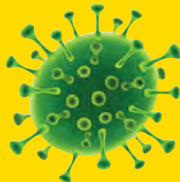


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EDITORIAL

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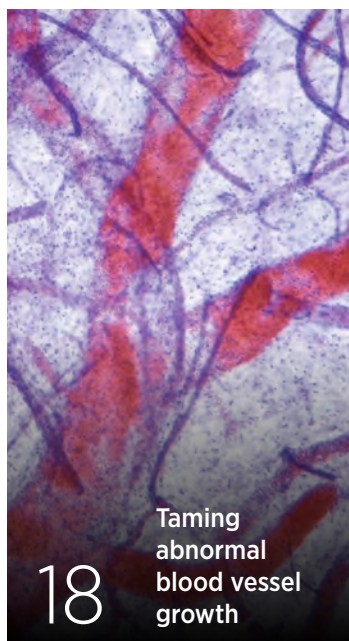
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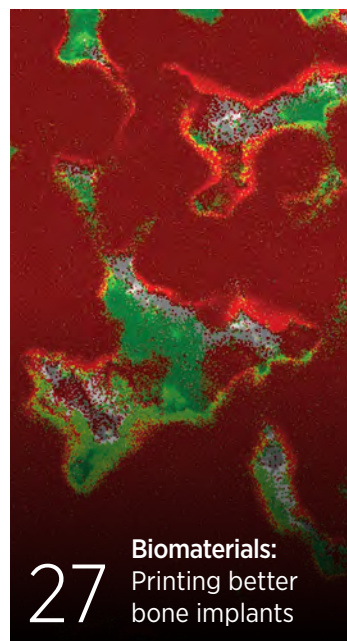
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EDITORIAL NOTES

For many around the world, 2020 has been a year of upheaval and disruption. Plans made at the start of the year have been abandoned or radically altered, while urgent new priorities have surged to the forefront. Now that we are ten months into the world-changing COVID-19 pandemic, the uncertainty of the early days has given way to a dogged determination to help humanity survive—and even thrive—in this new normal.

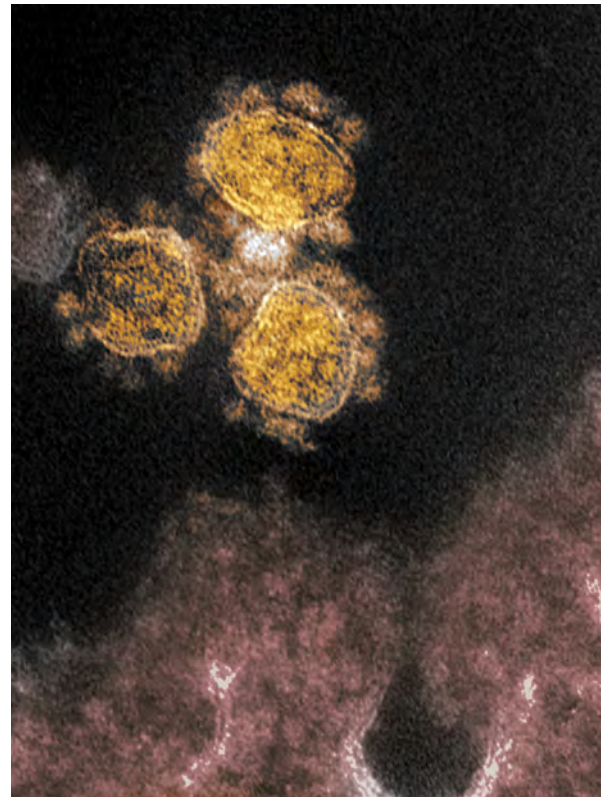
While it is one thing to describe this sentiment in words, quantifying emotions at a population level is another. Yet this is the challenge that a team at the Institute of High Performance Computing (IHPC) set for themselves: to capture the evolving emotions towards COVID-19 in real-time. In our cover story, ‘Sensing emotions in a crisis (p. 04),’ we find out how the researchers quickly adapted their existing algorithms to mine social media data for timely insights that could help policymakers communicate more effectively in times of crisis.

Similarly, expertise built up by A*STAR spin-off companies has helped them respond quickly to COVID-19. Take for example Curiox BioSystems (The Curiox case for better cell analysis, p. 10), an

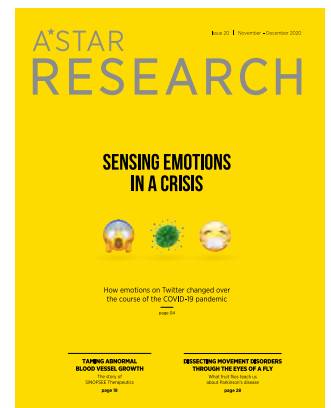
automated cell analysis company that adapted their technology to handle blood samples from COVID-19 patients. On the other hand, the story of SiNOPSEE Therapeutics in ‘Taming abnormal blood vessel growth (p. 18)’ illustrates the power of collaboration when moving research from the lab to industry.

Finally, consider the humble fruit fly, *Drosophila melanogaster*. Although flies are vastly different from human beings, they can nonetheless help us understand neurodegenerative diseases like Alzheimer’s and Parkinson’s Disease—with a little help from genetics and automated video analysis. Find out more in our interview with Sherry Aw of the Institute of Molecular and Cell Biology (IMCB) on p. 28!

In the final issue of *A*STAR Research* for this year, we would like to thank you for your readership and support. Drop us a note at our website www.research.a-star.edu.sg or on LinkedIn or Twitter to let us know what else you would like to see in this magazine come 2021!



Credit: NIAD-RML



On the cover

A*STAR researchers have developed algorithms that can track how emotions on social media change over time.

For the latest on A*STAR’s COVID-19 research, please visit: <https://research.a-star.edu.sg/tag/covid-19/>



SENSING EMOTIONS IN A CRISIS



Multidimensional emotion-sensing algorithms that analyze social media for the public's concerns during times of crisis could help improve policy and messaging from governments.

From Twitter to Facebook to Reddit, billions of people around the world use social media daily to connect with friends and family, as well as to share their stories, feelings and opinions about the state of the world around them. As such, social media has become a prime playground for social sensing—methods that use humans as ‘sensors’ to gather information.

The wealth of information on public sentiment available from social media is invaluable to governments. “The ability to understand the ground accurately and monitor changes in sentiment in a timely manner can help policymakers and communication professionals achieve greater timeliness, relevance and sensitivity to the nuances of the public’s needs,” noted Yinping Yang, a Principal Investigator at A*STAR’s Institute of High Performance Computing (IHPC). This is especially true and relevant during times of crisis, like the ongoing COVID-19 pandemic.

When COVID-19 first emerged in late 2019 and began spreading around the world in early 2020, social media was abuzz with activity about real-time issues like food hoarding and the use of masks. Yang and an international team of researchers responded to the urgent need to understand public sentiment during the rapidly unfolding health crisis by turning to social media, like many before them. What made their study unique was that it examined the multidimensional nature of emotions embedded in users’ messages.

THE POWER OF EMOTIONS

Several studies performed in the past decade have used social media to track public sentiment and trends in communication during health crises like Zika and the H7N9 avian influenza. However, these studies simply

tracked the volume and the positive and negative sentiment counts surrounding common topics of debate. Emotions, on the other hand, are psychological processes and more closely linked to behaviors.

“One thing we know from psychology is that human emotions arise to events that are important to our concerns and needs, be it feeling angry when being treated unfairly or feeling scared of getting infected by a deadly virus,” Yang said. In this way, emotions are more than just feelings; rather, they provide powerful insights into an individual’s and the public’s underlying concerns that matter to them. As such, government policies are most effective when they take into account the public’s emotional state.

Yang’s research program on affective and social intelligence has been focused on four distinct human emotions: fear, anger, sadness and joy. The choice is supported by a convergence in psychology literature, where fear, anger, sadness and joy are distinct emotions that are deemed ‘primary,’ meaning that they are common across cultures and age groups.

For example, although both fear and anger are unpleasant emotions that arise from uncertainty, fear is caused by circumstances while anger is caused by others. Meanwhile, sadness is a negative emotion that arises from unpleasant, uncontrollable events, while joy is a positive feeling that arises from certain and controllable events. Yang and her team hoped that understanding the deviations in these four basic emotions would provide generally applicable insights across various kinds of emotional experiences and application domains.

ALGORITHMS THAT MAKE SOCIAL MEDIA EMOTIONS CRYSTAL CLEAR

The researchers weren’t interested in simply extracting categorical information on emotions. “Traditional sentiment analysis treats an expression as a discrete, categorical construct—as either positive, neutral or negative, or either happy or not happy, sad or not sad,” she explained. “Such approaches are simply not able to provide insights about the complex, continuous and multidimensional nature of human emotional experiences.”

To gain a fuller understanding of human emotions, the researchers developed CrystalFeel, a collection of

“The ability to understand the ground accurately and to timely monitor the sentiment change can help policymakers and communication professionals achieve greater timeliness, relevance and sensitivity to the nuances of the public’s needs”

— **Dr. Yinping Yang**
Principal Investigator, A*STAR’s Institute of High Performance Computing (IHPC)

five algorithms that simultaneously analyze anger, fear, sadness, joy and the overall emotional valence on an intensity scale. In their research, Yang and her co-Principal Investigator and co-inventor Raj Kumar Gupta, experimented with features extracted from a variety of emotion-related lexicons or dictionaries, including their own in-house ‘Emotion Intensity’ lexicon, to predict the level of intensity associated with the four basic emotions in each sentence or message. “We found that including affective lexicon-based

features allowed the system to obtain strong prediction performance, while revealing interesting emotion word-level and message-level associations,” said Yang.

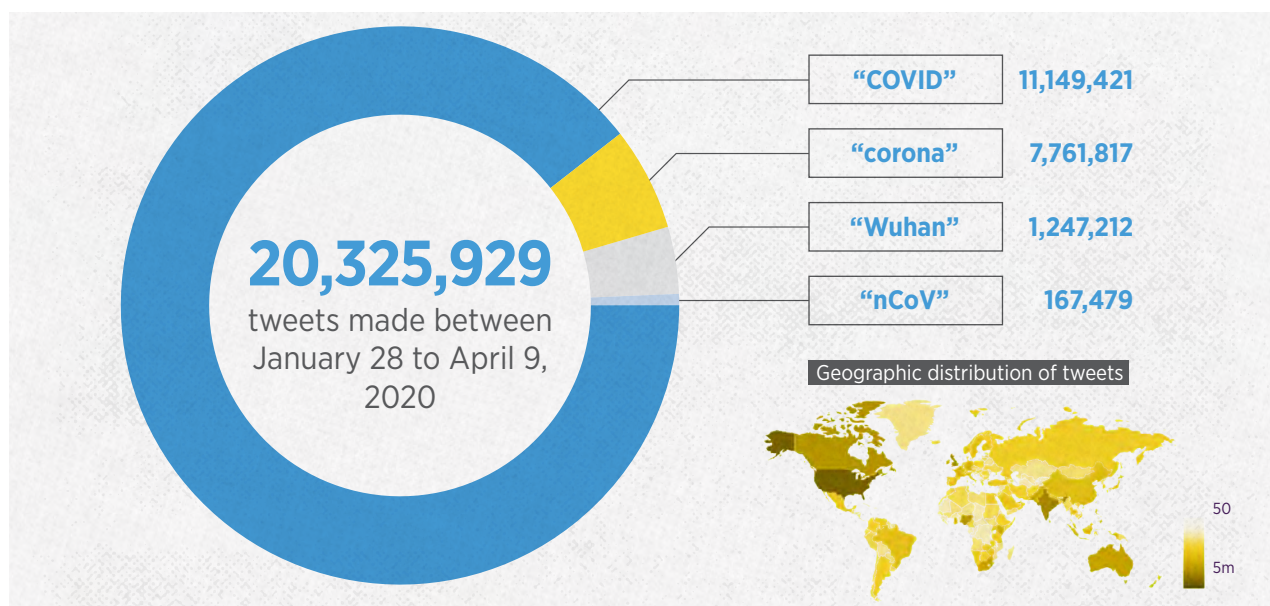
In addition to CrystalFeel, Yang and her team also developed Heartbeat, an all-in-one program that collects, analyzes and presents social media data. “A strong and rich algorithm is not enough,” explained Yang. “Users need lay user-friendly, end-to-end systems that can help them connect the sheer volume of raw data and well-integrated user interface.”

QUANTIFYING EMOTIONAL RESPONSES TO COVID-19 WORLDWIDE

By using Heartbeat and CrystalFeel, Yang and her team were able to leverage the power of social media to illuminate the change and dynamics of public emotions at a worldwide scale as early as late January 2020.

As their source of data, Yang and her team turned to Twitter. With more than 152 million active users worldwide as of the end of 2019, posts from Twitter—called tweets—provide geographically diverse insights into local and global events at the ground level. The researchers had collected more than 20 million publicly accessible tweets for analysis from 170 countries between January 28 and April 9, 2020.

In their COVID-19 analytic research program, done in collaboration with an international team led by May Oo Lwin, Chair of the Wee Kim Wee School of Communication and Information at Nanyang Technological University, Singapore, the researchers tracked emotions around the COVID-19 pandemic trajectory. One of their early findings was that public emotions underwent a strong shift from fear to anger in parallel with notable events, from the emergence



of COVID-19 at the end of January to the World Health Organization's pandemic declaration in early March and stay-at-home notices thereafter. While the researchers also observed signs of sadness linked to the loss of loved ones and joy in response to good health, negative emotions dominated the early months of the pandemic, with anger overtaking fear as the overriding emotion.

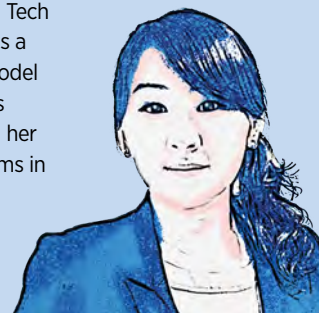
A CONTINUING COLLABORATIVE EFFORT

Yang and her team are continuing to collect and analyze data on the public's emotions in response to COVID-19, having now collected more than 100 million tweets. They are conducting more in-depth analyses to understand the differences in emotional responses among countries, and how cultural differences may play a role in this. The researchers are also seeking to make their databases and algorithms accessible to the broader scientific community, to enable researchers from all over the world to perform region-specific analysis. "We believe that fighting the pandemic requires a global-scale effort," Yang said.

