A*STAR
RESEARCH

TO BRING BIOLOGICS TO LIFE

Tackling production challenges in biotherapeutics development

POWERED BY SUNSHINE

Harnessing sustainable chemistry for a solar future

ELECTRIFYING ADVANCES IN SMART DEVICES

The IEEE fellows making waves in AI and ferroelectrics

CONNECTING THE DOTS

How A*STAR's strategic innovation engine drives partnerships within and beyond borders

A*STAR RESEARCH

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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.

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

A*STAR Infectious Diseases Labs (ID Labs)
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)
Horizontal Technology Coordinating Offices (HTCO):
  Agritech and Aquaculture (A2)
  Artificial Intelligence, Analytics and Informatics (AI³)
  Epidemic Preparedness (EP)
  Robotics
  Social Sciences and Technology (SST)
  Urban and Green Technology (UGT)
Institute of Sustainability for Chemicals, Energy and Environment (ISCE²)
Institute of High Performance Computing (IHPC)
Institute for Infocomm Research (I²R)
Institute of Molecular and Cell Biology (IMCB)
Institute of Microelectronics (IME)
Institute of Materials Research and Engineering (IMRE)
National Metrology Centre (NMC)
Singapore Immunology Network (SIgN)
Singapore Institute for Clinical Sciences (SICS)
Singapore Institute of Manufacturing Technology (SIMTech)
Singapore Institute of Food and Biotechnology Innovation (SIFBI)
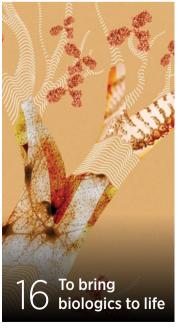
Contents

Issue 39 | January – February 2024

08 Connecting the dots

16 To bring biologics to life

22 Powered by sunshine

28 Electrifying advances in smart devices

Contents

Food Science: Mindful eating curbs blood sugar spikes
06

Genetics: Single-cell insights towards precision cancer care
14

Industrial Engineering: Seamless operations with machine health checks
27

Pharmacology: Millions of nature's secrets revealed
32

EDITORIAL NOTES

"**N**o man is an island," wrote the poet John Donne. The connections we make with others—whether as individuals or groups—are often the keys to successful endeavours. The work of innovation is no exception in this, as collaborations between industry, academia and government are critical to bring scientific solutions to living rooms and factory floors.

In this issue of *A*STAR Research*, our cover story, 'Connecting the dots (p. 08)', reviews A*STAR's multifaceted strategic efforts in driving vital partnerships between the key stakeholders of innovation at local and international levels.

Turning the lens to medicine, we examine how today's treatments are often inspired by our immune system's molecular tools. In our first feature, 'To bring biologics to life (p. 16)', Senior Scientist Sean Chia discusses his work in antibody biotherapeutics, as well as lessons from his tenure in industry and academia.

The sun's boundless energy could fuel our futures, but turning it into portable fuels for vehicles remains a challenge. For our second feature, 'Powered by sunshine (p. 22)', we speak to A*STAR scholar Celine Yeung about the potential for sustainable chemistry to create a greener Singapore.

Our third feature spotlights the achievements of two A*STAR researchers recently appointed as Fellows of the world-renowned Institute of Electrical and Electronics Engineers. In 'Electrifying advances in smart devices (p. 28)', Xiaoli Li and Kui Yao discuss their work in the fields of artificial intelligence and ferroelectrics.

Across this issue, we also review the latest findings at A*STAR's research institutes, ranging from gene editing technologies that destroy lethal viruses to self-assembling crystals that transform light. For more on these, turn to 'Gene editing cuts to the chase (p. 04)' and 'Growing polarisation control crystals' (p. 34).

For more of the latest developments from A*STAR researchers, visit our website at **research.a-star.edu.sg**. You can also stay up-to-date by following us on Twitter/X at **@astar_research**, LinkedIn at **A*STAR Research** and Telegram at **A*STAR Research**.
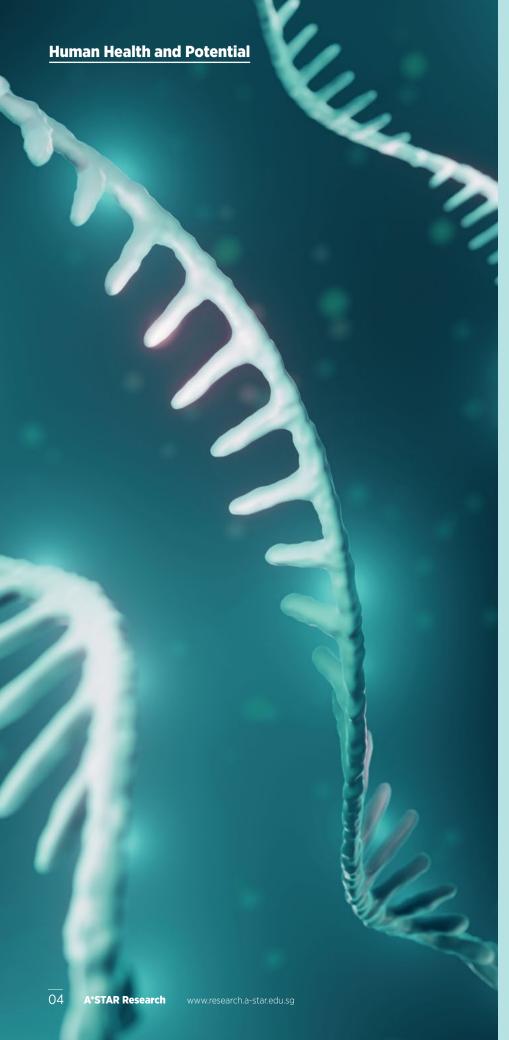
On the cover
A steady hand connects key nodes of innovation around the globe, generating new insights.

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Gene editing cuts to the chase

A programmable gene editing tool targets and eliminates a rapidly mutating RNA virus responsible for hand, foot and mouth disease outbreaks.

Some viruses are naturally adept at evading antiviral medicines. Take enteroviruses—a group of pathogens linked with a range of illnesses including hand, foot and mouth disease (HFMD). Thanks to their RNA genomes, these viruses are notorious for mutating rapidly, making them challenging targets for traditional therapies.

Wei Leong Chew, a Principal Scientist and Associate Director at A*STAR's Genome Institute of Singapore (GIS), believes that gene editing technologies have the precision and adaptability required to disarm these evolving viruses once and for all.

"CRISPR-Cas13 cuts RNA and can be easily programmed towards a user-defined RNA target sequence through a guide RNA (gRNA)," explained Chew, adding that this ease of programming can slash drug development timelines in the face of emerging viral strains.

Chew, along with a research team including Justin Chu and Thinesshwary Yogarajah from the National University of Singapore, as well as GIS Senior

Scientist Choong Tat Keng, developed a novel CRISPR-Cas13 system to target enterovirus-A71 (EV-A71), a common enterovirus that causes HFMD infections.

The precision of the CRISPR-Cas13 system hinges on its specific gRNA, which led the researchers to develop Cas13gRNAtor, a specialised bioinformatics tool for designing gRNAs. The RNA editing system was then packaged in a harmless adeno-associated viral vector (AAV) to deliver it to infected cells.

Results from tests on cell cultures showed that AAV-CRISPR-Cas13 treatment decreased viral replication by more than 90 percent. Data from animals with EV-A71 infections treated with AAV-CRISPR-Cas13 were equally exciting.

"One dose of AAV-CRISPR-Cas13 prevented death of infected mice," Chew said. "To go from an 80 percent mortality rate to almost zero percent is stunning beyond our expectations."
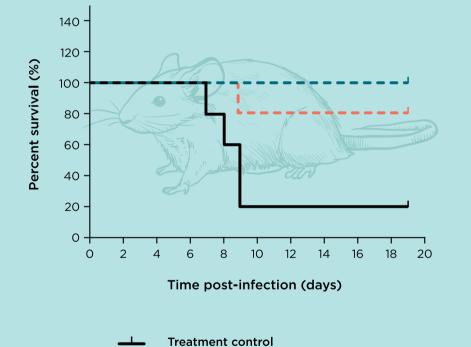
These findings underscore the unique potential of CRISPR-Cas13 antivirals to combat difficult-to-treat viral infections. "This is an antiviral mechanism that is distinct from other drug modalities such as small molecules and antibodies, which mainly target viral proteins," Chew said.

Despite the foreseeable hurdles in getting this potential therapy to patients, Chew said the recent approval of the world's first CRISPR-based therapeutic is highly encouraging.

Chew's team has filed two patents on their innovation and is currently developing similar approaches to target pathogens with pandemic potential. "Building our pandemic preparedness will help safeguard against the next Disease X," said Chew. ★

> ## "One dose of AAV-CRISPR-Cas13 prevented death of infected mice. To go from an 80 percent mortality rate to almost zero percent is stunning beyond our expectations."

Researchers
Wei Leong Chew, GIS
and Justin Chu, IMCB

IN BRIEF
A CRISPR-Cas13 system that targets the RNA genome and transcripts of enterovirus-A71 significantly reduces viral infection and death of mice.

Survival outcomes for mice with HFMD up to 19 days after a lethal infection. Treatments were given 24 hours after infection with EV-A71, a known cause of HFMD epidemics. Each mouse in the treatment group was injected with AAV-CRISPR-Cas13 with EV-A71 gRNAs at either a lower dose of 1×10^{11} viral genomes (vgs) or a higher dose of of 1×10^{11} vgs. Mice in the control group received 1×10^{12} vgs AAVDJ-GFPgRNA.

1. Keng, C.T., Yogarajah, T., Lee, R.C.H., Muhammad, I.B.H., Chia, B.S., *et al.* AAV-CRISPR-Cas13 eliminates human enterovirus and prevents death of infected mice. *eBioMedicine* **93**, 104682 (2023).

Mindful eating curbs blood sugar spikes

Research reveals that the way we chew can affect our blood sugar levels, offering improved strategies for managing blood sugar in people at risk for type 2 diabetes.

That first, relished bite of food when hunger strikes is invariably the most satisfying. Now, new research is showing that oral processing behaviours—specifically how food is chewed and how long it stays in the mouth before swallowing—may affect blood glucose levels after eating.

Ai Ting Goh, a Senior Research Officer at A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI), said that this early stage of digestion has been largely overlooked in metabolic health research.

Goh outlined various research-backed strategies for managing blood glucose levels in individuals susceptible to type 2 diabetes (T2D): "These include adding functional ingredients to carbohydrates, co-ingesting carbohydrates with macronutrients or manipulating the order of food during meal consumption."

There might also be metabolic benefits from changing one's chewing habits, Goh added, which would allow people with pre-diabetes to better manage their metabolism while still enjoying their favourite foods.

To test this theory, Goh teamed up with researchers from the National University of Singapore; Wageningen University and Research, the Netherlands; George Washington University, US; and Curtin University, Australia. In a trailblazing study, 26 participants with pre-diabetes were assessed both at home and in a tightly controlled laboratory setting to ascertain how their oral processing behaviours and salivary properties correlated with daily glucose readings.

