

A★STAR RESEARCH

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DELICIOUS INNOVATION IN THE SPOTLIGHT

Microbial factories for
food, flavors and fragrances

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UNPACKING THE POSSIBILITIES OF POLYMER SCIENCE

New materials with novel properties

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COMMEMORATING THE LIFE OF SYDNEY BRENNER

A tribute to a scientific pioneer

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EDITORIAL

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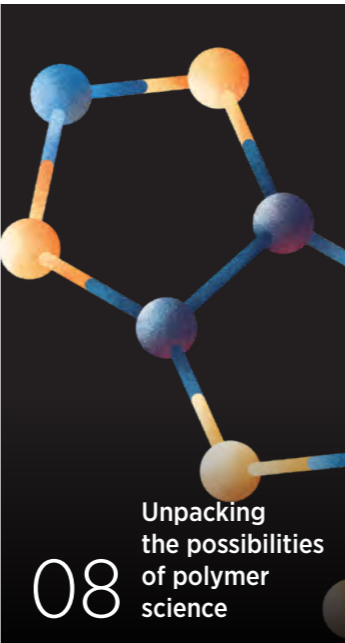
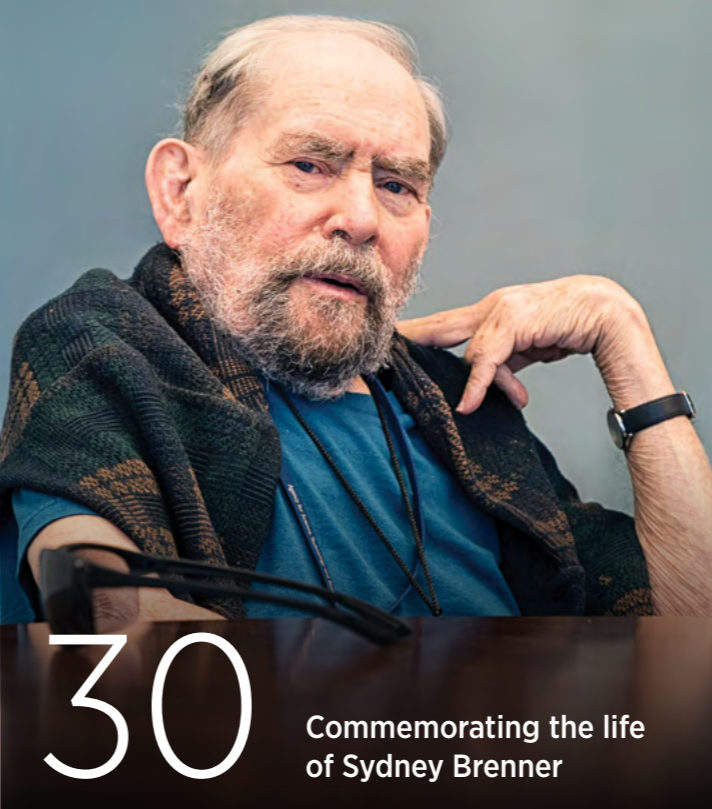
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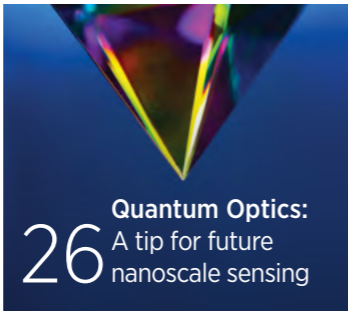
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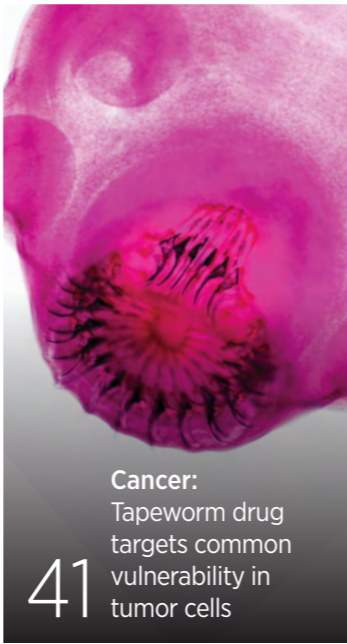
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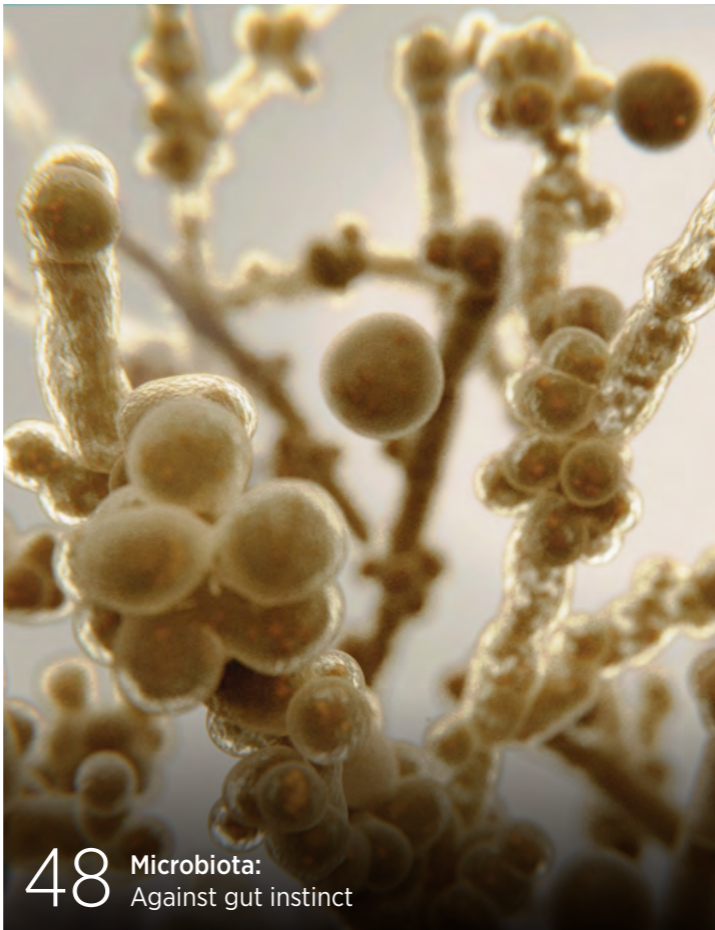
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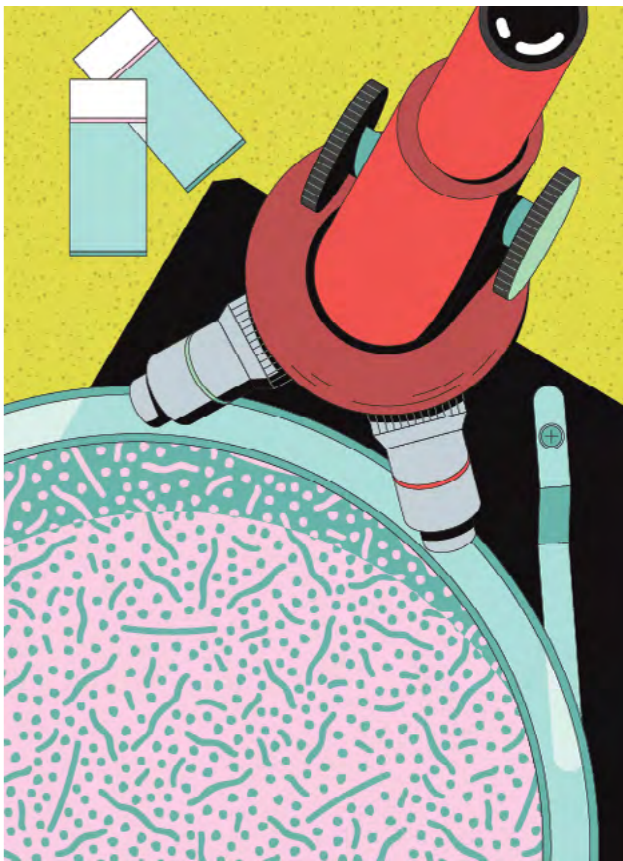
Much of what we consume and use comes from nature. But as we unravel the fundamental scientific concepts underlying how certain natural fragrances, medicines and materials come about, we begin to find ways to synthesize them at scale, improve on their properties, and even create novel substances that would never have been found outside the laboratory.

Exciting research such as these are being carried out under our BioTransformation Innovation Platform (BioTrans). Leveraging techniques such as metabolic engineering and mass spectrometry, A*STAR scientists are exploring a wide variety of natural products for the medical, food and personal care sectors. In our cover story ‘Delicious innovation in the spotlight,’ we find out how the humble gut bacteria, *Escherichia coli*, can be used to churn out 1,600 percent more of the antioxidant astaxanthin compared to previous methods.

Meanwhile, our second feature story delves into how scientists at the Institute of Chemical and Engineering Sciences (ICES) and the Institute of High Performance Computing (IHPC) are combining advanced computational approaches with experimental validation to unpack the possibilities of polymer science. From energy-harvesting materials to nanostructures for drug delivery, it is amazing how far imagination, coupled with scientific rigor, can take us.

In this issue, we also commemorate a dear colleague, Dr. Sydney Brenner, who passed away on April 5, 2019 in Singapore at the age of 92. Dr. Brenner was a visionary, and the field of molecular biology would not be where it is today without his seminal contributions to our understanding of how the genetic code is read. He was also instrumental in shaping Singapore’s research landscape, of which A*STAR is proud to be part of. He will be dearly missed by all of us.

But the march of science continues, and within these pages, you will find research highlights from scientific disciplines ranging from cancer biology to quantum optics, nanotechnology and machine learning. We hope you will enjoy reading the rest of this magazine, and for our latest stories, do visit us at our recently revamped website research.a-star.edu.sg, and follow us on Twitter at [@astar_research](https://twitter.com/astar_research) and LinkedIn at A*STAR Research.



On the cover
Microbes have become our allies in food innovation. (page 04)
© X-Tina / Shutterstock

DELICIOUS INNOVATION IN THE SPOTLIGHT

Tiny metabolically-engineered organisms could cheaply and sustainably produce ingredients for the medical, food and personal care sectors.

Is that floral-scented, natural shampoo from the health foods store good for the planet? Demand for organic food and fragrance is growing, but harvesting the ingredients used in natural products is putting a strain on limited environmental resources. One solution is to turn to microscopic organisms that produce ‘natural’ ingredients in vats of low-value fermented feedstock.

These microbes produce ‘nature-identical’ compounds; and while synthetics have a similar structure to naturally occurring compounds, they aren’t quite the same, explains A*STAR microbiologist Nic Lindley. In addition, a few tweaks to the metabolisms of the right microscopic organisms can power industrial-level production that often outperforms chemical synthesis or extraction in terms of production rates and cost-effectiveness.

Sharp output increases from yeast and bacteria are already being recorded at the BioTransformation Innovation Platform (BioTrans), the part of A*STAR’s Food, Nutrition and Consumer Care (FNCC) cluster focused on compounds for the health, seasonings and personal care sectors.

Lindley moved to Singapore from France two years ago to lead the platform. Since its launch in 2016, BioTrans has focused on five goals for the future of food, flavors and fragrances, says Lindley. These aims are to:

- Maximize product yields through its Microbial Metabolism Platform;
- Accelerate product development to get products to market faster via its Fermentation and Downstream Platform;
- Discover new compounds, biosynthetic pathways and microbial strains by trawling A*STAR’s vast Natural Product Library;
- Advance the development of healthier sweet, savory and other flavorings as part of the BioTrans Taste Receptor Platform;
- Investigate flavors, fragrances and metabolites by combining mass spectrometry with organoleptics (the study of sensory perception) to strengthen its Analytical Platform.

THE SWEET SMELL OF SUCCESS

Improvements in microbe production rates have steadily emerged from the BioTrans Microbial Metabolism Platform. In 2017, after increasing the output of a lycopene-overproducing *Escherichia coli* (*E. coli*) strain, researchers reported unprecedented yields of two high-demand natural aroma compounds¹—alpha-ionone, known for its sweet, violet-like aroma, and beta-ionone, which produces a scent often associated with violet or raspberry. On the upper end, BioTrans researchers beat a yeast’s proven beta-ionone production rate, improving output 80-fold using *E. coli*. The two ionones are used in everything from perfumes and oils to ice cream and maraschino cherries.

Lycopene, the carotenoid pigment that makes tomatoes red, is one of the main precursors of these types of apocarotenoids. Carotenoids have global market worth that is expected to reach USD 1.53 billion dollars by 2021. The complex metabolic characteristics of apocarotenoids have been a challenge to produce in the laboratory.

In their quest to optimize output, the BioTrans team divided *E. coli*’s apocarotenoid-producing biosynthetic pathway into four sections, or ‘modules,’ and optimized enzymatic steps in each module through genetic and enzyme engineering.

“In the future, biosynthesis will be on par with chemical synthesis.”

— Simon Congqiang Zhang,
A*STAR BioTrans Research Fellow

The group describes their method as a ‘plug-and-play’ system, meaning that “the platform is capable of producing various apocarotenoids simply by changing one or two genes, without perturbing the whole strains,” says lead author Simon Congqiang Zhang, a BioTrans research fellow, who supervises several translational research projects. This system has been shown to also work on a number of similar substances, including lycopene, beta-carotene, phytoene and retinol (vitamin A), an ingredient that will be familiar to those who use wrinkle creams or acne treatments.

Patenting the system is the next step, and Zhang reports that there are “quite a few companies in discussions with us to co-develop the bioprocess for commercialization.” Meanwhile, BioTrans scientists are also examining whether product range development can be pursued internally, with a view to spinning out their own commercial venture.

ACCELERATED ANTIOXIDANTS

In 2018, Zhang led another study building on his apocarotenoid work. The group used *E. coli* to produce a 1,600 percent improvement on current methods for producing the antioxidant astaxanthin², another type of carotenoid, and the red pigment that makes salmon and shrimp pink.

Astaxanthin exhibits strong antioxidant, anti-inflammatory and anti-cancer activity, and Zhang points out that its biological activities and benefits are supported by more than 50 human clinical trials and more than 1,000 papers published in leading journals. As a result, it is widely used in food, feed, nutraceuticals, cosmetics and medicine. The global astaxanthin market is predicted to reach USD 2.57 billion by 2025.

Most of the astaxanthin produced commercially is derived from algae such as *Haematococcus pluvialis*. This freshwater, unicellular green microalga transforms into red cysts under stress conditions, including nutrient deficiency, salinity and high temperatures, in combination with high irradiance.

But the algae is slow growing and usually produced in closed clear tubes (photobioreactors) to reduce cross-contamination from microorganisms such as microalgae, fungal parasites and zooplankton predators. As a result, producing astaxanthin requires a relatively large amount of land, and costs more than USD 7,000 per kilogram.

By building on the same modular approach used for apocarotenoids, the team from BioTrans and the National University of Singapore developed a complex self-learning system, known as a multidimensional heuristic process (MHP), capable of balancing the enzymatic activity within and among different modules simultaneously.

Using this approach, the team reported in *Nature Communications* a nature-identical astaxanthin production rate that was 16 times higher than the algae-based production rate, with an enantiomeric excess (a measure of purity) of 100 percent.

“The main advantage of the MHP is it enables a systematic but rapid optimization of biological systems to achieve high yield production of metabolites [such as astaxanthin],” Zhang explains.

This system is now on the cusp of commercialization. “Our current technology is able to produce astaxanthin at high concentrations and low cost on a small scale,” says Zhang. “The next challenge is to scale up our process in large fermenters, with a capacity of up to ten cubic meters, and to purify the compounds effectively.”

Zhang also points out that the team’s MHP has been used to optimize many different metabolic pathways

and molecules. Used with mathematical models, it could improve the performance of many microbes, he says. It has already been applied to produce nerolidol, well known for its fresh, woody scent and frequently used in shampoos, body lotions and soaps, as well as linalool, a compound with citrus tones used in many cleansing lotions, aftershaves and hair care products. With the MHP, *E. coli* produced linalool at 680 times the rate of a previously engineered yeast strain.

A*STAR'S BIOTRANSFORMATION INNOVATION PLATFORM



A*STAR's Natural Product Library

- 125,000 microbial strains
- 40,000 plant specimens



Taste Receptor Platform

- *In silico* structure-function modeling
- Cell systems mimicking the human tongue



Analytical Platform

- Gas chromatography/liquid chromatography-based workflows
- Organoleptics



Microbial Metabolism Platform

- Metabolic engineering methodologies
- Synthetic biology techniques



Fermentation & Downstream Platform

- 'Downscaling' for rapid early stage selection of robust microbes
- Bioprocess design and evaluation



Cosmetics



Food flavors



Fragrances



Food ingredients



Nutraceuticals

SEARCHING A TROVE OF TASTES

BioTrans researchers are also on the hunt for new food ingredients. Over at the BioTrans Taste Receptor Platform, senior research fellow Ann Koay and her colleagues mine A*STAR's rich resources for molecules that refine taste sensations—work that might provide people with more options so that they can make healthier choices.

To find these molecules, Koay trawls A*STAR's Natural Product Library (NPL), one of the world's largest resources for the study of biotechnologically useful microorganisms, genes, enzymes and other bioactive compounds. Established in 2013, the NPL houses more than 40,000 plant samples, 125,000 microbial strains, and 270,000 extracts derived from these specimens, collected from more than 100 countries. According to researchers at A*STAR's Bioinformatics Institute, who manage the NPL, the collection represents "57 percent of all known cultured fungal genera, 67 percent of the world's plant families, and 70 percent of filamentous bacterial genera." Genome sequence data for more than 150 microbial strains at NPL have already been uncovered, with potentially thousands more in the pipeline, and plans are underway to develop a digital database that will enable researchers to probe microbial genomes in even greater detail.

To make use of this huge resource, BioTrans researchers have developed cell systems that mimic human taste responses to sweet and bitter tastes, enabling researchers to quickly evaluate thousands of molecules for their taste-modulating properties. Cell systems are faster and cheaper than human sensory panels (groups of people who give feedback on taste and sensation). By further improving these high-throughput screening approaches, Koay hopes to accelerate discoveries of novel molecules, adding to the pipeline of molecules that are safe, healthy and effective for use in the food industry.

Of particular interest are molecules to help address increasing rates of diabetes. Half of Singapore's population will have Type 2 diabetes by 2050, according to a multi-institutional study published in 2014. To combat this disease, an increasing number of food companies are focusing on sugar reduction or replacing sugar in their products with sugar alternatives and sweet taste enhancers. The latter are molecules that increase the sweet taste sensation but do not taste sweet themselves. Even small amounts of such molecules can potentially replace or reduce the large amounts of table sugar currently added to processed foods, says Koay.

Koay and her colleagues are also looking at the other side of the coin, setting up a screening panel of bitter taste tests to search the library for bitterness blockers.

These can enhance naturally sweet flavors by blocking the interaction between bitter compounds and human taste receptors.

Sensations such as cooling, warming and tingling are also important to consumers, says Koay. People perceive quality and effectiveness of products from these sensations, so the researchers want to examine 'sensates'—molecules that correspond. These can send important underlying signals to consumers, who associate coolness with cleanliness, for example, or hotness with active ingredients. New and more potent ingredients—cooling agents for instance—can be utilized to improve products for the consumer care industry, Koay explains.

Researchers at the BioTrans Analytical Platform are already using mass spectrometry with organoleptics (the study of sensory perception) to look at the chemical compositions that affect the sensory aspects of flavors, fragrances and metabolites. Koay and researchers at the Taste Receptor Platform want to expand their repertoire of cell system tests to examine sensates for thermoreception and chemical sensitivity.

Once useful molecules are found and demonstrated to be safe and scalable, Koay says, then commercial level production can be assessed by colleagues, such as Zhang.

MICROBE ENGINE FOR INDUSTRY

While synthesis is still the main source of chemicals for the food and fragrance industries, Zhang firmly believes that in the future, "biosynthesis will be on par with chemical synthesis." Meanwhile, he will continue to focus on three main areas: the discovery of new enzymes and novel metabolites, such as terpenoids (the aromatics used in many scents); enzyme engineering for improved activity, stability and selectivity; and building on fundamental understandings of biosynthesis.

Lindley agrees that there are big changes ahead. He says that even capability-building projects, such as their work on lycopene, always aim for twin outcomes: "to expand our knowledge base and technological toolbox, and also to search for applications that we believe will have industrial potential."

But the biggest challenge has moved quickly to implementation. The conditions used in industrial processes are often far from the evolutionary pressure that has guided microbial evolution over millions of years, says Lindley. The platform will be carefully evaluating "how robust our metabolically engineered microbes will be when we transfer them into industrial-scale fermentation strategies." It means the hard science

at BioTrans must be supported by practical industrial considerations, he says, including rational projections and responsive development strategies. The team will also seek to use industrial side-streams by converting by-products and wastes into other value-added products.

