Making light work of measurement [p14]

Putting the brakes on accelerated aging [p26]
Small and powerful X-ray sources from graphene, plasmons and electrons [p38]
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Welcome to the second edition of the new format of A*STAR Research. This issue, covering highlights published between January and March 2016, is packed with exciting new research and we are thrilled to present a few sneak peeks in this editorial.

On page 23, A*STAR researchers from the Singapore Institute of Clinical Sciences (SICS) provide an insight on a problem that irks — literally — babies and their parents: eczema, or atopic dermatitis. New research shows that the disease has different and unexpected risk factors depending on the age of onset.

Lungs constantly move to keep us breathing, so they are particularly hard to image accurately — Soo Kng Teo and colleagues from the Institute of High Performance Computing (IHPC) have found a way to solve this technical challenge and produce high-resolution images of the lungs. This discovery has a strong clinical potential and is a brilliant example of engineering techniques applied to a health problem (see page 33). For a more everyday application of engineering research, Jinghua Teng and colleagues from the Institute of Materials Research and Engineering (IMRE) and the Data Storage Institute (DSI), came up with a photon sieve that can produce improved anti counterfeiting holograms, such as those used in banknotes (page 36).

Finally, to paraphrase a famous quote, Giulia Rancati and colleagues from the Institute of Medical Biology (IMB) discovered that some essential genes are more essential than others. More precisely, they found that, given enough time, yeast cells can undergo certain evolutionary processes and adapt to the absence of genes that were previously considered essential. Such genes were termed ‘evolvable essential’. This discovery has wide implications in drug discovery and development and also opens new perspectives on how evolution works (page 48).

There is all this and way more in the issue of A*STAR Research you are about to read, we hope you will enjoy it!
A*STAR researchers have developed the first selective probe for a marker of the stage before the brain plaques which characterize Alzheimer's disease are formed.

Alzheimer’s, which affects approximately 35 million people worldwide, is a neurodegenerative disease in which aggregates or plaques are formed by a protein called amyloid-beta. An A*STAR team has developed the first selective probe for amyloid-beta oligomers, the intermediate stage before plaque formation, and a promising AD biomarker.

“Amyloid plaques are the hallmarks of Alzheimer’s disease,” explains Chang Young-Tae from the A*STAR Singapore Bioimaging Consortium, “however there were doubts that they were a good biomarker for diagnosis,” he says. “You can’t tell much about the real situation of the disease — so people looked for other markers, such as the oligomer.” Oligomers are now generally believed to be the species responsible for Alzheimer’s disease pathogenesis.

An oligomer is an intermediate formed during the aggregation of amyloid-beta monomers into long fibrils and eventually plaques. “An oligomer is really a dynamic state,” explains Chang, “it can go back to a monomer state or can move to the aggregate state, that’s the real difficulty of studying oligomers”.

An A*STAR team has developed a fluorescence library (DOFL) — an in-house synthesized collection of 10,000 fluorescent molecules — to find a probe that would satisfy these criteria.

After testing 3,500 DOFL compounds, they found BoDipy-Oligomer, known as ‘BD-Oligo’. This showed a stronger response to amyloid-beta oligomers, with the signal decreasing once a
polymer started to form, which demonstrated to Chang and the team that they had found the first ever selective probe for oligomers.

With this fluorescent probe, the team was able to monitor oligomers in real time during the formation of fibrils. Additionally, in vivo tests on live mice revealed that BD-Oligo was able to cross the blood-brain barrier without any apparent toxicity.

The team patented the probe and is now focused on further developing it for in vivo or clinical applications. Chang notes there is the possibility of converting the molecule to a positron emission tomography (PET) probe which would be of greater clinical use. The development of a probe that preferentially detects amyloid-beta oligomers, rather than monomers or polymers, is promising for diagnostics aimed at detecting Alzheimer’s disease in its early stages. Such a tool would improve the ability of clinicians to choose the best treatment or palliative care for patients.


Chemistry:

LADDER POLYMERS STAND APART

MAKING MICROPOROUS, NON-STICK POLYMERS SOLUBLE IN LIQUIDS OPENS OPPORTUNITIES FOR TARGETED CLEAN-UP OF MOLECULAR IMPURITIES

Polymer chemists at A*STAR have synthesized materials with intrinsic, microscale porosity that are well suited for reusable gas and liquid separations because of their robust, ladder-like frameworks.

Polymers tend to pack tightly together in the solid state, easily filling any voids with their flexible chain structure. Recently, however, polymers of intrinsic microporosity (PIMs) have emerged that use rigid, fused organic ring structures to open up tiny voids in the plastic material. Researchers are considering PIMs as replacements for the activated carbons and zeolites used during industrial gas adsorption processes because they can be chemically tuned to specific contaminants, and do not require thermal regeneration.

Chemists can synthesize PIMs through a process, known as nucleophilic substitution, which enables covalent bonds to simultaneously form between two aromatic ring compounds. This type of polymerization tends to generate ‘ladder’ structures: two long parallel chains intermittently bridged by chemical ‘rungs’. While ladder polymers have an abundance of micropores for gas adsorption, the extra stiffness from the rigid ring components makes them notoriously difficult to dissolve for solution processing.

Ranganathan Krishnan and Anbanandam Parthiban from the A*STAR Institute of Chemical and Engineering Sciences tackled this problem by turning to a non-aromatic ring compound called octafluorocyclopentene (OFCP) that contains numerous fluorine atoms. Fluorine units can impart special characteristics to ladder polymers such as Teflon-like chemical resistance, improved solubility, and high thermal stability, notes Krishnan. As well, the team anticipated that the more flexible OFCP ring could lend sufficient ‘kinks’ to the polymer backbone to produce an organosoluble PIM.

Krishnan and Parthiban reacted OFCP with rigid benzene-type rings to synthesize fluorinated ladder polymers. Previous studies
Photonics: EXCITING SILICON NANOPARTICLES

SEPARATING THE ELECTRIC AND MAGNETIC COMPONENTS OF LIGHT SCATTERED BY SILICON NANOPARTICLES ENABLES MORE PRECISE CONTROL OF LIGHT

A method to characterize and design the optical properties of silicon nanoparticles for their use on silicon chips has been developed by A*STAR researchers in collaboration with colleagues from Russia, Israel and Australia\(^1\). The team were able to separate the electric and magnetic components of light resonances of silicon nanoparticles, promising new functionalities for optical components on silicon chips.

Thanks to their small size and shape, silicon nanoparticles have very different optical properties to those of larger slabs of the material, which allow them to be used as optical antennas to guide and direct light. “If you have silicon-compatible processes and computer chip nanolithography you can easily integrate good ideas into real devices using these silicon nanoparticles,” explains Boris Luk’yanchuk from the research team, pointing out silicon’s advantages over other optical materials.

The electric and magnetic components of a beam can be difficult to separate in the light scattered from the silicon nanoparticles, which prevents a full understanding of the nanoparticle properties. The experimental method developed by the team resolves this by combining different microscopy measurement techniques.

In the first step, polarized light of different wavelengths scattered by the nanoparticles when excited in the plane of the surface is studied using a regular microscope. In a second step, polarized light is used to excite the nanoparticles from underneath the surface, and the scattered light is collected by a small tip of an optical fiber. The combination of both experiments, where the silicon particles are excited at different angles, allows the electric and magnetic components of the scattered light beam to be determined.

The experimental approach promises the development of new applications, explains Luk’yanchuk. “The co-existence of strong electric and magnetic resonances, their interference and the resonant enhancement of the magnetic field in silicon nanoparticles

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brings new physics and entirely novel functionalities to the simple geometries of the nanoparticles."

Thanks to their ability to scatter light locally, the nanoparticles hold promise for the manipulation of light at length scales considerably smaller than the wavelength of light. This suggests that it may soon be possible to miniaturize silicon optical components as well as silicon electronic components. The ability to tune the electric and magnetic resonances separately permits a precise control over directivity and efficiency of the light scattering from the nanostructures.


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Immunology:

MONOCYTES SWITCH ROLES DURING SEPSIS

MONOCYTES ARE ‘REPROGRAMMED’ TO BE IMMUNOSUPPRESSIVE AS SEPSIS PROGRESSES

During the course of the deadly disease sepsis, monocytes — a type of white blood cell that helps the body stave off bacteria and viruses — undergo a profound change, A*STAR researchers show. This discovery will help scientists find effective strategies for treating the disease.

Sepsis is the one of the biggest killers of patients in intensive care units (ICUs). In the United States alone, it is responsible for more than 250,000 deaths each year, and the cost of treating it exceeded US$20 billion in 2011. Yet progress in fighting the disease has been painfully slow, with many seemingly promising therapies leading to disappointment.

One thing that makes sepsis so difficult to control is its ability to morph between two diametrically opposite responses: it initially stimulates the immune system, which it later suppresses. The initial overt inflammatory phase can generally be treated by antibiotics, but the subsequent immunosuppressive phase often proves fatal, as patients with lowered immunity succumb to secondary infections.

“Very often ICU patients get reinfected with hospital-borne bugs and can’t survive because their immunity has been compromised” explains Subhra Biswas of the A*STAR Singapore Immunology Network. “Epidemiological studies indicate this as one of the the main causes of mortality.”

Biswas and his co-workers have performed a comprehensive study that explored the transcriptomic, functional and mechanistic aspects of the role of monocytes — a neglected area of human sepsis.

By comparing monocytes from patients during sepsis with those after they had recovered, the team discovered that blood monocytes are ‘reprogrammed’ during the course of sepsis. Specifically, they change from being inflammatory to immunosuppressive, while still retaining their tissue remodeling and antimicrobial abilities. The researchers also pinpointed the culprit for this change — a transcription factor known as hypoxia-inducible factor-1α (HIF1α).