"Matching the same people's response in the lab and in their natural environment offers new opportunities to predict day-to-day fluctuations in glucose trajectories based on objective laboratory-based measures," said Goh.

The cohort was monitored via video during a test meal of eggs and rice. Samples of the chewed food, or bolus, were collected for analysis. Subsequently, the cohort spent a week wearing continuous glucose monitoring devices to track their blood glucose fluctuations. Participants also logged any kind of dietary intake in an app during the observation period.

The study revealed that an increase in saliva mixing with food during chewing often results in elevated surges in blood sugar levels. "This early glucose release is important as it stimulates early insulin release and can have a positive effect on maintaining euglycemia, or normal glucose levels," said Goh.

These insights suggest a new angle to optimal dietary practices for managing metabolic conditions; one that goes beyond restricting carbohydrates and sugary foods to maintain healthy glucose levels.

"[Our] ongoing research initiatives are looking closely at the impact of processed food structure on energy intake; the relationship between food texture, eating rate and satiety; and the potential link between bolus properties and the microbiome," Goh added. ★

> **"This early glucose release is important as it stimulates early insulin release and can have a positive effect on maintaining euglycemia, or normal glucose levels."**

Researcher
Ai Ting Goh,
SIFBI

IN BRIEF
Chewing patterns and saliva properties observed in individuals at risk for type 2 diabetes reveal a correlation between saliva uptake in chewed food and blood sugar spikes, potentially informing tailored dietary advice for better glucose management.

1. Goh, A.T., Yao, J., Chua, X.H., Whitton, C., van Dam, R.M., *et al*. Associations between oral processing, saliva, and bolus properties on daily glucose excursions amongst people at risk of type-2 diabetes. *Food and Function* **14** (4), 2260-2269 (2023).

Photo credit: SOCIAL.CUT / Unsplash

CANCER IMMUNOTHERAPY

Targeted therapy sparks childhood cancer hope

An experimental antibody therapy for solid tumours in adults also shows promise in improving quality of life for paediatric patients.

Photo credit: Charlein Gracia / Unsplash

The quest for effective cancer treatments has long been hampered by a crucial limitation: conventional approaches like chemotherapy can't differentiate between healthy and cancerous cells. This lack of specificity can damage healthy tissues along the way and trigger debilitating adverse effects.

According to Qi Zeng, a Research Director at A*STAR's Institute of Molecular and Cell Biology (IMCB), the crux of advancing cancer treatment lies in identifying molecular targets that are exclusively associated with tumours. This precision is especially critical for young children with cancer, who can be more vulnerable than adult patients.

In 1998, Zeng and colleagues first discovered PRL3: a cancer-specific protein that controls various cellular processes. As they traced PRL3's footsteps over the years, they found that it contributed to the spread of malignant cells in many different cancer types.

"Our lab has studied hundreds of adult tumour samples. We've found that approximately 80.6 percent of tumours in adults express PRL3, while adjacent normal tissue does not," said Zeng.

The team also pioneered the discovery of PRL3-zumab, the first humanised antibody therapy against PRL3, which showed a promising safety profile in adults during a clinical trial in 2017.

In their latest study, Zeng and IMCB colleague Min Thura teamed up with Amos Hong Pheng Loh, Shui Yen Soh and other experts from the KK Women's and Children's Hospital, Singapore and Duke-NUS School of Medicine, Singapore, to investigate the use of PRL3-zumab in treating paediatric cancers.

By analysing 65 tumour-derived and healthy tissues from paediatric patients, the researchers found that PRL3 was frequently expressed in soft tissue tumours in the muscles and kidneys, and in all neuroblastomas studied. Significantly,

the presence of PRL3-positive tumours correlated with heightened angiogenesis— the creation of blood vessels that support tumour growth and metastasis.

Spurred by these findings, the team was optimistic that PRL3-zumab might be as effective for children as it is in adults. "We did a first-in-child compassionate use trial of PRL3-zumab," said Zeng, adding that the treatment was administered to a seven-year-old in critical condition with recurrent rhabdomyosarcoma, a soft tissue cancer.

The team reported that PRL3-zumab, in combination with radiation therapy, temporarily stabilised the child's condition, prolonged his life by three months and enhanced his quality of life even in an advanced stage of cancer. "The boy was off morphine and supplemental oxygen; he left the ICU to return home, and was even able to go to school for three days," Zeng recalled.

These outcomes support further exploration of PRL3 expression as a prognostic cancer biomarker, as well as PRL3-zumab use in paediatric patients with aggressive cancers who have exhausted all standard options, Zeng said.

In December 2015, Zeng founded the spinoff biotech company Intra-ImmuSG, which is currently conducting phase 2 clinical trials with PRL3-zumab for adults with cancer in Singapore, China, the US and Malaysia. ★

Researcher
Qi Zeng, IMCB
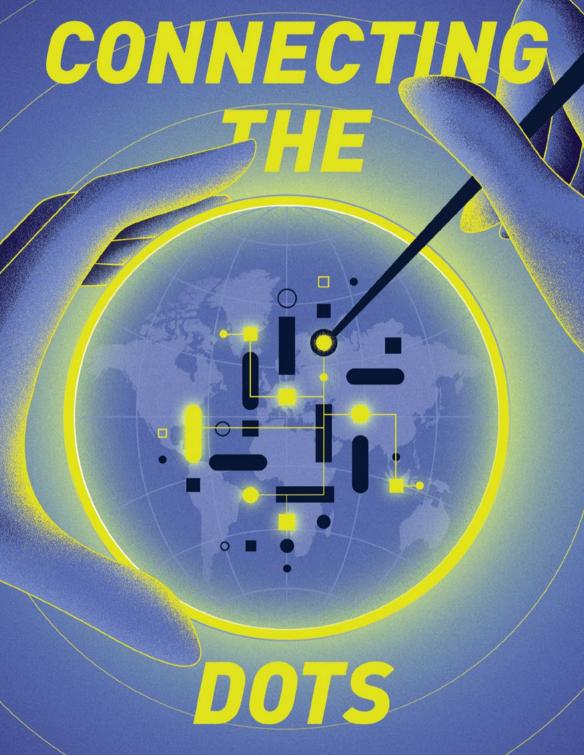
IN BRIEF
PRL3, a cancer-specific protein in adult patients, is differentially expressed in paediatric tumours. In a first-in-child, compassionate trial of novel humanised antibody PRL3-zumab, the drug specifically targeted cancer cells and improved clinical outcomes.

1. Loh, A.H.P., Thura, M., Gupta, A., Tan, S.H., Kuan, K.K.Y., *et al*. Exploiting frequent and specific expression of PRL3 in pediatric solid tumors for first-in-child use of PRL3-zumab humanized antibody. *Molecular Therapy Oncology* **30**, 153-166 (2023).

CONNECTING THE

DOTS

By contributing deep insights to Singapore's innovation ecosystem, A*STAR initiatives are helping to build strategic relationships with international partners and bridge the gaps in local capabilities.

Every day, cutting-edge discoveries make headlines: new drugs for deadly diseases, new alternatives to climate-changing fuels, new systems for smarter machines. Much of what was once science fiction is closer to reality than we might expect.

However, it's no simple process to turn these ideas into real-world solutions. "No matter how capable an individual, company or country may be, one rarely has all they need to productise research and development (R&D)," said Yee Chia Yeo, A*STAR Innovation and Enterprise (I&E) Assistant Chief Executive. "Therefore, when they find partners with complementary strengths, collaborations make sense to speed up and bring value to innovation."

Public agencies such as A*STAR act as innovation engines by locating and establishing relationships with such partners across diverse institutions and borders. These connections not only provide Singapore's researchers with problem statements, market guidance and commercial needs, but fill the gaps required to launch their proposed solutions beyond the laboratory.

"Our R&D teams solve high-value problems, making significant, scalable contributions to their fields," said Yeo. "In turn, our local and international partners help bring those solutions to market for greater societal impact."

To foster these two-way connections, A*STAR supports various initiatives based on its deep insights on the gaps in Singapore's innovation ecosystem. The agency helps drive the exchange of expertise and resources that both accelerate local innovation and propel it beyond Singapore's shores.

LANDING OFFSHORE

One of A*STAR's significant border-crossing platforms is the A*STAR Partners' Centre (A*PC), a launchpad for Singaporean tech startups to enter, expand and productise R&D within China's markets. Launched in late 2020 at the Singapore-Jiangsu Cooperation Council, A*PC is a strategic partnership between A*STAR, the Suzhou Industrial Park (SIP) Administrative Committee, the Singapore Economic Development Board (EDB) and Enterprise Singapore (ESG).

"A*PC acts as a platform to encourage interaction between Singapore and China's innovation communities," said Chuan Seng Tan, A*PC Director. "As of December 2023, A*PC has assisted 37 Singaporean companies to enter China through SIP, of which 30 are A*STAR-SIP Technology Support Grant awardees."

Beyond funding, A*PC's assistance also includes expertise and infrastructural support for startups in the biomedical sciences, advanced remanufacturing, green energy and new materials. Its 3,500 m² physical campus in Suzhou not only serves as a networking hub for ecosystem partners, but provides centralised research facilities for rapid product testing and customisation, as well as exhibition spaces, offices and other shared services.

"Member companies have accumulated a total of 147 intellectual property (IP) rights," said Tan. "As of December 2023, they have also achieved a cumulative turnover of around CN¥100 million, with a cumulative actual investment of around CN¥15 million."

A*PC member companies include machine vision specialists JM VisTec, which not only provides industrial solutions for Chinese manufacturing SMEs, but generates R&D linkages back to A*STAR's Advanced Remanufacturing and Technology Centre (ARTC) and Singapore Institute of Manufacturing Technology (SIMTech). Others include Vivo Surgical, which recently partnered with Shanghai-based CDMO Joymed to design and productise their robotic surgery products; and AiTreat Robotics, which has industrialised its soft tissue massage technology products in SIP.

TRAINING THE INNOVATORS

A*STAR's strategic partnerships have also introduced dynamic talent development programmes into Singapore's innovation ecosystem. One such platform is Singapore Biodesign (SB), a national platform to nurture innovators in health and medtech (HMT) based on the internationally-validated Biodesign methodology from Stanford University in the US.

"SB began in 2010 as Singapore-Stanford Biodesign (SSB), established in a joint partnership between A*STAR, EDB and Stanford," said Phin Peng Lee, SB Deputy Programme Director. "This was initiated when two Singaporeans, Ruey Feng Peh and Dorothea Koh, returned after their training as Stanford Biodesign Innovation Fellows. There was a desire to learn from that programme's success so as to build up the nation's HMT ecosystem."

Initially closely modelled after its parent programme, SSB would constantly evolve to address HMT needs unique to Singapore and Asia. In 2018, SSB officially transitioned into SB as it took on an implementation-focused approach, and continues to receive support from Stanford as well as regional partners in China, Indonesia and South Korea.