BioTrans, says Lindley, already has an edge in understanding and being able to exploit areas in which few laboratories have experience. "BioTrans was conceived as an industry-facing initiative, able to interact directly and resolve company problem statements efficiently and rapidly," he notes. "This gives us a clear competitive edge when we are discussing with companies their ambitious plans to put novel molecules on the market."

Singapore, he notes, is also ideally placed "to position itself as the hub for R&D aimed at the Asian consumer, and offers the opportunity to develop new molecules that may not be part of plans in the US or Europe." As a result, a new wave of Singapore-made, microbe-aided products are likely to hit the shelves in the near future.

"We have most of the world's leading food and cosmetics ingredients producers within a few minutes' drive from the lab and an equally rich diversity of nearby final end-user brand names," notes Lindley. Most, he says, are positioning themselves to service a growing middle class both in Asia and around the world, populations increasingly able to access information about the impacts of the ingredients they use, and willing to invest in healthy, sustainable and natural products. ★

1. Zhang, C., Chen, X., Lindley, N. D., Too, H. P. *et al.* A "plug-n-play" modular metabolic system for the production of apocarotenoids *Biotechnology and Bioengineering* **115**, 174–183 (2018)

2. Zhang, C., Seow V. Y., Chen, X., Too, H. P. *et al.* Multidimensional heuristic process for high-yield production of astaxanthin and fragrance molecules in *Escherichia coli* *Nature Communications* **9**, 1858 (2018)



UNPACKING THE POSSIBILITIES OF POLYMER SCIENCE

With a sound understanding of polymers, their properties and the methods to synthesize them, scientists can create novel materials for a wide range of practical applications.

From the DNA in living things to the plastics you use, a great many things in this world are made of polymers—individual chemical units strung together to form larger molecules with diverse shapes and unique properties.

For thousands of years, nature was the sole source of polymers that were of industrial utility and commercial interest. Cellulose and lignin, the two most abundant natural polymers, were essential for building and burning, while the silk threads produced by worms clothed royalty and led to the establishment of global trade routes, forever changing the economic trajectory of the world.

But by the 1800s, human civilization was no longer satisfied with what nature could provide. Seeking to enhance the properties of natural polymers or imbue them with new and useful characteristics, scientists and engineers began to make modifications to the materials at hand. By applying sulfur and heat to natural rubber, for instance, American chemist Charles Goodyear produced a stronger and more rigid polymer known as vulcanized rubber.

Then a more radical idea took root—what if we could produce polymers that had never been found in the natural world? The biological systems that produced natural polymers were, in essence, living, breathing vats of chemical reactions, so it may be possible to replicate some of that chemistry independently of life. The seminal work of German chemist Hermann Staudinger proved that possibility beyond doubt and paved the way for a systematic understanding of how synthetic polymers might be manufactured. Since then, polymer science has flourished as a formal research discipline, setting off a ‘Cambrian explosion’ of new polymers for various applications.

POWER TO THE POLYMERS

Scientists at A*STAR are adding to the ever-expanding repertoire of polymers with their research. One team, led by Shuo-Wang Yang at the Institute of High Performance Computing (IHPC), has invented a polymer that can convert changes in temperature into electrical energy—what is known as a thermoelectric (TE) material¹.

TE materials work by responding to temperature differences, which induce electric charge carriers to flow from the hot to the cold side of the material. An effective TE material needs to have high electrical conductivity, low thermal conductivity and a high ‘Seebeck coefficient’—the voltage generated per degree of temperature difference across the material. However, it is rare for any one material to satisfy all of these conditions, meaning that existing TE materials are limited in efficiency.

“One way of improving TE performance is to use doping, adding certain chemicals to the material to enhance its electrical conductivity by increasing charge carrier concentrations,” Yang explained. “However, doping can also interfere with the materials’ stability and performance, hence finding a dopant that works effectively is challenging. Identifying TE materials that work without doping could transform energy harvesting.”

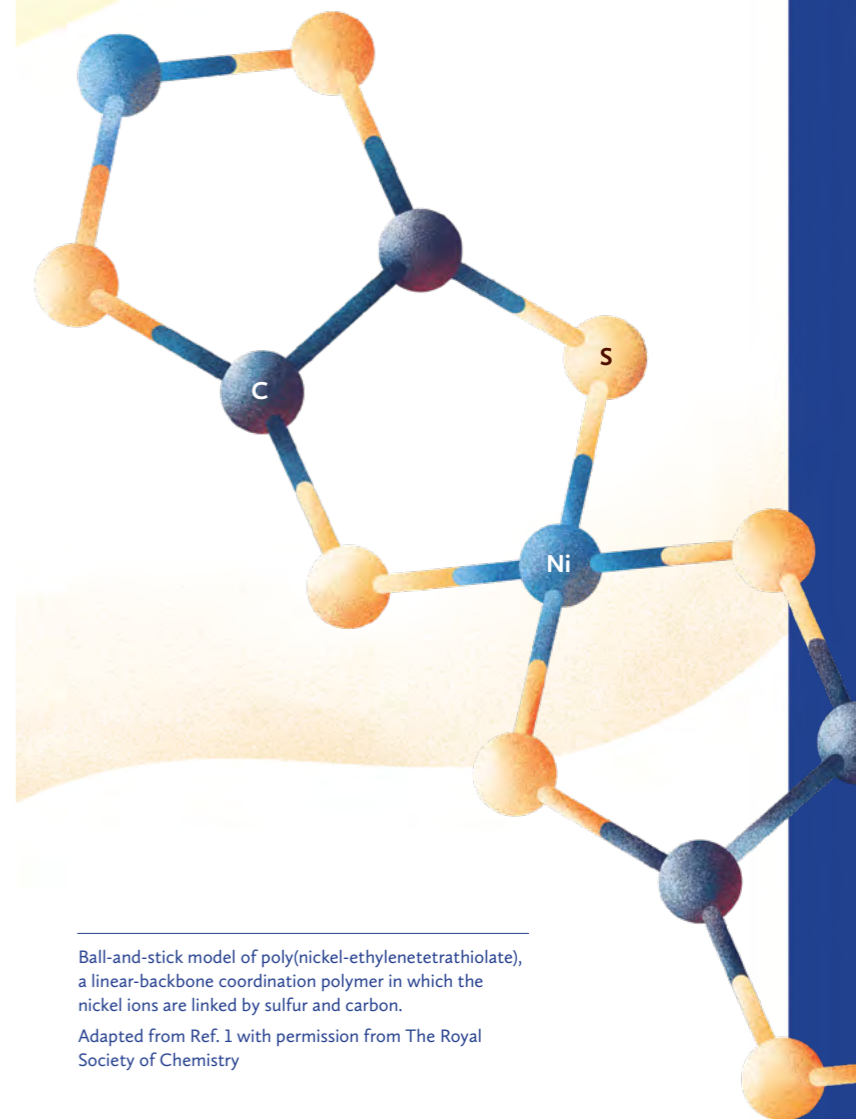
The team focused their attention on linear-backbone coordination polymers, structures containing metal ions linked by ligands, which can be built in the laboratory to specific designs. These polymers exhibit numerous advantages over conventional inorganic TE materials—they are flexible, have low thermal conductivity and are compatible with biological organisms. However, they have low electrical conductivity—a challenge that Yang and co-workers tried to overcome in their theoretical search.

“Based on first-principle molecular dynamics and structure optimization, we identified a polymer called poly(nickel-ethylenetetra-thiolate) and three associated

analogues which demonstrate intrinsically metallic behaviors and high electrical conductivity,” said Yang. “This is exciting as it suggests these polymers are potentially dopant-free TE materials.”

The team’s analyses suggested that the metallic behavior stems from the formation of dense, non-bonding molecular interactions between sulfur or selenium atoms within the polymeric structures. These interactions strengthen the forces between the atoms, decreasing electronic band gaps and encouraging the flow of electrical charge.

“Jianwei Xu, Kedar Hippalgaonkar and their teams at the A*STAR Institute of Materials Research and Engineering are now synthesizing these polymers,” Yang told *A*STAR Research*. “These materials are very promising, particularly in the applications of waste heat recovery and refrigeration near ambient temperature.”



Ball-and-stick model of poly(nickel-ethylenetetra-thiolate), a linear-backbone coordination polymer in which the nickel ions are linked by sulfur and carbon.

Adapted from Ref. 1 with permission from The Royal Society of Chemistry

A SURPRISING SOLUTION

Although research into polymer properties and products is important, processes to fabricate polymers simply and at scale are just as essential. Often, polymer synthesis involves the use of organic solvents or harsh conditions such as high temperatures or vacuum. This is in contrast to polymerization in nature, which takes place under ambient and aerobic conditions.

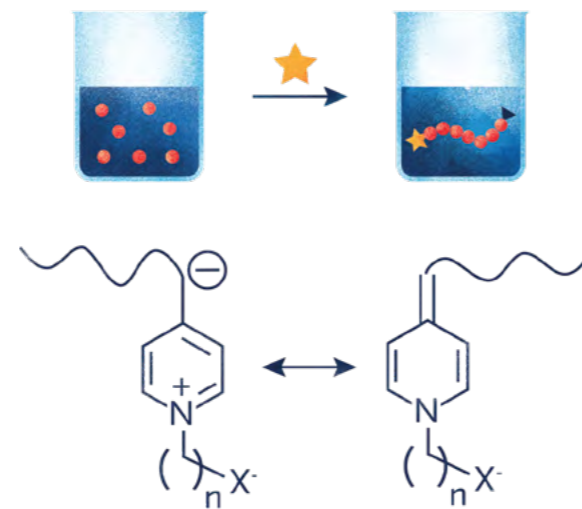
But now, a team led by Satyasankar Jana at A*STAR's Institute of Chemical and Engineering Sciences (ICES) has discovered a technique that allows them to grow polymer coatings made of zwitterions in water, at room temperature and in the presence of air². Zwitterions refer to molecules with both negative and positive charges, with a net charge of zero, that can assemble into long chains.

"It was a serendipitous discovery," Jana quipped. His team had been attempting to grow zwitterionic polymer coatings using a popular synthesis method called atom transfer radical polymerization, when they realized some reactions were not yielding the expected products. An amine, acting as a ligand on the catalyst used in the reaction, was unexpectedly found attached to the end of the polymer chains. "It took some time and a series of experiments to unfold the mystery of how it got there," Jana said.

Reaction kinetics observations, nuclear magnetic resonance spectroscopy and other analyses suggested that the amine kick-started the polymerization reaction via an anionic mechanism. These so-called anionic polymerizations are notoriously intolerant to water, methanol and air, but Jana's polymers were growing in the presence of all three, making the team doubt their findings. They eventually relied on computer models to understand what was going on.

"Density functional theory calculation results confirmed the proposed anionic polymerization mechanism," he said. "This is the first-ever example of an anionic solution polymerization of a vinyl monomer in aqueous media at ambient aerobic conditions."

His team has now used this approach to synthesize polymer coatings from four zwitterionic monomers and some other anion initiators, some of which are not amines. "In the future, we will use this methodology to generate anti-biofouling polymer coatings on large surface areas using a spray or dipping method," Jana noted, adding that such coatings could prevent harmful bacteria from attaching to medical devices, or inhibit mussels from adhering to ship hulls.



A*STAR scientists have devised a method to synthesize zwitterionic polymers in aqueous solution, at room temperature and in the presence of air, which could be used for the development of anti-biofouling coatings in the maritime and medical industries.

Adapted from Ref. 2 with permission from The Royal Society of Chemistry

DELIVERING ON A PROMISE

Although many polymers are used outside the body, recent research has unveiled classes of polymers that are biocompatible, which means that they are non-toxic and do not trigger adverse reactions when infused into living organisms. Improved synthesis methods have also allowed researchers to precisely control the size, shape, stability and function of such polymers. Alexander van Herk from A*STAR's ICES and Atsushi Goto from Nanyang Technological University are experts in this domain.

Together, they have created hollow polymer nanostructures that could serve as delivery systems for personal care products, drugs and chemicals used in agriculture³. There are two steps in their synthesis method, the first of which involves the polymerization of methylacrylic acid in the presence of iodine to make alkyl iodides. The poly(methacrylic acid) (PMAA) then initiates the polymerization of methyl methacrylate and the resultant formation of a block co-polymer comprising both PMAA and poly(methyl methacrylate) (PMMA). Sodium iodide is the catalyst in both stages.

Since PMAA is hydrophilic and PMMA is hydrophobic, the co-polymer self-assembles into hollow nanostructures in polar solvents such as ethanol and water. By varying the polymer proportions, van Herk and Goto could determine

"This is the first-ever example of an anionic solution polymerization of a vinyl monomer in aqueous media at ambient aerobic conditions."

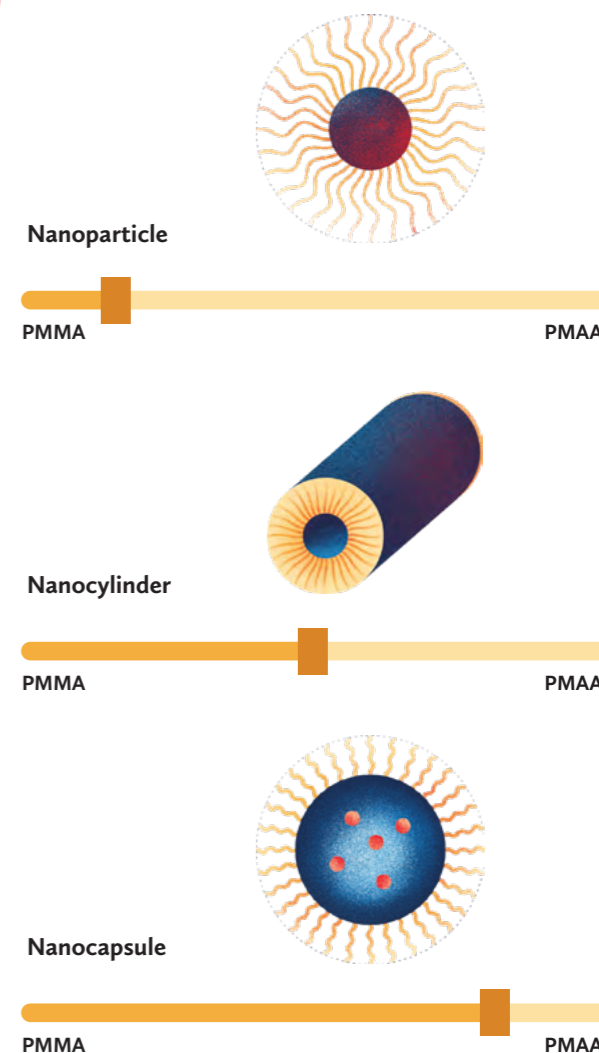
— Satyasankar Jana, Team Leader
A*STAR's Institute of Chemical and Engineering Sciences

the shape of the polymer nanostructures. The lowest ratio of PMMA to PMAA gave nanoparticles; boosting the PMMA content led to nanocylinders, then nanocapsules. The size and dimensions of the nanostructures could also be tweaked by varying the lengths of the two polymers.

The team also found that they could stabilize the nanostructures by including ethylene glycol dimethacrylate during the second polymerization step. "Crosslinking is important to 'freeze' the structure, to ensure it doesn't change during further handling," van Herk explained.

Going forward, the researchers plan to load their polymer nanostructures with active compounds such as vitamins and drugs, as well as test whether the nanostructures can deliver those compounds in a controlled manner. Their findings could pave the way for more effective treatments with fewer side effects.

Hence, like the individual chemical units that link up to give rise to polymers, new discoveries are constantly being added to the vast body of knowledge that is polymer science. With each new discovery, further possibilities and opportunities arise, waiting to be leveraged to improve lives and fuel economic growth. ★



ABOVE

Schematic of the various nanostructures that can be formed via reversible complexation-mediated polymerization and polymerization-induced self-assembly, depending on the ratio of PMMA and PMAA.

- Shi, W., Wu, G., Hippalgaonkar, K., Wang, J.-S., Xu, J. & Yang, S.-W. Poly(nickel-ethylenetetraolate) and its analogs: theoretical prediction of high-performance doping-free thermoelectric polymers. *Journal of the American Chemical Society*, **140**, 13200-13204 (2018).
- Jana, S., Klähn, M., & Parthiban, A. Nucleophile-initiated anionic polymerization of zwitterionic monomers derived from vinylpyridines in aqueous media under ambient aerobic conditions. *Polymer Chemistry* **9**, 3741-3753 (2018).
- Sarkar, J., Xiao, L., Jackson, A. W., van Herk, A. M. & Goto, A. Synthesis of transition-metal-free and sulfur-free nanoparticles and nanocapsules via reversible complexation mediated polymerization (RCMP) and polymerization induced self-assembly (PISA). *Polymer Chemistry* **9**, 4900-4907 (2018).

EVOLUTION

Biology of our ancient ancestor takes shape

Primitive microbes have cytoskeletal proteins that are structurally and functionally similar to those found in humans.

The recent discovery of a new lineage of microbes has overturned biologists' understanding of the evolution of complex life on Earth. Genomic studies of Asgard archaea revealed that they carry many genes previously thought to be found only in nucleus-bearing eukaryotes, suggesting they may be closely related to more complex life forms such as humans.

Two A*STAR scientists have now strengthened the case for this evolutionary scenario by showing that these small creatures have a dynamic network of cytoskeletal proteins, a feature that gives cells shape, and was previously thought of as specific to eukaryotes¹.

What's more, the A*STAR investigators found that one of these archaeal proteins,

profilin—that serves to bind and regulate the dynamics of a cytoskeletal protein called actin—had the same function as its counterpart in eukaryotes. The primordial profilin could even bind actin derived from a mammal.

“After around two billion years of divergent evolution, it is staggering that these proteins are compatible,” says Robert Robinson, a research director at the A*STAR Institute of Molecular and Cell Biology (IMCB), who led the study published in *Nature*.

Scientists in Sweden first identified Asgard archaea in 2015, from sediments taken deep below the Arctic Ocean, near a series of hydrothermal vents called Loki's Castle. Those microbes became known

as *Lokiarchaeota*, named after the Norse shape-shifting god, and every Asgard lineage found thereafter—as well as the word Asgard—gets its nomenclature from Norse mythology.

No Asgard archaea have yet been grown in the laboratory or observed under a microscope. So, Robinson and his graduate student Caner Akil took gene sequences encoding profilin proteins from a few Asgard lineages and inserted the DNA into an easily cultured bacterium. They then purified the profilins made by the bacterium and worked out the protein structures using X-ray crystallography.

Although these proteins shared little sequence similarity at the amino acid level with their eukaryotic counterparts, the researchers discovered that the overall shape of Asgard and human profilins were topologically alike—a sign of evolutionary links.

Robinson and Akil were not able to produce functional Asgard actin, profilin's binding partner, in their bacterial expression system. As an alternative, they used rabbit actin and tested whether Asgard profilin could bind to the actin and modulate its kinetics.

Indeed, the Asgard protein tethered and regulated the mammalian actin only slightly less efficiently than profilin from humans. These results indicate that Asgard archaea, unlike other organisms lacking a nucleus, harbor a primitive, but dynamic cytoskeleton, and thus probably shared a common ancestor with eukaryotes some two billion years ago.

“We are now comparing other eukaryotic-like Asgard proteins to the human counterparts,” Robinson says. “We hope to understand how the eukaryotic protein machineries became more sophisticated over time.” ★

1. Akil, C. & Robinson, R. C. Genomes of Asgard archaea encode profilins that regulate actin. *Nature* **562**, 439–443 (2018).

Photo credit: Christopher A. Salerno / Shutterstock



Asgard archaea can be found near underwater hydrothermal vents in the Arctic Ocean.



Photo credit: STILLFX / Shutterstock

ROBOTICS

Recognizing the right tool for the job

An algorithm gives robots an instinctive understanding of how to use tools.

A*STAR researchers working with colleagues in Japan have developed a method by which robots can automatically recognize an object as a potential tool and use it, despite never having seen it before.

For humans, the ability to recognize and use tools is almost instinctive. There are also many examples in which tool use seems hardwired into the brains of animals: some birds and primates use sticks or stones to obtain food, for example. One proposed reason for this neurologically embedded ability to use tools is that the animal's brain perceives the external object as an extension of its own body. Inspired by this idea, Keng Peng Tee and his colleagues

from the A*STAR Institute for Infocomm Research (I²R), along with Gowrishankar Ganesh from the CNRS-AIST Joint Robotics Laboratory located in Tsukuba, Japan, developed an algorithm that enables robots to recognize and immediately use tools that they have never seen before¹.