In the longer term, Yang and her team plan to extend the capabilities of their emotion-sensing algorithms to extract fine-grained information about long-term changes in the priorities, desires and values of the public. "We hope that the social sensing tools we developed can be used by more public agencies to help and empower policy analysts and communication professionals to gain more leverage for evidence-based, holistic and timely decision making and communication," concluded Yang. ★

ABOUT THE RESEARCHER:

Yinping Yang joined A*STAR's Institute of High Performance Computing (IHPC) in 2007. Yang currently leads the Affective and Social Intelligence Group as the Group Manager and the Digital Emotions Program as the Principal Investigator. As a founding member and Senior Scientist with the Social and Cognitive Computing Department since 2014, she works with a multidisciplinary team of scientists and engineers across diverse backgrounds including computer science, software engineering, information systems, psychology, linguistics, communication and design arts. Yang recently won a place in the Inaugural Singapore 100 Women in Tech List in September 2020 as a female leader and role model recognized in Singapore's tech sector. She obtained her PhD in Information Systems in 2008 from the School of Computing, National University of Singapore.



1. Lwin, M.O., Lu, J., Sheldenkar, A., Schulz, P.J., Shin, W., Gupta, R. and Yang, Y. Global Sentiments Surrounding the COVID-19 Pandemic on Twitter: Analysis of Twitter Trends. *JMIR Public Health Surveillance* **6**, e19447 (2020).
2. Gupta, R.K. and Yang, Y. CrystalFeel at SemEval-2018 Task 1: Understanding and Detecting Intensity of Emotions using Affective Lexicons. *Proceedings of the 12th International Workshop on Semantic Evaluation* (2018).



MATERIALS SCIENCE

Face-mask innovations, uncovered

From transparent masks to antimicrobial coatings, newer face masks in development will include advanced design features and materials.

Reminiscent of Shakespeare's famous quote, "To be or not to be," the question of whether "to wear or not to wear" a face mask began swirling around on social media at the start of the COVID-19 pandemic.

Fortunately for the rest of us, that debate has mostly been resolved in favor of wearing one. Not that the research wasn't clear in the first place—surgical masks, when used properly, are effective at reducing the spread of viral particles.

"Now that face masks have been thrown into the limelight, we seek to provide a deeper understanding of the different aspects of material selection and design, with the goal of safeguarding public health,"

said Xian Jun Loh, Executive Director at A*STAR's Institute of Materials Research and Engineering (IMRE).

Showcasing that necessity is the mother of invention, Loh and colleagues discuss in their review paper how improvements to mask design, material selection and mask reusability are urgently needed right now. Advanced features such as the ability for a mask to repel water and inactivate pathogens that land on it would also be useful, they suggest.

"Touching a mask surface can transfer some infectious microbes onto the hands," Loh said. "Thus, masks with antimicrobial activity can help to reduce the risk of contamination."

"We seek to provide a deeper understanding of the different aspects of material selection and design, with the goal of safeguarding public health."

Extrapolating into the future, newer face masks may be coated with metal-based nanoparticles, common household chemicals and organic compounds that have biocidal properties. Other materials, such as graphene-based composites with superhydrophobicity and potential for recycling, are also currently being evaluated.

It may be a lower priority at first, but an excellent feature for newer masks would be that of transparency—transparent masks would benefit hearing-impaired individuals who rely on lip-reading for communication, those in the service industry as well as facial recognition software.

"In addition to their key function of filtering viral particles, masks that incorporate multiple functionalities and new materials into their design open up incredible opportunities for us," Loh shared.

That said, the authors caution that masks are not a panacea to viral transmission—they offer no protection to the eyes, for example—and social distancing remains important. In addition, disposable face masks have been highlighted as a growing source of environmental pollution. ★

ABOVE

Innovations in nanotechnology and materials science could lead to safer and more effective masks.

1. Chua, M.H., Cheng, W., Goh, S.S., Kong, J., Li, B., *et al.* Face masks in the new COVID-19 normal - Materials, testing, perspectives. *Research* **2020**, 1-40 (2020).

MACHINE LEARNING

The battle of the bugs goes digital

A new machine learning technique can predict the dynamics between microbes and therapeutics with unprecedented accuracy.

Human beings play host to over 100 trillion bacteria and viruses that play a critical role in everything from digestion to immune protection. Besides these microbial friends, there are also the foes: pathogenic microbes that cause infection and disease. Maintaining this delicate human microbiome is a central focus in creating the next wave of precision therapeutics.

Previously, the drug development process relied heavily on time-consuming, expensive and labor-intensive screening methods. In recent years, however, the study of microbe-drug associations has gone digital, thanks to the advent of advanced machine learning and deep learning. By complementing traditional techniques with advanced machine learning, data scientists can rapidly model how microorganisms will respond to clinical interventions.

Xiaoli Li, a machine learning expert from A*STAR's Institute for Infocomm

Research (I²R), is among the team that has created a novel technique capable of predicting the clinical efficacy of newly developed and repurposed drugs with unprecedented accuracy. They've named it GCNMDA, short for Graph Convolutional Network-based framework for predicting human Microbe-Drug Associations.

One of the challenges with existing computational frameworks is that they struggle to make sense of complex, multidimensional datasets. Microbial and drug databases, for instance, have intricate layers of relationships, redundancies and associations that are difficult to 'teach' machine learning networks. Integrating multiple biological data sources into a single heterogeneous network is another hurdle.

GCNMDA has been the first to successfully overcome these limitations, thanks to a powerful secret weapon—Graph Convolutional Network with an embedded conditional random field (CRF)

layer. "The Graph Convolutional Network can learn accurate microbe and drug representations, while CRF is a probabilistic graphical model which possesses powerful capabilities for modeling pairwise relationships between nodes, such as microbe-drug associations," explained Li, the study's co-corresponding author.

This addition helped the technique to independently recognize semantic information such as similarities between groups of microbes and drugs, while simultaneously making accurate guesses as to microbe-drug associations. The GCNMDA's predictions were so accurate that they significantly outperformed seven state-of-the-art computational systems.

In one case study, the team used GCNMDA to test a suite of potential COVID-19 antivirals for their ability to interact with SARS-CoV-2, generating a list of the top 40 pharmaceuticals likely to be effective against the disease, including some drugs previously verified to be successful in clinical studies. In another case study, GCNMDA accurately identified potential microbe-drug associations for two antibiotic drugs, ciprofloxacin and moxifloxacin.

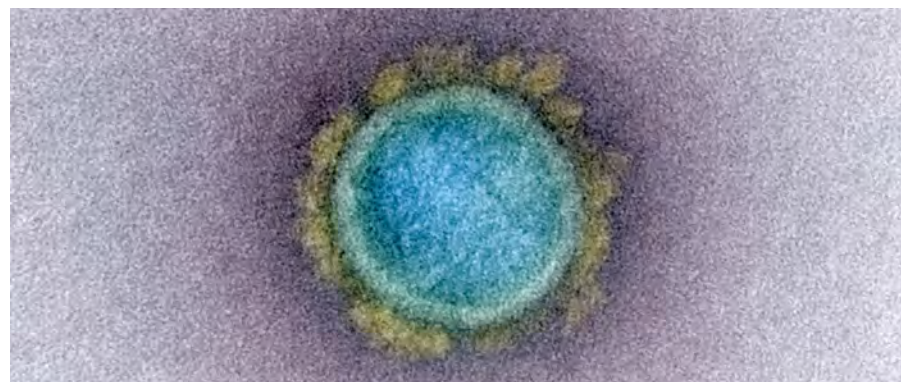
"We can use GCNMDA as a screening tool to narrow down the search space for candidate compounds, which can be developed as vaccines and drugs against drug-resistant microbes," Li said.

To enrich the predictive capabilities of the system, the team is feeding GCNMDA larger training datasets encompassing even more biological parameters. They also plan to tap into large volumes of unlabeled data, which could potentially lead to better predictive models. ★

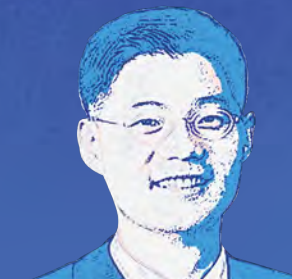
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Machine learning has helped to identify potential drug candidates to treat COVID-19.

1. Long, Y., Wu, M., Kwok, C.K., Luo, J., Li, X. Predicting human microbe-drug associations via graph convolutional network with conditional random field. *Bioinformatics*, btaa598 (2020).



THE CURIOX CASE FOR BETTER CELL ANALYSIS



Namyong Kim
CEO, Curiox Biosystems

Curiox Biosystems, an A*STAR spin-off company, specializes in automated and quantitative cell analysis. Its CEO, Namyong Kim, shares the story of the company's success.

In 1885, German biologist Wilhelm Roux took part of the brain from a chicken embryo and placed it in warm saline solution, keeping it alive for several days. Simple as the experiment was, it seeded the idea that biological tissue could be maintained, or cultured, outside the body, given the right conditions.

Over the years, scientists have refined their methods for keeping various tissues—and even individual cells—alive in petri dishes or cell culture plates. The ability to see, stain, probe and genetically engineer living cells *in vitro* has paved the way for a deeper understanding of how biological systems tick and formed the basis of screening tests for drugs against a plethora of diseases.

However, *in vitro* cell culture and the accompanying downstream analyses remain manual and tedious due to limited choices in methods for washing cells. Reagents are repeatedly added to cells and rinsed away with manual processes, sometimes resulting in the loss of biological material. At the same time, assay outcomes are highly dependent on the experience and technical capability of the researcher performing the experiment.

“There is currently a significant void in ensuring the consistency of cell analysis because practically all cell analysis is performed manually, leading to variation between operators, locations, times and so on,” said Namyong Kim, CEO of bioinstrumentation company Curiox Biosystems. “I believe that these problems can be solved with automation and quantification.”

Kim added that cell analysis is becoming more important in emerging areas of research, including the profiling of small populations of cells such as tumor-infiltrating leukocytes in dissociated tumor samples, or the sequencing of single-cell genomes. In these experiments, a robust and accurate system for handling and processing cells is critical, he said.

BRINGING DOWN WALLS

Kim joined A*STAR's Institute of Bioengineering and Nanotechnology (IBN) in 2004 with ideas for creating an automation system for cell analysis. Before that, he had been working with early-stage high-tech ventures and multinational companies in the US. His industry experience in developing biological assay platforms led him to realize that the assay format had a strong influence over the way downstream processing and analysis could be carried out.

Many high-throughput biological assays involve placing cells in plates consisting of 96 wells separated by walls. When reagents are added or removed from these wells, convective currents and turbulence arise, stressing cells and causing some of them to be washed away during rinsing steps.

Hence, his team at IBN conceived the idea of a wall-less plate that could still accommodate 96 distinct samples. "We developed a super hydrophobic (water-repellent) surface containing hydrophilic (water-'loving') spots positioned at regular intervals. Each hydrophilic spot stabilizes an aqueous droplet, giving rise to an array of sample droplets on a plate. This allows us to wash the samples by unidirectional laminar flow without convective effects or turbulence," Kim explained.

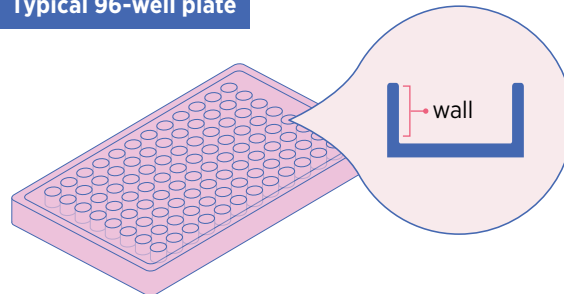
Harvesting the cells from the wall-less plate was also easier and less damaging to the samples. Kim noted that the use of laminar flow in lieu of centrifugal collection led to better consistency and cell viability, which in turn allowed for better resolution of cell populations and more effective debris removal—crucial parameters affecting data quality. The team eventually settled on two variants of wall-less plates: the DropArray and the Laminar Wash plate. These would go on to become the core technologies of Curiox Biosystems when Kim spun off the company from A*STAR in 2008.

MACHINES MAKE LIGHT WORK

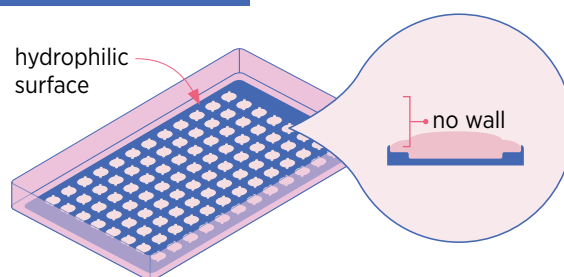
An improved assay format was only half of the equation. The next hurdle was to create a platform for dispensing reagents and performing the washing steps of assays automatically.

Working with engineers, Kim's team devised precise computer-controlled systems consisting of fluidics and robotics to allow researchers to place their DropArray or Laminar Wash plates into a machine, load the appropriate reagents, input the desired protocol, then just walk away and let the machine handle the rest.

Typical 96-well plate



Laminar Wash™ plate



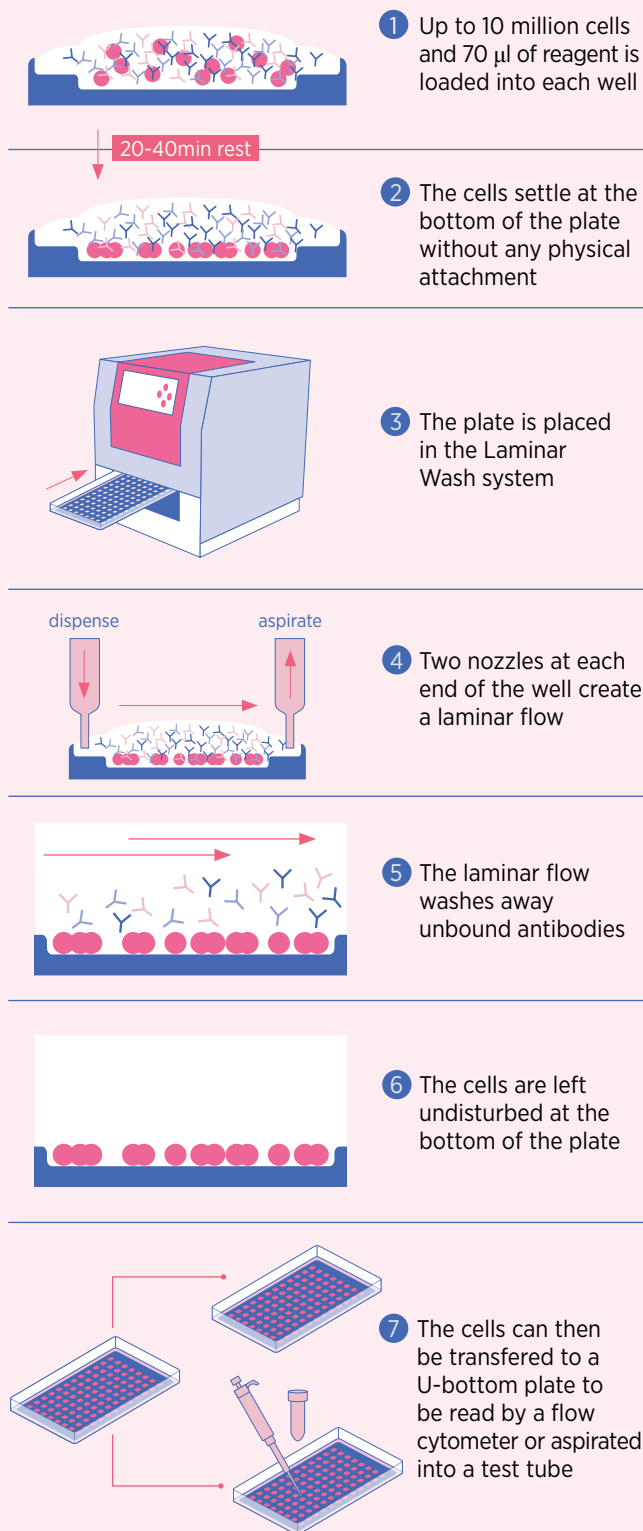
Curiox Biosystems has since launched a series of instruments and associated products enabling the laminar flow method in handling cells, including its Laminar Wash AUTO1000 workstation, a walk-away, fully automated cell analysis system.