The findings have important implications for treatment strategies. “We have to target sepsis according to the phase the patients are in,” says Biswas. “If they are in the overt inflammatory phase and you give an anti inflammatory drug, it should reduce inflammation. But if they are in the immunosuppressive phase and you give anti inflammatory drugs, it will tremendously increase the risk of secondary infection. Instead you have to boost the immune system.”

Existing drugs might be effective against sepsis. “Interestingly, there are drugs targeting HIF1α in clinical trials for cancer,” says Biswas. “So there is the option of re-purposing drugs that target this pathway.”

The team is currently developing interventions that can be combined with emerging immunotherapies.

A new technique for pinpointing the exact DNA regions that impact gene regulation lays the groundwork for identifying new drug targets and for developing diagnostics to predict disease risk, A*STAR scientists report.

“Once you know the actual causal variant, it’s easy to link it to a gene. That’s a key missing link in current drug target identification,” says Shyam Prabhakar, from the Genome Institute of Singapore, who led the work.

In trying to find the genetic underpinnings of disease, researchers often scan hundreds of thousands of markers across the genomes of thousands of people in search of specific variations associated with a particular health problem. However, the genetic associations they find are rarely the mutations that actually spur disease. The identified variants are usually only linked to the true causative mutations in DNA, and existing methods have struggled to identify those genetic drivers of disease, especially because the mutations often fall in regulatory regions, not in coding genes themselves.

Prabhakar and his colleagues decided to develop a new approach focusing on the parts of the genome that are associated with chemical markers known as acetyl groups. These chemical tags affect how tightly DNA is wound around its packing proteins. Looser chromosomes mean more gene expression. So the level of acetylation...
acts as an indicator or regulatory signal to indicate the activity of nearby genes.

The researchers used a method known as ChIP-seq in a novel fashion to identify DNA mutations at all acetylated regions in the genome — what Prabhakar calls ‘regulome sequencing’. He and his team created a statistical test to correlate differences in acetylation levels (and, by extension, gene regulation) with single-letter differences in the genome. They called it the genotype-independent signal correlation and imbalance (G-SCI) test.

By analyzing data from 57 cell lines, all derived from human B-cells, a type of cell involved in immunity, the researchers discovered dozens of DNA variants linked to mechanisms of autoimmune disease. “The beauty of our method is it does everything in one shot,” says Prabhakar. “It’s a really cheap and easy method. You don’t need any prior information.”

Prabhakar’s group is now applying the same method, and the G-SCI test, to post-mortem brain tissue in an effort to understand diseases such as autism and schizophrenia. The researchers are also looking at various kinds of blood cells to probe the genetics of susceptibility to infectious disease.


Diabetes:

INSULIN ON DEMAND

A BIOCHEMICAL EXPLANATION FOR THE SUCCESS OF BILLION-DOLLAR DIABETES DRUGS

The protein targets of a class of ‘blockbuster’ diabetes drugs have been identified by A*STAR researchers and may help explain varying type-2 patient responses to the drugs.

Diabetes affects more than 400 million people worldwide — 90 per cent of whom have developed type 2 diabetes — and the number is expected to surpass 600 million by 2040.

A study set out to determine why drugs that stimulate postprandial insulin secretion in people with type 2 diabetes have varying efficacy. “Understanding the mechanism of action of these drugs could help to explain why they are not as effective for particular subpopulations of diabetic patients,” explains Weiping Han from the A*STAR Singapore Bioimaging Consortium, who led the study, in collaboration with researchers at Stanford University.

A popular range of drugs for type 2 diabetes stimulates insulin secretion in a glucose-dependent manner.

Normally after food intake, elevated blood glucose levels trigger an increase in calcium in pancreatic beta cells and signal the release of insulin. Insulin is an essential hormone for clearing the blood of excess glucose that cells use as energy.

In patients with type 2 diabetes, however, this glucose-to-insulin relay does not perform correctly. Drugs containing metabolic hormones, such as glucagon-like peptide-1 (GLP-1), have proven effective at boosting insulin secretion and restoring glucose homeostasis in these patients. Han and his colleagues sought the biological reason for the drugs’ success.

Their previous study found that the membrane protein synaptotagmin-7 acts as a calcium sensor regulating insulin secretion in pancreatic beta cells1.

In their most recent investigation, the researchers discovered that the same protein is a key target of the GLP-1 class of drugs. Specifically, they found that in the presence of glucose and calcium, GLP-1 triggers the phosphorylation of synapototagmin-7, which enhances insulin release2. “This glucose dependence is ideal in preventing the risk of hypoglycemia,” says Han. “When glucose levels return to normal, no matter how you
A compact optical device that can rapidly and sensitively detect biomarkers in urine has been developed by A*STAR researchers. It has promise for developing simple point-of-care diagnosis of cancer and other diseases.

MicroRNAs are a newly discovered class of short (about 19 to 24 nucleotides in length) fragments of noncoding RNAs that are useful biomarkers for diagnosing various diseases, including cardiac disease and some cancers. Since they are surprisingly well preserved in fluids such as urine and blood, their detection is well suited to a rapid, point-of-care method.

modify the protein, you won’t stimulate insulin secretion.”

Han then used mass spectrometry chemical analysis to identify where on the protein phosphorylation occurs. Synaptotagmin-7 is made up of 403 amino acids with two large, distinct structural units responsible for binding to calcium. “We expected the phosphorylation to occur at one of these calcium binding sites, but it turned out to be at the linker region, serine-103,” says Han. “This leaves room for the phosphorylation site to interact with other proteins.” He is now trying to identify these interacting proteins.

The findings could also help explain other physiological functions where synaptotagmin proteins are at play, such as in the enhanced release of neurotransmitters from neurons during learning, memory and other higher-order brain activities, says Han.

Biosensors:

A LIGHT DIAGNOSIS

ON-THE-SPOT DIAGNOSIS OF CERTAIN CANCERS AND OTHER DISEASES IS CLOSER TO BECOMING A REALITY THANKS TO A SENSITIVE BIOSENSOR

Mikiyoung Park at the A*STAR Institute of Microelectronics and her co-workers have devised a silicon photonic biosensor that can detect tiny changes in the phase of a light beam, caused by hybridization between an immobilized DNA probe and target microRNAs in a sample.

A laser beam travels through a waveguide, which splits into two arms: a sensing arm in which the light interacts with the sample and a reference arm. The two light beams then rejoin each other. Binding between the DNA probe and the target microRNA alters the phase of the light traveling in the sensing arm, whereas the phase in the reference arm remains unchanged. The amount of target microRNA in the sample can be determined by monitoring the variation in the intensity of the output beam.

The device has many practical advantages, Park explains. “Existing methods to detect microRNAs are time consuming and require cumbersome machines, which limit their usefulness in clinical settings.”

The device is also highly sensitive and thus does not require labeling or amplification; it can deliver results within 15 minutes, eliminating the need for patients to return for their results; and it can potentially detect up to 16 targets in a single test.


To demonstrate the system Park and her team used it to detect two types of microRNAs in urine samples from three patients with late-stage bladder cancer; the tests involved a single reaction and took 15 minutes. The microRNA levels of the patients differed markedly from those of two healthy subjects.

The researchers are excited about the device’s potential. “The system can be expanded to detect a number of microRNAs of different species and should be useful for a variety of point-of-care clinical applications,” says Park. The team is currently working to boost the sensitivity of the device.


Antibodies:

A STICKY SITUATION

EXAMINING THE INTERMEDIATE STAGES OF ANTIBODY PURIFICATION PROVIDES INSIGHT INTO THE MANUFACTURE OF SAFER BIOPHARMACEUTICALS AT LOWER COST

Monoclonal antibodies are an important new class of drugs to treat cancer, heart disease and a range of other conditions. However, their production in mammalian cells introduces a large number of contaminants that are difficult to remove during purification. Now, by looking at how antibodies change chemically during purification, A*STAR scientists have identified a better way to eliminate contaminants

Protein A affinity chromatography is a technique that has dominated the field of antibody purification for the past 20 years, thanks to its remarkable ability to selectively bind to Immunoglobulin G (IgG). However, the purified antibody always contains more contaminants than it should. Previous studies compared IgG characteristics before and after protein A, and did not reveal why these contaminants persisted, but the technique still worked so well that there seemed little need to dig deeper.

Pete Gagnon and his team from the A*STAR Bioprocessing Technology Institute thought there was more to the question and decided to look more closely at what was happening to the antibody during the purification process, especially during elution when IgG is separated from protein A. Their findings came as a surprise.

“The antibodies became chemically ‘sticky’ under these conditions”, says Gagnon, “worse than that — they stuck to contaminants, and carried them along with them.”

Nothing could be done about the chemical conditions that cause the IgG to become sticky. But the team found a clever way out of this sticky situation — they discovered a class of contaminants called chromatin heteroaggregates that adhere to protein A even more strongly than IgG. “Chromatin is the operative element in a covert system for smuggling contaminants through purification methods — remove the chromatin in advance and there is nothing for the IgG to stick to,” says Gagnon.

By removing chromatin in advance, the team was able to achieve better purification with just protein A than most licensed manufacturing procedures can achieve with protein A and two additional steps. Gagnon cautions that this does not mean that purification of therapeutic antibodies can done with just one step, but it does mean that higher purity IgG can be achieved faster with less work and fewer materials.

Gagnon concludes: “Big improvements in process economics often demand compromises in performance, but here we have a situation where both economics and purification performance are improved. It’s all upside.”

Metabolism:

MATERNAL HEALTH LINKED TO CHILD’S RISK OF OBESITY

THE CULTURAL DIVERSITY OF SINGAPORE OFFERS INSIGHTS INTO ASSOCIATIONS BETWEEN BODY STATUS OF MOTHERS AND INFANTS

Women’s fat levels before and during pregnancy are linked to those of their infants in ways that can vary depending on a mother’s ethnicity, a Singapore-based study shows, and highlights the need for nuanced health advice.

