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A*STAR RESEARCH

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EDITORIAL

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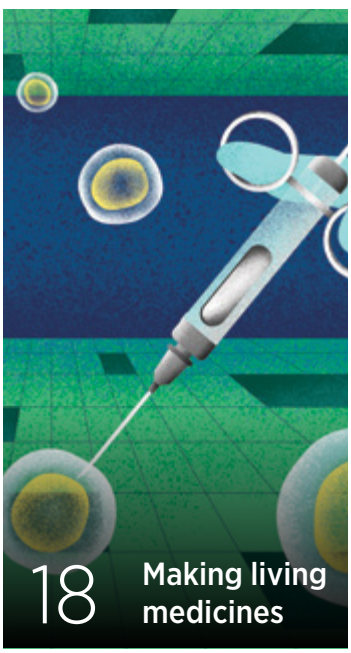

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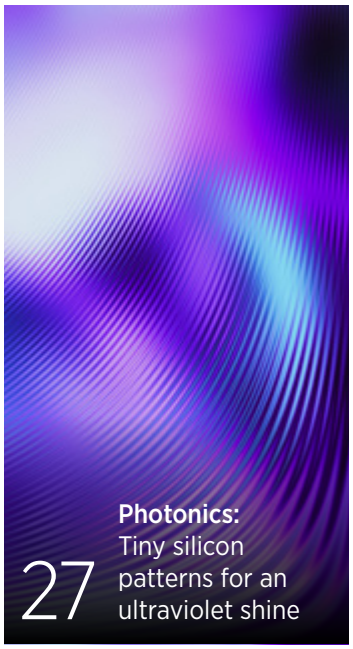

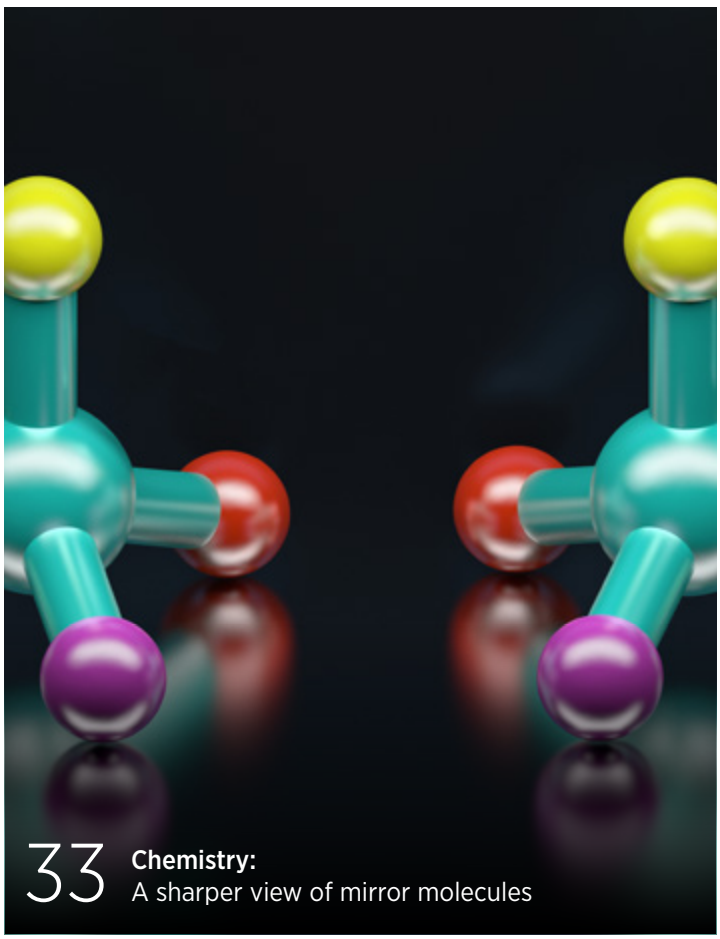

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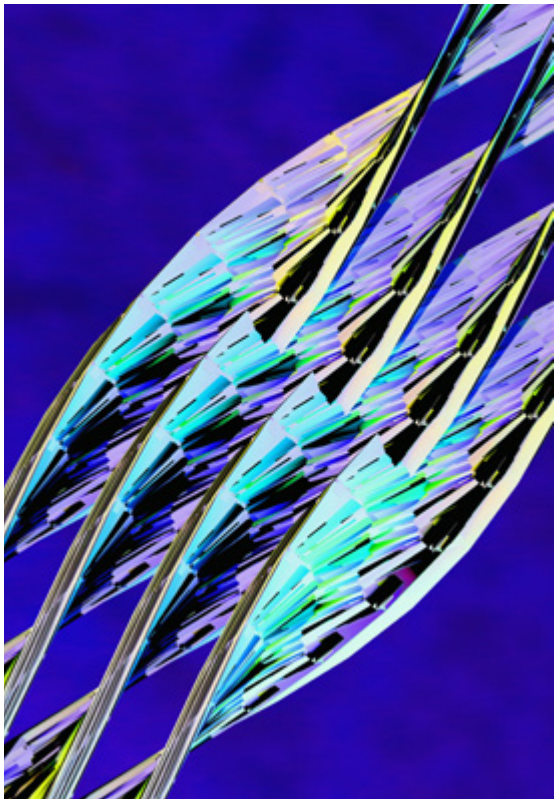

The first X-ray machines changed the face of medicine with the sweeping views they opened into our anatomy. Today, a new generation of tools is revolutionising the field once again with similarly holistic views into the very molecules that make us. Omics technologies now enable researchers to survey whole landscapes of our genes, proteins and cells, unlocking new insights into human health.

Our cover story this issue, 'Whole in one (p. 08)', takes a look at a broad spectrum of multi-omics technologies under development by A*STAR researchers and partners. By combining and analysing multiple layers of biological data, these tools are unearthing new biomarkers for underdiagnosed diseases; pinpointing the rare cells behind divergent cancer fates; and revealing the influence of our genes, lifestyle and microbial neighbours on individual health trajectories.

Diving deeper into one aspect of the omics revolution, we speak to A*STAR Bioprocessing Technology Institute Scientist Yu Hui Kang about his work in metabolomics and immunology. In our first feature, 'Making living medicines (p. 18)', Kang discusses how metabolomic insights are helping his team fine-tune the biomanufacturing of potent immunotherapies.

In our second feature, 'From code to cure (p. 28)', we speak to SINGA scholar Senuri De Silva about her scientific journey from computational biology studies in Sri Lanka to breast cancer proteomics at the A*STAR Institute of Molecular and Cell Biology in Singapore.

This issue also highlights groundbreaking developments taking place across A*STAR, such as a spatial genomic scoring system designed to more accurately predict liver cancer recurrence and a novel hydrogel that enables skin-like pressure sensors. These stories are explored in greater detail in 'Better TIMES for liver cancer patients (p. 04)' and 'Spongy sensors for a human touch (p. 24)'.

For more of the latest developments from A*STAR researchers, visit our website at **research.a-star.edu.sg.** You can also stay up-to-date by following us on X/Twitter at **@astar_research**, LinkedIn at **A*STAR Research** and Telegram at **A*STAR Research**.

On the cover
Overlapping glass windows symbolise the seamless integration of multiple layers of human biology enabled by multi-omics tools.

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CANCER

Better TIMES for liver cancer patients

A new spatial genomic scoring system outdoes existing tools at identifying patients at risk of recurring liver tumours.

Location, location, location: this guiding principle for homeowners when purchasing real estate also matters when treating cancer. Thanks to advances in biomedical tools, we can now capture the fine details of cell activity—from genes expressed to chemicals secreted—across different parts of a tumour. Such location-based data can help clinicians better predict a cancer's risk of recurring and adjust treatment plans accordingly.

That risk is particularly high in hepatocellular carcinoma (HCC), the most common form of liver cancer. "An estimated 70 percent of HCC cases see new tumours emerge after the initial ones are surgically removed," said Joe Yeong, Group Leader at the A*STAR Institute of Molecular and Cell Biology (A*STAR IMCB).

To change that statistic, researchers are eyeing immune cells known as natural killer (NK) cells. Studies have shown that higher levels of NK cell infiltration and activity within HCC tumours are tied to improved survival rates. The spatial distribution and expression patterns of these cells also seem to affect recurrence—but it's not clear how.

"Current prediction tools don't capture the full biological complexity of the tumour microenvironment," said Yeong. "They mainly stratify recurrence risk based on microscopic examinations of tumour tissue sections."

In pursuit of better tools, Yeong and A*STAR IMCB colleagues—including Denise Goh, Felicia Wee and Jeffrey Lim—collaborated with Nye-Thane Ngo, Tony Lim and their teams from Singapore General Hospital and Duke-NUS Medical School, Singapore; Cheng Sun, Gengie Jia and researchers from the University of Science and Technology of China; as well as other institutes in Singapore and China. Together, they conducted spatial multi-omics analyses on tumours from 61 patients with HCC.

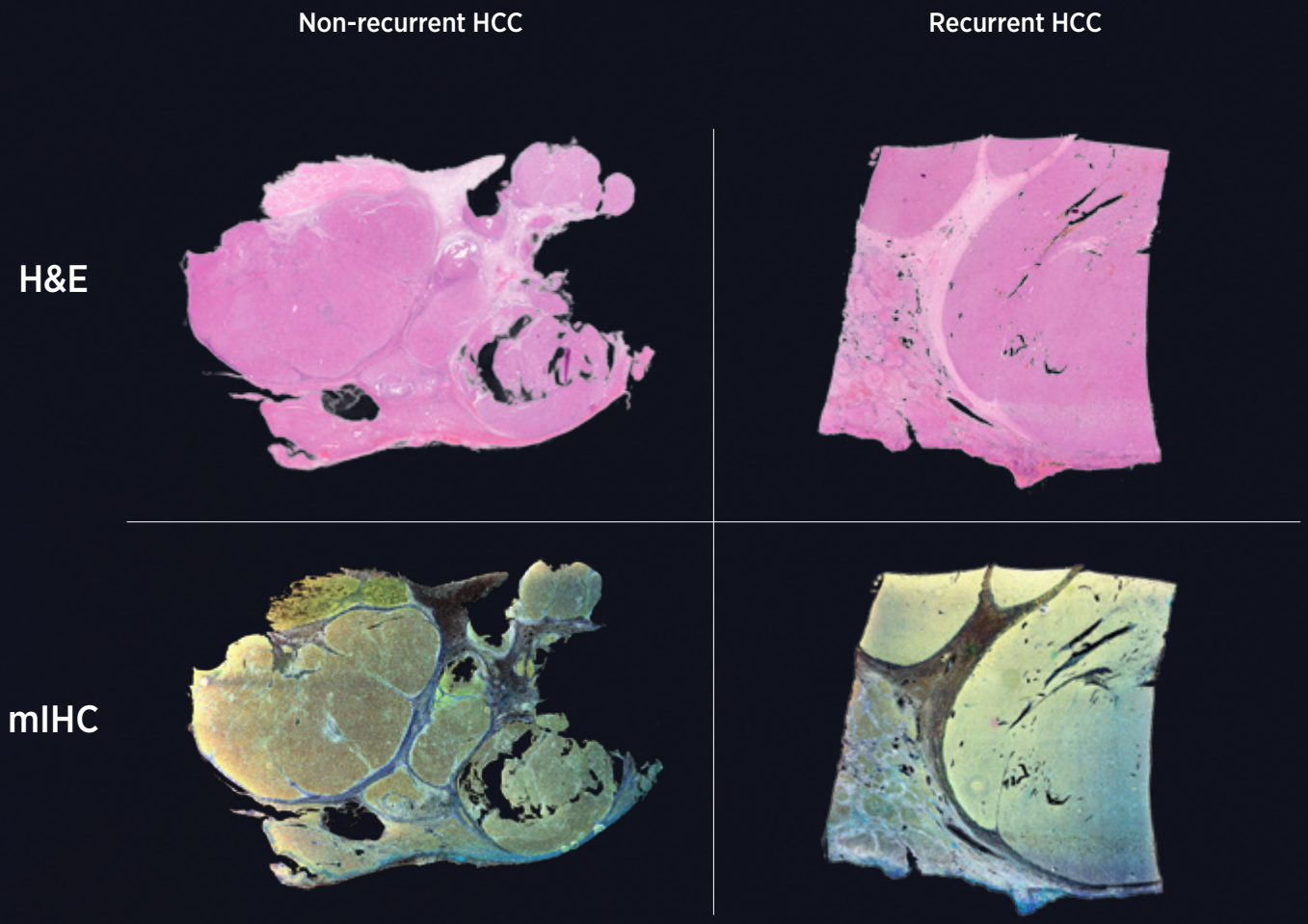
The researchers analysed over 75,000 spots from tumour tissue sections, looking at gene and protein expression levels as well as their spatial contexts. By comparing patients with recurrent versus non-recurrent HCC, they found that an increased presence of NK cells at a tumour's invasive front was linked with a better prognosis.

Zooming in on a subset of eight patients, they then analysed the spatial distribution of 18,677 genes in NK cells that had infiltrated tumours. They found five genes (*SPON2, ZFP36L2, ZFP36, VIM, HLA-DRB1*) whose corresponding protein levels and expression patterns could most accurately predict recurrence risk.

Based on their data, the team developed the tumour immune microenvironment spatial (TIMES) scoring system. Powered by artificial intelligence (AI), TIMES analyses histopathological images of tumours to map spatial expression patterns of the five identified biomarker genes, then generate a personalised recurrence risk score.

"Compared to 118 clinical factors, including established predictors, TIMES showed significantly stronger associations with disease-free survival and recurrence, even when the patient cohort was first

Photo credit: Vectormer / Freepik



Whole-slide hematoxylin and eosin (H&E) and multiplex immunohistochemistry (mIHC) images of representative hepatocellular carcinoma (HCC) samples. The H&E images show the tissue landscape, while mIHC detects spatial distributions of protein biomarkers, including SPON2 (green), CD57 (red), HLA-DR (cyan), ZFP36 (orange), ZFP36L2 (yellow) and Vimentin (white), with DAPI (blue) as the nuclear counterstain. (Adapted from images by: A*STAR Institute of Molecular and Cell Biology)

"Current prediction tools [for HCC recurrence] don't capture the full biological complexity of the tumour microenvironment."

stratified into subgroups based on established risk factors," said Yeong.

Yeong added that TIMES' strength lies in its integration of spatial immune information; the predictive power of the five biomarkers emerged only when their spatial context was considered.

Moving forward, the team hopes to further leverage AI and build an accelerated pipeline from biomarker discovery to assay development, potentially enabling rapid and personalised treatment selection for patients. ★

Researchers
Joe Yeong and Denise Goh,
A*STAR IMCB

IN BRIEF
The tumour immune microenvironment spatial (TIMES) scoring system analyses the spatial expression patterns of five biomarker genes to predict an individual's risk of hepatocellular carcinoma recurrence, aiding early intervention measures.

1. Jie, G., He, P., Dai, T., Goh, D., Wang, J., *et al.* Spatial immune scoring system predicts hepatocellular carcinoma recurrence. *Nature* **640**, 1031-1041 (2025).

MICROBIOLOGY

Microbial neighbours keep golden years shining

A large-scale gut microbiome study in elderly Singaporeans reveals new insights into the role of our resident microbes in healthy ageing.

As life expectancy rises across Asia, a key question remains: will people age in good health? With over a third of the region's population projected to be 60 years or older by 2050, understanding the factors that shape healthy ageing is increasingly urgent.

A key player might be our gut microbiomes. As we age, these microbial communities shift in ways linked to frailty and disease. Yet most studies so far offer only a low-resolution view of these connections, noted Aarthi Ravikrishnan, a Senior Scientist at the A*STAR Genome Institute of Singapore (A*STAR GIS).