Previous research by Ganesh has indicated that the human brain recognizes a limb not just by its physical features, but by its functionality. Building on this insight, Ganesh and the A*STAR team proposed that a robot can recognize the potential of a tool by comparing its shape with that of its own hand and arm when used to achieve this same task. They wrote an algorithm

based on this idea and tested it by setting a robot the task of moving, without grasping, a disk to a desired end point on a table. This involved the robot either pulling the disk toward itself, pushing it away, or shifting it sideways.

“The robot is programmed with the ability to complete the task by itself, represented by a hand shape template,” explains Tee. “When the task cannot be completed, because its arms aren't long enough, for example, the robot is able to recognize a viable tool by matching the tool shape with the hand shape template.”

Thus, the algorithm enabled the robot to successfully identify when a task cannot be performed without a tool, to identify an unknown object as a potential tool, and then to use the tool to complete the task. “Next we will look into automatic learning of the features that represent existing skills, rather than pre-defining hand shape templates,” says Tee. ★

ABOVE

By learning a ‘hand shape template,’ robots get a better grasp of which tool to use to accomplish a physical task.

1. Tee, K. P., Li, J., Chen, L. T. P., Wan, K. W. & Ganesh, G. Towards emergence of tool use in robots: automatic tool recognition and use without prior tool learning. IEEE International Conference on Robotics and Automation (ICRA), 2018.

MICROBIOME

Gut feelings are not for everyone

Gut bacteria in fruit flies do not have a major influence on behavior.

Microbial communities residing within the gut have been implicated in several aspects of health and disease. The mammalian gut microbiome, for example, not only influences metabolic functions and immune responses, but has also been found to affect mood, cognition, pain and anxiety. However, a recent study by Singapore-based scientists has shown this is not the case for flies¹.

Adam Claridge-Chang, a neurogeneticist at the A*STAR Institute of Molecular and Cell Biology (IMCB) and the Duke-NUS Medical School in Singapore, uses vinegar flies to study cognitive and emotional behaviors. Curious about the role of the gut microbiome in brain development and its contribution to anxiety and autism, he launched a project exploring how the removal of gut bacteria affects a range of fly behaviors.

The project was carried out in collaboration with Joanne Yew at Temasek Life Sciences Laboratory and the National University of Singapore, and Joel Selkig at Nanyang Technological University.

“I met Joel by chance at a symposium. He said that, in mice, it was hard to get sufficient sample sizes to get a useful estimate of the effects of removing germs from an animal,” explains Claridge-Chang.

Realizing that the sample size problem could be overcome by using flies, Selkig and Yew developed a bleaching method to completely remove gut bacteria from

“It will be interesting to test whether other fly behaviors are affected by the microbiome.”

the flies. Using this technique, germ-free offspring could be maintained for two generations.

When Claridge-Chang and colleagues compared anxiety-associated behaviors in these germ-free flies to conventional flies that developed with gut bacteria, they found no significant differences. Furthermore, microbe removal had almost no effect on the flies’ sleep. Similarly, the microbiome appeared to have almost no effect on sexual attractiveness: germ-free female bodies were only mildly more attractive to courting males than those of conventional females.

“Although we were surprised by the lack of effect on fly behaviors, this is an important finding in light of reports showing

the influence of the microbiome on brain function in other species,” said Yew.

These findings suggest that the microbiota–gut–brain axis is not conserved between mammals and flies. The researchers speculate that to accommodate the high energy demands of a large brain, mammals may have to be more reliant on gut microbe-derived nutrients and thus, are sensitive to changes in the microbiome.

“It will be interesting to test whether other fly behaviors are affected by the microbiome, as it has a much simpler composition than in mammals and could easily be manipulated genetically to identify bacterial products that impact higher order functions,” explains Selkig. ★

ABOVE

The fruit fly is an ideal model organism for studying fundamental biological processes, including the potential link between the microbiome and behavior.

1. Selkig, J., Mohammad, F., Ng, S. H., Chua, J. Y., Tumkaya, T. *et al.* The *Drosophila* microbiome has a limited influence on sleep, activity, and courtship behaviors. *Scientific Reports* **8**, 10646 (2018).

Photo credit: Peter Yeates / Shutterstock



IMMUNOLOGY

Ready, steady, fuse!

White blood cells in different subsets have varying propensities to fuse in response to inflammation.

White blood cells, also known as monocytes, play a key role in the immune system’s response to infection. They have been shown to fuse and form multinucleated giant cells (MGC) during inflammatory reactions, or in response to introduced materials such as medical implants, but little is known about the mechanisms underlying the fusion process and its functional significance. A collaborative study has shown that different monocyte subsets have varying propensities to fuse in response to inflammation.

The study, led by Siew-Cheng Wong from the A*STAR Singapore Immunology Network (SIgN) and Peter Monk from the University of Sheffield in the UK, examined

the fusion capacity of three different human monocyte populations¹. By sorting cells using flow cytometry, they purified classical, intermediate and nonclassical monocytes, which are defined based on the proteins found on their surface. “These subsets have different activities in diseases such as tuberculosis and so we expected to see significant differences in their capacities to form giant cells,” says Wong.

Wong and colleagues found that upon exposure to ConA, a sugar-binding protein that stimulates the production of fusion-triggering pro-inflammatory molecules, intermediate monocytes were able to fuse faster than the other monocyte subsets. These intermediate monocyte-derived

MGCs were also larger than those derived from the other populations.

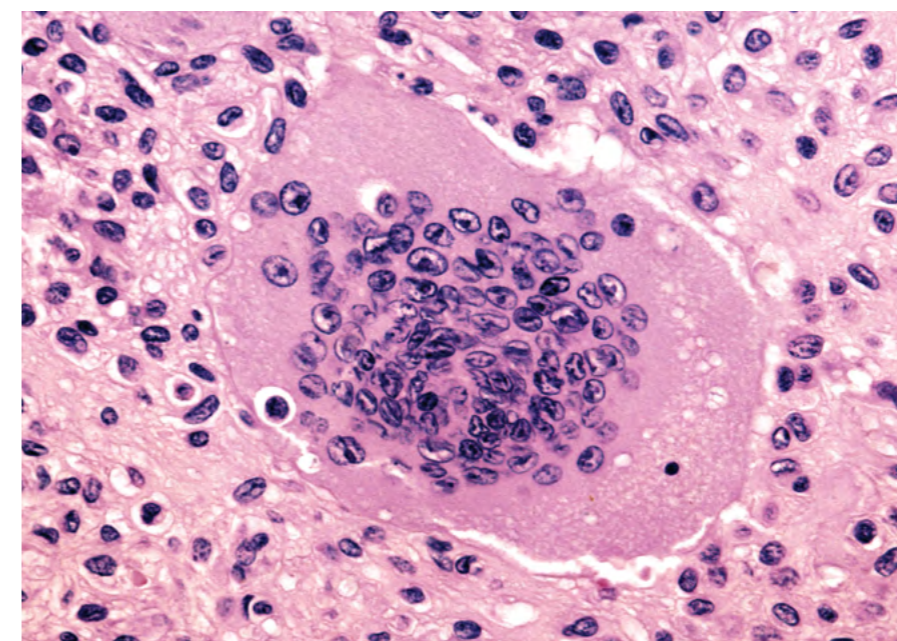
To determine what subset-specific factors could be influencing MGC formation in classical, intermediate and nonclassical monocytes, they examined the expression of various tetraspanins—proteins with four transmembrane domains that have been implicated in many membrane fusion events.

Although they were able to block intermediate monocyte cell fusion by targeting the tetraspanin CD63, they did not find a significant correlation between the expression of other tetraspanins and MGC formation. ConA exposure increased the production of the cytokine interleukin-1 in this subset, suggesting that pro-inflammatory signals contribute to the fusion process.

Analysis of other fusion-related membrane proteins showed that DC-STAMP, a protein with seven membrane-spanning domains that is involved in the maintenance of self-tolerance, was the only one that was expressed at significantly higher levels in intermediate monocytes than in both of the other subsets. The higher expression of DC-STAMP could be related to the greater fusion capacity of intermediate monocytes. The different propensity of monocyte subsets to fuse could have important implications for the treatment of disease and medical implant rejection. Further studies into different mechanisms of fusion in different contexts will help determine whether MGCs exacerbate inflammation or contribute to the removal of debris from tissues.

“By further understanding the fusion potential and mechanisms of monocyte subsets, we hope to learn how to harness these cells effectively to fight disease [and] prevent autoimmune reactions and medical implant rejection,” concludes Wong. ★

1. Champion, T. C., Partridge, L. J., Ong, S-M., Malleret, B., Wong, S-W. and Monk, P. N. Monocyte subsets have distinct patterns of tetraspanin expression and different capacities to form multinucleate giant cells. *Frontiers in Immunology* **9**, 1247 (2018).



Multiple monocytes fuse to give rise to a multinucleated giant cell during inflammatory reactions.

Photo credit: Jose Luis Calvo / Shutterstock

STEM CELLS

Making heart tissue ‘beat’

The key to efficient production of heart muscle from pluripotent stem cells lies in optimizing the density and replicative state of the starting material.

WHY THIS MATTERS

- Before stem cells can be used for regenerative medicine, specific treatments and procedures are needed to differentiate them into the appropriate cell type.
- Scientists have developed a protocol to consistently and efficiently generate heart muscle cells from stem cells.

The transformation of embryonic stem cells and their induced pluripotent counterparts into potentially limitless supplies of new heart tissue has been hindered by a lack of consistency from one stem cell line to the next, as well as a poor understanding of the differentiation process. Now, A*STAR scientists have shown that the key to efficient cardiac cell production lies in syncing the induction of differentiation with the cell cycle of the starting pluripotent material.

Although a widely used protocol for making heart muscle seems to work better with some stem cell lines than others, Steve Oh and his colleagues from the A*STAR Bioprocessing Technology Institute (BTI) found this same standard method can be made to work with all stem cells with high efficiency if the cells are first cultured at optimal densities and stages of the cell cycle ahead of cardiac induction¹.

“A stem cell bioprocess scientist, once understanding what to control, can differentiate any pluripotent stem cell line efficiently,” Oh says. “You must have actively cycling cells when you start differentiation—then efficiencies will increase.”

Discovering these lessons required Oh and his team to systematically try

differentiating five pluripotent stem cell lines into heart muscle tissue. The researchers varied the culture conditions and administered a drug that directs cells down a cardiac lineage. They found that cells grown in a less crowded environment and in the DNA-replicating or active division stages of the cycle responded favorably to the drug molecule and adopted a cardiac profile. By comparison, those lines with dense clusters of cells in the earliest quiescent phase of the cycle tended to die off in response to the drug treatment.

Individual stem cell lines are not locked into particular rhythms. By altering culture conditions or the timing and dose of the inducer drug, the researchers managed to devise protocols that worked reliably for each of the five lines.

The findings, says Oh, point to the need for scientists to fine-tune their differentiation methods based on the unique cell cycle profiles of their stem cell lines if they wish to obtain consistent, high-quality heart muscle cells in this way with an efficient yield. Their results could make it easier for researchers to study human heart development in a lab dish, discover new treatments for cardiac disease and, ultimately, develop new regenerative therapies for people with life-threatening heart problems. ★

RIGHT

Histological section of muscle cells, which can be derived from pluripotent stem cells.

IMPACT

With a reliable and renewable source of heart muscle cells, scientists can better understand human heart development and screen for drugs that can potentially treat cardiovascular disease.

1. Laco, F., Woo, T. L., Zhong, Q., Szmyd, R., Ting, S. *et al.* Unraveling the inconsistencies of cardiac differentiation efficiency induced by the GSK3β inhibitor CHIR99021 in human pluripotent stem cells. *Stem Cell Reports* **10**, 1851–1866 (2018).

Photo credit: Chokswatdikorn / Shutterstock



CANCER

New stem cell antibody targets cancer

An antibody that targets a protein on the surface of stem cells also binds to the same protein on some cancer cells.

An antibody that targets and is taken up only by certain types of cancer cells has been developed by A*STAR researchers. Combining this antibody with an anticancer drug could lead to a new treatment for some types of breast and ovarian cancers.

A team of researchers from the A*STAR Bioprocessing Technology Institute (BTI) wanted to develop monoclonal antibodies that could specifically target and kill cancer cells through one of a variety of potential mechanisms. Pluripotent stem cells and many cancer cells share some of the same proteins, called oncofetal antigens, on their surfaces. The researchers utilized this to develop monoclonal antibodies by injecting

human embryonic stem cells (hESCs) into mice, spurring their immune system into producing antibodies.

The team found that A19, one of the monoclonal antibodies produced, bound to Erbb-2, a receptor present on certain breast and ovarian cancer cells¹. Furthermore, the researchers noted that A19 not only bound to cancer cells' Erbb-2 receptors, but was also consumed by the cancer cells. The team wanted to test whether this process could be used for the targeted introduction of anticancer drugs into tumor cells.

They developed antibody-drug conjugates that were successfully taken up by ovarian cancer cells. The drugs were

“A19 could possibly be developed as an alternative or complementary treatment to Herceptin.”

released inside the cells, killing them, and reducing their overall numbers.

The team then implanted ovarian cancer cells under the skin of mice and injected the antibody-drug conjugates into their abdominal cavities. The tumor sizes were reduced by 60 percent in the treated mice compared to a control group.

Herceptin, another monoclonal antibody, is currently the gold standard for treating a specific type of breast and stomach cancer, called HER2-positive, and also binds to Erbb-2. The researchers found that A19 binds to a different form of Erbb-2 than Herceptin.

“A19 could possibly be developed as an alternative or complementary treatment to Herceptin,” says stem cell researcher Heng Liang Tan, the first author of this study. He noted that the drug would still need to go through toxicology testing and clinical trials.

Tan says the team hopes to collaborate with biotechnology companies to develop A19 into a clinically approved drug. They will also continue to use the same approach applied in this study to generate more antibodies that can be used as targeted therapies, or for diagnosing a variety of diseases. ★

ABOVE

Antibodies can be chemically linked to drug molecules to specifically target cancer cells in the body.

1. Tan, H. L., Yong, C., Tan, B. Z., Fong, W. J., Padmanabhan, J. *et al.* Conservation of oncofetal antigens on human embryonic stem cells enables discovery of monoclonal antibodies against cancer. *Scientific Reports* **8**, 11608 (2018).

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REGENERATIVE MEDICINE

Releasing the brakes on wound repair

A carefully defined balance of biomolecular signals stimulates healing by setting skin cells into motion.

After a flesh wound, skin cells march forward to close the gap and repair the injury. Findings from a team led by Leah Vardy at A*STAR's Skin Research Institute of Singapore (SRIS) now demonstrate how a carefully regulated set of molecular cues helps coordinate this healing migration¹.

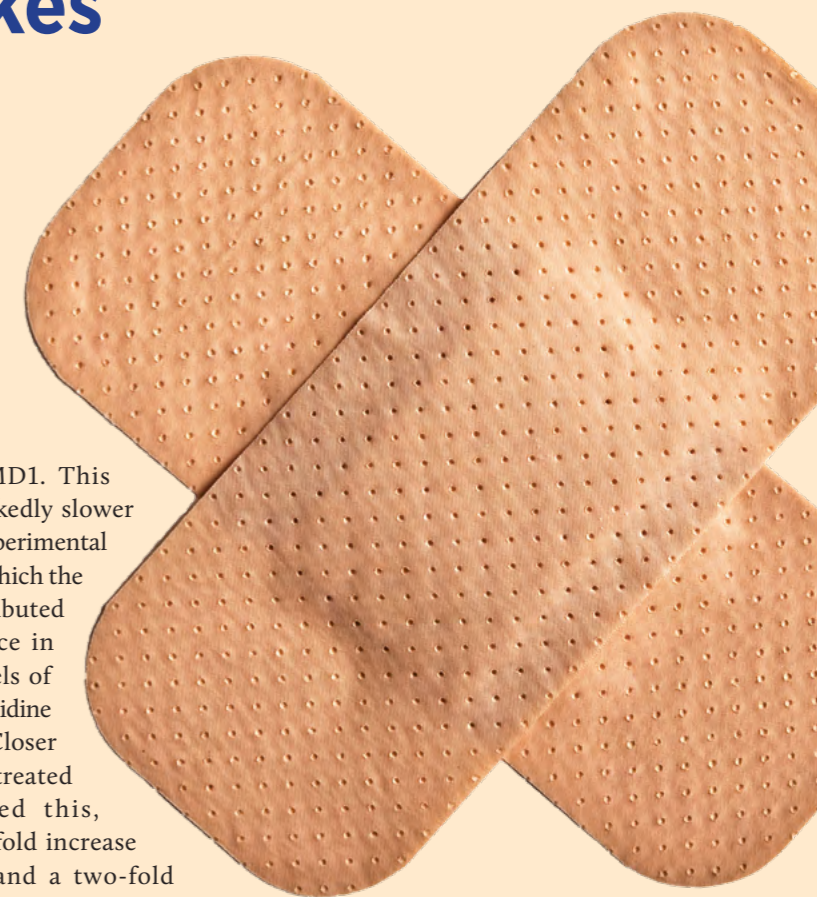
Vardy was particularly interested in a trio of organic molecules known as polyamines, which play a role in cellular proliferation. “They are well studied in cancer, but much less is known about how changes in their levels can drive normal cellular behavioral changes,” says Vardy. An enzyme called AMD1 facilitates the conversion of one polyamine, putrescine, into two other polyamines: spermidine and spermine. As this step is essential in determining the final balance of the three molecules within the cellular environment, Vardy's team examined what happens to AMD1 levels during wound healing.

To model skin damage, they put a scratch on a sheet of cultured human skin cells and observed a spike in AMD1 levels among cells near the edge of the wound within an hour of the injury. Although initially diffuse, AMD1 expression became more strongly focused within the outermost rows of cells over the next several hours. The researchers then subjected the cultured cells to a gene expression-modulating treatment that greatly reduced their ability

to produce AMD1. This resulted in markedly slower healing in the experimental wound model, which the researchers attributed to the imbalance in the relative levels of putrescine, spermidine and spermine. Closer analysis of the treated cells confirmed this, revealing a 2.7-fold increase in putrescine and a two-fold reduction in spermine levels, while spermidine levels remained relatively unchanged.

Strikingly, when Vardy and colleagues compensated for this imbalance by adding spermine back to the damaged skin cell cultures, they observed a clear increase in the rate of wound closure. “Low putrescine and high spermine levels are required for cell migration at the wound edge,” explains Vardy. They further determined that these polyamines appear to coordinate a reorganization of the cytoskeletal proteins that provide the infrastructure for cell migration during the wound healing process.

Vardy believes that this process may be disrupted in patients whose wounds won't heal after injury, and she is now looking into the potential for polyamine-based



therapeutics for wound care. “We are currently addressing the mechanism by which spermine promotes cell migration,” she says, “and working with clinicians here in Singapore to determine how polyamine levels are altered in non-healing wounds.” ★

ABOVE

A*STAR researchers have found that the ratio of three polyamines—putrescine, spermidine and spermine—regulates skin wound healing.

1. Lim, H. K., Rahim, A. B., Leo, V. I., Das, S., Lim, T. C. *et al.* Polyamine regulator AMD1 promotes cell migration in epidermal wound healing. *Journal of Investigative Dermatology* **138**, 2653-2665 (2018).

BLACK PHOSPHORUS

Wrinkles take the heat

Experiments on nanoribbons of black phosphorus reveal the origins of directional heat transport.

Single atomic sheets of black phosphorus are attracting attention for their potential in future electronics applications. A*STAR researchers have now completed experiments at the nanoscale to unlock the secret of this material's remarkable directional heat transport properties¹.

Black phosphorus has a layered honeycomb atomic structure that gives it some exotic physical and electronic properties. Its honeycomb lattice is not planar, but wrinkled, and its physical properties differ depending on whether they are measured across or along the wrinkles. Heat, for example, is transported

about twice as fast in the wrinkle or 'zigzag' direction compared with across the wrinkles, or the 'armchair' direction. Jing Wu and colleagues at the A*STAR Institute of Materials Research and Engineering (IMRE) used their state-of-the-art experimental facilities to discover the reason for this very unusual status.

"The strong anisotropy of heat transport in black phosphorus has been theoretically attributed to the dispersion or relaxation of lattice vibrations known as phonons, but the exact origin was unclear," says Wu. "Understanding this mechanism could help us better control heat flow in

nanoelectronic devices, which would be very useful in chip design for better heat dissipation."

The team started with the premise that the traveling velocity of phonons is equivalent to the speed of sound in a material, which in turn has a well-defined relationship to the material's stiffness. They used their expertise in high-precision material measurements to set up an experiment that allowed them to measure both heat transport and stiffness in the same system, using black phosphorus nanoribbons with either a zigzag or armchair orientation.