In a rare exploration of these issues in Asian populations, this research focused on ethnic maternal differences as well as on general trends\(^1\). These findings form one part of a large-scale and ongoing study of mothers and infants before and after birth — called ‘Growing up in Singapore Towards Healthy Outcomes (GUSTO)’ — from a collaboration by Singapore’s National University Health System (NUHS), KK Women’s and Children’s Hospital (KKH), and the A*STAR Singapore Institute for Clinical Sciences (SICS).

“The implications are that different advice and intervention may be appropriate for different Asian ethnic groups,” explains Yung Seng Lee of A*STAR.

With obesity a major public health problem, Lee explains that the GUSTO study group is trying to understand the ways in which a mother’s nutrition and lifestyle might determine if her child is at increased risk of obesity.

A particular advantage of the GUSTO study is that it is able to compare participants from the three major ethnic groups of Singapore — Chinese, Malay and Indian, explains Lee. These three groups have different rates of obesity, diabetes and cardiovascular disease. “We want to identify early life factors that account for these differences, and use our findings to inform clinical practice,” says Lee.

One example of ethnic differences is the link between a mother’s weight gain during pregnancy and an infant’s post-birth weight and length found in Chinese and Indian groups, but not in Malays. Also interesting is that a mother’s pregnancy weight gain and infant weight and fat level was independent of pre-pregnancy Body Mass Index (BMI). In other words the two factors in the mother — weight gain during pregnancy and BMI before pregnancy — need to be considered as distinct and independent contributors to possible obesity in their children.

Factors such as BMI before pregnancy and weight gain during pregnancy can be modified by nutritional and lifestyle changes and so
are useful for maternal health guidance. The discovery of ethnicity differences, however, emphasizes the need to explore these factors in more detail before assuming the same guidance will be appropriate for all groups.

“We now plan to investigate ethnic differences in more detail, and also look for underlying genetic and metabolic reasons behind them,” says Xinyi (Cindy) Lin, also of the SICS team.

It is now possible to grow large-area ultrathin sheets of molybdenum disulfide, a two-dimensional (2D) material promising for the next generation of electronic and optoelectronic devices, thanks to a new twist on a standard method developed by A*STAR scientists.

Molybdenum disulfide, one of a family of so-called semiconducting transitional metal dichalcogenides (TMDCs), has attracted considerable attention as a 2D material, thanks to its remarkable electronic and optoelectronic properties. But preparing large-area atomically thin layers of TMDCs is notoriously difficult, with conventional growth methods such as mechanical exfoliation and physical vapor deposition yielding single-layer films only a few micrometers in size.

To overcome the limitation of such a useful material, Dongzhi Chi and Hongfei Liu of the A*STAR Institute of Materials Research and Engineering searched for a way to modify a standard fabrication technique, to grow high-quality, millimeter-sized single-layer molybdenum disulfide nanosheets.

“The growth mechanism of 2D films is still not fully understood and is a major hurdle for their large-scale adoption in electronic applications,” says Chi. “Growing large-area 2D materials allows for large scale fabrication of integrated circuits using conventional semiconductor processing methods.”

By modifying chemical vapor deposition — a manufacturing tool used in everything from sunglasses to potato chip bags and fundamental to the production of much of today’s electronic devices — they were able to grow single-layer molybdenum disulfide nanosheets of greatly increased grain size.

“Smaller grain sizes result in structural defects, so devices fabricated with such materials perform poorly,” explains Chi. “Larger grain sized 2D TMDCs, however, minimize these defects and lead to improved performance.”

In a pressurized reaction chamber, powdered molybdenum trioxide and sulfur were vaporized. To create larger grain sizes, the researchers increased the temperature of the reaction chamber and used a silicon or quartz shadow mask, held over a sapphire substrate, to indirectly supply the molybdenum trioxide and sulfur vapors to the advancing molybdenum disulfide growth front on the substrate.

Ripples were introduced into the single-layer molybdenum disulfide nanosheets by illuminating them with a laser. These ripple structures are predicted to have a significant effect on the electronic, mechanical, and transport properties of single-layer molybdenum disulfide.

To compare the single-layer molybdenum disulfide nanosheets and their laser-induced ripple structures, the researchers used a number of characterization tools, including Raman scattering and photoluminescence spectroscopy as well as atomic-force microscopy.

“Studying these materials may lead to the discovery of new physics and also aid fabrication of electronic and optoelectronic devices with novel functions and improved performances,” says Chi.

Making light work of measurement

LIGHT-BASED TECHNOLOGIES ARE FINDING APPLICATIONS IN A DIVERSE RANGE OF FIELDS, AND MEASUREMENT IS AMONG THE MOST FUNDAMENTALLY IMPORTANT

Metrology — the science of measurement — plays an essential role in advancing science and technology. Precise definitions and measurements underpin almost all scientific and technological developments, from the astrophysical arena, such as sending a probe to Mars, through to the subatomic level, such as the discovery of the Higgs boson. What’s more, metrology has practical applications that directly affect our everyday lives, such as determining the lifetime of lighting sources and color matching paints.

LIGHT-BASED MEASUREMENTS

In addition to their work in electrical and mechanical metrology, A*STAR’s National Metrology Centre (NMC) metrologists conduct research and provide industrial services in an emerging field of metrology based on light, known appropriately enough, as optical metrology. Xuebo Huang, principal metrologist and assistant head of the Optical Metrology Cluster at NMC, has been working in optical metrology for 20 years. “Optics is a fascinating field of physics that has become very important due to various new applications,” he says.

Now, more than ever, visible light with its tiny wavelength, rapid oscillation and high manipulability is a vital component in a metrologist’s toolbox. It can be used both as a ruler, to measure distance, and as a clock to measure time. Some optical clocks are so stable and precise that it would take more than 15 billion years for their time to be out by one second.

In addition to using light to measure physical quantities such as distance and time, optical metrologists also measure the physical parameters associated with light itself. Examples include accurately determining ultraviolet radiation levels, spectra of light sources and evaluating the power of a laser beam. Huang notes that these types of optical measurements are critical for the design and manufacture of reliable and safe products in vital growth industries such as medical technology, energy and aerospace.

ADVANCING METROLOGY RESEARCH

One of NMC’s key responsibilities is to conduct research and development into the science of measurement to facilitate innovation in existing and emerging technologies. “One of our roles is to advance measurement science, and thus we conduct research to develop measurement technology and solutions to meet the emerging needs of industry,” Huang explains.

Huang’s research projects at NMC include establishing standards for laser power measurements, realizing a spectral responsivity scale, developing facilities for calibrating fiber optical measurement instruments and calibrating broadband ultraviolet radiometers, to name a few. He has also participated in several international comparisons and coordinated the Asia Pacific Metrology Programme comparison on irradiance responsivity of ultraviolet radiation detectors, the first such comparison in the world involving seven national metrology institutes.

Solar cell technology is advancing rapidly and many competing technologies are emerging. To objectively evaluate the efficiency and performance of solar cell devices, NMC has developed primary standards and...
Another active research area is the development of measurement technology for characterizing solid-state lighting sources such as light-emitting diodes. Solid-state lighting is predicted to replace conventional light bulbs and fluorescent lighting in the near future, and is increasingly being used in many applications including medical diagnostic devices and display monitors. Standards and methods for measuring their performance, quality and safety are hence important. Researchers at NMC has developed spectral radiance measurement technology, standards and calibration facilities, which are critical for accurately measuring luminance (brightness) and color, as well as assessing the photobiological safety of light sources.

Huang finds this aspect of his work highly stimulating. “Optical metrology is finding more applications in many industries, making it both exciting and challenging to undertake research in this area,” he enthuses.

ENSURING SINGAPOREAN INDUSTRY MEASURES UP

NMC is responsible for establishing and maintaining the national measurement standards of Singapore. Its mission is to enhance measurement quality in the industry by providing a world-recognized measurement infrastructure. Hence, NMC’s metrologists also deliver training courses, provide consultancy services and conduct calibration and measurement services, to constantly enhance the measurement quality.

Describing a typical day, Huang says he usually spends mornings talking with customers or visiting companies to gain a better understanding of their requirements and to support their measurement needs. “In the afternoons, I will perform measurements for maintaining optical standards or international comparison to ensure that our optical measurement standards and capabilities are comparable and equivalent to other national metrology institutes.” In addition, he provides regular training and consultancy on optical metrology with the aim of helping our industry partners to improve their skills in measurement science, calibration and uncertainty evaluation.

Looking to the future, Huang foresees that light-based technologies will be increasingly adopted in the medical industry. “With more applications of light sources in medical diagnosis and treatment, it is becoming more and more important to establish the safety of medical applications; this is an area in which optical metrology will play a critical role.”

The research and development conducted at NMC will ensure that Singapore maintains a strong international presence in this vital field, while the services and training it provides to industry are critical for ensuring that Singaporean industry remains competitive. Light-based measurement has never been so important.
A*STAR and the Nanyang Academy of Fine Arts created 17 science-inspired exhibits including paintings, digital art, photography, sculpture and more to celebrate Singapore’s Golden Jubilee. These artworks were exhibited at the ArtScience Museum during a two-day event called “Innovation Reconstructed”, giving the public an opportunity to meet the scientists and artists behind the work and participate in a series of interactive workshops and ‘pop-up’ talks by A*STAR scientists.
Electromagnetic reverberation chambers are used to test the safety of electrical devices and identify potential problems, such as interference with other devices, before they are released on to the market. Now, Singaporean researchers have developed a new algorithm that can analyze electromagnetic reverberation chambers data more than ten times faster than the best state-of-the-art commercial software.

Reverberation is fundamental to music recording. Sound engineers use acoustic reverberation chambers to produce a random sound field in which all frequencies echo with similar strength from the walls. Electromagnetic reverberation chambers do the same thing with electromagnetic radiation, using reflective surfaces to achieve high field strengths from a moderate input power.