"Older genomic methods, such as 16s rRNA sequencing, only detect microbes that match specific genes," Ravikrishnan said. "It's like assessing the variety of mixed Lego bricks by focusing on the most common colours."

To dive deeper, recent studies have turned to shotgun metagenomics, a next-generation DNA sequencing technique that breaks up all the genetic material present in a sample, then randomly sequences them, increasing the odds of catching rare species.

"Shotgun metagenomics is a powerful tool for studying the full diversity of complex microbial communities in detail," added Indrik Wijaya, a former A*STAR GIS Bioinformatics Specialist.

Still, many studies remain constrained by small cohort sizes, making it difficult to account for confounding factors such as diet, medication and lifestyle. To get a clearer view, Ravikrishnan and Wijaya worked with colleagues at A*STAR GIS including Niranjan Nagarajan, Associate Director and Senior Group Leader; the A*STAR Singapore Immunology Network (A*STAR SIgN); A*STAR Institute for Human Development and Potential (A*STAR IHDP); and Yong Loo Lin School of Medicine, National University of Singapore. They applied shotgun metagenomics on a large cohort from SG90: a decades-long population study of community-dwelling elderly persons in Singapore.

"[SG90] provided a rich health dataset which helped us effectively control for those confounding factors in our models," said Ravikrishnan.

With metagenomic profiles from over 200 SG90 participants, the team integrated data from younger Singaporean and Asian cohorts into statistical models, looking for age-related patterns.

"One thing that stood out was the age-related decline of *Faecalibacterium prausnitzii*, a key butyrate-producing bacterium. Butyrate maintains gut health by reducing inflammation, supporting gut barrier integrity and facilitating gut-brain communication," said the researchers.

They added, "Intriguingly, *F. prausnitzii's* decline came with the rise of *Alistipes* and *Bacteroides* species that teamed up to become major butyrate producers, potentially taking over *F. prausnitzii's* role in gut health. We saw these functional enrichments repeated in mouse models of healthy ageing, suggesting they may play similar roles in promoting that state."

Moving forward, the team plans to isolate and characterise key microbial strains linked with healthy ageing, and assess their effectiveness as supplements to reduce frailty. "We believe these experiments will provide critical insights and facilitate the translation of our findings into practical applications for improving healthy ageing," they concluded. ★

Researchers
Aarthi Ravikrishnan and Niranjan Nagarajan, A*STAR GIS

IN BRIEF
A deep shotgun metagenomics study on 234 community-living elderly persons in Singapore identifies species-level changes and key metabolic pathways linked to ageing.

1. Ravikrishnan, A., Wijaya, I., Png, E., Chng, K.R., Ho, E.X.P., *et al.* Gut metagenomes of Asian octogenarians reveal metabolic potential expansion and distinct microbial species associated with aging phenotypes. *Nature Communications* **15**, 7551 (2024).

Photo credit: Uwe Roscher / Unsplash

BIOINFORMATICS

Gluing together layers of molecular insights

A new spatial multi-omics tool merges different levels of biological data from the same tissue sample to better differentiate finer details at different health states.

Much like how a student synthesises lessons from different subjects to tackle complex real-world problems, scientists can acquire data from different levels of molecular biology to study the mechanics of health and disease. Thanks to experimental tools, the various fields of 'omics' today—epigenomics, transcriptomics, proteomics and more—can capture vast landscapes of molecular data that reveal every change to a cell or tissue's DNA; every message it writes in RNA; and every protein it expresses to adapt to its environment.

Ideally, such shifts are best studied in their spatial context—which genes in which part of the brain misfire in dementia, for example? However, today's computational tools typically analyse omics data without the spatial component, or process only a single omic modality at a time, potentially leaving out crucial information.

"The preservation of spatial information allows more accurate inferences on cell-cell interactions and localised changes in cell composition," said Jinmiao Chen, a Principal Investigator at the A*STAR Bioinformatics Institute (A*STAR BII). "We need tailored tools that can integrate complementary information from all omics layers while being spatially aware to extract systems-level features or signatures."

Aiming to fill that gap, Chen and A*STAR BII colleagues teamed up with researchers from the A*STAR Institute of Molecular and Cell Biology (A*STAR IMCB), A*STAR Singapore Immunology Network (A*STAR SIgN), National University of Singapore, and institutes in China and the US. Together, they created SpatialGlue, an analytical tool that uses an artificial intelligence (AI) model that integratively analyses spatial data from the epigenome-transcriptome and the transcriptome-proteome.

As omics data can be high-dimensional—a transcriptome, for example, can have over 10,000 measurable features—SpatialGlue first simplifies such data while ensuring it still captures the relevant biological variations. In parallel, the model constructs graphs that map the proximity of different molecule and cell types to each other.

"SpatialGlue then trains a deep learning AI model based on the simplified and mapped omics data, which adaptively combines the different modalities to learn an integrated representation of them," said Chen. "The model also learns the relative importance of each of these modalities to develop a final representation that fits different analytical needs, such as the clustering of certain cells with shared functions."

SpatialGlue was tested against a suite of five simulated datasets and 12 experimental datasets, which included molecular data from two species (mice and human) and four tissue types derived from four technology platforms.

The team found that SpatialGlue successfully captured more anatomical details and correctly distinguished tissue regions—such as brain cortex layers—at a higher resolution than existing methods. SpatialGlue also identified subtypes of immune cells in three spatial zones of the spleen, uncovering new information from the original dataset.

To enhance their model, the team plans to add imaging data from immunostaining experiments and other platforms that captures additional information about the cells, such as cell size and shape. They are also exploring collaborations to apply SpatialGlue for more in-depth studies of clinical samples.

"Analysis of spatial multi-omics data can deepen our understanding of the molecular underpinnings of diseases, aiding the discovery of biomarkers and therapeutic targets," said Chen. ★

Researcher
Jinmiao Chen,
A*STAR BII

IN BRIEF
SpatialGlue, a computational tool that integrates spatial epigenomic, transcriptomic and proteomic data, offers a more holistic view of cell and tissue properties over current multi-omics methods.

1. Long, Y., Ang, K.S., Sethi, R., Liao, S., Heng, Y., *et al.* Deciphering spatial domains from spatial multi-omics with SpatialGlue. *Nature Methods* **21**, 1658-1667 (2024).

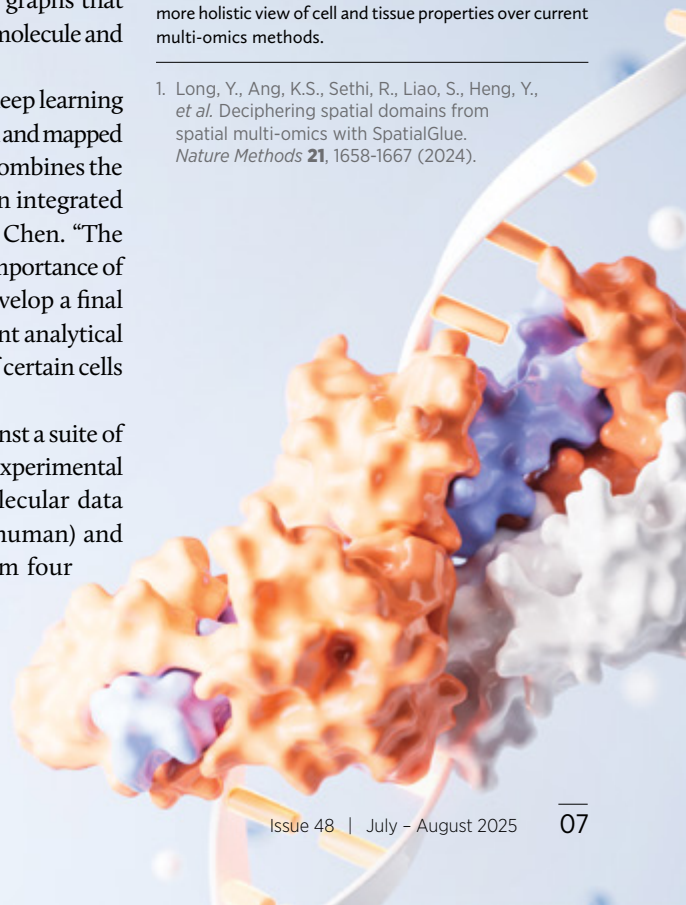


Photo credit: Vink Fan / Shutterstock

WHOLE IN ONE

Integrating molecular insights from several omics profiling approaches, A*STAR research initiatives are deepening our understanding of human physiology and unearthing new diagnostic and therapeutic opportunities.

Can a tree tell us about a rainforest's ecology, or a brick about a building's architecture? Given just a few puzzle pieces, can we clearly grasp the full picture they belong to?

Biomedical researchers face that struggle with the human body, given its trillions of cells and hundreds of thousands of protein variants, directed by instructions from around 20,000 unique genes. For decades, technological limitations meant scientists could only investigate a small fraction of these components to glimpse their complex relationships with each other and with health and disease.

Enter the multi-omics revolution: an emerging class of cutting-edge technologies enabling unprecedented holistic views of biology. These tools not only survey whole biological landscapes—every gene in a genome, every protein in a proteome—but also reveal hidden links between them. From high-throughput gene sequencing technologies to artificial intelligence (AI) models that harmonise different data modalities, multi-omics approaches are helping unearth fundamental biological insights and advance effective, tailored healthcare interventions.

"By integrating high-quality molecular data, multi-omics research provides deep insights into pre-disease and disease mechanisms, as well as population-specific biomarkers," said Lisa Ooi, Assistant Chief Executive of A*STAR's Biomedical Research Council (A*STAR BMRC).

Several A*STAR research groups are spearheading multi-omics initiatives with a focus on Asian populations to fill significant gaps in regional representation in international studies. Through active, cross-border collaborations with academia, industry and government, A*STAR teams are also contributing to Singapore's national precision health agenda and nurturing the growth of a regional multi-omics R&D hub.

"Given much of a tissue's function is encoded in how its cells interact, we need to know how its cells are arranged in living tissue."

— Shyam Prabhakar, Associate Director of the A*STAR Genome Institute of Singapore (A*STAR GIS)

TOOLS OF THE TRADE

Once extremely niche tools, omics profiling technologies are a cornerstone of many research institutions today. Whether genes, RNA transcripts, proteins or metabolites, the ability to sequence entire '-omes' has led to an explosive emergence of publicly-available datasets.

These treasure troves of omics data have likewise driven analytical innovations, as teasing out true biological signals—and therefore clinically-meaningful insights—amid the noise can prove difficult depending on data quality and quantity. Among these innovations are AI models, which are increasingly indispensable parts of omics analytical pipelines.

"Instead of looking at one measure at a time, AI systems can blend many layers of biological information to paint a fuller picture of health and disease, such as identifying which gene-protein combinations might signal early-stage cancer," said Dennis Wang, a Senior Principal Investigator at the A*STAR Institute for Human Development and Potential (A*STAR IHDP) and A*STAR Bioinformatics Institute (A*STAR BII).

These computational approaches are also helping uncover once-hidden insights from existing datasets. Researchers led by Jayantha Gunaratne, a Senior Principal Investigator and Deputy Division Director (Cell and Molecular Therapy) at the A*STAR Institute of Molecular and Cell Biology (A*STAR IMCB), developed a stepwise machine learning (ML)-based feature extraction pipeline called Unique Marker-AI (UMAI) to re-analyse published proteomics data. Through UMAI, they identified serum biomarkers of high-grade serous ovarian cancer, highlighting the translational value of AI-powered analytics in early disease detection.

"By integrating multiple validated algorithms, the pipeline effectively reduced analytical noise and prioritised biologically-relevant features. This led to the development of a novel four-biomarker panel that, when combined with current clinical markers, significantly enhanced diagnostic performance," said Gunaratne.

Such omics-powered workflows are already addressing unmet diagnostic needs through strong collaborations with local and international clinical partners. Gunaratne's clinical proteomics pipeline has uncovered biomarkers for several diseases, including a patent-pending urine biomarker panel for chronic kidney disease anchored on detecting earlier stages of kidney injury; prognostic serum markers predicting treatment response in chronic hepatitis B; and an immune-cold biomarker for breast cancer stratification. The group is also developing biomarker panels for a newfound high-risk subtype of breast and lung cancers.

PINNING LOCATIONS

Advancements in omics throughput (or processing rate) and resolution now allow researchers to read entire genomes within hours. Bulk sequencing and single-cell omics provide a wealth of data about how individual cells, tissues and organs function in health and disease, as changes in gene expression profiles reflect the up- and down-regulation of biological pathways.

However, these methods can be limited by their samples, which are typically cells removed from their original environments. Spatial omics—the latest arrival in omics innovations—now adds proximity and location into the picture, mapping cellular gene expression profiles to their anatomical locations.

"Given much of a tissue's function is encoded in how its cells interact, we need to know how its cells are arranged in living tissue," said Shyam Prabhakar, Associate Director of the A*STAR Genome Institute of Singapore (A*STAR GIS). "Spatial omics shows us both the physical proximity and the mix of molecules within and around those cells, allowing us to infer cell-to-cell communications."

With Singapore General Hospital (SGH)'s Tony Lim, the National Cancer Centre Singapore (NCCS)'s Iain Tan, A*STAR GIS's Kok Hao Chen and A*STAR BII's Hwee Kwan Lee, Prabhakar and colleagues spearheaded

the establishment of high-resolution spatial omics for colorectal cancer research at A*STAR GIS through the SCISSOR programme. From 2020 to 2024, the team built a full spatial omics pipeline, running from tumour sample collection and preparation to sequencing and data analytics. This led to the inhouse development and refinement of tools such as mFISH, a molecular probing technique to simultaneously profile thousands of gene targets within a tissue's spatial context; and BANKSY, an algorithm to analyse spatial omics data through integrated cell typing and tissue domain segmentation.

Through SCISSOR, the team discovered a rare invasive cell type that potentially drives tumour growth and metastasis in colorectal cancer. "As only a tiny population of this cell type exists in colorectal tumours, it was lost in the crowd of single-cell data. But spatial omics revealed that it forms a very thin, well-defined layer that pushes out from tumours into surrounding tissues," said Prabhakar, adding that further findings in this area were pending publication.

Following SCISSOR's success, A*STAR GIS, A*STAR BII, SGH and NCCS are jointly applying spatial omics to five cancers and two precancerous conditions through the TISHUMAP project, supported by a collaboration between A*STAR GIS and life science tech company 10x Genomics.

Across cancer types, profiles of a tumour's surroundings, or microenvironment, can provide insights on cancer's interactions with our immune system. Immune components such as natural killer (NK) cells play a critical role in disease progression, treatment response and even the risk of recurrence. For example, in hepatocellular carcinoma (HCC)—the most common form of liver cancer—NK cell infiltration into the tumour space is a key predictor of disease prognosis.

By combining multiple spatial omics methods, a team led by A*STAR IMCB Group Leader Joe Yeong and Senior Research Officer Denise Goh found a clinically-important subset of NK cells and five biomarkers whose spatial distribution patterns correlated with HCC recurrence. This led to the development of TIMES, a spatial immune scoring system that integrates spatial transcriptomics, spatial proteomics, multiplex immunohistochemistry and AI-driven analysis to generate a recurrence risk score based on the spatial expression of key biomarkers.

"TIMES enables the detection of molecular changes within specific cell types and tissue regions, allowing for more efficient identification of cancer biomarkers with biological relevance and spatial context," said Yeong and Goh.

