

# A\*STAR RESEARCH

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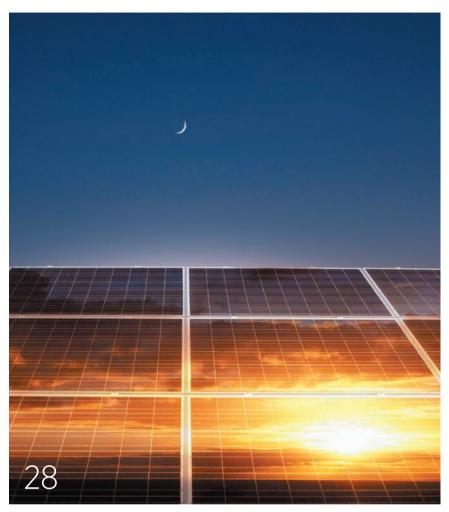
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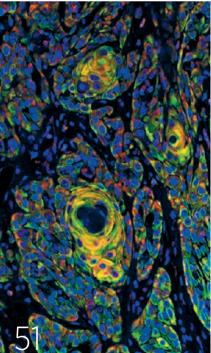
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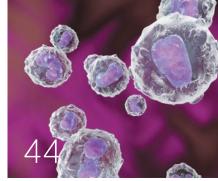
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elcome to the first edition of A\*STAR Research for 2018, where we highlight some of the latest cutting-edge research and innovations from A\*STAR.

Our cover story this issue introduces the Diagnostics Development (DxD) Hub — a nationally funded program led by ETPL, A\*STAR's commercialization arm, which accelerates the journey of diagnostics devices from lab to market (page 8). And continuing on from our previous issue's cover story, which discussed the insidious obesity problem in Asia, our second feature story this issue investigates an important but elusive problem — that of heart failure, which affects roughly 26 million people worldwide (page 4).

We also showcase exciting developments in the immunity field, including the identification of a new key immune cell subtype in human blood, 'pre-DC', as a precursor of dendritic cells (page 27), and the discovery of a potent antibody that can neutralize all

four serotypes of dengue (page 18) — both of which have important implications on vaccine development. And on the genetics side, while mutations are often detrimental to health, for example in a joint disorder called arthrogryposis (page 40), they can also occasionally offer protection against certain diseases, such as glaucoma (page 14).

A couple of interesting innovations in renewable energy materials are also presented a novel cathode material for lithium-ion batteries that can potentially increase battery capacity severalfold (page 39), and a simple and costeffective technique for manufacturing solar cells out of non-toxic common materials (page 28). And another group of researchers have found a way to make tunable magnetic skyrmions that could lead to next-generation memory and computing technologies (page 31).

There are many more fascinating and exciting stories from A\*STAR researchers in this issue, I hope you will enjoy the rest of our newly redesigned magazine.



**COVER IMAGE** Diagnostic tests are being fast-tracked by Singapore's DxD Hub. [page 8]

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# ATTRACTING THE BEST TO FIGHT HEART FAILURE

A new initiative will investigate the causes of heart failure in unprecedented detail.

n A\*STAR-led study into heart failure, the largest ever conducted in Singapore, is revealing new ways to predict death or admission to hospital for people who have suffered heart failure, as well as opening potential new avenues to reduce the risk of heart failure occurring.

It's all part of the Asian neTwork for Translational Research and Cardiovascular Trials (ATTRaCT), a S\$30 million government-backed initiative that for the first time has brought together leading cardiologists and heart disease researchers from A\*STAR, the National University of Singapore (NUS), the Duke-NUS Medical School and two national heart institutions (National University Heart Centre and National Heart Centre Singapore). Also involved are Singapore's Khoo Teck Puat Hospital, Tan Tock Seng Hospital, Changi General

Hospital and Singapore General Hospital. Together, this all-star cast is throwing the weight of Singapore's scientific expertise and resources at heart disease, one of the country's biggest killers, responsible for roughly 30 per cent of all deaths.

"ATTRaCT is the first integrated platform for translational cardiovascular research that leverages Singapore's competitive advantages to identify and validate novel targets in heart disease progression," says Carolyn Lam, a professor at the Duke-NUS Medical School and senior consultant cardiologist at the National Heart Centre Singapore, who is leading the program.

Launched in 2015, ATTRaCT builds on previous Singapore-led initiatives such as the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry, an 11-nation study of more than 6,000 heart failure patients. However, ATTRaCT goes much further, using advanced cardiac



Matthias Tunger/ Getty images





The study is the first large-scale trial in Asia that seeks to unravel differences in the two distinct forms of heart failure.

imaging, genetic and molecular studies to look at the root causes of heart diseases in patients and animal models.

#### **HEART OF THE MATTER**

The linchpin of the program is a nationwide prospective study involving Singaporeans with heart failure and healthy controls. Over three years, each of the trial's 1,200 participants will undergo a battery of sophisticated diagnostic tests. These include magnetic resonance imaging to view the heart's anatomy and the health of its tissues. Blood samples are also examined for novel molecular and immunologic indicators of disease. Also, geneticists are decoding the full genome sequence of each individual.

The clinical part of the study is yielding a wealth of data, so much

that leaders of the A\*STAR Bioinformatics Institute were enlisted to help with its management and analysis. Those clinical findings were then fed into the program's more basic discovery efforts.

The goal, says Lam, is to better understand the mechanisms underlying disease progression so researchers can identify molecular pathways that can be targeted to prevent heart failure. The ATTRaCT investigators also hope to develop new imaging modalities or blood-based tests for detecting early signs of pre-symptomatic disease, as well as reveal the genetic factors responsible for predisposing people to heart issues.

### AN UNMET MEDICAL NEED

The study is the first large-scale trial in Asia that seeks to unravel differences in the two distinct forms of heart failure, each of which is defined by the amount of blood pumped out of the heart with each beat.

For about half of patients with heart failure, blood volume is reduced, causing what is known as heart failure with reduced ejection fraction, or HFrEF, a problem that can be treated with drugs that help maintain fluid balance in the body. The other half maintain what seems like normal blood volumes. but the heart muscle thickens and becomes stiff, limiting its capacity to meet the body's needs. This is known as heart failure with preserved ejection fraction, or HFpEF, and it has no effective remedies — in part because so little is known about what drives this muscle thickening and why, for instance, women are more

#### THE TWO TYPES OF HEART FAILURE

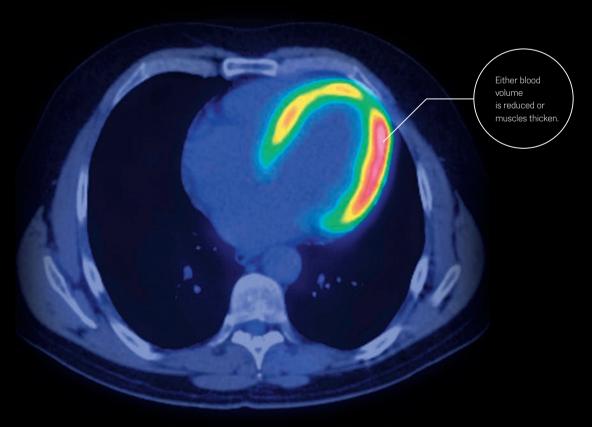
Heart failure with preserved ejection fraction (HFpEF)

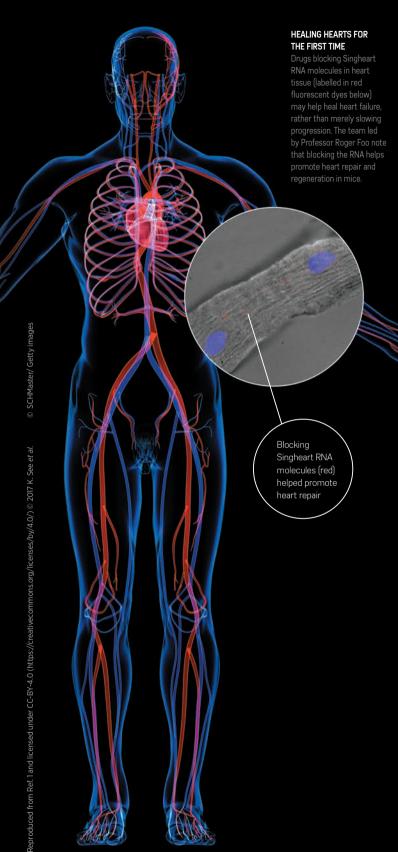
- and little understood

Heart failure with reduced

#### CARDIOVASCULAR FAILURE

with heart failure. The ATTRaCT program is the first large-scale trial in the world that seeks muscle thickens and





predisposed to HFpEF than men. "Fundamentally," says Roger Foo of the A\*STAR Genome Institute of Singapore, "we still need to understand what the biology of that disease is."

Foo is one of ATTRaCT's leaders, in charge of all research related to genetics and epigenetics. Other leaders include Patrick Cozzone, executive director of the A\*STAR Singapore Bioimaging Consortium, who runs the imaging track of the study, and Mark Richards, a cardiologist who directs the NUS Cardiovascular Research Institute and is heading efforts to discover blood biomarkers of disease. The ATTRaCT network also collaborates with several of the largest pharmaceutical companies in the world.

"It's an impressive research team-multi-national, multi-disciplinary and multi-institutional," says John McMurray, a cardiologist at the University of Glasgow's Institute of Cardiovascular and Medical Sciences in Scotland, who serves on the external scientific review committee for ATTRaCT. "I've reviewed initiatives like this in other countries, but this one is special, helped by charismatic, strong and focused leadership, and sympathetic and supportive government oversight."

#### **INITIAL FINDINGS**

ATTRaCT is only just past the halfway mark, but has already spurred a number of seminal discoveries. For example, the study investigators have filed to patent a new imaging technique that can track metabolism in the heart muscle like never before.

They've also pinpointed a molecule circulating in the bloodstream of patients that predicts outcomes specifically in women with HFpEF, potentially shedding light on the female predisposition to the disease.

Notably, the discovery of a molecule in the blood of patients with HFpEF, known to be the target of a drug that's already widely used for other types of diseases, suggests that the same drug could conceivably be repurposed to help deal with the unique pathology of HFpEF.

Foo and his colleagues also recently identified an RNA molecule (pictured left, in red) involved in regulating the heart's response to stress. This molecule, they reported in the journal Nature Communications, is active in diseased heart tissue from patients, and blocking it helped promote heart repair and regeneration in mice.1 Currently, notes Foo, no known therapies can do that—all existing heart medications merely slow disease progression. Now, he says, "the question is: can we heal the heart and cause recovery and reverse disease in patients?"

By mid-2019, when ATTRaCT has run its course, Lam hopes the platform will transform from an observational one for target discovery, to an interventional one for precision trials in heart disease. At that point, novel and repurposed drugs discovered in the first phase of the program should be ready for clinical testing in patients. "To achieve this," she says, "continued strong partnership among the clinical and research institutions, as well as between academia and industry, are essential."

 See, K., Tan, W.L.W., Lim, E.H., Tiang, Z., Lee, L.T., et al. Single cardiomyocyte nuclear transcriptomes reveal a lincRNA-regulated de-differentiation and cell cycle stress-response in vivo. Nature Communications 8, 225 (2017)

# DIAGNOSTIC TOOLS IN THE FAST LANE

Diagnostics tests are the key to the early detection and treatment of diseases — and Singapore's Diagnostics Development (DxD) Hub is accelerating the rate at which devices make it from the lab to market.

ancer could become a chronic condition rather than a terminal sentence with the right diagnostic tools, says Sidney Yee, CEO of the almost 4-year-old Diagnostics Development (DxD) Hub, a national initiative led by A\*STAR's commercialization arm, ETPL. "I strongly believe the key to managing oncology is early detection. And, if we can make minimally invasive or noninvasive tests, it's convenient, which means people can test more frequently if they have a high-risk profile." Sometimes, however, research that could make this possible isn't making it to doctors and patients.

Founded in 2014, the DxD Hub's role is to accelerate the process of taking diagnostic devices to market. The hub was seeded as part of the

Singaporean government's Innovation Cluster Programme, and its work covers a number of key areas: to make sure that researchers with intellectual property (IP) connect with the right business partners; to test their findings to make sure they are clinically reproducible; to design application devices that meet regulatory standards; to look for pain points in the adoption of a diagnostics tool; and, to mine data from Singaporean research spanning the last two decades for insights that could be turned into useful diagnostic tests. "We don't do any of the research," says Yee. "Instead we develop already existing IP that has sufficient evidence to support diagnostic use, meet clinical needs, and have a market demand. The output of that co-development is actually a regulatory dossier



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test (i.e. a test taken from a blood sample) for the early detection of gastric cancer. Gastric cancer, which kills more than 700,000 people worldwide only detectable via an uncomfortable inspection using a long tube called expensive and invasive for people with a high-risk profile to be doing these scope tests all the time. Some countries like Japan and Korea, with among some of the highest rates of gastric cancer in the world, hugely subsidize scope tests for at-risk parts of the population, yet we still see gastric cancers that are detected

biomarkers. The genome liquid biopsy test sprang from a microRNA platform that A\*STAR and the National University of Singapore had been developing for some years. That team partnered diagnostics company MiRXES, an early DxD Hub collaborator and a spin-off company from Technology Institute, to do some of the most extensive clinical trials of these types of tests in the world. GastroClear was recently approved for the European market of 32 countries, and the collaboration hopes to introduce the test to the Singapore market by the end of 2018.

that goes to the government regulatory authorities for approval."

The DxD Hub's framework means it invests in diagnostics all the way to the market stage. "My job is not finished when something gets regulatory approval. I also have to make sure that it reaches its intended patients," Yee says. This, as well as an accessible and standardized legal framework for sharing IP, signals to commercial partners that their initial input will quickly result in something useful to the market. From a national perspective, she says, that's an ideal outcome: "If research doesn't change clinical practice, it's probably not going to make any difference to patients."

From her experience as both the DxD Hub's CEO and an executive vice president at the ETPL, Yee observes that while scientific creators of IP possess



technological know-how, there is little awareness of how to turn that technology into a product. "DxD is a high-throughput engine to help startups and researchers develop diagnostic tests. Those startups may then later translate IP on their own or they can continue to work with us. So, the DxD Hub will have a multiplier effect too." Yee notes that it is often not appreciated that IP translation is an industrialized process that produces regulated diagnostics solutions, and requires the careful integration of biology, engineering and technology platforms. The hope is to educate and train people on how to translate research into new commercial products in companies all over Singapore, she says.

While the DxD Hub is led by A\*STAR's ETPL, it is a nationally funded program and many of its projects also come from external parties. Oncology diagnostics is currently its biggest portfolio, followed by cardiovascular and infectious diseases, metabolic diseases and neurological disorders. Currently, the hub is actively working on 25 diagnostic projects.

The DxD Hub is careful to keep their attrition rates in line with industry and select the right projects. The hub is in the preliminary stages of assessing over 400 different projects, with a projected attrition rate of approximately 90 to 95 per cent. That's roughly the same as commercial industry, Yee says. Of these 400, they will identify 150 that have the evidence to answer specific diagnostic questions, which will then be examined from a business development standpoint. At any one time, DxD Hub will be in discussions with potential business partners on 40 to 50 of the projects.