The introduction of every new electrical device poses a danger of interference with other gadgets to produce intense fields that could start fires or damage health. This prompted Huapeng Zhao, at the A*STAR Institute of High Performance Computing and Zhongxiang Shen at Nanyang Technological University, to find a way to improve analysis of important ‘electromagnetic compatibility’ information from electromagnetic reverberation chambers.
Stem cells are an effective tool for repairing or replacing damaged or diseased tissues, but only if they can be reliably developed from their flexible ‘pluripotent’ state into a mature ‘differentiated’ state. A*STAR researchers have learned how to control the state of stem cells by altering the physical environment in which they are cultured.

“An electromagnetic reverberation chamber consists of a large cavity with one or two stirrers inside,” says Zhao. “Rotating the stirrers creates a random environment in the cavity, which is useful for conducting statistical electromagnetic measurements.”

Modeling electromagnetic fields in such a complex environment is not easy, especially when a wide band of radiation frequencies is used. Zhao and Shen exploited the regular rectangular shape of the cavity to simplify the simulation geometry, and considered the stirrers as separate components affecting the field. The key to their success was using ‘adaptive frequency sampling’ (AFS) to identify peaks in electromagnetic fields that could be associated with interference. AFS responds to findings while analyzing the frequency bands, rather than uniformly sampling every frequency band.

“Uniform frequency sampling requires a large number of samples in order to accurately capture the sharp peaks in wide-band reverberation chamber simulations,” explains Zhao. “On the other hand, AFS adaptively chooses the location of samples so that the sharp peaks can be captured by using only a small number of samples. The simulation time is therefore reduced.”

Stem cells:

PATTERNING PLURIPOTENCY

INSIGHTS INTO HOW EXTERNAL MECHANICAL FORCES AFFECT STEM CELL BEHAVIOR COULD ADVANCE REGENERATIVE MEDICINE EFFORTS

Stem cells are an effective tool for repairing or replacing damaged or diseased tissues, but only if they can be reliably developed from their flexible ‘pluripotent’ state into a mature ‘differentiated’ state. A*STAR researchers have learned how to control the state of stem cells by altering the physical environment in which they are cultured.

Chemical signals and mechanical forces help determine which cells differentiate and which remain pluripotent. Researchers have gained several insights into the chemical ‘cues’, but are still struggling to understand how to manipulate the structure of stem cell colonies in order to control their behavior. “There has been a lot of trial and error because of the lack of engineering principles to guide the control of cellular responses,” says Hanry Yu of the A*STAR Institute of Bioengineering and Nanotechnology. His team focused on E-cadherin and integrin, two cellular adhesion proteins that are believed to be involved in regulating stem cell development. Intriguingly, both proteins act via a common signaling factor, Rho-ROCK-myosin II, raising questions about how they induce distinct cellular fates.

Initial experiments showed that cultured stem cells at the boundaries of colonies were more prone to undergo differentiation, supporting a previously proposed model in which stress-induced integrin signals at the edges actively promote differentiation (see image). However, further studies with cells cultivated on surfaces coated with patterns of these two proteins demonstrated that E-cadherin is actually the dominant signal, with the capacity to override integrin and compel stem cells to remain pluripotent. “At the colony center, E-cadherin-mediated strong cell-cell interaction inhibited stem cell differentiation,” says Yu. “Near the edge, the relatively less packed cells and higher stress caused a reduction in E-cadherin-mediated interaction that released the block on differentiation.” This process appears to be mediated in part by the...
preferential localization of Rho-ROCK-myosin II at sites of E-cadherin interaction, which prevents it from interacting with integrin. These findings could help clinical researchers to strongly control the population-scale behavior of stem cell cultures, maintaining them in a fully pluripotent or differentiated state. “It is difficult and costly to use impure cell sources for wound repair or regenerative medicine applications,” says Yu. In the future, he plans to extend the ‘micropatterning’ approach applied here to achieve even more precise modulation of stem cell behavior. “We plan to hijack the signaling process with soluble or patterned inhibitors to trigger controlled differentiation of human embryonic stem cells,” says Yu.


Pharmaceuticals:

TAKING CONTROL OF CRYSTAL FORMATION

A study by A*STAR researchers suggests the surface properties of the glass vessels in which pharmaceutical ingredients are prepared has an effect on how they crystallize.

When deciding how to control crystallization of an active ingredient during large scale production, drug companies consider many parameters, such as solvent type, solute concentration and temperature to ensure the right crystal form.

Different crystal forms (polymorphs) of active pharmaceutical ingredients exhibit different physicochemical properties and can behave very differently once inside the body, so reliable production of the required polymorph is vital.

In 2014, Sendhil Poornachary, at the A*STAR Institute of Chemical and Engineering Sciences, and colleagues, showed that the surface chemistry of modified glass vials influences nucleation and growth of selective crystal polymorphs of the anticonvulsant drug carbamazepine. While needle-shaped crystals preferentially formed in the cyano-functionalized vials, tetrahedral-shaped crystals formed in those modified with fluoro- and mercapto-groups. A mixture of the two forms was crystallized inside a control (unmodified) glass vial.

Now, the team has extensively studied the temperature ranges and solute concentrations at which the crystallization of carbamazepine occurs on different chemically-modified surfaces. By observing the crystal polymorph formed in these vials at a given temperature and concentration, the polymorph occurrence regions were plotted on a temperature-concentration phase diagram (see image). “This type of representation is important to the pharmaceutical industry in the context of defining the design space for a robust crystallization process development,” Poornachary says.

The impact of surface chemistry on the crystallization process was then investigated with the help of molecular models. “The experimental results were correlated with the results from a molecular modeling study, which revealed that specific chemical interactions between the crystal structure and functional groups on the template surface promoted nucleation of a particular polymorph,” explains Poornachary.

“We envisage that the insights from this work will help develop in silico models to predict the crystallization of [any] active...
A robust palladium catalyst developed by A*STAR researchers now offers the best way to couple certain forms of carbon-based molecules. The products of these reactions have chemical structures that are found in common pharmaceuticals, and the acclaimed catalyst is already commercially available.

The catalyst helps unite two types of organic chemical — aryl chlorides and alkynes — to generate a substituted alkyne. This structure is found in functional molecules such as tazarotene, a drug to treat psoriasis and acne. “We are essentially developing a tool for molecular assembly,” says Howard Jong of the A*STAR Institute of Chemical and Engineering Sciences, who led the research, along with his colleague Yong Yang.

The key component of the catalyst is the attached ligand, Cy*Phine, which is a phosphine-based molecule that is coordinated with the palladium center and controls reactivity; ligand properties directly influence how the catalyst interacts with other molecules during the reaction. Importantly, Cy*Phine contains an innovative chemical framework known as a meta-teraryl group, based on a chain of three benzene rings, which is designed to inhibit unwanted side reactions.

The team had previously made the catalyst by adding its precursors separately to the reaction mixture. More recently, they have pre-formed the catalyst as a yellow solid that is stable in the presence of air and moisture. Using such precatalysts tends to enable more reproducible results. Once in solution, Jong notes, the precatalyst is reduced, losing its two chloride atoms, and likely, one of its Cy*Phine units to become active.

The researchers tested their precatalyst under different conditions, and found that it worked best in a solvent called acetonitrile, along with a small amount of potassium phosphate.

The catalyst produced with this recipe gave much better results than other state-of-the-art commercial catalysts for the coupling reaction. It could connect a wide variety of different aryl chlorides and alkynes and mostly produced very high yields of the substituted alkyne product. It even worked well with electron-rich reactants, which other palladium catalysts have failed to couple in good yields. The team also found that adding an electron-donating group to the meta-teraryl group made the reaction run a little faster, although there was no increase in overall yield.

The palladium precatalyst and the Cy*Phine molecule are now being sold by Aspira Scientific. “Third parties who have extensively tested our products are extremely impressed,” says Jong. “We are encouraged by their responses and are hopeful our catalysts will continue to do well in the marketplace.”

Computational simulations:

ALL EYES ON THE CONDUCTOR

A ‘CONDUCTOR’ THAT ENSURES SIMULTANEOUS PROCESSING TASKS KEEP TIME COULD DRAMATICALLY INCREASE THE EFFICIENCY OF ‘CLOUD’ SIMULATIONS

In large-scale simulations that involve simultaneous computational tasks on distributed computers, the overall speed of the simulation is limited by the slowest link. By adaptively redistributing computational resources in real-time according to workload, a Singapore-based research team have shown how to overcome this ‘slowest link’ limitation. This approach could dramatically improve the speed and efficiency of simulations conducted across many computers — also called ‘cloud’ simulations.

“The problem of workload imbalance is very common in large-scale simulations, which involve a group of parallel distributed computers or ‘components’ that need to synchronize with each other to ensure that all simulation events are executed in time stamp order,” explains research leader Zengxiang Li, from the A*STAR Institute of High Performance Computing.

Parallel computing simulations involve a large number of events that must occur in order. These events are assigned to multiple parallel computing ‘nodes’ for simultaneous computation. When an event is processed, new events may be generated and inserted into the event processing queue. It is wasteful to let expensive computational resources lie idle waiting for work, so parallel processing schemes often allow each node to process events sequentially without waiting for events from other nodes.

The problem is, that if events from one node are late, the other nodes proceeding with their ‘optimistic’ execution of the next event have to discard their extra work and roll back to where the late node left off. “The entire simulation execution is held back by the slowest components,” says Li, “while faster components risk wasting time and resources on overoptimistic execution and execution rollbacks.”

To improve the efficiency of such simulations, Li and his colleagues developed a resource-conducting scheme called Adaptive Resource Provisioning Mechanism in Virtual Execution Environments, or ArmVee. This scheme acts transparently as middleware in the simulation environment to monitor workloads and task completion speeds on each node in real-time. ArmVee then dynamically reallocates resources, such as memory and processing cycles, to speed up the slowest links.