Curiously, Kim commented that developing an impressive range of technology was not the most difficult part of his journey from scientist to CEO—the biggest challenge was the application of the technology to meaningful biological assays. "It was not easy to find a counterpart in the field of biological sciences that was as excited about our technology as we were," he quipped.

Leveraging A*STAR's contacts, Kim managed to secure collaborations with the Singapore Immunology Network (SIgN) to validate the Laminar Wash technology for cell analysis and DropArray technology for protein analysis. For example, SIgN implemented Curiox Biosystems' DropArray system on the Institute's clinical immuno-monitoring platform. The researchers showed a five-fold reduction in assay reagent volumes and clinical sample usage, and 65 percent savings in overall clinical assay costs.

Another partnership with the Institute of Molecular and Cell Biology (IMCB) involved the optimization of the DropArray system for RNA transfection of cells in suspension. The findings not only helped refine Curiox Biosystems' technology, but also facilitated the discovery of fundamental biological mechanisms at IMCB.

Laminar Wash Technology for Flow Cytometry



INNOVATION CROSSING BORDERS

"Today, our DropArray and Laminar Wash technologies are being used by more than 80 percent of the 20 biggest biopharma companies, with many owning multiple units of our products," Kim said. "Our customer base ranges from R&D and process development to cell manufacturing and quality control, in both industry and academia."

Clinical labs have also adopted Curiox Biosystem's platforms because of the benefits of better and more consistent data, which is of crucial importance in organ transplant donor-recipient matching, he added.

The company's sustained success has caught the eye of investors. In 2010, Curiox received a large corporate investment by the Zicom Group, a Singapore-Australia conglomerate listed on the Australian Stock Exchange. More recently, in October 2019, Curiox Biosystems raised US\$15 million in series B funding led by top-tier bio venture capitals in South Korea. The latest injection of funds will be used to scale up and accelerate the commercialization activities of Curiox Biosystems globally.

Reflecting on the milestones that Curiox Biosystems' has achieved over the past twelve years, Kim acknowledges A*STAR's role in helping the company find its footing in a competitive global landscape of assay platforms. Even as it expands abroad, it continues to engage with A*STAR's research institutes.

"We are still in active collaboration with A*STAR—through our ongoing research collaboration agreement with SigN, we aim to harness the strengths of Laminar Wash technology to reduce cell loss, raise the viability and yield of cells, as well as increase the resolution of distinguishing immune subpopulations compared to conventional staining protocols," he said, adding that the findings from such studies will help to improve diagnostic immune-profiling, with implications for immunology and immunotherapies for cancer.

"Our work with SigN has also been awarded the prestigious IAF-ICP grant, which is governed by A*STAR, Enterprise Singapore and the National Research Foundation, Singapore. This is another testimony to the strong support available to local emerging companies," Kim concluded. ★

GENOMICS

Seeing glaucoma in a new light

A large-scale genome study suggests that Alzheimer's and an eye disorder called glaucoma share a common disease development pathway.

When pondering over the question of which of our five senses is most important, classical philosophers like Plato and Aristotle chose the sense of sight, because of its importance in our appreciation and understanding of the world.

Unfortunately, vision loss is a common problem facing the elderly due to a disease called glaucoma. Its root cause is traditionally understood to be increased pressure in the eyeball, which leads to optic nerve damage. While glaucoma can impact people of any ancestry, a form of glaucoma called open-angle glaucoma manifests more severely in individuals of African ancestry, although the reason for this is poorly understood.

To gain insight into the cause of this disparity, Chiea Chuen Khor, a Senior Principal Investigator at A*STAR's Genome Institute of Singapore (GIS), along with collaborators in the Genetics of Glaucoma in People of African Descent Consortium, performed a genome-wide association study to identify genetic variants specific to individuals of African ancestry that could be linked to increased risk of open-angle glaucoma.

The group first used genome-wide genotyping to scan the entire human genome for more than one million single nucleotide polymorphisms (SNPs), which are single-letter variations in DNA. In particular, the team found that a SNP in a



A gene associated with Alzheimer's disease has been linked to open-angle glaucoma, suggesting a common pathway between the two conditions.

gene named APBB2 was strongly associated with an increased risk of primary open-angle glaucoma. With more than 26,000 participants, the study's size enabled them to identify APBB2 with strong statistical certainty, explained Khor, who is the last author of the study published in *JAMA*.

Intriguingly, APBB2 is known to be linked to the production of a type of protein called beta-amyloid, which has been implicated in Alzheimer's disease. Armed with this clue, researchers next examined retinal and visual cortex tissue. They found that individuals who carried two copies of the APBB2 genetic

variant had more beta-amyloid in these tissues, suggesting a common pathway in disease development between open-angle glaucoma and Alzheimer's.

"Our findings suggest that glaucomatous optic nerve damage can be due to amyloid pathology, and not just due to pressure," Khor highlighted.

Future studies will involve much larger sample sizes to confirm a causal association between amyloid buildup and glaucoma, said Khor, who hopes that the work will lead to new therapeutic strategies for glaucoma. He also noted that pharmaceutical companies such as Galimedix have already developed eye drops to reduce amyloid buildup that are now in clinical trials. Taken together, these developments strongly suggest that drugs targeting amyloid deposition could help retard glaucomatous nerve damage, he said. ★

"Our findings suggest that glaucomatous optic nerve damage can be due to amyloid pathology, and not just due to pressure."

1. Genetics of Glaucoma in People of African Descent (GGLAD) Consortium. Association of Genetic Variants With Primary Open-Angle Glaucoma Among Individuals With African Ancestry. *JAMA* 322, 1682-1691 (2019).

DRUG DELIVERY

Delivering drugs in a pinch

Using magnets, scientists have developed an innovative pressure-based technique that represents a new frontier in needle-free drug delivery.

Though the world may be eagerly awaiting the arrival of a COVID-19 vaccine, there's one tiny snag in vaccine roll-out plans. Approximately 20 percent of the general population suffers from a paralyzing fear of needles known as trypanophobia, potentially derailing vaccine compliance.

But trypanophobia doesn't just affect vaccination rates. It can also affect treatment adherence—particularly for conditions like diabetes, where daily shots of insulin are needed to manage blood sugar levels. To overcome this barrier, researchers are continuously searching for non-invasive drug delivery strategies. However, many current methods irritate the skin or require specialized equipment, posing further challenges for patients.

Now, an international team of scientists including Xiaomeng Wang from A*STAR's

Institute of Molecular and Cell Biology (IMCB), David Becker from A*STAR's Skin Research Institute of Singapore (SRIS) and Chenjie Xu from the City University of Hong Kong, have found an innovative way of getting drugs across the skin: magnets.

Their unique approach was inspired by traditional Chinese medicinal massage called *tui na*, which involves applying pressure and herbal remedies to the body. The team sought to mimic the process by using two neodymium magnets to pinch the skin and subsequently apply drugs to the pinched area.

“With the use of magnets, we can control and optimize the pressure and application time to develop a reproducible technique to deliver drugs across the skin,” explained first author Daniel Lio, who did this research as part of his doctoral thesis

at Nanyang Technological University's School of Chemical and Biomedical Engineering, and is now working at A*STAR's Enterprise Group.

Testing their method on mice, Lio and his colleagues found that with just one minute of 0.28 MPa pressure, they were able to successfully deliver macromolecules and nanoparticles of up to 20,000 daltons and 500 nm, respectively. Further investigation showed that the pressure caused micropores to form on the skin surface, allowing the drugs to pass through.

Applying the technique to insulin delivery, the researchers showed that five minutes of pressure allowed the drug to enter the skin and make its way into the bloodstream, causing a gradual drop in blood sugar within 30 minutes following application. This pressure-based method could thus help diabetics manage their condition without the abrupt drop in blood sugar levels that is sometimes caused by insulin injections and linked to serious complications such as seizure and loss of consciousness.

As exciting as their discovery may be for trypanophobes, there's still much work to be done before their approach can be applied in the clinic. Moving forward, the researchers are now looking to optimize the method's parameters across a wider variety of animal models and other kinds of drugs.

To further enhance the patient experience, they are also working on a device that can automatically apply both pressure and the topical drug formulation. “Working with engineers at Nanyang Technological University, we have developed a 3D printable device which can deliver variable levels of pressure up to 45 Newtons without the use of magnets,” said Becker. ★

LEFT

Pinching the skin with magnets helps it to absorb drugs such as insulin.

1. Lio, D.C.S., Chia, R.N., Kwek, M.S.Y., Wiraja, C., Madden, L.E., *et al.* Temporal pressure enhanced topical drug delivery through micropore formation. *Science Advances* **6** (22), eaaz6919 (2020).



GENETICS

Reversing a cancer crisis

Researchers have pieced together a series of molecular events that trigger the progression of chronic myeloid leukemia to its acute phase—the ‘blast crisis.’

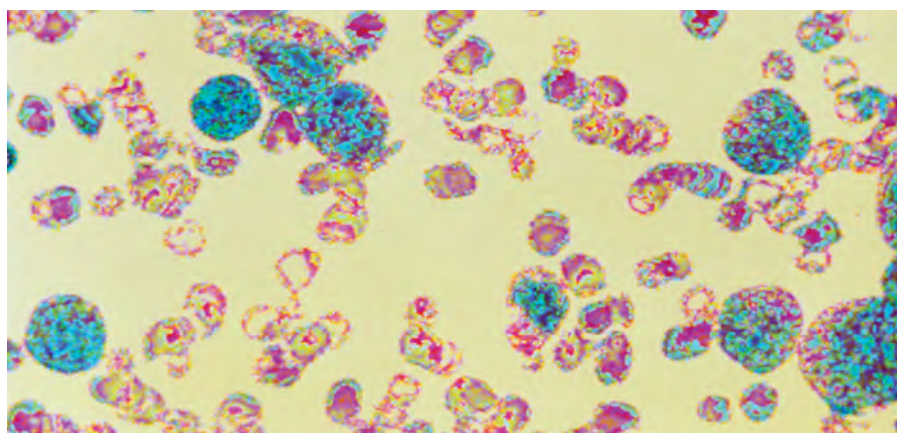
Unlike most types of cancer, which are assigned a stage based on tumor size and extent of spread, chronic myeloid leukemia (CML), a disease of the bone marrow, is measured by the number of immature white blood cells in the blood or bone marrow, which are commonly known as ‘blasts.’

Patients in the accelerated phase have 15 to 30 percent blasts, while patients in the acute phase—or ‘blast crisis’—have 20 percent or more blasts, some of which would have spread to other organs.

“CML patients in the blast-crisis phase no longer respond to the canonical treatment and have a poor prognosis. In particular, because of its rarity and daunting molecular heterogeneity, physicians quickly run out of effective treatment options,” explained Axel Hillmer, an Adjunct Group Leader at A*STAR’s Genome Institute of Singapore (GIS).

Hillmer, together with GIS colleague Asif Javed and Sin Tiong Ong at Duke-NUS Graduate Medical School Singapore, decided to map out a clinically relevant molecular model of CML transformation to blast crisis, which may help in identifying effective treatments and novel biomarkers for the disease.

Access to a rare cohort of 13 paired samples from patients who had progressed



Digitized colored light micrograph of cancerous blood cells in chronic myeloid leukemia (CML).

from the chronic phase to blast crisis provided an opportunity for the research team to study the samples using large scale ‘-omics’ approaches, ranging from whole genome and exome sequencing to chromatin immunoprecipitation and high-throughput sequencing.

Using transcriptome analysis, they found that the blast-crisis genome was significantly enriched for changes involving components of the polycomb repressive complex (PRC) pathway, regardless of the genetic background of the cells studied.

In blast-crisis samples, PRC1 mutations were shown to silence novel tumor suppressor genes, such as *NR4A2*, promoting cell survival and proliferation. PRC2 mutations, on the other hand,

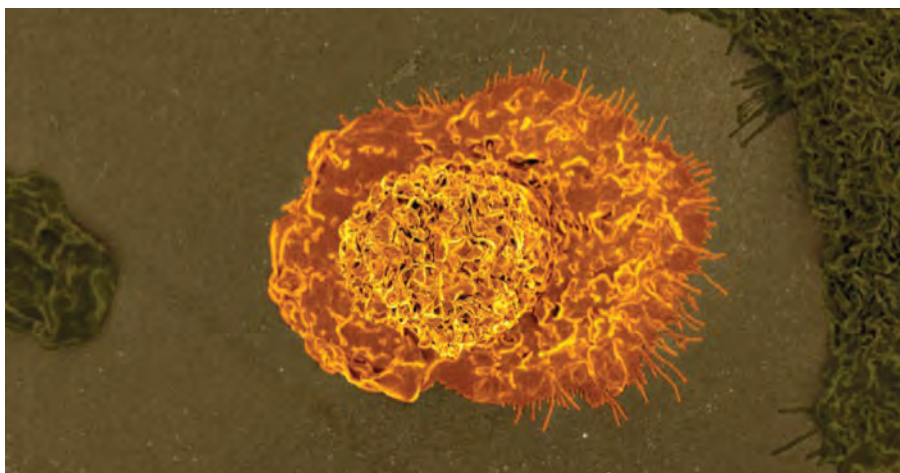
were shown to silence key genes involved in myeloid differentiation and tumor suppressor function by DNA hypermethylation, in a process called ‘epigenetic switching.’