#### **ASIAN RESEARCH COMING** OF AGE AND READY FOR **TRANSLATION**

With the acceleration of genomics and technology, Asian research as a whole is turning its attention to translation says Yee. There is currently a market of 700 million people or more

"We're also getting more information on how the Asian phenotype is unique and different..."

in Asia who are starting to spend as much, if not more, per head on medicine as their western counterparts. "We're also getting more information on how the Asian phenotype is unique and different, and so everything is coming together at a time when it's not just information we need, but also actionable information," she says. Fortunately, Singapore has been investing in biomedical research and engineering for many years. It will serve them well as clinical solutions customized for Asian populations become much more important to markets. "We were always developing healthcare solutions for a global population, but not really paying attention to the differences in the different populations. Now we need to look at solutions for Asian populations more specifically." The idea of personalized medicine like this is not new. says Yee, but it's only now possible because technologies like deep learning are converging with genomics.

The DxD Hub is very well placed geographically to use existing Asian data to look for these solutions and has already found some of

its ideas for diagnostic tools, such as the gastric cancer test (see left box) or staging and differentiating liver fibrosis for better treatment outcomes, in pre-existing A\*STAR research. "We don't do discovery of any genetic biomarkers or protein biomarkers, instead our job is to mine what has already been done in the ecosystem," Yee says.

The hub also hopes to curate existing data so that artificial intelligence (AI) is better able to deliver personal and multimodal healthcare solutions – a process that Yee calls "digital diagnostics".

"To do digital diagnostics, we need a lot of correlated and curated data. It would take us years to gather the data if we started from zero. So, we're looking back at what we've already done." Over the last few decades, Yee says, Singapore has invested heavily in medical research. "Now is the time to harvest tangible results."





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## CHROMOSOMES FIND THE PERFECT MATCH

A protein duo ensures that the chromosomes in reproductive cells find their significant other.

Reproduction is made easier by finding the right partner — and it's no different for the chromosomes inside reproductive cells. Now, an international team of researchers, including A\*STAR scientists, has revealed just how chromosomes find their perfect match.

The tightly-wound chromosomes that carry the genetic code inside living cells may float around the cell nucleus on their own, but they all have a genetically similar partner, or homolog, with one inherited from each parent.

During the life cycle of reproductive cells, these homologs need to find and dock to each other to ensure that the DNA is correctly distributed to the sperm or egg: a bad chromosome match can render the entire cell non-functional. Even worse, failure to distribute chromosomes correctly

can lead to a variety of inherited disorders.

In 2013, Brian Burke and Colin Stewart from the A\*STAR Institute of Medical Biology set out to discover how chromosomes find their match.

"The whole system is far more dynamic than one would appreciate from reading your average cell biology textbook!"

They revealed that a protein called KASH5 acts as an adaptor for a molecular motor which shuffles along the microtubule scaffolding of the cell. Mice modified to lack KASH5 were infertile.

The scientists proposed that KASH5 docks to the surface of the nucleus and teams up with another protein — SUN1 — which locks on to the ends of chromosomes inside the nucleus. With SUN1 and KASH5 attached, the chromosomes inside the nucleus would get dragged along the microtubule scaffolding randomly, allowing for the chromosomes to bump into their homologs.

For this paper, Burke teamed up with scientists at the University of Oklahoma to confirm the theory.

The team stained the DNA in living sperm precursor cells from normal mice and mice lacking KASH5, and imaged the cells' chromosome movements in three dimensions. Specialized algorithms revealed that, unlike normal cells, the chromosomes stop moving when KASH5 is lacking, which confirms the team's model. "This was really gratifying to see," says Burke.

The paper co-authors are now chasing leads on how mutations in either KASH5 or SUN1 could be causing infertility in humans and are investigating how similar protein duos may be working together to distribute the nuclei located in other cell types, such as skeletal muscle cell.

"We have to stop thinking of the nuclear envelope as just sort of a bag for genes which just sit there and do nothing but be transcribed," says Burke. "The whole system is far more dynamic than one would appreciate from reading your average cell biology textbook!"

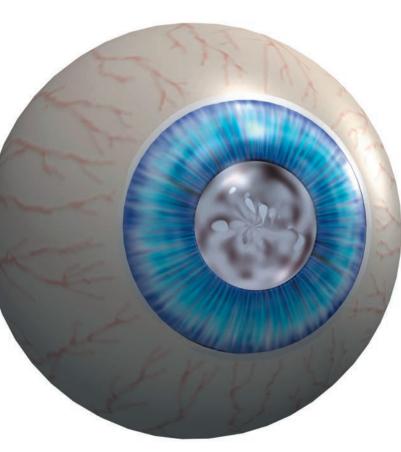
 Lee, C.-Y., Horn, H. F., Stewart, C. L., Burke, B., Bolcun-Filas, E. et al. Mechanism and regulation of rapid telomere prophase movements in mouse meiotic chromosomes. Cell Reports 11, 551-563 (2015).

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# EYES OPEN TO A PROTECTIVE MUTATION

A genetic mutation that protects against glaucoma has been uncovered during an international study into exfoliation syndrome.



A\*STAR researchers, together with an international team of scientists, uncover a rare, protective mutation that appears to prevent glaucoma and the progression of exfoliation syndrome.

A leading cause of glaucoma and blindness is exfoliation syndrome, or XFS, an age-related disorder that results in excess fibrous material building up. Now, A\*STAR scientists, along with an international research team, have found a novel mutation on the *LOXL1* gene that appears to protect against XFS and glaucoma, alongside five new locations on a chromosome associated with XFS1.

"This mutation has never been seen before, and it goes some way to explain why some people appear to be resistant to XFS' effects."

"We started a large-scale, international study of XFS in November 2012," explains Chiea Chuen Khor at the A\*STAR Genome Institute of Singapore, who led the research. "Despite the large sample size on this first project, we could only identify one other gene locus (CACNA1A) consistently associated with XFS to add to the known locus, LOXL1. XFS could not be explained by just LOXL1 and CACNA1A. There had to be more biological determinants."

As the body ages, molecules that provide both physical structure and biochemical support to all tissues and organs — the socalled 'extracellular matrix', or ECM — can begin to decline, resulting in abnormalities and the development of XFS. In XFS, cells are torn, or 'exfoliated', from the ECM; this is most prominent in the eye, and can severely damage

the ocular nerves and tissues.

The team conducted deep-sequencing analysis of both *LOXL1* and *CACNA1A* in samples from 5,570 XFS cases and 6,279 healthy controls from nine countries. Many of the participants were Japanese, and it was within this specific population that Khor's team found a rare, protective mutation in the healthy control group; the p.407F allele, located at the *LOXL1* gene.

"This mutation has never been seen before, and it goes some way to explain why some people appear to be resistant to XFS' effects," says Khor. "Although aging 'loads the gun' by inducing cell damage and potentially triggering the exfoliative process, the presence of the p.407F allele seems to markedly increase ECM material, and cells with the mutation bind together more strongly, delaying the progress of the disease."

The mutation at *LOXL1* considerably reduces the chances of developing glaucoma, and represents a promising target for future therapies to treat this widespread, debilitating condition.

"If we can stop cells from exfoliating, we may prevent the disease from occurring," says Khor. "The data gives us clues as to how we might target *LOXL1* to try to make this happen."

Khor's team also performed a genome-wide association study on a larger cohort from 24 countries, uncovering five new genetic loci associated with XFS susceptibility, which they will investigate soon.

 Aung, T., Ozaki, M., Lee, M. C., Schlötzer-Schrehardt, U., Thorleifsson, G. et al. Genetic association study of exfoliation syndrome identifies a protective rare variant at LOXL1 and five new susceptibility loci. Nature Genetics 49, 993–1004 (2017).

### **FAST FLOW TO SAFETY**

A new data structure developed at A\*STAR allows rapid tracking and policing of data flowing in and out of a network.



The way that network traffic is tracked has a huge effect on the speed at which it can be analyzed and checked for malicious activities. The REX data structure developed at A\*STAR is faster and more resilient against attacks than previous efforts.

To protect networks from malicious threats, cybersecurity solutions must track all the data flowing through the network — just like security guards checking travelers in airports. However, it is hard to design a solution that works fast enough to process all the information in real time, and to block threats before they can strike. Now, A\*STAR researchers have designed a way to structure data that is robust against cyber-attacks and allows it to be processed in record time.

The team's work improves on widely-used data structures called 'hash tables'. "A hash table maps values to specific locations, labeled with indices," explains Vrizlynn Thing from A\*STAR's Institute for Infocomm Research, who led the study. "To find a value, the hash table performs computations to quickly identify the indices and thus, its location. The challenges are that millions of values need to be stored, and the values are generated and transmitted extremely quickly."

Traditional hash tables are becoming inefficient as the internet grows and data flows get larger. Researchers have developed data structures known as Cuckoo and Peacock, but when they are under attack,

these hash tables fill up quickly, eroding performance.

### "We also utilized the special processing property of computer RAM."

The new data structure developed by Thing and her team is called REX. "The name REX stands for Resilient and Efficient data Structure (X for structure)" says Thing. Jokingly, Thing explained that this data structure was named REX (after Tyrannosaurus Rex) to

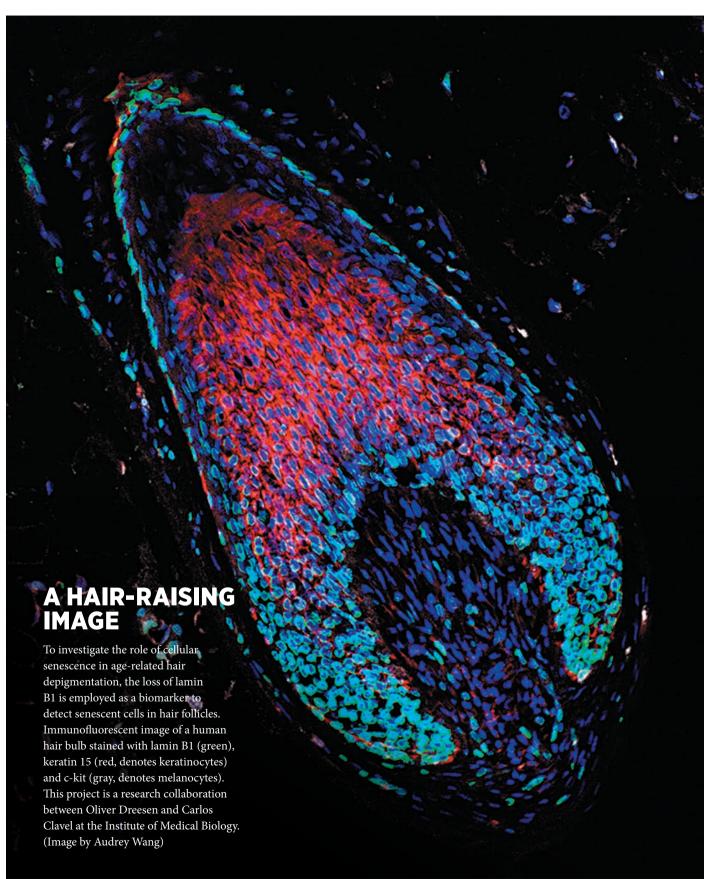
signify a stronger creature than the Cuckoo and Peacock as it outperforms both tables.

REX works by exploiting some inherent characteristics of internet traffic. For example, it takes into account the 'heavytail' behavior of data flows (there are a few large 'elephant flows' which contribute to a larger percentage of the total volume than the many small 'mice flows'), by employing a hierarchy of sub-tables increasing in size from top to bottom. This structure effectively segregates the different types of flows.

"We also utilized the special processing property of computer RAM," says Thing. "Our design features both fast, expensive Static RAM and slower, cheaper Dynamic RAM." The faster SRAM is used to process the few large, important flows, allowing fast tracking and frequent updates, while DRAM handles the low priority flows in secondary sub-tables.

In tests using real recorded network traffic, REX was faster and more efficient at analyzing data than Cuckoo and Peacock. "We will further investigate the efficiency and scalability of this new data structure for security analysis in larger scale environments," says Thing.

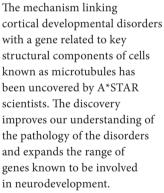
1. Divakaran, D. M., Ko, L. L., Su, L. & Thing, V. L. L. REX: Resilient and efficient data structure for tracking network flows. Computer Networks 118, 37-53 (2017).



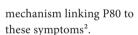
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## WHAT MAKES **BRAINS GROW SMOOTH AND SMALL?**

Researchers uncover how a microtubule-related gene affects neural development.



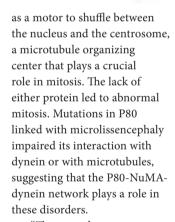
Microcephaly and lissencephaly are disorders in which brains develop to be abnormally small or abnormally smooth, respectively. In 2014, Bruno Reversade's team at the A\*STAR Institute of Medical Biology and Chris Walsh's lab at Harvard showed that patients with both disorders - microlissencephaly - carry a mutated version of the P80 gene, which encodes a subunit of the KATNB1 gene1. In a follow-up paper, the Reversade lab and their collaborators in Japan have uncovered the



The study began with a search for proteins that interact with P80. To the researchers' surprise, they discovered an interaction with NuMA, a well-studied protein which organizes microtubules during mitosis. They also confirmed that P80 binds to dynein, a molecular motor associated with microtubules that had already been identified as a P80 partner.

"With each gene causing a similar phenotype, we are adding more pieces to the puzzle."

The researchers then investigated how these proteins regulate microtubules during mitosis. They showed that P80 and NuMA use dynein



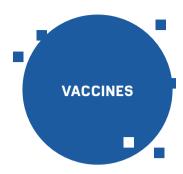
"The most elegant assay we did was the in vitro aster formation," says Oz Pomp, a scientist in the Reversade lab who co-led this project. Asters are microtubule arrays formed during mitosis around the centrosome, an organelle which forms microtubules and regulates the cell cycle, and Pomp was amazed to find that combining P80, NuMA, dynein, microtubules, and the energy-storage molecule ATP in a test tube was enough for asters to form.

Finally, the team showed

that P80 and NuMA activity in the centrosome is essential for neural development. In mouse embryos, neurons lacking either protein differentiated early, divided insufficiently, and migrated abnormally.

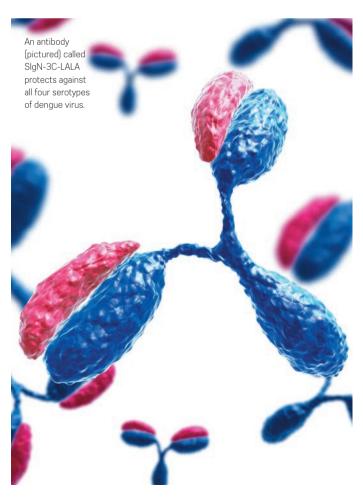
"With each gene causing a similar phenotype, we are adding more pieces to the puzzle. By connecting the dots we will eventually get the big picture of how a human brain is built," says Reversade. In the meantime, each gene they identify improves the prospects of genetic counseling and screening and provides a new avenue for researchers studying brain disorders.

- 1. Hu, W. F., Pomp, O., Ben-Omran, T., Kodani, A., Henke, K. et al. Katanin p80 regulates human cortical development by limiting centriole and cilia number. Neuron 84, 1240-1257 (2014).
- 2. Jin, M., Pomp, O., Shinoda, T., Toba, S., Torisawa, T. et al. Katanin p80, NuMA and cytoplasmic dynein cooperate to control microtubule dynamics. Scientific Reports 7, 39902 (2017).



# A DENGUE TREATMENT THAT IS ONE 'FOUR' ALL

An antibody that targets all four strains of the virus renews hope for effectively treating and preventing dengue.



A vaccine candidate that blocks infection and confers protection against all four strains of dengue virus has been uncovered by Katja Fink and Cheng-I Wang from the A\*STAR Singapore Immunology Network, in collaboration with colleagues from across Singapore.