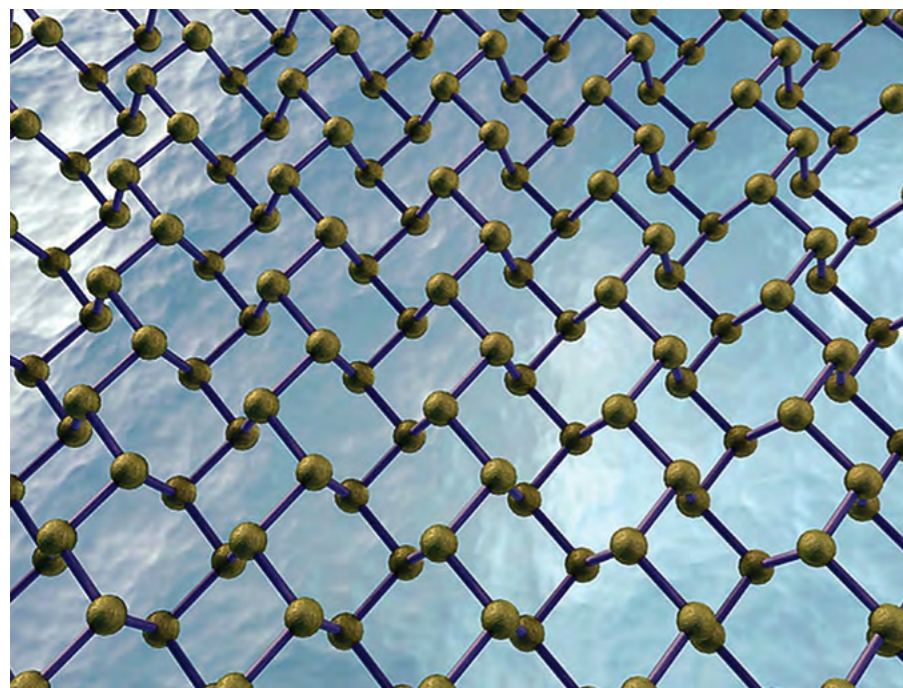
"Probing the heat transport and stiffness of the nanoribbons was very challenging," says Wu. "We fabricated two orientations of nanoribbons by using electron-beam lithography on a thin film of black phosphorus. We then picked up the nanoribbons using nano-manipulators under a scanning electron microscope, and transferred them to our lab-built micro-electro-thermal system where they were tested using an atomic force microscope. These are techniques we have been developing and using for more than eight years."

These experimental measurements confirmed a physical link between the thermal transport and a measure of stiffness, known as the Young's modulus, providing the first direct information on the origin of phonon transport anisotropy in black phosphorus.

"The ratio of thermal conductivity between the zigzag and armchair nanoribbons is almost identical to the ratio of the corresponding Young's modulus values and corresponds to the relationship theorized by first principles calculations," says Wu. ★

1. Zhao, Y., Zhang, G., Nai, M. H., Ding, G., Li, G. *et al.* Probing the physical origin of anisotropic thermal transport in black phosphorus nanoribbons. *Advanced Materials* **30**, 1804928 (2018).

Photo credit: Robert Brook / Science Photo Library



Understanding the basis of heat transport in black phosphorous could lead to better control of heat flow in nanoelectronic devices.

LUPUS

From suspected instigator to unlikely hero

A*STAR researchers have revealed the mechanism behind the way receptor TLR-9 protects against lupus.

When the pathogen-sensing intracellular receptors TLR-7 and TLR-9 were implicated in systemic lupus erythematosus (SLE), it was suspected that their removal would lessen the severity of the disease. However, while this held true for TLR-7, removing TLR-9 in mice unexpectedly caused severe SLE with an inflammatory kidney disease called glomerulonephritis.

"Everyone was scratching their heads: all the signs of autoimmunity were there but no one had any idea why it happened," recalls A*STAR's Anna-Marie Fairhurst. The two receptors share similar expression and signaling patterns, and their aberrant expression is implicated in SLE, but their absences caused opposite effects.

Fairhurst's team at A*STAR's Singapore Immunology Network (SIgN) has now revealed the stabilizing action of TLR-9, and how its depletion boosts pathogenic levels of TLR-7 which leads to the production of antibodies that act against the body's own genetic material¹.

SLE is an autoimmune disease—a condition in which a person's immune system turns on its host's own cells and

tissues. SLE's exact causes aren't fully understood, however, it is thought that a combination of inherited risk factor genes and a trigger—such as an infection—could precipitate it.

In their paper, published in *Arthritis and Rheumatology*, Fairhurst and her team explain that, in SLE, complexes of host-attacking antibodies and genetic material embed in organs and cause irreversible damage. When these complexes activate infection-sensing toll-like receptors (TLRs), the result is an exacerbating and damaging inflammatory response.

"It's the anti-RNA antibodies coming together with TLR-7 on dendritic cells to really drive inflammatory events that slowly, but surely, destroy the kidney."

The researchers bred lupus-prone, TLR-9 deficient mice to establish the impact. The mice exhibited a systemic increase in TLR-7, including within the immune system's dendritic cells. Dendritic cells with increased TLR-7 expression infiltrated the kidneys, where TLR-7 played an initiative role in the development of glomerulonephritis.

Mice lacking TLR-9 also developed increased autoantibodies that targeted a form of genetic material known as RNA, a nucleic acid involved in carrying instructions from DNA to control protein synthesis. Fairhurst's team report in their paper that this loss of 'tolerance' to a host's own RNA is thought to be a key stage in the transition to active autoimmune disease.

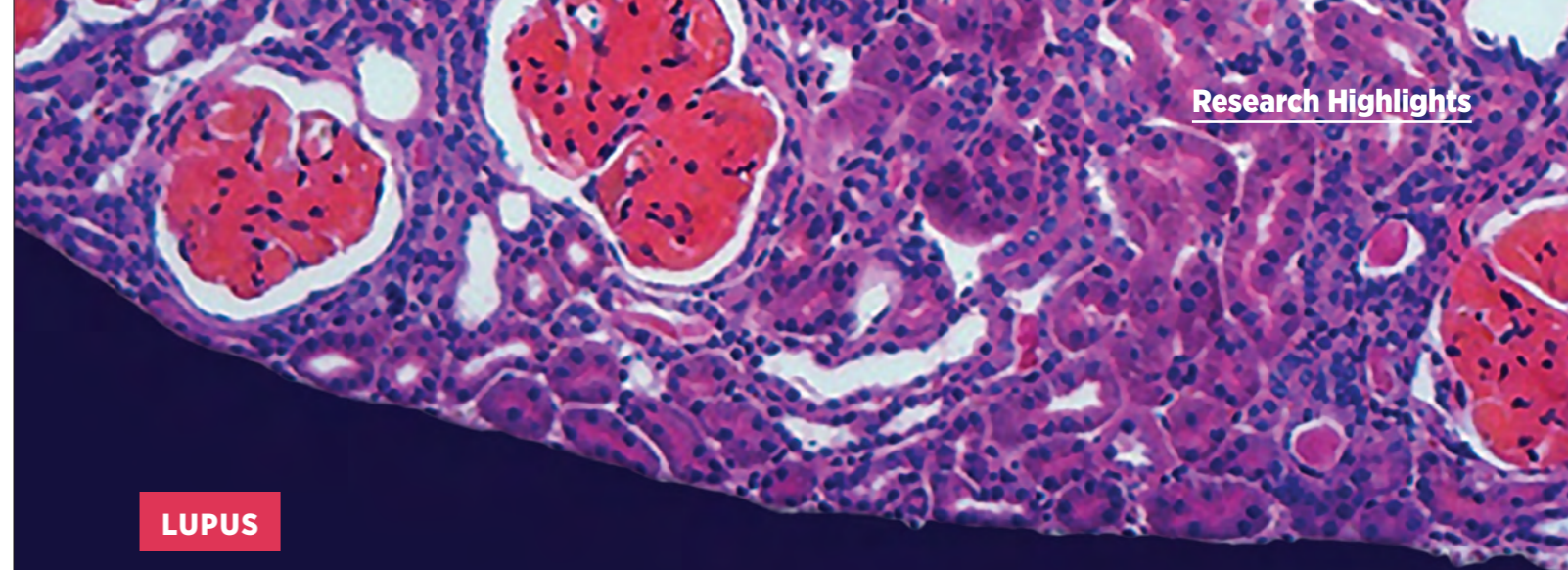
"It's really two things coming together. It's the anti-RNA antibodies coming together with TLR-7 on dendritic cells to really drive inflammatory events that slowly, but surely, destroy the kidney," says Fairhurst.

"This research points to targeting this pathway for patients with lupus," she adds. ★

ABOVE
Kidney damage can occur in patients suffering from systemic lupus erythematosus, and researchers still do not fully understand the underlying molecular mechanisms.

1. Celhar, T., Yasuga, H., Lee, H. Y., Zharkova, O., Tripathi, S. *et al.* Toll-Like Receptor 9 deficiency breaks tolerance to RNA-associated antigens and up-regulates Toll-Like Receptor 7 protein in *Sle1* mice. *Arthritis & Rheumatology* **70**, 1597-1609 (2018).

Photo credit: Steve Gschmeissner / Science Photo Library



MATERIALS

Ceramic holds promise for greener optical devices

Scientists have developed an environmentally friendly ceramic material.

WHY THIS MATTERS

- Lanthanum-modified lead zirconate titanate is one of the most widely used electro-optic ceramics, but the lead contained in the material can cause environmental harm.
- Lead-free versions of the material would pave the way for greener optical sensors and switches.

A lead-free ceramic that could be used in applications ranging from optical sensors and switches to creams for protecting against ultraviolet (UV) light has been developed by A*STAR researchers.

Ceramics made from potassium sodium niobate (KNN) are promising alternatives to lead-based ceramics in electro-optical applications. However, it is both challenging and costly to improve KNN’s performance by ensuring it has a high density, fine-grained, chemically uniform microstructure.

Known as PLZT, lanthanum-modified lead zirconate titanate is one of the most widely used electro-optic ceramics. Yet, there are serious ecological concerns regarding toxicity to the environment and living organisms once devices made with it are discarded. As PLZT contains around 60 percent of lead (by weight), the search is on to find lead-free replacements for PLZT.

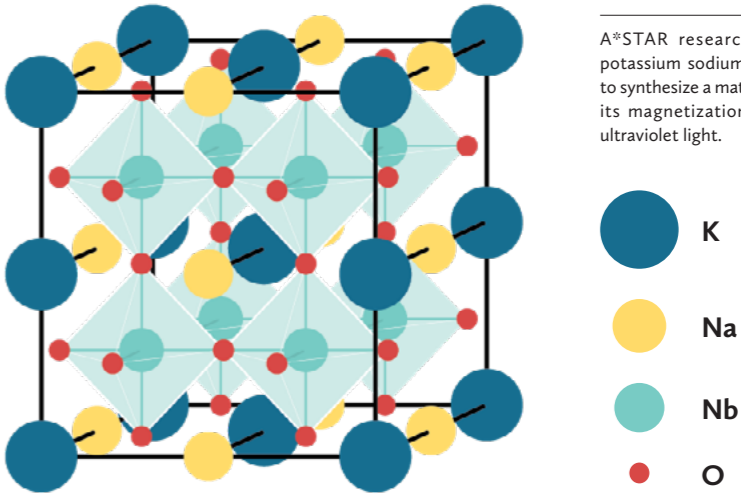
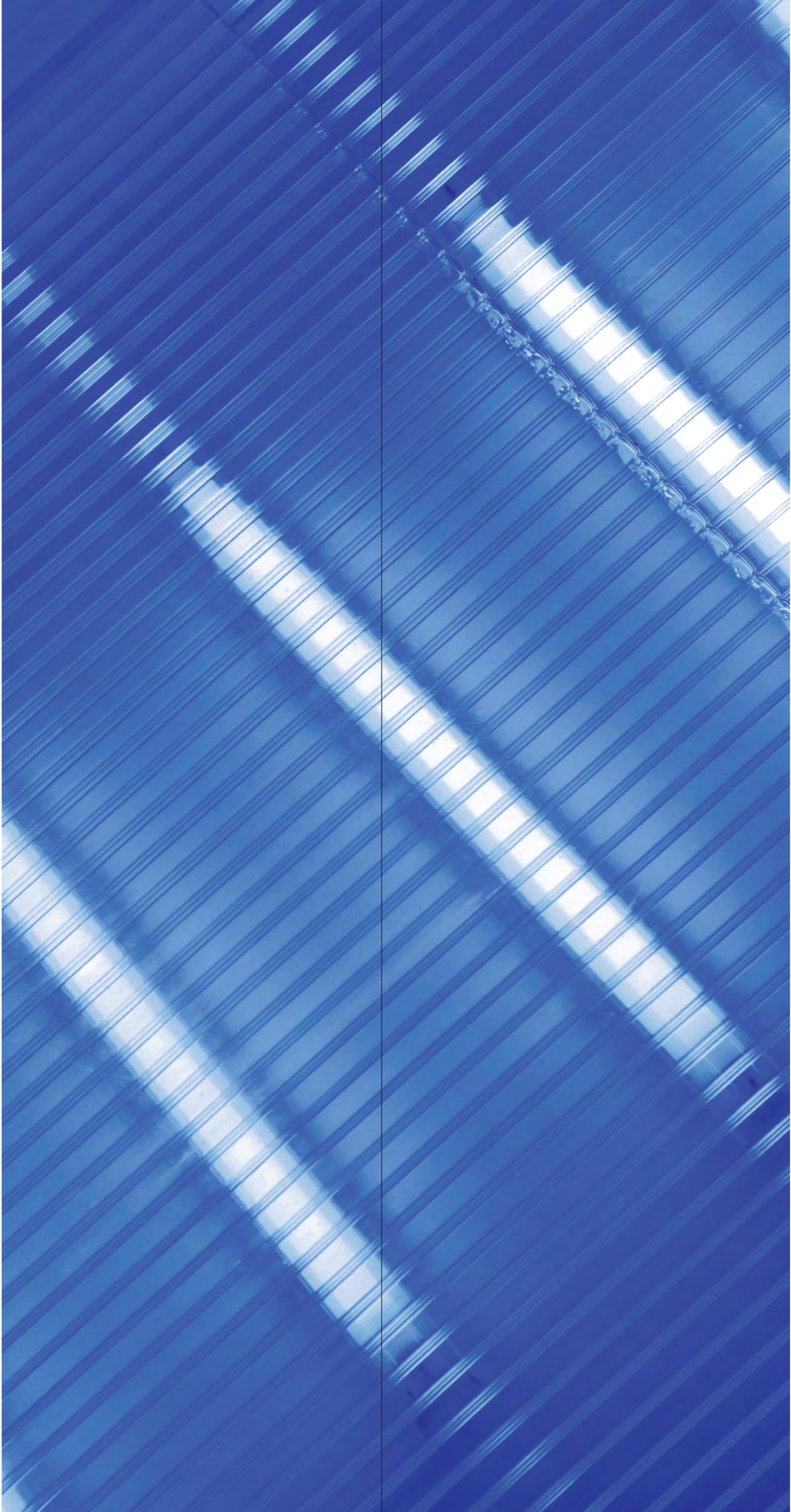
Santiranjan Shannigrahi, and his colleagues from A*STAR’s Institute of Materials Research and Engineering (IMRE) and Institute of High Performance

Computing (IHPC), have developed a method for making a KNN-based ceramic material that has the potential for replacing PLZT¹.

“Developing a lead-free, stable ceramic for practical applications was our key aim,” explains Shannigrahi. “For some time now KNN has shown promise as a potential alternative to PLZT, but KNN-based ceramics suffer from a number of intrinsic issues, such as the low density of large, cube-shaped particles that allow moisture to be absorbed, making them unstable and therefore unsuitable for practical use.”

The KNN crystals are modified into nano-sized, nearly spherical particles arranged in a perovskite lattice arrangement. Potassium and sodium ions are located at the corners of the cubed-shaped lattice, oxygen ions at the faces, and niobium ions at the center. The researchers then replaced a proportion of the niobium ions with lanthanum ions, changing the crystal size and structure and creating a completely new material whose magnetic and optical properties can be tuned when exposed to UV.

Photo credit: Evannovostro / Shutterstock



A*STAR researchers have used potassium sodium niobate crystals to synthesize a material that changes its magnetization in response to ultraviolet light.

The new material completely absorbs UV light when illuminated, turning into a deep blue color. This is accompanied by a significant increase in magnetization. Interestingly, it returns to its original color and magnetization once illumination ceases.

“These modifications produced a semitransparent ceramic with nano-sized, spherical particles with a density of approximately 98 percent of the theoretical potential,” says Shannigrahi.

The new material could be used in a range of applications, including powerless UV sensors, optical switches and detectors, and for UV protection in sunscreens.

“Our work could lead to a more environmentally friendly alternative to PLZT, and we are now engaging industrial partners for further development,” says Shannigrahi. ★

IMPACT

Potassium sodium niobate crystals could replace environmentally toxic PLZT in electro-optic devices.

LEFT

Ultraviolet light is a double-edged sword, useful for optical and electronic applications but potentially harmful to health.

1. Shannigrahi, S., Khoong, H. K., Laskowski, R., Chee, K. I. T., Sharma, M. *et al.* Lead-free perovskite ceramics with ultraviolet-tunable optical and magnetic properties at room temperature. *Journal of Applied Physics* **123**, 234901 (2018).

BIOCHEMISTRY

Finding a stinky source

Newly discovered enzyme uses an unusual mechanism to generate a molecule with an eye-wateringly awful smell.

The malodorous molecule—skatole—that gives animal manure its repugnant stench is so potent that the human nose can detect it in the air at a concentration threshold of just 0.00056 parts per million. Bacteria living in the gut of animals, including humans, produce skatole by breaking down indoleacetate, which itself is a breakdown product of tryptophan, an amino acid from dietary protein. The bacterial enzyme that converts indoleacetate into skatole has never been identified, although the enzymes that break down related aromatic amino acid metabolites are known.

Now, the skatole-producing enzyme has been found by an international research team, co-led by Huimin Zhao at the A*STAR Institute of Chemical and Engineering Sciences (ICES)¹. “We are interested in identifying new enzyme-catalyzed chemical reactions in nature and exploring the corresponding enzymes for practical applications,” said Zhao.

The team relied on comparative genomics in their search for the enzyme. “We were fortunate that the genome sequences of two skatole-producing bacteria were already available in public databases,” adds Yifeng Wei, a member of Zhao’s team at A*STAR.

The researchers compared the genes of the two bacteria, looking for unknown enzymes that both species possessed, related to enzymes known to break down other aromatic amino acid metabolites. They quickly identified a candidate enzyme in the genetic data, and a biochemical assay confirmed the enzyme’s ability to convert indoleacetate into skatole.

Away from the oxygen-free environment of the gut, the indoleacetate decarboxylase enzyme required careful handling. “The most challenging part of this project, conducted mainly by our collaborators in Tianjin University, was the biochemical characterization of the oxygen-sensitive enzyme,” Zhao says. To ensure it remained active, the enzyme had to be kept and handled in a glove-box, under oxygen-free conditions, at all times.

Identifying indoleacetate decarboxylase has many potential practical applications, Zhao says. The enzyme’s genetic sequence can be used as a marker to identify skatole-producing organisms. “Once identified, steps can be taken to eliminate or replace these organisms, or to create conditions that suppress their specific skatole-producing metabolism,” Zhao says. The applications extend far beyond agriculture. “We noticed that this enzyme is present in certain sequenced human oral bacteria, which could provide an avenue to treat certain aspects of bad breath,” adds Wei. Mosquitoes that carry human diseases such as Japanese encephalitis and West Nile virus are also known to be attracted by skatole.

Furthermore, the gut—an oxygen-free environment—is potentially a rich source of enzymes possessing unique biochemical reactivity involving highly reactive ‘free radical’ intermediates. Therefore, the team next plans to study the free-radical mechanism for indoleacetate decarboxylation in more detail, and characterize other enzymes in the skatole-producing metabolic pathway, Zhao says. “In the long-term, we plan to continue discovering new enzymatic free-radical chemistry in environmental and human gut bacteria.” ★

1. Liu, D., Wei, Y., Liu, X., Zhou, Y., Jiang, L., *et al.* Indoleacetate decarboxylase is a glyceryl radical enzyme catalysing the formation of malodorous skatole. *Nature Communications* **9**, 4224 (2018).

BELOW

Skatole is responsible for the unpleasant stench of manure. A*STAR scientists now know which enzyme produces the foul compound.



Photo credit: shurkin_son / Shutterstock

CANCER BIOLOGY

Drug resistance in the hot seat

Thermal stress elicits genomic changes that can make cancer cells resistant to chemotherapy.

Harsh treatments that fail to eliminate tumors can make them more resilient, a new A*STAR study finds¹. Elevated temperature, nutrient deprivation or other environmental stressors can cause cancer cells to acquire large-scale genomic changes, some of which make them resistant to the drugs commonly used in cancer care.