"Today, SB provides a full suite of training offerings and innovation support for healthcare professionals and engineers at varying competency levels, with a curriculum adapted for local and regional contexts," said Lee. "In recognition of our success and sustainability, we were also the first Biodesign programme in Asia—and one of only two worldwide—to be conferred the Global Affiliate status by the Stanford Byers Center for Biodesign."

Apart from talent development, SB provides prototyping support for alumni to develop proofs of concept. For alumni-led projects or startups aimed at US markets, SB works with nonprofit incubator Fogarty Innovation in the BOLT Initiative: a bespoke mentoring and coaching programme that includes a three-week visit to Fogarty's Silicon Valley campus to learn directly from successful healthtech domain experts.

SB also invests in community building to boost professional relationships and experience sharing. "Through our fellowships, workshops and classes, we have a strong, active network of over 1,500 SB alumni, who also enjoy access to the wider global Biodesign network," said Lee.

"We've gone from creating two spinoffs a year in the past to approximately 15 a year now."

— Kai Hoo Quek, Chief Investment Officer at A*STAR Innovation and Enterprise (I&E)

CROSS-BORDER EDUCATION

To advance Singapore as a global nexus of scientific talent, the A*STAR Graduate Academy (A*GA) also offers a suite of scholarships and fellowships at undergraduate, PhD and postdoctoral levels. To date, A*GA has supported over 4,215 scholarships and awardees—almost half of them international students—to A*STAR research institutes and 90 universities across 14 countries, with top host countries being Singapore itself (3,234), the US (585) and the UK (330).

ACCELERATING VENTURES

Since the 1990s, over 200 companies have spun off A*STAR innovations, according to I&E Chief Investment Officer Kai Hoo Quek. "There's been a ramp-up in recent years as we've focused on spinoffs as a key mode to commercialise IP developed within A*STAR," said Quek. "We've gone from creating two spinoffs a year in the past to approximately 15 a year now."

To boost their momentum, I&E recently embarked on Project Carrier, a deep tech venture building programme that provides pre-spinoffs with protected time and resources to incubate their startups and bring them closer to market, aiming to boost their odds of success after emerging from A*STAR. Carrier unifies previously siloed efforts in mentorship, gap funding, IP and talent matching under a structured programme that aims to be more deliberate around venture creation.

Prefer, a spinoff from the Singapore Institute of Food and Biotechnology Innovation (SIFBI), is the first to take off from Carrier. With incubation support and funding, the company uses biofermentation to upcycle food waste into bioflavours; their flagship bean-free coffee product is now sold in Singaporean cafes.

To prepare deep tech startups for further shores, A*STAR's open innovation platform A*StartCentral (A*SC) takes a further two-pronged approach of venture building and ecosystem building.

"As part of I&E's Venture Creation and Growth division, A*SC gears its programmes to grow globally investible deep tech startups," said Anthony Chong, A*SC Deputy Director. "We provide a continuum of support throughout the venture building life cycle, helping new innovators move from initial ideation to business plan validation, spinoff creation and market access."

A*STAR has supported over 250 A*STAR spinoffs and external startups via A*SC and other programmes and events. One key initiative is A*SC's Essentials Bootcamp, a 20-week venture building programme where prospective spinoff teams can identify markets for entry, and calibrate business plans that are scalable and harness global markets. "The Bootcamp brings in mentors with global experience to assist the teams, providing them a realistic lens," said Chong.

Such mentors can make a significant impact, as in the case of Revivo Biosystems, an A*SC-incubated SIMTech spinoff specialising in 4D human skin models. "To mentor Revivo founder Massimo Alberti, we engaged Bert Grobben, P&G's former Director of Open Innovation, who then joined Revivo as Chief Business Officer," said Chong. "The company has since received investment from German MNC Evonik to develop human skin models as alternatives to animal testing. With clients from Europe and ASEAN, Revivo is poised for the international market."

Chong also highlighted A*SC's Elevate programme, which facilitates market access for deeptech startups within A*SC's ecosystem. Elevate's four-part structure comprises peer sharing and market awareness; insights and workshops on overseas business operations; in-market immersion to engage funders, customers and partners; and market entry strategy and decision.

In 2023, Elevate's inaugural cohort was prepared in collaboration with A*PC, ESG, GIA Partners, Xnode, China-Singapore Suzhou Industrial Park Development Group and other ecosystem partners. "Our collective efforts and knowledge superseded that of any individual contributor, with insights and workshops providing considerations in IP protection, business-government interactions, international trade and hiring," said Chong.

An ongoing member of A*SC's support continuum is BioActivx, a spinoff of A*STAR's Institute of Materials Research and Engineering (IMRE) geared for advanced wound care solutions. "Bioactivx had gone through our Open Mike, Essentials and Elevate programmes," said Chong. "In November 2023, we coached them for a pitch at the 2023 Jinji Lake Innovation and Partnership Competition in Suzhou, where they received an award and investor interest."

TAKING FLIGHT — OTHER A*STAR-SUPPORTED INNOVATORS AT DIFFERENT GLOBALISATION STAGES

LOCAL

Plasma Science

Developers of air sanitisers under Trident Air in collaboration with IMRE and partners; I&E support led to their product showcasing at the 2024 Consumer Electronics Show in Las Vegas, US.

Xinterra

High-throughput sustainable materials engineering with AI platforms developed by IMRE, National University of Singapore (NUS) and Nanyang Technological University. Winners of the Vogue Singapore x BMW Innovation Prize 2023 for COzTERRA, a line of carbon dioxide-absorbing clothing textiles.

REGIONAL

Neeuro

Non-invasive health neurotechnology with IP licensed from the Institute for Infocomm Research (I^2R); now exploring markets in Vietnam, Belgium, China and Scotland.

Ampotech

AI-enabled Internet of Things (IoT) energy management solutions; a spinoff from A*STAR and the University of Illinois Research Institute, US. Raised S$1.7 million in a 2023 funding round led by Vietnam's Earth Venture Capital; to set up first international office in 2024.

INTERNATIONAL

MiRXES

Developer of non-invasive, blood-based microRNA test kits for early detection of cancer and other diseases. In 2023, received the US Food and Drug Administration's Breakthrough Device Designation for its flagship product GASTROClear; filed listing application with the Hong Kong Stock Exchange after raising US$50 million in Series D funding.

Immunoscape

Pre-clinical biotechnology company focused on the development of next-generation T cell receptor (TCR)-based cell immunotherapies. Introduced to University of Tokyo Edge Capital and Anzu Partners for initial venture capital funding; in 2022, raised US$14 million in new financing led by Anzu.

Augmentus

Intelligent, adaptive industrial robotics solutions sold worldwide. In 2023, the ARTC spinoff raised an oversubscribed Series A round led by Silicon Valley-based venture capital firm Sierra Ventures.

"By uniting differentiated capabilities across domains, we achieve greater objectives. This is the power of partnership."

— Yee Chia Yeo, Assistant Chief Executive at A*STAR Innovation and Enterprise (I&E)

NATION TO NATION

Strategic innovation relies not only on collaboration between institutes and industries, but between nations. Under A*STAR I&E, the International Operations and Relations Office (IORO) works with the Office of Grants Administration (OGA) and other teams to help bolster R&D partnerships between Singapore and other countries.

An example of such bilateral partnerships is the '2+2', wherein both countries fund four-way, public-private partnerships that provide R&D grants in thematic areas of interest. "In 2018, to deepen the nexus between public and private R&D performers in both countries, A*STAR and Germany's Federal Ministry of Education and Research (BMBF), together with Singapore's EDB and ESG, launched the Singapore-Germany 2+2 Cooperation Framework," said IORO representatives.

Other partnerships have been conducted with Australia via the A*STAR-CSIRO 2+2 Partnership, established in 2020 with the Commonwealth Scientific and Industrial Research Organisation (CSIRO); and Italy via the Italy-Singapore Executive Programme for Scientific and Technological Cooperation, established with Italy's Ministry of Foreign Affairs and International Cooperation (MAECI).

From 2018 to 2020, A*STAR-BMBF launched three rounds of joint grant calls in three thematic areas, with nine projects awarded in total. In 2020, the first A*STAR-CSIRO joint grant call was issued in four areas, with four projects awarded; a second grant call is planned for launch in early 2024. Meanwhile, the first grant call under A*STAR-MAECI was launched in 2022, with 10 projects awarded under seven areas.

STRATEGIC BILATERAL R&D PARTNERSHIPS

THEMATIC AREAS

A*STAR-BMBF, Germany
- Advanced manufacturing
- Blockchain technology in manufacturing and supply chains
- Smart urban mobility

A*STAR-CSIRO, Australia
- Circular economy and low emission technologies
- Digital and environment
- Food and health
- Future materials in advanced manufacturing

A*STAR-MAECI, Italy
- Artificial intelligence
- Food technology
- Health
- Hydrogen research
- Photonics
- Quantum technology
- Robotics

STEERING THE ENGINE

Whether between individuals or countries, collaboration is key to develop truly successful innovations that address increasingly global problems. To that end, A*STAR continues to facilitate partnerships that bring together the right people for the right purpose.

"We want to attract strong partners to Singapore. Rather than relying on serendipity, we adopt a strategic and intentional approach, especially in economically vital sectors such as healthcare and electronics," said Yeo.

For Yeo, the value of A*STAR's work in facilitating cross-border innovation is exemplified by the evolution of equipment manufacturer Applied Materials' presence in Singapore. Established in 1991 as a regional manufacturing operations centre, Applied Materials South East Asia has since formed four joint R&D labs in partnership with A*STAR research institutes and NUS, with significant support from A*STAR I&E.

"Ultimately, collaborations are about leverage: they multiply force and shorten time. By uniting differentiated capabilities across domains, we achieve greater objectives. This is the power of partnership," said Yeo. ★

Single-cell insights towards precision cancer care

Researchers perform a comprehensive genetic sequencing of individual tumour cells to refine existing colorectal cancer classifications.

We're on the cusp of a new era of precision cancer care; a revolution driven by gene-profiling technologies is slowly phasing out one-size-fits-all standard treatments such as chemotherapy.

To design personalised treatment protocols for patients with colorectal cancer (CRC), clinicians currently rely on a consensus molecular subtype (CMS) classifier: a system used to categorise tumours based on their genetic and molecular characteristics.

However, researchers say that because CMS analyses tumour cells in bulk, it lacks resolution. Today's CMS can be compared to classifying cars into broad categories such as 'sports cars' or 'utility vehicles', which overlooks the unique features and capabilities of individual models.

Iain Tan, a Principal Investigator at A*STAR's Genome Institute of Singapore (GIS), said that single-cell RNA sequencing (scRNA-seq) technologies can help to fill the gap. "We can identify malignant cell subtypes and their properties, as well as understand their interactions with other cells in the tumour microenvironment,"

said Tan, adding that this provides a clearer view of CRC heterogeneity.

Tan was part of a cross-functional team including researchers from the National Cancer Centre, Singapore; Singapore General Hospital; and experts from Singapore, Switzerland, Belgium, South Korea and the US that aimed to revamp the current CMS with the help of transcriptomics.