CHOOSE YOUR FIGHTER (DRUG)

Just as the same disease can progress differently in different people, the same medication can elicit varying responses based on a whirlwind combination of genetics, metabolic processes, immune profiles and environmental factors. By shedding light on such diversity, multi-omics profiling stands as a critical enabler of both drug development and treatment selection within Singapore's precision health agenda, starting with the issue of individual drug resistance.

"People tend to think resistance is the result of random mutations that change drug targets after starting treatment, but we're starting to see resistance can be there before treatment begins," said Sin Tiong Ong, a Professor at Duke-NUS Medical School's Cancer and Stem Cell Biology (CSCB) Programme, as well as an A*STAR GIS Principal Investigator.

Ong explained that patients with chronic myeloid leukaemia (CML) carry the BCR::ABL1 driver gene mutation, creating an abnormal protein kinase that prompts the cancer's aggressive growth. Tyrosine kinase inhibitors (TKI) are drugs designed to inhibit these proteins; however, actual treatment responses can vary from highly effective to dangerously ineffective between patients, with some leukaemias transforming into a treatment-resistant blast crisis stage.

To investigate this variability in CML patient response, Ong teamed up with Shyam Prabhakar and A*STAR GIS researchers, as well as SGH Senior Consultant Charles Chuah, Duke-NUS Principal Research Scientist Vaidehi Krishnan, and Immunoscape Associate Director Florian Schmidt.

"People tend to think resistance is the result of random mutations that change drug targets after starting treatment, but we're starting to see resistance can be there before treatment begins."

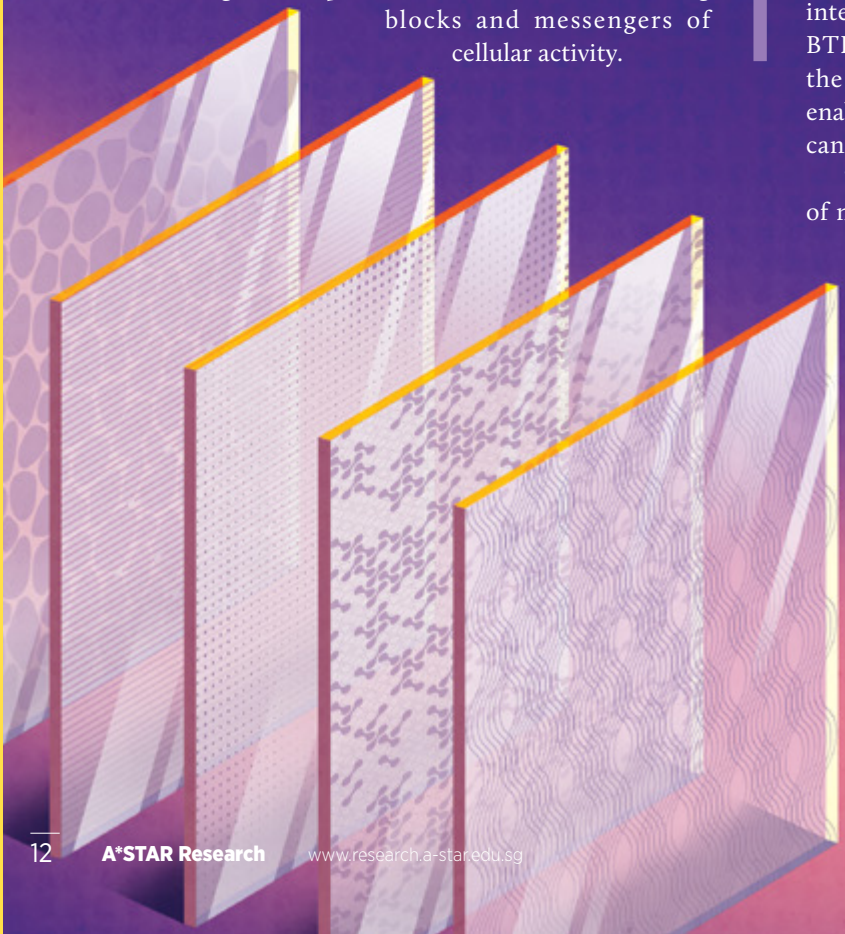
— Sin Tiong Ong, Professor at Duke-NUS Medical School's Cancer and Stem Cell Biology (CSCB) Programme, and A*STAR GIS Principal Investigator

By combining single-cell RNA sequencing, flow cytometry and computational methods, they found that leukaemic stem cells—especially certain transcription factors within them that guided their differentiation trajectory—were significant predictors of TKI response. Patients who responded well tended to have stem cells destined to become red blood cells rather than white blood cells.

"That revealed a whole new way of thinking: the types of stem cells in which CML occurs could determine a patient's sensitivity to TKIs," Ong explained. "They can help us predict which patients are likely to undergo blast crisis months, even years ahead. We can then stratify these patients for closer monitoring and transplant them in earlier CML phases, potentially boosting survival rates."

The team is now is developing a flow cytometry kit to identify those at high risk of blast crisis transformation. Employing a cocktail of antibodies developed with A*STAR GIS data by the Duke-NUS CSCB team, including Research Fellow Mengge Yu, the kit is being validated in patients from Singapore and Australia, the latter in collaboration with Tim Hughes, Clinical Director of Precision Cancer Medicine at the South Australian Health and Medical Research Institute.

Given that evolving cell fates and functions are also critical to how patients react to drugs, Ying Swan Ho and researchers at the A*STAR Bioprocessing Technology Institute (A*STAR BTI) are harnessing a range of omics technologies to map metabolites: the chemical building blocks and messengers of cellular activity.



"Metabolic processes provide insights into how cells operate under normal conditions and how they change in response to disease and treatment, which allows us not only to discover drug targets, but ensure that new drugs are effective and safe," said Ho, an A*STAR BTI Senior Principal Scientist.

Metabolomics can be critical when developing biotherapeutics. A class of products comprising antibodies, cells, RNA and other complex biological structures, biotherapeutics face ongoing challenges in production due to variability in quality and performance between manufacturing batches.

Ho believes that an expanded understanding of cell behaviour and advanced profiling techniques could make biotherapeutics production more consistent by identifying key quality indicators. For instance, metabolite data that reflects intracellular states and nutrient use can help producers optimise cell culture media to mimic bodily environments, promoting healthy and consistent cell growth.

To meet these needs, A*STAR BTI's BioStream programme features a comprehensive suite of proteomics, metabolomics and glycomics capabilities to characterise biotherapeutics and the processes needed to manufacture them at scale. Supported by AI integration and mechanistic modelling in collaboration with Yang Zhang, Professor of Computer Science at the National University of Singapore, BioStream's integrated approach is also complemented by A*STAR BTI's proprietary display-and-secretion system for the widely-used CHO immortalised cell line, which enables high-throughput screening of complex biologic candidates as full molecules.

"This multi-dimensional analysis and preservation of molecular structural integrity helps us understand how structure, function and process conditions interact, enabling more informed development decisions," Ho said.

HEALTH ACROSS THE LIFESPAN

Beyond uncovering the mechanisms behind disease progression and treatment responses, multi-omics can be powerful trackers and predictors of health trajectories, supporting more preventive and proactive national healthcare models.

"Longitudinal multi-omics profiling platforms can reveal how factors like diet, lifestyle,

microbiome and drug interventions interact to influence individual health, helping to identify disease risk even before symptoms emerge. These insights drive preventive health efforts that optimise health and promote healthy longevity," Lisa Ooi said.

Ooi noted how research findings from the nationwide GUSTO birth cohort study have directly informed policymaking for gestational diabetes, a condition that poses both acute and long-term health risks for mother and child. National clinical guidelines were revised to now recommend universal screening during pregnancy, allowing for earlier detection and interventions against this glucose tolerance disorder.

"Beyond risk screening, GUSTO also uses omics data to uncover molecular drivers of maternal and child health," Ooi added. "For example, linking fetal cord DNA methylation to maternal glucose levels of GUSTO mother-infant pairs revealed distinct epigenetic signatures associated with specific glycaemic traits, suggesting that different types of maternal hyperglycaemia can uniquely programme the neonatal epigenome and potentially influence early-life metabolic disease risk."

Proteomics data from GUSTO also led Dennis Wang and A*STAR IHDP colleagues to discover the involvement of a protein called ephrin-A4 in early linguistic development, tracing its role to pathways that promoted myelination in brain regions for language-related functions. Myelination is a vital process not just during neurodevelopment but also in ageing, as it wraps lipid-rich sheaths around nerve fibres to enable rapid signal transmission and provide metabolic support to brain cells.

"Our findings are not just relevant for children; they may also help stratify dementia patients facing language difficulties," Wang said.

To forecast evolving health conditions, Wang and colleagues are also building ML-based platforms such as GenMetS, a prediction model using genomic data for metabolic health status in young and healthy Asian adults. GenMetS has been validated in over 680,000 individuals from diverse cohorts including the UK Biobank, Japan Biobank, Chinese Kadoorie Biobank and Singapore's ATTRaCT.

"We found that GenMetS can forecast a person's risk of cardiometabolic disorders up to 30 years before clinical onset, and remains predictive across their lifespan, highlighting its potential for early intervention and lifelong health monitoring," said Wang.

IN BRIEF: A*STAR MULTI-OMICS STRATEGIC PARTNERSHIPS

- **Public healthcare clusters** *(SingHealth, NUHS, NHG)*
- **National programmes** *(STCC, CADENCE)*
- **National translation platforms** *(MedTech Catapult, DxD Hub, NATi, EDDC)*
- **Public-private partnerships** *(Biopharmaceutical, life science tools and AI companies)*

DRIVING CLINICAL TRANSLATION

Omics continues to reveal new depths to human diversity with powerful implications for precision healthcare. "What is 'normal' in a healthy population, when populations can be very different?" said Shyam Prabhakar.

Referring to the recently-published Asian Immune Diversity Atlas (AIDA), which found that immune cell compositions could vary as widely between Asian ethnic groups as between the sexes, Prabhakar highlighted the need to broaden clinical research coverage to more diverse and often underrepresented groups. Launched in 2019, AIDA's initial collaborators included A*STAR GIS, RIKEN Japan and the Samsung Genome Institute.

Through projects such as AIDA, A*STAR research groups and partners across academia, industry and clinics continue to expand the foundation on the dynamic mechanics behind health and disease, advancing precision healthcare approaches for Singapore and beyond.

"Discoveries enabled by multi-omics can translate to risk-based screening and precision therapeutics, enabling earlier detection and targeting the right individuals at the right time with the right interventions," Ooi said.

For Ooi, these tight clinical linkages and strong national translation platforms, further empowered by emerging AI capabilities, position A*STAR as a key innovation player in domestic and global multi-omics spaces. Whether through diagnostics, health monitoring or therapeutic innovations, A*STAR groups and collaborators jointly act as a translation engine to transform foundational omics research into improved clinical outcomes, simultaneously promoting scientific advances, bolstering the biotech scene and nurturing healthier communities. ★

NEUROSCIENCE

Bedtime battles now, big feelings later

A long-term study reveals that sleep problems in early childhood impact emotional well-being in later childhood, especially among 'night owl' children.

We all need our sleep, but not all of us are morning people. Our varied preferences for sleeping and waking periods over a 24-hour cycle—what's known as our chronotype—reflect the diversity of human biology. However, much of society tends to be structured around 'early birds', which means 'night owls' compelled to wake early for school and work might not get as many hours of restful sleep as their peers.

The effects of chronotype on sleep problems—which include fragmented sleep, poor sleep quality and daytime sleepiness—can be particularly concerning for young children, according to Derric Eng, a Senior Research Officer at the A*STAR Institute for Human Development and Potential (A*STAR IHDP).

"Evening chronotype in children isn't only linked to increased sleep problems, but to greater socioemotional problems later in life, such as difficulties with handling feelings and getting along with others," said Eng.

Alongside researchers from institutes in Singapore, Finland, Canada and the Netherlands, Eng and A*STAR IHDP colleagues including Principal Scientist Shirong Cai set out to investigate the long-term associations between chronotype, sleep problems and socioemotional outcomes in children from the ages of four to seven.

Previous studies have often focused on investigating the individual relationships between each factor within the same timepoint during childhood. The team drew on the ongoing Growing Up in Singapore Towards healthy Outcomes (GUSTO) study, which provided more than a decade's worth of detailed health observations on over 1,200 pregnant Singaporean women and their children. This allowed the team to observe the pathway linking all three factors together over time as the same children grew up.

The team found that sleep duration did not account for the association between chronotype and socioemotional problems at primary school age. Instead, quality of sleep mattered more: negative socioemotional outcomes were more strongly associated with increased sleep disturbances seen in children with greater evening preferences.

"It was fascinating to confirm our hypothesis that early sleep problems may be an important factor linking chronotype with later socioemotional problems," said Eng.

The team's findings aligned with previous studies which implied that socioemotional problems faced by 'evening' children are due less to their chronotype, but more to social jetlag: the misalignment between a person's biological clock and social schedule.

"Our findings imply that children with evening preferences are not necessarily 'doomed' to develop socioemotional problems," Cai said. "However, sleep problems may be a more appropriate target for early intervention than sleep duration."

While the current study relied on reports by caregivers, Eng suggested that future studies could use more objective measures of sleep. The team may also extend their work to adolescence, being another important period linked to profound changes in sleep habits and socioemotional development. ★

Researchers
Derric Eng and Shirong Cai,
A*STAR IHDP

IN BRIEF
Data from the GUSTO early childhood cohort shows sleep problems at preschool age mediate the link between chronotype and socioemotional problems at primary school age, suggesting that sleep quality interventions may reduce risk of negative socioemotional development in later years.

1. Eng, D.Z.H., Tham, E.K.H., Jafar, N.K., Tan, J.S.Y., Goh, D.Y.T., *et al.* Sleep problems in preschool mediate the association between chronotype and socioemotional problems at school-age. *Sleep Medicine* **124**, 174-186 (2024).

Photo credit: Laura Lee Moreau / Unsplash

BIOENGINEERING

Lipid tweaks for better vaccines

A*STAR researchers discover how subtle changes to a packaging component of mRNA vaccines can boost their efficacy and safety.

There's no denying that packages sway our shopping decisions. Marketing teams know that good package designs help ensure products reach their intended users: for example, bright colours and cartoon characters catch children's eyes, while sleek patterns and elegant text appeal to sophisticated tastes.

A similar idea applies to mRNA vaccines, which rely on lipid nanoparticles (LNPs)—tiny, bubble-like 'packages' of fatty molecules—to reach their intended cells. A small but critical part of LNPs is a class of lipids known as PEGylated lipids (PEG-lipids), which help anchor LNPs to their targets.

"While PEG-lipids help stabilise LNPs and extend their internal circulation time, they can also affect where LNPs go in the body, how well they enter cells, and how the immune system reacts to them," explained Yi Yan Yang, a Distinguished Principal Scientist at the A*STAR Bioprocessing Technology Institute (A*STAR BTI). "PEG can also sometimes trigger unwanted immune reactions and limit how long mRNA-LNPs stay active internally."

Yang added that as PEG-lipid choice and design can affect mRNA delivery efficiency, a better understanding of PEG-lipid varieties would allow researchers to fine-tune LNP formulations, enabling safer, more effective and longer-lasting mRNA vaccines.

With this goal in mind, Yang teamed up with colleagues from A*STAR BTI and the A*STAR Genome Institute of Singapore (A*STAR GIS) to clarify the effects of different PEG-lipid types on mRNA-LNPs in human cell lines and mouse models.

The team prepared and characterised 48 different LNP formulations with varying amounts of PEG-lipids, lengths of PEG-lipid tails, and chemical linkages between PEGs and lipids. They then assessed the LNPs' various properties, including their mRNA packaging efficiency, serum stability, uptake by cells, and resulting protein expression in mice.