“We use a self-adaptive auto-regressive-moving-average model — commonly used in control theory — to capture the relationship between simulation performance and resources,” says Li. “This allows ArmVee to predict the dynamically changing simulation workload and to align the execution speeds of simulation components proactively so that each advances in simulation time with comparable speed.”

Importantly, ArmVee can be used transparently in standard simulation architectures without any simulation recoding or interruption. This makes it ready for implementation in standard parallel and distributed simulations.

An eco-friendly strategy has been developed by A*STAR researchers to stop the collection of bacteria and marine organisms on objects immersed in seawater. Working under the Innovative Marine Antifouling Solutions program, the scientists have created a safe polymer-based coating.

Marine fouling badly damages ships, seawater filtration systems, and harbor installations, and leads to expensive and time-consuming repairs. Fouling also corrodes ship hulls which increases their fuel consumption. It has proven destructive for high-performance devices specific to the maritime industry, such as underwater communication equipment and buoy sensors.

Traditional measures against marine fouling rely on coatings that release substances known as biocides, which deter or kill these microorganisms. But, these compounds also harm the marine habitat, especially in shallow bays and harbors, leaving an extensive ecological footprint.

In their search for alternative coatings to biocides, Anbanandam Parthiban, and co-workers from the A*STAR Institute of Chemical Engineering Sciences and Institute of Materials Research and Engineering have discovered so-called poly(methyl oxazoline) (PMOx) polymers that prevent microorganisms.
from sticking to surfaces and, where there is contact, facilitate their detachment.

According to Parthiban, low-adhesive polymers that form hydration layers on coated surfaces have emerged as potential antifouling agents. “Poly(methyl oxazoline) is the third generation of hydrophilic polymers under focus,” he adds. Parthiban described a peptide-like chemical backbone, which shows greater resistance to oxidation than its widely-studied predecessor polyethylene glycol. This makes it attractive for long-term performance — a major challenge in the design of antifouling agents.

Parthiban explains that PMOx is typically anchored on surfaces through electrostatic interactions, which can be nullified by charge screening in high-ionic-strength solutions, such as seawater. To preempt this issue, the researchers covalently attached the polymer chains to surfaces by curing precursors functionalized with reactive end groups using ultraviolet light.

After an initial reduction in thickness, the coatings remained intact when immersed in a seawater proxy for two months. They effectively reduced the settlement of barnacle larvae and algae, regardless of polymer mass and surface charge.

The coatings may also have biomedical applications, as they reduced the attachment of bacteria Staphylococcus aureus and Escherichia coli. “Bacterial adhesion showed a strong response to surface charge,” adds Parthiban.

The researchers are talking to potential industrial partners about the possible implementation of these new coatings in high-value applications. Also, in a continued effort to come up with biocide-free technologies, they are creating coating materials that satisfy the diversity of organisms in various water bodies.

Immunology:

UNDERSTANDING INFANTS’ ITCHY SKIN

The age at which eczema appears in young children may indicate its cause

A*STAR researchers have shown that eczema has different risk factors depending on its age of onset, after evaluating more than 1,000 Asian newborns over in an 18-month study.

Eczema, or atopic dermatitis, is a chronic condition characterized by dry, itchy skin that is prevalent all over the world. Understanding its cause can help clinicians choose the most appropriate treatment.

To determine the factors involved in eczema onset, Evelyn Xiu Ling Loo from the A*STAR Singapore Institute for Clinical Sciences and colleagues analyzed 18 months of data collected as part of the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) study. Healthy pregnant mothers donated cord blood and placenta samples after delivery and information on signs of eczema development was collected at regular intervals. At the end of the 18-month period, the children were tested for common allergens. The patients’ lifestyle and family history of allergy were also considered.

The team found that eczema can be activated by different triggers depending on the age of the sufferer at onset. Early onset occurs before the age of six months and was found to be associated with a maternal history of allergies. For the second type of eczema, occurring in children between six and twelve months of age, one of the risk factors was childcare attendance. This is a surprising result, Loo notes, since exposure to higher microbial load during childhood normally protects from diseases later in life. She says other studies, however, have reported similar findings indicating a higher presence of allergens in these settings might sensitize some children to allergies. Finally, late onset atopic dermatitis, which develops in children over the age of 12 months, was found.
Stem cell activity in the outer lining of the ovary, now identified in mice by A*STAR researchers, will elucidate normal ovarian activity and offer insights into the origins of disease.

Ovarian cancer kills more than 140,000 women globally each year, but the molecular and cellular events behind it remain unclear. “We need to understand the normal cell biology of the ovary before we can begin to understand what goes wrong during cancer, for example,” says Loo.

The team next plans to examine how factors like diet and weight gain in addition to the presence of environmental allergens and chemicals in house dust may also influence the development of allergic diseases in children.

Loo explains that early intake of antibiotics may disrupt the gut’s microflora, which is important for shaping the immune response, and may also suppress the production of small proteins called cytokines, ultimately making the child more prone to allergic reactions.

“Knowledge that taking antibiotics may increase the risk of development of late onset atopic dermatitis could be used to develop a preventive strategy to reduce its prevalence,” says Loo.

The team next plans to examine how factors like diet and weight gain in addition to the presence of environmental allergens and chemicals in house dust may also influence the development of allergic diseases in children.

source of epithelial cancers of the stomach and intestine.

Next Barker and his team plan to create targeted mutations in specific genes and analyze the possible role of these mutations in ovarian cancer. They also hope to build on the work with mice by purifying and growing human ovarian stem cells and epithelia in culture, providing insights that will be directly relevant to medical applications. “This basic research is a prerequisite for eventually being able to develop more targeted and more effective therapies to treat ovarian disease,” says Barker.


Immunology:

FINE-TUNING IMMUNE CELL FUNCTION

B cells are immune cells that generate antibodies against foreign antigens and play an important role in fighting pathogens. The overproduction of antibodies is a cause of the autoimmune disease lupus, leading to kidney dysfunction. Now A*STAR researchers have identified a small cluster of RNAs that regulate antibodies in mice, shedding light on how B cells are regulated.

The team, including Shengli Xu from the Bioprocessing Technology Institute at A*STAR, identified a genomic cluster of six short noncoding RNAs, called mir-17-92, that regulates the function of mature B cells.

Short noncoding RNAs modulate the expression of a number of target genes by binding specifically to complementary mRNA transcripts and affecting their stability, or their ability to be translated into protein. While the mir-17-92 genomic cluster was known to influence the early development of B cells, its role in mature B cells was not understood.

Xu and colleagues produced a mouse that lacked mir-17-92 only in mature B cells, and observed that more antibody-producing plasma cells — derived from B cells — ended up in the bone marrow during immune responses than in normal mice. They showed that this was because mir-17-92 normally reduced the expression of a receptor called sphingosine 1-phosphate receptor 1 (S1PR1) that is known to drive bone marrow homing by plasma cells. The absence of mir-17-92 meant S1PR1 expression went up, leading to increased plasma cell homing to bone marrow.

The mice lacking mir-17-92 also produced less of a certain class of antibody called IgG2c, which is the most prevalent type of antibody against self molecules in mouse models of lupus. The researchers identified the mir-17-92 gene target responsible for suppressing the production of IgG2c in mice is the protein IKAROS. Levels of this protein are elevated in mir-17-92-deficient mice: bringing its levels back to normal also brought IgG2c production back to normal levels.

Because of the significance of IgG2c antibodies in mouse models of lupus, the team also wanted to know if reducing mir-17-92 could affect disease in the mice. By deleting mir-17-92 in the mouse model of lupus, they found diminished autoantibody production and kidney injury in mice lacking mir-17-92 compared with controls.

“These findings lead to better understanding of the role of mir-17-92 for normal B cell function, and also pave the way for development of new treatments for some B cell-related diseases in humans, such as multiple myeloma and lupus,” explains Xu.

Telomeres are to chromosomes what aglets are to shoelaces — protective caps that stop the tightly wound strings from unraveling. Every time a cell divides, its telomeres are trimmed, eventually becoming so short that the cell goes into an unproductive state of senescence. Lifestyle changes can slow or hasten this biological clock, which has become a popular area of research in the last few years. Scientists are looking at the link between aging and telomeres from all angles, from genetics to diet and lifestyle choices.

Researchers at the A*STAR Institute of Medical Biology (IMB) are examining another factor — the presence of a mutant protein known as progerin. The protein is produced by children with a rare genetic disease that causes premature aging, called Hutchinson-Gilford progeria syndrome. “The length of the telomeres in these children is about the same as that of an 80 or 90-year-old,” says Colin Stewart, a lead researcher in the study. “Somehow, progerin is accelerating this aspect of the aging process.”

This study offers one of the best pieces of evidence that damaged telomeres and premature senescence is detrimental to the body,” says Oliver Dreesen, another lead researcher, discussing the work’s implications for aging in general. “Maintaining the integrity of your telomeres is extremely important.”

But, probing further, the A*STAR team discovered something even more significant. By introducing to the mutant cells a specific protein found in the cell nucleus, telomere damage was prevented and the cells saved from early aging.

“That really blew me away,” says Dreesen. TELOMERE LINK

Hutchinson-Gilford progeria affects one in every four million babies. Children with the disease typically show signs of aging from their first birthday, are bald by their second or third year, and die in their teens of heart failure or stroke. They are thinner and more fragile than their contemporaries, but remain mentally astute.

Early in his career, Stewart developed a keen interest in the new genetic manipulation techniques being used to create mouse models of various diseases. He focused on a fibrous protein found inside the nuclear lamina called lamin-A. “I became very interested in why this one rather boring protein in the nucleus, when mutated in different ways, leads to so many different types of disease.” One of those diseases happened to be progeria, in which a single mutation in the gene that codes for lamin-A produces the mutant progerin. In 2003 Stewart produced the first mouse model of the premature aging syndrome. A few years later he moved to Singapore to develop new ‘disease-in-a-dish’ models of progeria using human embryonic stem cell technologies, which were advancing rapidly in the country.

