EDITORIAL
03 Editorial notes

FEATURES
08 The roadmap to RIE2025
16 The dark side of antibiotics
28 Towards the next generation of computing devices

RESEARCH HIGHLIGHTS
COVID-19
04 Immunology: Forecasting a (cytokine) storm
05 Diagnostics: Capturing antibodies in asymptomatic COVID-19 patients
06 Data Science: Did Singapore’s ‘circuit breaker’ work?
07 Infectious Disease: The purifying power of plants

HUMAN HEALTH AND POTENTIAL
12 Immunology: Not all brain macrophages are alike
13 Genetics: Providing closure in anencephaly research
14 Developmental Biology: A tough choice for embryo cells
15 Cancer Biology: How EBV guts us in new ways

URBAN SOLUTIONS AND SUSTAINABILITY
20 Materials Science: An EPIC search for new materials
21 Materials Science: Designing binders for the batteries of tomorrow
22 Nanotechnology: A tiny step forward for sustainability
SMART NATION AND DIGITAL ECONOMY

24 Machine Learning: Taking fashion from streets to shops

25 Nanotechnology: Bringing nanolasers in from the cold

26 Materials Science: Spinning a way to flexible energy harvesters

MANUFACTURING, TRADE AND CONNECTIVITY

32 Artificial Intelligence: A man-machine winning team

33 Additive Manufacturing: Shaping 3D-printed bones for better implants

34 Nanotechnology: Mixing it up with smart nanoparticles

35 Synthetic Biology: A fine taste for resveratrol

NEXT ISSUE

36 A sneak peek of Issue 23
A strong scientific base doesn't develop spontaneously; rather, it is the product of consistent investment over many years. Since the first Research, Innovation and Enterprise (RIE) plan was launched in 1991, Singapore's research landscape has grown from strength to strength, a testament to the country’s careful planning and forward thinking.

In December 2020, RIE2025 was launched with a S$25 billion budget—the biggest so far. RIE2025 will support research in four domains, namely: manufacturing, trade and connectivity (MTC); human health and potential (HHP); urban solutions and sustainability (USS); and Smart Nation and digital economy (SNDE). As the lead government agency for scientific research, find out how A*STAR is driving research across these domains in our cover story on p. 08.

One notable effort in the HHP domain is the collaborative Growing Up in Singapore towards healthy Outcomes (GUSTO) study, which has tracked over one thousand mother-offspring pairs in the past decade. By analyzing GUSTO data, A*STAR researchers have examined for the first time the impact of antibiotics on the gut bacteria of infants and adults. Dig deep into their results through our feature ‘The dark side of antibiotics (p. 16).’

Elsewhere, scientists like Anjan Soumyanarayanan from the Institute of Materials Research and Engineering (IMRE) are developing faster and more powerful computers. In ‘Towards the next generation of computing devices (p. 28),’ read about how A*STAR researchers are harnessing novel particles called skyrmions to surpass the limits of modern computing.

Aside from advances in human health and digital innovation, research at A*STAR also touches upon sustainability with ‘Designing binders for the batteries of tomorrow (p. 21)’ and manufacturing with ‘Shaping 3D-printed bones for better implants (p. 33).’

Discover the many ways A*STAR scientists are contributing to Singapore’s research efforts by visiting our website at research.a-star.edu.sg or following us on Twitter at @astar_research and LinkedIn at A*STAR Research. Stay tuned for more exciting developments from A*STAR this year!

For the latest on A*STAR’s COVID-19 research, please visit: https://research.a-star.edu.sg/tag/covid-19/
Forecasting a (cytokine) storm

These novel immune signatures identify patients most at risk for developing severe COVID-19 symptoms.

The influx of COVID-19 patients has overwhelmed hospitals around the globe. Managing resources is particularly challenging, considering the course of infection differs significantly between patients. Some present with relatively mild symptoms, while others can quickly enter a downward spiral, ending up in the intensive care unit (ICU) battling life-threatening respiratory distress.

Early interventions can help, but the question is, which patients need them? In general, older patients and those with underlying medical conditions are known to be more vulnerable. However, the biological mechanisms controlling infection severity are still poorly understood and screening protocols to more accurately categorize patients are not yet available.

Ginhoux and his team first obtained blood samples from a cohort of COVID-19 patients experiencing the full spectrum of infection severity: from a mild fever and cough to respiratory distress requiring ventilation. Using high-throughput flow cytometry and single-cell sequencing, they found that immune cells from patients with severe infections appeared to be out of place—their blood contained markedly elevated levels of neutrophils at the very early stages of their maturation. This was a red flag, considering that these cells are typically found only in the bone marrow.

Additionally, the team observed striking differences in the levels of calprotectin in the blood of patients with severe COVID-19. “Calprotectin is a very well-known marker of inflammation,” explained Ginhoux, adding that its levels also spike in the case of other infectious diseases. “It stood out as one of the most upregulated markers in severe patients.”

“The detection of these markers would allow patients to receive earlier treatment such as oxygen, corticosteroids and anticoagulants, which may slow down disease evolution and prevent critical situations requiring hospitalization in the ICU,” said Ginhoux. Follow-up studies will focus on more in-depth statistical and mechanistic analyses of these newfound predictive biomarkers, he added.

Measurable inflammatory biomarkers are key pieces of this puzzle, said Florent Ginhoux, a Senior Principal Investigator at A*STAR’s Singapore Immunology Network (SIgN). An exaggerated immune response is a hallmark feature of severe COVID-19, in which inflammatory proteins flood the body—a process known as the cytokine storm.

In collaboration with Eric Solary and Michaela Fontenay from Gustave Roussy and Institut Cochin respectively, Ginhoux tested whether specific immune molecules could represent early warning signs that such a storm is brewing. Their study, published in Cell, suggests that the presence of a specific type of white blood cell and elevated levels of an inflammatory protein called calprotectin were tightly linked to greater disease severity.

Capturing antibodies in asymptomatic COVID-19 patients

Using flow cytometry, researchers have developed a sensitive and specific test for COVID-19 that can identify asymptomatic carriers.

With the COVID-19 pandemic raging into its second year, it has become increasingly clear that completely eradicating SARS-CoV-2 will not be possible. Instead, containing the virus and mitigating its impact will be key to resuming ‘normal’ life, making the routine detection of SARS-CoV-2 background levels important.

Serology-based tests, which detect antibodies against the virus rather than the virus itself, will play a crucial role in identifying asymptomatic patients and those who have recovered. However, existing serology tests typically use only a fragment of the virus’ most exposed protein, the spike protein, detecting antibodies specific to each fragment rather than the full range of antibodies produced against the virus.

Now, a team of researchers led by Laurent Renia, Executive Director of A*STAR’s Infectious Diseases Labs (ID Labs), has developed a serology test that not only captures the full repertoire of antibodies against the spike protein that covers the surface of SARS-CoV-2, but also distinguish between the antibody subclasses detected.

“Being able to distinguish between IgG and IgM subclasses, for example, might inform us about which stage of infection the patient is at. This could be particularly important for asymptomatic patients,” said Renia. “Similarly, the assay could be used to detect functional IgG1 and IgG2, which are important in virus neutralization.”

To develop their assay, the researchers first introduced the full-length spike protein gene into cells, causing them to stably express the protein on their surface. They then incubated the cells with patient plasma, allowing any antibodies present to bind to the spike protein. Finally, fluorescent-labeled secondary antibodies that can distinguish between the antibody subclasses were added and detected using a technique called flow cytometry.

When tested on samples that were confirmed to be positive using the gold-standard polymerase chain reaction test, the assay was able to detect 97 percent of the infections in pre-symptomatic and asymptomatic patients, despite the lower antibody levels in these patients. In contrast, commercially available serology tests only indicated results in 32–35 percent of pre- or asymptomatic patients.

The team is currently using the assay to support Singapore’s COVID-19 surveillance efforts and investigate the immune response to SARS-CoV-2 over time, with studies planned to follow patients for up to 18 months after the onset of illness.

“As the assay is based on full-length spike protein, it will likely still be able to detect antibodies against the spike protein even in cases where there are point mutations,” said Renia, adding that the group is currently developing a parallel assay to detect both UK and South African variants.

Did Singapore’s ‘circuit breaker’ work?

Lockdown measures not only reduced the number of COVID-19 cases but also resulted in a temporary improvement in air quality, study finds.

When governments first scrambled to control the spread of COVID-19 in early 2020, they faced a crisis with very little precedent. To protect their populations, many governments tried containment measures like lockdowns despite limited data about whether such measures would be effective against SARS-CoV-2. One year on, insights from spatial and temporal data are now allowing policymakers to assess the effectiveness of lockdown measures while making evidence-based forecasts for possible future outbreaks.

