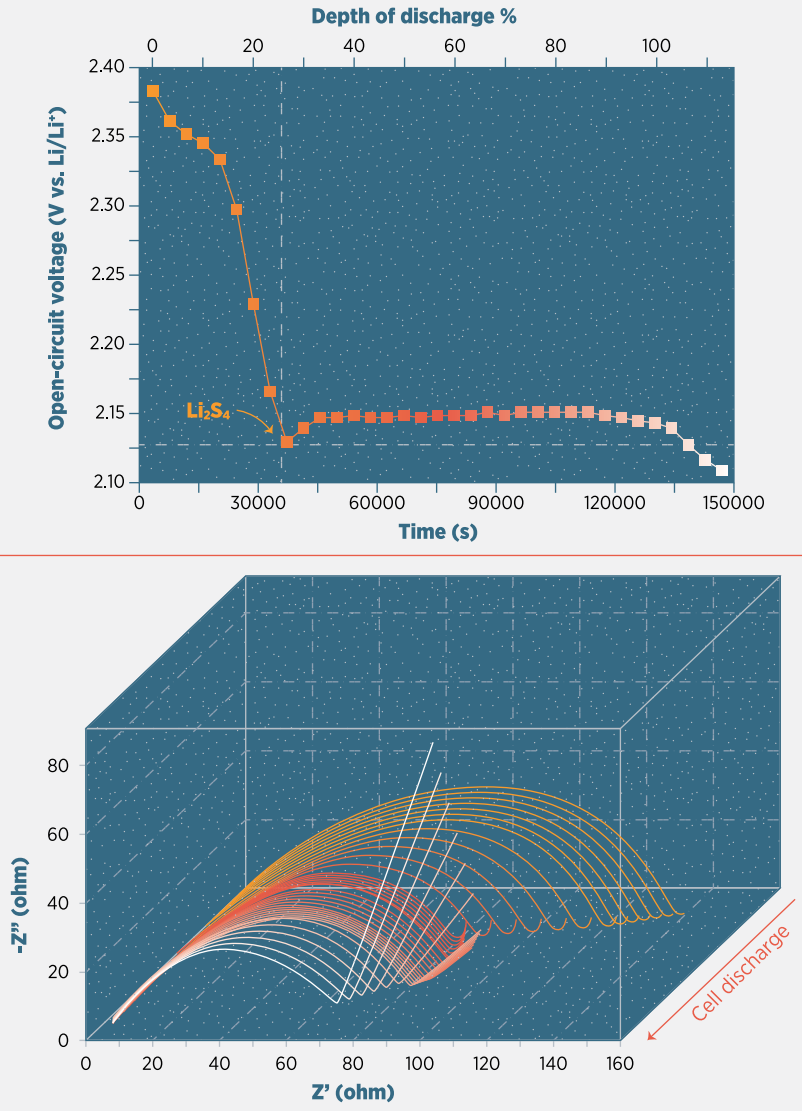
To overcome these limitations, Liu and colleagues took a closer look at the electrochemical reactions that cause Li-S batteries to drain their charge so quickly. They looked for specific chemical factors that influence Li-S cell deterioration using electrochemical impedance spectroscopy (EIS) to measure the battery resistance change during discharging.

"The reduction from sulfur to lithium sulfide forms various intermediates, including Li_2S_8, Li_2S_6, Li_2S_4, Li_2S_3 and Li_2S_2," explained Liu. "The discharge capacity and output current are mainly determined by the conversion of these intermediates during discharge."

Using EIS, the team observed two distinct voltage dips over time, coinciding with the transition from Li_2S_4 and Li_2S_2. According to Liu, these sudden voltage drops correspond to energy barriers, proving to be the culprit behind sulfur's poor conductivity.

With this leap forward in the understanding of chemical dynamics in batteries, the researchers have their sights set on making a better Li-S battery.

"Our research facilitates the development of Li-S batteries, especially fast-discharging sulfur batteries," noted Liu. "We will continue to explore effective catalysts for sulfur reduction." ★



Electrochemical impedance spectroscopy confirmed voltage drops correspond with two energy barriers in sulfur reduction during discharge.

"Our research facilitates the development of Li-S batteries, especially fast-discharging sulfur batteries."

Researcher
Zhaolin Liu, IMRE

IN BRIEF
With their superior specific energy and resistance to overheating, lithium-sulfur batteries are ideal for use in transportation and aviation.

1. Ding, N., Schnell, J., Li, X., Yin, X., Liu, Z., *et al.* Electrochemical impedance spectroscopy study of sulfur reduction pathways using a flexible, free-standing and high-sulfur-loading film. *Chemical Engineering Journal* **412**, 128559 (2021).

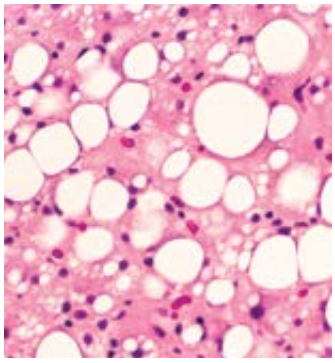
NEXT ISSUE

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

COVID-19

WHAT'S THE BEST WAY TO REUSE AN N95 MASK?

By identifying the best way to decontaminate N95 masks, A*STAR scientists are helping solve the environmental consequences of disposable masks.



STEM CELLS

SEARCHING FOR GOOD FATS' ORIGINS

Researchers have identified a stem cell marker that influences fat cell development, unlocking exciting therapeutic opportunities for chronic diseases.

ARTIFICIAL INTELLIGENCE

COPYING THE HOMEWORK OF MACHINE LEARNING ALGORITHMS

A new method for eliminating irrelevant data in training models could boost the adaptability of deep neural networks.

MATERIALS SCIENCE

A MODERN TWIST TO ANCIENT ALLOYS

Machine learning and computational platforms lend a hand in developing robust protocols for manufacturing an emerging class of strong, super lightweight alloys.

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REIMAGINE RESEARCH

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