Oliver Dreesen moved to A*STAR in 2009, having spent the last few years studying telomeres in a parasite that causes sleeping sickness. “One of the first discussions I had when I came to Singapore was with Colin, who told me about progeria,” says Dreesen. “And I said to him: we have to look at telomere length.” By that time, researchers had already established that telomeres played a role in the normal aging process. But those working on progeria were more preoccupied with the morphed structure of the cell nucleus, which projects like tiny bubbles from the original oval.

Together, Dreesen and Stewart developed a model of progeria using connective tissue cells known as fibroblasts in which they could gradually increase the dose of progerin. When progerin levels reached about 30 to 40 per cent of normal lamin-A levels, the cells began to exhibit some strange and pathological behavior: the nuclei lost its original shape, the telomeres showed signs of damage and the cell went into a state of senescence.

“They just sit there,” says Dreesen to describe the irreversible growth arrest. “They are not dividing but are metabolically active and start to secrete all sorts of junk that breaks down the extracellular matrix.” Dreesen and Stewart had published a study in 2013 in which they identified a specific biomarker for senescence that made these cells easy to detect. Different types of cells accumulate progerin...
at different rates, which means that they arrive at this dangerous threshold sooner (as with blood vessel cells) or later (as with neural cells). The findings explained why children with progeria were more likely to die of cardiovascular diseases, while their mental capacity appeared unaffected. “Children who have progeria typically die from a heart attack or a stroke, which is associated with accelerated calcification of the blood vessels and also some types of atherosclerosis,” says Stewart, describing, at the same time, a common cause of death worldwide. “Progeria may give us insights into how the normal vascular system ages.”

**TO THE RESCUE**

Dreesen and Stewart then tried to see if they could prevent these progerin-induced cellular deteriorations. Their first candidate was an enzyme known to lengthen telomeres, called telomerase, which they introduced to the cells. To their surprise, telomerase prevented most of the deviant behavior of progerin-expressing cells, but it did not explain how it led to such detrimental outcomes.

To address this question they sought the aid of a colleague, Brian Burke, also at the IMB, who had developed a ‘BioID’ technique for studying how proteins interact. The technique involves tagging a protein of interest — in this case lamin-A or the mutant progerin — with a sticky substance that irreversibly attaches to any protein it comes within nanometers of. “It’s like going fishing,” explains Stewart. “You throw out a longline of your favorite protein, and then pull it in to see what proteins have hooked on to the line.” The researchers compared the proteins that stuck to lamin-A with those that stuck to progerin.

Compared with lamin-A, progerin interacted significantly less with a protein also found in the nuclear lamina — lamin-associated polypeptide-α (LAP2α). The difference was significant enough to consider it a potential contender for preventing the accelerated biological aging. “I didn’t think it would work, to be honest. We were looking for a needle in a haystack,” says Dreesen.

As with telomerase, they introduced LAP2α to the progeric cells. To their amazement, the cells grew faster, had less DNA damage, and did not become unproductive prematurely. “We just couldn’t believe it,” says Dreesen. “We reproduced the experiment about seven times, but every time we did this, the cells grew better.”

Using super-resolution microscopy, they further discovered that LAP2α was found in closer proximity to telomeres in normal cells than in progeric cells by almost 200 nanometers. This mislocalization of LAP2α might be responsible for the progerin-induced telomere defects.

The majority of telomeres in both types of cells were found within 250 nanometers of the nuclear lamina (see image). When taken as a whole, these findings set the scene for the pathology of progeria in which telomeres and the nuclear lamina play a prominent role.

Understanding how this process works could show scientists a way to prevent progeric cells from deteriorating and dying, says Dreesen. Ultimately, the researchers want to know how the changes observed in progeria apply to normal aging.

Artificially engineered materials called metamaterials can be used to manipulate light for a range of applications, but often require complicated three-dimensional structures with features as small as a few tens of nanometers. Now, A*STAR researchers have constructed a simpler, two-dimensional ‘metasurface’ for state-of-the-art high-transmission light manipulation.

Yefeng Yu and his co-workers from A*STAR’s Data Storage Institute have created a metasurface that can alter a property of light known as phase (see image). Light can be thought of as a wave with successive peaks and troughs. Moving this wave, to delay or hasten the peaks and troughs, is known as a phase shift. The metasurface designed and created by Yu and the team is capable of complete control over the phase of visible light. By creating certain phase shift distributions it is possible to focus light or even create on-demand holographic images.

The team’s metasurface comprised a square array of silicon disks. Each was 130 nanometers tall with a center-to-center separation of 360 nanometers. Light striking the surface of the structure passed through to the other side, but was deflected by approximately...
ten degrees. The phase change imparted to the transmitted light by the metasurface was dependent on the radius of the silicon disks. The team showed that varying the radii between 120 and 155 nanometers could produce any desired phase shift.

The main drawback of previous approaches to such optical components has been the low fraction of light transmitted. The structure created by the team reached a peak transmission of almost 90 per cent. “Most previous approaches are based on plasmonic nanoparticles, which have strong losses in the visible spectrum and typically have only an electric resonant response,” explains Yu. “The silicon particles we use can have both electric and magnetic resonances.” The researchers have nearly eliminated both losses and optical reflection from their metasurface.

“To make metasurfaces interesting for practical applications it is important to tune them and dynamically control the phase of incoming light,” says Yu. “This is something our group is now working on.”


Immunology:

CONFIRMING THE ORIGIN OF MACROPHAGES

A long-held misconception over the origin of macrophages, a type of white blood cell that plays a vital role in development and immunity, has been dismissed. Researchers at A*STAR used state-of-the-art technology to verify that adult tissue-resident macrophages stem from two sources in the early stages of embryonic development.

Macrophages are key components of the body’s major organs, including the brain, lungs, and gut. They patrol the body for pathogens, trigger defense mechanisms, and devour damaged cells. They can also turn against the body during various diseases and have been implicated in the growth of cancerous tumors. Therefore, new therapies could either limit or enhance the activity of macrophages, according to the necessary response.

Until 2010, scientists thought that all macrophages were replenished from a continuous supply of monocytes, another form of white blood cell. Then, Florent Ginhoux at the A*STAR Singapore Immunology Network and co-workers proved that microglia, a type of macrophage resident in the brain, actually originates from embryonic yolk sac macrophages.

“Following this discovery, we proposed a systematic study of macrophage development from the embryo onwards, to settle the debate,” says Ginhoux. “We employed a ‘fate-mapping’ technique that allowed us to genetically tag progenitors (developmental precursors derived from stem cells) and follow them from their origins right through to adulthood.”

The team developed a mouse model in which fetal macrophage progenitors were tagged to emit fluorescence when triggered by an injection. This allowed the researchers to follow the cells as they moved and differentiated.

“Our biggest challenge was the speed of biological processes during early embryogenesis,” states Ginhoux. “Given such a specific target, we had to be incredibly
The team’s precision paid off. It allowed them to verify that yolk sac macrophages and fetal monocytes derive from early- and late-stage ‘erythro-myeloid’ progenitor cells. Yolk sac macrophages give rise to microglia, while fetal monocytes colonize other tissues before differentiating into adult tissue-resident macrophages. The macrophages then self-renew throughout life, without the need for a supply of monocytes from the bloodstream.

“The next question to answer is whether the origin of macrophages actually matters,” explains Ginhoux. “Essentially it is the ‘nature versus nurture’ debate – do their origins influence their behavior and functions in later stages of development, both under normal circumstances and in disease? These details will be of crucial importance in the quest to cure cancer, for example.”


**Therapeutics:**

**POP IN A SHOCK PROTEIN TO PEP UP PRODUCTION**

A protein produced by cells in response to stress can improve the production of biological medicines

Production of an antibody can be doubled without loss in quality by genetically modifying special cells to overexpress heat shock protein 27 (HSP27), a Singaporean research team has shown, bringing efficient production of therapeutics a step closer.

Cultures of Chinese hamster ovary (CHO) cells are used to produce large quantities of biological medicines known as recombinant biologics. DNA is artificially constructed with specially chosen gene sequences and inserted into CHO cells. The ‘recombinant DNA’ instructs the cells to produce proteins that are then used for medical purposes.

Scientists from A*STAR’s Bioprocessing Technology Institute (BTI) and the National University of Singapore have now genetically modified CHO cells to overexpress heat shock protein 27. Under typical conditions, CHO cells die in culture, due to build-up of waste by-products, which limits the amount of recombinant biologics they can produce.

By studying gene and protein expression in CHO cultures BTI researchers previously found that HSP27 levels were low when the growth of CHO cells was slow. “We speculated that more HSP27 in the CHO cells could prolong the culture’s life and accordingly increase the concentrations of the biologics they produce,” says BTI bioprocess scientist Janice Tan Gek Ling.

To demonstrate the concept, the team overexpressed HSP27 in CHO cells engineered to produce an antibody that binds to an antigen, called Rh factor, which is commonly present on red blood cells. This antibody can prevent Rh disease, where Rh incompatibility between a pregnant mother and her fetus can lead to a dangerous breakdown in the newborn baby’s red blood cells — acute cases can kill the baby *in utero*.

Together with their previous study that used CHO cells engineered to produce recombinant human interferon gamma — a therapy for hereditary immune and bone diseases — the team has shown that use of overexpressed HSP27 can improve the production of different recombinant biologics.

“Companies developing new biologic products can choose to implement this technology by using a host cell line designed to overexpress HSP27,” says BTI staff scientist Ng Say Kong. In future, rather than having to engineer the cell lines from scratch, there
could be new additives to add to CHO cultures which would simplify using this technology in existing manufacturing plants. The team is now pursuing a more in-depth understanding of how HSP27 works. “With this knowledge, we can further engineer the CHO cell cultures to have an even longer culture life and higher cell growth leading to higher production of biologics,” says Ng.