The team analysed a massive 370,000 transcriptomes from 63 patients across five cohorts, generating one of the largest single-cell CRC datasets to date. A subset of about 50,000 epithelial cell transcripts formed the nexus of their inquiry, as these cells are known to be the origin of most CRCs.

Their analyses revealed that malignant epithelial cells were divided into two intrinsic-molecular subtypes—iCMS2 and iCMS3—characterised by distinct signalling pathways and mutational profiles. They also found that one-third of microsatellite stable tumours share more in common with microsatellite instability-high tumours in terms of their genetic activity and biological

pathways—a finding that challenges the traditional classifications of CRC.

With this, the existing CMS went from four broad categories to five distinct subtypes, which now include data on a tumour's intrinsic epithelial subtype, microsatellite instability status and fibrosis.

In addition, the researchers offered unprecedented insights on the existing classifier, CMS4, known to represent fibrotic tumours that are particularly prone to post-treatment relapse.

"CMS4 tumours are evenly split between iCMS2 and iCMS3, [and are] not a distinct subgroup," explained Tan. "CMS4 cancers with iCMS3 epithelium have particularly poor outcomes."

These new frameworks to stratify CMS4 tumours provide a more nuanced understanding that can reshape diagnostic and treatment strategies for patients with CRC. For example, iCMS3 cancers have an inflammatory and immune-activated tumour microenvironment and may therefore be more susceptible to immunotherapies.

Moving ahead, the researchers will continue exploring the early development and immunological makeup of iCMS2 and iCMS3 tumours. "We are also performing biological and clinical studies to prevent CRC metastasis," Tan added. ★

Researchers

Iain Tan and Shyam Prabhakar, GIS

IN BRIEF

Single-cell RNA sequencing of over 370,000 transcriptomes revealed two intrinsic epithelial subtypes of colorectal cancer, offering a refined classification system that can help enhance personalised treatment approaches.

1. Joanito, I., Wirapati, P., Zhao, N., Nawaz, Z., Yeo, G., *et al*. Single-cell and bulk transcriptome sequencing identifies two epithelial tumor cell states and refines the consensus molecular classification of colorectal cancer. *Nature Genetics* **54** (7), 963–975 (2022).

Photo credit: gopixa / Shutterstock

Clean water and a cleaner planet

A first-of-its-kind recyclable water filtration membrane enables more sustainable practices in wastewater management.

Photo credit: Peter Milto / Shutterstock

Singapore, an island nation surrounded by seas, faces the paradox of water scarcity. The availability of potable water largely depends on wastewater reclamation and seawater desalination, processes that hinge on membrane filtration technology.

"The substantial application of membrane technology accounts for 70 percent of Singapore's current water supply, a figure projected to increase to 85 percent by the year 2060," commented Bofan Li, a Scientist at A*STAR's Institute of Sustainability for Chemicals, Energy and Environment (ISCE^2).

However, the frequent replacement of filtration membranes—essential for optimising efficiency—results in over 28,000 tons of waste annually, significantly contributing to CO_2 emissions. Sustainable wastewater treatment practices have, in recent years, pivoted towards biodegradable membranes. Still, challenges in the design

phase and in end-of-life management have hindered progress, particularly in procedures to recycle used membranes.

Li's team at ISCE^2 worked with colleagues at the National Taiwan University of Science and Technology to address these challenges head-on, exploring sustainable materials and membrane structures resilient enough to withstand the demanding conditions of wastewater treatment. For example, Li listed high mechanical, thermal and chemical stabilities alongside effective separation performance as prerequisites for industry-ready membranes.

"Our focus extended beyond just assessing the thermal and mechanical properties of the materials," said Li. "We also considered their stability for practical uses and on-demand recyclability."

Drawing on covalent adaptable networks (CAN) with thermally reversible Diels-Alder adducts, Li and colleagues

developed robust, adaptable polymer-based materials for water filtration membranes. As CANs are held together by special heat-reversible chemical bonds, the molecular structures of CAN membranes break down into polymers when heated, allowing contaminants to be removed. After cleaning, new membranes can be refabricated using the recycled polymers, restoring their structure.

This recyclable process enables CAN membranes to be reused multiple times, reducing waste and improving sustainability in water purification. Li's team also demonstrated that their new membranes featured comparable filtration performance to conventional membranes for at least three cycles.

This breakthrough ushers a new era in eco-friendly wastewater treatment membranes, which Li said addresses both disposal concerns and aligns with circular economy principles.

Aiming for industrial-scale, accessible and affordable production of their CAN membrane design, the team is currently optimising its performance and manufacturing consistency. "Our roadmap ahead is to go from establishing structure-performance relationships, to morphology control, to application exploration and finally, to industrialisation," said Li. ★
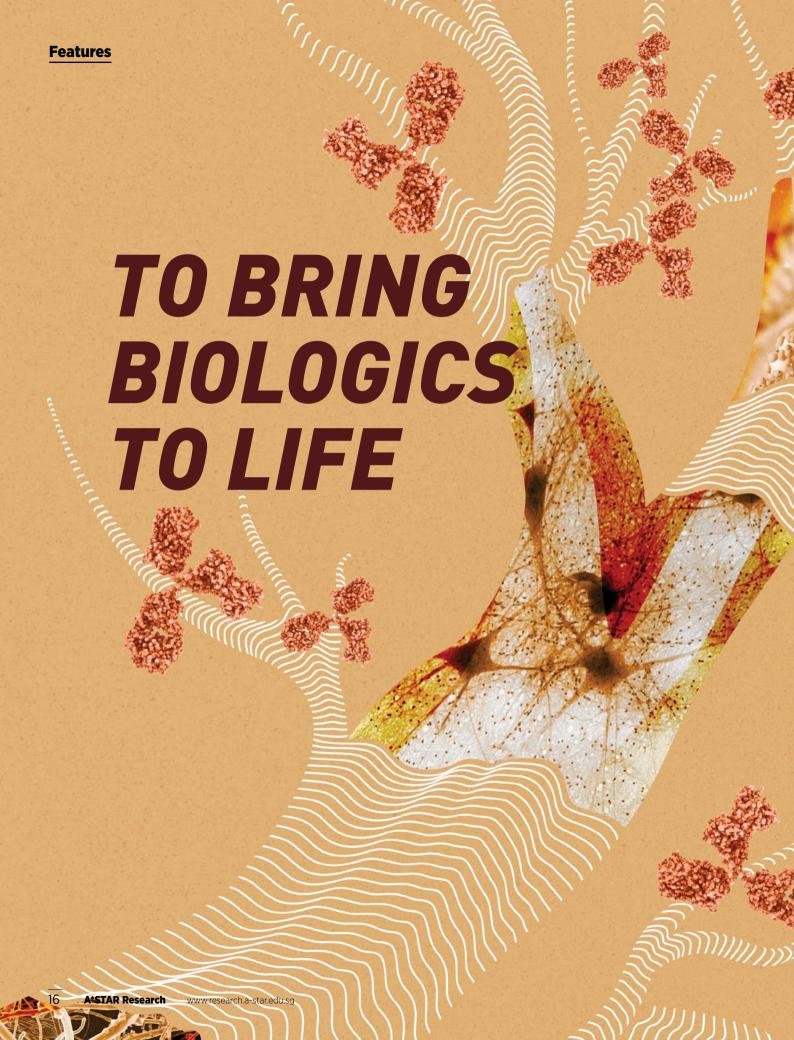
Researchers
Bofan Li and Zibiao Li,
ISCE^2

IN BRIEF
Water purification membranes based on covalent adaptable networks with thermally reversible Diels-Alder adducts can be reused multiple times without losing effectiveness, thereby reducing waste.

1. Li, B., Wang, S., Loh, X.J., Li, Z. and Chung, T.-S. Closed-loop recyclable membranes enabled by covalent adaptable networks for water purification. *Proceedings of the National Academy of Sciences* **120** (15), e2301009120 (2023).

TO BRING BIOLOGICS TO LIFE

Taking lessons from an eye-opening stint in industry, Sean Chia is tackling the challenges of biotherapeutics manufacturing to help bring game-changing antibody treatments to more patients.

*T*hey quench the fires of inflamed joints; they latch onto stealthy tumours, marking them out for our body's defenders to destroy. Whether they're boosting immune systems against cancer or suppressing them in rheumatoid arthritis, biotherapeutic products have transformed the way we treat many diseases, improving lives across the world.

Also known as biologics, biotherapeutics are a class of medicines based on organic molecules made by living cells. Ranging from hormones to antibodies, biotherapeutics can be more effective than traditional small-molecule drugs as they're designed to bind to specific disease-related targets without hitting unintended pathways along the way.

However, efficacy isn't the only factor behind a drug's clinical success, or developability. Two others are key: its safety for use in humans, and its manufacturability at an industrial scale. However, the same molecular complexity that makes biotherapeutics effective treatments can often also make them more fragile and expensive to produce compared to the simple chemical compounds of small-molecule drugs.

Among those tackling this issue are researchers like Sean Chia, a Senior Scientist at A*STAR's Bioprocessing Technology Institute (BTI). During his PhD studies, Chia studied the aggregation of amyloid-beta (Aβ) peptides: proteins linked to the progression of Alzheimer's disease. Moving from academia to industry, Chia worked on drug development for protein misfolding-related diseases in a biotech company before joining BTI, where he is developing new analytic tools to study biotherapeutic developability. In 2022, Chia was awarded the Singapore Biodesign (SB) Innovation Fellowship and dove into the field of health technology innovation.

In this interview with *A*STAR Research*, Chia shares his reflections on the diverse experiences in his scientific journey, their influence on his current research, and the promise of biotherapeutics for future innovation in Singapore.

Q: WHAT SPARKED YOUR INTEREST IN BIOTHERAPEUTICS?

My PhD degree was focused on understanding the biophysical principles behind protein misfolding and aggregation in the context of human diseases, such as neurodegenerative conditions. From there, I was keen to explore the other problems that these concepts could be applied to.

As it turned out, I found that biotherapeutics development was one such relevant area. It's fascinating to learn about how protein structures that cause disease, and those that treat disease, share some of the same fundamental principles, yet differ greatly in other aspects.

For me, what adds to the fascination of biotherapeutics development is how it's an ever-evolving area that operates right at the intersection between basic and applied research. You get to learn a lot of things beyond scientific discoveries!

Q: TELL US MORE ABOUT YOUR CURRENT WORK AT A*STAR.

A big challenge in manufacturing biotherapeutics, such as antibodies, is that their structures haven't naturally evolved to endure the stressful conditions that occur in industrial production. As a result, they often destabilise during the production process, causing unwanted protein aggregation—an effect where proteins unfold and tangle together into clusters, causing efficacy and safety issues.

At BTI, we're studying the developability properties—such as the specificity and aggregation propensity—of next-generation antibody therapeutics like multispecific antibodies. As part of this work, we design new assays and computational models to assess these therapeutic molecules and optimise their properties.

I find this project particularly exciting as it requires an interdisciplinary approach to effectively tackle what is currently one of the biggest challenges faced in the field. I am fortunate to be collaborating with a talented group of experts; we hope to contribute to the development of faster and more efficient drug discovery processes.