The mosquito-borne dengue virus currently has no specific vaccine or treatment. Originally confined to Southeast Asia, the dengue virus has now spread to southern China, Africa, Indonesia, Australasia, Latin America and the United States. Millions of people are infected by the virus each year and usually develop mild flu-like symptoms and a characteristic skin rash. However, around one in every thousand cases is fatal due to dengue hemorrhagic fever or dengue shock syndrome.

The development of a safe and effective small molecule drug or vaccine against dengue has been elusive, partly due to the complexity of the virus itself. There are four strains or 'serotypes' and each produces different immune responses by interacting with antibodies in human blood serum. Fink's team have been working to develop a therapeutic agent that is effectively a combination of four treatments.

Their first step was to isolate an antibody (SIgN-3C) produced by a naturally-infected dengue patient that is able to bind to all four dengue virus serotypes and prevent their replication in cells. When administered to mice, SIgN-3C reduced bloodvirus levels after exposure to any of the four dengue serotypes. If administered before exposure, it conferred protection against infection.

Similar findings were reported with SIgN-3C-LALA,

an intentionally mutated version of the antibody that stops antibody-virus complexes from entering cells, thereby preventing enhancement of dengue infection. This phenomenon known as 'antibody-dependent enhancement' helps to explain why patients who have been infected by dengue before are more likely to experience severe symptoms when they are infected subsequently by a different serotype. This is a major barrier for developing therapeutic antibodies against dengue virus.

# "The key to this cross-reactivity lies in the unique virus-antibody binding site."

Fink concedes that they were surprised at the efficiency of SIgN-3C-LALA against all four dengue serotypes. "Usually, very potent neutralizing antibodies are specific against one virus serotype, [while] cross-reactive antibodies are usually less potent" she explains. The key to this cross-reactivity lies in the unique virus—antibody binding site. SIgN-3C-LALA targets a site that is conserved across serotypes and is crucial for virus integrity.

With a grant from the Global Health Innovative Technology Fund, the team continues to investigate the mechanism of action of the antibody and are working with Chugai Pharmaceuticals to evaluate its suitability for the treatment of dengue in humans.

 Xu, M., Zuest, R., Velumani, S., Tukijan, F., Toh, Y. X. et al. A potent neutralizing antibody with therapeutic potential against all four serotypes of dengue virus. npj Vaccines 2, Article number: 2 (2017).

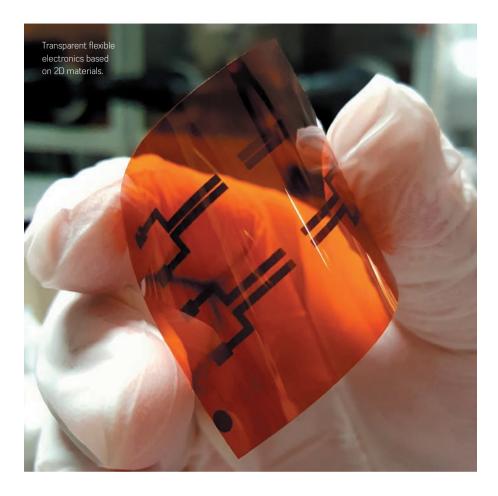
## PRODUCING TOP-NOTCH 2D MATERIALS

Mass producing ultrathin nanosheets could lead to nextgeneration electronic and optoelectronic devices.

Molybdenum trioxide (MoO<sub>3</sub>) has potential as an important two-dimensional (2D) material, but its bulk manufacture has lagged behind that of others in its class. Now, researchers at A\*STAR have developed a simple method for mass producing ultrathin, high-quality MoO<sub>3</sub> nanosheets.<sup>1</sup>

Following the discovery of graphene, other 2D materials such as transition metal dichalcogenides, began to attract considerable attention. In particular, MoO3 emerged as an important 2D semiconducting material because of its remarkable electronic and optical properties that hold promise for a range of new applications in electronics, optoelectronics and electrochromics.

Liu Hongfei and colleagues from the A\*STAR Institute of Materials Research and Engineering and Institute of High Performance Computing



have sought to develop a simple technique for mass producing large, high-quality nanosheets of MoO<sub>3</sub> that are flexible and transparent.

"Atomically thin nanosheets of molybdenum trioxide have novel properties that can be utilized in a range of electronic applications," says Liu. "But to produce good quality nanosheets, the parent crystal must be of very high purity."

By first using a technique called thermal vapor transport, the researchers evaporated MoO<sub>3</sub> powder in a tubefurnace at 1,000 degrees Celsuis. Then, by reducing the number of nucleation sites, they could better match the thermodynamic crystallization of MoO<sub>3</sub>, to produce highquality crystals at 600 degrees

Celsius without the need for a specific substrate.

"In general, crystal growth at elevated temperatures is affected by the substrate," explains Liu. "However, in the absence of an intentional substrate we could better control the crystal growth, allowing us to grow molybdenum trioxide crystals of high purity and quality."

After cooling the crystals to room temperature, the team used mechanical and aqueous exfoliation to produce submicronthick belts of MoO<sub>3</sub> crystals. Once they subjected the belts to sonication and centrifugation, they were able to produce large, high-quality MoO<sub>3</sub> nanosheets.

The work has provided new insights into the interlayer electronic interactions of 2D MoO<sub>3</sub> nanosheets. The crystal growth and exfoliation techniques developed by the team could also be helpful in manipulating the band gap — and therefore the optoelectronic properties — of 2D materials by forming 2D heterojunctions, interfaces between two layers of different materials.

"We are now attempting to fabricate 2D molybdenum trioxidenanosheets with larger areas, as well as exploring their potential use in other devices, such as gas sensors," says Liu.

 Liu, H., Cai, Y., Han, M., Guo, S., Lin, M. et al. Aqueous and mechanical exfoliation, unique properties and theoretical understanding of MoO<sub>3</sub> nanosheets from free standing a-MoO<sub>3</sub> crystals: Raman mode softening and absorption edge blue shift. Nano Research advance online publication, 10 August 2017 (doi: 10.1007/s12274-017-1733-x).



# LIKE FATHER LIKE CHILD FOR WEIGHT GAIN

A father's weight is just as relevant as the mother's in determining a child's risk of obesity.

It's not only women who should be concerned about the impact of their weight on their children's health. A\*STAR researchers have identified a set of factors, including the father's weight, that combine to increase a child's risk of obesity up to 11-fold<sup>1</sup>.

The period between conception and a child's second birthday is crucial in determining his or her future risk of obesity. Previous studies have identified several factors that can boost obesity risk during this window, but most only considered them in isolation. "Few studies have looked at how risk factors combine to influence a child's risk of obesity, which is important because many of them are interlinked," says Izzuddin Bin Mohd Aris of the A\*STAR Singapore Institute for Clinical Sciences. For example, if the mother is overweight, she's more likely to have higher blood sugar levels during pregnancy, which in turn could cause the fetus to gain more weight.

"The most important thing is that all these risk factors are modifiable."

To investigate these relationships in more detail, Aris and his colleagues assessed 1,247 women during pregnancy and when their children were four years old, scoring them against the following criteria: mother overweight/obese; father overweight/obese; excessive weight gain during pregnancy; raised blood glucose during pregnancy; breastfeeding for less than four months; and introducing solid food before four months. They also

looked at how the child's size at four years related to this combined score.

The team found that the more risk factors a family had, the more likely their child was to be overweight or obese. Surprisingly, the weights of both parents made an equal contribution. "If either the mum or the dad was overweight, the contribution was similar, but if both parents were overweight, the probability of the child being overweight doubled," says Aris. Compared to children whose families had no risk factors, those with four or more risk factors were 11 times more likely to be overweight. Parents' weight made the greatest contribution to a child's obesity risk, followed by pregnancy weight gain, breastfeeding duration, timing of solid food introduction, and maternal glucose levels.

The researchers note that while fathers could be transmitting genetic, or epigenetic factors that influence obesity risk, their weight could also be a more general indicator of family diet and exercise levels.

"The most important thing is that all these risk factors are modifiable," says Aris. "Targeting only one of them will have a limited impact, but if we can target them in tandem then we should be able to reduce the risk of obesity even further." Advice and support could also be directed at families where many of these factors are present.

 Aris, I. M., Bernard, J. Y., Chen, L. W., Tint, M. T., Lee, Y. S., et al. Modifiable risk factors in the first 1000 days for subsequent risk of childhood overweight in an Asian cohort: Significance of parental overweight status. International Journal of Obesity advance online publication, 28 July 2017 (doi: 10.1038/ijo.2017.178).





The team modeled the

two dozen mutated proteases

that clinicians found made

HIV resistant to any one of

drugs. These mutations arose

in patients who were taking

just one of these drugs, but

they impacted the efficacy of

other protease inhibitors, too.

cross-resistance can develop

easily across five of the seven

says Chinh Tran-To Su,

a postdoctoral fellow in

Gan's lab, "could help guide

the selection of drugs for the

first and subsequent lines

Take the protease

example. The analysis found

that resistance to any other

inhibitor lopinavir, for

the other two.

of treatment."

protease inhibitors, but less so for

That kind of information,

The A\*STAR team showed that

seven different protease-blocking

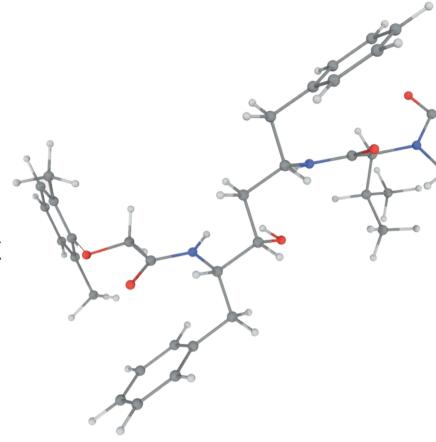
structures of more than

## **MAKING HIV DRUGS WORK LONGER**

Computational modeling of drug resistance could help guide treatment decisions for people infected with HIV.

A bioinformatic examination of HIV mutations could help guide the selection of antiretroviral therapies in such a way that the onset of drug resistance could be delayed. This would "prolong drug effectiveness, improve quality of life and lower treatment costs," says Samuel Ken-En Gan, from the A\*STAR Bioinformatics Institute.

Through structural modeling and computational analyses, Gan and his team have shown how changes in the HIV genome that make the virus resistant to one antiretroviral drug can often induce resistance more broadly to other drugs of the same class. The findings suggest that some of these drugs should be prescribed before others. This includes drugs that block critical viral proteases — enzymes that break down proteins — called protease inhibitors.



protease inhibitor would probably induce resistance to lopinavir as well. That means it's not very useful if taken by patients after other drugs have started to fail. However, since resistance to lopinavir does not seem to affect how well the other six protease inhibitors will work, Gan and Su conclude that lopinavir should be considered as the drug of choice for patients who are getting their

"These drugs impacted the efficacy of other protease inhibitors, too."

first protease inhibitor.

Should resistance then emerge to lopinavir, the analysis indicates that patients should try one of the four other protease inhibitors that are prone to cross-resistance, while saving the two that are least affected by cross-resistance as agents of last-resort.

Computational mod-

eling suggests that

a HIV drug called lopinavir (pictured)

should be used before others of the

same type to avoid

cross-resistance.

Clinical implementation of these recommendations will be needed to test the predictions of the computational modeling. But as Gan notes, the insights gleaned from his group's structural analysis would be hard to come by any other way. "This paper," he says, "represents a landmark analysis using bioinformatics to go where experimental labs and clinical trials cannot easily investigate."

1. Su, C. T., Ling, W. L., Lua, W. H., Haw, Y. X. & Gan, S. K. Structural analyses of 2015-updated drug-resistant mutations in HIV-1 protease: an implication of protease inhibitor crossresistance. BMC Bioinformatics 17, 500 (2016).



### BUILDING A BARRIER AGAINST OXIDATION

Chemically stabilizing atomically flat materials improves their potential for commercial application.

Two-dimensional materials could underpin a novel family of flexible, low-power electronic devices, but their success depends on ensuring the layers are chemically stable. A\*STAR researchers now show that one 2D material, phosphorene, can be stabilized with the right choice of substrate and an electric field.

Graphene, a single layer of carbon atoms, deserves its reputation as a supermaterial; it's strong, hard, light, and has excellent electronic and thermal properties. It is the archetypal 2D material. More recently scientists

have created single layers of other materials — tin, germanium, boron, silicon and phosphorus — with their own signature properties. For example, while graphene is a semi-metal without a band gap, phosphorene is a semiconductor like silicon, which makes it useful for electronic devices. However, phosphorene has a notorious drawback: the material oxidizes in air and its quality is rapidly degraded.

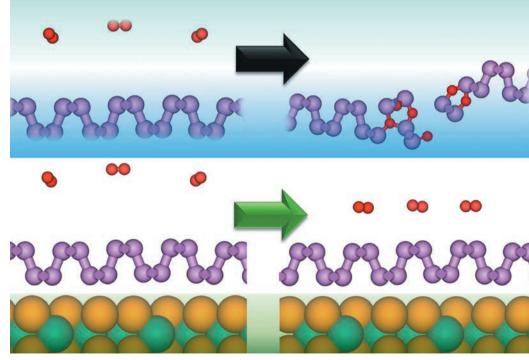
In search of a viable approach to overcome this, Junfeng Gao and colleagues from the A\*STAR Institute of High Performance Computing used first-principles calculations to demonstrate that placing phosphorene on a molybdenum diselenide substrate and applying a vertical electric field can drastically increase its resistance to oxidation.

"The interaction and charge transfer between substrate and phosphorene can be tuned by an external electric field, causing a change in surface activity and suppressing the oxidation of phosphorene," explains Gao.

Their study shows that the dominant process involved in the degradation of phosphorene in air is the absorption of oxygen. The fast oxidation of freestanding phosphorene in ambient conditions is due to a low energy barrier for oxygen absorption of about 0.57 electronvolts: oxidation can occur in less than a minute.

When this analysis is repeated with phosphorene overlying molybdenum diselenide, the energy barrier is much higher. The model also shows that the presence of the molybdenum diselenide substrate enables more effective tuning of the properties of the phosphorene with an electric field. This increases the oxidation energy barrier even further. Under a suitable vertical electric field, the barrier can increase to 0.91 electronvolts. This lifetime of the phosphorene against oxidation can be 105 times greater than that without treatment.

Gao's approach to achieve air-stable phosphorene may greatly promote its use in practical devices. "We will explore more substrates for their ability to stabilize phosphorene," says Gao. "In particular, we want to find out if such a substrate is suitable for epitaxial growth of phosphorene."



The absorption of oxygen (red) damages phosphorene (purple, top), but the phosphorene is protected when on a molybdenum diselenide substrate (bottom).

Vastly enhancing the chemical stability of phosphorene by employing an electric field. *Nanoscale* **9**, 4219 (2017).

1. Gao, J., Zhang, G & Zhang, Y.,-W.

2017 A\*STAB Inctitute of High Borformance Computing



## SEEING THE BIG PICTURE

A system that identifies malicious patterns in network traffic could help create a more secure internet.

The majority of cyber security solutions that stand between us and increasingly sophisticated malware target only specific attacks or subsets of attacks, meaning that users may have to buy and install many different products to protect themselves. Now, A\*STAR researchers have developed a system that instead gathers evidence across a wide stream of internet traffic and identifies links and correlations related to suspicious activity<sup>1</sup>.