In Singapore’s case, one might ask: how can we measure the impact of lockdowns like the government’s ‘circuit breaker’ policy? This challenge was taken on by Xiuju Fu, a Senior Research Scientist at A*STAR’s Institute of High Performance Computing (IHPC). With collaborators from Delft University, Brno University of Technology and Singapore’s Ministry of Health, Fu and her team looked at how mobility-curbing measures affected variables like COVID-19 exposure risk and air quality.

However, collecting spatio-temporal mobility data about walking, driving or public transport is difficult, so the researchers turned to a near real-time, open-source dataset—the availability of car-park lots—as a proxy for mobility. “Compared to other mobility data, driving mobility data from residential car-park records is readily available, accurate and continuously updated, which saves us time-consuming data collection and validation,” Fu explained.

Using an extended Bayesian spatial-temporal model that considered data uncertainties, Fu’s team found that the ‘circuit breaker’ immediately reduced driving mobility by 13.4 percent, reaching a peak reduction of 36.4 percent by April 12. This reduction in mobility was associated with an average reduction of potential COVID-19 exposure risk by 37.6 percent and a 55.4 percent average reduction in transportation-related emissions.

These changes happened after a six-day post-lockdown ‘lag effect,’ where a preceding phase with near-exponential rates of increase in COVID-19 cases steadily slowed down and eventually made a turnaround. “Our results indicate that the circuit breaker not only keeps residents safe but also leads to environmental changes with reduced transportation pollution,” Fu said.

This information is useful for policymakers because it not only shows that mitigation measures can control the explosion of COVID-19 cases, but also when and how this might happen. The methods used in the study can help inform governments and citizens alike of the appropriate kinds of mitigation strategies and when to use them. “For example, residents working from home can even acquire more online information through predictive analytics on crowd distribution and select the most suitable time to go out to minimize transmission risk,” Fu said. ★

The purifying power of plants

Plant-based ionizers are surprisingly effective at removing aerosols and could play an important role in preventing COVID-19 transmission.

Before the pandemic, few of us would have given thought to whether the air in a grocery store or our offices was safe. But now that we have to be concerned about the airborne transmission of COVID-19, air quality can sometimes be all we think about.

Air purifiers, such as ionizers, can help allay some of our concerns about air quality. Ionizers emit static electricity that helps draw floating particles towards surfaces where they will not be inhaled. Unfortunately, many ionizers emit harmful ozone gas as they operate.

Taking a leaf from nature, a team of scientists from A*STAR’s Institute of Materials Research and Engineering (IMRE) and Institute of High Performance Computing (IHPC) investigated whether plant-based ionizers could play a role in the fight against COVID-19. Plant-based ionizers are small devices attached to living plants that use the plant’s leaves to create an ionizing effect. Unlike normal ionizers made from mechanical parts, plant-based ionizers do not emit ozone.

Surprisingly, the team led by IMRE group leaders Ady Suwardi and Dan Daniel found that plant-based ionizers were even more effective than traditional ones. They found that it took 24 minutes for 95 percent of the aerosols in a room to dissipate with no ionizers running, a figure that dropped to 15 minutes with a traditional ionizer. However, it took just six minutes for a plant-based ionizer to achieve the same effect.

“In a windowless room, it may take up to 30 minutes for human-generated aerosol to clear,” said Daniel. “With proper usage of plant-based ionizers, the time it takes to clear the aerosol can be easily reduced to as low as six minutes.”

The team also used sophisticated simulations to show how efficient different types of plant-based ionizers would be in different spaces. The models showed that a large plant-based ionizer could provide enough clear air for a room as large as 40 square meters.

Currently, the researchers are working on other techniques for reducing the spread of COVID-19 indoors, like adding surfaces to a room so that aerosols will be more likely to settle on them.

“We are also actively involved in testing the efficacy of various mitigation measures on venues such as churches, restaurants and meeting rooms,” said Suwardi. “We work hand in hand with our sister institute, IHPC, which uses computational fluid dynamics to simulate the aerosol and airflow patterns in various settings.”

Researcher
Ady Suwardi, IMRE (left)
Dan Daniel, IMRE (right)

BACKGROUND
Plant-based ionizers are small devices attached to living plants that are highly effective at removing aerosols.

A*STAR is poised to contribute towards Singapore’s Research, Innovation and Enterprise 2025 plan across all four strategic domains. Having bagged the title of Asia’s most innovative economy for seven years running, it’s hard to believe that Singapore’s research and development (R&D) journey began just a little over thirty years ago. After all, it was only in 1991 that the National Science and Technology Board (NSTB)—A*STAR’s predecessor—was formed. That same year, the first-ever National Technology Plan was launched.

Now known as the Research, Innovation and Enterprise (RIE) plan, these strategies lay the groundwork for the country’s science and technology efforts every five years. As the nation faces its biggest crisis yet, capabilities built over the previous RIE plans have helped Singapore emerge stronger through the pandemic. Indeed, with one of the world’s lowest COVID-19 mortality rates, Singapore’s steady R&D investments have paid off.

Last December 2020, RIE2025 was launched with a S$25 billion budget—the largest sum so far dedicated to R&D in Singapore’s history. Of this amount, 29 percent or S$7.3 billion will go towards strengthening Singapore’s core capabilities in universities and A*STAR’s research institutes, signifying the country’s sustained, long-term commitment to R&D through economic cycles.

This time around, RIE2025 will be organized across four domains, namely: manufacturing, trade and connectivity (MTC); human health and potential (HHP); urban solutions and sustainability (USS); and finally, Smart Nation and digital economy (SNDE). As the lead public sector R&D agency in Singapore, A*STAR remains one of the crucial drivers of RIE2025 efforts—as it has always been from its earliest days as NSTB.

THE MANUFACTURING MAKEOVER

While Singapore is popularly known as the ‘little red dot,’ it is actually the world’s fourth-largest exporter of high-tech goods. This remarkable feat was partly achieved through
pioneering initiatives like the A*STAR Model Factories at the Advanced Remanufacturing and Technology Centre (ARTC) and the Singapore Institute of Manufacturing Technology (SIMTech). Since its launch, the Model Factory Initiative has deployed close to 2,600 Industry 4.0 technologies to over 100 local companies in a never-ending quest for business efficiency.

To maintain its position as a global manufacturing hub, RIE2025 will see Singapore deepen its capabilities in MTC by tapping on frontier technologies like artificial intelligence (AI). At A*STAR, the Accelerated Materials Development for Manufacturing (AMDM) program is leading the way, by combining tools like AI with high performance computing and automation to optimize materials R&D.

Singapore’s success as a manufacturing hub can also be attributed to its strategic location along global major trade, shipping and aviation routes. But as COVID-19 has proven, even the most robust supply chains can be disrupted without adequate preparation. With the country hoping to become a regional node for vaccine distribution, A*STAR is developing technologies to make air traffic safer and more productive.

Collaborating with the Civil Aviation Authority of Singapore, A*STAR researchers created a digital assistant that can recognize and transcribe voice conversations between air-traffic controllers and pilots for safety and training purposes. In-house researchers have also developed tools to better allocate assets on the ground and harvest energy from runway sensors. Together, these tools should enable air-traffic controllers to handle complex scenarios with ease and efficiency.

Beyond aviation, the maritime industry has also benefitted from A*STAR’s R&D expertise. Consider the VHF Data Exchange System, developed by A*STAR’s Institute for Infocomm Research’s (I2R) Satellite Team and ST Engineering. By enabling communication regarding from ship-to-ship and ship-to-shore, the system prevents potential collisions and even facilitates search-and-rescue operations. With support from horizontal technology program offices like AI, Analytics and Informatics (AI3), more exciting innovations in the MTC domain are set to arise over the next five years.

GETTING A HEADSTART ON HEALTH

The Republic’s bustling biomedical sector traces its origins to the year 2000, when the Biomedical Sciences initiative was launched to develop life sciences as a key economic pillar. Over twenty years later, A*STAR now counts milestones like homegrown cancer drug ETC-159 and the COVID-19 diagnostic kit Fortitude on its list of achievements.

Developed over mere weeks, Fortitude’s speedy deployment was made possible through the combined efforts of Tan Tock Seng Hospital along with A*STAR’s Diagnostics Development (DxD) Hub, Bioinformatics Institute (BII) and Experimental Drug Development Centre (EDDC). Together, these institutes comprise the Health and Medical Technologies (Medtech) horizontal technology program office, which aims to encourage innovation in biomedical companies with A*STAR’s expertise.