Q: WHAT MOTIVATED THE DIFFERENT ENDEAVOURS IN YOUR SCIENTIFIC JOURNEY?

I am a firm believer that science and research are multifaceted. Hence, I was curious to understand it in different contexts, such as in academia and industry. I am thankful for these experiences, as they really helped me develop a diverse skillset and a broader appreciation for research.

Q: HOW HAS YOUR TIME IN INDUSTRY SHAPED YOUR APPROACH TO RESEARCH?

I think that my exposure to the fast-paced environment of a biotech startup has instilled a sense of practicality in my approach to research. I tend to have a more pragmatic perspective nowadays, as I've learnt to focus not only on identifying theoretical solutions, but also on figuring out how they can be practically translated to real-world applications. My exposure to the business side of science has also made me more aware of the complexities involved when trying to materialise relevant solutions for commercial purposes.

> "For me, what adds to the fascination of biotherapeutics development is how it's an ever-evolving area that operates right at the intersection between basic and applied research. You get to learn a lot of things beyond scientific discoveries!"

— Sean Chia, Senior Scientist at A*STAR's Bioprocessing Technology Institute (BTI)

Sean Chia

Senior Scientist

Bioprocessing Technology
Institute (BTI), A*STAR

Q: TELL US ABOUT YOUR EXPERIENCES AS AN SB INNOVATION FELLOW.

I was interested in the fellowship as I wanted to acquaint myself with health and medtech innovation, as well as gain a more general understanding of startups within the ecosystem.

One of the biggest takeaways for me was learning about the business aspects of health and medtech, such as market sizing, intellectual property and regulatory affairs. It was also a fantastic experience to work with and learn from my fellow team of clinicians and the SB mentors, who helped nurture a collaborative and entrepreneurial mindset, and defined my experience in the SB fellowship.

Q: HOW MIGHT YOUR WORK ADVANCE SINGAPORE'S BIOTHERAPEUTICS CAPABILITIES?

With the recent emergence of novel therapeutic modalities, there's a need to evolve our current approaches accordingly so as to characterise these agents and determine how to develop them further.

I hope our research in analytical development that is targeted specifically towards these new molecules will allow us to contribute to Singapore's growing biomedical manufacturing industry. In particular, we hope to attract biopharmaceutical companies to further their R&D and manufacturing activities here in partnership with us.

Q: WHAT'S YOUR ADVICE FOR SCIENTISTS AIMING FOR REAL-WORLD IMPACT?

Identifying problem statements and market needs are a crucial aspect of developing real-world solutions. To tackle a specific problem in a field, it's important to identify what exactly the relevant 'needs' are, as opposed to the 'wants'.

For this, I think it's always useful to read widely and talk to other people working on the same problem. Doing so will help you better understand and frame the problem, which then allows you to develop a solution that is both innovative and applicable to it. ★

Nanocatalysts ignite greener fuel cells

Novel nanoparticles promise a safer, more powerful alternative to commercial catalysts used in direct formic acid fuel cells.

Just as smartphone batteries wear down with heavy use, catalysts—the chemical drivers of numerous chemical reactions—also deteriorate over time. This steady drop in efficiency can hamper the reactions they're designed to accelerate, indicating when it's time for them to be replaced.

One such catalyst-driven chemical reaction takes place in direct formic acid fuel cells, or DFAFCs. These fuel cells, which transform formic acid's chemical energy directly into electricity, are noted for their high efficiency and environmentally-friendly attributes, making them ideal for portable power solutions.

However, current DFAFC designs have a common setback. "Palladium (Pd) electrocatalysts, often used in DFAFCs, are prone to causing carbon monoxide (CO) poisoning," said Zhaolin Liu, a Senior Principal Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE).

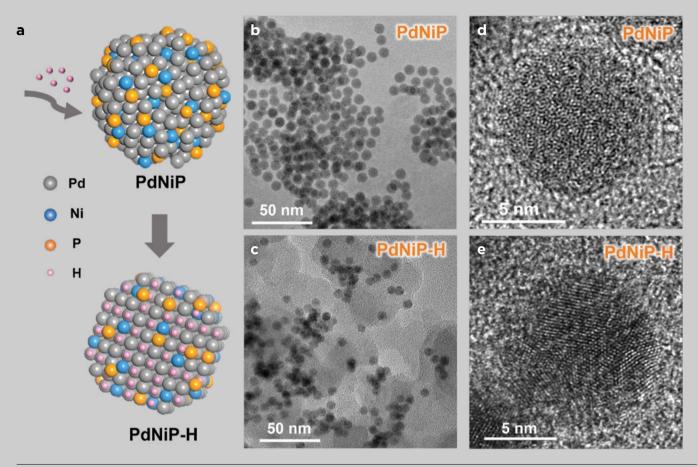To circumvent this issue, Liu said that incorporating hydrogen (H) into Pd electrocatalysts to form Pd hydrides (PdH_x) alters their molecular structure, which has been shown to improve their ability to boost DFAFC reactions.

Together with researchers from Tongji University, China, Liu's team went further by experimenting with other elements like oxygen-loving nickel (N) and phosphorus (P) to counter CO production during the catalytic process. With hydrogen in the mix, the researchers generated nano-sized PdNiP-H particles that presented a more uniform structure for enhanced fuel cell performance.

Liu added, "Alloying phosphorus into the catalyst introduces more amorphous structures, which serve as active sites crucial for facilitating the necessary reactions during formic acid oxidation."

In validation experiments, the novel PdNiP-H nanoparticles achieved a peak power output which was 63.4 percent higher than systems using commercially available Pd catalysts. In addition, these nanoparticles demonstrated enhanced stability against

(a) A schematic illustration of hydrogen particles being incorporated into a PdNiP nanoparticle. (b-c) Low-magnification transmission electron micrography (TEM) images of (b) PdNiP nanoparticles and (c) carbon-supported PdNiP-H nanoparticles. (d-e) High-resolution TEM images of (d) a single PdNiP nanoparticle and (e) PdNiP-H nanoparticle.

"Alloying phosphorus into the catalyst introduces more amorphous structures, which serve as active sites crucial for facilitating the necessary reactions during formic acid oxidation."

CO poisoning, thereby increasing DFAFCs' efficiency and durability.

These new-and-improved catalysts can position DFAFCs as a preferred alternative to hydrogen fuel cells, particularly because of formic acid's lower cost, ease of handling and green profile.

For now, the team is focusing on optimising their PdNiP-H nanoparticles for industrial-scale applications. "We still observe notable a decline in performance over time, which may be linked to the partial dissolution of the alloying elements," Liu said. "We plan to develop even more robust electrocatalysts by designing structures with enhanced stability, such as core-shell configurations, and using more durable support materials." ★

Researchers
Zhaolin Liu and Xian Jun Loh, IMRE
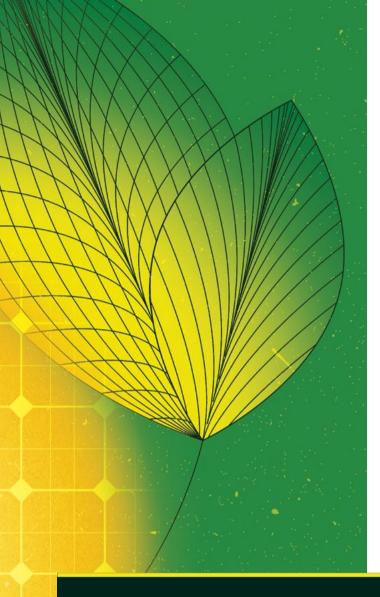
IN BRIEF
Nanoparticles composed of palladium, nickel, phosphorus and hydrogen were shown to outperform conventional electrocatalysts used in direct formic acid fuel cells, offering more durable and efficient green energy solutions.

1. Cheng, H., Zhou, J., Xie, H., Zhang, S., Zhang, J., *et al*. Hydrogen intercalation-induced crystallization of ternary PdNiP alloy nanoparticles for direct formic acid fuel cells. *Advanced Energy Materials* **13** (14), 2203893 (2023).

POWERED BY SUNSHINE

To power our future cities, A*STAR Scholar Celine Yeung is exploring 'artificial leaf' devices that transform solar energy into sustainable fuels.

Drawing inspiration from photosynthesis—the process through which plants turn sunlight into food—Yeung is one of many researchers working on 'artificial leaf' devices that combine light absorbers and catalysts to convert water and waste carbon dioxide into sustainable fuels. While much work remains to optimise their efficiency and ensure they're made from eco-friendly materials, these devices may bring us closer to a solar-powered world.

In this interview with *A*STAR Research*, Yeung looks back on her enduring fascination with science, shares her deep passion for sustainable chemistry, and offers valuable advice for aspiring STEM graduates.

Q: WHY DOES SUSTAINABLE CHEMISTRY MATTER TO YOU?

Sustainability is a complex, multifaceted topic that needs collaboration and input from various stakeholders. To me, sustainable chemistry is a subset of this overarching goal, where scientists leverage the tools of chemistry to design and manufacture new systems that reduce our ecological footprint.

Quoting the United Nations' 1987 Brundtland Report, we aim to "meet the needs of the present without compromising the ability of future generations to meet their own needs". This implies moving beyond bench-scale processes to develop industrial systems that are not only economically viable, but relevant to wider communities. The inextricable link between sustainable chemistry and our daily lives makes it a worthwhile endeavour to pursue.

Q: TELL US ABOUT YOUR SCIENTIFIC JOURNEY.

My interest in science began early; I spent school holidays joining science workshops at local community centres and signing up for mini-research projects in high school. I have fond memories of making ice cream and baking soda volcanoes, cultivating hydroponic *kangkong* plants (our mums whipped up tasty dishes afterwards!) and growing copper sulfate crystals with my project buddies.

With the A*STAR Undergraduate Scholarship, I pursued chemical engineering at the National University of Singapore (NUS). While there, I refined my research skills by taking on various projects with domain experts from IMRE, A*STAR's Singapore Institute of Manufacturing Technology (SIMTech) and NUS itself.

*A*lthough fossil fuels—coal, oil and natural gas—have helped to build our modern world, the emissions they produce stand as the greatest driver of the ongoing climate crisis, while the plastics they make linger in our soils and oceans. These problems have spurred researchers worldwide to accelerate our shift towards cleaner energy and greener materials.

"Whether it's upcycling recalcitrant plastics, designing recyclable batteries or finding new uses for waste CO_2, the possibilities of sustainable chemistry are endless," said Celine Yeung, an A*STAR National Science Scholar previously based at A*STAR's Institute of Materials Science and Engineering (IMRE).

Like plants, scientists like Yeung are turning to the sun for inspiration. A significant power source, solar energy already generates over five percent of the world's electricity today. However, unlike oil or coal, it remains challenging to store solar energy or convert it into industrial materials at a vast scale.

After graduation, it was natural to continue with the A*STAR National Science Scholarship (PhD). For my one-year research attachment, I returned to IMRE's Soft Materials Department; I'd previously spent a great summer interning with Shermin Goh, and this time I got to work at a fume hood adjacent to her, under Jason Lim in the Sustainable Supramolecular Materials Group.