Chromosomal abnormalities are a hallmark of most tumors, and genetic mutations can lead cancer cells to develop growth differences, survival advantages, or increased resistance to therapeutic pressures. Working with human colon cancer cell lines, Giulia Rancati and her team at the Institute of Medical Biology (IMB) induced changes in chromosomal numbers in three different ways.

The investigators blasted the cells with an extra five degrees Celsius of heat

(compared with normal culture conditions) for a few hours every day. Separately, they starved the cells of fetal cow serum, an essential supplement for cellular growth, for days. They also maintained another batch of cells at oxygen concentrations well below healthy levels.

All three culture conditions elicited strong stress responses in the cells, which led to defects in cell division. Consequently, when a cancer cell splits in two, pairs of matching chromosomes failed to sort properly.

This problem was most pronounced in cells exposed to heat stress, and the researchers found that the shock of the added temperature impaired a molecular safeguard that normally ensures faithful chromosome transmission during cell division. As a result, cells failed to separate, despite having already doubled their

genomes, generating a ‘super-cell’ with twice the usual number of chromosomes—a condition known as tetraploidy.

The A*STAR team, which included Zhihao Tan from the Genome Institute of Singapore (GIS), and Norman Pavelka from the Singapore Immunology Network (SIgN), grew both the tetraploid super-cells and the normal diploid cells in lab dishes containing various chemotherapy medications. Compared to the cells with the usual chromosome count, the super-cells—which contain more DNA—persisted at greater concentrations of doxorubicin, and in the presence of drugs such as bleomycin and daunorubicin, that would otherwise have proven deadly.

Many cancer clinics around the world perform a kind of ‘thermal therapy’ in which heat is applied locally, regionally or to a patient’s entire body to enhance the effects of radiation or drug treatment. However, the data from the new study suggest that thermal therapy can backfire for patients under certain circumstances. Because of the heat stress, Rancati says, “there might be cells that are able to survive the treatment, change their genome and become resistant.”

One solution may be to add a drug that blocks cell division to the mix to negate the potential for genome doubling presented by the thermal pressure. Ultimately, however, heat regimens will have to be re-evaluated in light of the risk revealed by the A*STAR scientists. Rancati next hopes to confirm the findings from her cellular investigations in mouse models of cancer. ★

ABOVE

When grown at elevated temperatures, cancer cells fail to segregate their genetic material properly during cell division, with implications for chemotherapy resistance.

1. Tan, Z., Chan, Y. J. A., Chua, Y. J. K., Rutledge, S. D., Pavelka, N. *et al.* Environmental stresses induce karyotypic instability in colorectal cancer cells. *Molecular Biology of the Cell* **30**, 42–55 (2019).

QUANTUM OPTICS

A tip for future nanoscale sensing

The tiny diamond pyramid tips used for atomic force microscopy may also prove to be highly useful for nanoscale, quantum sensing.

The idea of using ‘color centers’—optically-active atomic defects in diamond—as a probe for taking highly sensitive nanoscale measurements of quantities such as electromagnetic field, temperature or strain is well known. In practice, however, these experiments often required the expensive fabrication of custom-designed diamond nanostructures. Furthermore, it is a challenge to collect the very weak optical signal that the color centers produce.

Now, a study published by Victor Leong and colleagues from A*STAR’s Institute of Materials Research and Engineering (IMRE) and the Institute of High Performance Computing (IHPC), suggests that the use of commercial pyramid-shaped diamond atomic force microscopy (AFM) tips that contain silicon vacancy centers could help¹. The approach has several advantages.

Firstly, the team’s experiments with a confocal microscope and diamond tips

arranged in different orientations show that the pyramid shape of the diamond tip acts as a highly efficient collector of the weak infrared (738 nanometer) photoluminescence generated by the color center. Due to geometric effects, a larger portion of the emitted photoluminescence was channeled to the base of the pyramid,

“We plan to deploy these tips in practical nanosensing applications. Current ideas include nanoscale magnetic sensing and surface studies.”

resulting in a signal of up to eight times stronger than in other directions.

“In many nanosensing applications, the signal is inherently very weak, and this poses a fundamental limit to the sensitivity,” explained Leong. “The ability to collect and detect a larger signal improves many performance metrics such as minimum detectable signal, resolution and measurement time, for example.”

Secondly, the diamond tips used in this study are commercially available and compatible with AFM and microscope equipment, offering a path to practical implementation. “These off-the-shelf diamond AFM tips are easily available and inexpensive. They cost around SGD 100 each,” commented Leong. “The lower cost and easy availability could help promote the rapid development and uptake of quantum technological applications.”

The extremely small size of the diamond tips, which have a tip radius of approximately 10 nanometers and length of around 15 micrometers, means that they can be brought extremely close to the sample to be studied, maximizing measurement sensitivity and spatial resolution. To date, the team has focused on investigating diamond tips featuring silicon vacancy color centers, but Leong says that it is possible to also introduce nitrogen vacancy color centers which are popular in magnetometry studies.

Now that the team has shown that enhanced optical readout is possible from the diamond tips, the next stage of the research will be to optimize performance and then perform some actual sensing experiments. “We plan to deploy these tips in practical nanosensing applications. Current ideas include nanoscale magnetic sensing and surface studies,” said Leong. ★

ABOVE

Diamond atomic force microscopy tips allow for high measurement sensitivity and spatial resolution when analyzing the surface properties of materials.

1. Choi S., Leong V., Alagappan G. & Krivitsky L. Enhancing optical readout from diamond AFM tips for quantum nanosensing *ACS Photonics* **5**, 4244–4248 (2018).

Photo credit: optinaric / Shutterstock

SCIENCE POLICY

A decline in gene discoveries

The rate of discovery of human gene functions has fallen significantly.

The number of papers reporting new protein-function discoveries in 2017 declined by two-thirds compared with output in 2000, according to research led by A*STAR¹.

While the Human Genome Project has made the entire human genetic code available to researchers, making sense of this vast trove of data is challenging.

“For many biologists, the discovery of a gene function completely changes their lives—it is their main scientific achievement,” says Frank Eisenhaber, director of A*STAR’s Bioinformatics Institute (BII), who led the study.

The BII team, together with Lars Juhl Jensen from the University of Copenhagen, wanted to explore how the rate of new gene structure and function discoveries changed between 1901 and 2017 by looking at how many papers and patents appeared in the biomedical literature describing previously unknown gene and protein-function discoveries.

To do this, they came up with a score, called a ‘full publication equivalent’ or FPE, representing the published equivalent of one whole paper dedicated solely to a single genomic entity, be it a gene, a protein, or a non-coding RNA.

Overall, they found references to 17,824 human proteins and 2,641 human

noncoding RNAs in the literature over that period. Of these proteins, 1,610 proteins (nine percent) scored more than 500 FPEs and accounted for 78 percent of all relevant papers published. Some of the most frequently mentioned proteins included insulin, serum albumin, tumor necrosis factor and p53.

A further 16 percent of the literature was dedicated to another 3,207 proteins (18 percent of the total), which scored between 100 and 500 FPEs. Just over one-third of all proteins mentioned in the literature—6,439 genomic entities—had 10–100 full FPEs. But only six percent of the literature was left to cover more than 13,000 genomic entities.

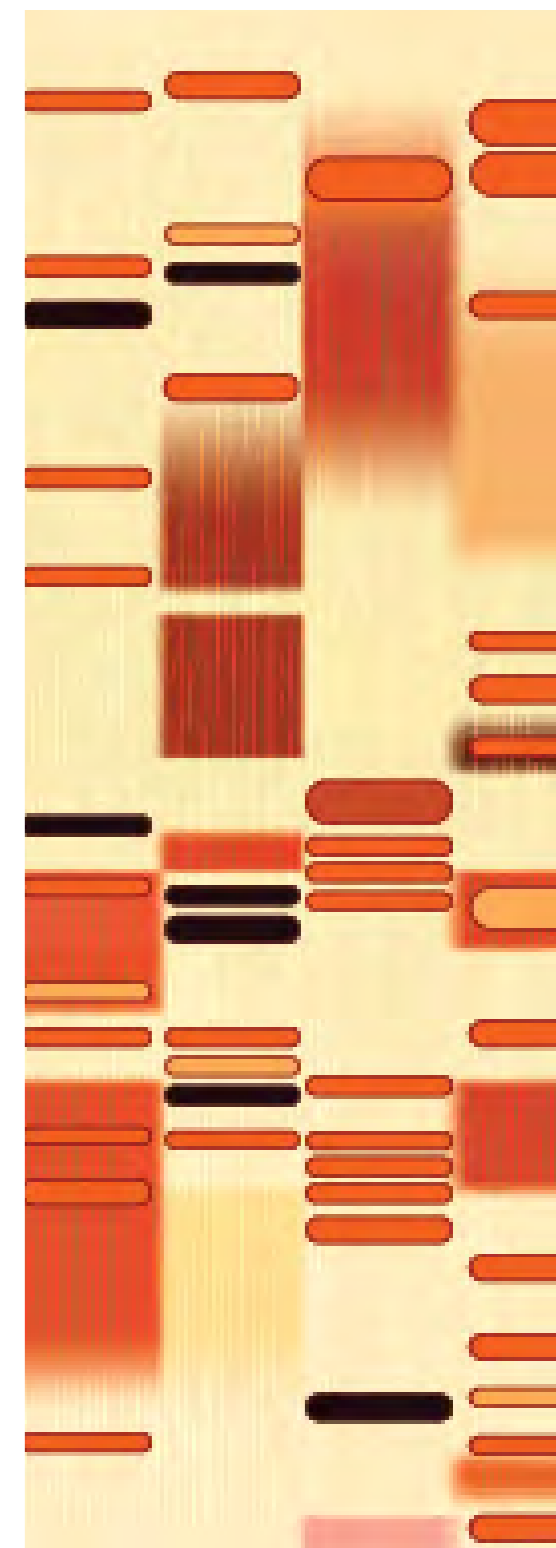
The rate of protein function discoveries over time steadily increased from 1980–2000, such that by the year 2000, there were around 500 new protein names being reported in the literature each year.

Then in 2000, things changed. Despite the fact that the draft human genome sequence became available in 2001, which should have made genomic discoveries easier, the publication rate underwent a sustained decline. In 2017, the number of genes appearing in the literature for the first time was one-third of the number of genes that appeared in the literature in 2000.

“That’s a huge drop,” Eisenhaber says. “And since function discoveries mainly come from elite institutions, it means they are also affected on a great scale, and that this is a worldwide phenomenon.”

He suggests that the decline in new gene and protein publications may be the result of a diversion in research funding from core budgets towards more short-term, grant-based funding, as well as shorter contracts for academic and research staff. ★

1. Sinha, S., Eisenhaber, B., Jensen, L. J., Kalbuajji, B., & Eisenhaber, F., Darkness in the human gene and protein function space: Widely modest or absent illumination by the life science literature and the trend for fewer protein function discoveries since 2000. *Proteomics* **18**, 1800093 (2018).



An illustration of DNA fragments separated by electrophoresis. Despite advances in molecular biology techniques, the discovery of new gene structures and functions is in decline.

IMAGE ANALYSIS

Helping computers find ‘Waldo’

New program picks out targets in a crowd quickly and efficiently.

WHY THIS MATTERS

- Training computers to identify specific objects in a complex image remains a challenge in the field of computer image analysis.
- By mimicking how humans perform object recognition, scientists could make computer image analysis ‘smarter’ and faster.



It can be harder for computers to find ‘Waldo,’ an elusive character that hides within crowds in a popular children’s book series, than it is for humans.

Now, an A*STAR researcher and her colleagues have developed a biologically-inspired program that could enable computers to identify real-life ‘Waldos’ and other targets more efficiently¹.

Computer image analysis is routinely used in medicine, security and rescue. Speed is often critical in these efforts, says Mengmi Zhang, a computer scientist at A*STAR’s Institute for Infocomm Research (I²R), who led the study. She cites the use of computers to help find victims of natural disasters, such as earthquakes.

But these efforts are often hampered because computers lack human intuition. A person can quickly spot a dog in a crowded space, for instance, even if they have never seen that particular dog before. A computer, by contrast, needs to be trained using thousands of images of different dogs, and even then, they can falter when looking for a new dog whose image they have not encountered previously.

This weakness could be particularly problematic when scanning for weapons, says Zhang. A computer trained to look for knives and guns might overlook another sharp object. “If there is one sharp metal stick which has not been seen in the training set, it doesn’t mean the passenger should be able to take it on board the airplane,” says Zhang.

Current computer searches also tend to be slow because the computer must scan every part of an image in sequence, paying equal attention to each part. Humans, however, rapidly shift their attention between several different locations in an image to find their target. Zhang and her colleagues wanted to understand how humans do this so efficiently.

They presented 45 people with crowded images and asked them to hunt for a target, say, a sheep. They monitored how the subjects’ eyes darted around the scene, fixating briefly on different locations in

the image. They found that, on average, people could locate the sheep in around 640 milliseconds. This corresponded to switching the location of their gaze, on average, just over two and a half times.

The team then developed a computer model to implement this more human-like search strategy to seek out an image of a dog. Rather than look for a target identical to an image of a dog given beforehand, the model was trained to identify something that had similar features to the example image. This enabled the model to generalize from a single dog image to the “general concept of a dog” and quickly pick out other dogs it had not seen before, explains Zhang.

The researchers tested how effective the new computer visual search model was by measuring the number of times the computer had to fixate on different locations in a scene before finding its target. “What surprises us is that by using our method, computers can search images as fast as humans, even when looking for objects they’ve never seen before,” says Zhang. The computer was even as good as humans at finding Waldo.

The team is now programming their model with a better understanding of context. For example, humans naturally understand that a cup is more likely to be sitting on a table than floating in the air. Once implemented, this should improve the model’s efficiency even further, says Zhang, adding, “Waldo cannot hide anymore.” ★

BACKGROUND

A*STAR scientists have developed a computer visual search model that is more efficient and effective at identifying specific targets in complex images.

1. Zhang, M., Feng, J., Ma K. T., Lim, J. H., Zhao, Q. *et al.* Finding any Waldo with zero-shot invariant and efficient visual search, *Nature Communications* 9, 3730 (2019).



IMPACT

Fields such as medicine, security, and search and rescue, could stand to gain from speedy and precise computer image analysis.

Commemorating the life of



Sydney Brenner

Dr. Sydney Brenner, the visionary molecular biologist and Nobel laureate who turned a humble soil worm into one of the most-studied organisms in biology, passed away on April 5, 2019 in Singapore. He was 92.

Few scientists make their mark on even one specialized field of research, but Dr. Sydney Brenner—visionary molecular biologist and Nobel laureate—charted a scientific career marked by versatility. A contemporary of Francis Crick and James Watson (who together with other researchers deduced the double helix structure of DNA in 1953), Brenner was instrumental in deciphering the basic principles of the genetic code—the instructions by which DNA codes for proteins.

As biologists went from studying individual genes to scanning entire genomes, Brenner would go on to invent new methods for reading DNA on a large scale. These later became the basis for the high-throughput DNA sequencing now routine in many laboratories.

MEDICINE'S LOSS, SCIENCE'S GAIN

Brenner was born on January 13, 1927 in Germiston, South Africa, to Jewish immigrants from Eastern Europe. In 1942, after an accelerated grade school career, he enrolled in the University of the Witwatersrand in Johannesburg to study for a medical degree.

By his own admission a poor student of medicine, Brenner was instead captivated by courses in the natural sciences. A gap year, taken because he was deemed too young to qualify to practice medicine, solidified his passion for scientific research—Brenner spent it working in a laboratory, learning physical chemistry, neurology, microscopy, anthropology and paleontology from senior researchers. (“This was heaven,” he later wrote in his Nobel autobiography.)

Photo credit: Bryan van der Beek / Wildtype Media

After scraping through medical school, Brenner won a highly competitive scholarship to pursue his PhD at Oxford University in the UK. He moved there in 1952 to work in the laboratory of physical chemist Cyril Hinshelwood, who suggested that he study how bacteria develop resistance to bacteriophage (viruses that infect bacteria).

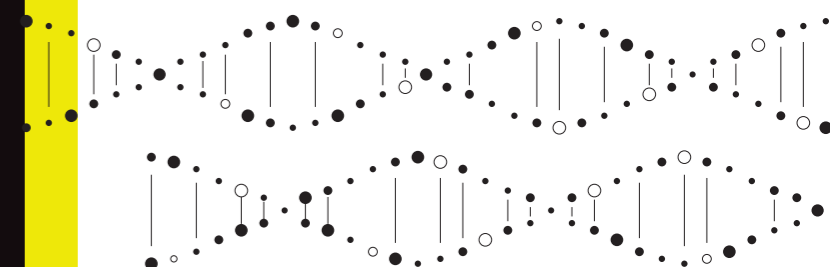
DECODING DNA

In 1953, Crick and Watson proposed the DNA double helix, a structure formed by paired chains of the nucleotide bases A, C, G and T. This milestone marked the start of the ‘golden age’ of molecular biology—over the next decade and a half, researchers would painstakingly work out the rules of the genetic code, the very basis of life.

That year, Brenner drove to Cambridge to see Crick and Watson’s model of DNA, an occasion he described as a watershed moment in his scientific career. “The moment I saw the model and heard about the complementing base pairs, I realized that it was the key to understanding all the problems in biology we had found intractable—it was the birth of molecular biology,” he wrote.

Still, the question of how just four bases could encode enough information to make all the proteins necessary for life remained unsolved. In 1956, Brenner joined Crick at the UK Medical Research Council’s laboratory in Cambridge—where they would share an office for the next 20 years—to work on cracking this puzzle.

In 1961, Brenner, Crick and others used a bacteriophage system to show that the genetic code is composed of non-overlapping triplets. Three bases, or a codon, are required to encode one amino acid, the basic building block of proteins. Turning next to the question of how information contained in DNA is communicated to the cell, Brenner collaborated with Matthew Meselson and François Jacob to demonstrate the existence of messenger RNA, an intermediate molecule that carries genetic messages from DNA in the nucleus to ribosomes—the cell’s protein-making machinery—in the cytoplasm of the cell.



A CAN OF WORMS

By the mid-1960s, Brenner and Crick believed that the central problems of molecular biology had been solved; the details could be left to the many young scientists who were now entering the field. It was time to look for new and bigger problems.

Brenner, who was interested in the genetics of how complex organisms develop and nervous systems are wired, began to hunt for the right experimental organism to answer these questions. The nematode worm *Caenorhabditis elegans* (*C. elegans*) fit the bill: the worm could be grown by the hundreds on petri dishes in the laboratory; its diminutive size meant that it would fit within the field of view of an electron microscope; and its translucent body made it easy for scientists to follow and observe biological processes. In a 1974 paper, Brenner laid out key aspects of *C. elegans* genetics, along with methods for studying it in the laboratory.

By tracking the lineages of every one of *C. elegans*' 959 cells, scientists were able to link specific genes to key processes such as cell differentiation and organ development. The humble worm—more complex and hence more informative than bacteria and yeast, and yet easier to study than flies and zebrafish—turned out to be a powerful experimental system that today continues to be

used by laboratories all over the world. In 2002, Brenner shared the Nobel Prize in Physiology or Medicine with H. Robert Horvitz and John E. Sulston for their work in *C. elegans* on the genetics of programmed cell death.

FROM GENES TO GENOMES

Brenner's scientific contributions continued well into the genomic era. In the mid-1980s, he became a strong supporter of efforts to sequence the human genome, but believed the project was not yet feasible given the sequencing technology of the day. Further, he also believed that most of the human genome—some 97 percent of its three billion bases—was junk DNA, meaning that it didn't code for anything; it did, however, make life difficult for scientists who were sifting through it for genes.

"My view at the time was that we should treat the human genome like income tax and find every legitimate way of avoiding sequencing it," Brenner, who was also known for his dry wit, said in his Nobel lecture.

If not the human genome, then what? Brenner started a project to sequence the genome of the *Takifugu rubripes* puffer fish, known in Japan as fugu. Humans and fugu share the same basic vertebrate body plan and similar repertoires of genes, but the fish's genome, for reasons yet unknown, contains almost no junk DNA. Like *C. elegans*, the compact fugu genome—published in 2002—was an ideal model for studying larger and more complex organisms like humans. Plus, it was cheaper, too—Brenner dubbed it the "discount genome," as it offered researchers a 90 percent discount on the cost of sequencing.

At the same time, Brenner also wanted to improve on existing DNA sequencing techniques, recognizing that the ability to read genomes on a large scale would be needed to move the field forward. Together with Applied Biosystems founder Sam Eletr, he developed a technique for sequencing large numbers of DNA molecules in parallel by anchoring them to microscopic beads. Lynx Technologies, the company focused on commercializing this invention, was later acquired by Illumina, and the technology now forms the basis of what today is known as next-generation sequencing.