"Our aim is to develop a framework to gather as much evidence as possible from a set of traffic and indicate malicious anomalies, regardless of the type of attacks," says Vrizlynn Thing from the A\*STAR Institute for Infocomm Research, who led the study.

Thing and her team designed their new framework to look out for the fundamental characteristics of the malicious activities that stalk unsuspecting users through the evolving cyber landscape. Through this approach, the framework is robust against new threatening software and gathers only relevant evidence on the threats. For example, the system looks out for data flows that arrive at fixed time intervals, because attack bots are much less random than ordinary human-generated internet activities. The model also identifies sources that try to communicate with a large number of destina-



tions in a short time, which is indicative of a botnet.

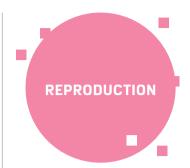
"The main challenge was devising ways to build up a large set of possible patterns which could serve as potential evidence for detecting a wide variety of anomalies," says Thing. "We capture the persistent characteristics of the malicious activities in transit, and represent them in observable sequential forms. This has allowed us to detect very fundamental patterns related to malicious traffic."

### "We could trigger the disconnection of infected hosts, curbing the rampant growth of botnets."

The team tested their new evidence-gathering system on recorded internet traffic, and found it could quickly identify many notorious botnets such as Andromeda, Zeus and Sality, with very few false positives. Given this success, Thing is hopeful that by improving their detection patterns, their system could defend networks against a much wider variety of attacks than has previously been possible.

"If we can detect malware infections by analyzing network traffic, we can prevent malware from further spreading," she says. "We could also trigger the disconnection of infected hosts, thereby curbing the rampant growth of botnets."

 Divakaran, D. M., Fok, K. W., Nevat, I. & Thing, V. L. L. Evidence gathering for network security and forensics. *Digital Investigation* 20, S56–S65 (2017).



## A PROTEIN TO MAKE SPERM

A protein essential for spermatogenesis may help combat male infertility and lead to new methods of contraception.



AVID MACK/Gettv in

"Infertility is generally perceived to be mostly a female problem, but this is wrong," says Philipp Kaldis, researcher from A\*STAR. Kaldis studies the development of human sperm, his work could one day lead to the treatment of male infertility and help develop chemical contraception methods for males.

To set his work in context, Kaldis points to studies reporting a 50-60 per cent fall in sperm counts between 1973 and 2011. "Claims that this trend could lead to the extinction of the human race may be exaggerated," he concedes, but they do indicate a need for understanding male fertility.

The importance of a protein called Emi2 for generating sperm in mice has now been shown by Kaldis, working with colleagues at the A\*STAR Institute

of Molecular and Cell
Biology and collaborators
elsewhere in Singapore and
in Taiwan, the USA and
Europe<sup>1</sup>. They say this indicates
that the protein may play
a similar role in humans.
The researchers were able to
identify the crucial role for
Emi2 in testes by creating
mice in which the gene that
codes for the protein was
knocked out. The mice were left
sterile, but suffered no other
major effects.

"Nobody had previously studied the role of this protein in testes," says Kaldis, noting that the protein has been shown to be involved in controlling the cell divisions that produce egg cells in ovaries, but that its activity has not been detected in other tissues. This all suggests that it is an important player in human reproduction.

"The next step is to figure out all of the functions of Emi2 in making sperm," says Kaldis. The work so far suggests that it is essential, but has not fully revealed why.

There are hints, however, from the protein's known role in the ovary. There, it regulates meiosis, an essential cellular process for halving chromosome numbers to make egg and sperm cells that will combine to form a fertilized egg cell.

Any applications of the research to devise treatments for male infertility, or contraceptives, would require much further research, but Kaldis' work lays the foundations for major medical advances.

 Gopinathan, L., Szmyd, R., Low, D., Diril, M. K., Chang, H-Y. et al. Emi2 is essential for mouse spermatogenesis. Cell Reports 20, 697–708 (2017).

## POLYMERS ARE TOUGH ON MICROBES, SOFT ON SKIN

Polymers that kill germs rapidly and effectively will help in the fight against multidrug-resistant microbes.

Inexpensive antimicrobial polymers that are gentle on the skin and highly effective in killing microbes have been developed by A\*STAR researchers¹. They have promise for use in surgical scrubs and disinfectants.

Most antibiotics work by disrupting the specific biochemical pathways microbes use to make the proteins and enzymes which are essential for their survival. This strategy makes them lethal to microbes but safe to the cells of humans and other mammals. However, it is easy for microbes to develop resistance to such antibiotics, which has led to the widespread problem of multi drug-resistant microbes.

The antimicrobial compounds of the body's immune system use a different tactic — they fight microbes by destroying their membranes. Since this approach is based on the inherent electrical properties of the cell membrane, it is much harder, if not impossible, for microbes to develop resistance.

Now, Yi Yan Yang of the A\*STAR Institute of Bioengineering and Nanotechnology and her co-workers, in collaboration with IBM Almaden Research Center, have developed powerful antimicrobial polymers that employ the same strategy. The polymers with optimized structures killed almost 100 per cent of microbes within two minutes. They were also softer on the skin of mice than commercial surgical scrubs that are currently used in clinical settings.

"Our polymers kill a broad spectrum of microbes, especially the difficult-to-kill *Pseudomonas aeruginosa*, faster than any of the many antimicrobial peptides and polymers reported to date," comments Yang. "With their superfast bactericidal effect and skin compatibility, these polymers are promising candidates for use as surgical

scrubs, hand washes and disinfectants," she adds.

The polymers have two key components: positive charges and hydrophobic parts. Their positively charged components interact with the negatively charged membranes of pathogenic microbes, while the hydrophobic parts of the polymers enter the two layers of fat cells inside membranes. This double action ruptures the membrane and destroys the microbe. Since the surfaces of mammalian cells are less negatively charged than those of microbes, cells such as red blood cells are immune to the polymers' action.

The researchers found that repeated use of the polymer at sub-lethal doses did not lead to bacterial resistance. In addition, the polymers are inexpensive to make and can be synthesized from commercially available starting materials.

"Building on this work, we are developing biodegradable versions of the polymers," says Yang. "They are designed to degrade into benign, environmentally-friendly compounds. Such biodegradable antimicrobial polymers may be used as preservatives in cosmetics and even food products."



 Liu, S., Ono, R. J., Wu, H., Teo, J. Y., Liang, Z. C. et al. Highly potent antimicrobial polyionenes with rapid killing kinetics, skin biocompatibility and in vivo bactericidal activity. Biomaterials 127, 36–48 (2017).

## **UNRAVELING** THE COMPLEXITY

Powerful new technologies shed light on the origin and maturation process of key immune system cells.

subtype. The comprehensive

process of the immune system's

dendritic cells could lead to new

analysis of the maturation

potential targets for more

effective immunotherapy

treatments and vaccines.

Pathogens such as

bacteria and viruses trigger

an immediate, nonspecific immune response. Dendritic

cells are immune system cells

a longer, specific and more

re-infection with the same

pathogen. "Characterizing

the immune system's key

to improve the efficacy of

vaccines and develop better

therapeutics for devastating

multiple sclerosis or lupus"

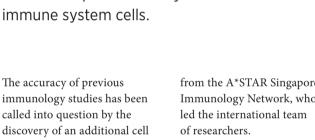
explains Florent Ginhoux,

autoimmune diseases such as

that 'decide' whether to mount

complex immune response that will protect against subsequent

decision-making cells is crucial



There are two main types of dendritic cells: plasmacytoid DCs (pDCs) (see image), which promote antiviral immune responses through the production of interferons, and conventional DCs (cDCs). The latter come in two flavors or subsets: cDC-1 and cDC-2 and have crucial roles in mounting immune responses to intracellular and extracellular

about the origin of dendritic cells and the mechanisms through which they become specialized to carry out these functions.

Until now, dendritic cells have been identified and characterized based on the expression of particular proteins or surface markers. Ginhoux and colleagues took a different

rely on prior knowledge, to re-examine the classification and interrelationship of dendritic cells.

2µm

"We were amazed to find this cluster of cells with unique properties between those of dendritic cell precursors and plasmacytoid dendritic cells."

They applied two powerful technologies: single-cell RNA sequencing and cytometry by time-of-flight to a fraction of human blood cells containing dendritic cells and dendritic cell precursors (pre-DCs) (see image), and analyzed the entire gene expression and protein profile of these cells.

They identified pre-DCs that share surface markers

with pDCs, but that are functionally distinct as they are able to mature into cDC1 and cDC2 cell types but not pDCs. "We were amazed to find this cluster of cells with unique properties that lie between those of pre-DCs and pDCs" says Ginhoux.

Electronic microscopy images of pre-DCs (top) and

pDCs (bottom).

2µm

These findings bring into question results from many studies that have relied on a small set of markers to isolate pDCs. "It is likely that such studies were contaminated with pre-DCs" Ginhoux explains.

Further analyses confirmed previous findings in mice that the pre-DC population can be split into pre-cDC1 and pre-cDC2 lineages as the precursors start to commit to a particular lineage.

from the A\*STAR Singapore Immunology Network, who

pathogens, respectively. However, little is known

approach, which does not

Günther, P., McGovern, N. et al. Mapping the human DC lineage through the integration of high-dimensional techniques. Science 356, eaag3009 (2017).

1. See, P., Dutertre, C. A., Chen, J.,

www.research.a-star.edu.sg



## **A SPUTTERING STEP CLOSER TO CHEAPER SOLAR CELLS**

A simple, low cost technique that uses common materials could lead to significantly cheaper solar cells.

In the search for alternatives to silicon-based solar cells, A\*STAR researchers are investigating a new material that is cheaper and easier to make, and could lead to better performing solar cells.1

Silicon solar cells are highly efficient, converting up to 25 per cent of sunlight into electricity, but fabricating the silicon wafers, which need to be around 300 microns thick to absorb all the sunlight that falls on them, is an expensive process that requires temperatures of around 1,200 degrees Celsius.

A cheaper alternative to silicon is cadmium telluride; however, it is highly toxic and known to cause cancer. This spurred Goutam Dalapati and colleagues from the A\*STAR Institute of Materials Research & Engineering to investigate a copper-zinc-tin-sulfide (CZTS) compound, which offers the optical and electrical properties required in solar cells, but is made from non-toxic, widely

available materials that are cheaper than silicon to process.

"CZTS is a semiconducting compound with a higher absorption coefficient than silicon," says Dalapati, "so it's able to absorb more visible light and produce more electricity than silicon, and can be used for very large-scale applications, like roofs and solar farms."

"Using a single-step sputtering target we produced a thin film with a uniform composition and smooth surface."

Solar cells made from CZTS have potential for up to 30 per cent efficiency, but require high-quality, thin films of CZTS with no impurities, and a suitable material for the 'buffer'

or interface layer that sits underneath the CZTS, helping to collect electrical charge.

A technique called quaternary sputtering was used to grow thin films of CZTS, where a single target made from CZTS was used as a source for depositing the film. This method offers several advantages over other deposition methods, including excellent uniformity over large areas and reduced reliance on toxic precursors. The researchers then investigated the effect of sulfurization temperature on the formation of a molybdenum sulfide (MoS.) interfacial layer.

"The composition and structural properties of the CZTS layer depend on the deposition process and the sulfurization," explains Dalapati. "By using a singlestep sputtering target we were able to produce a thin film with a uniform composition and smooth surface, which limits the formation of defects, and is a highly reproducible process."

The researchers found that the amount of molybdenum lost, referred to as out-diffusing, during the MoS layer formation varied significantly with changes in sulfurization temperature, and that the overall efficiency of the solar cell was improved by nearly five times when the sulfurization temperature was raised from 500 to 600 degrees Celsius.

"We achieved a solar efficiency of nearly five per cent, and are aiming for around 15 per cent by investigating a suitable buffer and interface layer," says Dalapati.

<sup>1.</sup> Dalapati, G. K., Zhuk, S., Masudy-Panah, S., Kushwaha, A., Seng, H. L. et al. Impact of molybdenum out diffusion and interface quality on the performance of sputter grown CZTS based solar cells. Scientific Reports 7, 1350 (2017).





### HEAVY LEGACY OF MUM'S SWEET TOOTH

The babies of women who consume carbohydrate-rich foods during pregnancy have an altered growth-trajectory.



Babies born to women who have a sugary diet during pregnancy have a higher body mass index, according to a new study by Singaporean researchers.

Childhood obesity
has steadily increased in
recent decades, and is
associated with a higher risk
of cardiovascular disease
and type 2 diabetes in
later life. Although there's
some evidence that gaining
substantial amounts of
weight during pregnancy
can increase the child's
obesity risk, little is known
about how the specific foods
a woman eats affect her
baby's weight.

To investigate, Ling-Wei Chen at the National University of Singapore, and his colleagues, Mary Chong and Yung Seng Lee at the Singapore Institute for Clinical Sciences interviewed 1,127 women of Chinese, Malay or Indian background when they were 26–28 weeks pregnant about their diet during that period.

"One of the novelties of this study is that it is performed on an Asian population, where there is a lack of research."

Once their babies were born, they were weighed at regular intervals to track their growth. The childhood body mass index (BMI) curve is characterized by a peak occurring around 6 to 12 months, and previous research has shown correlation between a higher peak at this age and later adverse health outcomes.

The team found that a woman's carbohydrate intake, particularly the amount of sugar she consumed, during pregnancy, was associated with more rapid weight gain and a higher peak BMI during infancy — even though it didn't significantly affect the babies' birth weight. A high carbohydrate intake was also associated with a higher BMI when the children were assessed at 2, 3 and 4 years of age, suggesting the effect may be long-lasting — although follow-up studies are needed to confirm this. The children in the study are now seven, and continue to be monitored. Women's fat and protein consumption had no apparent impact on children's BMI.

"One of the novelties of this study is that it is performed on an Asian population, where there is a lack of research," says Chen. "It's also important, because Asians tend to have higher risk for diseases such as cardiovascular disease, even at the same BMI."

Given that high sugar intake during pregnancy is already known to associate with excessive pregnancy weight gain and higher risk of gestational diabetes, Chen says it may be prudent for pregnant women to avoid foods and beverages high in sugar. The World Health Organization recommends getting no more than ten per cent of total daily energy intake from free sugars.

 Chen, L.-W., Aris, I. M., Bernard, J. Y., Tint, M.-T., Lee, Y. S. et al. Associations of maternal macronutrient intake during pregnancy with infant BMI peak characteristics and childhood BMI. The American Journal of Clinical Nutrition 105, 705–713 (2017).



# UNLOCKING MAGNETIC SKYRMIONS

An innovative technique for making tunable magnetic skyrmions could lead to next-generation memory and computing technologies.

Magnetic skyrmions offer the promise of next-generation memory and computing technologies, such as cache memory devices and cloud computing. Now A\*STAR researchers have developed an innovative technique for making tunable skyrmions that could help unlock their potential.<sup>1</sup>

Only recently discovered, skyrmions are tiny structures that are formed in magnetic materials and behave like nanoscale magnetic particles. This means they can selforganize into ordered arrays or lattices, and can be created, moved, and erased using electrical currents. To become

a viable technology, however, requires the ability to modulate these properties and to achieve their electrical detection under ambient conditions.

This led Anjan
Soumyanarayanan and
colleagues from the A\*STAR
Data Storage Institute and
Institute of High Performance
Computing, in collaboration
with Nanyang Technological
University, Singapore and
Lawrence Berkeley National
Laboratory in the United
States, to develop an innovative
technique for making
ultrathin films for hosting
tunable skyrmions.