On reflection, I'm grateful to all the inspiring teachers, scientists and professors I've met along the way who encouraged me to follow my dreams and passion for science. What makes scientific research exciting is that there isn't one fixed correct answer, and no two projects are identical; each has its own unique challenges and creative solutions.

Q: WHY SHOULD WE TRANSFORM PLASTIC WASTE INTO FUNCTIONAL MATERIALS?

During my time at IMRE, we focused on developing different strategies to chemically upcycle waste plastics. Tapping into these underexplored resources—rather than sending them to landfills or incineration plants—can reduce our carbon footprint. If we continue our current levels of waste generation, Singapore's only landfill, Pulau Semakau, is expected to be fully filled by 2035.

One issue is that non-biodegradable plastics, such as polyolefins, have strong C–C and C–H bonds that can't be easily broken down by chemicals or enzymes. Our research at IMRE has shown a viable solution: we can transform these waste plastics into functional materials such as anti-fungal polymers and catalysts for biomass conversion, thereby giving them a new lease of life.

Celine Yeung
A*STAR National Science Scholar

"Whether it's upcycling recalcitrant plastics, designing recyclable batteries or finding new uses for waste CO_2, the possibilities of sustainable chemistry are endless."

Q: TELL US ABOUT YOUR CURRENT WORK.

In the autumn of 2021, I joined Erwin Reisner's group at the University of Cambridge's Chemistry Department for my PhD studies. Despite being half the globe away from my sunny island home, I am exploring a topic close to my heart: solar energy.

Inspired by nature, my work revolves around developing photoelectrochemical devices to produce solar fuels. These devices mimic photosynthesis by coupling synthetic light absorbers with suitable catalysts to directly harness, convert and store solar energy in the form of chemical fuels—all using water or waste CO_2 as starting materials. Those fuels can then be transported and used on demand to power fuel cell electric vehicles, like hydrogen-based ones, or produce commodity chemicals.

From solar panels on the rooftops of HDB flats to floating solar farms on the Tengeh Reservoir, there is an immense future potential for solar energy research in Singapore. My goal is to transition us away from existing precious metal or lead-based prototype devices and, through rational design, create high-performing standalone systems fully powered by sunlight.

Q: WHAT EXCITES YOU ABOUT YOUR JOURNEY AHEAD?

Singapore's dynamic, progressive and ever-changing research landscape. That vibrant ecosystem is essential for exploring new ideas and forming collaborations. A*STAR also provides a good platform for conducting interdisciplinary work as it oversees a diverse talent pool that spans 17 different research institutes.

Speaking with friends of various nationalities, I realised how fortunate we are to have extensive funding for R&D, with A*STAR and local universities housing state-of-the-art equipment for cutting-edge research. In the near future, I hope to apply the skills I've learnt abroad to the Singaporean context and contribute in unique ways.

Beyond research, I believe it's also important to pay it forward and mentor the next generation of budding scientists during my deployment. The A*STAR scholarships allowed me to pursue world-class education both locally and abroad without financial worries, providing opportunities to work under scientists with different mentoring styles. From revising my first manuscript to tagging along for departmental seminars, these experiences have shaped my scientific perspective and prepared me well to embark on a PhD degree.

> ## "It's always the darkest before dawn, but find the burning passion within yourself to stay motivated even when you're at your lowest."
>
> — Celine Yeung, A*STAR National Science Scholar

Q: WHAT ADVICE WOULD YOU GIVE THOSE PURSUING SIMILAR STEM JOURNEYS?

I would like to share a quote by the late Stephen Hawking, a British physicist and cosmologist: "Science is not only a disciple of reason but, also, one of romance and passion." Research is indeed an arduous but rewarding journey because you are stepping into the unknown, constantly adapting and always learning something new.

I had a tough start to my PhD, given that it was my first foray into optoelectronics and electrochemistry; I spent countless nights troubleshooting in the lab. I do remember my excitement when I finally made my first working device—I immediately fabricated at least three more copies to assure myself that I wasn't dreaming!

It's always the darkest before dawn, but find the burning passion within yourself to stay motivated even when you're at your lowest. Along the way, do reach out and seek support from your principal investigator and lab mates; their fresh perspectives will help you grow and mature as a scientist. ★

Intelligent machines sum up the chit-chat

Researchers develop a more efficient artificial intelligence model for summarising conversations by innovatively enhancing underutilised computational components.

It seems like we've reached a pivotal moment in bridging the gap between complex human communication and computational understanding. Advances in natural language processing (NLP) have spawned innovative platforms such as ChatGPT, which facilitate remarkably natural and seamless human-computer interactions.

At the heart of these NLP breakthroughs is a transformer-based model known for its 'multi-head attention mechanism'. According to Zhengyuan Liu, a Lead Research Engineer at A*STAR's Institute for Infocomm Research (I²R), this model works much like how our brain simultaneously processes different types of information—transformers focus on different parts of the input data at the same time, significantly enhancing context understanding and task efficiency.

However, in task-specific modelling like dialogue summarisation, the model's attention heads are not uniformly used. Liu, alongside A*STAR Senior Principal Scientist Nancy Chen, developed a novel technique for repurposing these underused heads to infuse new capabilities into transformers and bump up their computational efficiencies.

"Redundant attention heads can be replaced with featured weights, which is much more computationally efficient than introducing additional neural components," explained Liu.

Their method involved training a base model to identify the attentive parts that were not contributing much during the task of summarising conversations.

They then improved these underperforming parts by giving them additional information about how personal named entities in a conversation refer to each other; this helped the model to better understand the flow and context of the dialogue.

The researchers then experimented with a benchmark dataset and found that their enhanced transformer model not only improved upon the base model but also held its own against state-of-the-art models, all while being more computationally economical. In addition, of the coreference information integration techniques tested, the nearest-neighbour approach proved superior.

In practical terms, this can lead to more effective summarisation of legal documents, medical records or customer service interactions, where both clarity and context are crucial.

"There are many directions that we are exploring," said Liu, speaking on next steps. These include investigating the effectiveness of attention mechanisms in multiple modalities such as vision, speech and text, as well as improving the accountability of these models, which are crucial for sensitive applications such as healthcare. ★

Researchers
Zhengyuan Liu and Nancy F. Chen, I²R

IN BRIEF
Reallocating underutilised attention heads to encode coreference resolution information significantly enhanced a transformer-based model's dialogue summarisation capabilities while maintaining computational efficiency.

1. Liu, Z. and Chen, N.F. Picking the underused heads: a network pruning perspective of attention head selection for fusing dialogue coreference information. *ICASSP 2023 - 2023 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, 1-5 (2023).

Photo credit: Clayton Cardinalli / Unsplash

INDUSTRIAL ENGINEERING

Seamless operations with machine health checks

A new algorithm accurately predicts when industrial machines will need maintenance, which can greatly improve efficiency and reduce costs.

Peering into the future like a digital crystal ball, artificial intelligence (AI) is transforming the way industries operate. Specialised algorithms can predict when a machine will require maintenance, or its remaining useful life (RUL), thereby reducing operational downtime and saving costs.

Ruibing Jin and Zhenghua Chen, Scientists at A*STAR's Institute for Infocomm Research (I²R), are at the helm of AI-driven methodologies to forecast RUL with greater precision, pushing the boundaries of what's possible in industrial efficiency and proactive maintenance.

"After reviewing existing approaches for RUL prediction, we find that these methods show unstable performances in different subsets which include different conditions and fault models," said Jin.

Jin explained that traditional static neural networks typically have fixed architectures; these networks may not always 'learn' effectively from the changing behaviours of machines, hindering their ability to provide the most accurate and up-to-date information on a machine's health and lifespan.

To navigate this challenge, Jin and Chen introduced a first-of-its-kind adaptive and dynamic neural network called AdaNet. This approach was designed to better capture sequential information in time series data and keep pace with evolving patterns of machine behaviour, thereby improving RUL prediction accuracy.

"To the best of our knowledge, we are the first to propose a dynamic network for RUL prediction," said Jin.

The team ventured into other research domains to find a solution for adaptive network architectures. Their efforts culminated in the successful adaptation of deformable convolution techniques, typically used for visual data, to sequential time series data.

AdaNet distinguishes itself by altering its neural network kernels and selectively activating channels based on the incoming data, significantly honing its data extraction capabilities.

When benchmarked against the C-MAPSS dataset—which simulates a large commercial jet engine—AdaNet outclassed other models in all six conditions, showcasing its superior early prediction capabilities.

"An early prediction of RUL allows industries to replace parts in a timely manner, circumventing industrial failures," said Jin.

While AdaNet's immediate implications for RUL prediction are profound, its potential spans across other applications involving time series data, such as monitoring human activities. Currently, the research team is engaging with industrial partners to explore practical deployments of AdaNet, signalling a new horizon in the application of AI for industrial prognostics. ★

> **"An early prediction of RUL allows industries to replace parts in a timely manner, circumventing industrial failures."**
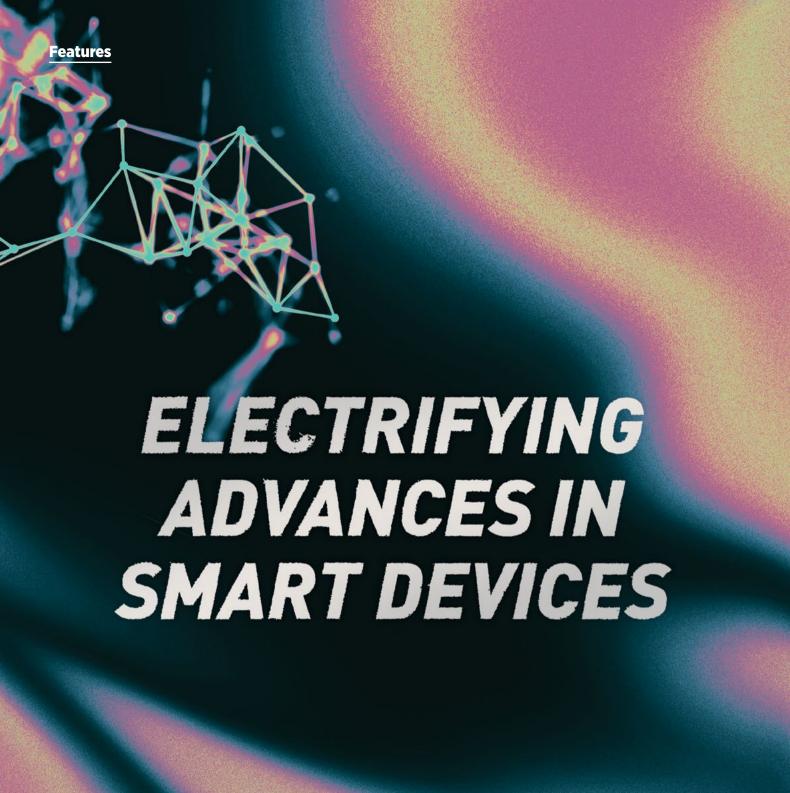

Researchers
Ruibing Jin and Zhenghua Chen, I²R

IN BRIEF
AdaNet, an adaptive neural network that dynamically adjusts its architecture for enhanced time series prediction of machinery's remaining useful life, outperformed traditional fixed-architecture models.