THE SINGAPORE CONNECTION

Brenner worked on the fugu genome from his laboratories at the University of Cambridge and at the Institute of Molecular and Cell Biology (IMCB) in Singapore. But before that, he had been advising the Singapore government on scientific policy since the early 1980s. At that time,



the country's leaders were eager to diversify its economy from low-cost manufacturing into more highly skilled industries such as biotechnology.

On a visit to Singapore in 1984, Brenner met then prime minister Kuan Yew Lee, and proposed setting up a molecular biology research institute to train Singaporean PhDs. When Lee remarked that Singapore was a nation of technicians and not of scientists, Brenner replied with trademark candor: "Prime minister, if you don't do something like this, you will remain a nation of technicians."

Singapore took his advice. The IMCB, set up in 1987, was followed by a host of other biomedical research institutes managed by the Agency for Science, Technology and Research (A*STAR), all located in a hub called the Biopolis—a name coined by Brenner. In 2003, he was made an honorary citizen in recognition of his contributions towards putting Singapore on the biomedical research world map.

One Biopolis research center in particular bears Brenner's mark. In 2009, he established the Molecular Engineering Laboratory (MEL), which according to

ABOVE
Sydney Brenner's 10-on-10: *The Chronicles of Evolution*, a book documenting ten logarithmic scales of evolution from the Big Bang to modernity, was Dr. Brenner's brainchild.
Photo credit: Wildtype Media Group

him was one of the first in the world to institutionalize molecular engineering, an interdisciplinary field focusing on the design and manipulation of molecules for myriad applications.

Brenner hoped MEL would serve as a training ground for Singapore's next generation of talent. There, scientists, even the junior ones, were expected to be independent; in return, they got to work on problems that really interested them. Brenner applied this same philosophy during his tenure as the founding president of the Okinawa Institute of Science and Technology Promotion Corporation, Japan, from 2005–2011.

"Ninety percent, maybe even more, of what goes on in research and development is essentially routine," he said. "And that's fine. But you also need the talent to do something new."

A CHRONICLE FOR THE FUTURE

Brenner remained a magnetic presence in Singapore's scientific research scene up until his death. In 2016, he co-founded the Evolution Club, aimed at stimulating discussion in that field among scientists, scholars and the public. He envisioned ten seminars spanning ten billion years of evolution; these would follow a logarithmic time scale beginning 10^{10} years ago with the Big Bang, then moving to the origin of biological life 10^9 years ago, and so on, up to the development of modern human society in the present, or 10 years.

The result was the 2017 public lecture series '10-on-10: The Chronicles of Evolution.' Experts on each evolutionary milestone—many of them friends or collaborators of Brenner's—were invited to Singapore, where they gave talks to packed lecture halls.

Brenner himself, then 90, bookended the series. In the opening lecture, he dispelled the common misconception that biological evolution is an upward progression with a fixed purpose; at the series' conclusion, he detailed his plans to construct genome maps of every organism that had been sequenced, in order to trace their evolutionary history.

"The big lesson to learn here is that in science, only mathematics is the art of the perfect. Physics is the art of the optimal, and biology is the art of the satisfactory: if it works, you keep it; if it doesn't, you get rid of it," he said. A book based on the lecture series has since been published. Brenner, who was married to his wife May for 58 years until her death in 2010, is survived by their three children, Stefan, Belinda and Carla. His stepson, Jonathan, passed away in 2018. ★

ABOVE
In October 2003, Dr. Sydney Brenner received the inaugural Honorary Singapore Citizen Award from the late Mr. S. R. Nathan, who was then Singapore's President. (First row, from left: Mrs. May Brenner, Dr. Sydney Brenner, Mr. and Mrs. S. R. Nathan, and Mr. George Yeo.)
Photo credit: Institute of Molecular and Cell Biology

MACHINE LEARNING

A five-star review system

New algorithm mines users' most relevant reviews to better predict their tastes.

Online reviews of products, venues and services can help other consumers choose among the many options available on the market. But such reviews also reveal information about the reviewer's own tastes, which go beyond their purchase history.

Websites thus mine reviews to refine future recommendations they make to each reviewer. This is a good idea, in principle, says Anh Tuan Luu, a computer scientist at A*STAR's Institute for Infocomm Research (I²R). However, existing recommender systems tend to miss the mark because most of them combine all reviews that a user has ever written in one document, regardless of the product or service they are discussing. Similarly, they combine all reviews about an item written by other users in another single document. The system then compares these two documents, making recommendations based on any overlaps of interest it spots.

This strategy makes the mistake of weighting all reviews written by a user equally, even if they are about vastly different things, says Luu. "A user's bad review about a coffee shop should be mostly irrelevant when deciding if a spa is a good match," he says. "Not all reviews are created equal."

Another problem is that documents listing every review written by a person can become unwieldy, as more irrelevant

data is included until eventually it hits an arbitrary cut-off. "The squashing of reviews into a single document is unnatural and ad-hoc," says Luu.

Luu and his colleagues have devised a new algorithm which gives added weight to reviews that are directly related to the service or product in question¹. So when deciding if a coffee shop is a good match for a user, only the user's previous reviews of eateries are considered, while their reviews of, say, car mechanics, are ignored.

The algorithm also looks for matches on a word-by-word level. For instance, if the reviewer mentions that they like cocoa, the algorithm would surface to them products containing the word chocolate which have received positive reviews.

The team tested their algorithm on 24 benchmark datasets supplied by Amazon, including reviews for digital music, Android apps, video games and gourmet food, and on business reviews from Yelp. They evaluated their system's performance by predicting user ratings for particular items and services and then comparing them with the actual ratings given by those users. Their system outperformed two state-of-the-art systems, TransNet and DeepCoNN, by 19 and 71 percent respectively.

The team was surprised to find that while the system needed to use many reviews to correctly match-up food and businesses preferences, it was able to correctly predict the reviewers' tastes in apps and electronic games based on just one or two particularly insightful reviews.

"We hope that our model can be applied in current commercial websites," says Luu. ★

LEFT

A*STAR researchers have developed a recommender algorithm that better matches products to personal preferences by analyzing reviews on e-commerce platforms.

1. Yi, T., Luu, A. T. & Hui, S. C. Multi-pointer co-attention networks for recommendation, *Proceedings of the ACM SIGKDD Conference on Knowledge Discovery and Data Mining (KDD)*, pp. 2309-2318 (2018) DOI: 10.1145/3219819.3220086 (2019).

Photo credit: Black Salmon / Shutterstock

CANCER

Better imaging leads to more precise surgery

A new imaging method could reduce the number of repeat operations for breast cancer.

Surgeons removing breast tumors must excise enough tissue to ensure all the cancer is gone, while retaining as much healthy tissue around the edges, or margins, of the tumor as possible. A new method, developed by an A*STAR-led team, is able to better distinguish cancerous from non-cancerous breast tissue in real-time¹.

"You want to remove as much of the tumor as possible, but you need to be very precise in the amount of healthy tissue you have to remove," says Malini Olivo, a principal investigator with the A*STAR Singapore Bioimaging Consortium (SBIC).

The current approach is to remove the tumor, then send it to a pathologist for analysis using conventional ultrasound and light microscopy—a process which can take a week or two. If it is found that the surgery didn't remove the entire tumor, the patient must undergo the procedure again. The probability of this outcome

in breast cancer is as high as 40 percent, Olivo says. Furthermore, there is a chance that the tumor could progress during the required healing period between the first and second surgery.

Multispectral optoacoustic tomography, or MSOT, uses different light wavelengths to excite the molecules in the tissue sample, such as fats, water molecules or other compounds. When excited with light, these compounds give off distinctive soundwaves that can penetrate deeper into the tissue and be picked up by an ultrasound detector. This enables researchers to build a 3D picture of the tissue around the edge of the excised tumor.

"Ultrasound cannot tell you the difference between lipids in the tissue and water in the tissue, it cannot tell you the difference between oxygenated and deoxygenated blood, it cannot tell you where the blood vessels are," she says.

"Ultrasound is not a functional-based imaging technique, whereas MSOT, like magnetic resonance imaging, is."

The technique can be applied in any scenario where tumors need to be surgically removed. In this study, the research group used the imaging method to examine the margins of a breast tumor that had been surgically removed.

While conventional ultrasound showed the tumor within the surgically removed specimen, the MSOT even identified the biochemical makeup of the specimen, including the fats and hemoglobin. This revealed that there was a good margin of normal breast tissue around the removed tumor, a conclusion that was also supported by a pathologist. A larger study in 90 patients has recently been completed.

"The goal would be—if we image as many patients as possible and use artificial intelligence to assess those images—that eventually we will have the confidence that we don't need histopathology during the operation," Olivo says. ★

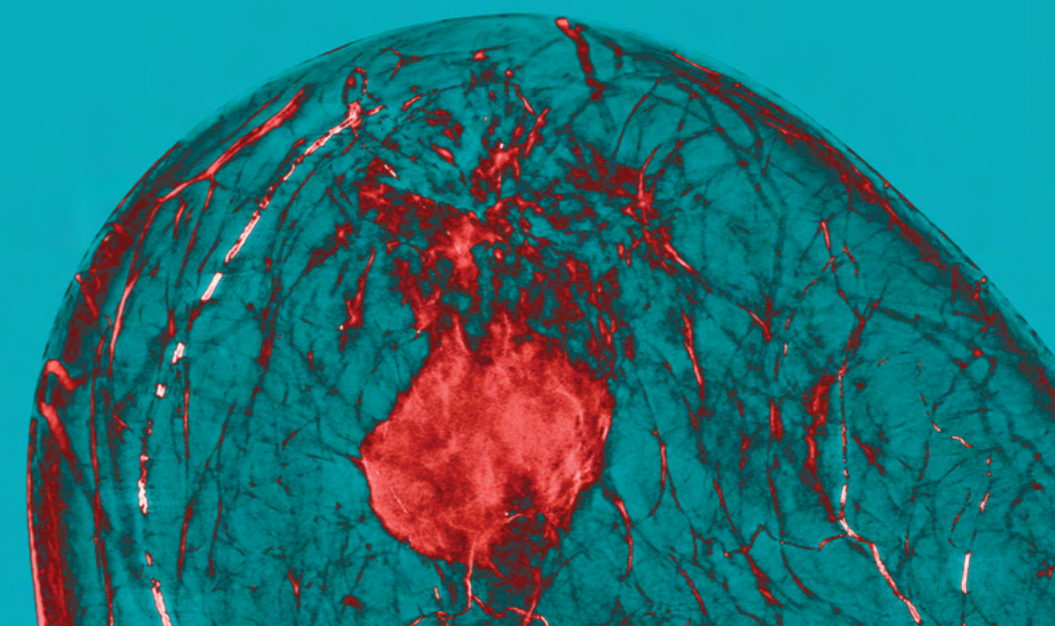
BELOW

Mammogram identifying a breast tumor. During surgery, a 'buffer zone' of normal tissue around the tumor is typically excised to prevent cancer relapse.

1. Goh, Y., Balasundaram, G., Moothanchery, M., Attia, A., Li, X. *et al.* Multispectral optoacoustic tomography in assessment of breast tumor margins during breast-conserving surgery: A first-in-human case study. *Clinical Breast Cancer* **18**, e1247-e1250 (2018).

Photo credit: Centre Jean Perrin, ISM / Science Photo Library

"You want to remove as much of the tumor as possible, but you need to be very precise in the amount of healthy tissue you have to remove."



CARBON FIBER MATERIALS

On board for aircraft repairs

A process that improves repair of carbon fiber airplane components may benefit Singapore's avionics industry.

Carbon fiber structures are strong enough to replace avionic parts typically made from steel. But when damaged, these lightweight materials require special repair techniques to ensure they can still bear mechanical loads. Technicians normally cut wedge-shaped chunks from the defective site, and glue in pre-made patches. Finally, components are placed in pressurized ovens called autoclaves to remove volatile gases and cure the adhesives.

Autoclave-based repair techniques, however, are impractical for the maintenance of extra-large components, such as wings or fuselages, that cannot be removed from the aircraft. Stefanie Feih and co-workers from A*STAR's Singapore Institute of Manufacturing Technology (SIMTech) have now investigated a technique for patching carbon fiber structures while they are still in place on the aircraft¹.

The team studied a double vacuum debulking process that places a rigid box containing an inner flexible vacuum bag on top of a patch. By creating a second and different vacuum level within this chamber, volatile gases can be quickly removed from the repair material. The patch is then transferred to the aircraft to complete the curing step.

"Double vacuum debulking adds an additional step to an already very complex repair scenario," says Feih. "Repair processes require highly accurate surface-temperature control over surfaces with generally complex internal features. Performing large scale repairs further complicates the process."

High porosity in the final patch is a significant issue during carbon fiber repair, because voids can lessen mechanical strength. The researchers found that

the adhesive films used to bond repair patches can also trap volatile gases to create additional voids. The double vacuum debulking process, however, was found to almost completely eliminate porosity in both the adhesive film and repair patch for all repair geometries.

"These findings highlight why you need a highly skilled workforce in an avionic hub city," says Feih. "It's crucial for attracting operators to Singapore, and we undertook this project to improve the understanding of repair processes for composite structures among local companies."

Feih and colleagues also examined the impact of patch geometry by mechanically testing configurations ranging from simple laminate films to more complex wedge shapes. Here, circular 3D repairs proved inherently stronger than simplified 2D shapes when under tension. Further study is needed to determine optimal improvements under complex conditions experienced by real components during flight. ★

BELOW

Smarter materials and methods are revolutionizing the way aircraft parts are repaired.

1. Chong, H. M., Liu, S. L., Subramanian, A. S., Ng, S. P., Tay, S. W. *et al.* Out-of-autoclave scarf repair of interlayer toughened carbon fibre composites using double vacuum debulking of patch. *Composites: Part A* **107**, 224–234 (2018).



Photo credit: trationg / Shutterstock

METALLURGY

Strength in numbers for 3D printing

Hierarchical microstructure improves the performance of metallic material.

Cobalt-chromium-iron-nickel-manganese (CoCrFeNiMn) is known as a high entropy alloy. Discovered in 2004, it is particularly good at withstanding fractures under harsh environmental conditions, such as low temperatures. To make an object from the alloy, researchers typically pour the molten metal into a cast, allow it to cool, and then machine it into the desired shape. However, this can be a time-consuming and costly way of making complex components. In principle, additive manufacturing could skip the machining step to directly fabricate complex components.

A team led by Sharon Mui Ling Nai of the A*STAR Singapore Institute of Manufacturing Technology (SIMTech) has shown that an additive manufacturing method, called selective laser melting, is well suited to building components from

CoCrFeNiMn¹. The researchers first created a pre-alloyed powder of CoCrFeNiMn, containing particles that were an average of 36 micrometers across. They then used laser melting to craft the particles into 10-millimeter-wide cubes, or flat bars of 90 millimeters. They also varied the laser's power, and the speed at which it scanned over the alloy particles, to understand how different printing conditions affected the alloy's performance.

The researchers further noted that their sample contained microscopic melt pools, rather like miniature welds, that held the material together. It also contained elongated crystalline grains that were roughly 13 micrometers across. These grains were subdivided into smaller 'cells' less than one micrometer wide, which played a crucial role in strengthening the

alloy because the crystal structure of each grain may not line up with its neighbors, so any atomic dislocations stop as soon as they reach a grain boundary.

One of the printed alloys, prepared using optimized printing conditions, could withstand 510 megapascals of stress before it started to permanently deform. This is almost twice the stress that a conventionally prepared CoCrFeNiMn alloy can handle.

When the researchers heated their 3D-printed objects at 900 degrees Celsius for one hour under an inert atmosphere, the material's strength decreased, but it became more ductile and could deform further. They plan to tweak the 3D-printing processes to further enhance the mechanical properties of the materials, and intend to use selective laser melting to fabricate other high-performance alloys.

"With this understanding, we will be better equipped to tailor their properties for industrial application and help to accelerate the adoption of additive manufacturing," says Nai. ★

ABOVE

Using a high resolution laser, A*STAR researchers melted CoCrFeNiMn powder to additively manufacture 3D objects with high mechanical strength.

1. Zhu, Z.G., Nguyen, Q.B., Ng, F.L., An, X.H., Liao X.Z. *et al.* Hierarchical microstructure and strengthening mechanisms of a CoCrFeNiMn high entropy alloy additively manufactured by selective laser melting. *Scripta Materialia* **154**, 20–24 (2018).

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TISSUE ENGINEERING

Sweetening the deal on bone repair

The size and composition of protein-binding sugars in the extracellular matrix play a crucial role in bone repair.

Repairing bone tissue hinges on the action of bone morphogenetic proteins (BMPs), a family of cell signaling proteins that regulate numerous cellular processes in the body. Specifically, BMPs control key developmental processes, such as skeletal development, and can also induce bone formation and regeneration in adults. This makes them appealing for treatment in cases where the normal healing process is stalled or delayed.

BMP signaling relies on first coupling to the sugar heparan sulfate, a tissue component that often gets damaged during bone injury. Specifically, the linear polysaccharide, whose sugar chains are anchored to the extracellular matrix or cell surface, binds proteins and cell receptors to form signaling complexes that instruct stem cell fates and drive reparative cascades within tissues. However, the mechanics behind these coupling interactions, especially the contribution of the sugars to the stability, concentration and configuration of the resulting complex, remain unclear.

“Bio-inspired heparan sulfate materials can be readily formulated into scaffolds using advanced manufacturing practices to produce patient-customized bone implants.”

In the present study, a team led by Simon Cool and Raymond Smith from A*STAR’s Institute of Medical Biology (IMB) determined what elements are necessary for heparan sulfate to maximize the bone repair activity of BMP-2, which is produced at bone injury sites¹. The researchers assessed how the structural features of smaller, more defined heparan sulfate-like structures regulate BMP binding and signaling. They also evaluated

the interactions of BMP-2 with heparan sulfate analogs, including heparin and several heparin-derived oligosaccharides of varying chain lengths and sulfate content.

“This work would allow us to create bone-relevant heparan sulfate variants with higher potency and tissue specificity by enhancing the actions of BMP-2 produced at bone injury sites,” Cool says.

The team demonstrated that BMP-2 binding and BMP-2-mediated bone formation can be strongly enhanced when BMP-2 complexes with heparan sulfate-like structures of defined size and charge. “This provides an opportunity to generate more bone tissue-relevant heparan sulfate structures and improve self-healing cascades,” Cool says.

The binding assays revealed that the sugars needed at least ten-unit-long chains to effectively bind BMP-2. Longer chains also enhanced the thermal stability of the protein. Moreover, *in vitro* and *in vivo* tests confirmed the influence of sugar chain length and sulfate functionalization on BMP-2-mediated bone repair. Chain lengths exceeding ten units were particularly necessary to prolong and maintain BMP-2-induced signaling reactions in the cells, while also enhancing the transcription of osteogenic genes.

“Such bio-inspired heparan sulfate materials can be readily formulated into scaffolds using advanced manufacturing practices to produce patient-customized bone implants,” says Cool. His team is now fabricating bone implant materials with enhanced growth factor-binding performance. These materials will be evaluated in various bone tissue repair models before plans for commercialization. ★

ABOVE

Bone morphogenetic proteins (BMPs) regulate bone repair. Researchers at A*STAR now know how to enhance BMP activity using protein-binding sugars of varying chain lengths and structures.

1. Smith, R. A. A., Murali, S., Rai, B., Lu, X., Lim, Z. X. H. *et al.* Minimum structural requirements for BMP-2-binding of heparin oligosaccharides. *Biomaterials*, **184**, 41–55 (2018).

Photo credit: Crevis / Shutterstock

CANCER IMMUNOTHERAPY

Reprogramming T cells to attack solid tumors

A two-pronged genetic manipulation of T cells could lead to more effective cancer treatments.

Hepatocellular carcinoma (HCC) is a common form of liver cancer and a leading cause of cancer deaths worldwide. It often arises in people with chronic liver damage associated with hepatitis B virus (HBV) infection.

Immune cells such as T cells often have difficulty infiltrating solid tumors like those that occur in HCC. Hence, researchers led by Itziar Otano, a former visiting researcher at A*STAR’s Institute of Molecular and Cell Biology (IMCB), sought to modify T cells to grant them greater anticancer potency. They first engineered T cells to express a cell surface protein called a T cell receptor (TCR), which was tailored to recognize HBV-infected liver cancer cells¹.

“The TCR ‘hook’ links with a corresponding HBV-derived hook on the cancer cell,” says project co-leader Andrea Pavesi of IMCB. “By using genetic engineering, we effectively increase the pool of T cells potentially able to ‘see’ and attack solid tumors.”