The LNPs were then put to the test: loaded with mRNA encoding the SARS-CoV-2 Delta spike protein, their biological performance was benchmarked against commercial ALC-0159 LNPs currently used in Pfizer/BioNTech COVID-19 vaccines.

Overall, the researchers found that subtle changes in PEG-lipid content and structure—especially lipid tail length—significantly influenced the performance of mRNA-LNP vaccines, including their distribution in the body and immune response profile.

"Longer-tailed PEG-lipids such as C16-Ceramide-PEG and the 18-carbon DSPE-PEG elicited significant anti-PEG antibody responses," said Yang. "In contrast, shorter-tailed PEG-lipids such as C8-Ceramide-PEG and ALC-0159 induced minimal immune responses, which highlights the role of lipid anchor design in reducing immunogenicity."

The team also discovered that both C8-Ceramide-PEG and ALC-0159 LNPs built up similarly in mouse lymph nodes—the command centres of immune response—and triggered comparable desired immune responses against SARS-CoV-2. However, C8-Ceramide-PEG LNPs built up less in the liver compared to ALC-0159, potentially indicating less liver toxicity.

Looking ahead, Yang's team is exploring ways to replace PEG-lipids with biodegradable counterparts. "By engineering smarter and safer PEG-free materials, we aim to create next-generation LNP platforms more suited to long-term repeat use in mRNA vaccines and therapeutics," said Yang. ★

Researcher
Yi Yan Yang, A*STAR BTI

IN BRIEF
A comprehensive study of mRNA-LNP PEG-lipids reveals how PEG-lipid content, lipid tail length and chemical linkages can affect vaccine immune responses and change mRNA-LNP accumulation patterns in the body.

1. Zhang, L., Seow, B.Y.L., Bae, K.H., Zhang, Y., Liao, K.-C., *et al.* Role of PEGylated lipid in lipid nanoparticle formulation for *in vitro* and *in vivo* delivery of mRNA vaccines. *Journal of Controlled Release* **380**, 108-124 (2025).

Photo credit: Amir Taheri Ghafarokhi / Shutterstock

POLYMERS AND PLASTICS

Ionogels charge on to greener wearables

A new generation of flexible polymers could pave the way for more easily recycled bioelectronics.

Whether as sleek smartwatches or blocky wristbands, fitness trackers are an increasingly common sight in Singapore, as even public initiatives like the National Steps Challenge promote their adoption. These devices could soon evolve beyond rigid cases into soft, skin-conforming patches, allowing users to wear them comfortably day and night.

However, flexible bioelectronics like these could also create new environmental issues, according to Zibiao Li, Director of the Resource Circularity Division at the A*STAR Institute of Sustainability for Chemicals, Energy and Environment (A*STAR ISCE²). Even today, simpler soft sensors—such as electrodes for heart monitors—mostly end up in landfill due to their non-recyclable plastic content.

"The growing environmental concerns associated with electronic waste highlight a pressing need for sustainable alternatives," said Li.

Li added that soft polymers such as ionogels are currently a promising base material for flexible bioelectronics. Unlike traditional counterparts such as hydrogels, ionogels are more durable and electrochemically stable, making them ideal for long-term outdoor use. Some are even recyclable—but at a cost.

"Existing recyclable ionogels are held together by reversible, non-covalent bonds, which typically reduce their strength and stability," said Xian Jun Loh, Executive Director at the A*STAR Institute of Materials Research and Engineering (A*STAR IMRE). "This significantly limits their practical use in wearables that demand durability and flexibility."

In collaboration with Nanyang Technological University, Singapore, Li, Loh and colleagues including A*STAR ISCE² Scientist Xiaotong Fan and A*STAR IMRE Senior Scientist Yifei Luo aimed to tackle that performance-recyclability tradeoff.

Photo credit: Yiistocking / Freepik

“The growing environmental concerns associated with electronic waste highlight a pressing need for sustainable alternatives.”

Combining expertise in materials sustainability and polymer chemistry, the team explored a new ionogel system based on covalent adaptable networks (CANs).

CANs contain dynamic bonds which allow their mesh-like polymer structure to temporarily break down at certain heat, light or pH levels, then reform once those stimuli are removed, all without the need for toxic catalysts. “This strategy allowed us to design a closed-loop, recyclable ionogel system that also exhibits robust mechanical properties,” said Fan, the study’s lead author.

The result was a transparent film that proved not only physically stronger than other reported recyclable ionogels, but on par with non-recyclable designs. The team found that a 0.05 g film, measuring 0.2 mm thick and 0.3 cm wide, could easily lift a 1 kg object. The ionogels also maintained their properties after up to 10 rounds of recycling.

The team was surprised to find that lithium ions, originally added to improve their system’s conductivity, also boosted its mechanical strength by ‘gelling’ it together. Ion-dipole interactions made the lithium ions act both as a bonding agent and a conductor, creating a ‘sweet spot’ of performance and durability.

“These interactions resolve another long-standing tradeoff in ionogels; one between their electrical and mechanical properties,” said Luo.

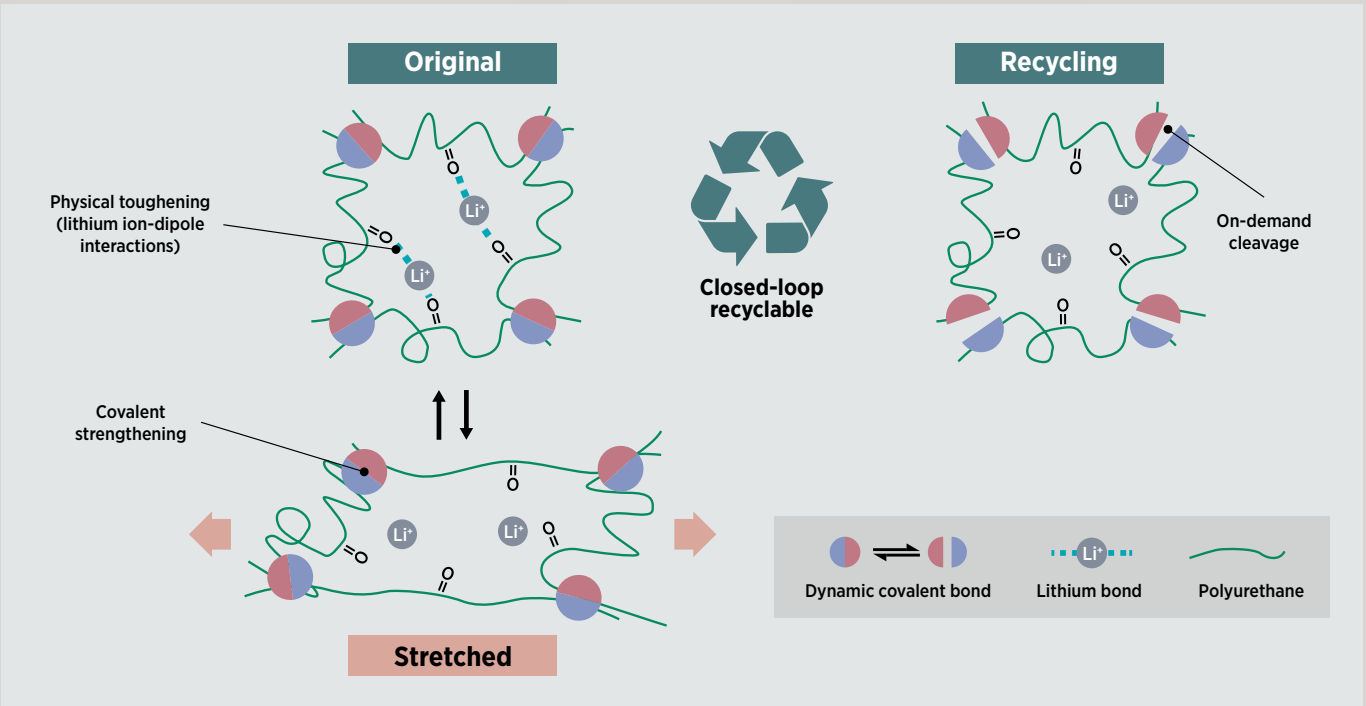
Moving forward, the team aims to upgrade the adhesive properties of recyclable ionogels. “Stable long-term skin contact would enhance user comfort and ensure more accurate health monitoring, especially during motion and perspiration,” Luo added. ★

Researchers
Zibiao Li, A*STAR ISCE² and A*STAR IMRE
and Xiaotong Fan, A*STAR ISCE²

Researchers
Yifei Luo and Xian Jun Loh, A*STAR IMRE

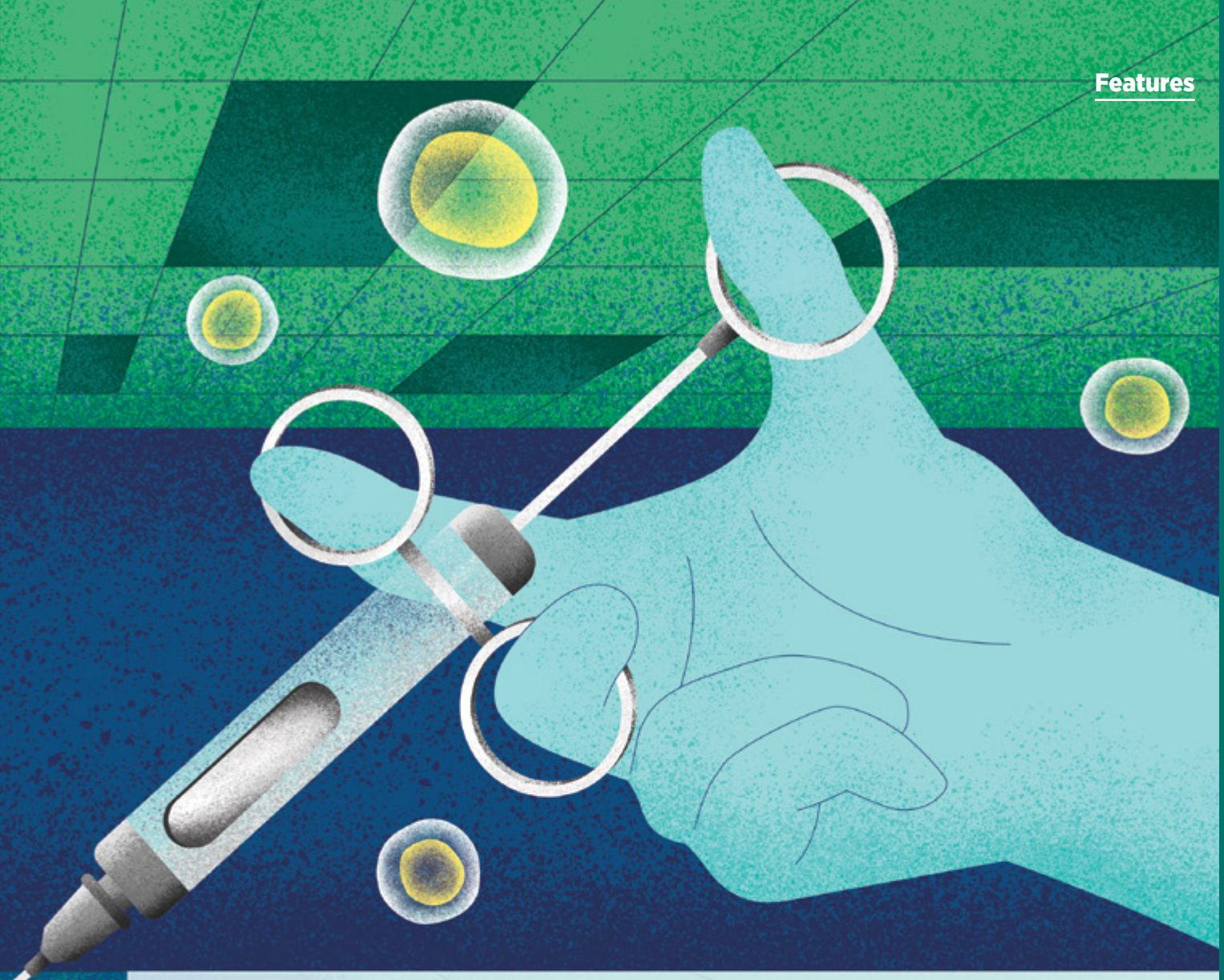
IN BRIEF
Ionogel designs that integrate covalent adaptable networks and lithium ion-dipole interactions demonstrate repeatable recyclability as well as improved electrical and mechanical properties.

1. Fan, X., Luo, Y., Li, K., Wong, Y.J., Wang, C., *et al.* A recyclable ionogel with high mechanical robustness based on covalent adaptable networks. *Advanced Materials* **36** (44), e2407398 (2024).



Schematic illustration of the proposed polymer network design for a robust and recyclable ionogel, based on covalent adaptable networks. (Adapted from Fan *et al.* 2024)

MAKING LIVING MEDICINES



Combining biology and analytical chemistry, Yu Hui Kang is developing cell infusions to fight cancer and autoimmune diseases.

Doctors today have more options in their medical toolkit to treat diseases, with advances in healthcare adding living cells to their arsenal. In cell-based immunotherapy, human immune cells are grown, modified and infused into patients, harnessing our body's natural defenders to target cancer and other difficult-to-treat diseases.

However, an effective cell-based therapy doesn't only depend on the type of cells used, but also on the nutrients the cells consume and how those nutrients are used. Known as metabolism, this vast network of chemical reactions occurs in every living cell and changes dynamically to modulate cellular function. The small molecules involved in these reactions are known as metabolites.

To design potent cell-based immunotherapies, A*STAR Bioprocessing Technology Institute (A*STAR BTI) Scientist Yu Hui Kang aims to understand both the biology of immune cells and the chemical reactions involving their metabolites. By building bridges between immunology and metabolomics, Kang and colleagues are optimising the metabolic networks of immune cells so that they can carry out the best cellular processes to combat disease.

In this interview with *A*STAR Research*, Kang discusses his interdisciplinary academic journey, how his experiences influence his work, and the role of metabolomics in advancing healthcare research.

Q: TELL US ABOUT YOUR JOURNEY IN SCIENCE.

I first pursued a traditional path in immunology as I wanted to work on a topic that was relevant to multiple diseases. Doing my PhD degree at a paediatric hospital allowed me to stay connected to that goal and gradually led me to value patient impact over journal publications—though we always strived for a balance between the two. I'm grateful to A*STAR for both its scholarship support and its strong emphasis on applying research for the benefit of Singapore.

Later, inspired by an A*STAR colleague, I decided to pivot towards analytical chemistry—metabolomics in particular. I'd been interested in how metabolism can shape immune cell function during my PhD studies, but found it difficult to understand metabolomics, a field that is critical to generating that insight. With my supervisor's help, I joined the lab of a metabolic expert with in-house metabolomics capabilities. This marked the beginning of my interdisciplinary training; beyond metabolomics itself, I acquired a better understanding of the analytical, precision-focused approach to science—the skills of which I continue to apply today.

Q: WHY DO YOU THINK METABOLOMICS IS AN EXCITING FIELD TO BE IN?

Far from the static pathways you might have learned about in school, metabolism is a highly dynamic network, constantly changing to meet the body's needs and functions. You can compare this network to road traffic, which shifts as traffic marshals direct different junctions. We are still discovering new ways in which metabolic traffic moves; metabolomics allows us to not only study these movement patterns, but to also reveal potential targets (junctions) for new therapeutics.