1. Jin, R., Zhou, D., Wu, M., Li, X. and Chen, Z. An adaptive and dynamical neural network for machine remaining useful life prediction. *IEEE Transactions on Industrial Informatics* **20** (2), 1093-1102 (2023).

ELECTRIFYING ADVANCES IN SMART DEVICES

From artificial intelligence to smart materials and sensors, A*STAR scientists Xiaoli Li and Kui Yao have spearheaded scientific breakthroughs that have led to their recognition as Fellows of the Institute of Electrical and Electronics Engineers (IEEE).

Since Benjamin Franklin's kite, advances in our understanding of electricity—and the ways we can harness it—have brought the stuff of science fiction into modern-day life. Sensors made from piezoelectric materials can generate electricity from movement, ultraviolet (UV) radiation and heat; in turn, they give rise to ultrasound probes, Internet of Things (IoT) devices, and UV and thermal detectors. Self-powered sensors are also possible thanks to ferroelectrics, a subgroup of piezoelectrics that often have stronger properties and, in principle, need no external power supply.

The integration of artificial intelligence (AI) to analyse sensor data collected over time is also helping to create the next generation of smart devices and useful tools. AI unravels patterns and enhances decision-making for machines that optimise manufacturing processes, monitor equipment health and improve healthcare diagnostics.

*A*STAR Research* speaks to Xiaoli Li from the Institute for Infocomm Research (I²R) and Kui Yao from the Institute of Materials Research and Engineering (IMRE), who were both recently conferred Fellows of the Institute of Electrical and Electronics Engineers (IEEE) for their trailblazing work in their respective fields. The researchers discuss their research journeys, their proudest scientific achievements, and the collaborations made all of it possible.

Q: WHAT SPARKED YOUR INTEREST IN YOUR FIELD?

XL: I was initially drawn to AI due to its transformative potential in solving complex problems. In 1976, AI successfully proved the Four-Colour Theorem; by the 90s, AI was winning games like checkers and chess. These breakthroughs have showcased AI's computational prowess and ability to intelligently tackle complex problems.

I developed a deep-seated curiosity about AI, especially how it gains knowledge or creates models from data through machine learning (ML). Witnessing AI's impact on various industries fuelled my passion.

KY: My research focuses on ferroelectrics and piezoelectrics—from materials to device applications. Since my PhD studies, I've found ferroelectrics attractive due to their extraordinary material properties and the rich physics underlying them.

Though there are billion-dollar markets for their commercial applications, ferroelectrics have greater unexplored potential in advanced sensors, transducers, memories and intelligent systems. There's ample room for improvement even in our fundamental understandings of ferroelectric-related phenomena.

Q: TELL US ABOUT THE SCIENTIFIC CONTRIBUTIONS YOU'RE MOST PROUD OF.

XL: They include the development of advanced ML models for processing time-series sensor data, which has potential applications across diverse domains from manufacturing to healthcare.

In 2011, I led an I²R team that worked with Boeing to build a data-driven model for portable machine fault detection. As existing signal processing approaches to learn time and frequent domain features had limited accuracy, we began to explore AI, focusing on time-series sensor data analysis. We pioneered a novel deep learning (DL) method that could automatically extract representative features from high-dimensional sensor signals, which generated much better outcomes than previous approaches. The resulting paper from this work has received over 1,000 citations.

I hope these models will see wider real-world applications, ranging from equipment health diagnosis to human activity recognition.

KY: I'm pleased with what we've done to advance ferroelectric film materials, including coatings for innovative piezoelectric sensors; and our exploratory work on bulk photovoltaics in ferroelectric films, which has led to robust ferroelectric UV sensors.

After I joined IMRE, our work on such films started with research projects jointly supported by the institute and industry. My initial efforts involved basic, yet vital lab-based engineering work to determine, reliably and efficiently, a film's piezoelectric and bulk photovoltaic properties. Eventually, I became the main inventor for several piezoelectric and ferroelectric sensors and UV dosimeters produced in collaboration with my colleagues and our industry licensees.

I hope to see wider applications for the ferroelectric materials and devices we've developed, particularly as advanced electromechanical sensors and ultrasonic transducers.

Q: WHAT PARTNERSHIPS WERE KEY TO YOUR SCIENTIFIC SUCCESSES?

XL: I'm glad to have had opportunities to work with world-class scientists through international conference networks. I've also had the privilege of leading key initiatives in partnership with aerospace, semiconductor and manufacturing companies, which not only provided problem statements driven by real-world use cases, but helped translate theoretical advancements into practical, domain-specific solutions.

KY: I appreciate the guidance, leadership and unwavering support of my mentors, international peers, as well as A*STAR and IMRE's management and colleagues. The contributions of my team members, students and collaborators have been invaluable to our shared achievements.

Q: WHAT ARE SOME INTERESTING PROJECTS YOU'RE WORKING ON?

XL: I currently spearhead my AI Singapore project, "Self-Aware Continuous Learning Models" (SACoLM), which aims to create AI models capable of lifelong learning: a crucial skill for dynamic decision-making. Unlike traditional DL models that assume known distributions, SACoLM addresses the challenge of adapting to unknowns. Our models maintain awareness of representations; identify novel distributions and estimate their complexity; and adapt while retaining previous learning.

Our approach has highly relevant engineering applications, such as defect detection, fault diagnosis and engineering asset prognosis, as it uses IoT sensor data to manage systems with drifting characteristics.

I also work on sustainable AI, which aims to reduce the carbon emissions and huge computing power consumption associated with developing and deploying large-scale AI models.

KY: My team is currently developing ferroelectric materials with superior piezoelectric properties, and producing advanced electromechanical sensors and transducers for ultrasonic structural health monitoring and healthcare. Another goal is to create eco-friendly, lead-free alternatives to lead-based piezoelectric materials that are toxic but are currently widely used. To boost our impact, we're striving to enhance our collaborations with A*STAR's Institute of Microelectronics (IME) and industry partners.

"I hope to see wider applications for the ferroelectric materials and devices we've developed, particularly as advanced electromechanical sensors and ultrasonic transducers."

— Kui Yao, Senior Principal Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE)

Kui Yao

Senior Principal Scientist

Institute of Materials Research and Engineering (IMRE), A*STAR

> **"In the ever-evolving AI landscape, it's imperative to continually learn and adapt."**
>
> — Xiaoli Li, Senior Principal Scientist and Department Head at A*STAR's Institute for Infocomm Research (I²R)

Xiaoli Li

Senior Principal Scientist and Department Head

Institute for Infocomm Research (I²R), A*STAR

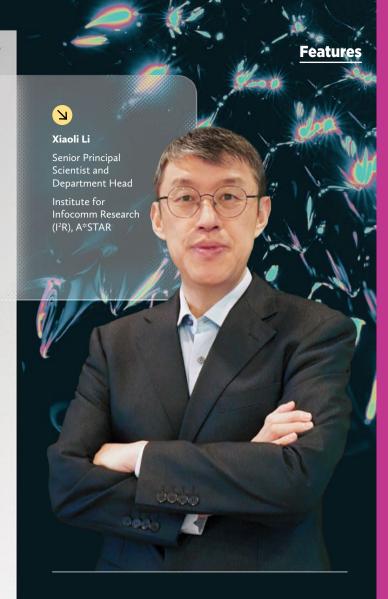## Q: WHAT DOES YOUR ELEVATION TO IEEE FELLOW MEAN TO YOU?

XL: It's a significant honour that recognises our team's collective efforts in advancing ML and AI, and bolsters my dedication to advancing knowledge in these domains. The IEEE Fellowship offers a platform to engage with a global community of experts and cultivate an environment conducive to innovative thought and idea exchange. Regardless of the title, I remain committed to working with our A*STAR colleagues to fulfil our mission of translating research into real-world impacts.

KY: I appreciate IEEE's recognition of my technical contributions to ferroelectrics and their sensor applications; I'd like to share it with my A*STAR colleagues, students and collaborators in this area, who have made it possible together. This recognition increases the visibility of our research and strengthens my resolve to continue our efforts therewith.

Q: WHAT DO YOU THINK MAKES GOOD SCIENCE?

XL: A delicate balance between rigorous methodology and a creative, open-minded approach; a commitment to pushing the boundaries of knowledge, coupled with a genuine curiosity to explore the unknown; and transparency, reproducibility, and a dedication to ethical practices. It's not only about answering existing questions, but asking the *right* questions, challenging assumptions, and inspiring others to join the pursuit of knowledge.

KY: Curiosity, passion, collaboration, perseverance and courage to overcome various difficulties on the way.

Q: WHAT ADVICE WOULD YOU GIVE OTHER SCIENTISTS LOOKING TO CREATE IMPACT?

XL: Delve into research topics grounded in real-world problems with tangible applications. It's also crucial to collaborate with expert stakeholders to bridge gaps between theory and practice.

In the ever-evolving AI landscape, it's imperative to continually learn and adapt. While striving to discover, we should also commit to making tools and insights accessible to the broader community. Ultimately, our work's true measure is its ability to address real-world challenges and improve society.

KY: I'm still learning how to work more effectively and impactfully. Align your interests with your job; work hard with vision and strategy; appreciate and respect those who have supported you; and collaborate with the right people to achieve your goals. ★

Millions of nature's secrets revealed

A*STAR scientists use advanced computer models to create a massive database of natural products for drug discovery and beyond.

Nature serves as a bountiful source of compounds poised to revolutionise human health and wellbeing. The rich chemical diversity present in plants and fungi have presented us with molecules that can combat pathogens and enhance longevity.

Still, there remains a wealth of nature yet to be discovered. According to Dillon Tay and Shi Jun Ang, Research Scientists at A*STAR's Institute of Sustainability for Chemicals, Energy and Environment (ISCE[2]) and Institute of High Performance Computing (IHPC), there's profound value in delving deeper into the universe of naturally derived

chemicals; but existing approaches are notoriously slow and offer no guarantee of uncovering anything of worth.

"The traditional approach to natural product discovery is through experimental screening of natural samples like plant extracts in the hopes of finding hits with the desired bioactivity," said Tay and Ang.

However, artificial intelligence (AI) can circumvent these limitations. "We can now design 'fit-for-purpose' natural products by pairing the generation of novel natural product-like structures with activity prediction models," Tay and Ang added.

Working with other IHPC and ISCE[2] colleagues, they employed a machine learning (ML) architecture, based on long short-term memory (LSTM), to generate a natural product database. The LSTM architecture is adept at managing sequential data, which enables the retention of information over extended sequences: a critical feature to accurately generate complex molecular structures. Additionally, the structures generated had to be novel, chemically sound and diverse, spanning a broad physiochemical spectrum. These stringent criteria ensured the quality and diversity of the database, Tay and Ang explained.