The next challenge the team faced was the gradual loss of T cell efficacy that occurs due to repetitive T cell stimulation—a phenomenon known as T cell exhaustion. The receptor protein PD-1 is a central mediator of T cell exhaustion and a target of checkpoint inhibitor therapy.

“We reasoned that an elegant solution would be to genetically knockdown PD-1

just on T cells of the desired specificity,” says Otano.

The researchers then used an innovative 3D microfluidic device to test the cancer-killing efficacy of their doubly modified T cells.

“The beauty of our microfluidic device is that it allows us to study cancer cell killing by T cells with minimal experimental noise,” explains Pavesi. “More generally, the use of microfluidic devices to test possible treatments under conditions mimicking those of target tissues could reduce clinical trial failures.”

The researchers observed enhanced killing activity in T cells that targeted HBV-infected liver cancer cells. However, the anticancer activity of the T cells still waned eventually.

“Future work must address the emergence of alternative inhibitory pathways,” cautions Pavesi. “Nevertheless, our study provides proof of principle that a dual approach to genetically reprogram human T cells can invigorate their ability to attack solid tumors.” ★

“Our study provides proof of principle that a dual approach to genetically reprogram human T cells can invigorate their ability to attack solid tumors.”

BACKGROUND

A colorful battle: Live human liver cancer cells (green) are attacked by engineered T cells (blue), resulting in dead liver cancer cells (red). White blood cells called monocytes (orange) can prevent T cells from reaching and killing the cancer cells. The image is taken with confocal microscopy inside the 3D tumor microenvironment region of the microfluidic device.

1. Otano, I., Escors, D., Schurich, A., Singh, H., Robertson, F. *et al.* Molecular recalibration of PD-1+ antigen-specific T cells from blood and liver. *Molecular Therapy* **26**, 2553–2566 (2018).

DISEASE MODELS

Spinal organoids mimic neurodegenerative disease

New spinal cord-like cell clusters could be used to study and find treatments for nerve cell degeneration.

Spinal muscular atrophy (SMA) is a degenerative disease of motor neurons that mainly affects children. It is caused by a gene mutation that leads to a protein deficiency that affects spinal motor neurons, causing nerve degeneration in skeletal muscles, arrested childhood developmental milestones, paralysis and ultimately, in severe cases, premature death.

To better understand how SMA develops and progresses, researchers at A*STAR's Institute of Molecular and Cell Biology (IMCB), with colleagues in Singapore and China, developed spinal organoids from pluripotent stem cells

derived from healthy people, and from patients with SMA¹.

"We are one of the first labs to report the formation of spinal organoids," says IMCB principal investigator Shi-Yan Ng. "Our study presents a new method for culturing human spinal-cord-like tissues that could be crucial for future research."

The stem cells were coaxed into differentiating into spinal cord precursor cells using a chemical cocktail. They were then encapsulated in a gel that was rich in extracellular matrix. The spinal organoids that ultimately developed demonstrated characteristics of the developing spinal cord, with diverse types of cells, including

motor neurons, the nerve cells that send nerve impulses from the brain or spinal cord to skeletal muscles; interneurons, which transmit impulses between nerve cells; and astrocytes, star-shaped cells that play various support roles within the nervous system.

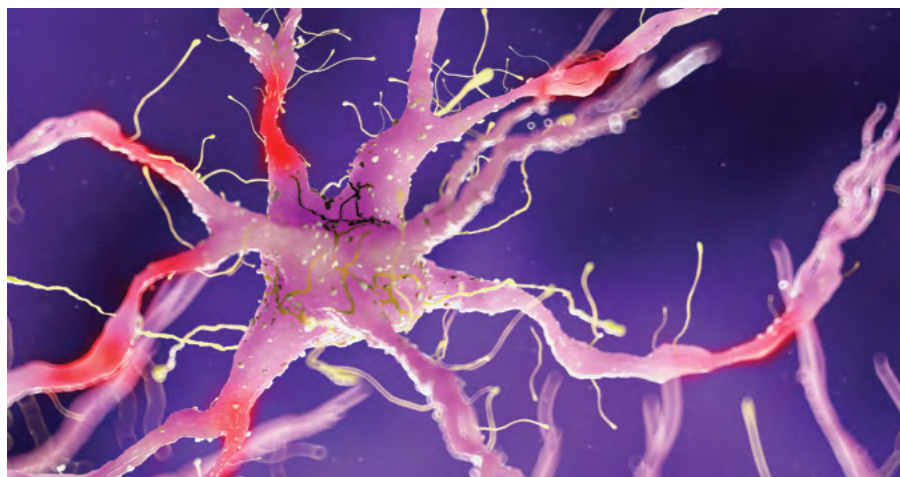
The researchers demonstrated that their spinal organoids mimicked the progression of SMA *in vitro*. Importantly, the motor nerve cells in SMA-afflicted spinal organoids began to degenerate only between day 28 and 35 of culture, suggesting that SMA may not be a disease that occurs during nerve development as was previously believed.

Further investigations showed that the protein deficiency that leads to SMA causes motor nerve cells—which don't normally divide—to begin dividing again, ultimately leading to their death. When the researchers used a small molecule inhibitor to block a group of enzymes involved in triggering this 're-entry of the cell cycle,' a larger number of motor neurons were able to survive.

"We believe that some neurons re-enter the cell cycle as a means to overcome cellular stress," says Ng. "Other publications reported that neurons in other neurodegenerative diseases, such as Alzheimer's disease, also re-enter the cell cycle."

Ng and her colleagues are now conducting in-depth analyses on the cellular composition of their SMA spinal organoids to find out if other nerve cells contribute to the disease. They are also using spinal organoids to study amyotrophic lateral sclerosis, a progressive neurodegenerative disease that currently has no effective treatment. ★

1. Hor, J. H., Soh, E. S., Tan, L. Y., Lim, V. J. W., Santosa, M. M. *et al.* Cell cycle inhibitors protect motor neurons in an organoid model of spinal muscular atrophy. *Cell Death & Disease* **9**, 1100 (2018).



Pluripotent stem cells differentiated into spinal organoids *in vitro* shed light on the progression of spinal muscular atrophy.

Photo credit: Sebastian Kautzki / Shutterstock

CANCER

Tapeworm drug targets common vulnerability in tumor cells

Drug screen reveals safe, potent, broad-spectrum anticancer compound.

More than half of human cancers carry a mutation in the tumor suppressor gene p53, making it an attractive target for cancer therapy. Many research efforts have focused on directly or indirectly restoring p53 function in mutated cells, but the team, led by Chit Fang Cheok of A*STAR's Institute of Molecular and Cell Biology (IMCB), took a different approach.

Instead of trying to fix p53, which mutates in hundreds of ways in cancers, they exploited the differences between wild-type and p53-deficient cells to develop a treatment based on the vulnerabilities of p53-deficient cancer cells¹.

The team tested the effect of 1,600 FDA-approved compounds on cultured colon cancer cells with normal and mutated versions of p53. The compound that was best at killing p53-deficient cells, rather than cells with p53, was niclosamide, a

drug used to treat tapeworm infections. Subsequent tests showed that niclosamide was also effective against other p53-deficient cancer cell lines.

Niclosamide is known to affect cells by interfering with energy production in mitochondria (an effect known as 'mitochondrial uncoupling') and causing changes in fatty acid metabolism. The researchers thus examined the metabolic profile of niclosamide-treated cells and found that the p53-deficient cells had significantly higher levels of a fatty acid known as arachidonic acid. They revealed that the mitochondrial uncoupling caused by niclosamide increases the calcium concentration in a cells, which boosts the production of arachidonic acid.

Elevated arachidonic acid in p53-deficient cells triggered the release of a molecule known as cytochrome c from the

cells' mitochondria, leading to programmed cell death. Future work may identify other drugs that activate the same pathway and could also be used to treat p53-deficient cancers.

To confirm their model, the researchers knocked out two genes that break down arachidonic acid, ALOX5 and ALOX12B, in cells with a working copy of p53. They found that the engineered cells were more sensitive to niclosamide treatment even though they had a functioning p53 gene. Likewise, knocking out ALOX5 and ALOX12B in p53-deficient cells did not increase their niclosamide sensitivity.

Finally, the team confirmed that niclosamide is effective against p53-deficient cancers in animals, and not only in cultured cells. Niclosamide reduced tumor growth by 50 percent in mice which had received p53-deficient cells, but had no effect on tumors in mice injected with p53-positive cells.

Based on their findings, the researchers have filed a patent for the use of niclosamide to treat p53-deficient cancers. Since this approach targets deficiency rather than a specific mutation, Cheok expects it to be effective against a broad spectrum of cancers. ★

ABOVE

By screening 1,600 FDA-approved compounds, A*STAR researchers discovered to their surprise that a tapeworm drug may be effective in the treatment of cancers harboring p53 gene mutations.

1. Kumar, R., Coronel, L., Somalanka, B., Raju, A., Aning, O. A., *et al.* Mitochondrial uncoupling reveals a novel therapeutic opportunity for p53-defective cancers. *Nature Communications* **9**, 3931 (2018).

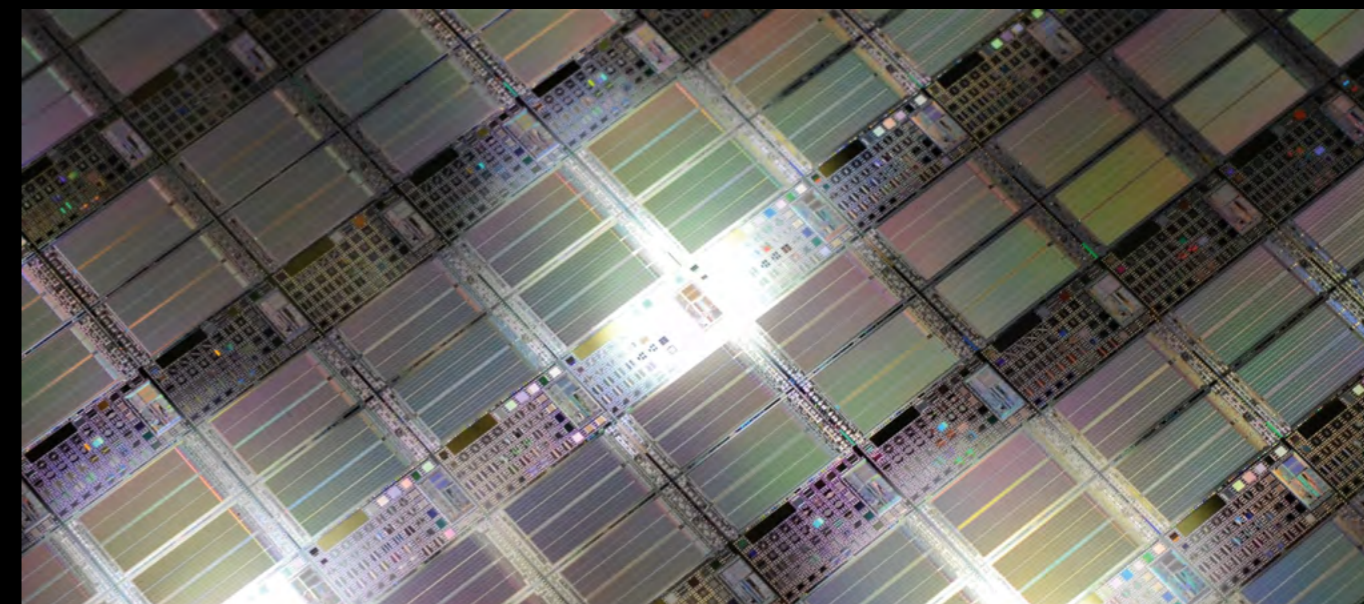
NANO-OPTICS

Mass manufacturing of metasurfaces

Advanced display technologies based on nanostructures could be mass manufactured by introducing existing techniques from the semiconductor electronics industry.

WHY THIS MATTERS

- Earlier methods of creating metasurfaces are not amenable to production at an industrial scale.



Metasurfaces are synthetic, two-dimensional materials covered in tiny individual shapes with sizes and spacings smaller than the wavelengths of visible light. These 'sub-wavelength' structures enable scientists to precisely control the propagating shape, or wavefront, of light beams. As such, metasurfaces show promise for many applications from high-resolution imaging and color printing to controlling light polarization.

Previously, metasurfaces were mainly fabricated using electron beam lithography (EBL), which is not applicable to mass production. "With EBL, the focused electron beam moves slowly, step by step, across the metasurface substrate. Metasurfaces with millions—and possibly billions—of elements require a very long time to be patterned via EBL. We desired a faster and more efficient way of patterning," Ting Hu explains.

Hence, his research group at A*STAR's Institute of Microelectronics (IME) drew inspiration from existing techniques in semiconductor fabrication to develop a method of building silicon-based metasurfaces in a more scalable fashion¹. The alternative strategy is based on 'immersion lithography,' which has long

been used to etch patterns onto electronic components.

With multiple exposures, complex patterns can be built up. The researchers used ultraviolet-based (UV) lithography for initial patterning onto silicon substrates, followed by plasma etching to form the designs in small pixel blocks that were assembled into a 12-inch display surface. Using their approach, they were able to design new metasurfaces for high-resolution red-green-blue (RGB) color displays.

"Our UV lithography tool is a scanner that can pattern a whole 12-inch wafer with designed devices within half an hour," says Hu. "We designed the physical dimensions of the nano-pillar arrays of the metasurface to accurately display colors, with fantastic results, for example displaying the letters I, M and E in red, green and blue respectively."

Hu and the team hope to optimize their design and improve the etching process to minimize losses induced by light scattering and defects in the nano-structure arrays. They are also making efforts to realize flat, lightweight 'meta-lenses' and dot projectors with potential uses in facial recognition technologies. ★

ABOVE

A*STAR researchers can now make metasurface displays using existing semiconductor fabrication techniques, paving the way for mass production.

IMPACT

Techniques adopted from the semiconductor industry could help create industrially viable metasurfaces for applications such as high-resolution imaging and color printing.

1. Hu, T., Tseng, C-K., Fu, Y. H., Xu, Z., Dong, Y. *et al.* Demonstration of color display metasurfaces via immersion lithography on a 12-inch silicon wafer. *Optics Express* **26**, 19548–19554 (2018).

DATA VISUALIZATION

An algorithm to rule them all

A powerful machine learning technique enables biologists to analyze enormous data sets.

The mind-boggling size and complexity of biological data sets make it extremely challenging for scientists to uncover meaningful relationships between parameters. Measurements on single cells alone can generate huge data sets that have anywhere from 20 to more than 20,000 parameters.

Mathematicians have developed statistical techniques that simplify complex data sets by grouping data according to their similar characteristics. The most well-known technique is principal component analysis (PCA), which was developed in the early 20th century. Recently, more powerful techniques that harness the power of machine learning have been developed.

Now, a team led by Evan Newell and Florent Ginhoux at the Singapore Immunology Network (SIgN), have used single-cell data to test six such machine learning techniques and discovered one that stands out from the rest in terms of speed, quality of analysis and reliability¹. This technique is called the uniform manifold approximation and projection, or 'UMAP.'

"When Evan and Etienne Becht in his group at SIgN started to benchmark UMAP,

we realized that it was much more powerful than anything we had used before," recalls Ginhoux.

An analysis that might take days using other methods can be done in a few hours using UMAP, which will allow scientists to investigate larger data sets. "With UMAP, we can analyze data for two or three million cells, whereas we generally avoid going beyond 100,000 cells with other methods," says Newell, adding that UMAP grouped similar cells in the most intuitive way, making it easier to interpret its results.

"I think it's really groundbreaking," says Ginhoux. "Researchers I meet at conferences are already starting to use it."

In an earlier study, the group showed UMAP's power by using it to discover a new population of cells in blood. Newell notes that UMAP is highly versatile and can be applied to data generated in fields as diverse as astronomy and crystallography. "Basically, any data that can be expressed in matrices can be analyzed by UMAP," he says.

In addition to using UMAP to analyze data daily, the team plans to continue to work with informaticians to tailor UMAP to their needs. ★

"With UMAP, we can analyze data for two or three million cells, whereas we generally avoid going beyond 100,000 cells with other methods."

BACKGROUND

As biological data becomes increasingly voluminous, machine learning techniques can help researchers uncover relevant insights more effectively.

1. Becht, E., McInnes, L., Healy, J., Dutertre, C.-A. et al. Dimensionality reduction for visualizing single-cell data using UMAP. *Nature Biotechnology* **37**, 38–44 (2019).

Photo credit: pinkeyes / Shutterstock

THERMOCHROMISM

Smart liquid goes dark in the heat

Nanowires that form and disperse as the temperature changes make for a robust thermochromic liquid.

A*STAR researchers have developed a smart liquid that darkens dramatically in response to rising temperature—what is known as a thermochromic liquid. Previous thermochromic liquids have usually been based on organic dyes or liquid crystals. Although amenable to industrial-scale production, organic dyes tend to degrade upon exposure to light, while liquid crystals require encapsulation to avoid degradation in air.

To overcome these challenges, researchers led by Wen-Ya Wu at the A*STAR Institute of Materials Research and Engineering (IMRE), in collaboration with researchers at the National University of Singapore, developed nanowire-based thermochromic liquid¹. Wu's research

is mainly focused on semiconductor nanocrystals, which form a colloidal suspension in certain solvents, and which are known for their broad light absorption and high photostability.

"While exploring the synthesis of colloidal antimony selenide (Sb₂Se₃) nanoparticles, we serendipitously discovered that they formed crystalline nanowires upon heating and dissolved into their molecular precursors upon cooling, in a certain mixture of solvents," Wu says.

Thanks to their broad light-absorbing behavior, a vial of Sb₂Se₃ nanowires formed by heating can appear very dark. But a solution of their molecular precursors, which the nanowires revert to upon cooling, are relatively transparent.

"This phenomenon formed the basis for developing these materials as liquid-based thermochromics," Wu says.

The team showed that the thermochromic liquid's color-changing behavior is long-lived and robust. A solution of the molecular precursors was stable even after two years in ambient conditions, and could be heated and cooled hundreds of times without any loss of performance. An additional advantage was that the color change transition temperature could be tuned to anywhere between 35 and 140 degrees Celsius, simply by adding a small amount of tin chloride to the mixture. The tin species interact with the selenium precursor, lowering the temperature needed for nanowire growth.

When the researchers coated filter paper with their thermochromic solution, they showed that it could differentiate between cooler and hotter regions of an irregularly heated surface. "Our liquid-based thermochromic system potentially allows coating onto a large variety of surfaces," Wu says. One potential application is self-regulating windows that darken on hot days.

The team next plans to use transmission electron microscopy to study the mechanism of reversible nanowire growth, to aid the rational design of new colloidal nanomaterial thermochromics. ★

LEFT

The thermochromic liquid changing color in reaction to a change in temperature.



1. Wu, W.-Y., Xu, Y., Ong, X., Bhatnagar, S., Chan, Y. Thermochromism from ultrathin colloidal Sb₂Se₃ nanowires undergoing reversible growth and dissolution in an amine–thiol mixture. *Advanced Materials* **31**, 1806164 (2019).

SHAPE MEMORY ALLOYS

Finding a premium blend

In shape memory alloys, the right combination of crystal grains can achieve high strength and still retain memory.

Shape memory alloys (SMAs) are materials that can revert to an original shape by heating after being deformed at low temperature. This property makes them useful in applications such as nanoscale switches, and in medical devices such as stents and braces.

However, shape memory alloys lose their functionality when the size of the constituent crystal grains goes below a certain limit, typically a few tens of nanometers.

“An additional surface is created between the transformed memory phase within the grain and the untransformed phase at the grain boundary, eventually leading to the suppression of memory transformation altogether at very small grain sizes,” says Jerry Quek at A*STAR’s Institute of High Performance Computing (IHPC). Because of this, SMAs, like most polycrystalline metals, become strong at very small grain sizes but lose their shape memory properties.

“Our findings could be useful in situations where both strength and shape memory effect are important.”

Seeking to create a material with high strength while retaining shape memory, Quek’s team ran computational simulations of various materials and grain sizes in SMAs, making use of the high performance computing capabilities of Singapore’s National Supercomputing Centre¹. “We were primarily interested in the reversible austenite–martensite phase transformation,” explains Quek. “The austenitic and martensitic phases have different atomic arrangements, and shape memory is possible if the material can be reversibly switched between the two phases, such as by changing temperature.”

The team simulated and observed how the martensitic phase developed by quenching an initial iron–palladium alloy in the austenite state. By studying a wide range of grain size combinations, the researchers were able to show that introducing a population of larger grains amid nano-sized grains reintroduces the shape memory effect while retaining the high strength of the nanoscale structure.

“We also showed that for a certain combination of grain sizes, we can obtain a microstructure in which one region undergoes phase transformation to martensite while other regions remain austenitic, which offers the possibility of designing materials with a varying degree of shape memory functionality across a material,” says Quek.