One hypothesis is that patients with a poor prognosis can be reverted to a lower risk category by inducing the re-expression of PRC-controlled genes. In cell culture experiments, the researchers demonstrated that two PRC inhibitors—decitabine and PTC209—both independently lowered the viability of blast-crisis cells. Used in combination, they reduced colony formation by 90 percent, opening up an avenue for combination treatments.

“We found that epigenetic reprogramming is responsible for the transition from benign chronic-phase CML to fatal blast-crisis CML. Our cell culture experiments suggest that epigenetic drugs may improve CML treatment, but its efficacy remains to be determined in clinical studies,” Hillmer said. ★

“We found that epigenetic reprogramming is responsible for the transition from benign chronic-phase CML to fatal blast-crisis CML.”

1. Ko, T.K., Javed, A., Lee, K.L., Pathiraja, T.N., Liu, X., *et al.* An integrative model of pathway convergence in genetically heterogeneous blast crisis chronic myeloid leukemia. *Blood* **135** (26), 2337-2353 (2020).



IMMUNOLOGY

A fatal flaw in the immune system

Clinicians and scientists have discovered a rare mutation that impairs the immune system, and are using their findings to devise treatment strategies.

It is notoriously one of the most complex systems in the natural world, but its complexity is there for good reason. By guarding against and responding to foreign microbes, our immune system keeps us alive. Primary immunodeficiency disorders, characterized by defects in the immune system, turn every infection into a life-threatening one.

This was the scenario that challenged clinicians Enrica Tan, Woei Kang Liew, Ah Moy Tan and colleagues at the KK Women's and Children's Hospital (KKH): a one-week-old baby was hospitalized for a variety of infectious diseases that required urgent antimicrobial treatment.

"When doctors from KKH admitted an infant patient with recurrent infections alongside lung, skin and liver damage, they recruited scientists at A*STAR's Institute of

Molecular and Cell Biology (IMCB) to help determine the cause of this unprecedented disease and devise a treatment strategy," said John Connolly, a Research Director at IMCB and co-corresponding author on the study with KKH's Liew.

The team was quick to recognize that they were dealing with a primary immunodeficiency disorder: a novel heterozygous mutation in the *NFKB1A* gene that appeared to be unlike any other *NFKB1A* mutation.

"Mutations in *NFKB1A* are normally characterized by defective T and B cell responses," Connolly explained. "But the *NFKB1A* mutation we found caused pathological changes in myeloid cell cytokine production."

NFKB1A encodes a protein called I κ B α , which inhibits the activation and transport

of the NF- κ B protein complex. Whole-exome sequencing confirmed that the missense mutation occurred at a site on the I κ B α protein critical for its degradation. As the mutation prevented I κ B α degradation, it caused severe defects in downstream NF- κ B signaling and cytokine production.

"We believe the mutation acts in two parts. Firstly, it limits immune responses in fibroblasts and macrophages, via the suppression of pro-inflammatory cytokines IL-6 and TNF α ," said Connolly. "Secondly, it fails to limit immunopathological responses, over-producing IL-1 β which increases neutrophil activity, causing liver damage and inflammation."

Functional and phenotypic characterization of the patient's white blood cells revealed an abnormally high production of a key pro-inflammatory cytokine, IL-1 β . Replicating the mutation in mice and myeloid cells differentiated from the patient's induced pluripotent stem cells confirmed that this mutation was the cause of IL-1 β hyper-production.

With the genetic cause pinpointed, the team decided on a treatment strategy. A bone marrow transplant temporarily stabilized the patient's condition, but the re-emergence of the patient's white blood cells sent IL-1 β levels soaring again. Treatment with anakinra, a recombinant IL-1 receptor antagonist, briefly halted disease progression but had to be withdrawn due to side effects.

Although unable to save the patient, the researchers made the important discovery of a rare mutation and the role of I κ B α in IL-1 β production. These findings have implications for the development of treatments against liver disease and cancer that target the NF- κ B pathway, Connolly added. ★

ABOVE

Scientists have identified a novel mutation that causes an over-production of pro-inflammatory cytokines in macrophages.

1. Tan, E.E.K., Hopkins, R., Lim, C.K., Jamuar, S., Ong, C. *et al.* Dominant-negative *NFKB1A* mutation promotes IL-1 β production causing hepatic disease with severe immunodeficiency. *Journal of Clinical Investigation* (2020).

IMMUNOLOGY

Where immune cell reinforcements come from

A molecular marker called Ms4a3 can help scientists trace the origins of immune cells that reside in tissues and organs.

Like policemen patrolling a residential estate, immune cells known as macrophages can be found within tissues and organs, constantly keeping a lookout for foreign microbes and rogue cells. After an inflammatory response, these tissue-resident macrophages (RTMs) may need to be replenished.

Some replacement RTMs are thought to be derived from monocytes—another type of immune cell circulating in the blood. However, without a way to track monocytes and their precursors as they mature, researchers found it difficult to estimate the relative contribution of circulating monocytes to RTM numbers.

Now, scientists led by Florent Ginhoux, a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SIgN), have discovered a gene (or marker) that faithfully maps the development path

of monocytes. Working with colleagues in China and Germany, Ginhoux's team profiled immune cells and found that Ms4a3 was specifically expressed by monocyte-committed progenitor cells—precursor cells that are fated to become monocytes.

“One can think of Ms4a3 as a switch that is only turned on in monocyte-committed progenitor cells,” Ginhoux said.

The researchers also demonstrated that macrophages themselves do not express Ms4a3. This was an important finding because it meant that any RTMs expressing Ms4a3 originated from monocyte-committed progenitor cells.

Using Ms4a3 as a marker, Ginhoux's team was able to quantify the extent to which monocytes contributed to RTMs in various organs. In a mouse model of inflammation, the researchers reported that the proportion of Ms4a3-expressing

circulating monocytes decreased while the proportion of Ms4a3-expressing RTMs increased as inflammation progressed. This suggested that circulating monocytes were recruited to the site of inflammation, where they subsequently matured into RTMs. The researchers further noted that factors such as sex, age and diet impact the extent of monocyte contribution to RTMs.

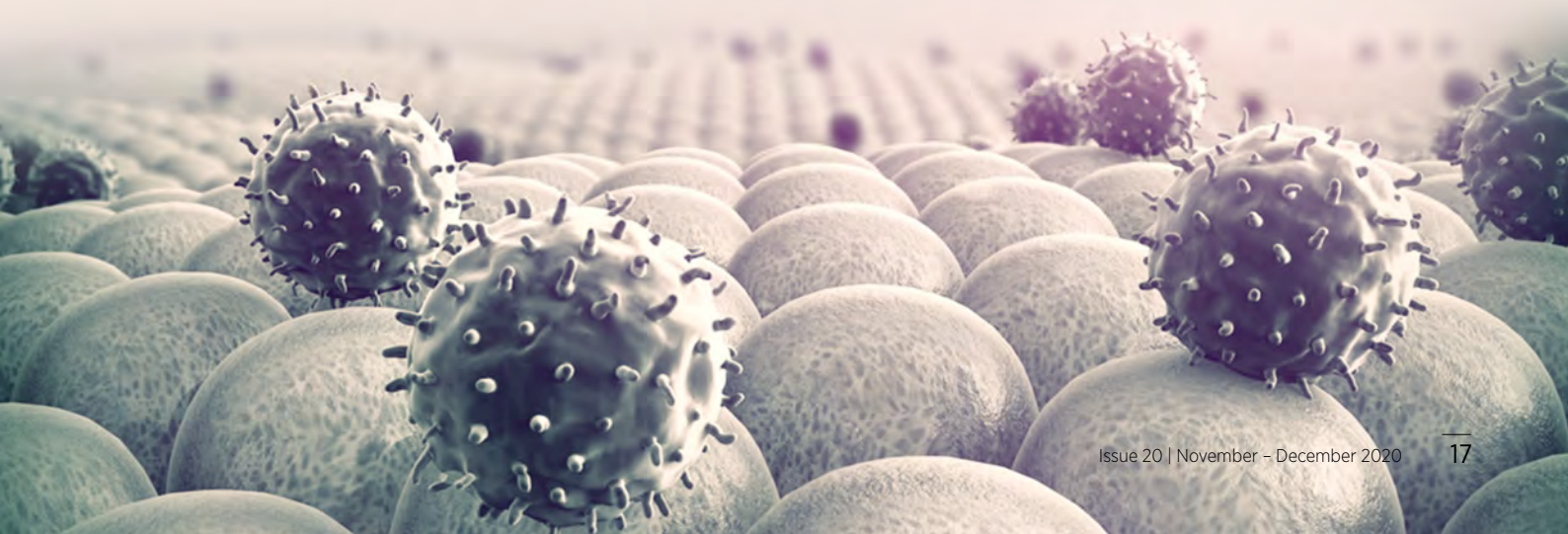
Ginhoux added that the discovery of specific immune cell markers such as Ms4a3 will pave the way for a more holistic understanding of the immune system. “Rather than define immune cell populations only by their function, we can now also define them by their origins, since we can trace their lineage and map their fates,” he explained.

This broader definition could offer clues into the body's immunological responses to cancer, something that Ginhoux is keen to explore in the future. “We already have clear evidence that tumor-associated macrophages play an important role in the progression of mouse and human cancers. By exploring the origins of those immune cell populations, we may be able to better target them to treat cancer,” he said. ★

BOTTOM

Immune cells that reside in tissues and organs may sometimes need to be replenished after an immune response to infection.

1. Liu, Z., Gu, Y., Chakarov, S., Blieriot, C., Kwok, I., *et al.* Fate mapping via Ms4a3-expression history traces monocyte-derived cells. *Cell* **178** (6), 1509–1525.e19 (2019).



TAMING ABNORMAL BLOOD VESSEL GROWTH

Uttam Surana shares how SiNOPSEE Therapeutics, the biopharmaceutical startup he co-founded, is developing drugs to block angiogenesis in cancer and degenerative eye conditions.

Life is maintained by a delicate balance of interactions among molecules, cells, tissues and organs. For instance, blood vessels are essential for delivering blood rich in oxygen and nutrients to all parts of the body. Angiogenesis—the sprouting of blood vessels—is important during growth, development and wound healing.

However, aberrant angiogenesis can also result in disease. For example, in the eye, the overgrowth of blood vessels can give rise to a condition known as wet age-related macular degeneration (AMD), whereby the vessels leak blood and fluid into the retina. Similarly, in cancer, solid tumors secrete factors that promote angiogenesis so that the tumor receives nourishment and can sustain its growth, while also gaining an ‘escape route’ to metastasize to other parts of the body.

An A*STAR spin-off company, SiNOPSEE Therapeutics, aims to tackle the problem of unwanted angiogenesis with its pipeline of small molecule drugs that block the downstream signaling from angiogenic factors. A*STAR Research spoke to Uttam Surana, one of SiNOPSEE Therapeutics' four founding members and a Research Director at A*STAR's Institute of Molecular and Cellular Biology (IMCB), about how he is taking his research from bench to bedside.

Q: WHY ARE YOU INTERESTED IN MOLECULAR TARGETS THAT REGULATE ANGIOGENESIS?

My research primarily focuses on networks that control the dynamics of cell division. Hence, anticancer therapeutics that can inhibit tumor cell division and trigger cell death have always been on my radar.

Angiogenesis is important in this context because blood vessels supply nutrients and oxygen to tumors, helping them grow, survive and invade other tissues. Furthermore, abnormal blood vessel formation is also involved in debilitating ocular diseases such as AMD, which can lead to complete blindness.

Thus, we had reasoned that by targeting angiogenesis, we would serve the therapeutic need simultaneously for two major disease domains: oncology and ophthalmology.

Q: WHAT ARE SOME OF THE MOLECULAR TARGETS THAT SiNOPSEE THERAPEUTICS IS DEVELOPING DRUGS AGAINST?

A major class of molecules we target are the receptor tyrosine kinases (RTKs), which regulate many signaling pathways involved in cell growth and division. Some of the targets in this group, like PDGFR, VEGFR and Flt3, are involved or implicated in tumor growth and angiogenesis.

Besides RTKs, our repertoire of molecular targets also includes regulators like cyclin-dependent kinases (CDK). CDK 8 and CDK19, for example, control transcription and are frequently deregulated in colon, prostate and breast cancer. As they are considered an important group of therapeutic targets, we intend to develop drugs against them.

Q: COULD YOU DESCRIBE THE PROCESS OF DRUG DISCOVERY AND DEVELOPMENT AT SiNOPSEE THERAPEUTICS?

We first use 'humanized' yeast strains (developed with the help of a Singapore Therapeutics Development Review grant from A*STAR) to identify inhibitors against various disease targets, such as RTKs or metabolic enzymes, before testing them on human cells. By humanized, I mean yeast strains that have human proteins or pathways integrated into the yeast genome through genetic engineering.

Essentially, we took humanized Baker's yeast (*Saccharomyces cerevisiae*) and used them as a platform for designing drug screening strategies that can rapidly identify inhibitors against disease-causing proteins or pathways. These experiments eventually evolved into a collaborative project with the company MSD, where we sought to identify inhibitors against metabolic enzymes that are implicated in lung cancer.

During this process, my long-time collaborator Hong Hwa Lim and I developed a close collaboration with Chandra Verma and Srinivasaraghavan Kannan at A*STAR's Bioinformatics Institute (BII). We employed computational methods for improving the efficacy and selectivity of our system, and the four of us eventually became the co-founders of SiNOPSEE Therapeutics.

Finally, to build our chemical compound library, we received generous support from Kong Peng Lam, Executive Director of A*STAR's Bioprocessing Technology Institute (BTI), and Wanjin Hong, Executive Director of IMCB. Our computational efforts were supported by Frank Eisenhaber, Executive Director of BII. These events ultimately helped to establish the current drug pipeline we now have.

Q: HOW MIGHT SMALL MOLECULE INHIBITOR DRUGS BE SUPERIOR TO OTHER DRUG TYPES IN THE CONTEXT OF ONCOLOGY AND/OR OPHTHALMOLOGY?

For wet-AMD, as an example, the current standard of care for the condition involves injecting antibodies into the eye

every few months. Even then, 30 to 40 percent of the patients do not respond well to this form of treatment.