For RIE2025, the HHP domain will build upon existing biomedical capabilities, but with a focus on furthering human potential. As Singapore’s greatest resource is its people, ensuring that residents have healthy and meaningful lives is a national priority. In 2009, the Growing Up in Singapore Towards health Outcomes (GUSTO) study was launched to uncover how Singaporeans can get a good start in life and reach their highest potential.

Co-led by researchers from A*STAR’s Singapore Institute for Clinical Sciences (SICS) along with the National University Health System and KK Women’s and Children’s Hospital, GUSTO tracks over 1,200 local mothers and their children from early pregnancy until the children reach the age of ten. Moving forward, a key priority for GUSTO will be to track children as they mature to better understand the links between early development and adolescence. Researchers will also study the effects of sleep and digital media use on cognitive development and growth.

Healthier and more meaningful lives can also be achieved through precision medicine, a key focus of A*STAR’s Genome Institute of Singapore (GIS). In 2019, GIS spearheaded the creation of the world’s biggest Asian genetic database. Insights from the database could lead to earlier and more accurate diagnoses, as well as targeted treatments to improve patient quality of life. With these HHP initiatives in place, people in Singapore can truly exemplify living live to the fullest.

SUSTAINABILITY TAKES THE SPOTLIGHT

Though COVID-19 may be the topic of the hour, a global climate crisis will still be imminent in the absence of decisive action. To ensure that Singapore is spared from the worst effects of climate change, the USS domain of
RIE2025 will focus on reinforcing the city-state’s livability, resilience and sustainability.

The Integrated Environmental Modeler (IEM) is one notable A*STAR effort already being deployed. Developed by the Institute of High Performance Computing (IHPC) and I2R researchers along with Singapore’s Housing and Development Board, the IEM is a ‘digital twin’ that simulates the effects of environmental factors on Singapore’s housing estates. Insights gained from the IEM will be used to design cooler and more livable estates with a reduced carbon footprint.

Novel decarbonization technologies and initiatives such as zero waste and building a circular economy are two other cornerstones of the USS domain. At A*STAR, the aptly-named Urban and Green Technology horizontal technology program office guides the development of solutions for energy efficiency to waste management. Meanwhile, to cultivate a circular economy, scientists at A*STAR’s Institute of Materials Research and Engineering (IMRE) are creating sustainable materials and extending the life cycle of various wastes.

For Singapore to truly become resilient, however, it must lessen its near-total dependence on imported food. Hence, by 2030, Singapore intends to produce locally 30 percent of its nutritional needs—with the goal fittingly called ‘30 by 30.’ To achieve this goal, A*STAR has launched several initiatives: In 2018, for instance, A*STAR’s Institute of Chemical and Engineering Sciences (ICES), in collaboration with local SME Westcom Solutions, developed a microbial treatment that could break down one ton of food waste into organic fertilizer in 24 hours.

More recently, the S$144 million Singapore Food Story R&D program was launched with the Singapore Food Agency in 2020 to drive innovation in sustainable urban food production, future foods and food safety science. In April 2020, the Singapore Institute of Food and Biotechnology Innovation (SIFBI) was subsequently established to conduct studies on everything from food process engineering to food waste conversion.

The A*STAR Agritech and Aquaculture horizontal technology program office will also focus on building expertise in areas like the Internet of Things and smart lighting, to help farmers monitor crops in real-time and better detect contaminants. Continued research in these areas will surely help move the country towards a more climate- and food-resilient state.

**DIVING DEEP INTO DIGITAL**

Echoing Singapore’s big biomedical bet, RIE efforts in the digital realm first took shape in the early 2000s, with the Smart Nation initiative following in 2014. While these efforts have since created a thriving tech ecosystem—with local unicorns like ride-hailing juggernaut Grab—it was only during the COVID-19 pandemic that the benefits of digitalization truly became apparent.

As digitalization accelerates across all sectors, the SNDE domain in RIE2025 will continue to drive digital

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**Examples of research at A*STAR supporting the Research, Innovation and Enterprise 2025 (RIE2025) plan:**

**Manufacturing, Trade and Connectivity (MTC)**

- Accelerated Materials Development for Manufacturing (AMDM)
- Air traffic control digital assistant (in partnership with the Civil Aviation Authority of Singapore)
- VHF Data Exchange System (FR)

**Human Health and Potential (HHP)**

- Health and Medical Technologies (Medtech) horizontal technology program
- Growing Up in Singapore Towards healthy Outcomes (GUSTO)
- SG100K (GIS)

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**Features**

- Diagnostics Development Hub (DxD)
- Bioinformatics Institute (BII)
- Experimental Drug Development Centre (EDDC)
IME and I2R are teaming up with local semiconductor component supplier arQana Technologies to develop supporting infrastructure for 5G applications like drone detection radars and satellite communications.

**TRAINING TOP-TIER TALENT**

With RIE2025 underway, researchers at A*STAR and beyond can expect a flurry of research activities dedicated to advancing the four domains. Of course, fulfilling such an ambitious agenda is only possible with a robust manpower base as well as collaboration among the many local and international scientific players. Accordingly, S$2.2 billion has been set aside in RIE2025 for dedicated talent development activities. Part of this amount will go into increasing the number of A*STAR postgraduate scholarships and traineeships, as well as introducing the Research Internship Awards for undergraduate students interested in interning at A*STAR’s research institutes. Focused initiatives like the Singapore Biodesign Program—jointly launched by A*STAR, the Singapore Economic Development Board and Stanford University—will also train the country’s next generation of medtech innovators.

In the lead up to 2025, A*STAR—and indeed, the entirety of Singapore’s scientific ecosystem—is set to be a hotbed for exciting research and innovation over the next five years. Stay tuned for more developments across the four domains! ★

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Adoption and support the development of emerging technologies. Doing so will allow Singapore to harness new opportunities in the digital economy—advancing its Smart Nation ambitions along the way. Indeed, previous RIE investments have already boosted the public sector’s digital capabilities.

Consider SG Translate, a machine learning-powered translation engine that specifically caters to Singapore’s unique linguistic context. Created by I2R in collaboration with the Ministry of Communications and Information, the engine has produced over 100,000 translations for government agencies. During COVID-19’s peak, SG Translate reduced the time needed to translate the government’s public WhatsApp messages by up to 50 percent.

Through program offices like AI³ and its capabilities across data analytics, computer vision and natural language technologies, among others, A*STAR will continue helping both the public sector and industry address their many needs. Frontier technologies like blockchain and AI are also being used by I2R to improve cybersecurity and detect threats. Meanwhile, researchers at IHPC and IMRE are exploring how quantum effects manifest in different materials, in hopes of building newer and more powerful quantum devices.

Finally, any conversation about the digital future would be incomplete without 5G, the next frontier of ultra-fast mobile wireless technology. With the ongoing nationwide 5G rollout, A*STAR’s Institute of Microelectronics (IME) and I2R are teaming up with local semiconductor component supplier arQana Technologies to develop supporting infrastructure for 5G applications like drone detection radars and satellite communications.
Not all brain macrophages are alike

Being able to distinguish between different types of macrophages in the brain could shed light on inflammatory diseases such as Alzheimer’s.

Unlike most other organs in your body, the brain is shielded from immune cells circulating in the blood, protecting it from potentially harmful immune responses. However, that is not to say that immune cells are completely absent from the brain; in fact, cells called macrophages migrate to the brain very early on during fetal development and play a crucial role in its proper development and functioning.

While studying the proteins expressed on the surface of brain macrophages in mice, Florent Ginhoux, a Senior Principal Investigator at A*STAR’s Singapore Immunology Network (SIgN), and colleagues quickly realized that there were two distinct populations of macrophages resident in the brain: cells called microglia found in the brain itself, and border-associated macrophages (BAMs) found peripherally in the membrane surrounding the brain.

“People tend to think that all brain macrophages are the same,” said Ginhoux, who collaborated on this study with Melanie Greter at the University of Zurich, Switzerland. “But recent studies have revealed that different types of macrophages reside in parts of the brain, surrounded by different types of cells that can confer completely different functions.”

Although microglia are relatively well-studied and have been linked to several diseases, much less is known about BAMs as they were previously assumed to be the same as microglia.

Using flow cytometry and single-cell transcriptomics to investigate these cells in greater detail, Ginhoux and colleagues identified markers that revealed an early bifurcation in the development of brain macrophages: microglia require TGF-β for development, while BAMs do not.

They also traced the origins of both cell types back to the yolk sac, suggesting that they diverge from each other early during development. “While we showed in 2010 that microglia arise from the yolk sac, we always thought—perhaps naively—that BAMs would come after,” he said. “We were surprised to find that the BAM lineage is also decided very early on, even before the brain itself is fully formed.”