Using an LSTM ML model trained on the COCONUT database, an open-source library of known natural product molecules, the team successfully built a new database comprising over 67 million natural product-like structures, massively surpassing

the roughly 400,000 known natural products registered in COCONUT. Their computationally generated database also boasts the advantage of being substantially more cost-effective than commercially available natural product libraries.

To validate their model, the researchers compared the generated library with a dataset of 81,384 COCONUT entries that had not been used for the model's training. The library successfully reproduced 37 percent of the held-out natural products. The team also demonstrated that the generated molecules closely resembled known natural products in COCONUT in terms of structural likeness scores and biosynthetic pathway distributions, providing further validation.

Having demonstrated the utility and potency of deep generative ML models in natural product discovery, the researchers are already looking towards future prospects across a variety of industries.

For example, the generated library of molecules holds promise for uncovering novel sustainable bio-alternatives to existing fossil fuel-based chemicals. "We are excited to explore the potential of our generated natural products for various applications including insect repellents and therapeutics, as well as an aid for more precise analytics," said Tay and Ang. ★

Researchers
Dillon Tay, ISCE[2]
and Shi Jun Ang, ISCE[2] and IHPC

IN BRIEF
A generative artificial intelligence based on long short-term memory architecture produces a vast database of 67 million natural product-like molecules, exponentially increasing the number of candidate molecules for potential medicinal, agricultural and industrial applications.

1. Tay, D.W.P., Yeo, N.Z.X., Adaikkappan, K., Lim, Y.H. and Ang, S.J. 67 million natural product-like compound database generated via molecular language processing. *Scientific Data* **10**, 296 (2023).

Photo credit: Palle Knudsen / Unsplash

MATERIALS SCIENCE

Alloy advancements defy traditional limits

Using an innovative approach, researchers discover how special metal blends remain exceptionally strong and flexible in extreme environments such as those in jet engines and nuclear reactors.

Complex metal alloys have physical properties that keep them sturdy even under intensely extreme conditions. They can withstand the operating conditions of jet engines, for instance, where extraordinarily hot temperatures would melt most typical metals; or the cores of nuclear reactors, where radiation would degrade their 'pure' counterparts.

Refractory high-entropy alloys (RHEAs) are a prime example: the combination of several heavy-duty elements enables them to endure in the most challenging industrial environments. These exceptional qualities of RHEAs are, paradoxically, a product of their intrinsic imperfections.

"In common metals, all atoms are identical, leading to predictable behaviour," said Zachary Aitken, a Senior Scientist at A*STAR's Institute of High Performance Computing (IHPC). Conversely, RHEAs are a mosaic of different atoms in a random arrangement. This randomness fosters short-range ordering (SRO), which introduces localised zones with a propensity for dislocations: tiny irregularities in the metal's crystal structure that affect its strength and flexibility.

Understanding these nuances is crucial for predicting RHEA behaviour under stress. According to Aitken, prior research offered contradictory insights into how two key dislocation types—edge and screw—proliferate in alloys.

"Experiments have indicated that unlike conventional metals, which have less complex compositions, RHEAs have a prevalence of edge dislocations," said Aitken.

Working with researchers from the University of Hong Kong, the City University of Hong Kong, and the University of Tennessee, US, Aitken and colleagues took a synergistic approach to investigate an alloy composed of molybdenum, tantalum, titanium, tungsten and zirconium. Combining density-functional theory, Monte Carlo simulations and molecular dynamics, this approach enabled them to conduct an unprecedented, atomic-level examination of dislocation dynamics in the presence of SRO.

Their findings revealed that SRO prompted the emergence of a pseudo-composite microstructure within RHEAs which not only comprised clusters with distinct energy levels, but promoted unexpected types of dislocations.

"The low-energy clusters, being more stable, resist deformation and contribute to the alloy's strength," said Aitken. "On the other hand, the high-energy clusters, due to their instability, facilitate plasticity, while the medium-energy clusters form the alloy's matrix."

The team's discovery of how SRO affects the dominance of dislocations in RHEAs may be instrumental for engineering alloys that marry strength with ductility, overcoming the long-standing trade-off between strength and brittleness.

Moving forward, Aitken and colleagues aim to extend these findings to practical applications, focusing on how SRO and dislocation dynamics at high temperatures can be harnessed to refine RHEAs for even broader applications, such as in advanced turbine technologies. ★

Researchers
Zachary Aitken and Yong-Wei Zhang, IHPC

IN BRIEF

Advanced computer simulations revealed that edge dislocations are more dominant in refractory high-entropy alloys, offering new possibilities for their use under high-stress industrial conditions.

1. Chen, S., Aitken, Z.H., Pattamatta, S., Wu, Z., Yu, Z.G., *et al*. Short-range ordering alters the dislocation nucleation and propagation in refractory high-entropy alloys. *Materials Today* **65**, 14-25 (2023).

Photo credit: QinJin / Shutterstock

Growing polarisation control crystals

Researchers develop a novel approach for 'growing' crystals to create miniaturised devices with optical technology applications.

Polarised sunglasses that shield the eyes from damaging rays have a chemical coating to selectively block certain light orientations, reduce glare and enhance visual clarity. Such manipulation of light, pivotal in optical technologies, is also central to applications from medical imaging and telecommunications to quantum computing and virtual reality.

However, a pressing challenge in optics is the miniaturisation of waveplates: crucial components for manipulating how light polarises. Conventional methods involve precisely cutting and shaping large quartz crystals,

a process that is often expensive, inefficient and imprecise.

"Rather than relying on the conventional top-down approach of working with large chunks of crystals, our team focused on a 'bottom-up' synthesis method," said Qian Wang, a Senior Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE). "We chose to work with ferrocene, a compound containing iron from the metallocene family, due to its unique properties conducive to our objectives."

Together with researchers from La Trobe University and RMIT University

in Australia; Institute of Biointelligence Technology, China; Université Montpellier, France; and the National University of Singapore, the team selected ferrocene for its optical anisotropy—its unequal refraction of light in different directions—which allows waveplates to modulate the polarisation state of light.

Ferrocene crystals have added benefits: they're transparent, allowing light to pass through with minimal loss; and can self-assemble under controlled conditions, aligning their growth direction with the crystal's principal refractive axis.

"This ability to self-assemble is especially important, as it means that once the ferrocene crystals achieve the desired thickness during preparation, they are immediately usable as miniaturised true zero-order waveplates, eliminating the need for further processing," explained Wang. "This makes our bottom-up approach particularly effective for producing high-quality, micron-scale waveplates."

Wang and colleagues discovered that their self-assembled ferrocene crystals can change the phase between two perpendicular polarisation components of a light wave (high birefringence) without absorbing light (low dichroism),
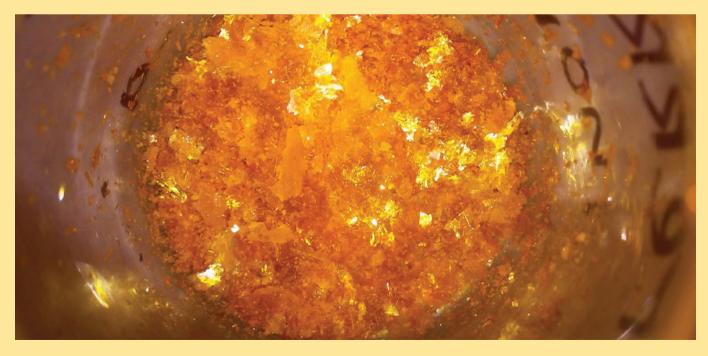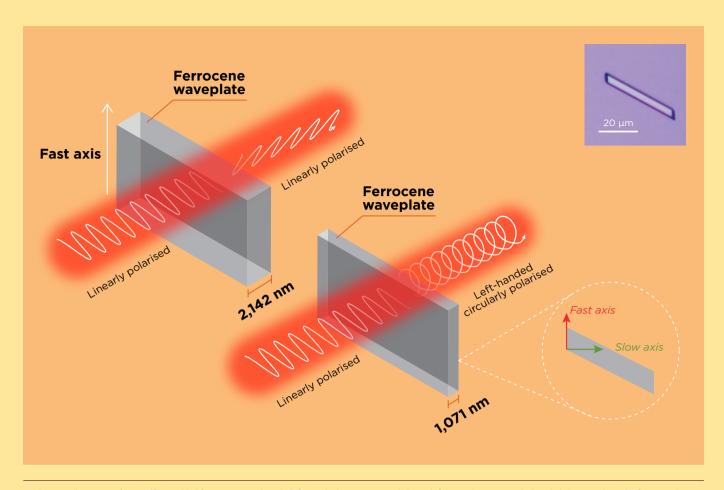

Photo credit: Thomas Finkelnberg / Wikimedia Commons

A schematic illustration of how self-assembled ferrocene crystals with different thicknesses convert light to different polarisations, which include linear and circular forms. Each crystal has a fast axis that runs along a natural edge, making it readily useable as a miniature true zero-order waveplate. Top right: an optical microscope image of a ferrocene crystal.

"Once the [self-assembled] ferrocene crystals achieve the desired thickness during preparation, they are immediately usable as miniaturised true zero-order waveplates."

making the crystals prime candidates for use in miniaturised waveplates.

These advancements have the potential to change how optical devices are made, particularly in the field of nanophotonics, which requires ultra-thin, compact components for optical communication and neural computing applications.

"Our current focus is on harnessing surface tension at liquid-liquid interfaces to drive the self-assembly and crystallisation of ferrocene, a technique we plan to extend to other materials," said Wang.

In addition, the team is investigating the optical traits of other metallocene compounds, opening exciting avenues in next-generation optical technologies. ★

Researchers

Qian Wang, Xuezhi Ma and Zhipeng Li, IMRE

IN BRIEF

Self-assembling ferrocene crystals generated using a bottom-up synthesis method had high birefringence and low dichroism, making them ideal for compact and efficient optical polarisation control components.

1. Li, Z., Ma, X., Wei, F., Wang, D., Deng, Z., *et al*. As-grown miniaturized true zero-order waveplates based on low-dimensional ferrocene crystals. *Advanced Materials* **35** (32), 2302468 (2023).

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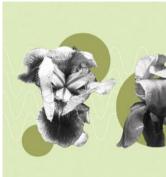
Here's a sneak peek of the material covered in the next issue of *A*STAR Research*

OPHTHALMOLOGY
EYEING VISION-SAVING BREAKTHROUGHS

A polymer-based drug delivery innovation aims to replace invasive eye treatments for retinal diseases.

BIOTECHNOLOGY
SUSTAINABLE SCENTS INSPIRED BY NATURE

Researchers develop a novel and more efficient bioprocess to synthesise a highly valued plant extract used in the fragrance industry.

MECHANICAL ENGINEERING
FLOAT LIKE A BUTTERFLY, STING LIKE A BEE

Built from nanowires and polymers, a new 'soft' robot design fully mimics the natural movements and optical features of jellyfish.

COMPUTER NETWORKS AND COMMUNICATIONS
COVERT WHISPERS BEHIND DIGITAL CURTAINS

A new approach to secure direct communication between devices enhances privacy by preventing eavesdropping.