Unlike antibodies, our most advanced lead candidate does not bind to the ligand that promotes angiogenic growth as antibodies do. Instead, the candidate is a small molecule that inhibits three RTK receptors (PDGFR α , PDGFR β and VEGFR2) responsible for the abnormal growth of blood vessels. This difference in mechanism of action allows us to administer the drug as an eye drop, which is not possible with current antibody-based therapies.

Q: *WHAT WERE SOME OF THE HURDLES YOU AND YOUR TEAM FACED WHILE FOUNDING SiNOPSEE THERAPEUTICS?*

Once we had identified, optimized and tested the first set of inhibitors against our targets, we decided to develop them as well-optimized, preclinical development candidates for wet-AMD. At that time, A*STAR's Experimental Therapeutics Centre (ETC) did not yet have measures in place to develop such therapeutics. Our other option, then, was to start a spin-off company and attract funding from angel investors to develop these lead molecules. So the four of us took the plunge and registered SiNOPSEE Therapeutics in December 2017.

Having no prior experience in running a start-up, a major hurdle was familiarizing ourselves with various administrative processes, like business registration, share distribution, licensing agreements and patents. We had to slowly learn the ropes while running our respective labs. We also assembled a Scientific Advisory Board with three eminent members to guide SiNOPSEE Therapeutics through its developmental path: Alex Matter, a drug discovery and development expert; Sir Tom Blundell, a renowned structural biologist; and Dorairajan Balasubramanian, an eminent scientist and the Director of the L. V. Prasad Eye Institute, India.

The greatest challenge, however, was finding investors who would provide funding to sustain our research. In this regard, we received some help and guidance initially from A*ccelerate, the commercialization arm of A*STAR, and subsequently from our personal contacts. A*STAR is a stakeholder in SiNOPSEE Therapeutics and has helped to connect us with various investors.

Q: *WHAT IS THE CURRENT STATUS OF SiNOPSEE'S LEAD DRUG CANDIDATES AND WHAT ARE THE COMPANY'S FUTURE PLANS?*

SiNOPSEE Therapeutics has now advanced the development of the drug molecules it licensed out from A*STAR. New chemical modifications have been introduced to increase the efficacy and selectivity of these compounds, and a new intellectual property filing has been made that is wholly owned by our company.

Meanwhile, our lead candidate against wet-AMD has been tested in both mouse and rat models. We have also 'tuned' its structure such that its pharmacokinetic parameters, such as ocular toxicity, are within a characteristic range for a good drug candidate, without compromising on drug efficacy.

Most notably, we have developed a proprietary eye-drop formulation for the efficient administration of our lead candidate. Given that the current standard-of-care for wet-AMD is the bimonthly eye-injection of an antibody marketed by Bayer, Novartis and Genentech, a therapeutic eye drop could be a game changer in the wet-AMD therapeutics domain.

We are now planning to test the lead candidate, in combination with our eye-drop formulation, in a monkey model, followed by a Phase 0, first-in-human trial. In addition to the wet-AMD project, we are looking to further develop our anticancer therapeutics and will be raising series A funding in the near future. ★

ABOUT THE RESEARCHER:

Uttam Surana received a PhD degree in 1986 from the University of Arizona, US. After research stints at the University of Cambridge, UK, and the Institute of Molecular Pathology in Vienna, Austria, Surana joined A*STAR's Institute of Molecular and Cell Biology (IMCB) in 1992 where he is currently a Research Director. He is also an Adjunct Professor at A*STAR's Bioprocessing Technology Institute (BTI), as well as at the Yong Loo Lin School of Medicine and the Synthetic Biology for Clinical and Technological Innovation (SynCTI), National University of Singapore. For his outstanding contributions to the understanding of control circuits that regulate cell division, Surana was awarded Singapore's National Science Award in 2007.





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AGING

Stopping premature aging in its tracks

DNA damage associated with premature aging in Hutchinson-Gilford Progeria Syndrome can be prevented if the abnormal protein progerin is removed before DNA replication.

Every February 29, a date befitting the rarity of the diseases it highlights, Rare Disease Day is held to raise awareness for rare diseases around the world. Although rare, these diseases can be devastating, such as in the case of Hutchinson-Gilford Progeria Syndrome (HGPS), a genetic condition that causes children to age—and die—prematurely. Importantly, these diseases provide a unique glimpse into potential mechanisms that trigger cell and organismal aging.

HGPS is caused by a mutation in the *LMNA* gene, creating an abnormal version of the Lamin A protein called progerin. Progerin is known to cause signs of accelerated aging such as DNA damage

and the loss of heterochromatin, a densely packed form of DNA located near the nuclear lamina. However, it was unclear if DNA damage and heterochromatin loss were linked and whether therapeutic interventions that remove progerin would be able to rejuvenate these cells.

A team from A*STAR's Skin Research Institute of Singapore (SRIS) and Institute of Medical Biology (IMB) has now shown that heterochromatin loss is actually a prerequisite for progerin-mediated DNA damage, and that DNA damage can be prevented altogether if progerin is removed before the cells replicate their DNA.

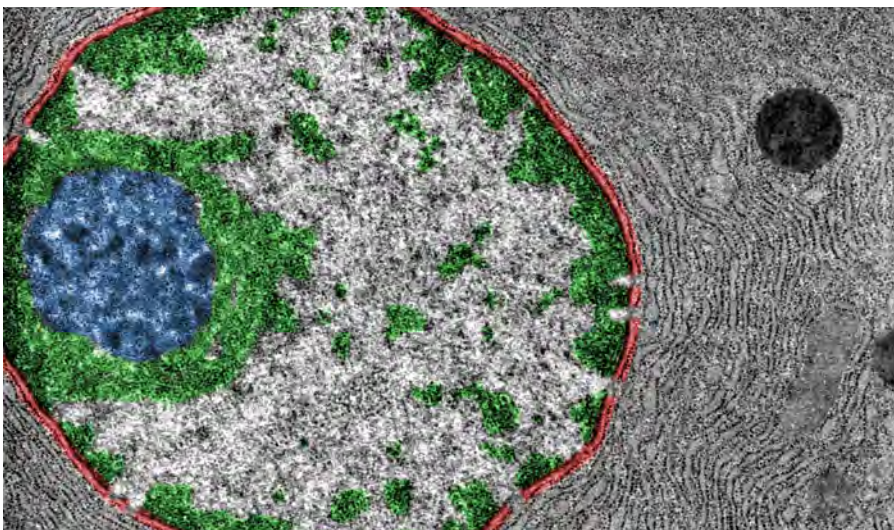
Using immunofluorescence microscopy to measure the levels of heterochromatin,

DNA damage and progerin in cells arrested at different stages of the cell cycle, the team found that progerin-expressing cells in the non-dividing (G1) stage of the cell cycle lost heterochromatin but did not accumulate DNA damage. In contrast, progerin caused DNA damage exclusively during the late stages of DNA replication and preferentially in cells with low levels of heterochromatin.

This discovery is in line with the team's previous findings that progerin-induced DNA damage can be alleviated with telomerase. "Telomerase is active only during DNA replication," explained study corresponding author Oliver Dreesen, a Principal Investigator at SRIS. "This finding made me think that progerin-induced DNA damage may have happened during replication—or else telomerase would not have been able to prevent it."

In agreement with their hypothesis, the team found that DNA damage occurred during the very late stages of replication, and that removing progerin from non-dividing cells could restore the levels of heterochromatin. "Importantly, based on the assays we used, these cells now behave like cells that never were exposed to progerin," added Dreesen.

"This study provides a proof of concept that removing progerin from non-dividing cells or tissues would leave no permanent damage and fully restore cell function," said Brian Kennedy, Director of the National University Health System Centre for Healthy Ageing in Singapore. "This takes us one stage closer in therapeutic development." ★



LEFT

A false color transmission electron microscopy image showing a cell's nuclear envelope (red), chromatin (green) and nucleolus (blue). Hutchinson-Gilford Progeria Syndrome has been linked to DNA damage.

1. Chojnowski, A., Ong, P.F., Foo, X.R.M., Liebl, D., Hor, L., *et al.* Heterochromatin loss as a determinant of progerin-induced DNA damage in Hutchinson-Gilford Progeria. *Aging Cell* **19**, e13108 (2020).

IMMUNOLOGY

When immune cells aren't immune after all

Researchers at A*STAR have uncovered a new role for a subset of immune cells in HIV infection and transmission.

Anyone who has seen an Avengers movie knows that superhero teams consist of members with complementary strengths and weaknesses. Likewise, our immune system consists of a constellation of cell types, each with their specialized function.

When facing a foe as dangerous as the human immunodeficiency virus (HIV), two immune cell types are known to be particularly susceptible—CD4⁺ T cells and macrophages, and, to a smaller degree, dendritic cells (DCs).

This has been the prevailing belief until a recent study by Florent Ginhoux, a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SiGn). Together with the team of Philippe Benaroch at the Curie Institute in Paris, Ginhoux discovered that a rare subset of DC precursors has unique properties that make them three or four times more readily infected by HIV than other DC populations.

In particular, the expression of a viral receptor called Siglec-1 on this population of DC precursors piqued the curiosity of Ginhoux's team.

"When we discovered pre-dendritic cells (pre-DCs), we did not immediately think about HIV. But then we noticed that they showed a high expression of a molecule called Siglec-1. This triggered our interest because Siglec-1 is known to bind to HIV," said Ginhoux.

To identify the role Siglec-1 plays in HIV infection, the researchers used an antibody

to block the Siglec-1 receptor on pre-DCs. This prevented the pre-DCs from being infected by the HIV-1 virus to varying extents: 35 percent inhibition for CCR5-tropic strains, and 85 percent inhibition for CXCR4-tropic strains.

One option for stopping HIV infection would be to make pre-DCs resistant to viral fusion and replication. However, pre-DCs made resistant to viral fusion were still able to capture viral particles on their surface via Siglec-1, and transmit the virus to CD4⁺ T cells in a replication-independent manner.

Nonetheless, Ginhoux thinks that the answer to stopping HIV infection and transmission is more complex than just blocking the Siglec-1 receptor—doing so would allow other infections to pass by undetected, sacrificing the immune system's general antiviral response.

"We noticed that the pre-dendritic cells showed a high expression of a molecule called Siglec-1. This triggered our interest because Siglec-1 is known to bind to HIV."

Findings from this study have broader implications for other infectious diseases, which Ginhoux's team is keen to explore in the future. "It would be interesting to look into whether pre-DCs play a similar role in the spread of viral diseases like dengue and chikungunya," he said. ★

ABOVE

A subset of dendritic cells that express high levels of a protein called Siglec-1 are three to four times more readily infected by HIV than other dendritic cells.

1. Ruffin, N., Gea-Mallorquí, E., Brouiller, F., Jouve, M., Silvín, A., *et al.* Constitutive Siglec-1 expression confers susceptibility to HIV-1 infection of human dendritic cell precursors. *Proceedings of the National Academy of Sciences of the United States of America* **116**, 21685–21693 (2019).

CANCER BIOLOGY

Exposing the weakness of a tough drug target

By targeting a metabolic vulnerability caused by a mutation in a gene called SALL4, researchers have identified drugs that could potentially eradicate an aggressive form of liver cancer.

Finding the right drug to target a specific molecule is like finding a small needle in a giant haystack. With thousands of drug compounds to screen through in a short period of time, scientists start the search with a process known as high-throughput cell-based screening, thereby sieving out a small handful of candidate compounds for further detailed testing.

The challenge is intensified in the case of hepatocellular carcinoma or liver cancer, for which the most aggressive form express high levels of a fetal oncogene known as SALL4. Existing screening methods use either patient-derived cells or cells genetically engineered to express high levels of SALL4; each approach has its own drawbacks.

“Cells from genetically distinct patients could have oncogenes other than SALL4 at varying levels, so we cannot conclude if the compounds identified are truly targeting SALL4,” explained Justin Tan, a Junior Principal Investigator at A*STAR’s Genome Institute of Singapore (GIS). “On the other hand, while engineering allows us to compare cells that are genetically identical other than their SALL4 levels, the compounds found could be interfering with the upregulation mechanism and not have anything to do with the underlying cancer biology.”

“To overcome the disadvantages of both systems, we simply combined both into our screening platform,” Tan said. By comparing the responses of both types of SALL4-overexpressing cells, the team was able to tease out the impact of genetic variability induced by genetic manipulation while providing biologically relevant findings.

“It also increases the efficiency and effectiveness of drug discovery. This saves time and money since fewer compounds need to be validated after the screen,” said Tan.

“To overcome the disadvantages of both systems, we simply combined both into our screening platform.”

From an initial panel comprising more than 22,000 small molecules and natural product extracts, the team identified five compounds that killed SALL4-overexpressing liver cancer cells. Of the five, four were found to inhibit an oxygen-dependent energy generating process called oxidative phosphorylation, suggesting that SALL4-expressing cells are in fact metabolically distinct from other liver cancers.

“Our results showed that more aggressive liver cancers and even non-small cell lung cancer are ‘addicted’ to this pathway for their metabolic needs, potentially making them more sensitive towards inhibitors of the SALL4 metabolic pathway,” added Wai Leong Tam, one of the senior investigators of the study.

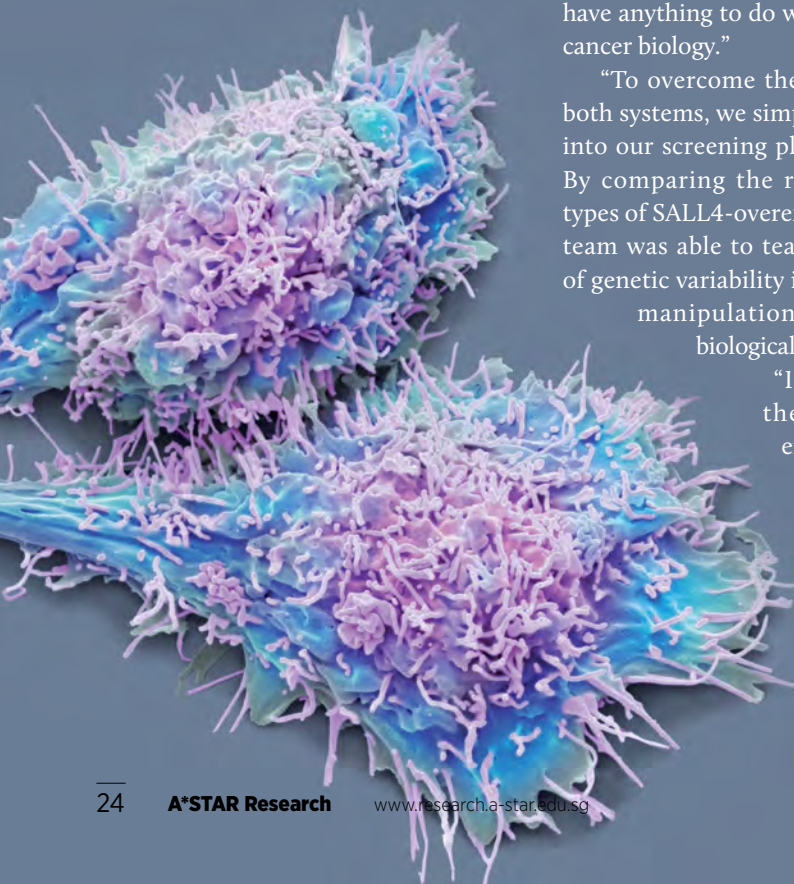
Further testing showed that one of the compounds, oligomycin, when used in combination with sorafenib, the current standard-of-care drug for liver cancer, was more potent at suppressing SALL4-expressing tumors in mice when compared to sorafenib alone.