Since microglia are thought to be more involved in brain development while BAMs are believed to perform more of an immune function, having a way to identify the cells could help us understand diseases such as Alzheimer’s and complications related to Zika fetal infection during pregnancy, which have been linked to inflammation in the brain, Ginhoux added.

“The next exciting thing we would like to work on is establishing what are the cues that make these cells adopt one fate versus another in humans,” he said. For that, Ginhoux says he would need to develop an in vitro model, such as a 3D brain organoid model from induced pluripotent stem cells.
A lot happens in the first month of conception: Between day 17 and 30 after conception, a dynamic process called neural tube closure occurs, giving rise to the baby’s spinal cord, spine, brain and skull.

When the neural tube fails to close properly, the developing brain or spinal cord is left exposed to the amniotic fluid. If the upper end of the neural tube fails to close, the brain either never completely develops or is absent, causing a common neural tube defect called anencephaly. Pregnancies affected by anencephaly often result in miscarriage and infants who are born alive die very soon after birth.

“While neural tube defects—including its most severe form of anencephaly—are common in humans, a genetic etiology of anencephaly in humans has never been established,” said Bruno Reversade, a Research Director at A*STAR’s Genome Institute of Singapore (GIS) and Institute of Molecular and Cell Biology (IMCB).

Reversade was a co-corresponding author on the study, which discovered a genetic cause for the devastating condition.

Reversade’s team first learned about a Turkish first-cousin couple that had three consecutive fetuses with anencephaly, suggesting a possible genetic origin. Curiously, no other extended family members had similarly affected offspring. By carrying out exome sequencing of the couple’s DNA and one of their terminated fetuses, they were able to highlight a potential gene candidate: NUAK2.

Each parent only had one mutated copy of NUAK2, but the fetus had two, implying that this form of anencephaly was recessive.

NUAK2 had previously been studied in the context of cancer, its role in brain development was not known. The NUAK2 gene encodes a kinase, which is an enzyme that catalyzes the transfer of phosphate groups to other proteins. Using in vitro kinase assays, the team observed that the loss of seven critical amino acids in the αC-helix of the NUAK2 protein resulted in the loss of its catalytic activity.

To understand NUAK2’s link with anencephaly, the team mimicked neural development in vitro using 3D cell cultures called cerebral organoids, which were derived from affected fetus skin cells. The researchers found that the loss of NUAK2 enzyme activity led to decreased activity in the downstream Hippo-YAP signaling pathway—a critical pathway that controls cell shape during neural tube folding.

Moving forward, the team intends to explore the relationship between folic acid and NUAK2 function. “Given that folic acid and vitamin supplementation before and during pregnancy has been shown to reduce neural tube defects by 50-70 percent, it would be interesting to use our in vitro models to assess whether the presence of folic acid could rescue the loss of Hippo-YAP signaling in mutant cells,” said Carine Bonnard, currently the Head of Operations at the Skin Research Institute of Singapore (SRIS). Bonnard was both first and co-corresponding author in this study.

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A tough choice for embryo cells

Keratin, a tough and insoluble fibrous protein, plays a surprising role in determining mouse embryonic cell fate.

It may come as a surprise to learn that some new parents consume the placenta after birth, by processing it into capsules or cooking it. Other mammals do it too, for reasons that remain unclear. Regardless of one’s postpartum degustation choices, we can at least take solace in the fact that there’s a difference between the placenta and fetal tissue, although they arise from the same embryo.

But how are such cell-fate decisions made, and how do embryonic cells coordinate their choices among themselves? Cell fate is determined very early in embryonic development, even before the embryo gets implanted into the uterine wall. The prevailing theory of cell polarity proposes that cell fate is determined during cell division, by the asymmetric inheritance of cytoskeletal components that help to keep track of cell polarity.

In 2018, researchers from A*STAR’s Institute of Molecular and Cell Biology (IMCB) made an observation that suggested there might be other cytoskeletal components besides F-actin and microtubules that determine cell polarity during embryonic development.

“Nobody knew exactly what keratin did in a developing embryo during preimplantation development,” said Plachta. “We discovered that keratins function as asymmetrically inherited factors specifying which cells of the embryo go on to be the precursor of the placenta.”

Using immunofluorescence imaging, the team studied the keratin subtypes in live mouse embryos that are predominantly expressed during the preimplantation stage. They observed that keratin filaments help in decision making by providing a memory of cell polarity: keratin filaments are inherited only by daughter cells that retain an outward face, suggesting that they serve as a physical memory of apical-basal polarity.

“The discovery that keratins function as symmetrically inherited fate determinants provides a mechanism to understand how embryonic cell lineage fate is influenced at cell divisions during the early stage of development,” said Plachta. “This extends the idea that the fate of early blastomeres is predictable and validates a key aspect of the cell-polarity model.”

How EBV guts us in new ways

The Epstein-Barr virus can cause epigenetic changes that persist even after the infection has been cleared, highlighting why prevention is better than cure when it comes to gastric cancer.

“While EBV infection is known to be associated with 8-10 percent of gastric cancers, the exact manner by which EBV causes gastric cancer remains poorly understood,” said Patrick Tan, Executive Director of GIS and Professor at Duke-NUS Medical School. While other cancer-causing viruses are known to cause disease by integrating into the genome and disrupting the host DNA, Tan and his team have shown the EBV can affect gene regulation without integrating its DNA.

Instead of looking for cancer-induced changes at the level of individual genes, the researchers investigated epigenetic alterations and changes in the 3D structure of DNA. “Using a technique called Hi-C, we identified paired regions of the genome that lie in close physical proximity to one another in 3D space, that would otherwise exist far apart if the DNA sequence is interpreted as a linear sequence of base pairs,” Tan said.

By comparing these 3D chromatin structures between healthy and cancerous stomach cell lines, the researchers identified a novel mechanism for tumor formation, which they termed ‘enhancer infestation.’ In the enhancer infestation model, the virus unleashes normally silenced enhancers, which are short pieces of DNA that augment gene expression, allowing them to activate nearby tumor-enhancing genes by loosening their tightly packed chromatin structure. “This is a new paradigm where viral DNA, even when not integrated, can nevertheless interact with the human genome to affect gene regulation, particularly in genes related to the development of cancer.”

Further work showed that EBV modified chromatin topologies by altering the epigenetic ‘tags’ on histone H3, a DNA packaging protein. Interestingly, the group found that these tags persisted even after EBV DNA was eliminated. “These results suggest that for such genes, the ‘epigenetic damage’ caused by EBV is largely fixed and that infected cells are committed to the development of cancer,” Tan added.

The group, led by Tan and Atsushi Kaneda of Chiba University, Japan, is now investigating if the enhancer infestation model applies to other EBV-related cancer types. Moreover, having identified several novel genes linked to gastric cancer using this approach, the researchers are now investigating whether these genes are suitable drug targets.

Epigenetics has revealed that the Epstein-Barr virus can cause gastric cancer by altering gene expression without causing mutations to the underlying sequence.

THE DARK SIDE OF ANTIBIOTICS
And what we can do about it
As early as the 13th century, scholars proposed that diseases were caused by ‘invisible entities’ unseen to the naked eye. However, it was not until the 1670s when Antonie van Leeuwenhoek made his microscope did the theory gain traction. Just as seeing tiny ‘animalcules’ zipping around under the microscope enabled the field to advance, it has taken development of the right tools to enable 21st century scientists to uncover the full impact that microorganisms have on human health.

Observational studies have long suggested a link between microorganisms in the gut and metabolic diseases. However, without the tools to prove what many had observed, the role of the gut microbiome was a major blind spot in biomedical research. Only in the past few decades—with the advent of high throughput sequencing and sophisticated analytical methods—have researchers been able to perform cause-and-effect studies, helping this key area of research finally flourish.

Since then, research has revealed that disruptions to the delicate balance of microorganisms in the gut can have wide-reaching effects on health and disease. Dysbiosis, or perturbations to the gut microbiome, has not only been linked to common metabolic disorders like diabetes, but can have effects that extend to autoimmune disorders like multiple sclerosis, cancer, and even cognitive disorders like Alzheimer’s disease.

While various factors can cause dysbiosis in the gut, one particular culprit stands out: antibiotics. Despite having saved millions of lives since the famed, fateful accident that led Alexander Fleming to discover penicillin nearly a century ago, antibiotics have proven to be a double-edged sword. Because they kill bacteria non-discriminately—good and bad alike—antibiotics use can lead to a tipping of the balance in these communities, causing a myriad of problems, one of which is obesity.

Understanding the impact of antibiotics on both infants and adults could help restore the delicate balance of the gut microbiome.
These findings have important implications for medical practice, Karnani said. Although antibiotics may be necessary in some circumstances, physicians and caregivers should balance the benefits and risks of administering antibiotics to children, she explained.