Chemistry:

MAKING MOLECULES THAT TWINKLE

SINGLE STEP PROCESS TRANSFORMS CARBON DIOXIDE INTO STAR-SHAPED MOLECULES THAT ARE PROMISING BUILDING BLOCKS FOR USEFUL POLYMERIC MATERIALS

The power of carbon dioxide has been harnessed by A*STAR researchers to make two symmetrical star-shaped molecules in a single step. These molecules could be used to build complex, functional polymeric materials useful for catalysis, coatings and drug delivery.

Carbon dioxide is a cheap and accessible base material, explains lead researcher He-Kuan Luo from the A*STAR Institute of Materials Research and Engineering. “Therefore, many people are searching for efficient methods to transform carbon dioxide into useful molecules,” he explains. “But transforming carbon dioxide is not typically easy.”

His team has developed a simple route to use carbon dioxide to make aromatic compounds that can be used as building blocks for more complicated materials. They created symmetrical benzene rings with three or six identical arms comprising carbonate groups terminated by carbon–carbon triple bonds, or ‘alkynes’. “We can integrate the carbon dioxide into the molecule without the need for high temperatures or high pressure,” says Luo.

The molecules were made in a single step. The team introduced carbon dioxide from dry ice to an alcohol with an alkyne end group and benzene rings decorated with either three or six alkyl bromide groups. “At the beginning, however, only some of the branches reacted so we could not get the desired compound,” Luo explains.

The team fine-tuned the process and found the reactions worked most efficiently at room temperature, with the carbon dioxide at atmospheric pressure and with the addition of both a promoter tetrabutylammonium bromide (TBAB) and the base potassium carbonate. “We tried many times and after a few months, we finally got [the bromide groups in] all six branches to react [with the alcohol],” he says.

Adding the promoter to the mix doubled the amount produced. “It is likely that the tetrabutylammonium cation enhances the rate of carbon dioxide incorporation by stabilizing the carbonate anion,” says Luo.

The reaction time is also vital. “We needed to be patient and let the reaction run to completion to ensure that all the branches reacted.” The synthesis of the three-armed and six-armed star-shaped molecule took two and four days respectively.

The alkynes on the end of each arm in these molecules should theoretically be able to react with a host of different molecules using simple click chemistry — to produce a range of complex or functional materials. “We are currently trying to use the six-armed branched molecule to build more functional star-shaped molecules, which may find applications in catalysis, coatings and drug delivery,” says Luo.

The classes of RNA molecules encoded by DNA sequences previously considered non-functional may play a vital role in cell stress responses, and could one day lead to cancer treatments. A*STAR researchers have identified a class of the long noncoding RNAs responding upon oxidation stress and characterized and specified their functions across stress stimuli and cell types.

Human skin and lung cells were subjected to oxidative stress by the research team, stimulating cellular pathways of repair and survival. While protein-coding genes were generally inhibited, stress caused noncoding genomic regions to produce thousands of RNA molecules called ‘long noncoding RNAs (lncRNAs)’.

Author Igor Kurochkin says the role of lncRNAs is a mystery. “We don’t know their function, or even if they function at all.” They may act in the evolution of new genes; in helping cells respond to stress; in interaction with genes or proteins; or, says another author, Vladimir Kuznetsov, “all of these at once!”

Unexpectedly, lncRNAs were found to accumulate at structures, known as polysomes, where proteins are assembled. According to Kuznetsov, “it’s possible that lncRNAs interfere with protein production at polysomes.”

He finds this interaction fascinating: “The cross-regulation of coding and noncoding RNAs lies at the intersection of many questions and may provide a major mechanism for evolutionary adaptation”, says Kuznetsov. “The field of studying protein-RNA interactions is huge and growing fast.”

The researchers, from several disciplines, could not exclude the intriguing possibility that lncRNAs actually code for proteins. Certainly some encode smaller molecules, known as polypeptides, made from the same building blocks as proteins. Many of these polypeptides are functional, for instance as hormones. The team now intends to study their role.
in combating oxidative stress. Kurochkin describes this as "a work in progress".

The implications of these findings can be linked to medical conditions from chronic stress to neurodegenerative diseases. Some types of IncRNAs are common in cancer cells and could be a direct target for treatment. Kuznetsov explains: "Our study is very simple because it uses well-organized cells. In cancer, this organization is disrupted, unregulated, but the same machinery is at work."

Kurochkin agrees. "We need first to develop more complex experimental designs, models and interpretations," he says. "Eventually we’ll learn how to manipulate it."

Their research turns on its head the whole concept of noncoding DNA. In fact, Kuznetsov says, "There is no 'junk DNA'. At least 80 per cent of the human genome initiates RNA production. RNA, DNA and proteins are now equal partners, we just don’t yet understand their complementary roles."


Medical imaging:

**SHARP IMAGES OF MOVING TUMORS**

LUNG TUMORS CAN BE ACCURATELY IMAGED BY A METHOD THAT COMBINES THE BEST ASPECTS OF TWO EXISTING IMAGING TECHNIQUES

By cleverly combining two medical imaging techniques, A*STAR scientists have found a way to produce images of the lungs that are both high resolution and account for lung movement due to breathing. The method is expected to greatly assist clinicians when they target tumors in the lungs during radiotherapy. Cancerous tumors in the lungs are often treated by irradiating them with high-energy X-rays, but this therapy is complicated by the fact that tumors are moving targets, due to the expansion and contraction of the lungs as the patient breathes.

Currently, two biomedical imaging techniques are used to help clinicians locate tumors in the lungs, both of which have their advantages and disadvantages. Three-dimensional computed tomography (3D-CT) provides high-resolution images, but it can only provide snapshots in time and there are safety concerns surrounding exposure to X-rays. In contrast, four-dimensional magnetic resonance imaging (4D-MRI) does not employ ionizing radiation and allows continuous tracking of the lung motion, but its low spatial resolution yields blurred images.

Now, Soo Kng Teo and co-workers at the A*STAR Institute of High Performance Computing in Singapore have combined these two techniques to realize the best of both approaches — a high-resolution imaging method that accurately accounts for lung movement.

The researchers used 3D-CT to obtain a sharp static image of the lungs. They mathematically combined this static image with the four-dimensional (the three spatial dimensions plus time) information extracted from images obtained using 4D-MRI. This enabled them to achieve a high spatial resolution to realize excellent clarity and
show movement of a lung tumor over several breathing cycles (see image).

They tested their imaging technique on six lung-cancer patients and obtained impressive results: the average error was less than two millimeters.

As with all medical innovations, adoption of the technique in hospitals depends on obtaining the backing of medical equipment companies and meeting the many regulatory requirements. “The biggest hurdle will be convincing equipment manufacturers to adopt the imaging method,” says Teo.

There is much scope to extend the study. For example, Teo explains, the imaging technique could be applied to other organs or other imaging modalities. “Encouragingly, some clinicians are thinking of applying our method to other organs, such as the liver, which also moves significantly with breathing,” says Teo. “Also our computational method can combine information from different imaging methods to produce more comprehensive data sets”.

The team is exploring both possibilities.

For precision engineering systems, such as CD and DVD players, anti-lock braking systems and computer hard disk drives, vibration can significantly affect performance. Now, A*STAR engineers have developed an efficient and reliable method for eliminating a major source of vibration.

Vibration is a significant destabilizing source that can seriously degrade the operation, lessen the working life, and, in some cases, lead to catastrophic failure of mechatronic — integrated mechanical, electrical and computer systems — devices. Produced internally from sources of noise such as motors, bearings and other moving parts as well as from electrical noise, unwanted vibration should be eliminated or compensated for.

Mechanical resonant modes — frequencies that match those of one or more of a system’s mechanical components, the effects of which can be felt when a part of a car begins to vibrate at a particular speed — whose natural frequencies are above a specific frequency for a sampled-data mechanical system, referred to as the Nyquist frequency, are reflected back at low frequencies and become indistinguishable from the output signal. Such signals are tricky to isolate and therefore not easily extracted.

Yan Weili and colleagues at the A*STAR Data Storage Institute have developed a powerful mathematical model that identifies mechanical resonance modes above the Nyquist frequency that lead to vibration, so they can potentially be eliminated, leading to better performing mechatronic systems.

“Our method can potentially be implemented on mechatronic systems without the requirement for any external equipment, such as a laser Doppler vibrometer, or external excitation signals,” says Yan. “It is less time-consuming and not as computation-heavy as analog methods, and can be applied to ultra-high performance mechatronic systems and advanced motion control for nano-positioning systems.”

The researchers used a mathematical method based on statistical modeling, known as a polynomial transformation technique-based recursive least-squares algorithm, to first generate a mixed-rate model using fast sample rate inputs and slow-sample rate outputs that identifies the mechanical resonances beyond the Nyquist frequency.

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and then to derive a fast-rate model involving fast sample-rate inputs and fast sample-rate outputs from which the unwanted frequencies can be extracted.

To evaluate their approach, the researchers used a voice coil motor actuator in a commercial hard disk drive — a typical mechatronic component that contains many mechanical resonant modes — and used simulation and experimentation to verify its effectiveness.

“The outputs from the simulation and experimentation were in good agreement, confirming that the parametric identification approach is efficient, consistent, and can be realized online,” says Yan.


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Cancer:

**BETTER DIAGNOSIS FOR A RARE SYNDROME**

**A REARRANGEMENT IN A TUMOR SUPPRESSOR GENE COULD BE THE KEY TO A FIRM DIAGNOSIS FOR FAMILIES PRONE TO CANCER**

Understanding Li–Fraumeni syndrome (LFS) — a genetic disorder that substantially increases the risk of a young person developing cancer, such as the bone cancer osteosarcoma — is a first step to improving diagnosis and counseling.

LFS diagnosis is currently based on empirical factors such as having two first-degree relatives who develop cancer before the age of 40. For Axel Hillmer at the A*STAR Genome Institute of Singapore, this was a crude approach to diagnosis. Along with David Virshup at Duke-National University of Singapore, he led an international team to improve it.