We now know that metabolism is a critical driver of many diseases, rather than a passive bystander. Obesity, diabetes and other common diseases in Singapore are linked to metabolic defects—the same ones that medicines such as metformin and GLP-1 agonists are designed to help restore. Further research is underway to test if these metabolic drugs also work for immune-based diseases.

Q: WHAT IS THE MOST MEMORABLE ASPECT OF YOUR INTERDISCIPLINARY JOURNEY?

The most memorable part of my experience is cultivating a core trait of interdisciplinary researchers: the ability to integrate different fields to tackle key problems.

We conducted the metabolomics research alongside biological experiments on immune cells, which allowed me to refine the analytical or biological aspects as needed. Sometimes, this meant formulating new methods to detect specific metabolites; at other times, it involved utilising different approaches—such as bioinformatics and perturbation experiments—to validate the metabolomics. This constant crosstalk between disciplines helped us better understand each field and generate useful insights into the metabolic pathways immune cells use in diseases such as cancer.

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

I work in A*STAR BTI's Analytical Science & Technology (Metabolomics) group, where my main focus area is cell-based immunotherapy. These therapies remain complex and costly to manufacture, as cells are labour-intensive

"Metabolic pathways can be modified affordably through dietary changes or small molecules that target key enzymes."

— Yu Hui Kang, Scientist at the A*STAR Bioprocessing Technology Institute (A*STAR BTI)

to generate and can vary significantly across processes and donors.

As cellular metabolism is an important source of this variability, a key part of my work involves monitoring and optimising metabolites during the biomanufacturing process to ensure product quality and reduce costs. We look for early indicators of successful metabolic states so that unsuccessful cultures can be terminated early, thereby minimising resource wastage. We also rationally fine-tune their diet (the media they grow in) to improve the odds of generating cells with ideal metabolic states.

This role is a great fit for my interdisciplinary skills as it allows me to apply immunology to understand the biological context behind processes, and analytical chemistry to improve precision and consistency in biomanufacturing.

Q: WHAT ARE YOUR BIG GOALS IN HEALTH RESEARCH?

One of my goals is to foster a greater adoption of metabolism as an area of therapy. A common approach to disease treatment today is to alter biological pathways by modulating genes and proteins. While exciting and important, these modalities can be expensive. In contrast, metabolic pathways can be modified affordably through dietary changes or small molecules that target key enzymes. It would be great to see metabolism play a more prominent role in disease treatment, perhaps as a cost-effective addition to conventional approaches.

My second goal is to encourage greater consideration of the metabolite environment—culture media, for example—in immunology research and the development of immune-based medicines. When I was solely focused on immunology, I tended to prioritise cells and proteins, while metabolites were often an afterthought. Now, knowing that metabolites play an active role in immune function, I believe it's essential for researchers to consider and optimise the environments in which our cells reside, to develop medicines that work potently within the body.

Q: WHAT ADVICE WOULD YOU GIVE TO OTHER RESEARCHERS INTERESTED IN MULTIPLE FIELDS?

First, find out more about the interdisciplinary path you're interested in. This path can offer opportunities for innovation by breaking silos and revealing gaps that exist across fields. However, it's important to find an environment that values boundary-spanning breadth. Research systems are typically organised around disciplines with emphasis on depth within a specific field, thus interdisciplinary researchers—who often don't fit neatly into conventional lanes—may need to actively articulate the value of their integrative contributions. I'm grateful to have found a place at A*STAR BTI that values multidisciplinary collaboration.

Next, have a purposeful narrative when choosing your areas of focus. This will help you and others make better use of your skills, which is especially important when navigating less conventional paths.

Finally, try to connect with like-minded individuals. Interdisciplinary researchers are relatively uncommon in discipline-organised systems, so finding a community of people who share your interests can be incredibly helpful. I'm always happy to connect and continue these conversations. ★

Yu Hui Kang
Scientist
A*STAR Bioprocessing Technology Institute (A*STAR BTI)

MATERIALS CHEMISTRY

Swift systems seek out thorny battery solutions

Through machine learning-aided design, A*STAR scientists discover new additives to suppress hazardous metal deposits in high-performance lithium metal batteries.

Lithium-ion (Li-ion) batteries have reshaped our world thanks to their ability to pack immense amounts of electricity into small and light devices. Yet as the world tips towards renewable energy, there's a growing need for batteries with better capacities, performance and reliability, which would make them more viable for power grids and vehicles.

One avenue for improvement involves fixing an old 'thorny' problem with Li-ion batteries. After prolonged use, battery anodes tend to form needle-like, electrically-conductive growths known as dendrites, which can pose safety risks.

"Lithium dendrites are formed due to unevenly-deposited lithium ions during the charging and discharging process. They can increase the chances of a battery short-circuiting, materially degrading or catching fire," said Andy Man-Fai Ng, a Principal Scientist at the A*STAR Institute of High Performance Computing (A*STAR IHPC).

To suppress dendrite growth, most commercial Li-ion batteries use graphite anodes with lithium salt and electrolytes, but this stability can cut the battery's maximum capacity down to a tenth of its potential. In theory, lithium metal batteries (LMBs)—which use lithium itself as the anode—offer a significant boost to capacity, but this alternative design forms dendrites too rapidly for safe and practical use.

To overcome this, Ng and A*STAR IHPC colleagues worked with the National University of Singapore in a computational search for novel electrolyte additives that can help regulate lithium ion movement and level out dendrites in LMBs.

"Electrolyte additives can add to the formation of a stable and robust solid electrolyte interphase (SEI) that guides smooth lithium deposition," Ng explained. "This reduces the risk of dendrite formation and allows the use of lithium-metal anodes with much higher specific capacities."

Using an inverse design strategy, the team combined machine learning (ML) approaches and Bayesian optimisation (BO) to screen over 2.6 million molecules from the PubChemQC database for potential electrolyte additives. They trained their ML model to identify molecules with specific desirable properties, particularly dendrite suppression based on interaction energies with lithium metals. Meanwhile, BO guided the model's search through the database's vast chemical 'space', tagging promising molecules for further evaluation and using them to enhance the model's accuracy.

"Through an iterative process, we formed an active learning loop which gradually improved the model while its algorithm converged toward the search space's global optimum," said Ng.

Over the course of their study, the researchers identified 62 potential SEI-forming molecules and 106 levelling molecules that were predicted to perform better than similar electrolyte additives in current literature.

"To our knowledge, this work is the first instance of the use of computational inverse design combining ML, BO and atomistic modelling to discover electrolyte additives," said Ng.

The team is now working on generalising their approach to other applications, such as screening novel materials for other types of batteries and enabling molecular engineering through designing more efficient energy storage components. ★

Researcher
Andy Man-Fai Ng, A*STAR IHPC

Photo credit: Brookhaven National Laboratory / Flickr (CC BY-NC-ND 2.0)

IN BRIEF
An inverse design strategy involving machine learning and Bayesian optimisation enables the discovery of electrolyte additives that mitigate lithium dendrite growth on lithium metal anodes, paving the way for higher-capacity lithium metal batteries.

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FOOD SCIENCE

Good things happen when microbes meet soy

Scientists dig into tempeh to uncover how microbial action breaks down soybean proteins into smaller, more digestible and more nutritious forms.

Fermented foods such as yoghurt, kimchi and kombucha are often celebrated for their digestive and health benefits. But what is it about fermentation that gives these foods their supposedly healthy edge? How do their nutrients differ before and after?

In a recent study, a team of researchers from the A*STAR Institute of Molecular and Cell Biology (A*STAR IMCB) and A*STAR Singapore Institute of Food and Biotechnology Innovation (A*STAR SIFBI) took a dive into tempeh fermentation to examine its molecular-level effects on the humble soybean.

"Tempeh is more than just soybeans inoculated with *Rhizopus* fungi. Its microbial complexity, culinary potential and nutritional depth are more sophisticated than people realise," said Jayantha Gunaratne, a Senior Principal Scientist and Head of the Translational Biomedical Proteomics lab at A*STAR IMCB. "The right fermentation and preparation techniques can not only improve tempeh's flavour and texture, but also enhance its protein profile in ways we're only starting to understand."

Gunaratne and colleagues—including Jia Yee Wu, formerly of A*STAR SIFBI and now a Scientist at A*STAR IMCB, and A*STAR Senior Adviser Christiani Jeyakumar Henry—used advanced proteomics and peptidomics tools to study how soybean proteins are broken down by *Rhizopus* and other microbes during tempeh production. They analysed the mix of peptides—chains of amino acids—released as such proteins are digested by microbial enzymes. The peptides were then compared to those in commercial soybeans.

A major hurdle for the team was the absence of a complete protease database for *Rhizopus* with which to identify enzymes responsible for protein degradation. Instead, they used a non-specific enzyme search strategy to infer the types of proteases involved, applying advanced spectral processing and peptide analysis to analyse protein cleavage sites and detect patterns in protein breakdown.

"This approach revealed peptides typically overlooked by conventional analysis, shedding light on the diverse proteolytic activities of the microbes involved," said Gunaratne.

The team identified over 48,000 peptides derived from soybean proteins after microbial digestion. They also mapped the combined roles of several fungal and bacterial enzymes in enriching tempeh's nutritional and functional profiles.

Gunaratne highlighted the role of mass spectrometry-based proteomics in their study's novel findings. These included the reduction of allergenic proteins in tempeh compared to soy, which highlights its potential as a hypoallergenic plant-based protein; as well as the release of insulin-like peptides during microbial digestion that may enhance insulin sensitivity and support metabolic health.

"Proteomics allows us to pick up subtle changes in food composition that conventional methods often miss, making it a powerful tool not just for nutrition research, but also for improving food safety and quality control," said Gunaratne.

Next, the team aims to investigate the fate of microbially-digested tempeh peptides in the human gut, particularly their interactions with gut cells and microbiota, as well as their potential influence on immunity or gut health. ★

Researchers

Jayantha Gunaratne and Jia Yee Wu, A*STAR IMCB

IN BRIEF

Advanced proteomics and peptidomics show *Rhizopus* fermentation enriches tempeh's proteins by pre-digesting them, producing insulin-like peptides and reducing allergens, with implications for enhanced nutrition and gut health.

1. Wu, J.Y., Wee, S., Ler, S.G., Henry, C.J. and Gunaratne, J. Unraveling the impact of tempeh fermentation on protein nutrients: An *in vitro* proteomics and peptidomics approach. *Food Chemistry* **474**, 143154 (2025).

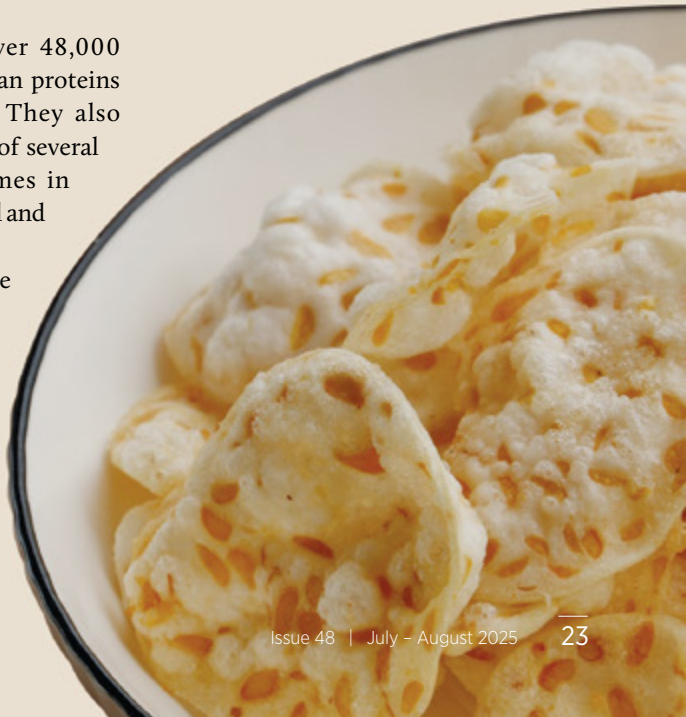


Photo credit: Jepretualang / Unsplash

ELECTRONICS

Spongy sensors for a human touch

Inspired by sponges and trees, a novel hydrogel design paves the way for a new generation of multi-functional electronic soft sensors.

Soft sensors that boast the 'human touch' have long been the holy grail for makers of soft electronics, robotics and healthcare devices. However, the challenge is more than capturing a squeeze or a stretch; like our skin, such sensors should ideally be versatile enough to simultaneously detect not just the presence of pressure, but its degree, location and even the type of object creating it.

A team of researchers including Junhua Kong, a Senior Scientist at the A*STAR Institute of Materials Research and Engineering (A*STAR IMRE), has recently invented a new hydrogel-based sensor to do the job. "We aimed to create something that was as human-like as possible. Something simple, sensitive and multi-functional, yet not reliant on expensive materials or complex testing methods," said Kong.

Drawing inspiration from nature, Kong and colleagues from A*STAR IMRE, the A*STAR Institute of High Performance Computing (A*STAR IHPC) and Nanyang Technological University's School of Materials Science and Engineering, Singapore, fabricated a polymeric hydrogel made of polyvinyl alcohol reinforced with cellulose nanofibres (CNF) to mimic the elasticity of sponges and the structural toughness of wood. A freeze-casting technique gave the material long, one-way channels that allow water and ions to flow freely.

"The hydrogel works like a basic resistive sensor—it's essentially a 'noodle' connected to two electrodes," Kong explained. "When touched or stimulated, it responds by changing its electrical properties; it 'feels' the touch electronically."

Infused with an ionic solution and coated with a thin sodium alginate film, the sensor functions using alternating current impedance measurement: a method that reads changes in a material's electrical resistance without the drawbacks of traditional direct current systems, such as electrode corrosion.