“Understanding the factors linked to dysbiosis in gut microbiota in early life and its relationship with metabolic adversities can help early intervention and reduce the burden of obesity on society,” Karnani added.

**RESTORING THE BALANCE**

Gut microbiome sequencing studies, like the one performed by Chen and colleagues, have been made possible by recent advances in technology. The ability to determine the profile of microorganisms living within a given environment like the gut—known as metagenomics—allows researchers to compare populations and the effects of interventions. On the flip side, researchers can also use this information to develop ways to manipulate microbiomes for therapeutics.

For example, Niranjan Nagarajan, a Senior Group Leader at A*STAR’s Genome Institute of Singapore (GIS), used metagenomics to identify ‘keystone’ bacteria, species that would promote the healthy re-colonization of the gut following antibiotic treatment. Comparing gut microbiome of patients from Singapore, Canada, England and Sweden given different classes of antibiotics,
Nagarajan and his team found that the patients could be grouped into ‘recoverers’ or ‘non-recoverers.’²

“Recoverers exhibited a ‘U-shaped’ diversity profile where their gut microbiome diversities rebounded within a specified period post-antibiotics treatment,” Nagarajan said. “Non-recoverers, on the other hand, continued to have low gut microbiome diversities within the same specified period post-antibiotics treatment.”

Classifying patients in this way allowed the researchers to search for bacterial species that may aid the recovery of microbiome diversity. They discovered 21 recovery-associated bacterial species, or RABs, so-called because they were significantly linked to the recovery of the gut microbiome after treatment with antibiotics in at least two of the four patient cohorts studied.

Just like food webs in oceans or rainforests, the different species of bacteria in the gut form complex interactions, with a few primary species proving to be essential for the survival of the many secondary and tertiary species, which are more synergistic in nature. Using a computational method to fit the RABs into the gut microbial food web, the researchers identified both primary and tertiary species among the 21 RABs.

Testing the practical applications of their results, the team found that inoculating mice with both primary and tertiary RABs bolstered the recovery of absolute microbial abundance by 100-fold. These mice also had higher gut microbiome diversity after receiving treatment with antibiotics compared to mice that received just a tertiary species or control substance.

“These findings are critical for improving our understanding of how gut microbiomes recover and the type of microbial species that play a crucial role in this process,” Nagarajan noted. “The 21 RAB species can potentially be used for therapeutic and diagnostic purposes for restoring the gut microbiome post-antibiotics perturbation.”

WORKING HAND IN GLOVE

While both studies examine the gut microbiome through the lens of antibiotics, they do so through different but complementary lines of inquiry: the impact on human health and the potential for finding therapeutic and diagnostic solutions.

These diverse but linked lines of research are made possible through A*STAR’s integrative research infrastructure and the establishment of various health and technological initiatives. For example, the institute’s involvement in seminal collaborative population-wide studies like GUSTO provides researchers the opportunity to investigate the effects of the gut microbiome in a range of settings and across a variety of populations, factors and diseases.

Meanwhile, initiatives like A*STAR’s integrated Omics research program complement these studies by facilitating the development of new and improved tools—like OPERA-MS, which was developed by researchers at GIS to enhance metagenomics methods—to transcend the possibilities of researchers’ endeavors. Aided by these tools, A*STAR researchers are advancing our understanding of the gut microbiome, just as van Leeuwenhoek’s homemade microscope first opened human eyes to the existence of microorganisms nearly four centuries ago. ★

ABOUT THE RESEARCHER:

Neerja Karnani is a Senior Principal Investigator and the Systems Biology Lead at A*STAR’s Singapore Institute for Clinical Sciences (SICS) and an Adjunct Associate Professor at the National University of Singapore’s Yong Loo Lin School of Medicine. She received her PhD degree in 2002 from Jawaharlal Nehru University, India, where her research was recognized with the C. R. Krishna Murti Memorial Young Scientist Award.

Niranjan Nagarajan is an Associate Director and a Senior Group Leader at A*STAR’s Genome Institute of Singapore (GIS), and an Associate Professor at the Department of Medicine and Department of Computer Science at the National University of Singapore. His research focuses on developing cutting edge genome analytic tools and using them to study the role of microbial communities in human health.

A high-throughput screening method could significantly shorten the discovery cycle for new thermoelectric materials.

If you live on the equator, you may rely on the ubiquitous air conditioner to get relief from the oppressive heat and humidity. These devices can perform their important functions of heat harvesting and refrigeration thanks to a family of thermoelectric materials called bismuth telluride (Bi$_2$Te$_3$) alloys.

For decades, materials scientists have been trying to recreate their blockbuster success with bismuth telluride by searching for novel thermoelectric materials from over half a million inorganic compounds. They have made very little traction, despite the potential upside for industries as wide-ranging as cold storage, computing, automotive and aerospace.

“Finding new thermoelectric materials is time consuming, inefficient and expensive. Thus, limited progress has been made in the discovery of high-performance candidates, which is a bottleneck for thermoelectric technology,” explained Shuo-Wang Yang, a Senior Scientist at A*STAR’s Institute of High Performance Computing (IHPC) and a co-corresponding author on the study.

A new computational method developed by Yang and colleagues—called Energy-dependent Phonon- and Impurity-limited Carrier Scattering Time AppRoximation, or EPIC STAR—can identify promising high-performance thermoelectric materials in less than one-tenth of the time taken by other methods.

“Our benchmark shows that, compared with the widely used electron-phonon Wannier (EPW) interpolation method, EPIC STAR can provide results with the same accuracy in less than one-tenth of the computational time,” Yang said.

Instead of a trial-and-error, brute-force approach to the discovery of thermoelectric materials, EPIC STAR bypasses the challenges posed from the calculations of electron-phonon coupling, a time-consuming but essential calculation that is necessary to predict the thermoelectric performance of a candidate material.

To speed up their calculations, the researchers simplified the numerical integrations that are conducted in the Brillouin zones, which explain the behavior of an electron in a perfect crystal but become increasingly complex at every stage.

Yang and his team have used EPIC STAR to identify a low-cost, high-performance thermoelectric candidate, NaInSe$_2$, which could be experimentally tested by industry partners for thermoelectric and electronic applications.

“The composing elements of NaInSe$_2$ are more abundant than bismuth- and tellurium-based materials. Therefore, NaInSe$_2$ and its analogs may have useful applications as a new low-cost, high-performance thermoelectric material,” Yang said.

To facilitate the screening of thousands of inorganic materials in a high-throughput manner, the team is leveraging on computational resources at the A*STAR Computational Resource Centre (ACRC) and the National Supercomputing Centre Singapore (NSCC).

“We expect to find new high-performance candidates and design principles that could enable breakthroughs in the field,” Yang shared. “The data we collect will be used to build an open-source database for machine learning-aided materials design.”

Researcher
Shuo-Wang Yang,
IHPC

ABOVE
High-throughput screening has helped to identify new thermoelectric materials.

Sodium-sulfur batteries could help make renewable energy a reality by making energy storage more scalable.

Driven in part by pandemic-related slowdowns, renewable energy reached a new milestone in 2020, surpassing coal-generated energy for the first time. For all the gains that renewable energy generation has made, it’s easy to forget that any power produced needs to be stored. Despite leaps in lithium-ion battery technology, we are reaching the theoretical and practical energy limits of battery technology; lithium is also too expensive and too scarce to meet our energy storage needs, more so if scaled up to meet demand.

Lithium’s abundant and inexpensive chemical cousin, sodium, is its prime successor. When built into room-temperature sodium-sulfur batteries (NaSBs), it theoretically holds triple the energy density of lithium-ion batteries. But NaSBs have their flaws, said Zhi Wei Seh, a Senior Scientist at A*STAR’s Institute of Materials Research and Engineering (IMRE). “Issues that plague lithium–sulfur batteries continue to affect NaSBs,” he said. For one, NaSBs burn out fast: the sodium anode gets smothered by sulfur intermediates from the cathode, while the cathode disintegrates from repeated expanding and contracting during use.

To tackle both issues, Seh and his IMRE colleague, Alex Yong Sheng Eng, focused on the battery binder, the material used to hold the battery together. Though it forms only a small part of the overall battery, the binder plays a crucial role, giving structure to the battery and affecting the stability and performance of the electrodes.

Since the discharge products of NaSBs are ionic and polar, the researchers hypothesized that a polar binder would help the battery maintain its structure and perform better. In collaboration with Man-Fai Ng from A*STAR’s Institute of High Performance Computing (IHPC), the team used simulations to show that polar binders would indeed stabilize a sulfurized cathode and prevent sulfur intermediates from reaching the anode at the same time.