"Our initial goal was to understand skyrmion formation, establish their electrical detection, and control their physical properties," explains Soumyanarayanan. "We are now examining skyrmions in nanoscale devices for their potential as bits in memory applications."

By using a technique called magnetron sputtering — a process in which atoms are ejected from a source material and then deposited on to a substrate — the researchers

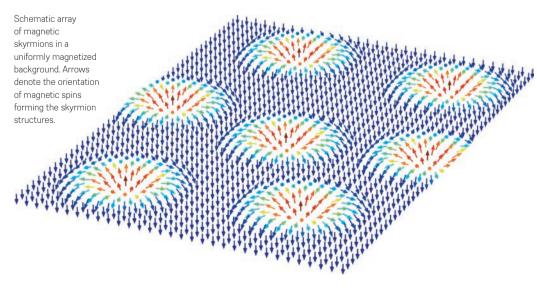
fabricated an ultrathin film with sequential layers of iridium, iron, cobalt, and platinum on a silicon substrate.

Harnessing the large and opposite signs of the chiral magnetic interaction between the iridium-iron and cobaltplatinum interfaces, referred to as the Dzyaloshinskii-Moriya interaction, allowed the team to establish a platform for nanoscale-sized skyrmions. And by varying the thickness of the layers, the team was able to modulate the physical properties, such as the size, density, and stability of the skyrmions.

"The platform allows us to directly control the magnetic interactions that govern skyrmion properties by simply varying the thickness of the constituent layers, and provides skyrmion configurations tailored to the specific requirements of a range of different applications," says Soumyanarayanan.

The work demonstrated, for the first time, the electrical detection of ambient skyrmions, and could lead to stable and highly scalable skyrmion-based memory and computing technologies, explained Soumyanarayanan. These could then be easily integrated into microchips using existing manufacturing processes commonly used in the electronics industry.

"Our next steps will be to stabilize the skyrmions in nanostructures at zero magnetic field, and to demonstrate their electrical reading and writing in electronic devices," says Soumyanarayanan.



 Soumyanarayanan, A., Raju, M., Gonzalez Oyarce, A. L., Tan, A. K. C., Im, M. Y. et al. Tunable roomtemperature magnetic skyrmions in Ir/Fe/Co/Pt multilayers. Nature Materials 16, 898–904 (2017).

## A BIT OF PERFECTION

The optimum drill geometry for creating deep, narrow holes is determined using a computational model.

Computational fluid dynamic simulations of a chip falling through a fluid enables optimization of gundrill design.

Improving the design of drills capable of excavating deep holes should increase their performance and longevity. Scientists from A\*STAR develop a computational model that can determine the ideal drill design, achieving significant savings.

In designing a drill, a crucial consideration is the effective removal of material, known as chips. A standard drill bit, the part of the drill that excavates the hole, removes chips by having a spiral shape that carries the chips up the length of the bit and out of the hole entrance. But there is a limit to the depth that can be reached by spiral drill bit, usually a distance between five to ten times the bit diameter.

An alternative approach, known as gundrilling, can create holes with a depth-todiameter ratio of more than three hundred. The unusual shape of the tip of a gundrill bit gives it a single cutting edge that enables the drill bit to self-center and ensures deep and straight holes. Chips in a gundrill are removed by forcing a fluid through the bit at high pressure. This fluid also acts as a coolant to prevent damage to both the cutting surface and the drill bearings.

Guan Leong Tnay from the A\*STAR Singapore Institute of Manufacturing Technology and colleagues now achieve this by developing a novel methodology to simulate gundrill coolant flow based on a technique called computational fluid dynamics. "Gundrill geometry is complicated; changing any single parameter could affect the coolant flow," explains Tnay. "To improve the

drilling process, it is necessary to understand the coolant flow behavior."

Tnay and co-workers started by experimentally measuring the resistance exerted on a chip falling through a tube filled with the cooling fluid. The team then developed their computational fluid dynamics model to recreate the drag coefficients determined by these experimental results. Once they knew the model worked, the researchers could compute the fluid flow and chip transport in gundrills with different geometries.

"Roughly a
30 per cent
improvement
in tool life
is achieved
compared to
the current
commercial
gundrill design."

They considered the overall shape of the tip, referred to as the nose grind contour, the number and shape of the coolant flow holes running inside the drill bit, and the angle of the cutting edge. Their results indicated that the optimum design has a kidney-shaped cooling holes, a zero-degree shoulder angle and a nose grind contour known as N4. "With this optimization of tool geometry, roughly a 30 per cent improvement in tool life is achieved compared to the current commercial gundrill design," says Tnay.

Woon, K.S., Tnay, G.L., Rahman, M., Wan, S. & Yeo, S.H. A computational fluid dynamics (CFD) model for effective coolant application in deep hole gundrilling. *International Journal of Machine Tools & Manufacture* 113, 10–18 (2017).

## LUPUS LINK TO STIMULATORY PROTEINS

Lupus patients exhibit altered cell proteins, a discovery with potential implications for diagnostics and studies into the disease's origins. Monocytes white blood essential rol us from patt can also ove excitatory p associated will upus. It's ye whether this sion contribidisease, or j its presence.

Monocytes (pictured), or white blood cells, play an essential role in protecting us from pathogens, but can also overexpress excitatory proteins associated with systemic lupus. It's yet to be seen whether this overexpression contributes to the disease, or just indicates its presence.

Autoimmune diseases such as lupus — in which the body attacks its own cells and tissues — are on the rise, according to A\*STAR's Anna-Marie Fairhurst. Her team is the first to observe that patients with lupus exhibit an increased number of a specific type of protein on the surface of certain white blood cells. This finding may help diagnosticians in detecting the disease, or reveal new avenues of research into its causes.

"Systemic lupus erythematosus, or SLE, is the archetypal autoimmune disease, and affects the whole body," says Fairhurst. Common symptoms include fever, swollen joints, and fatigue, though the exact presentation and severity vary from patient to patient.

Fairhurst's research group, including scientists from the Singapore Immunology Network and the Institute of Molecular and Cell Biology, recently discovered a link between SLE and the increased prevalence of a cell-surface protein that modulates immune responses, called 'Siglec-14'.

# "Every discovery in research is a stepping stone."

The team assessed
39 patients with SLE and
found that, compared to a
cohort of healthy individuals,
the patient group expressed
significantly more Siglec-14
proteins on a class of white blood
cells, called monocytes. SLE
disease severity also increased
in tandem with the monocyte
levels of Siglec-14 among the
study group.

Most Siglec proteins are inhibitory, dampening immune

responses upon recognizing the body's own molecules. This is thought to be an innate mechanism that prevents the body from attacking itself. Siglec-14, however, differs in that it's an excitatory molecule that stimulates host defenses. "An increased expression of Siglec-14 would create a greater stimulatory signal," says Fairhurst. It's not fully understood how much the increased protein contributes to the disease: "The increase could either amplify inflammation or just be an indicator of disease," says Fairhurst.

In a previous study into Siglec-14 and chronic obstructive pulmonary disease, a gene variation causing the loss of Siglec-14 expression resulted in a reduced risk of inflammatory response that could exacerbate the disease. Fairhurst's results on SLE

showed no disparity in SLE disease severity/prevalence between those with, or without, the gene variant.

This paper is the first to explore the relationship between SLE and monocyte Siglec expression, and Fairhurst hopes that other institutions will start to look at the relevance of Siglec proteins to disease: "Every discovery in research is a stepping stone, and since this study is the first of its kind, I'd like other researchers to be able to reproduce these results, and then build on them to find out why this happens, and better understand human disease."

 Thornhill, S. I., Mak, A., Lee, B., Lee, H. Y., Poidinger, M. et al. Monocyte Siglec-14 expression is upregulated in patients with systemic lupus erythematosus and correlates with lupus disease activity. Rheumatology 56, 1025–1030 (2017).

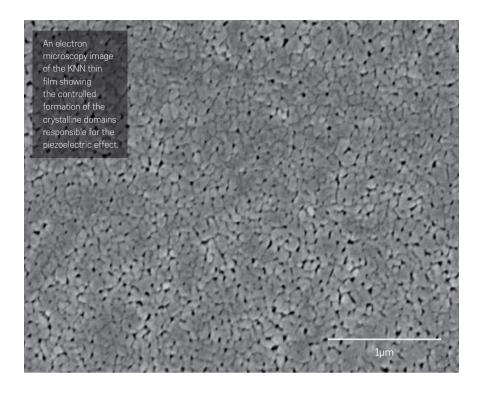
# LEAVING LEAD BEHIND

Thin films of a leadfree piezoelectric finally match the performance of the lead-bearing standard.

An advance in fabrication technology greatly improves the material quality and performance of thin films of a lead-free 'piezoelectric' material<sup>1</sup>. This development by A\*STAR researchers promises to unlock a lead-free alternative to the lead–zircon–titanate (PZT) standard.

Piezoelectrics are remarkable materials that deform on application of an electric field and, conversely, produce an electric current when compressed. They are used in many electronics applications, including as electromechanical actuators and as sensors for strain and acceleration. Thin films of piezoelectric materials are also being integrated into microelectromechanical systems (MEMS) circuits and devices.

For decades, PZT was the piezoelectric material of choice, since it offered the degree of deformation or sensitivity needed for practical



applications. However, PZT contains 60 per cent lead — a toxic metal, which although once commonly used in electronics, has been banned.

"It has been challenging to achieve excellent piezoelectric properties in KNN-based thin films."

An alternative material, which is based on a potassium–sodium–niobate composition and is known as KNN, is being used as a replacement for PZT in many bulk applications. Yet thin films of KNN are problematic because they are subject to a breakdown of composition control and the atomic ordering needed to produce the piezoelectric effect.

Now, Kui Yao and colleagues from the A\*STAR Institute of Materials Research and Engineering, in collaboration with National University of Singapore researchers, have shown that a solution-based fabrication method using a painstakingly formulated cocktail of chemical agents can produce thin films of KNN with a piezoelectric performance comparable to PZT.

"It has been challenging to achieve excellent piezoelectric properties in KNN-based thin films because the phase conditions needed for the piezoelectric effect depend very sensitively on composition," explains Yao. "In KNN, it has been difficult to suppress the loss of volatile elements needed for these conditions."

Yao and his team overcame this problem by adding a blend of chemical stabilizing agents — refined over more than ten years of research — to the precursor solution used to prepare the KNN thin films.

The interactions between the volatile alkali ions in solution and the stabilizing agent suppressed volatilization, allowing the compositions of the resulting films to be well controlled.

"With the film composition under control, we were able to study the phase transitions in the material and their dependence on the chemical composition and stress in the KNN-based thin films," says Yao.

Through laser measurements combined with theoretical analysis from first-principles simulations, the team confirmed that the performance of their piezoelectric films makes them a viable lead-free alternative to PZT.

 Wang, Y., Yao, K., Qin, X., Mirshekarloo, M. S., Liu, X., Tay, F. E. H. High piezoelectric performance and phase transition in stressed lead-free (1–x)(K,Na)(Sb, Nb) O<sub>3-x</sub>(Bi,Na,K)ZrO<sub>3</sub> thin films. Advanced Electronic Materials 3, 1700033 (2017).

## INVISIBILITY IS WITHIN SIGHT

The theoretical discovery of transparent particles that break the previously accepted limit of visibility opens a new door in the search for perfect transparency.

Transparent particles with extraordinarily high refractive indices can become almost invisible at wavelengths longer than the particle size, an A\*STAR-led theoretical study has shown¹. The discovery challenges the accepted wisdom around the limits of light scattering and visibility, and could lead to a new class of 'invisible' materials.

The scattering of sunlight from gas molecules in the atmosphere is what makes the sky look blue, allowing us to effectively see what would otherwise be a transparent medium. This process, known as Rayleigh scattering, occurs when molecules or particles are smaller than the wavelength of

light that hits them. It has long been accepted that all particles undergo Rayleigh scattering, and that the minimum amount of scattering occurs when the refractive index — a measure of the 'slowness' of light passing through a medium compared with a vacuum — is less than two. Water, air and glass all meet this condition, suggesting that the Rayleigh scattering that makes the sky blue is the least visible state physically achievable.

Boris Luk'yanchuk and colleagues from the A\*STAR Data Storage Institute, in collaboration with researchers from the Australian National University, have now upset this status quo with the discovery that Rayleigh scattering can

be suppressed in transparent particles at wavelengths longer than the particle scale if their refractive index is extraordinarily high.

"This phenomenon could be used to design ultratransparent optical materials."

"There have been many attempts to reduce scattering," says Luk'yanchuk. "For example, suppression of the back reflection of radar signals has been widely studied as part of the development of stealth technology. Yet even very small

transparent particles have some degree of scattering. We have been able to reveal a new phenomenon that could be used to design ultra-transparent optical materials."

Rayleigh scattering occurs when light is absorbed by a molecule — producing a separation of positive and negative charges known as an electric dipole — and re-emitted by the dipole at the same energy. This can occur at all wavelengths, but is more efficient at short wavelengths, which is why the sky is more blue (short wavelength) than red (long wavelength).

"In our theoretical study we found that for very high refractive index materials, the contribution of the electric dipole becomes vanishingly small," explains Luk'yanchuk. "Specifically, we found that the electric dipole mode in small particles of such materials is suppressed by the emergence of another dipole mode, resulting in ultra-weak scattering below the Rayleigh limit. The challenge now is to find or develop materials with a high enough refractive index at the wavelength of interest to suppress Rayleigh scattering."



 Luk'yanchuk, B., Paniagua-Domínguez, R., Kuznetsov, A. I., Miroshnichenko, A. E. & Kivshar, Y. S. Suppression of scattering for small dielectric particles: anapole mode and invisibility. *Philosophical Transactions A* 375, 20160069 (2017).

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## THE ROLE OF CRYSTALS IN THE 'DISEASE OF KINGS'

Gout is associated with unhealthy living, but its underlying mechanism has been a mystery.

An attack of gout is said to be like your joint catching fire, and someone slamming it with a hammer to put out the flames. Now A\*STAR researchers have identified how the build-up of monosodium urate (MSU) crystals in the joints triggers such excruciating pain, raising the prospect of new treatments.

Gout has been dubbed the disease of kings, because it is sometimes — but crucially, not always — associated with the overconsumption of alcohol and fatty or protein-rich foods. These boost levels of blood uric acid, which crystalizes in the joints: but it was unclear how these crystals caused severe inflammation.

One clue came with the discovery of inflammasomes, complexes of molecules within cells that respond to environmental "danger signals" by mediating the release of active message molecules called

cytokines. These rally immune cells, which release further substances, resulting in excessive inflammation and pain.

"Complement is involved in initiating inflammation," says Khameneh, "targeting it may benefit gout sufferers."

Inflammasomes can become activated in response to bacterial or viral invaders, but they also respond to particulate structures such as MSU crystals. To investigate how MSU activates inflammasomes, a team led by Alessandra Mortellaro of the A\*STAR Singapore Immunology Network turned to the complement system, a group of more than 20 proteins circulating in blood and tissue

fluids which act as first line of immune defense.

One way of mimicking what happens in gout is to inject MSU crystals into the peritoneal cavity of mice; this usually triggers an influx of immune cells and inflammation. It also raises levels of two complement proteins, C3a and C5a, the team found.

Experiments revealed that incubating immune cells in the presence of C5a, but not C3a, increased levels of the cytokines, IL-1 $\beta$  and IL-1 $\alpha$ . "This is a hallmark of inflammasome activation," says Hanif Khameneh, one of the lead investigators.