“Our findings could be useful in situations where both strength and shape memory effect are important,” he adds. ★

LEFT

Shape memory alloys reversibly undergo changes in shape when subjected to specific conditions.

1. Mikula, J., Quek, S. S., Joshi, S. P., Wu, D. T. & Ahluwalia, R. The role of bimodal grain size distribution in nanocrystalline shape memory alloys. *Smart Materials and Structures* **27**, 105004 (2018).

Photo credit: lenabelova / Shutterstock

POLYMERS

Radical steps toward clean encapsulation

Chemists use free radicals to produce polymers strong enough to encapsulate drugs while remaining degradable.

Star hyperbranched polymers are formed when linear chains stretch out from a central cross-linked core. The internal cavities of these core-shell structures can be used to encapsulate smaller, hydrophobic molecules. Studies indicate that the strong chemical bonds in these materials prevent the premature ‘burst release’ of cargo.

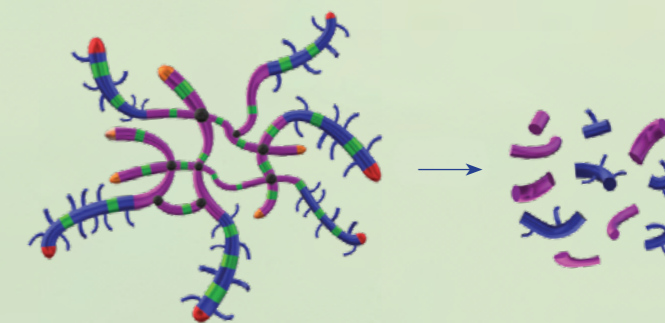
The robust nature of these polymers, however, also creates ecological and toxic hazards at the end of their useful life. Alexander Jackson from the A*STAR’s Institute of Chemical and Engineering Sciences (ICES) and colleagues have now synthesized star hyperbranched polymers that can both encapsulate drug molecules, and then biodegrade into smaller components¹.

Jackson explains that chemists have developed several tools to synthesize degradable polymers, one of which involves cyclic molecules known as ketene acetals. These compounds can be opened and linked into polyesters using free radical polymerization, this approach introduces carbon-oxygen bonds into the polymer chain which facilitate degradation reactions.

“Radical ring-opening polymerizations of cyclic ketene acetals have been

understood for about 30 years,” says Jackson. “The really exciting aspect of this research was to take this chemistry and combine it with modern techniques using ‘living’ polymer chains.”

Living polymerizations are so-called because they will continue to grow outwards upon addition of different building blocks. This gives chemists precise control over chain lengths and composition—critical features that are needed for advanced delivery devices.



ABOVE

A polymer that can both self-assemble into star-shaped nanoparticles and break down when no longer needed could impact chemical encapsulation technology.

Adapted from Ref. 1 with permission from The Royal Society of Chemistry

Initially, the researchers used living radical polymerization to prepare methacrylate-based structures. Experiments showed that these materials could reversibly swell and contract with changes in pH, as well as switch between individual particles and larger nanoscale aggregates, by simply changing the solution temperature. These triggers were used for controlled release of hydrophobic cargo.

Next, the A*STAR-based team optimized the conditions needed to perform ring-opening of cyclic ketene acetals simultaneously during the living methacrylate polymerization. This created a degradable analog of the initial stimuli-responsive structure.

“We will use this approach to develop even more of these kinds of polymers, including degradable polystyrene and other acrylates,” says Jackson. “This will prevent undesirable accumulation of these materials after they have delivered their cargo.”

Currently, the ICES scientists are helping manufacturers expand the possibilities of recyclable polymeric materials with the assistance of two industry alignment fund projects that focus on reaction engineering and encapsulation technologies. ★

1. Wais, U., Chennamaneni, L. R., Thoniyot, P., Zhang, H. & Jackson, A. Main-chain degradable star polymers comprised of pH-responsive hyperbranched cores and thermoresponsive polyethylene glycol-based coronas. *Polymer Chemistry* **9**, 4824–4839 (2018).

MICROBIOTA

Against gut instinct

By turning a pathogenic yeast into an immunity-conferring symbiont, a team of A*STAR researchers is unraveling the mysteries behind gut evolution and universal vaccines.

While attempting to increase a yeast's pathogenicity towards a non-native host, A*STAR researchers unexpectedly transformed the fungi into a symbiotic gut microbe that supported its host's survival instead of fighting it¹. This revelation implicates a recently discovered 'trained' immunity and could shed light on the origins of the mammalian gut microbiome.

"My first hypothesis was completely wrong," says Norman Pavelka at A*STAR's Singapore Immunology Network (SIgN). He had hoped that by taking the human-pathogenic yeast *Candida albicans* and exposing it repeatedly to a new host (mice), he could select and re-inoculate the best growers and force the evolution of a mouse-pathogenic strain. This process is known as serial passaging and is similar to the way classic 'live-attenuated' vaccines, such as those for polio and smallpox, are produced. By forcing pathogens to repeatedly adapt to new species, they lose their virulence towards humans.

Surprisingly, the passaged *C. albicans* lost, rather than gained, pathogenicity to their new host. Pavelka realized that their approach of using the mouse gut as the

selective environment, as opposed to the bloodstream, was probably to blame. "The gastrointestinal tract is where we make peace with microbes, not war. The selective pressure is completely different," he explains. Many animals, mice included, eat each other's feces, providing a transmission vector for pathogens. Microbes that evolve to thrive in their host's gastrointestinal tract without causing death are more likely to be passed to new hosts.

The team also found that the mutualistic mutations of *C. albicans* were hindered by the presence of other gut microbes, indicating its need to retain virulence to survive in a competitive environment. This also explains why *C. albicans* does not have a symbiotic relationship with its natural host, humans, as it is outcompeted by other microbes.

Mice colonized by or vaccinated with evolved *C. albicans* survived an otherwise-lethal injection—not only of wild-type, virulent *Candida* fungus, but also of other unrelated pathogenic fungi and bacteria. In fact, the team found that the evolved symbiotic fungi trained the mice's immune system via a pathway completely separate from traditional adaptive immunity, in which a host recognizes previously encountered pathogens via identifying structures called antigens. Instead, the response is indicative of a recently discovered process dubbed 'trained immunity.'

As trained immunity can offer broad protection against pathogens not previously encountered, Pavelka says this revelation could fuel investigations into 'universal' vaccines that could even protect patients with otherwise-compromised immune systems. Now, the team is working to reveal the scope of this cross-protection, and the mechanisms underpinning trained immunity. ★

1. Tso, G. H. W., Reales-Calderon, J. A., Tan, A. S. M., Sem, X., Le, G. T. T. *et al.* Experimental evolution of a fungal pathogen into a gut symbiont. *Science* **362**, 589–595 (2018).

Photo credit: Juan Gaertner / Shutterstock

A strain of fungus introduced into the gut of mice became 'trained' to support its host's survival.

CHEMORESISTANCE

Poised for survival

State-of-the-art single-cell RNA sequencing technologies shed light on the mechanisms through which cancer cells become resistant to tumor-treating drugs.

Drug resistance is a leading cause of cancer-associated deaths. Although many types of cancers initially succumb to chemotherapy, over time, a small subpopulation of cells stop responding to treatment and continue to proliferate and metastasize.

Exploring the survival strategies adopted by tumor cells when exposed to a cancer-treating drug, researchers led by Ramanuj DasGupta at the A*STAR Genome Institute of Singapore (GIS), in collaboration with N. Gopalakrishna Iyer at the National Cancer Centre Singapore, have identified mechanisms of drug-resistance only triggered when cancer cells experience selection pressure from cisplatin, a common anticancer therapeutic¹.

The team took advantage of recent advances in single cell transcriptomics to explore how changes in gene expression in individual, patient-derived primary cells contribute to drug resistance. They analyzed the RNA sequences of oral squamous carcinoma cells before and after exposure to cisplatin.

The molecular profiles of drug-treated cells grown in the laboratory were remarkably similar to those of tumor cells in the same patient's body. "By mimicking the clinical conditions and tracking the behavior of individual cancer cells, we are able to precisely predict and identify mechanisms of tumor evolution in the clinic," says DasGupta.

They found that upon drug treatment, some cancer cells continue to proliferate even when treated with high drug doses, and even start to express genes associated

with drug resistance and metastasis. Part of this transition to a resistant state involves epigenetic programming.

The researchers reported transcription-regulating chromatin marks on resistance-associated genes, indicating that those genes are epigenetically poised to be switched on or off. Exposure to cisplatin caused the cancer cells to increase the addition of acetyl groups on histone H3 (H3K27ac), which allows for the recruitment of transcription factors to otherwise inaccessible sites.

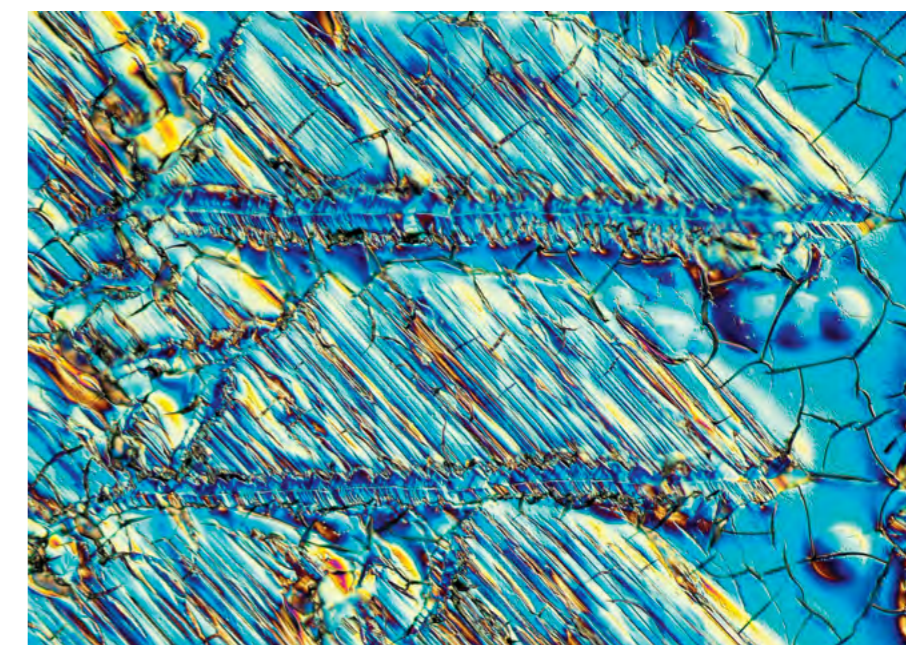
Probing deeper, the team further identified that drug-induced resistant cells

are characterized by the loss of stem-cell factor SOX2 and a gain of SOX9 expression. The specific enrichment of SOX9 at H3K27ac sites underscores the role of this factor in the epigenetic reprogramming that drives drug-induced cancer resistance in homogeneous tumors.

Inhibiting the histone acetyltransferase BRD4 with the small molecule epigenetic drug JQ1 reduced H3K27ac and the cisplatin-induced cell-fate switching, thus reversing drug-resistance. This result highlights the exciting possibility of using epigenetic inhibitors along with targeted therapies to prevent or delay the emergence of drug resistance.

"Our next steps will involve looking at the evolution of different cancers under a variety of selective stresses and at the cell-cell interactions within the tumor to determine how they influence the evolution of different cell types," concludes DasGupta. ★

1. Sharma, A., Cao, E. Y., Kumar, V., Zhang, X., Leong, H. S., *et al.* Longitudinal single-cell RNA sequencing of patient-derived primary cells reveals drug-induced infidelity in stem cell hierarchy. *Nature Communications* **9**, 4931 (2018).



Polarised light micrograph (PLM) of cisplatin crystals. Resistance to cisplatin, a commonly used drug in cancer therapy, can arise due to epigenetic programming in cancer cells.

Photo credit: Alfred Pasiaka / Science Photo Library

METASURFACES

Tuning terahertz transmission

A metasurface whose optical properties change in response to electricity provides precise control over the reflection and transmission of radiation.

The ability to manipulate light on a subwavelength-scale could lead to a revolution in photonic devices such as antennas, solar panels, and even cloaking devices. Nanotechnology advances have made this possible through the development of metasurfaces, materials covered in features smaller than the wavelength of the light.

Now, a team led by A*STAR researchers has produced a metasurface that can be precisely controlled using a conventional electrical circuit so that it reflects and transmits different amounts of radiation¹.

“Terahertz radiation can penetrate a wide variety of non-conducting materials, but is blocked by liquid water or metals,” explains Lu Ding, who led the work with Jinghua Teng at the A*STAR Institute of Materials Research and Engineering (IMRE). “This means that terahertz beams can be used for material characterization, layer inspection and the production of high-resolution images of the interior of solid objects. It is non-ionizing radiation, and safer than X-rays.”

Previous metasurfaces have been designed to manipulate the reflection of terahertz radiation. However, their application has been limited, as Ding explains: “Conventional terahertz antireflection surfaces are passive and often employ an ultrathin metal coating that, once fabricated, becomes fixed and can’t be actively tuned to improve performance.”

“An electrically tunable metasurface would produce more versatile devices and render more flexibility in system design,” Teng adds.

The researchers fabricated their metasurface on a silicon wafer, using a process entirely compatible with the complementary metal-oxide semiconductor (CMOS) technologies that underpin most electronics. The exposed metasurface contains stripes of semiconducting silicon doped with other elements. These stripes are alternately n-type, in which the moving charge carriers are electrons, and p-type, in which the carriers are positively-charged ‘holes’ in the electron structure. When the

voltage supplied to the p-n junctions is changed, the reflection and transmission of the radiation also change.

The team realized that the reflection coefficient of their metasurface increased in response to a temperature rise caused by the applied voltage. Meanwhile, the transmission showed a more complex response depending on the voltage polarity, which affected the type of charge carrier that became dominant. Using terahertz time-domain spectroscopy, the team showed that certain voltage conditions caused the echo pulse from the metasurface to vanish, representing complete antireflection.

“Another big advantage is for our research looking into how 2D materials interact with 2D metamaterials or metasurfaces, a topic in our project under A*STAR’s 2D Semiconductors Pharos Program,” says Teng. “The atomically smooth surface makes the transfer and formation of 2D silicon heterostructures much easier than the patterned surfaces of nano-sized pillars or disks seen on conventional metasurfaces.”

“We could further exploit this type of metasurface by independently biasing the p-n junctions or designing modular functions, meaning that we would have pre-programmable metamaterials,” says Ding. ★

BELOW

Solar panels could benefit from metasurfaces that interact with light in unique ways.

1. Ding, L., Luo, X., Cheng, L., Thway, M., Song, J. *et al.* Electrically and thermally tunable smooth silicon metasurfaces for broadband terahertz antireflection. *Advanced Optical Materials*, 1800928 (2018).

Photo credit: KhanunHaha / Shutterstock

INFECTIOUS DISEASES

The coincidental complications of coinfection

Malaria infections may be masking the extent of the emerging chikungunya epidemic.

The chikungunya virus is rapidly spreading around the world and encroaching into areas already plagued by malaria, which means that more people are falling ill with both mosquito-borne infections. That might sound dire, but according to a new study by A*STAR scientists, prior exposure to malaria may help protect against complications of chikungunya.

That is the good news. The downside, according to Lisa Ng, a viral immunologist at A*STAR’s Singapore Immunology Network (SIgN) who co-led the study, is that the protective benefit is probably masking the true scale of the global chikungunya epidemic. “In co-endemic regions, a reduction in malaria cases could indirectly result in an increase in clinical cases of chikungunya fever,” she says.

To explore the health effects of co-contagion, Ng collaborated with Laurent Rénia at SIgN to infect mice with both the chikungunya virus, which causes fever and severe joint pain, and two forms of rodent *Plasmodium* parasite responsible for malaria.

Reporting in *Nature Communications*, the team found that mice pre-infected with *Plasmodium* and then exposed to chikungunya virus four days later did not exhibit joint inflammation¹. Mice that had been infected with *Plasmodium* prior to chikungunya virus exposure also showed

reduced levels of the chikungunya virus in the blood.

The protective effects were less pronounced among mice infected with both malaria and chikungunya at the same time. In that case, peak joint swelling declined, but the amount of chikungunya virus in the bloodstream was the same as in mice exposed to chikungunya virus alone. No beneficial effects were seen in mice that had completely recovered from a malarial infection, or when malaria was introduced four days after the chikungunya virus when the latter infection was already in full swing.

To explain their observations, the researchers looked closely at the immune mechanisms by which prior or concurrent exposure to malaria parasites safeguards against chikungunya virus-induced joint damage. They found that *Plasmodium* infection stimulated the production of a critical immune-modulating molecule called interferon-gamma that primed joint cells to be on the alert for viruses like chikungunya. The prior *Plasmodium* exposure also limited the number of pro-inflammatory T cells that normally infiltrate joint tissue and drive swelling in response to the virus.

Nonetheless, the researchers noted that co-infection with *Plasmodium* could restrict the maturation of B cells

that are needed to make chikungunya-fighting antibodies. To recreate only the immunological benefits of co-infection without the negative consequences for B cells, Ng suggested using drugs to target a cell signaling receptor protein called CXCR3, which plays a role in the immune response to infection by both pathogens.

“Currently, there are several small molecules that could antagonize CXCR3 in patients,” Ng says. “Perhaps the use of CXCR3-targeted therapies could be considered in regions where the diseases are co-endemic.” ★

ABOVE

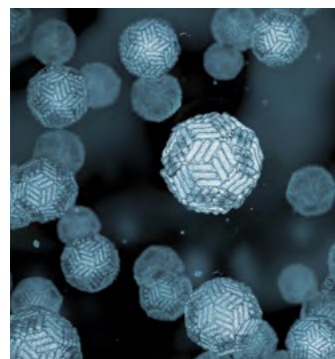
Mosquitoes help spread several disease-causing microbes, and co-infections may sometimes have unexpected health impacts.

1. Teo, T. H., Lum, F. M., Ghaffar, K., Chan, Y. H., Amrun, S. N. *et al.* *Plasmodium* co-infection protects against chikungunya virus-induced pathologies. *Nature Communications* 9, 3905 (2018).

Photo credit: frank60 / Shutterstock

NEXT ISSUE

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



DIAGNOSTICS ONE TEST TO DETERMINE THEM ALL

A*STAR researchers have devised a method that can detect and distinguish closely related flaviviruses with 100 percent accuracy.



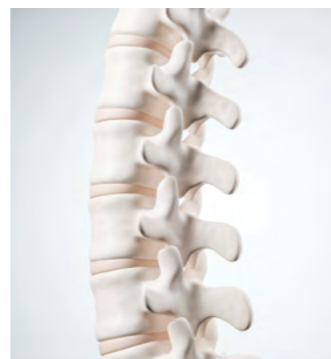
NANOTECHNOLOGY CREATING COLORS WITHOUT DYES

Nanofabricated metallic structure arrays produce a kaleidoscope of bright colors.



ENVIRONMENT SIMULATIONS SHED LIGHT ON AIR FILTER DEPLOYMENT

Using computational tools, A*STAR researchers are learning how best to deploy air treatment systems across large urban areas.



STEM CELLS GROWING A 'SPINE' ON A CHIP

Microfluidic device allows for precise control of growth factor gradients, mimicking natural spinal cord development *in vitro*.

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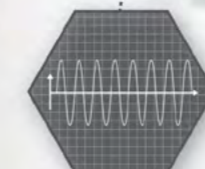


Agency for
Science, Technology
and Research

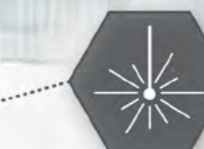
X-ray sources used in medicine and other industries have remained virtually unchanged for over a century. Leveraging the unique properties of novel 2D materials, Dr. Wong Liang Jie and a team of collaborators have conceived a method to generate intense, continuously tunable X-rays on a microchip scale. The laser beam-like quality of the X-ray output also allows for more precise pinpointing of medical and dental X-rays, enabling lower dosages and leading to safer, more efficient and less costly X-ray sources in the future.

CHIP-SCALE SOURCES OF POWERFUL X-RAYS MAY SOON BECOME A REALITY

Infrared or optical light creates nanoscale electromagnetic structures on the surface of 2D materials such as graphene.



Nanoscale electromagnetic structures induce wiggling in electrons sent through them.



Rapid wiggling in modestly relativistic electrons produces high quality, hard X-rays.



INDUSTRIAL QUALITY
CONTROL



BIOMEDICAL IMAGING

[KEY APPLICATIONS]



MEDICAL TREATMENT



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Dr. Wong Liang Jie

Scientist, Singapore Institute of Manufacturing Technology
PhD and Postdoctoral Fellow, Massachusetts Institute of Technology

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