To test their predictions, the researchers constructed NaSBs using common and naturally derived carboxyl-rich polymer binders such as polyacrylic acid, carboxymethyl cellulose or sodium alginate. The result was a more robust battery that outperformed traditional cathode binders in longevity and stability tests at 1,000 cycles, which is among the best performance for such batteries to date.

The team is now working on developing other battery configurations and improving the safety and charging rate of their batteries, with an eye to commercialization within the next five years.

“Our findings can not only be applied to portable batteries, but also to stationary grid storage, to store excess renewable energy and release it on demand during times of shortfall,” Seh said. “This will enable us to decarbonize our energy landscape and power a sustainable energy future based on renewable energy.”

From catalysis to diagnostics and targeted drug delivery, new and exciting applications in nanotechnology have emerged over the past two decades. Because of their distinctive features—an incredibly high surface area to volume ratio for catalytic reactions, in addition to their capacity for carrying drugs and imaging agents—nanoparticles have provided novel solutions to many industrial and healthcare challenges.

Their potential notwithstanding, polymeric nanoparticles in use today are often non-biodegradable, which means that they accumulate in the environment and eventually enter the food chain. Preparing ultra-small nanoparticles in the sub-30 nanometer size range can also prove extremely challenging, with current methods (such as self-assembly) resulting in nanoparticles in the 100-nanometer size range or larger.

A rising interest in biodegradable and ultra-small nanoparticles due to their intriguing similarity with natural systems like proteins and other biological molecules inspired researchers at A*STAR’s Institute of Chemical and Engineering Sciences (ICES) to turn to single-chain technology, a method of synthesizing nanoparticles with a high level of precision that allows for individual copolymer chains to be folded and collapsed into single-chain nanoparticles. This method gives rise to ultra-small nanoparticles that are sub-30 nanometer in size.

“Our approach is experimentally robust and a straightforward route for the preparation of degradable single-chain nanoparticles,” said the lead investigator of the study, Praveen Thoniyot, a Senior Scientist and Team Leader at ICES. “Since the linear polymer precursor is prepared under free-radical conditions, it is easy to introduce a very large number of functionalities compared to other polymerization methods.”

Starting with a degradable linear polymer precursor containing cyclic ketene acetal-derived ester moieties and cross-linkable functional groups throughout the chain, the nanoparticles were formed via intramolecular chain folding and

“Non-degradable and environmentally persistent polymer nanoparticles are harmful to the biosphere. Introducing degradability into polymer chains can be one of the first steps towards achieving true sustainability.”
cross-linking. The degree of chain folding corresponded to the quantity of diamine cross-linker added for amide bond formation, while degradation into branched oligomers was attained through main-chain ester hydrolysis. Thoniyot and colleagues confirmed that they produced single-chain nanoparticles via light scattering and size-exclusion chromatography.

Due to their small diameters and higher diffusion rates compared to larger conventional nanoparticles, degradable nanoparticles have great potential to be used in a variety of applications including catalysis, nanoreactors, sensing and nanomedicine, said co-corresponding author Alexander William Jackson, a Scientist at ICES.

“Sustainability is a key driver of all technological innovations today,” added Thoniyot. “Non-degradable and environmentally persistent polymer nanoparticles are harmful to the biosphere. Introducing degradability into polymer chains can be one of the first steps towards achieving true sustainability.”

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When it comes to fashion, online shopping is the new black. Convenience, competitive prices and a seemingly endless array of the season’s latest trends are driving more consumers to online stores than ever before. From a customer’s perspective, the online shopping experience is vastly different from walking into a brick-and-mortar fashion outlet. With no fitting rooms, it is nearly impossible to answer the question, “Do these jeans look good on me?”

In a bid to make e-shopping more interactive and intuitive, the fashion industry is looking to next-generation clothing image synthesis technologies. While current fashion image generation platforms work for basic items, clothes with intricate textures, patterns or logos are often too much for existing imaging technologies to handle. The rendered image ends up looking distorted and fine details are lost, making it frustrating for retailers and shoppers alike.

To overcome this bottleneck in imaging quality, a team led by computer vision and machine learning researcher, Huijing Zhan from A*STAR’s Institute for Infocomm Research (I2R), has created the Pose-Normalized and Appearance-Preserved Generative Adversarial Network (PNAP-GAN). This computing framework could revolutionize how shoppers interface with online stores, bringing the retail experience into their living rooms.

“Three scenarios motivate our research into clothing imaging technologies: Firstly, can we generate a novel image from a street image captured on a mobile phone? Secondly, can we find online listings based on user-submitted photos? Finally, can we visualize the clothes on the customer virtually?” Zhan explained.

The team focused on designing an algorithm to teach computers how to ‘scan’ fashion elements from a visual input source, such as a photograph. In Stage I of their two-stage approach, the algorithm guides the system to capture the global structure of the garment, recognizing particular landmarks and creating a general image representation. In Stage II, this visual is refined. Fine details are added, making it easier for the system to accurately and interchangeably depict how the piece would look either on a model or on a virtual clothes rack.

“For example, when customers go window shopping and see a cool blazer worn on others, they would like to know how the blazer looks on them. PNAP-GAN makes it possible to try on the item virtually by pasting your profile image onto the synthesized image, which is also free of the deformation regardless of the pose,” said Zhan.

While this study describes PNAP-GAN’s exciting potential across an array of sweaters, tops and dresses, further enhancements to the technology are already in the pipeline. Zhan says follow-up studies will focus on further fine-tuning the platform to preserve fabric textures and patterns in more elaborate pieces.★

Researcher
Huijing Zhan,
I2R

Algorithms can help you visualize how clothes worn by others might look on you.

The laser is a staple of modern technology, finding uses from optical communication and surgery to barcode scanners and laser printers. But most modern lasers still follow a basic blueprint developed more than sixty years ago: a material to convert input energy into light, sandwiched between two finely-tuned mirrors to select and emit a narrow range of light wavelengths.

To make lasers more compact and energy efficient, researchers have in recent years tried to replace these mirrors with sophisticated solutions based on nanotechnology. These novel designs, however, suffer from impractical requirements, such as the need for cryogenic cooling. Now, a group of scientists led by Arseniy Kuznetsov, a Principal Scientist at A*STAR’s Institute of Materials Research and Engineering (IMRE), has combined two optical nanotechnologies to create a room-temperature nanolaser, in collaboration with Hilmi Volkan Demir and the Luminous! Centre of Excellence for Semiconductor Lighting and Displays at Nanyang Technological University, Singapore.

Kuznetsov and his group had previously shown that lasers could be built using ‘nanoantenna arrays,’ periodic arrangements of nano-scale cylinders etched into a material. When the spacing between cylinders is carefully controlled, these arrays emit light at specific wavelengths, allowing them to replace the traditional mirror-based cavity resonators. “These nanoantenna arrays are simpler and cheaper to manufacture than standard solid-state lasers, and may even be integrated into flexible devices,” explained Kuznetsov.

However, Kuznetsov’s first generation of nanolasers only worked at negative 70 degrees Celsius or colder, as the nanoantenna arrays were too inefficient at converting pump energy into light at higher temperatures. This was a problem that Demir could solve with his group’s expertise—growing ‘nanoplatelets’ of cadmium selenide just a few molecules wide. These nanoplatelets convert energy into light very efficiently thanks to quantum effects.

Combining the two technologies by coating the nanoantenna arrays with nanoplatelets resulted in a nanolaser that could lase at room temperature, overcoming the energy conversion inefficiency that had plagued earlier versions. Kuznetsov and his group also showed that the wavelengths of emitted light could still be tuned by changing the spacing of the nanoantenna array in this new, hybrid version.

So far, Kuznetsov’s nanolaser can emit light in short pulses, and his group is currently working on extending this to continuous operation, followed by achieving electrical instead of optical energy input. “If we succeed, this would open up opportunities for multiple potential applications, including flexible displays, sensors, wearables and many more,” Kuznetsov said. ⚫

**“These nanoantenna arrays are simpler and cheaper to manufacture than standard solid-state lasers, and may even be integrated into flexible devices.”**
Flexible polymers capable of turning physical movement into electricity may usher in the future of wearable devices.

Recall how your hair would cling to a plastic comb or the feeling of being zapped by the handrails of an escalator. Static electricity may be annoying, but it could play a role in powering emerging applications such as wearable devices. These devices demand materials that are both flexible and able to convert physical movement into electrical energy.

While piezoelectricity results in the electricity that stems from mechanical pressure, triboelectricity comes from materials shifting against each other, such as when you pull a plastic comb away from your hair.