While seeking industry partnerships to develop candidate compounds for clinical testing, the team is also utilizing this screening strategy in combination with whole-metabolome CRISPR knockout screens and genomic analyses to target genes involved in other cancers. ★

LEFT

Colored scanning electron micrograph of hepatocellular carcinoma cells showing numerous filopodia. Targeting a gene called SALL4 could help treat aggressive liver cancers.

-
1. Tan, J.L., Li, F., Yeo, J.Z., Yong, K.J., Bassal, M.A., *et al.* New high-throughput screening identifies compounds that reduce viability specifically in liver cancer cells that express high levels of SALL4 by inhibiting oxidative phosphorylation. *Gastroenterology* **157**, 1615-1629.e17 (2019).



MICROBIOLOGY

New tools in the fight against malaria

Scientists are one step closer to developing effective treatments against *Plasmodium vivax* parasites, thanks to the ability to culture one of its closest cousins.

Malaria has existed since the days of the Roman Empire—in fact, the disease was so widespread throughout the empire that one of its monikers was ‘Roman fever.’ More than a millennium later, malaria remains a significant health concern in many parts of the world, especially warm, humid regions that encourage the breeding of mosquitoes, which transmit the disease to humans.

Although malaria can be caused by several parasites from the *Plasmodium* genus, both *P. falciparum* and *P. vivax* top the list of clinical importance, owing to the high mortality and morbidity rates they cause. But the two species are polar opposites when it comes to how easy they are to grow in the lab; *P. falciparum* does well in *in vitro* cultures but *P. vivax* does not.

The primary challenge, explained Pablo Bifani, a Principal Investigator at A*STAR’s Singapore Immunology Network (SIgN), is that how *P. vivax* invades cells is not known. Furthermore, the parasites selectively invade a minute population in the blood, known as the reticulocytes, rendering them difficult to culture in the laboratory. To get around this problem, Bifani and collaborators at the University of Otago, New Zealand, developed an *in vitro* culture system for studying *P. cynomolgi*, the simian malaria that most closely resembles *P. vivax*.

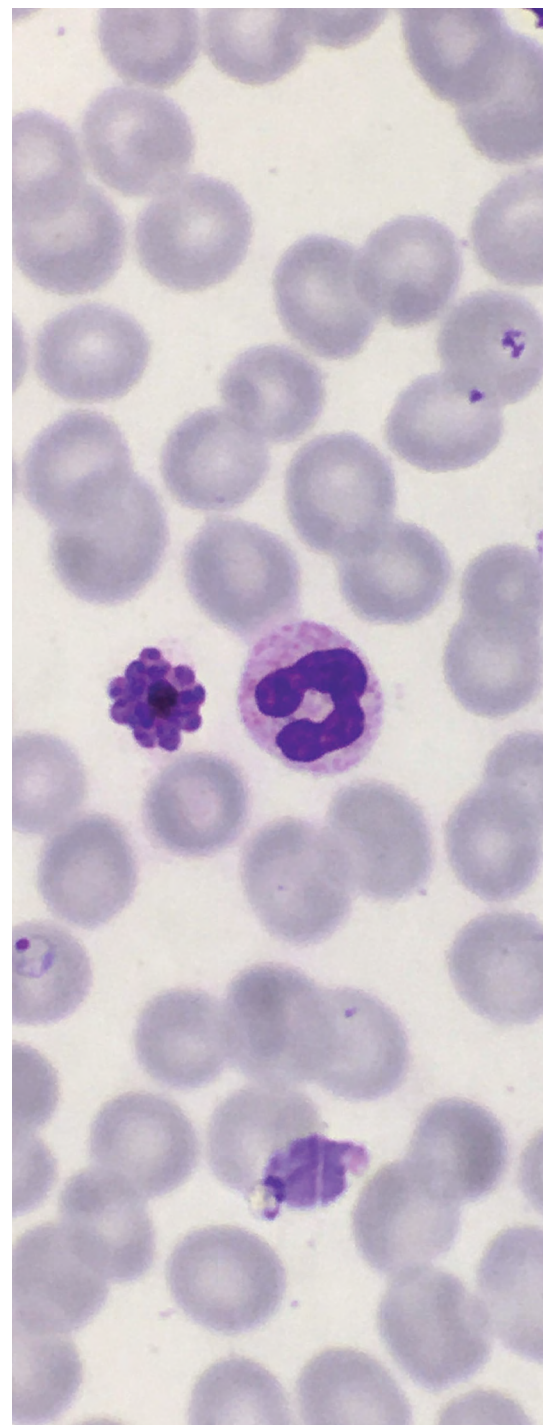
“We found that *P. cynomolgi* in culture shares several morphological and

phenotypic features with *P. vivax*, such as the display of caveolae structures, tightly attached rosettes, and, most notably, similar patterns in drug susceptibility profiles which sometimes differ from those observed in *P. falciparum*,” he highlighted.

“With the model that we established, we now have for the first time an opportunity to study the development of *P. vivax*-like malaria at each stage of their life cycle,” Bifani said. “Previously, we could only study *P. vivax*-like malaria by either obtaining blood samples from infected patients or laboratory monkeys.”

Together with SIgN colleague Adeline Chua and international collaborators, Bifani and his team are now using their *P. cynomolgi* culture system as a platform to understand how *P. vivax* develops resistance to drugs and to screen for novel antimalarials. “Both are of particular importance due to the rise in drug-resistant *P. vivax* in the region,” he said.

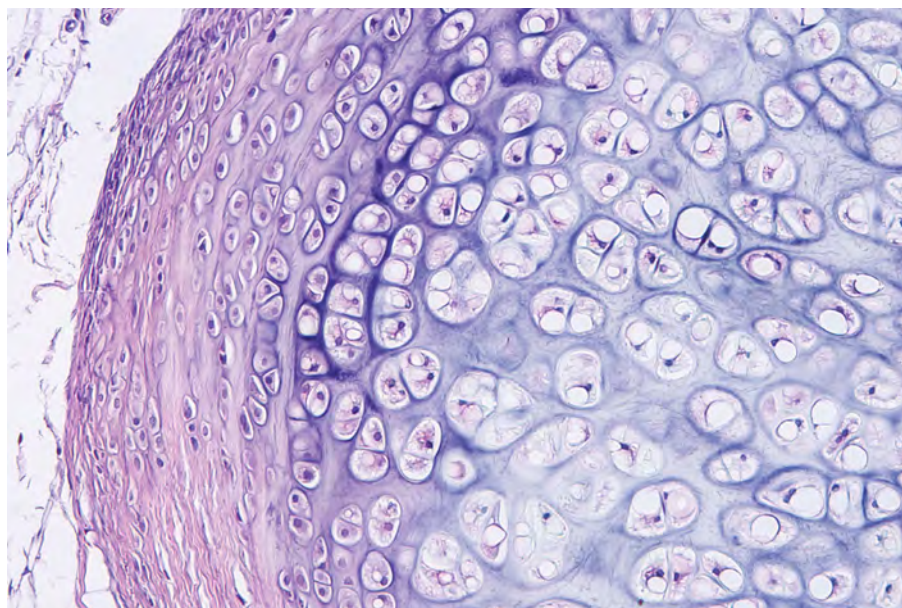
Their work has now been shared with more than 16 labs worldwide, thanks to support from the Medicine for Malaria Venture and the Bill and Melinda Gates Foundation. “Some of our collaborators are investigating gene expression at different life-cycle stages, while others are studying the mechanism of invasion and development. We hope our findings will help to refine the drug discovery process in *P. vivax*,” Bifani said. ★



ABOVE

By studying a closely related parasite, scientists can now understand how *Plasmodium vivax* behaves at each stage of its life cycle.

1. Chua, A.C.Y., Ong, J.J.Y., Malleret, B., Suwanarusk, R., Kosaisavee, V., et al. Robust continuous *in vitro* culture of the *Plasmodium cynomolgi* erythrocytic stages. *Nature Communications* **10**, 3635 (2019).



STEM CELLS

Scaling up stem cell production

By enhancing stem cell proliferation, this newly developed bio-additive lowers the barriers to regenerative medicine.

High impact sports such as soccer and basketball place athletes at risk for injuries called osteochondral defects. These defects occur when the soft tissue between joints—known as cartilage—become damaged, causing pain and a limited range of motion that could threaten an athlete's career.

Current approaches in repairing osteochondral defects, including microfracturing and grafting, provide only limited success. Next-generation stem cell therapy using human mesenchymal stem cells (hMSCs) could help restore worn out cartilage. However, obtaining enough stem cells to achieve therapeutic

efficacy has long been a major obstacle to this approach.

An international collaboration by scientists at A*STAR's Institute of Medical Biology (IMB), the National University of Singapore and the Mayo Clinic in the United States has now made significant strides towards making stem cell therapy feasible by developing an ingenious method for enhancing *in vitro* hMSC proliferation. Their findings have been patented in the US.

Human MSCs require certain growth factors to support their proliferation, one of which is fibroblast growth factor 2 (FGF2). However, FGF2 is expensive

and its ability to induce proliferation is short-lived. At the same time, previous work has shown that prolonged FGF2 supplementation can adversely affect the therapeutic potential of hMSCs, said Simon Cool, a Senior Principal Investigator at IMB and the study's senior author.

Harnessing the knowledge that hMSCs themselves produce low levels of FGF2, Cool and colleagues developed a heparan sulfate glycosaminoglycan bio-additive to stabilize and prolong the proliferative effects of FGF2.

"Our inventive step was to utilize affinity chromatography, a very efficient and cost-effective technique, to manufacture a particular heparan sulfate variant with increased binding potential for FGF2," said Cool.

This variant, named HS8, enabled hMSC cultures to produce about 2.6 times more cells than cultures without HS8. By studying animal models of osteochondral defects, the team demonstrated that HS8-expanded hMSCs produced significant improvements, based on a widely used clinical grading system.

Besides repairing sports-related injuries, HS8-expanded hMSCs could also be used to supply hospitals with large numbers of highly potent stem cells to treat a rapidly aging population in need of cellular therapy, Cool added.

The team is currently investigating changes in cell and tissue aging pathways and whether HS8 affects these processes. "Mechanistic studies are underway to determine whether FGF2-HS8 complexes bind and then maximally activate FGFR1, and whether this relationship is altered in the context of cellular aging," he said. ★

ABOVE

A heparan sulfate-based additive can increase the proliferation of cartilage stem cells by nearly three times.

1. Ling, L., Ren, X., Cao, X., Hassan, A.B.M., Mah, S., *et al.* Enhancing the efficacy of stem cell therapy with glycosaminoglycans. *Stem Cell Reports* **14**, 105-121 (2020).

BIOMATERIALS

Printing better bone implants

A composite of porous titanium and magnesium could be the future of orthopedic implants.

As populations age, the incidence of conditions such as osteoarthritis and osteoporosis inevitably increase, in turn precipitating a growing demand for orthopedic implants. Although titanium (Ti) has been widely used in bone replacements, the metal does not always integrate readily with the surrounding bone, resulting in implant failure.

Porous Ti materials containing magnesium (Mg)—an essential element for bone formation—may encourage bone growth by releasing Mg ions and allowing bone cells to enter the pores of the implant. However, it is difficult to synthesize a strong network of interconnected pores using conventional fabrication methods.

In the present study, researchers led by Sharon Nai, a Senior Scientist at A*STAR's Singapore Institute of Manufacturing and Technology (SIMTech), fabricated Ti + Mg composite implant parts using 3D

“3D printing enables fast, accurate and cost-effective fabrication of porous biomedical implants with improved fit and load distribution specific to patients’ requirements.”

printing and characterized their strength, resistance to corrosion as well as toxicity to cells. The biocompatibility studies were done in collaboration with researchers at the National University of Singapore.

“3D printing enables fast, accurate and cost-effective fabrication of porous biomedical implants with improved fit

and load distribution specific to patients’ requirements,” said Ganesh Kumar Meenashisundaram, a Scientist at SIMTech and the lead author of the study.

The team 3D-printed porous Ti parts in two different shapes: the first was a cylinder, and the other was a cylinder with a cup structure attached to one end. “Post 3D printing, the Ti parts were cured at 150 °C for two hours and thermally debinded and sintered at 1200 °C under argon gas atmosphere,” Meenashisundaram explained.

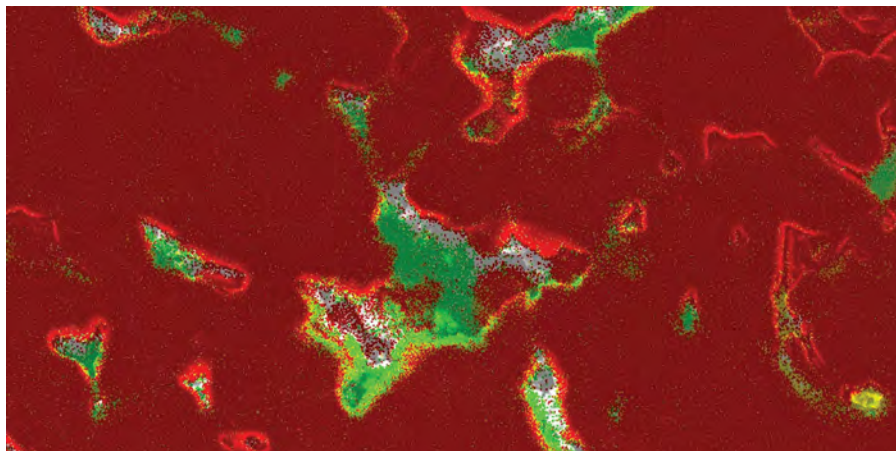
Microscopy revealed that the porous Ti material contained well-interconnected pores. The team then successfully infiltrated these pores with molten Mg to create Ti + Mg composites.