Using their simple sensor format, the team demonstrated three distinct capabilities: measuring pressure via deformation, pinpointing the location of a touch and identifying different materials based on their unique impedance signatures. They then combined these functions into several practical devices, including a motion-sensitive interface for minimally-mobile patients; a 3D touchpad; and a robotic

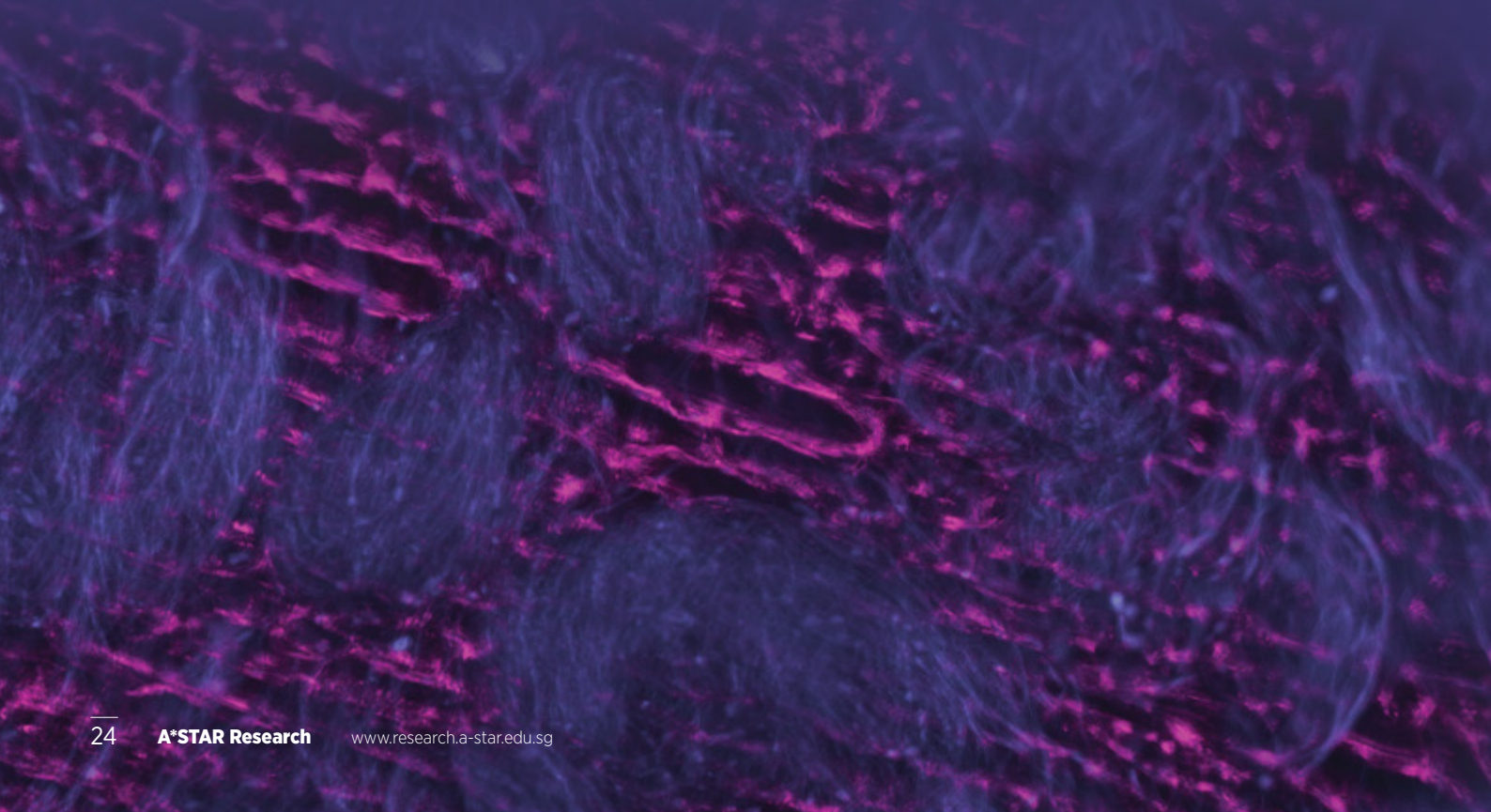
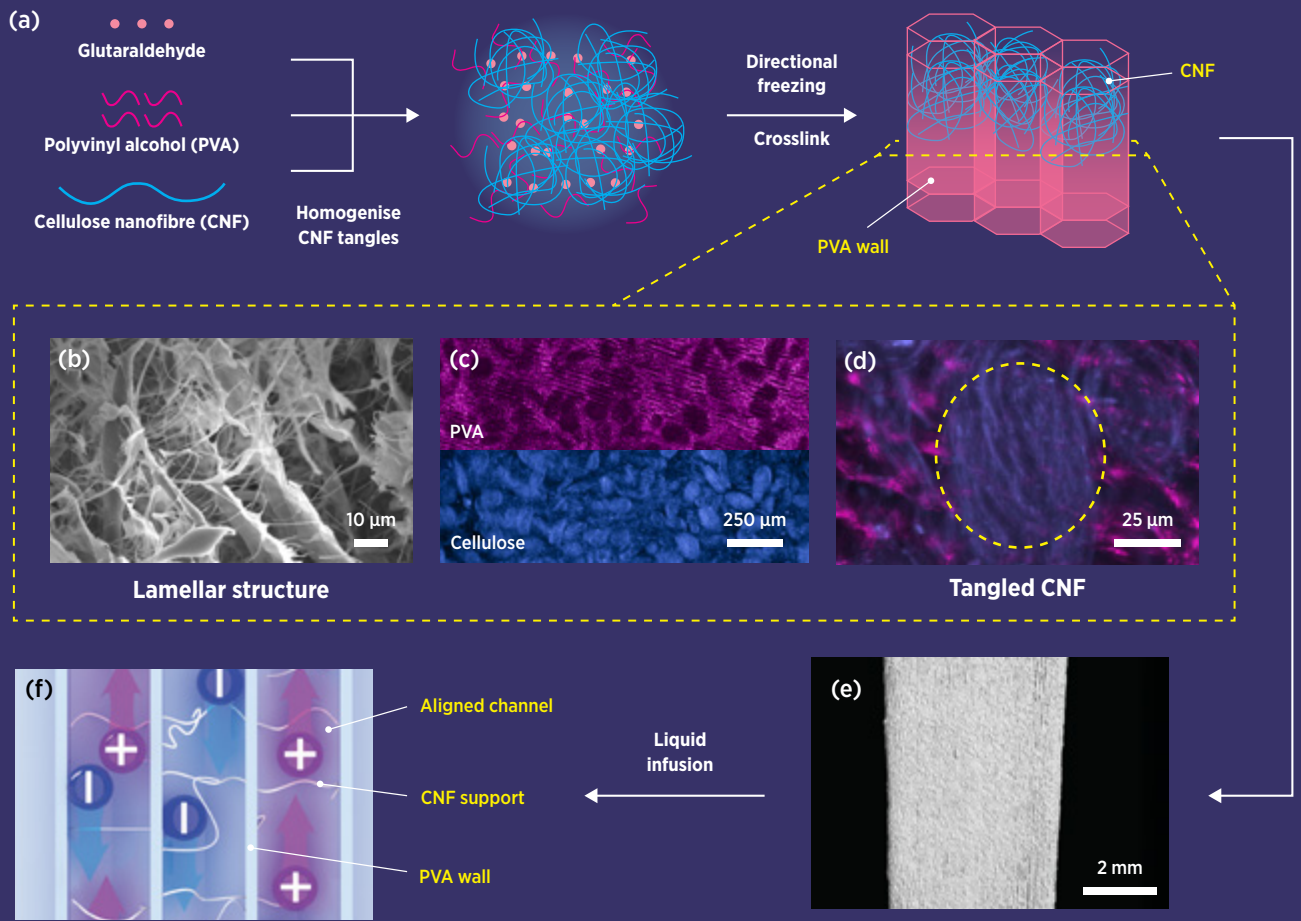


Photo credit: Xiangyu Duan / Nanyang Technological University / A*STAR Institute of Materials Research and Engineering



Design, fabrication and structural study of the sponge hydrogel. **(a)** Schematic illustration of the fabrication process. **(b)** Cross-sectional view of an as-fabricated sponge hydrogel through scanning electron microscopy. **(c)** Cross-sectional views of the hydrogel when wet, showing directional PVA walls (top) and randomly-distributed CNF tangles (bottom), through confocal laser scanning microscopy (CLSM). **(d)** Stacked CLSM images showing both PVA and CNF structures. **(e)** Micro-CT scan of the hydrogel when dry, showing aligned channels. **(f)** Schematic of the hydrogel's internal structure when infused with salt solution. (Adapted from Duan *et al.* 2025; images by Xiangyu Duan)

gripper that distinguished between metal, plastic and organic items.

"What surprised us was how much information we could extract from a single point of touch," Kong said. "With such a simple setup, we picked up differences in impedance between materials that created a rich dataset for sensing possibilities."

"What surprised us was how much information we could extract from a single point of touch."

The team was also surprised to discover that the hydrogel's CNF content had tangled up in tumbleweed-like structures, causing them to act like elastic springs. "We didn't set out to create these tangles," said Kong, "but they turned out to be key to the hydrogel's exceptional elasticity and recovery after being compressed."

The hydrogel's softness and conformability make it potentially suited to wearable health monitors and bioelectrodes. Looking ahead, the team plans to explore alternative materials to further enhance the hydrogel's performance, as well as its applications beyond sensing, including biomedicine and energy storage. ★

Researcher
Junhua Kong, A*STAR IMRE

IN BRIEF

A porous, elastic hydrogel with directional polyvinyl alcohol channels and spring-like cellulose support enables soft electronic pressure sensors that detect subtle pressure changes, precise touch positions and different originating materials using electrical impedance.

1. Duan, X., Mi, Y., Lei, T., Ma, X.Y.D., Chen, Z., *et al.* Highly elastic spongelike hydrogels for impedance-based multimodal sensing. *ACS Nano* **19** (2), 2909-2921 (2025).

LANGUAGE MODELS

Doctor AI on call

An AI-based framework adds a personal touch to medical dialogues, supporting the health management plans of patients with diabetes.

If you have ever dreamt of having your own robot healthcare assistant like Baymax from *Big Hero 6*, the idea may not be as farfetched as you think. Amidst advancements in generative artificial intelligence (AI) such as the algorithms that power ChatGPT and Gemini, researchers are also leveraging large language models (LLMs) to develop AI assistants that can converse with patients.

"Personalised medical dialogue generation can improve medical care by tailoring conversations to patients' specific needs, medical histories and preferences," said Zhengyuan Liu, Tech Lead of the Multimodal Generative AI Group at the A*STAR Institute for Infocomm Research (A*STAR I²R).

These LLM-based agents can be particularly beneficial in supporting follow-up health communications beyond the clinic, such as diabetes management plans.

According to Liu, personalising these conversations can help encourage patients to adhere to treatment plans, taking into account, and adapting to, changes in their lifestyle or day-to-day health condition.

With the support of the Diabetes Clinic of the Future initiative, Liu and A*STAR I²R colleagues including Senior Principal Scientist Nancy F. Chen developed a generative AI-based medical dialogue system to provide customised coaching for patients with diabetes. To optimise the model, they analysed 856 telehealth conversations between nurses and patients with diabetes to identify essential topics covered in follow-up calls.

"Our approach uses topic-focused summarisation to distil core information from lengthy dialogues, making it better at handling the long conversational contexts that are typical in medical settings," Liu explained. The framework also incorporates patient profiles from demographic data and health condition changes, all leading up to more personalised dialogue generation.

When compared against real-life healthcare calls, the researchers found that their system effectively extracted key information from noisy dialogue contexts to guide the subsequent conversation flow. This contextualised approach significantly enhanced dialogue generation quality based on standardised metrics for language models, representing a step towards more human-centred AI.

"By adapting to individual patient contexts and preferences, the framework creates more natural, relevant and empathetic healthcare conversations that respect the uniqueness of each patient's situation," said Liu. For example, the model might ask more specific follow-up questions on the patient's diet based on their dietary habits.

"Emotion-aware text-to-speech generation could enhance dynamic and empathetic interactions between the system and patients."

The team now aims to expand their personalised dialogue generation system, with one potential development being speech capabilities. "Emotion-aware text-to-speech generation could enhance dynamic and empathetic interactions between the system and patients," Liu said. ★

Researchers
Zhengyuan Liu and Nancy F. Chen,
A*STAR I²R

IN BRIEF
A personalised medical dialogue generation system takes into account the uniquely evolving conditions of patients with diabetes, enabling customised health coaching.

1. Liu, Z., Salleh, S.U.M., Krishnaswamy, P. and Chen, N.F. Context aggregation with topic-focused summarization for personalized medical dialogue generation. *Proceedings of the 6th Clinical Natural Language Processing Workshop*, 310-321 (2024).

2. Liu, Z., Salleh, S.U.M., Oh, H.C., Krishnaswamy, P. and Chen, N.F. Joint dialogue topic segmentation and categorization: A case study on clinical spoken conversations. *Proceedings of the 2023 Conference on Empirical Methods in Natural Language Processing: Industry Track*, 185-193 (2023).

Photo credit: DC Studio / Freepik

PHOTONICS

Tiny silicon patterns for an ultraviolet shine

A new crystalline silicon metasurface harnesses asymmetric design to efficiently generate deep-UV light, advancing chip-scale photonic applications.

For many people, the words 'ultraviolet light' or 'UV light' might bring to mind sunburn or skin cancer. You might be surprised to find UV lights in a range of helpful applications today, ranging from medical equipment sterilisers to indoor farm lighting.

One form of UV light, known as coherent deep-UV (DUV), already plays key roles in making nanoelectronics and purifying water. Researchers such as Omar Abdelraouf, a Research Scientist at the A*STAR Institute of Materials Research and Engineering (A*STAR IMRE), think coherent DUV could do a lot more if it could be generated on compact chips, rather than via bulky and power-hungry laser equipment.

"We're aiming for on-chip, energy-efficient, ultracompact light sources for DUV nanophotonics applications," said Abdelraouf, referring to a new generation of light-based computer circuits that could run faster than today's electronics.

Abdelraouf and A*STAR IMRE colleagues including Hong Liu, Group Leader of A*STAR IMRE's Intelligent Nano-optics Group, teamed up with Nanyang Technological University, Singapore, to develop a crystalline silicon (c-Si) metasurface to produce coherent DUV from a low-power laser light source. Comprising a sapphire sheet dotted with rows of fin-shaped c-Si structures—each a hundred times thinner than a human hair—their metasurface relies on third harmonic generation (THG), an optical process which combines a trio of low-energy photons into a single high-energy photon.

The team had to negotiate a delicate balancing act with their metasurface, which Abdelraouf compared to a magnifying glass for focusing sunlight. "Tiny imperfections in c-Si structures, like round edges, reduce their ability to trap and amplify light," said Abdelraouf. "On the other hand, if you turn up the laser's power to increase DUV output, the system breaks."

Central to their metasurface's design was a deliberate breaking of its structural symmetry, causing it to activate specialised light-trapping phenomena called bound states in the continuum (BIC). Abdelraouf noted that this approach not only boosted the metasurface's capacity to confine and convert light energy, but allowed more fine-tuning than existing methods of enhancing BIC resonance, which rely on changing materials or geometric shapes.

Through careful fabrication and tuning, the team achieved a 14-fold increase in THG power and a conversion efficiency to DUV of 5.2×10^{-6} percent, outperforming other metasurface designs in current literature.

"Tiny imperfections in c-Si structures, like round edges, reduce their ability to trap and amplify light."

To address light 'leaks' and other performance issues from minor structural flaws, the team used advanced nanofabrication techniques and robust, error-tolerant designs. This aligned their experimental results with simulation data, bringing their silicon platform one step closer to being a part of practical, chip-based DUV light sources.