Obtaining both piezoelectric and triboelectric effects, and getting them to work constructively in a flexible material, is a challenge that researchers from A*STAR’s Institute of Materials Research and Engineering (IMRE) and the National University of Singapore are trying to solve. Their solution is a flexible film from electrospun-aligned polyvinylidene fluoride (PVDF) fibers that can produce a giant electric output in response to mechanical vibration.

On its own, PVDF is the most commonly used piezoelectric polymer. To further increase its flexibility and electromechanical coupling performance, a team led by Kui Yao, a Principal Scientist at IMRE and the corresponding author on the study, conducted electrospinning under high voltage to shape the PVDF material into flexible fibers and induce the fibers to align in a desired orientation.

“Electrospinning enabled us to tune the fibers’ electron affinity with different polarization terminals. This results in strong and constructive piezoelectric and triboelectric responses within a single PVDF composition.”

The team tested the fiber film’s electromechanical conversions under different frequencies and input levels. In their experiments, they were able to obtain maximum effective piezoelectric strain and voltage coefficients of up to -1065 pm V\(^{-1}\) and -9178 V mm N\(^{-1}\).
respectively. They then proposed a theoretical model to explain their experimental observations.

“Our theoretical analyses and experimental results showed the potential of the electrospun-aligned polar PVDF fiber material for mechanical energy harvesting,” said Yao.

Yao foresees that these fiber materials could someday provide electrical power in wearable devices by converting natural body movement into electrical energy. ★

ABOVE

PVDF fibers are electrospun onto a layer of aluminum and then coated with copper, which acts as the top electrode. The result is a flexible device that uses both piezoelectricity and triboelectricity to generate electricity.

Towards the Next Generation of Computing Devices

Computing devices are finally reaching their limits. But recently discovered particles called magnetic skyrmions could redefine these limits, according to Anjan Soumyanarayanan.

Ever noticed how our smartphones and computing devices become faster within short spans of time? You can thank Moore’s law for that. Back in 1965, Intel co-founder Gordon Moore predicted that the processing power of computers would double about every two years, and incredibly, this empirical rule-of-thumb has held on for over five decades.

However, modern computing technology is now reaching its scaling limits, potentially bringing Moore’s law to a screeching halt. Meanwhile, the demand for computing power continues to grow rapidly—in part due to the advent of artificial intelligence.

Circumventing these restrictions on memory and computing power is the need of the hour, and it requires one to look beyond conventional devices and computing architectures. Behold one of the candidates: tiny magnetic quasi-particles called skyrmions, which may offer a way to surpass conventional processing limits.

Because the information storage memory and decision-making functions of computers are typically kept separate, performing even the simplest of tasks consumes energy. Skyrmions, one of the candidates that may combine the two functions, are opening the doors to faster processing and real-time decision making with reduced power.

Discovered over a decade ago, magnetic skyrmions have proven tricky to control. But not anymore, thanks to a breakthrough technique pioneered by Anjan Soumyanarayanan and his colleagues at A*STAR’s Institute of Materials Research and Engineering (IMRE). Through their method, the team managed to finetune the size, density and stability of the skyrmions, drawing them closer to realizing energy-efficient computing.

For literally putting a fresh spin on skyrmions and harnessing quantum phenomena for nanoelectronics, Soumyanarayanan received the Young Scientist Award at the 2018 President’s Science and Technology Awards. Soumyanarayanan, who is also an Assistant Professor at the National University of Singapore and the 2018 recipient of the IEEE Magnetics Society Early Career Award, takes us on a closer look at skyrmions and the role they could play in next-generation computing.
**Q:** HOW DID YOU BECOME INTERESTED IN STUDYING MAGNETIC SKYRMIONS?

The formation of magnetic skyrmions relies on three key ingredients: spin-orbit coupling, magnetism as well as the unique topology at certain material surfaces and interfaces. These concepts are central to several emergent phenomena discovered over the last 10-15 years. In 2010, these concepts were the backbone of a successful grant proposal that I co-wrote with my PhD advisor to support my thesis work on topological materials. Upon returning to Singapore, A*STAR’s deep capabilities in magnetic thin films provided a natural pivot towards skyrmions. I am glad that it came with challenges in materials science and device engineering—both of these have proven to be valuable learning opportunities.

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

Moore’s law, or the exponential growth of computing power with time, is reaching its limits after a five-decade reign as the cornerstone of modern electronics. One promising alternative is to use electron ‘spin’ instead of charge to store, process and transfer information. Spin electronics, or spintronics, may offer devices faster processing speeds while drastically reducing power consumption.

Of late, my research efforts have focused on magnetic skyrmions. Recently discovered in industry-compatible materials, skyrmions are nanoscale arrangements of electron spins that behave like individual magnetic particles. They have promising attributes as base elements for next-generation computing. We are developing thin-film materials hosting such skyrmions and investigating their behavior in nanoscale devices.

**Q:** WHAT ARE SOME SEMINAL FINDINGS IN YOUR FIELD THAT YOU INTEND TO BUILD UPON?

First, spintronic devices require the ability to electrically detect (‘read’) and manipulate (‘write’) spins to form ‘0’ and ‘1’ states—to represent the binary system used in conventional computer code. Discovered three decades ago, these capabilities were recognized with the 2007 Nobel Prize and are commercially used in modern hard disk drives and magnetic random access memory (MRAM).

More recently, the coupling between electron spin and momentum—known as spin-orbit coupling (SOC)—has emerged as an attractive ingredient in industry-compatible thin films. On one hand, SOC enables the creation of magnetic skyrmions and other novel phenomena. On the other hand, it provides a fast and energy-efficient means for electrical writing.

Finally, we hope that such devices may find use in mimicking the biology of neurons, thereby realizing brain-inspired or ‘neuromorphic’ computing. This burgeoning topic is seeing numerous device proposals to achieve recognition, pattern-matching and decision-making capabilities mimicking the human brain.

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

Though magnetic skyrmions show great promise as a nanoscale data-processing element, they’re not the easiest to work with. In fact, till recently magnetic skyrmions were observed only at low temperatures. Therefore, our initial efforts on this topic focused mostly on establishing and tailoring their room temperature properties in thin...
HOW DO YOU SEE YOUR RESEARCH AREA EVOLVING IN THE NEXT DECADE?

Use-inspired research areas, including ours, are evolving rapidly in how problems are defined and tackled. For example, defining problems requires increased and sustained engagement with stakeholders across the entire value chain. Likewise, solving complex, large-scale problems requires forming interdisciplinary teams comprising materials scientists, physicists, electrical engineers and computer scientists. Notably, machine learning techniques are now playing an increasingly vital role in the prediction, design and analysis of materials and device parameters. These and other emerging factors will help shape our research area in the near future.

WHAT ARE SOME OF THE INDUSTRIAL OR SOCIAL IMPLICATIONS OF YOUR RESEARCH? WHO WILL BENEFIT FROM THE FINDINGS?

Our research aligns with broader efforts in the field of spintronics. Spintronic technologies are commercially used in hard disk drives and magnetic memory. Future discoveries from spintronic research could enable new computing architectures, in addition to low power device operation at extremely fast speeds. Such devices could help us achieve energy-efficient computing platforms.

This could potentially manifest in data centers with reduced power consumption. Alternatively, they could be used to develop personal or ‘edge’ computing devices with AI capabilities. Eventually, such research may be applied in diverse domains ranging from manufacturing to healthcare and surveillance, as it can aid in monitoring as well as recognizing faults for intervention.

“Machine learning techniques are now playing an increasingly vital role in the prediction, design and analysis of materials and device parameters.”

ABOUT THE RESEARCHER:

Anjan Soumyanarayanan is a Senior Scientist at A*STAR’s Institute of Materials Research and Engineering (IMRE) and an Assistant Professor at the National University of Singapore. Soumyanarayanan obtained a BA degree in 2005 from Cambridge University, UK, and a PhD degree in 2013 from the Massachusetts Institute of Technology, US. His research interests are in topological and quantum phenomena in thin-film materials. In 2018, he received the IEEE Magnetics Society Early Career Award and the Singapore Young Scientist Award for his spin-orbitronics work.
A*STAR is Singapore's lead public sector science and technology agency. A*STAR has a strategic R&D agenda, driving use-inspired basic research, advancing translational programmes, spearheading economic growth and advancing social well-being through scientific discovery, technological innovation and talent development.

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Leveraging both artificial intelligence and field knowledge may prove to be a superior strategy for predicting machine health.

Just as all of us are advised to undergo regular health check-ups, machines are no different. To keep endless rows of factory machines in tip-top condition, a valuable parameter that can be tracked is a machine’s remaining useful life (RUL), which predicts the health of a machine component or system.