The researchers showed that their 3D-printed porous Ti and 3D-printed Ti + Mg composites were similar in strength to human bone and could withstand high strain without fracturing. When immersed in a saline solution of 0.9 % sodium chloride to simulate exposure to chloride ions in the body, the researchers observed negligible corrosion of both materials. Neither material was toxic to bone cells, and in the case of Ti + Mg composites, the leaching of Mg ions from the composites stimulated bone cell infiltration and proliferation.

“Moving forward, we will perform *in vivo* tests to confirm the suitability of Ti + Mg composites as a potential implant material. We also plan to optimize the 3D printing parameters and investigate the use of biomedical-grade titanium alloys,” said Meenashisundaram, adding that the findings from this study may pave the way for the design of orthopedic implants with improved implant success rates. ★


LEFT

Element mapping showing titanium (red), magnesium (green) and oxygen (cyan) in a 3D-printed bone implant.



1. Meenashisundaram, G.K., Wang, N., Maskomani, S., Lu, S., Anantharajan, S.K., *et al.* Fabrication of Ti + Mg composites by three-dimensional printing of porous Ti and subsequent pressureless infiltration of biodegradable Mg. *Materials Science & Engineering C* **108**, 110478 (2020).

DISSECTING MOVEMENT DISORDERS THROUGH THE EYES OF A FLY



In the search for new therapeutics and diagnostic tools, Sherry Aw is unraveling the biology behind movement disorders using the humble fruit fly.

Every time we move, electrical impulses are channeled along neuronal highways, jumping from nerve cell to nerve cell until they reach a muscle, causing it to contract. Because muscle movement depends on neuronal function, neurodegenerative diseases can sometimes result in debilitating symptoms like tremors or rigidity.

Neurodegenerative diseases, which include Alzheimer's and Parkinson's disease (PD), affect millions worldwide. Importantly, a group of these diseases, known as movement disorders, are essentially incurable, significantly affecting a patient's quality of life.

Sherry Aw, an Independent Fellow and a Group Leader at A*STAR's Institute of Molecular and Cellular Biology (IMCB), leads a research group that studies the biology behind movement disorders. Using the fruit fly (*Drosophila melanogaster*) as a disease model, her group aims to understand the pathology behind these disorders and devise new therapeutic and diagnostic strategies.

Photo credit: Cornel Constantin / Shutterstock

In this interview with *A*STAR Research*, Aw shares about her work and how she plans to dissect the science behind movement disorders like PD.

Q: WHY DID YOU CHOOSE TO STUDY NEUROSCIENCE, AND IN PARTICULAR, NEURODEGENERATIVE DISEASES?

My interest in neuroscience began from a place of curiosity: despite great advances in understanding neurophysiology, there is still so much to discover about how the brain functions. Even now, we still do not really understand how the brain does what it does as a whole.

It was later during my post-doctoral training at Professor Stephen Cohen's lab at IMCB that I developed a more specific interest in neurodegenerative diseases. In particular, I study a class of neurodegenerative diseases called movement disorders, which, broadly speaking, are diseases that lead to loss of control over voluntary movement. Not only are these conditions highly debilitating for the patient, but they are also of growing socioeconomic impact in aging societies like ours. There are also no disease-modifying cures for most of these disorders at the moment, which can be partially attributed to our lack of understanding at the level of their basic biology.

Q: WHAT ARE THE KEY PROBLEMS YOU HOPE TO SOLVE WITH YOUR RESEARCH?

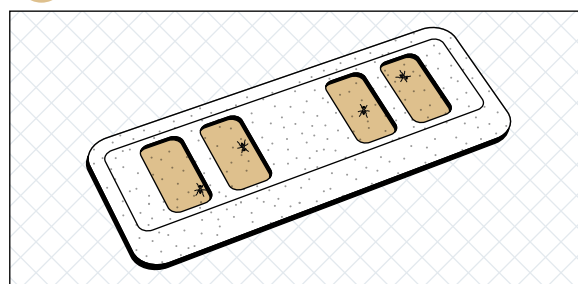
Movement disorders are characterized by difficulties in controlling voluntary movements, resulting in certain signs like hand tremors. For example, patients with spinocerebellar ataxia 3 (SCA3), a rare genetic movement disorder, suffer from worsening coordination of their gait, hands, speech and eye movements.

However, the specific changes in movement control are distinct between one condition and another. For example, while SCA3 is associated with excessive, involuntary movement like jerkiness and poor coordination, PD leads to rigidity and slowness of movement. These different behaviors likely arise from the different types of neuronal circuitry affected. Hence, we aim to characterize these vulnerable neuron types and dissect their underlying neurogenetic and molecular mechanisms.

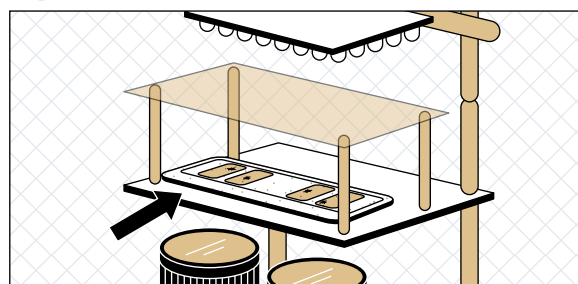
Feature Learning-based Limb segmentation and Tracking (FLLIT)

Sherry Aw's lab at IMCB developed a fully automated machine learning-based program to track fruit fly leg movements.

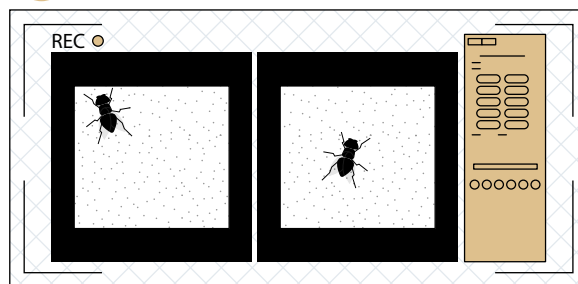
1 Place flies in chambers secured by glass slide



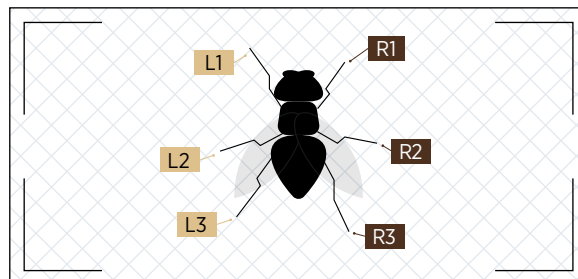
2 Place chamber under camera



3 Record video, focusing on the leg tips of flies



4 FLLIT automatically labels each leg and tracks their movements



Q: WHY ARE FRUIT FLIES A SUITABLE MODEL FOR STUDYING HUMAN MOVEMENT DISORDERS?

Despite the obvious differences between the two species, the fruit fly has helped to illuminate numerous conserved mechanisms of human brain function and neurodegenerative diseases. We use the fruit fly as a disease model for human movement disorders because very fundamental principles of neuronal function are conserved from fly to human, not just at the molecular and cellular levels, but even up to the level of neuronal circuitry.

We found these similarities in a previous study using a fully automated machine learning-based program that we developed for tracking fruit fly leg movements, called Feature Learning-based Lmb segmentation and Tracking (FLLIT). In that study, we showed for the first time that there is a close resemblance between the gaits of fly PD and SCA3 models compared to human patients with those respective diseases. Importantly, these findings suggest that the motor neuronal circuitry is well-conserved between flies and humans. Since the fruit fly possesses a million times fewer neurons than humans, studying these questions in the fruit fly model allows us to investigate the complex mechanisms underlying these movement disorders in a more simplified model.

Q: WHAT ARE SOME OF THE RESEARCH QUESTIONS YOU ARE TACKLING NOW?

Using FLLIT, we reported the first measurement of leg tremors in flies and discovered that those with SCA3 exhibited strong tremors when walking. Currently, we intend to follow up on these findings to elucidate the molecular and cellular mechanisms behind these tremors. Specifically, we are trying to understand how dysfunctions in the underlying neuronal circuitry in flies with SCA3 can lead to tremors.

Other than that, we are also working to optimize a microRNA sensor that we developed, called *Pandan*. MicroRNAs are a promising group of biomarkers for many diseases, including neurodegenerative diseases. However, current methods for microRNA detection require advanced training and costly equipment. By enhancing the sensitivity and specificity of *Pandan*, our microRNA sensor could potentially be used as a low-cost clinical diagnostic tool for movement disorders and other diseases in the future.

Q: WHAT ARE SOME OF THE IMPLICATIONS YOUR RESEARCH WILL HAVE FOR NEURODEGENERATIVE DISEASES?

We hope that by understanding the basic mechanisms underlying movement disorders, we will be able to identify new therapeutic and diagnostic strategies against neurodegenerative diseases. For example, our research could potentially unravel the biochemical pathways whose dysfunctions contribute to specific movement disorders, enabling us to identify novel candidate genes that can serve as the basis for new clinical therapeutics.

Q: GOING FORWARD, WHAT OTHER RELATED RESEARCH QUESTIONS WILL YOU BE PURSUING?

I believe our work will evolve in two directions. First, we hope to expand and validate the neurogenetic mechanisms that we are discovering in flies using mammalian animal models over the next five to ten years. Second, we aim to put a greater focus on translational research, especially in the area of drug development. For example, we are using FLLIT to study the cellular mechanisms that underlie tremors, which are very prevalent but poorly understood. We plan to apply our method towards behavioral phenotype-based drug screening, in order to identify potential druggable targets that underlie movement disorders. ★

ABOUT THE RESEARCHER:

Sherry Aw obtained her Bachelor's degree in biochemistry from the University of Wisconsin-Madison in 2003 and completed her doctoral studies at Harvard Medical School in 2009. During her postdoctoral training in Steve Cohen's lab at A*STAR's Institute of Molecular and Cell Biology (IMCB), she developed an interest in understanding the pathophysiology of neurodegenerative diseases and is now a Group Leader at the Institute. She is a co-inventor on two patents, and was awarded the L'Oréal-UNESCO Singapore For Women in Science National Fellowship in Life Sciences 2017.



CANCER BIOLOGY

Green tea-based compound takes the fight to cancer

A compound derived from green tea could enhance the safety and effectiveness of cancer treatment.

Step into a Japanese restaurant and the odds are you will be offered a cup of green tea to accompany your meal. More than just a popular drink, green tea contains a compound known as epigallocatechin-3-O-gallate (EGCG), which can be used as a nanocarrier for anticancer drugs.

Administered on their own, many small molecule inhibitor drugs used in cancer treatment cause side effects because they are readily taken up by both healthy and cancer cells. Hence, researchers led by Motoichi Kurisawa, a Principal Research Scientist at A*STAR's Institute of Bioengineering and Nanotechnology (IBN), decided to encapsulate the anticancer drug sunitinib in EGCG and test if they could improve the efficacy of cancer treatment while reducing the off-target toxicity of sunitinib administered on its own.

“We hope to develop our green tea-based nanocomplexes for commercialization.”

The encapsulation process involved chemically linking EGCG to the biologically compatible material poly(ethylene glycol), resulting in PEG-EGCG. The researchers then mixed sunitinib with PEG-EGCG, reporting that the compounds self-assembled into nanocomplexes comprising a sunitinib core and a PEG-EGCG shell.

The amount of sunitinib within the core, and the size of the nanocomplexes, could be varied by controlling the temperature of the self-assembly reaction.

“We proceeded to evaluate the efficacy of nanocomplexes using appropriate mice models for liver cancer, breast cancer and kidney cancer,” said Kurisawa.

For example, testing their nanocomplexes in mouse models of kidney cancer, the researchers showed that the treatment effectively inhibited cancer cell proliferation, induced cancer cell death and blocked blood vessel formation in tumors. The researchers noted that the tumor growth inhibition by their nanocomplexes was significantly higher (75.4 percent) than sunitinib administered on its own (0.9 percent).

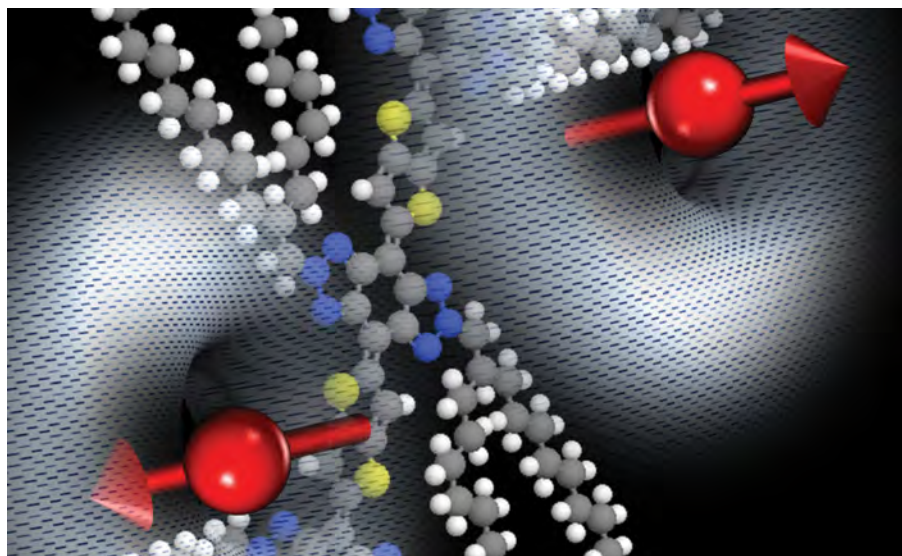
Furthermore, the nanocomplexes accumulated more readily in the tumors compared to other organs. Hence, 21.3-fold lower doses of sunitinib (encapsulated in the nanocomplexes) were required to achieve anticancer effects, and this corresponded with fewer toxicity symptoms. According to Kurisawa, the findings from this study lay the foundation for developing safer and more effective drug delivery complexes to improve cancer treatment.

“We are interested in evaluating our nanocomplex in large animals and in humans. Moving forward, we hope to develop our green tea-based nanocomplexes for commercialization,” he concluded. ★

BOTTOM

A compound in green tea known as epigallocatechin-3-O-gallate (EGCG) has been used to deliver anticancer drugs, increasing the efficacy of treatment while reducing side effects.

1. Yongvongsoontorn, N., Chung, J.E., Gao, S.J., Bae, K.H., Yamashita, A. *et al.* Carrier-enhanced anticancer efficacy of sunitinib-loaded green tea-based micellar nanocomplex beyond tumor-targeted delivery. *ACS Nano* **13** (7), 7591-7602 (2019).