"Our next steps include exploring novel optical materials with strong nonlinearity for DUV THG enhancement; advanced nanofabrication techniques for higher accuracy and conversion efficiency; as well as integration technology for on-chip devices," Abdelraouf said. ★

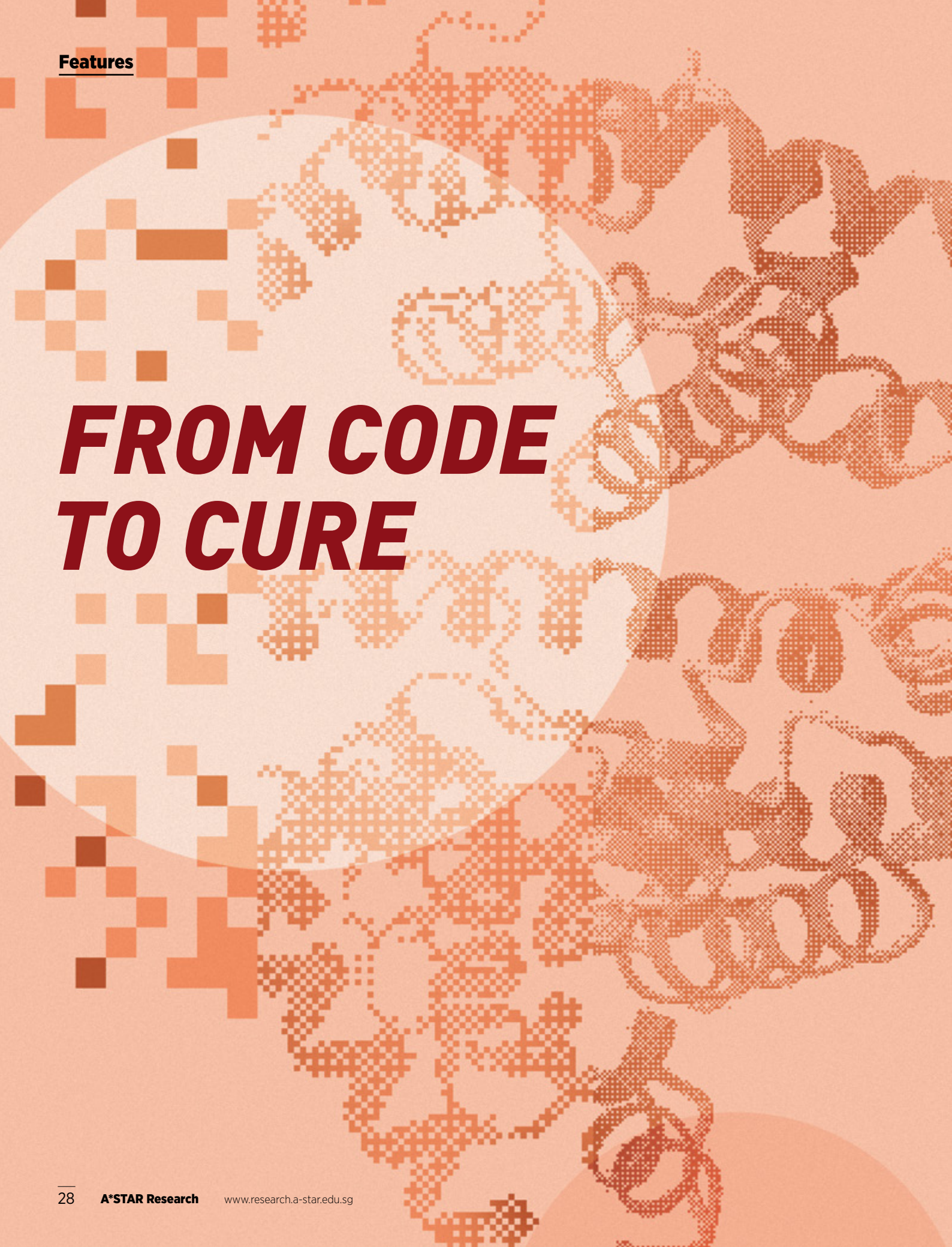
Researchers
Omar A. M. Abdelraouf and Hong Liu, A*STAR IMRE

IN BRIEF
Symmetry-breaking in a crystalline silicon metasurface enhances light confinement and conversion into deep ultraviolet (DUV) wavelengths through bound states in the continuum, enabling stronger third harmonic generation for compact DUV emitters.

1. Abdelraouf, O.A.M., Anthur, A.P., Wang, X.R., Wang, Q.J. and Liu, H. Modal phase-matched bound states in the continuum for enhancing third harmonic generation of deep ultraviolet emission. *ACS Nano* **18** (5), 4388-4397 (2024).

Photo credit: Golubovy / Shutterstock

FROM CODE TO CURE



SINGA scholar Senuri De Silva merges computational biology with translational science to unlock protein-level insights into the mechanisms of disease.

To understand biology in motion, we must look to the proteome—the full set of proteins expressed in a biological system at a given moment. DNA may be a master blueprint for life, but it's proteins that act as tireless builders, executing that blueprint through cellular machinery. Today, proteomics provides a powerful lens into real-time biological activity, revealing not just which proteins are produced under various conditions, but also how they behave, interact and transform.

At the A*STAR Institute of Molecular and Cell Biology (A*STAR IMCB), Senuri De Silva is on a mission to decode these protein behaviours across diverse disease contexts. A recipient of the Singapore International Graduate Award (SINGA), her research aims to identify early diagnostic biomarkers, monitor disease progression and uncover new therapeutic targets to ultimately guide the development of more effective treatments.

In this interview with *A*STAR Research*, we speak with De Silva on the rare intersection of computational biology and translational science which drew her to proteomics. She also reflects on a scientific career spanning one island nation to another, the impact of her work along the way, and her advice for early-career scientists.

Q: SHARE WITH US HOW YOU WENT FROM SRI LANKA TO SINGAPORE.

I grew up in Sri Lanka, a country known for its breathtaking landscapes and rich biodiversity. Frequent childhood trips to the countryside—from lush forests to vibrant coral reefs—sparked my early curiosity about nature and biology. At the same time, Sri Lanka was rapidly embracing technology; as computers became more common in schools and homes, I was excited to experiment with them. It felt like discovering a whole new world.

With a math-loving mother and an engineer father, pursuing computer science and engineering at the University of Moratuwa, Sri Lanka, felt like a natural path. A course in computational biology helped clarify my aspirations: to use computing to solve complex biological problems. Later, a final-year project combining computing and biology strengthened both my technical skills and my interest in translating science to medicine.

I wanted to go beyond computational predictions to understand how they manifest at the molecular level. As I explored relevant opportunities worldwide, Singapore stood out for its thriving scientific ecosystem, the presence of world-class research institutes such as A*STAR and the National University of Singapore, and a scholarship opportunity that would fully support my studies. The research project I joined also provides a meaningful chance to contribute to impactful biomedical research while dissecting the molecular mechanisms behind disease.

> **"I wanted to go beyond computational predictions to understand how [biological problems] manifest at the molecular level."**
>
> — Senuri De Silva, SINGA Scholar at the A*STAR Institute of Molecular and Cell Biology (A*STAR IMCB)

Q: TELL US ABOUT THE ADHD PROJECT YOU PREVIOUSLY WORKED ON.

For my final-year undergraduate project, I teamed up with two close friends to develop a support system for the early detection of attention-deficit hyperactivity disorder (ADHD), a condition we felt was underdiagnosed in our community.

Guided by our supervisor Dulani Meedeniya at the University of Moratuwa, we used a multimodal approach that combined brain scan data from functional magnetic resonance imaging (fMRI)—which tracks brain activity during task performance—and subtle eye movement patterns detected by a machine learning (ML)-based model we built. This provided objective, data-driven support for clinical diagnosis of ADHD, which is often based on subjective assessments.

In our deep learning analysis of imaging data, we found people with ADHD had reduced functional connectivity in the default mode network: a brain region linked to rest and mind-wandering states, which was consistent with findings from other emerging studies. A key novelty of our work was its ability to generate an objective score using either or both data types, allowing minimally-invasive and child-friendly ADHD screening.

We consolidated these features into a web-based tool called ADHD-Care, which we piloted in local clinical settings. A senior psychologist praised its usability and translational potential; it was later presented at international conferences and published in peer-reviewed journals, and went on to win the university's Best Final Year Project in Computer Science and Engineering award in 2020.

Q: WHAT ARE YOU WORKING ON AT A*STAR IMCB?

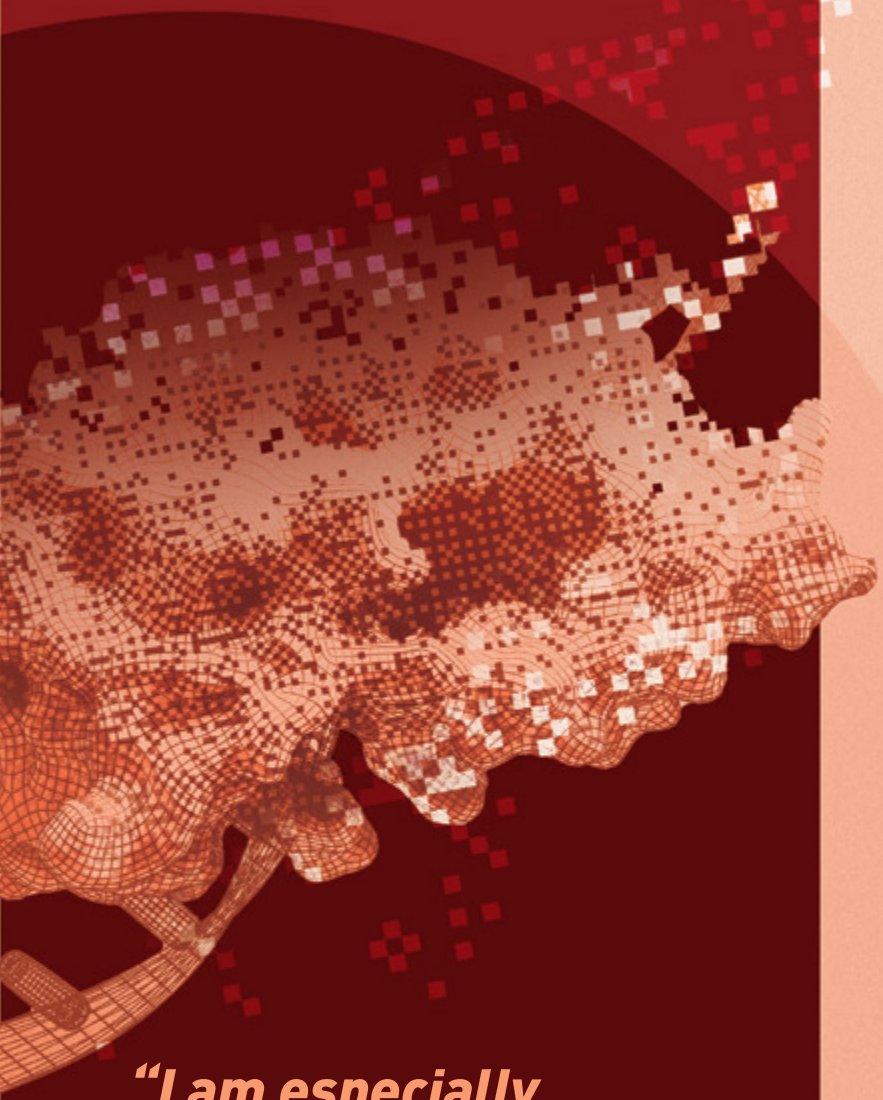
At Jayantha Gunaratne's A*STAR IMCB lab, my work primarily focuses on integrating in-house experimental data with large-scale public proteomics datasets to uncover meaningful patterns in protein expression. Specifically, I investigate the proteomic landscape of breast cancer, with a focus on aggressive and hard-to-treat subtypes.

Over the past three years, our research has led to several exciting findings. We identified a previously uncharacterised breast cancer subtype linked to poor prognosis, along with distinct molecular signatures that improve patient stratification. We've since found this subtype in other cancer types as well, which prompted us to develop novel computational methods capable of extracting robust features with high sensitivity and specificity.

This effort culminated in the creation of several open-source, user-friendly statistical and ML tools—now widely adopted both in our lab and the wider community—to support biomarker discovery from proteomics data. Crucially, these tools have also enabled the discovery of highly specific, previously unrecognised biomarkers in diseases including high-grade serous ovarian cancer, chronic kidney disease, triple-negative breast cancer and eye disease. Our discoveries have led to two patent filings; I've been privileged to present our work at multiple international conferences.

Senuri De Silva

A*STAR Institute of Molecular and Cell Biology (A*STAR IMCB)



"I am especially intrigued by the 'dark proteome': regions of the protein universe often uncharacterised or mislabelled due to algorithmic limitations."

— Senuri De Silva, SINGA Scholar at the A*STAR Institute of Molecular and Cell Biology (A*STAR IMCB)

Q: WHAT BIG QUESTIONS IN SCIENCE DO YOU HOPE TO ANSWER?

A central question in my research, especially for complex diseases like cancer and neurological disorders, is how to identify novel, non-invasive biomarkers and therapeutic targets that have remained overlooked. I see immense potential for computational methods, given their rapid advancement, to improve disease diagnosis, inform treatment strategies and advance precision medicine in scalable and accessible ways.

I am especially intrigued by the 'dark proteome': regions of the protein universe often uncharacterised or mislabelled due to algorithmic limitations. Mapping this underexplored space with improved computational techniques could be a transformative step that helps connect previously unseen biological relationships and address longstanding questions across multiple disease contexts.

Q: WHAT ADVICE DO YOU HAVE FOR YOUR PEERS AND JUNIORS IN SCIENCE?

I often reflect on a quote by physicist Richard Feynman in his Nobel Prize interview: "I have already got the prize. The prize is the pleasure of finding the thing out, the kick in the discovery, the observation that other people use it." This sums up perfectly what drives me in science: the joy of discovery and the fulfilment of contributing something meaningful, even in small ways.

My advice is to actively seek mentorship and stay open to learning at every stage. We are all lifelong learners, and the right mentors can guide, inspire and shape your scientific journey. Seminars, scientific events and informal discussions are also opportunities to engage with brilliant minds, broaden your thinking and remember the human side of science.

Above all, find joy in what you do, and pursue it with curiosity and purpose. Science can be challenging, but it is also deeply rewarding when approached with passion and openness. Stay inspired, remain humble and never stop learning. ★

DIGITAL HEALTH

Decoding emotions online for mental health needs

A big data study reveals that shifts in emotional expressions on social media can predict changes in demand for mental health care services.

Social media has long been a space to share life's highlights and everyday struggles. A post about feeling overwhelmed, a discussion thread about stress or a comment venting frustration all offer glimpses into how people are coping emotionally with difficult events.

Yet it can be challenging to assess population-wide mental health needs without timely, accessible and effective indicators, noted Yinping Yang, a Senior Principal Scientist at the A*STAR Institute of High Performance Computing (A*STAR IHPC).

The COVID-19 pandemic saw 6,600 calls to Singapore's National Care Hotline within two months, and a record high of reported suicides in 2020. These highlighted the need for proactive ways to detect emerging mental health issues, as demand for support can rapidly outpace available resources in a time of crisis.

Yang and A*STAR IHPC colleagues including Senior Scientist Chitra Panchapakesan, Senior Research Engineers Nur Atiqah Othman, Brandon Loh and Mila Zhang, and Principal Scientist Raj Kumar Gupta turned to social media to fill the information gap. Working with collaborators from Singapore's Ministry of Health (MOH), MOH Office for Healthcare Transformation (MOHT) and Institute of Mental Health (IMH), they investigated whether emotions expressed in public posts or 'tweets' on Twitter (now known as X) could be early indicators of rising public mental health needs.

"Mental health conditions often go undetected unless individuals actively seek help, which introduces significant underreporting," said Mythily Subramaniam, Assistant Chairman of IMH's Medical Board (Research) and study collaborator. "Traditional survey methods—while valuable—face logistical limits and often only capture people's feelings after a crisis unfolds."

To effectively decode emotions online for assessing mental health needs, the team used CrystalFeel, an in-house emotion analysis engine developed at A*STAR IHPC, to analyse 2.5 years of local tweets, filtering out advertisements and influencer content. CrystalFeel counted, measured and classified the intensity of four primary emotions—fear, anger, sadness and joy—based on language use across 140,598 tweets.

"These emotional indicators were then compared with two key outcome indicators of mental health needs: the number of mindline.sg website users showing signs of crisis, and IMH emergency visits," said Othman and Panchapakesan.

The team found that changes in emotional expressions in tweets significantly enhanced the predictions of mindline crisis and IMH visits. Joy intensity and anger count strongly predicted IMH visits, while sadness count, joy intensity, anger count and joy count did likewise for mindline crisis states. In contrast, situational indicators, such as COVID-19 case numbers, were less effective.

"MOHT started mindline in response to COVID-19, and the stresses on all walks of life were evident," said Robert Morris, MOHT Chief Technology Strategist. "We subsequently saw changes in psychological wellness as the pandemic waxed and waned, but this study's extra signals from social media made the effects and their nature much clearer."