With accurate RUL prediction, businesses can reduce maintenance costs by performing maintenance only when necessary, and improve system reliability by minimizing machine downtime and maximizing machine lifetime. However, it is challenging to model these systems accurately, as different mechanical systems have their distinct mechanisms.

To boost the performance of RUL prediction, a research team that included Xiaoli Li, a Principal Scientist at A*STAR’s Institute for Infocomm Research (I2R), built a new RUL prediction framework that combines learned features derived from deep-learning algorithms, with handcrafted features derived from manual inputs by a data scientist.

“Both deep learning and handcrafted features with domain knowledge are important for accurate RUL prediction,” Li explained. “However, the effective combination of these two types of features is non-trivial.”

Their strategy, which they call an ‘attention-based deep learning framework,’ combines the best of both learned and handcrafted features: First, a ‘long short-term memory (LSTM) network’ is used to learn characteristic features in sequence; second, an ‘attention network’ automatically assigns larger weights to more important features; and third, a ‘feature fusion framework’ combines LSTM with handcrafted features.

In two real-world datasets, the researchers applied their attention-based deep learning framework to describe the deterioration of an aircraft engine. Based on two widely used criteria for evaluating RUL prediction performance, they showed that their approach outperformed current ‘state-of-the-art’ methods based on artificial intelligence (AI) algorithms.

“People often say deep learning can achieve the best prediction results,” said Li. “Our research demonstrates that human domain knowledge is equally valuable and critical for boosting system performance. By integrating AI and human intelligence, we can achieve the best possible prediction outcomes.”

In real-world scenarios where each machine operates under different working conditions, models trained under specific conditions may not generalize well to other machines. As such, the researchers plan to incorporate transfer learning in their RUL predictions, to overcome an assumption in machine learning that training data and test data share the same basic patterns and distributions. By developing an AI model that can self-adapt to new working environments, it will be possible to develop RUL predictions that more accurately predict complex interactions found in the real world.

Shaping 3D-printed bones for better implants

Porous metallic bones designed to be 3D-printed in unusual shapes could be the future of permanent orthopedic implants.

Gyroids are oddly shaped objects: their curved geometrical structures contain no straight lines and never self-intersect, and yet they remain infinitely connected. These gyroid structures can also be found in nature, as photonic nanostructures in the wings of the *Calliphrys rubi* butterfly.

The highly curved surfaces in gyroids also make them excellent candidates for artificial bone implants. The only problem? Getting their pore sizes right remains a challenge—if the pores are too big, bone cells cannot attach to the scaffold; if the pores are too small, the transport of nutrients to the bone tissue is hindered.

To enhance the biocompatibility of 3D-printed bone implants, researchers in Singapore designed a heterogeneous gyroid structure that solved both problems: millimeter-scale pores for nutrient and oxygen exchange, and micrometer-scale pores for cell adhesion and growth.

“Biostructural and mechanical compatibility are the most important factors for the success of an artificial implant in the human body,” said Pan Wang, a Scientist at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech) and the lead author of the study. “In addition, the implants also need to have similar stiffness and strength to bone to avoid stress-shielding effects, which will lead to the loss of surrounding bone mass.”

While searching for an ideal artificial bone implant, the team reviewed an internally developed database for suitable initial gyroid structures. Using a simulation technique called finite element modeling, they then developed modified gyroid 3D lattices with the desired pore size and mechanical properties using detailed visualizations of stress distribution patterns.

Next, the researchers selected a Ti-6Al-4V alloy for their implant material and successfully fabricated five types of gyroid structures by electron beam melting, a type of metal 3D printing. The lattices had variable cell wall thicknesses and pore sizes, and possessed a range of Young’s modulus from 8 to 15 GPa and compressive strength from 150 to 250 MPa. These mechanical properties are well within the range observed with human bone, Wang noted.

Introducing numerous pores within the gyroid structures also distributed stress more evenly, allowing the implants to deform more stably and avoid brittle failure. Furthermore, these pores also enhance the biological function of metallic lattices, Wang added. “After implantation, the metallic ‘skeleton’ populated with cells will grow with the femur and its mechanical properties will gradually change to a bone-like one,” he said.

Wang believes that their research findings will support the development of more biocompatible implants as well as further knowledge into lattice design and 3D printing. “Our target is to develop permanent orthopedic implants that can fully eliminate stress shielding and last beyond a patient’s lifetime,” he said.  

Mixing it up with smart nanoparticles

Self-assembled nanoparticles can stabilize oil-brine emulsions under extreme conditions, paving the way for enhanced oil recovery and other industrial applications.

“Pickering emulsions,” where nanoparticles take the place of surfactants to stabilize small droplets, are particularly useful in industrial applications where surfactants may not perform well under harsh conditions. These nanoparticles can kinetically stabilize emulsions at the liquid-liquid interface, overcoming instability issues associated with high temperatures and salinity.

In this proof-of-concept study, Vasantha used simple chemistry to bond brine-soluble zwitterions—molecules with negatively and positively charged fragments—with oil-soluble styrene monomers. Subsequently, when these hybrids were combined with unmodified styrene monomers using a one-step emulsion copolymerization, they self-assembled into small spherical polystyrene nanoparticles covered in a mesh of zwitterions.

“These zwitterionic nanoparticles can be made with one-step copolymerization, removing the need for complex manufacturing and purification processes,” said Ludger Stubbs, a Senior Research Scientist at ICES and a co-author on the study. In addition to being simple to manufacture, the zwitterionic nanoparticles remained stable in industrial salt concentrations and at elevated temperatures.

“Microscope images showed that the nanoparticles indeed formed a rigid, protective barrier between oil and brine, making this the first time such stable emulsions have been prepared using zwitterionic nanoparticles without further chemical additives,” Hadia explained.

Moving forward, the researchers hope to create nanoparticles that are highly responsive to their chemical environments, resulting in smart nanofluids that can form or break emulsions on demand. Such nanofluids would have significant technological applications, from biological environments to oilfield deployment, enhancing the capabilities of industrial chemistry. ★

A fine taste for resveratrol

A highly sensitive biosensor may aid in the production of high-value compounds in microbial cell factories.

If you’ve heard that a glass of red wine a day is good for your health, you may wonder what exactly makes red wine beneficial. It turns out that a chemical compound in grape skin, called resveratrol, confers onto red wine a variety of biological properties ranging from anti-aging to cardiovascular protection.

As would be expected, resveratrol quickly garnered attention from the nutraceutical and beauty industries for its use as a dietary supplement. But attempts to commercially manufacture resveratrol using genetically engineered *Escherichia coli* and *Saccharomyces cerevisiae* have met with little success to date.

“Engineering microbial cell factories for the sustainable production of important chemicals is often limited by the lack of high-throughput detection methods,” said Ee Lui Ang, now a Team Leader in the Discovery and Transformation division at A*STAR’s Singapore Institute of Food and Biotechnology Innovation (SIFBI). “This means that researchers are unable to screen through vast libraries of genetic variants generated by mutagenic methods to find the variants with higher production titers.”

Looking to find a way to produce valuable chemicals sustainably, Ang and colleagues sought to develop a biosensor that enables the high-throughput screening of resveratrol production in microbial cells.

Transcription factors are nature’s biosensors, triggering a cellular response when bound to specific compounds. However, before this study, there were no transcription factors known to be responsive to resveratrol. Therefore, the researchers searched for novel transcription factors by mining the genome of a bacterium called *Novosphingobium aromaticivorans*, which is known to break down resveratrol naturally.

“We hypothesized that *N. aromaticivorans* may have a sensing mechanism to detect resveratrol compounds,” said Ang. Genome analysis revealed a putative transcription factor gene upstream of a known resveratrol degradation enzyme, which the research team incorporated into their biosensor.

Characterization studies of the candidate transcription factor confirmed its sensitivity to resveratrol. The biosensor could accurately distinguish resveratrol from its precursors, p-coumaric acid and trans-cinnamic acid, and detect other biologically active stilbenes and cannabinoids.

When coupled to resveratrol biosynthesis enzymes, the biosensor sensed changes in resveratrol production in cells, demonstrating a 667-fold enrichment in one round of fluorescence-activated cell sorting. This suggests that the biosensor can potentially be used to identify genetic variants associated with high production titers in directed evolution experiments.

The researchers are looking to develop similar biosensors for other high-value compounds by mining the genome of microbes for new transcriptional regulators.

“At this point, we are working on establishing biosynthetic routes for other valuable compounds, such as alkaloids. We see the potential for using this strategy to discover new biosensors once we have established their production strains,” Ang shared.

**Researcher**

Ee Lui Ang, SIFBI

**BACKGROUND**

A biosensor that can detect high-value compounds like resveratrol could make the screening of microbial cell factories more efficient.

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

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