Next, the team used mice engineered without receptors for either complement protein. Those lacking C5a receptors, but not C3a receptors, failed to show the usual infiltration of immune cells, and inflammation in response to MSU crystals. Treating mice with a drug that blocks C5a receptors produced a similar result. C5a most likely triggers inflammasome activation by boosting cellular levels of reactive oxygen species, which are toxic at high levels.

The discovery could have consequences for gout treatment. Current drugs merely dampen pain and inflammation, rather than addressing its root cause. "At least in our mouse model, we've shown that complement is involved in initiating inflammation," says Khameneh. "Targeting complement may therefore benefit gout sufferers.

 Khameneh, H. J., Ho, A. W. S., Laudisi, F., Derks, H., Mortellaro, A. et al. C5a Regulates IL-1β Production and leukocyte recruitment in a murine model of monosodium urate crystal-induced peritonitis. Frontiers in Pharmacology 8, 10 (2017).

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Altered gene promoters in gastric cancer cells (blue) helps them evade

detection by cells of the immune system

### **HOW STOMACH TUMORS HIDE**

Alterations in gene regulation make gastric cancer cells less visible to the immune system.

Gastric cancer cells are helped to evade the immune system by alterations in gene regulation, according to new work by A\*STAR researchers. This mechanism might apply to a wide range of cancers, and could be exploited to improve cancer treatments.

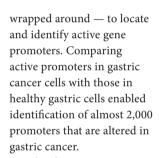
Gastric cancer is among the most common and deadly forms of the disease and has limited treatment options. The impact of gastric cancer means that its genetics have been studied extensively. Patrick Tan, from the A\*STAR Biomedical Research Council, and an international research team, now provide new insight by studying variation in gene promoters, components of DNA that regulate gene expression.

"Promoters act as multifaceted switches that turn genes on or off, regulate the amount of gene expression and control a gene's output," explains Aditi Qamra from the A\*STAR Genome

Institute of Singapore, primary author of the study. "More than half of the genes in the human body have more than one promoter controlling them, and cancer cells often exploit this by using abnormal promoters to drive malignancy. We wanted to identify which promoters are abnormally activated or silenced in gastric cancer cells."

"Studying the tumor promoter profiles of gastric cancer patients can help to identify suitable candidates for immunotherapy."

The researchers used a technique called Nano-ChIP-Seq that uses molecular tags on histones — proteins that DNA molecules are



The alterations in promoters not only conferred cancerous properties, but also reduced the expression of proteins in tumor cells that would enable the immune system to detect them. This mechanism helps the cells evade the immune system, but also reduces the effectiveness of immunotherapy, which exploits the immune system to attack the tumor. Ultimately, the findings could be used to improve treatment.

"Studying the tumor promoter profiles of gastric cancer patients can help to identify suitable candidates for immunotherapy," explains Qamara. "Also,

the reversible nature of promoter activity can be exploited to modulate the immunogenicity of gastric cancer tumors and make them more sensitive to immunotherapy."

Furthermore, analysis of a cancer genetics database revealed many similar promoter alterations in other cancers - colon cancer, kidney renal clear cell carcinoma and lung cancer — suggesting that similar mechanisms apply to many cancers. The researchers now aim to determine the cellular pathways involved in the function of the altered promoters. "Targeting these pathways can potentially increase the response rates of gastric cancer patients to immunotherapy," says Qamra.

1. Qamra, A., Xing, M., Padmanabhan, N., Kwok, J. J. T., Zhang, S. et al. Epigenomic promoter alterations amplify gene isoform and immunogenic diversity in gastric adenocarcinoma Cancer Discovery 7, 630-651 (2017).



### UNLEASHING **SULFUR'S POTENTIAL**

Sealed sulfur particles show promise for renewable energy storage technology.

Hollow sulfur nanospheres wrapped inside sheets of molybdenum disulfide could form the ideal cathode material for the next generation of lithium-ion batteries, research from A\*STAR suggests1.

The amount of energy a lithium-ion battery can hold is partly determined by the amount of lithium ions its cathode can absorb. Sulfur's high chemical affinity for lithium ions means a lithium-sulfur battery could hold five times the energy of today's lithium-ion batteries.

Sulfur does have drawbacks, however. Once 'lithiated', it becomes soluble in the battery's electrolyte, and so can break away from the cathode. Sulfur also swells by up to 80 per cent when soaking up lithium. Both processes shorten the cathode's life.

Complicating matters, the process by which sulfur absorbs lithium is hard to study in situ. Sulfur has a high vapor pressure, which means that its atoms rapidly sublime under the high vacuum conditions required for imaging techniques, such as transmission electron microscopy.

With an initial aim of getting a better look at sulfur during lithiation, Guangyuan Wesley Zheng from the A\*STAR Institute of Materials Research and Engineering co-led an international effort to seal sulfur nanoparticles inside sheets of a 2D nanomaterial to suppress sublimation. The team selected nanoflakes of molybdenum disulfide (MoS<sub>2</sub>), a material known to have a good binding interaction with sulfur and lithium sulfide, to encase the particles.

"We are currently working with a battery company to develop a commercial prototype."

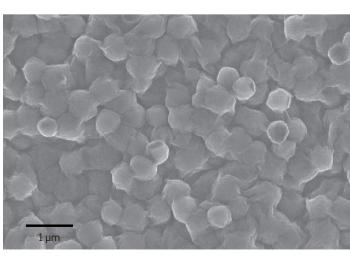
The researchers were then able to examine the nanoparticles using transmission electron microscopy. "The most significant insight we gained related to the 'lithiation kinetics' of sulfur particles," Zheng says. "We observed relatively fast lithium reaction kinetics —

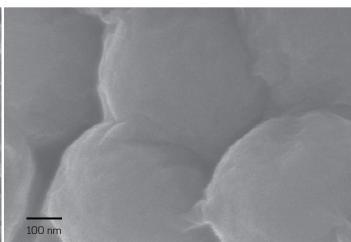
quite a surprise, as the common understanding is that sulfur is highly insulating, and it is difficult to directly lithiate sulfur particles."

As well as gaining fundamental insights into lithium's interaction with sulfur, the team showed the MoS,-wrapped hollow sulfur nanoparticles could become more than just a study tool. Sealing the sulfur within MoS, restricted the damaging volume change and the loss of lithiated sulfur into the electrolyte, avoiding the two key hurdles blocking the use of sulfur in lithium-ion batteries.

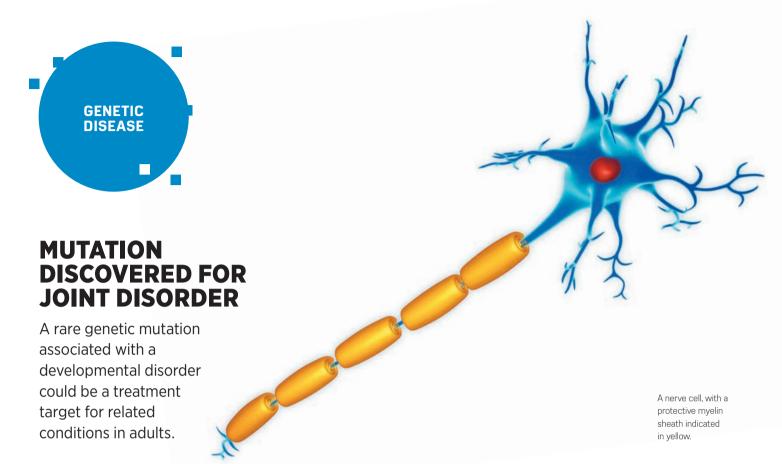
"I do believe there is practical application for the technique in batteries, if we can further improve the MoS production process," Zheng says. "We are currently exploring the scaled-up production of the encapsulated sulfur particles, and working with a battery company to develop a commercial prototype battery," he says.

1. Tang, W., Chen, Z., Tian, B., Lee, H.-W., Zhao, X., et al. In situ observation and electrochemical study of encapsulated sulfur nanoparticles by MoS, flakes. Journal of the American Chemical Society 139, 10133-10141 (2017).





Scanning electron microscopy image showing a sheet of the MoS<sub>2</sub>-wrapped sulfur nanoparticles.



The discovery of a rare genetic mutation associated with a devastating developmental disorder called arthrogryposis multiplex congenita could also provide researchers with a new treatment target for a group of related neurodegenerative diseases, including multiple sclerosis, in adults.

Arthrogryposis multiplex congenita is a common birth defect, affecting around 1 in 3,000 live births. Babies with the disorder have stiff joints and their limbs become locked into awkward positions because of a lack of movement in the womb.

The disorder can be caused by crowding in utero — for example with twin pregnancies — but it also occurs when genetic mutations affect the normal development of muscles and nerves.

A study led by researchers from A\*STAR looked at a group of families affected by a severe form of arthrogryposis that

resulted in several fetuses dying before birth or soon after.

"We knew that it was probably going to be genetic because many of these families had multiple individuals with this condition," says Shifeng Xue from the A\*STAR Institute of Molecular and Cell Biology.

"We're hoping we can develop LGI4 as a therapeutic biologic to stimulate myelination."

But when the researchers looked at the families' genomes, they couldn't find any of the known mutations associated with arthrogryposis.

Instead they discovered a new mutation in the gene coding

for a molecule called LGI4. This molecule is secreted by Schwann cells, which produce the fatty sheath called myelin that covers and insulates nerve cells, and enables them to conduct electrical impulses quickly and effectively. It suggests that LGI4 plays a key role in the myelination process.

LGI4 and Schwann cells operate in the peripheral nervous system — the parts that don't include the brain and spinal cord - which controls movement and sensory function.

This new mutation stopped the LGI4 gene from functioning altogether, so those affected by it didn't have any myelin on their peripheral nerve cells. This caused severe malformation of their limbs and also affected the muscles of the diaphragm so their lungs didn't develop properly.

The discovery means the mutation could be screened for in the early stages of pregnancy, and people with a family history of the disease could be offered genetic counseling before pregnancy. It also opens the door to research that could help adults with degenerative diseases such as multiple sclerosis, where the immune system attacks and destroys myelin.

"We're hoping that by identifying LGI4 as being important for Schwann cell development, differentiation and myelination, we can possibly develop it as a therapeutic biologic to stimulate myelination," says Bruno Reversade, research director at the A\*STAR Institute of Medical Biology.

1. Xue, S., Maluenda, J., Marquet, F., Shboul, M., Quevarec, L. et al. Lossof-function mutations in Igi4, a secreted ligand involved in Schwann cell myelination, are responsible for arthrogryposis multiplex congenital. The American Journal of Human Genetics 100, 659-665 (2017).



## PANCREATIC STEM CELLS ON TAP

Growing pancreatic stem cells will help research on diabetes.

A new cell culture procedure developed by A\*STAR will assist the study of diabetes and facilitate better treatments<sup>1</sup>. "Our discovery will enable studies of how the pancreas forms and why certain cells malfunction in diabetes," says Jamie Trott from the A\*STAR team.

Type 1 diabetes occurs when insufficient insulin is released into the bloodstream by the beta cells of the pancreas. Insulin promotes the uptake of glucose from the blood by the body's cells. Diabetes therefore results in high blood glucose levels, which can be fatal if not controlled. The levels are controlled by administering synthetic insulin, but if too much is given, there is a risk of low blood glucose. These and other risks of diabetes can lead to long-term complications, including problems with vision and the circulatory system.

Researchers use cultured

cells to explore what goes wrong in beta cells and to develop new ways to control or correct the problems. It has proved difficult and time-consuming, however, to generate suitable cell lines. Pluripotent stem cells — those able to develop into a wide range of mature cell types — can be guided through stages that mimic embryonic development, leading to the formation of beta cells. Unfortunately, this procedure

yields considerable variability in the cells, which can make it difficult to interpret the results of different studies. It also involves many time-consuming steps.

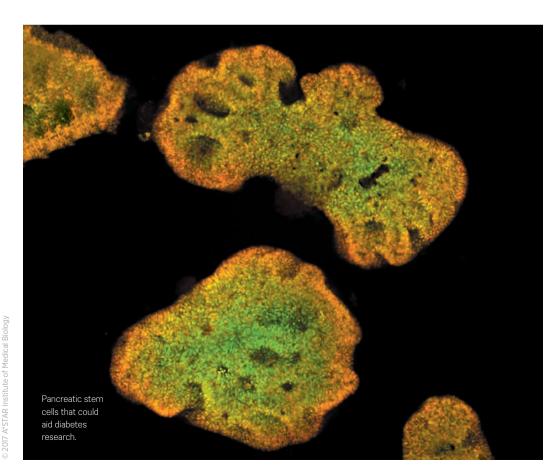
Researchers at the A\*STAR Institute of Medical Biology and the Genome Institute of Singapore have developed a new method that reduces the number of steps and ensures a more consistent supply of beta cells, by generating pancreatic stem cells and expanding them.

"We found a way to propagate pancreatic stem cells, which are developmentally much closer to the beta cells we need," says Trott. The researchers explored modifications to the cell culture conditions in which these stem cells developed, eventually discovering a cocktail of signals that enabled the cells to grow.

"Seemingly minor differences in culture conditions turned out to be the difference between success and failure," says Trott. "It took a while to identify the importance of these variables and to control their effects."

A key feature of the new procedure is that the pancreatic stem cells are self-renewing, so they can be expanded repeatedly to generate an enormous supply of beta-like cells, without the frequent need to go through the many stages of embryonic development. This should make it easier, faster and cheaper to produce supplies of beta cells for scientists investigating diabetes.

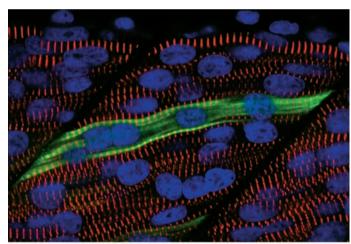
The researchers plan to improve their technique and investigate the molecular factors controlling the cells' development.

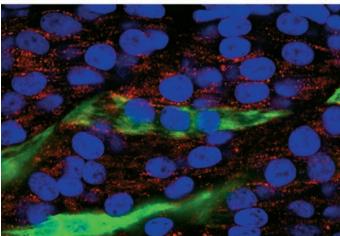


 Trott, J., Tan, E. K., Ong, S., Titmarsh, D. M., Denil, S. L. I. J. et al. Long-term culture of self-renewing pancreatic progenitors derived from human pluripotent stem cells. Stem Cell Reports 8, 1675–1688 (2017).

## FISHING FOR A DISEASE GENE

Mutant zebrafish help explain the cause of a rare muscledegenerating disorder.





Fast-twitch skeletal muscle from normal zebrafish larvae (top) shows the characteristic striated pattern formed by the long chains of sarcomeres within each fiber, whereas muscle from frozen mutant larvae of the same age (bottom) lacks any striation.

An immobile mutant zebrafish first described by scientists more than 20 years ago turns out to have defects in the same gene as people with a rare muscledegenerating disorder called nemaline myopathy, an A\*STAR study has found.

The study points to a central role of the faulty gene, known as *myo18b*, in the assembly of sarcomeres, the force-generating component of the muscle cell. It also helps explain the poor motor function seen in patients who have mutations in this gene — an insight that mouse models could not provide, because mouse embryos that lack *myo18b* die before their skeletal muscle has developed.

"The zebrafish mutant provides the only animal model for studying the effects of the myo18b mutation on skeletal muscle."

As Philip Ingham, head of the Developmental and Biomedical Genetics Laboratory at the A\*STAR Institute of Molecular and Cell Biology, points out: "The zebrafish mutant provides the only animal model for studying the effects of the *myo18b* mutation on skeletal muscle."