"Predictive models based on such new tools could enable authorities to make more proactive, informed decisions in resource allocation, such as staffing plans in future crises," added Kelvin Bryan Tan, MOH Principal Health Economist. ★

Researchers

Yinping Yang, Nur Atiqah Othman and Chitra Panchapakesan, A*STAR IHPC

IN BRIEF

Emotion indicators from Twitter posts are found to be helpful in forecasting online mental health portal use and hospital visits, suggesting that trends in social media emotions can potentially aid in planning population-wide mental health services.

1. Othman, N.A., Panchapakesan, C., Loh, S.B., Zhang, M., Gupta, R.K., *et al.* Predicting public mental health needs in a crisis using social media indicators: a Singapore big data study. *Scientific Reports* **14**, 23222 (2024).

Photo credit: Domingo Alvarez E / Unsplash

CHEMISTRY

A sharper view of mirror molecules

Adjustments to a key chemical reaction could improve the selective production of mirror-image molecules with differing properties for better chemical design.

Chemical reactions underpin our ability to build molecules for all sorts of compounds, from life-saving drugs to advanced materials. In the S_N2 reaction, for example, a molecule called a nucleophile attacks the carbon atom of a second molecule, typically a halogen element, allowing an exchange of atoms to form a new molecule.

While the S_N2 reaction is well-established, it is only able to produce half the maximum amount of enantiomers: chemicals that have the same composition but are structurally mirror images of each other, which may mean they have completely different properties. A slightly different reaction pathway, S_N2X, gives chemists greater control over producing a desired enantiomer through a process called dynamic kinetic resolution (DKR).

"DKR works a bit like a recycling loop, where the unwanted enantiomer is continuously converted back into the starting material until the desired one is made. This method helps us produce safer, more effective medications and other important chemicals," explained Choon Wee Kee, a Scientist at the A*STAR Institute of Sustainability for Chemicals, Energy and Environment (A*STAR ISCE²).

In collaboration with Choon-Hong Tan and colleagues from Nanyang Technological University, Singapore, Kee sought to better understand the conditions for optimising S_N2X reactions to produce specific enantiomers.

Their quantitative studies revealed that the DKR process, which typically involves nucleophile-halogen interactions, can also occur when sulfur is used instead. In the S_N2Ch reaction, the nucleophile interacts with sulfur via a chalcogen bond. This forms an intermediate molecule that allows DKR to proceed, leading to the production of the desired enantiomer.

As such reactions often rely on catalysts to speed up the process, the researchers also looked into the role of these additives. They found that bromide ions, often present in common catalysts in S_N2X reactions, can step in and enable DKR. The team's findings show how the DKR-based strategy can be flexible and suited to different situations, including those where the nucleophile and halogen pair are not naturally well-matched.

"Our discoveries open up powerful new ways to control how molecules are built," Kee noted. "These insights will help chemists design cleaner, more selective and more efficient reactions, which in turn leads to safer drugs, better agricultural chemicals and more sustainable industrial processes."

Next, the team plans to explore how their findings might apply to other chemical reactions, especially those that involve more complex molecules. The surprising role of bromide in S_N2X reactions has also prompted the team to study other common additives more closely.

"We want to better understand and eventually control these subtle but powerful effects on reaction outcomes," Kee said. ★

Researcher
Choon Wee Kee, A*STAR ISCE²

IN BRIEF
An investigation into halogen-nucleophile interactions uncovers a previously unknown intermediate reaction pathway and identifies an unexpected beneficial role for a common chemical additive.

1. Kuo, L.-H., Ban, X., He, J.-H., Pham, D.N.P., Kee, C.W., *et al.* A quantitative study of the halogenophilic nucleophilic substitution (S_N2X) reaction and chalcogenophilic nucleophilic substitution (S_N2Ch) reaction. *Journal of the American Chemical Society* **146**, 34609-34616 (2024).

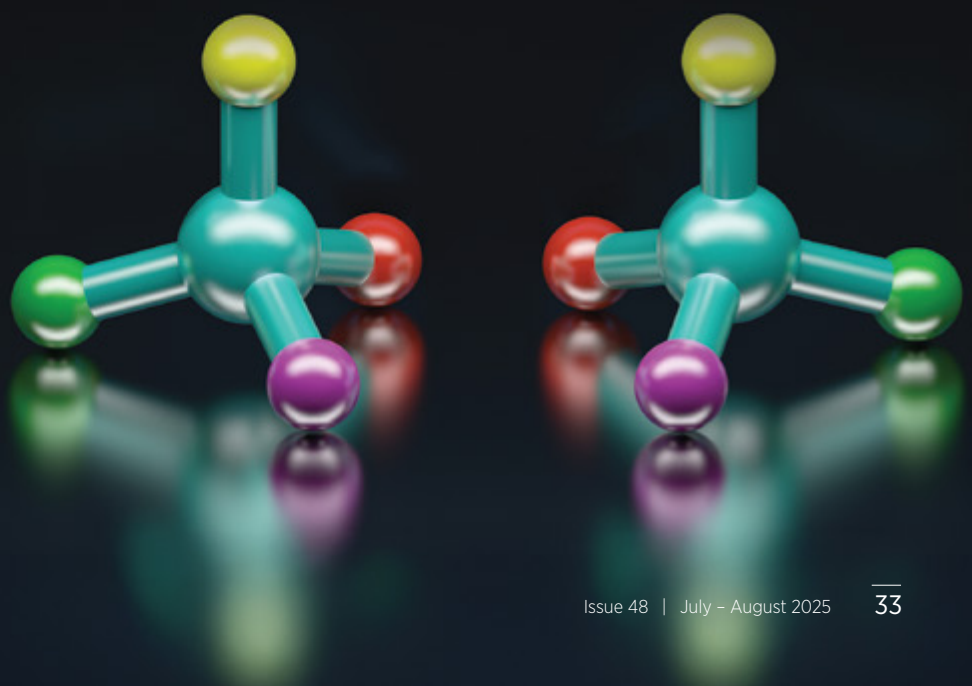


Photo credit: DariaRen / Freepik

OPTICS

X-ray detection gets a scintillating glow-up

A new molecular modification helps a class of light-emitting materials capture lost radiation energy, boosting their efficiency as X-ray detectors.

As useful as X-rays are in modern medicine, astronomy and engineering, they can also be energy-intensive tools and invisible health hazards. To detect and visualise this form of ionising radiation, some devices make use of scintillators: special materials that, when hit by high-energy X-ray particles, absorb their energy and turn it into a vibrant glow.

Scintillators often contain rare elements with unique optical properties, known as lanthanides. However, most lanthanide-based scintillators only capture a small portion of energy from the original (primary) X-rays; the rest is often lost as heat or non-radiative decay, said Xiaogang Liu, a Principal Scientist II at the A*STAR Institute of Materials Research and Engineering (A*STAR IMRE).

"Lanthanide ions have trouble harvesting the full cascade of secondary X-ray energy that's released after primary X-ray irradiation," said Liu. "This inefficiency prompted us to rethink the energy transfer pathway between X-rays and these ions."

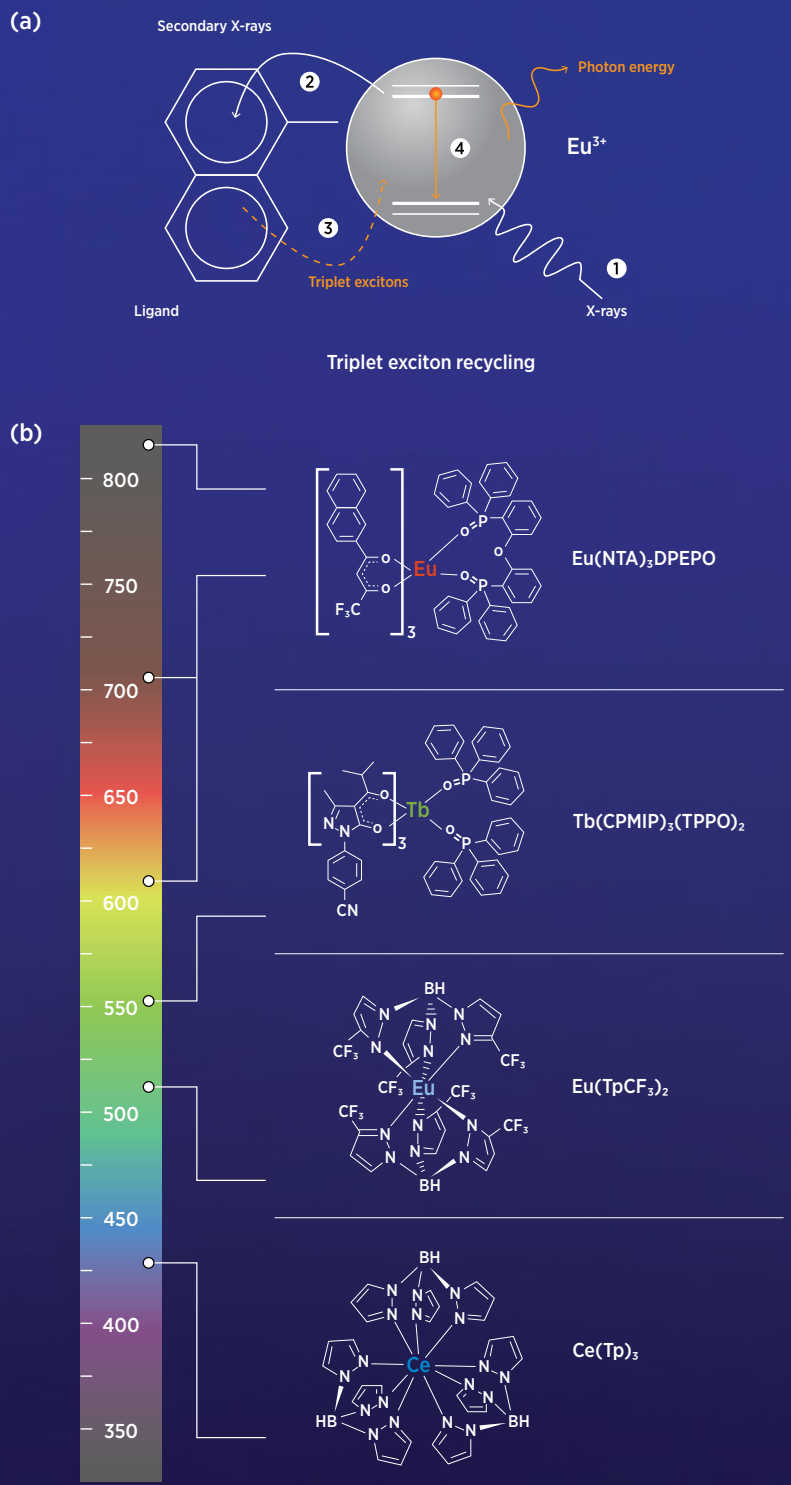
Working with researchers from Xiamen University, Fujian Normal University and other institutes in China, Liu and A*STAR IMRE colleagues sought to improve this system through a mechanic called triplet exciton recycling.

"Excitons are bound pairs of electrons and holes that are generated when a material absorbs energy, such as from X-rays," said Liu. "We theorised that triplet excitons—longer-lived than singlets, and often called 'dark' because they don't emit light efficiently on their own—could act as efficient mediators to capture and redirect secondary X-ray energy to lanthanide cores."

The team strategically designed and attached small organic molecules (ligands) to much larger scintillator molecules. Like radio antennae, these ligands were precisely tuned to capture waves of escaping

"Our goal is to enable the uniform and efficient labelling of biological tissues for high-resolution molecular imaging, with minimal background interference."

Photo credit: Denis Larkin / Shutterstock



(a) Schematic of triplet exciton recycling in a europium (Eu)-based organolanthanide molecule, showing energy transfer from an organic ligand 'antenna' to its lanthanide centre. (1) X-ray irradiation triggers a cascade of secondary X-rays, which are (2) captured by the ligand, then (3) transferred back into the molecule. Once excited by the secondary X-rays, (4) hot charge carriers in the molecule relax, leading to the formation of optical excitons. **(b)** Molecular structures of four typical organolanthanide scintillators based on cerium (Ce), Eu and terbium (Tb), showing full-colour radioluminescence from ultraviolet to infrared light wavelengths. (Adapted from Xu *et al.* 2025)

secondary X-ray energy, convert them into dark excitons, then transfer the excitons to the scintillators' lanthanide cores.

Compared to existing inorganic and organic scintillators, the team's system proved to be several orders more efficient at emitting visible light. The team was also surprised by a stark performance difference when they tested their ligands with different lanthanide systems.

"We found f–f lanthanide complexes outdid d–f systems in efficiency despite the latter's theoretically higher yields," said Liu. "Our studies showed that f–f systems rely more on triplet exciton recycling, while d–f systems rely on direct energy capture by the luminescent centre."

Liu added that these results highlight how strong light emissions don't always translate to efficient scintillation, with exciton recycling instead playing a more decisive role.

Looking ahead, Liu noted that the team's fully molecular-level system design could be a part of next-generation scintillators, optoelectronics and radiation detection platforms. The team hopes that their work may also enhance biomedical imaging probes and phototherapeutic systems.

"We're improving our scintillator materials to be more compatible with in-body environments," said Liu. "Our goal is to enable the uniform and efficient labelling of biological tissues for high-resolution molecular imaging, with minimal background interference." ★

Researcher
Xiaogang Liu, A*STAR IMRE

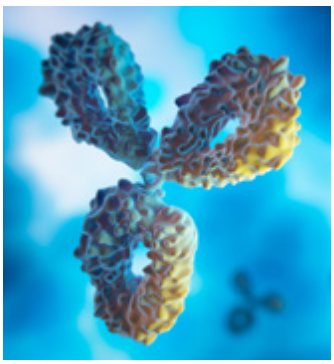
IN BRIEF
A new organic ligand design enables triplet exciton recycling of secondary X-rays by lanthanide-based scintillators, raising their light-emitting efficiency and performance under primary X-ray irradiation.

1. Xu, J., Luo, R., Luo, Z., Xu, J., Mu, Z., *et al.* Ultrabright molecular scintillators enabled by lanthanide-assisted near-unity triplet exciton recycling. *Nature Photonics* **19**, 71-78 (2025).

Next Issue

SNEAK PEEK

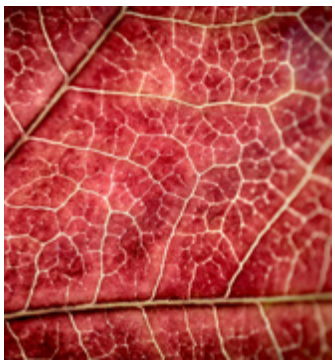
A brief look at upcoming research highlights in the next issue of A*STAR Research



BIOENGINEERING

UNRAVELING STICKY SITUATIONS WITH ANTIBODIES

New insights on heat and acidity's role in monoclonal antibody clumping pave the way for improved biotherapeutics production methods.



FOOD SCIENCE

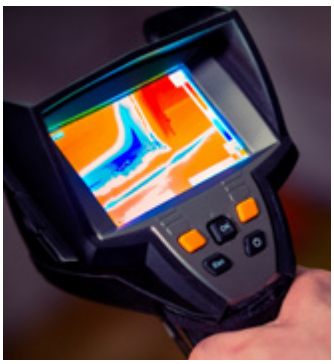
DIGESTING THE DIFFERENCE WITH PLANTS AND ANIMALS

A study of animal and plant-based meats uncovers key nutritional differences for future food innovations.

SENSORS

SEA-ING INTO MACHINES' FUTURE LIFE

A new computational framework aligns data from multiple sensors across time, boosting the accuracy of machine failure predictions.



OPTICS

SEEING THE INVISIBLE

Devices that transform near-infrared light to visible light can open new possibilities in medical imaging and security systems.

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