MATERIALS SCIENCE

Smoothing the path for conductive polymers

Polymers with a special property called proquinoidal character can be used to make organic conductors a thousand to a billion times more conductive.

You may have learned in school that metals conduct electricity and plastics don't, but for more than thirty years, scientists have been developing organic conductors and semiconductors that break those rules. Organic light-emitting diodes are now commonplace in LED screens, and conductive plastics could unlock a new wave of flexible electronic technologies, from electronic paper and bendable displays to printed circuitry using conductive ink.

However, even the best organic polymers are still far worse electrical conductors than their inorganic counterparts. "Typically, these polymers contain a backbone with alternating single and double bonds, making a path for electrons to hop between

successive carbon atoms," explained Dexter Tam, a Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE). "But the polymer backbone can bend and twist, slowing down any electrical conduction—just like a car would slow down on a road that is winding and bumpy."

"Proquinoidal monomers can flatten out the backbone of an organic polymer, making it a better conductor."

Tam was interested in chemical components that could address this problem, eventually settling on a property called proquinoidal character, exhibited by special rings of carbon and nitrogen atoms. "These structures can stabilize a string of alternating single and double bonds," Tam said. "Thus, their presence can flatten out the backbone of an organic polymer, making it a better conductor."

In collaboration with colleagues from A*STAR's Institute of High Performance Computing (IHPC) and Nanyang Technological University, Singapore, Tam was able to synthesize conjugated polymers containing BBTa26, a candidate proquinoidal monomer. When he tested these new polymers, he found that he had a new semiconducting material, which was a thousand to a billion times more conductive than other organic semiconductors.

The team was able to improve the conductivity further by adding an impurity to supply more charge carriers, a common modification for both organic and inorganic semiconductors. "When we did this, our final products had conductivities reaching 100 S/cm, a thousand times better than other widely researched and used commercial conducting polymers," Tam stated.

Looking forward, Tam hopes to further improve conjugated polymers using a variety of other proquinoidal monomers. "We are always interested in finding new material properties to incorporate into our conjugated polymers," Tam said. "Our latest versions incorporate high-spin electronic states that could further improve performance and allow for new applications in spintronics." ★

ABOVE

Special rings of carbon and nitrogen atoms exhibit a property called proquinoidal character, which can make the resulting polymer a much better conductor.

1. Tam, T.L.D., Ng, C.K., Lim, S.L., Yildirim, E., Ko, J., *et al.* Proquinoidal-conjugated polymer as an effective strategy for the enhancement of electrical conductivity and thermoelectric properties. *Chemistry of Materials* **31** (20), 8543-8550 (2019).

POLYMER SCIENCE

Helping devices take the heat

A new class of organic conductors shows high thermoelectric efficiency, thanks to an unusual arrangement of electrons inside its bonds.

Imagine a T-shirt that could charge a power bank from your body heat—or draw power from a battery to keep you cool. Such inventions could become a reality thanks to the thermoelectric effect, in which solid-state semiconductors can convert thermal energy into electricity and back again.

However, scientists working on thermoelectric devices such as these have struggled with a fundamental trade-off—materials that generate higher voltages between hot and cold temperatures are unfortunately also poor electrical conductors, and vice versa. This limits the rate at which heat and electricity can be interchanged.

Now, Jianwei Xu and Dexter Tam, scientists at the A*STAR Institute of Materials Research and Engineering (IMRE), have shown that a new class of organic semiconductors they discovered previously, called proquinoidal polymers,

“Proquinoidal structures imbue polymers with rapidly switching double bonds, giving them high electrical conductivity.”

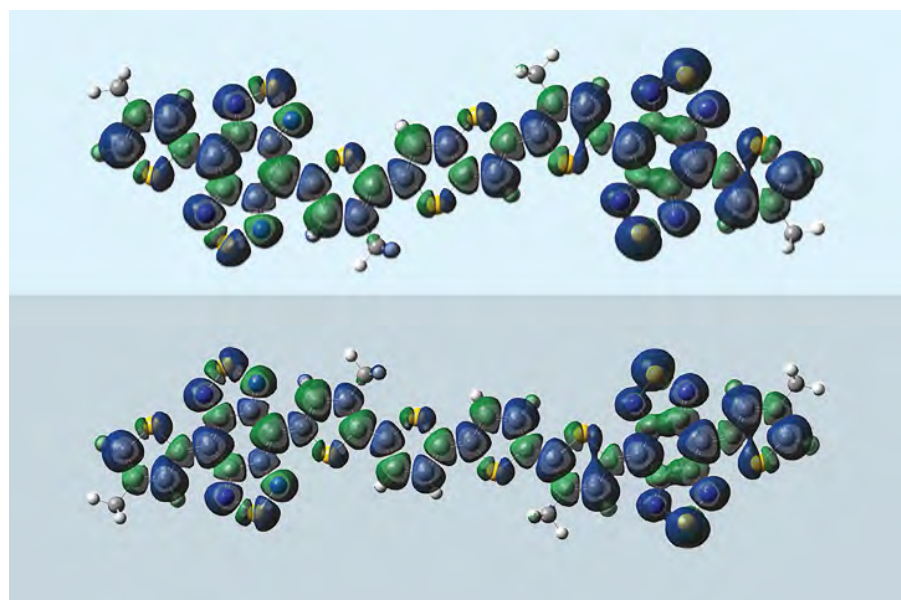
avoid this constraint, thanks to an unusual arrangement of electrons that give them excellent electrical conductivity.

“Scientists around the world are trying different tricks to increase the power factor of materials, by increasing conductivity without compromising too much on the Seebeck coefficient (thermoelectric sensitivity). However, our previous work on the highly-conductive proquinoidal polymers suggests that they might naturally have a high Seebeck coefficient as well, thanks to how electrons behave within them,” Tam said.

As Tam explains, proquinoidal structures imbue polymers with rapidly switching double bonds, giving them high electrical conductivity. Together with Shuo-Wang Yang at A*STAR’s Institute of High Performance Computing (IHPC), the researchers showed how these rapid switches also occasionally separate the tightly-bound pairs of electrons that make up chemical bonds.

When these separated electrons ‘spin’ in the same direction, forming a ‘high-spin triplet state,’ they respond more effectively to thermal energy, resulting in high Seebeck coefficients in addition to high conductivity. Under testing conditions, the doped proquinoidal semiconductors showed power factors exceeding $50 \mu\text{W m}^{-1} \text{K}^{-2}$ —among the highest ever reported for organic semiconductors.

“Our findings provide design strategies to improve both conductivity and Seebeck coefficient simultaneously for thermoelectric applications,” Tam said, adding that they hope to further explore the application of proquinoidal polymers in spintronics and thin-film soft magnets. ★



LEFT

Triplet spin densities of the dimer of pBBT-2T-TT (above) and pBBT-2T-2T (below).

1. Tam, T.L.D., Wu, G., Chien, S.W., Lim, S.F.V., Yang, S.W. and Xu, J. High spin pro-quinoid benzo[1,2-c;4,5-c']bisthiadiazole conjugated polymers for high-performance solution-processable polymer thermoelectrics. *ACS Materials Letters* **2** (2), 147-152 (2020).

NANOTECHNOLOGY

Electrons marching one by one, hurrah!

Researchers have found quantum dots lurking inside nanoribbon transistors, suggesting that nanoribbons could one day be used for quantum computing.

An electrical current flowing through a wire typically involves billions upon billions of electrons moving as one. But as electronic devices become ever smaller, the current flowing through them also shrinks to a trickle, approaching the quantum regime where electrons suddenly behave as individual particles and display very different properties.

A team led by Principal Investigator Kuan Eng Johnson Goh and Dharmraj Kotekar-Patil at A*STAR's Institute of Materials Research and Engineering (IMRE) saw this happen in their prototype nanoribbon transistors, demonstrating that they had inadvertently manufactured quantum dots in the process.

"Quantum dots are nanostructures which confine electrons in all three dimensions," explained Dharmraj Kotekar-Patil, a scientist in Goh's team and first author of the study. "They are small enough for electrons to travel through them one at a time. In the process, the electrons repel other electrons and prevent them from passing through at the same time, leading to a 'Coulomb blockade' that reduces the current flow."

Kotekar-Patil and his team were studying monolayer molybdenum sulphide nanoribbons, tiny semiconductor strips just one to a few molecules high and a few dozen molecules wide. At room temperature the nanoribbons functioned

as transistors, smoothly increasing their current as the voltage was increased. But when the nanoribbons were cooled to ultra-low temperatures, the electrical current initially disappeared at low voltages, and then jumped in a stepwise fashion as the voltage was increased—tell-tale signs of quantum behavior.

"This Coulomb blockade showed the existence of discrete energy levels that only allowed single electron transport," Kotekar-Patil said. This in turn demonstrated that quantum dots had been formed, either at the jagged edges of the nanoribbon or in the rough surface underneath.

These quantum dots could be a blessing or a curse. Nanoribbon transistors are meant to transmit a smooth electric current, and their performance could be degraded if electrons get trapped instead of passing through smoothly. "We could eliminate these quantum dots by using atomically flat surfaces under the nanoribbon, or chemically smoothing out the nanoribbon edges," Kotekar-Patil said.

However, Kotekar-Patil also believes that these quantum dots could be harnessed for quantum computing, a new paradigm that could lead to much faster and more powerful computers. "We could manipulate confined single electrons using additional contacts on top of the nanoribbon and encode quantum information using their spin states," he continued. "This would contribute to the development of quantum computing, which would be much faster than existing classical computers at several important computational tasks." ★

LEFT
Electrical currents flowing through tiny electronic devices show quantum behavior.

1. Kotekar-Patil, D., Deng, J., Wong, S.L. and Goh, K.E.J. Coulomb blockade in etched single- and few-layer MoS₂ nanoribbons. *ACS Applied Electronic Materials* 1 (11), 2202–2207 (2019).

Photo credit: Dmitry Rybin / Shutterstock



MACHINE LEARNING

Expecting the unexpected from AI

Researchers are simulating real-world complexity in machine learning models to ensure their safety before they are deployed in the wild.

When we think of artificial intelligence (AI) going rogue, prime examples from the movies include HAL 9000 from *2001: Space Odyssey* and Skynet from *The Terminator*, which were mainframe computers that reacted to real-world problems in unexpected ways.

From industrial manufacturing to autonomous vehicles, machine learning models are becoming increasingly embedded in our lives. Researchers are thus exploring pre-emptive ways to avoid harm from unexpected AI decisions made by machine learning models deployed in real-world situations—an area of machine learning known as reinforcement learning (RL).

“While deep RL has indeed been very successful in achieving state-of-the-art performance in curated academic environments, it has yet to be thoroughly tested in the presence of real-world complexities,” said Abhishek Gupta, a Scientist at A*STAR’s Singapore Institute of Manufacturing Technology (SIMTech) and one of the study’s senior authors.

The work, which was principally conducted by Nanyang Technological University (NTU) graduate student Xinghua Qu and jointly overseen by Gupta and A*STAR’s Chief AI Scientist Yew-Soon Ong, focused on the performance of vision-based AI, which is likely to be critical for the safe use of AI in applications such as autonomous vehicles.



Atari video games have helped researchers identify weaknesses in reinforcement learning models when it comes to real-world situations.

Using six Atari video games, including the classic game of Pong, the group simulated visual perturbations by altering a small number of pixels in selected frames in the game environment. They then examined how well the algorithm performed in the perturbed environment by measuring the ‘accumulated reward,’ a barometer of how optimal an algorithm’s decisions are.

Stunningly, they found that a mere one-pixel change to input images was often enough to cause the accumulated reward to

significantly plummet for all four algorithms tested, including widely used algorithms such as Deep Q Networks. These results indicate that although RL models thrive in familiar, standardized environments, they would be poorly equipped to handle an environment that is highly variable, like roads and heavily populated areas, potentially to the detriment of safety.

“Most of the work has focused on achieving highly accurate AI or deep learning models,” Gupta said. “However, this vulnerability needs to be considered before these AI are put into operational use, to ensure the integrity and reliability of AI deployment.”

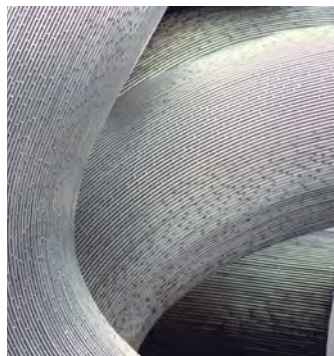
The research team is now investigating more efficient techniques for generating adversarial perturbations in real-time RL applications. “This constitutes a critical step of knowing your enemies before defeating them,” Gupta said. ★

“Researchers are thus exploring pre-emptive ways to avoid harm from unexpected AI decisions made by machine learning models deployed in real-world situations.”

1. Qu, X., Sun, Z., Ong, Y.S., Wei, P., Gupta, A. Minimalistic attacks: How little it takes to fool deep reinforcement learning policies. *IEEE Transactions on Cognitive and Developmental Systems* (2020).

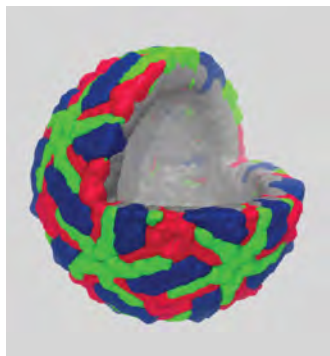
NEXT ISSUE

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



ADDITIVE MANUFACTURING
SMOOTHING THE WAY
FOR 3D-PRINTED METAL
PARTS

Thin-walled metallic parts built via additive manufacturing are weaker than expected.



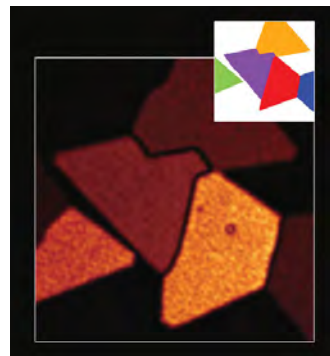
VIROLOGY
VIRUS SHAPE-
SHIFTERS

Studying how viruses change their shapes at different temperatures could lead to more effective vaccines.



CANCER IMMUNOTHERAPY
TURNING
IMMUNOTHERAPY
INSIDE OUT

A novel targeting strategy may make pave the way for effective cancer immunotherapy against previously 'undruggable' targets.



NANOELECTRONICS
SIMULATING
THE SHAPES OF
NANOFLAKES

New computer models show how semiconductor flakes with fancy shapes grow from simple starting points and rules.

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