Ingham worked with postdoctoral fellows in Singapore and England to characterize a particular strain of mutant zebrafish first identified by German researchers in 1996. At the time, the scientists were looking for gene mutations that affect zebrafish motility, and they found one that meant the

developing fish embryos were without fast-twitch muscle fibers, bundles of long and slender cells that are needed for bursts of rapid movement.

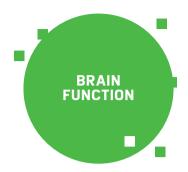
They named the mutated gene *frozen*. However, they had no idea where the gene was in the zebrafish genome or what kind of protein it encoded.

Ingham and his team have now filled in those missing details. They used a series of genetic markers and fish breeding experiments to narrow down the location of *frozen* to a relatively short stretch of around 1.4 million DNA letters long on chromosome 10. The researchers then compared this small region with matching DNA from other fish species, including tilapia and pufferfish.

They found that what had been called *frozen* is actually the zebrafish version of a known gene, *myo18b*, which encodes a poorly characterized member of the myosin motor protein family. In the zebrafish, the protein-coding portion of the myo18b gene was about 50 per cent identical to its human counterpart, which has been linked to rare genetic muscle disorders.

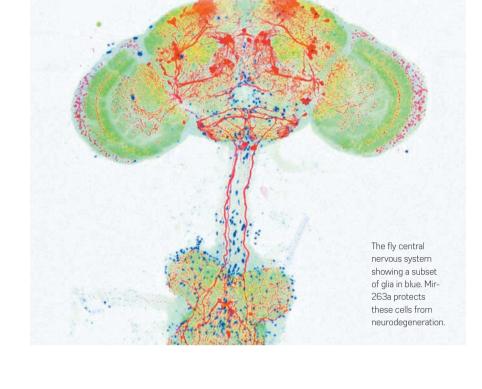
Detailed analyses of these *myo18b*-deficient fish provide the first definitive evidence that this motor protein is needed for proper skeletal muscle development. Ingham says the fish can now serve "as a model for better understanding the role of MYO18B in the assembly of the sarcomere," and he hopes they can help scientists find ways to treat myopathy disorders in people.

 Gurung, R., Ono, Y., Baxendale, S., Lee, S. L., Moore, S. et al. A zebrafish model for a human myopathy associated with mutation of the unconventional myosin MYO18B. Genetics 205, 725–735 (2017).



### **FINE-TUNING EXCITATION FOR SURVIVAL**

A small molecule plays a big role in protecting the nervous system's support cells from excessive stimulation.



Glutamate is the primary excitatory neurotransmitter of the central nervous system. In excess it causes cells to become overexcited, which contributes to neuron death in neurodegenerative disease. Now, a study of flies led by Sherry Aw, at the A\*STAR Institute of Molecular and Cell Biology, highlights the importance of also curbing glutamate stimulation in glia. Glia are generally considered the nervous system's support cells, although important contributions to brain signaling have also recently been described.

Although glia account for 90 per cent of the cells in the human brain, research on the molecular mechanisms of neurodegenerative disease mainly focus on neurons. In their article in Cell Reports, Aw and colleagues show that a small RNA that regulates glutamate receptor expression in glia, mir-263a, protects flies from developing a movement defect associated with neurodegeneration.

"A single microRNA can target a family of genes with a similar molecular function."

Flies lacking the gene encoding mir-263a were unable to climb up the walls of a cylindrical vial when flipped from a horizontal to vertical position. The climbing defect worsened with age, reflecting a progressive decline in nervous system function. The authors were surprised when they examined the expression pattern of mir-263a as they found that it is predominantly expressed and functional in glia, rather than in neurons.

They found that mir-263a depletion triggers glial cell death and that restoring mir-263a expression in a subset of glia not only promotes cell survival, but remedies the flies' impaired climbing.

Mir-263a is a small non-coding RNA molecule (microRNA) that suppresses the expression of multiple target genes. In the brain of mir-263a mutant flies, the authors detected an increase in the expression of over 70 genes, including several encoding for glutamate receptors. When the authors reduced the expression levels of these receptors in glia of flies lacking mir-263a, glia cell numbers were restored and the movement defects were suppressed. "MicroRNAs can be an efficient mode of gene regulation as a single microRNA can target a family of genes with a similar molecular function" explains Aw.

Previous studies have shown that glia express all the major types of glutamate receptors and that they contribute to maintain neuronal function by clearing extracellular glutamate, but little is known about the effects of glutamate on glia themselves. This study shows that glia, like neurons, are susceptible to glutamate overstimulation, and highlights a key role for mir-263a in fine-tuning the levels of glutamate receptor expression in glia and thus, their sensitivity to the neurotransmitter.

It will be interesting to determine whether a similar mechanism contributes to neurodegenerative diseases in humans and to explore the exciting possibility of developing microRNA-based therapeutics to treat them, says Aw.

<sup>1.</sup> Aw, S. S., Lim, I. K. H., Tang, M. X. M. & Cohen, S. M. A glio-protective role of mir-263a by tuning sensitivity to glutamate. Cell Reports 19, 1783-1793 (2017).



## NEW HOPE FOR ECZEMA SUFFERERS

Scientists have scratched the surface of the genetics behind an irritating skin condition.

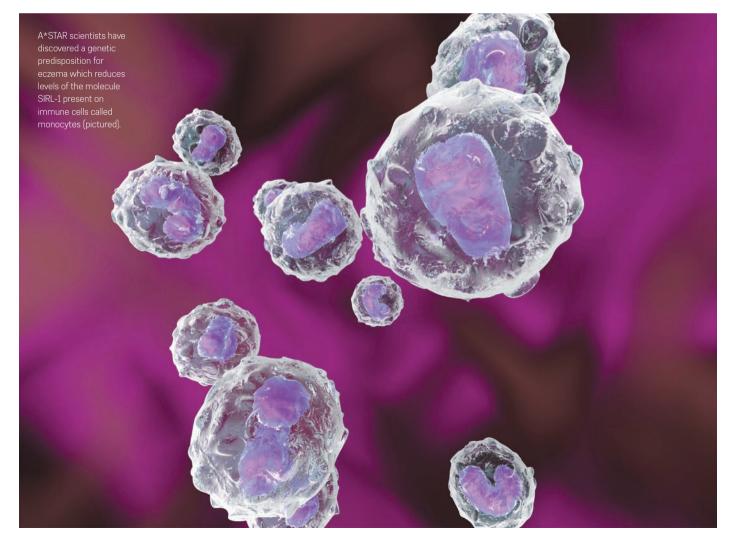
Everyone who has ever had to endure eczema knows just how irritating the symptoms are. Now A\*STAR researchers have pinpointed a genetic predisposition to the condition, opening possibilities for new treatments.

The itchy, red and cracked skin typical of atopic dermatitis, otherwise known as eczema, is an inflammatory condition which affects up to one in five children, many of whom continue to suffer into adulthood.

Topical corticosteroid creams and other medication can treat persistent symptoms and severe cases, but can induce side-effects. With the number of cases increasing, scientists are searching for what causes the condition.

Now, Olaf Rotzschke and his team at the A\*STAR Singapore Immunology Network have uncovered a common genetic mutation which increases the risk of atopic dermatitis. As part of a large study aimed at identifying drug targets for allergies and other immune conditions, Rotzschke's team collected blood samples and clinical data from 600 Singaporean residents.

The scientists analyzed the activity of more than 30,000 genes in each of the blood samples and compared



Westend61/Getty

this to 5 million common genetic mutations, referred to as single nucleotide polymorphisms (SNPs), for each individual.

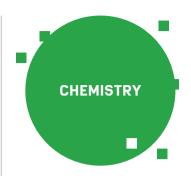
After analyzing this extensive database, the researchers discovered that the activity of the gene *VSTM1*, which encodes a protein called SIRL-1, was heavily dependent on a specific SNP. This mutation, analysis revealed, lowered SIRL-1 levels on a subset of immune cells called monocytes and increased the risk of atopic dermatitis by 30 per cent.

SIRL-1 is a molecule found on the surface of monocytes, and other immune cells, and functions to regulate the defense against invading pathogens. It is not currently known which molecule, or ligand, naturally docks to SIRL-1 inside the human body, but identifying such a molecule could result in new intervention strategies for eczema, Rotzschke explains.

"Our Dutch colleagues are very active in the hunt of the ligand," he says. "Topical application of this compound through a cream or ointment could help suppress rashes and other symptoms."

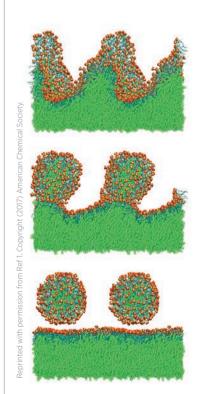
His own team is casting a wider net, investigating the genetic profile of *VSTM1* and how this gene could be involved in other conditions. "We have already looked in a subset of potential diseases but the search is by no means exhausted," he says.

 Kumar, D., Puan, K. J., Andiappan, A. K., Lee, B., Westerlaken, G. H. A., et al. A functional SNP associated with atopic dermatitis controls cell type-specific methylation of the VSTM1 gene locus. Genome Medicine 9, 18 (2017).



### SIMULATING SURFACTANTS

Small changes to a surfactant's structure influence its ability to encapsulate oily molecules.



A surfactant (shown in red, yellow and turquoise) with a 14-carbon 'tail' forms an undulating layer between water (colorless) and decane (green), which develops into buds (middle) and then free micelles (lower).

The properties of surfactants, substances that lower the surface tension of a liquid, can be fine-tuned by tweaking their molecular structure, according to a recent A\*STAR study¹. This method could help researchers develop better surfactants for a variety of applications, from aiding drug delivery, or improving the efficiency of oil drilling, to boosting the cleansing ability of soap.

Surfactants are molecules with split personalities. They typically have a hydrophilic 'head' that attracts water, and a hydrophobic 'tail' that prefers oily molecules. Surfactants can surround tiny oily droplets to form a structure called a micelle, which allows the oily molecules to be dispersed and stable in water.

Freda Lim and colleagues at the A\*STAR Institute of High Performance Computing have now shown that rearranging the atoms in a common surfactant can have a big impact on its ability to form micelles.

The team performed computer simulations of a family of six different alkyl benzenesulfonate molecules, surfactants that, due to their cost-effectiveness and biodegradability, are widely used in the detergents and petroleum industries. These molecules sport alkyl 'tails' containing 12, 14 or 16 carbon atoms, and some have short alkyl groups in various positions on their benzenesulfonate 'heads'.

The researchers first simulated how the surfactants behaved in a single-molecule layer, trapped between water and a colorless, oily hydrocarbon called decane. As the concentration of surfactant molecules increased to the point where the layer was packed with

surfactants, those with more compact heads and longer tails remained in a flat layer, while those with bulkier heads and shorter tails began to buckle into undulating waves. In general, the behavior of the surfactant also depended on the position of chemical groups around its head.

# "Our simulations provide a guideline on choosing the types of surfactants depending on the specific applications."

The researchers then continued to increase the concentrations of surfactants in the intermediate layer. Those with more compact heads and longer tails formed bud-like structures filled with decane, but did not release free micelles. In contrast, those with the bulkier heads and shorter tails formed buds that eventually broke free from the surfactant layer (see image).

"The selection of surfactants depends on the purpose for which it is used, so there is really no 'best' surfactant," explains Lim. "Our simulations provide a guideline on choosing the types of surfactants depending on the specific applications." The team now plans to study how different stimuli trigger the rupture of the surfactant micelle structures, and how the substances trapped within these structures can be released for applications.

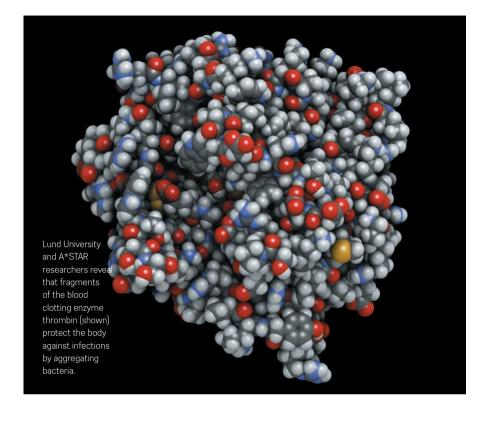
 Tan, J. S. J., Zhang, L., Lim, F. C. H. & Cheong, D. W. Interfacial properties and monolayer collapse of alkyl benzenesulfonate surfactant monolayers at the decane-water interface from molecular dynamics simulations. *Langmuir* 33, 4461-4476 (2017).

### NEW STRATEGY FOR FIGHTING INVADERS

A surprise finding shows in skin wounds fragments of a blood clotting enzyme collect and consume bacteria and their toxins.

A previously unknown mechanism used by the body to prevent wound infections has been discovered by team of researchers from A\*STAR, Lund University, Nanyang Technological University, and Copenhagen University¹. This finding could provide scientists with a new way to fight infection, a critical development when many microbes are becoming increasingly resistant to antibiotics.

Skin wounds are open doors for bacteria to enter the body and cause infections. The body uses a range of different strategies to protect itself against this threat, including blood clotting and immune responses. In a surprising find, Jitka Petrlova at Lund University, Sweden, together with Peter Bond's team at the A\*STAR Bioinformatics Institute, have discovered a strategy that the body uses to neutralize invading microbes.



Using an array of techniques, including biophysical, biochemical, and microbiological methods, fluorescence and electron microscopy, and computer modeling, the team found that an enzyme secreted by immune cells such as neutrophils and macrophages cuts up thrombin, an enzyme that plays an important role in blood clotting, into fragments. These thrombin fragments then collect bacteria and their toxins together. This occurs rapidly in a wound, and the invaders are gobbled up by inflammatory cells. This phenomenon was not seen in normal blood plasma; it was observed only in wounds.

The discovery suggests a new approach for fighting bacteria. "Perhaps, we don't need to kill bacteria with antibiotics. Instead, we could simply gather them together and give the body a helping hand in combating

infection," says Petrlova. "We believe this to be a fundamental mechanism for taking care of both bacteria and their toxins during wound healing."

"Compared to antibiotics, innate immunity has been around for millions of years, and we should consider the application of these concepts in an era of increasing antibiotic resistance."

Petrlova says: "Nature has effectively created different defense mechanisms, and wound healing provides a rich source of new discoveries.

The ability to effectively heal

wounds is of evolutionary significance to our survival. Compared to antibiotics, innate immunity has been around for millions of years, and we should consider the application of these concepts in an era of increasing antibiotic resistance."

The team's finding could also have implications for diseases such as Alzheimer's and Parkinson's. "Various aggregating proteins can cause amyloid diseases in the skin or internal organs such as the brain," says Petrlova. "Such degenerative diseases could be caused by over-activation of a mechanism that is supposed to protect us from infections."

 Petrlova, J., Hansen, F. C., van der Plas, M. J. A., Huber, R. G., Mörgelin, M. et al. Aggregation of thrombin-derived C-terminal fragments as a previously undisclosed host defense mechanism. Proceedings of the National Academy of Sciences USA 114, E4213—E4222 (2017).



### **BETTER PROPERTIES FOR A MAGNESIUM ALLOY**

Optimized processing improves the mechanical strength and workability of magnesium alloy as a lighter alternative to aluminum alloy.

Magnesium alloy can be made stronger and more workable by hot pressing under optimized conditions to produce an ultra-fine crystalline structure, A\*STAR researchers have shown<sup>1</sup>. The improved material means magnesium alloy will have broader applications as an ultra-light structural material.

Aluminum alloy is currently

the go-to light metal for many structural applications, from aircraft fuselages to smartphone bodies. It is light, corrosionresistant and is relatively easy to shape, weld and work. Alloys of magnesium are up to onethird lighter than alloys of aluminum, and are particularly promising for applications where weight is critical: they

have the added benefit of being more dent resistant and more machinable, and better able to shield electromagnetic radiation and dampen vibrations, than aluminum alloys.

The trade-off with magnesium is that it is notoriously difficult to work with, requires high temperatures for formability and has generally lower strength. Finding a way to improve the mechanical properties and workability of magnesium alloys could open many new applications for the material with real-world benefits like improved fuel economy in aircraft, watercraft and land vehicles, and lighter mobile phones.

Kai Soon Fong and colleagues from the Singapore Institute of Manufacturing Technology and Nanyang Technological University have now devised a pre-processing method that significantly improves the mechanical strength and ductility of AZ31, the most widely used magnesium alloy.

"We have shown that the properties of commercial AZ31 magnesium sheet can be enhanced by severe plastic deformation using an orthogonal constrained groove pressing technique with fast post-annealing," says Fong.

Constrained groove pressing involves repeated pressing of a thin sheet of metal, such as the magnesium alloy, between heated, finely corrugated dies. This stretches — or strains — the material over very narrow domains, causing plastic deformation while preventing damage and inducing the microscopic crystal grains to recrystallize into a finer microstructure. By turning the sheet by 90 degrees between each pressing step, the material is repeatedly strained until the entire sheet has been processed.

"This processing led to improved mechanical strength and ductility, making it tougher and easier to shape at room temperature."

The material is then heated, or annealed, to remove residual stress, but at a faster heating rate and shorter time than usual, to prevent the grains from enlarging again.

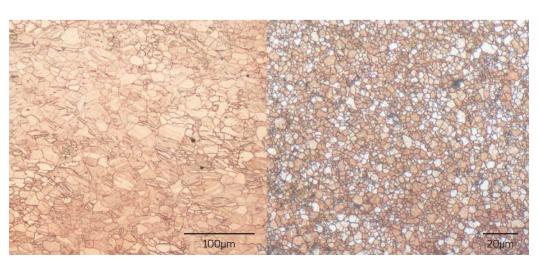
"By optimizing the processing temperature and strain rate, we were able to achieve an ultrafine-grained microstructure, which does not physically change the alloy, but improves its mechanical properties through grain refinement," says Fong. "This processing led to improved mechanical strength and ductility, making it tougher and easier to shape at room temperature."

1. Fong, K.S., Danno, A., Tan, M.J., & Chua, B.W. Tensile flow behavior of AZ31 magnesium alloy processed by severe plastic deformation and

Processing Technology 246,

235-244 (2017).

post-annealing at moderately high temperatures. Journal of Materials



Orthogonal groove strain pressing and fast annealing dramatically shrinks the grain size of AZ31 magnesium alloy, resulting in increased strength and room temperature ductility. Before processing (left), after processing (right).



### **BETTER WAYS WITH X-RAYS**

Low-energy X-rays are surprisingly effective at killing bacterial spores, offering improved sterilization techniques.

Low-energy X-rays are able to sterilize materials, offering a potentially cheap and effective alternative to current techniques, A\*STAR researchers have shown.

The effect of the X-rays on bacteria when they are in a spore state, a dormant condition in which they are able to survive harsh conditions, was examined by Derrick Yong and colleagues at the Singapore Institute of Manufacturing Technology, in collaboration with researchers from other Singapore universities.

They showed that surprisingly low doses of X-rays can kill spores: but that the X-rays can also activate spores<sup>1</sup>. Fine-tuning the procedure is key. "If the exposure is long enough we can kill all of the spores, including those that we unintentionally wake up," says Yong.

Yong explains that the investigations were prompted by conversations with local

manufacturers, who seek improved sterilization processes during the production and use of medical equipment and in the food industry.

"If the exposure is long enough we can kill all of the spores, including those that we unintentionally wake up."

"We typically picture sterilization as involving extreme conditions such as high temperatures, toxic chemicals or deadly radiation sources," says Yong. An alternative, the research suggests, is that a small and low-hazard tabletop X-ray source could do the job more conveniently and at lower cost.

The researchers began by firing X-ray beams of different

energies at the bacterium Bacillus pumilus, a sporeforming bacterium common in soil.

The first results threw up a troubling surprise. "When we looked at the data we couldn't understand why we ended up with more bacteria than we started with," says Yong. The researchers assumed there must have been some error in the experiment, but when they repeated the process, the same thing happened.

"This got us excited," adds Yong.

Further investigation revealed that short duration exposure was 'waking up' the spores rather than killing them. But then came a second and much more useful surprise. In runs of longer duration the lower energy X-rays were more effective at killing the spores than higher energy rays. This was the crucial breakthrough that allows the new, safer and more convenient sterilization system.

More work is needed to learn how to keep the X-ray energies as low as possible, while adjusting the length of exposure to ensure that all bacterial spores and free-living bacteria are killed. Yong reports that they have already run trials of the system on dried food products and small medical devices. "We are also working on new ways to generate the X-rays and methods to accelerate and scale up the whole process," he adds.

<sup>1.</sup> Ha, T. M. H., Yong, D., Lee, E. M. Y., Kumar, P., Lee, Y. K. & Zhou, W. Activation and inactivation of Bacillus pumilus spores by kiloelectron volt X-ray irradiation. PLoS ONE 12, e0177571 (2017).





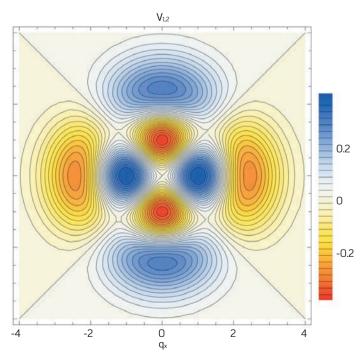
www.research.a-star.edu.sg A\*STAR RESEARCH 49

## A GUIDEBOOK FOR EXOTIC STATES

A theoretical model will allow systematic study of a promising class of peculiar quantum states.

Research on the fragile states of matter that could give traction to the many promises of quantum computing has been given a boost by a comprehensive set of theoretical tools developed by A\*STAR researchers¹.

Long theorized but notoriously difficult to achieve in practice, quantum computers



A universal theoretical framework will help guide research on exotic topological states, shown here in terms of the spatial distribution of electron states, which could be used to realize practical quantum computers.

rely on a mechanism in quantum physics by which an object can simultaneously exist in a fuzzy superposition of multiple states. This and other complementary quantum processes could theoretically be utilized to perform complex operations many times faster than in classical computers. Yet despite significant research and investment, quantum computers are still undeveloped, with only a handful of rudimentary computing platforms demonstrated experimentally. One of the principal reasons for the lack of progress is the fragility of the quantum states that support mechanisms like superposition.

Electrons and light, the typical 'information carriers' of quantum computing systems, both have quantum properties that could be exploited, but the trick is to create a physical material system that provides the interactions needed to make the quantum phenomena appear. This takes researchers into uncharted physics territory.

Bo Yang and Ching
Hua Lee from the A\*STAR
Institute of High Performance
Computing, in collaboration
with researchers from China and
the UK, have now developed a
general theoretical framework
for a promising class of
quantum material systems
that will provide a universal
language for researchers in this
pioneering field.

"Our framework describes a class of exotic phases of matter consisting of a very thin sheet of electrons subject to a strong perpendicular magnetic field," explains Yang. "Unlike conventional phases of matter such as liquids or solids, these phases are defined by specific patterns of electrons 'dancing' around each other."

Different 'dancing patterns' produce different two-dimensional states, or 'topological order', in the same manner that pin pricks in a piece of paper produce different patterns. And while quantum mechanical properties are generally very fragile, those manifested through topological order are very robust and could theoretically be utilized for practical applications such as topological quantum computers.

"Unlike conventional phases of matter such as liquids or solids, these phases are defined by specific patterns of electrons 'dancing' around each other."

By analyzing the algebraic structures of various simple models and validating their results against large-scale numerical computations, Yang and his team developed a model that allows physicists to study these topological states over a wide range of conditions, including states that are common in real materials.

"Our work can help both theorists and experimentalists to understand and realize highly interesting new phases of matter," says Yang.

Yang, B., Hu, Z. X., Lee, C. H., Papić, Z. Generalized pseudopotentials for the anisotropic fractional quantum Hall effect. *Physical Review Letters* 118, 146403 (2017).



### HOW A COMMON CANCER HIJACKS A WOUND-HEALING SWITCH

Understanding how head and neck squamous cell carcinomas takes over wound-healing processes could yield new treatments.

A\*STAR researchers have identified the molecular means by which a common form of cancer hijacks wound-healing processes to help it spread. The team hope their findings could lead to more effective treatments.

Head and neck squamous cell carcinoma (HNSCC) is the sixth most frequently-occurring cancer worldwide. It is caused by the uncontrolled growth of squamous cells — thin, flat, scale-like cells — in the outer layer of skin called the epidermis.

Upon injury, epidermal cells called keratinocytes proliferate and migrate toward wounds, a process that normally stops when healing is complete. In 2013, Prabha Sampath's group at the A\*STAR Institute of Medical Biology discovered a molecular switch that triggers the production of a microRNA called miR-198 in healthy skin, and, upon injury, of the protein follistatin-like 1 (FSTL-1).

Given that uncontrolled cell growth and migration are hallmarks of cancer and a primary cause for metastasis, Sampath's team set out to test their hypothesis that a defective wound-healing switch could facilitate HNSCC.

They used a technique called fluorescent *in situ* hybridization to show that miR-198 was expressed in abundance in

tongue cells from healthy patients, but absent from those from HNSCC patients. Their finding of elevated FSTL1 expression in HNSCC samples suggested the molecular switch was indeed defective. In the absence of miR-198, they also found increased expression of Diaphanous-1 (DIAPH1), another protein elevated following skin wounding.

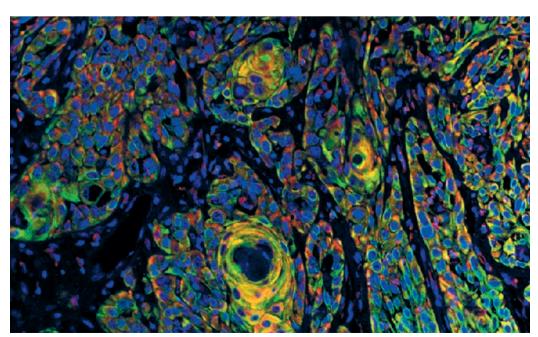
Using biochemical and cell culture experiments, the researchers went on to show that a protein that triggers cell growth and differentiation called epithelial growth factor (EGF), which is often elevated in HNSCC, acts as a regulator

of the defective switch. They revealed the precise molecular mechanism involved.

Sampath's group further showed that blocking FSTL1 and DIAPH1 individually not only thwarts the ability of HNSCC cancer cells to migrate, but also limits the spread of metastatic tumors in immunodeficient mice. Notably, knocking out both genes simultaneously prevented formation of metastatic tumor nodules. Analysis of The Cancer Genome Atlas (TCGA) data base showed the survival of HNSCC patients who expressed elevated levels of both FSTL1 and DIAPH1 was significantly shorter than those who expressed them at lower levels.

Further investigation revealed FSTL1 and DIAPH1 promote HNSCC metastasis by blocking the actions of other proteins that normally prevent cell migration.

The findings provide new targets for therapeutic intervention. "Additionally, we are trying to identify biochemical modulators of this defective molecular switch which could serve as novel and alternative drugs to effectively treat this deadly disease," says Sampath.



Elevated expression of DIAPH1 protein (shown in red) in a squamous cell carcinoma patient.

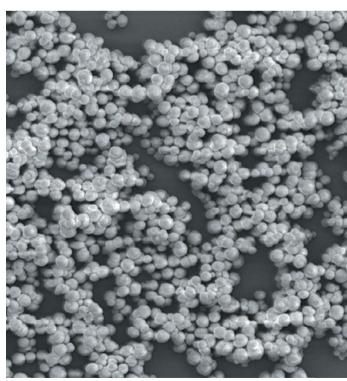
 Sundaram, G. M., Ismail, H. M., Bashir, M., Muhuri, M., Sampath, P., et al. EGF hijacks miR-198/FSTL1 wound-healing switch and steers a two-pronged pathway toward metastasis. Journal of Experimental Medicine 214, 2889–2900 (2017).

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### **GETTING A FUNCTIONAL PROTEIN** FROM A TO B

A milk protein contained in gastro-resistant microcapsules could be used to give foods cancer-fighting, immune-boosting properties.



Microcapsule-protected functional proteins could one day form a key part of human nutrition. Pictured: Calcium carbonate microparticles. After absorbing a functional molecule such as lactoferrin, these microparticles act as the core around which layers of gastro-protective coating can be built.

Scientists from A\*STAR have developed a system to transport a functional protein to the tissues of the digestive tract where it may confer a range of health benefits. This overcomes previous obstacles where the molecules broke down before they could reach their target receptors.

Lactoferrin, found naturally in breastmilk, is a biologically active protein that provides vital support during early infancy. It also has antimicrobial, anti-inflammatory and cancer-fighting properties, and can even help with weight loss. Adults, however, cannot benefit from dietary lactoferrin because the digestive enzymes and acid in their mature stomachs degrade the protein before it can reach the small intestine. It's there, says A\*STAR's Maxim Kiryukhin, that lactoferrin's receptors are thought to absorb the protein and transport it to the lymphatic system, where it provides its beneficial effects.

Kiryukhin, from the Institute of Materials Research and Engineering and his team have succeeded in protecting lactoferrin molecules on their journey through the stomach by coating them in layers of gastric-resistant casing. "We start with calcium carbonate microparticles. These are porous and absorb lactoferrin to produce a 'core' around which we can build our protective shell," says Kiryukhin. "Then, we dissolve the calcium carbonate, leaving the lactoferrin contained within micrometer-sized shells, designed to be stable within gastric fluid, but to degrade in intestinal fluid."

The shell utilizes eight alternating layers of bovine serum albumin and tannic acid grouped into four 'bilayers,' which, aside from offering protection, are also safe and cheap. Tannic acid also has its own antioxidant properties.

"We're in discussions with several companies with regard to how we can move our technology forward."

Kiryukhin's team then performed both in vitro and in vivo studies, first using simulated digestive enzymes to verify the capsules' desired properties, before testing them in mice. In their mouse model, the scientists fluorescently labeled the protein so they could track it through the stages of digestion, finding high levels of lactoferrin in the small intestine and liver. Lactoferrin's presence in the liver verifies the protein's ability to survive gastric digestion and be absorbed into the tissues of the intestine.

Kiryukhin says that his team is now assessing whether their process is commercially viable: "We're in discussions with several companies with regard to how we can move our technology forward."

<sup>1.</sup> Kilic, E., Novoselova, M. V., Lim, S. H., Pyataev, N. A., Pinyaev, S. I. et al. Formulation for oral delivery of lactoferrin based on bovine serum albumin and tannic acid multilayer microcapsules. Scientific Reports 7, 44159 (2017).

The Agency for Science, Technology and Research (A\*STAR) is Singapore's lead government agency dedicated to fostering world-class scientific research and talent for a vibrant knowledge-based economy.

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Singapore Institute of Manufacturing Technology (SIMTech)

Singapore Immunology Network (SIgN)

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