The researchers sequenced the whole genome of four osteosarcoma patients and looked for large rearrangements in chromosomes of the tumor cells. “We tried to find commonalities across these four tumors,” says Hillmer. The only gene that was affected in all four was *TP53* which encodes a protein essential for a cell’s response to DNA damage.

The genomic rearrangement they saw featured a break at the beginning of *TP53*, in a region called intron 1, which led to a fusion of the front segment of a gene with distant genomic regions. This resulted in a *de facto* loss of the gene. “It cannot be transcribed any more,” explains Hillmer.

The team identified this type of rearrangement in more than 10 per cent of osteosarcoma patients. Significantly, it has not been seen in other cancer types, even though *TP53* is a gene commonly mutated or deleted in many tumors.

Given the specificity of the rearrangement for osteosarcoma, Hillmer and his colleagues wondered whether the *TP53* rearrangement is present in LFS, which could explain the 30 per cent of cases where no genetic cause can be found with standard methods. They analyzed a family with 12 members affected by LFS and found the same *TP53* rearrangement in all affected individuals. “For the first time, we see LFS patients where the *TP53* intron 1 rearrangement is in the germline,” says Virshup.

“We can now make a clear diagnosis.”

While not yet having implications for treatment changes, the diagnosis will improve genetic counseling.

Hillmer wants to screen more LFS families to strengthen the link between the rearrangement and the disease. He will also investigate what triggers the initial break in *TP53*’s intron 1 specifically in bone cells. “We plan to identify features in that region that are different in the osteoblast lineage compared to other tissues and cell types,” explains Hillmer.

Holography: NANO SCALE SIEVES SNARE WOULD-BE THIEVES

BIO-INSPIRED ALGORITHMS ENABLE A PATTERN OF THOUSANDS OF NANO SCALE HOLES INTO METAL FILMS FOR HIGH-TECH OPTICAL SECURITY

Bank notes and credit cards may soon feature improved anti counterfeiting holograms thanks to a ‘photon sieve’ developed by A*STAR researchers and co-workers.

Holograms contain complex, three-dimensional image information that makes them difficult — but not impossible — to counterfeit. One way to improve their security is by using sophisticated devices that enhance holographic resolution. Nanophotonic devices deploy arrays of nanoscale light scattering pixels that encode additional layers of information through ‘near-field’ optical interactions between lasers and the pixels.

Recently, researchers have shown nanoscale holes carved into thin metal sheets to be effective light scattering pixels. Surprisingly, when these nanoholes are arranged randomly, instead of periodically, the generated hologram becomes more uniform. Designing devices with randomly arranged components, however, is technically challenging, as parameters such as nanohole radius and spacing can vary over a wide range of values.

To overcome these obstacles, Jinghua Teng from the A*STAR Institute of Materials Research and Engineering and colleagues devised a theoretical method that deconstructs the complex diffracted field from a single nanohole into simple analytical expressions that can be solved exactly. By superimposing the solutions together, they can calculate local, specified electric fields instead of expending significant computational resources to numerically simulate the entire nanophotonic array.

The researchers turned to genetic algorithms to efficiently arrange the holes in a photon sieve arrangement. By repeatedly pairing, crossing, and mutating ‘chromosomes’ containing different ‘genes’ — labels of different nanohole sizes and positions — an aperiodic pattern evolves that optimizes holographic light control based on the simplified electric field calculations.

Next, the team used electron-beam lithography to turn their design into a practical device by etching over 34,000 aperiodic nanoholes into a thin chromium film (see image). The resulting prototype boosted diffraction efficiency by nearly 50 per cent compared to conventional nanophotonic devices with image resolution hundreds of times better. Common holographic errors or ‘artefacts’ such as twin images were also eliminated through this technique.

“The high-quality holographic images are promising for applications like anti counterfeiting, optical encryption and portable information identification system,” says Teng. “For example, it could be used in anti counterfeiting in banknotes, with its ultra-compact size, high-quality, and even multi level holographs.”
The researchers demonstrated another application of their approach by designing a ‘superfocusing’ system that can resolve objects smaller than the wavelength of light. With the nanoholes arranged into concentric rings, the photon sieve lens focuses light down to spots just 200 nanometers wide — scales useful for biological imaging and optical manipulations.


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**Genomics:**

**UNLOCKING THE MYSTERY OF AN AGE-OLD SECRET**

It’s not quite the mythical elixir of youth, but A*STAR scientists have found a way to control aging at a cellular level. Researchers have pinpointed the gene in human egg cells that can block the process that causes cells to age.  

The discovery could be the first step toward rejuvenating dying tissues and organs in the body, says Ng Shyh-Chang from the A*STAR Genome Institute of Singapore.  

The breakthrough was made as Ng and his team tried to unravel the mystery behind the 1996 cloning of Dolly the sheep, who was created when stem cell researchers combined the nucleus of an adult cell with an egg cell. While scientists knew the egg cytoplasm contained special factors that can reprogram adult cells into embryonic stem cells, the underlying mechanism remained unclear.

“When you put a cell nucleus into an egg something magical happens, but people don’t understand why it works,” he says. This lack of knowledge was highlighted in 2006 when Japanese researcher, Shinya Yamanaka, showed that any adult cell could be turned into a stem cell through a process known as induced pluripotent stem cell reprogramming (iPSC).

However, Ng says there was a vast difference in the effectiveness of the iPSC reprogramming and the cells it produced compared with the approach that created Dolly. Ng believed a better understanding of what happened when Dolly was cloned could resolve these problems.

“We wanted to revisit the old system in pioneering cloning and find what other genes and factors in the egg can facilitate this reprogramming process, what helps it become more efficient, more accelerated,” Ng says.

Their work revealed old mitochondria — the oxygen-consuming engines in cells — blocked cellular rejuvenation. But they also found that the gene, Tcl1, which is highly abundant in egg cytoplasm, binds to a mitochondrial enzyme PnPase that regulates mitochondrial growth. By increasing the amount of Tcl1 in the egg, the researchers were able to control the aging rate of the cells.

“We found if we suppress mitochondrial growth, we could set the stage for the cells to be rejuvenated back to their embryonic state,” says Ng.

He says the findings have direct implications in generating better stem cells without the ethical implications associated with using cells from human embryos. Ng says the findings could also be the important ‘first step’ in reversing the aging process in human organs such as the heart.

“To figure out how to rejuvenate cells that are on their way to death and rescue them back would be the holy grail,” he says.

Since their discovery in 1895, X-rays have led to significant advances in science, medicine and industry. From probing distant galaxies to screening at airport security and facilitating medical diagnosis, X-rays have allowed us to look beyond the surface and see what lies beneath.

Now, a collaboration between the A*STAR Singapore Institute of Manufacturing Technology (SIMTech) and the Massachusetts Institute of Technology (MIT) in the United States has proposed a versatile, directional X-ray source that potentially could fit on a laboratory bench and is based on the intriguing two-dimensional material, graphene.

**COMPACT YET TUNABLE**

X-rays are high-frequency electromagnetic waves that can be generated using X-ray tube technology dating back to the 19th century or from huge sources like synchrotrons and kilometer-long free electron lasers.

X-ray tube sources, popularly used in medical diagnostics, emit radiation in all directions. But since only X-rays generated in the forward direction can be used for imaging, a significant amount of the generated X-rays are wasted. Moreover, they are not ‘tunable’, meaning that a different X-ray source has to be installed in a diagnostic device for each desired wavelength.

Kilometer-long free electron lasers, on the other hand, can produce intense, tunable X-rays by accelerating free electrons to extremely high energies and then causing them to ‘wiggle’ with an undulator stage. But these enormous X-ray sources only exist in a few places in the world and are housed in very large, expensive and over-subscribed facilities.

An X-ray source that is both small and powerful has been much sought after for some time. This challenge intrigued Liang Jie Wong from SIMTech and his collaborators at MIT: Ido Kaminer, Ognjen Ilic, John Joannopoulos and Marin Soljačić.

“We wanted to combine the best of both worlds by creating something that is compact and also capable of producing very intense X-rays,” says Wong. “Essentially, we wanted to implement the concept behind the enormous free-electron-laser sources on a scale small enough to fit on a laboratory table or even a microchip.” This goal led the researchers to the wonder material graphene, the subject of the 2010 Nobel Prize for Physics.

**X-RAY WIGGLES**

Graphene is a one-atom-thick sheet of carbon atoms arranged in a honeycomb-like fashion.
Its suite of enviable properties include high mechanical strength and near optical transparency, as well as excellent thermal and electrical conductivity. But more importantly for Wong and his MIT collaborators, the two-dimensional material can also support plasmons — collections of electronic oscillations that can be used to confine and manipulate light on scales of around ten nanometers.

The idea for a graphene plasmon-based free electron X-ray source was born toward the end of Wong’s postdoctoral fellowship at MIT, where he met several scientists studying plasmons in graphene. Together, they realized that graphene might be the key to realizing the long-standing goal of a compact and powerful X-ray source. “Graphene plasmons were a natural option because they are capable of confining electromagnetic radiation to very small scales,” Wong explains.

In November 2014, Wong joined SIMTech and began working on the project together with his MIT collaborators. His first steps were to develop a robust ab initio simulation tool that models the exact physics of electrons interacting with a plasmon field, which is sustained on a graphene sheet deposited on a piece of dielectric. By performing numerical simulations, the SIMTech–MIT team showed that this set-up induces a ‘wiggling’ motion in electrons fired through the graphene plasmons, causing the electrons to produce high-frequency X-ray radiation (see image). The simulations agreed with the analytical theory the team had developed to explain how electrons and plasmons interact to produce X-rays.

One standout characteristic of such a source will be its directionality, or ‘pointability’, which will increase efficiency and hence reduce costs by ensuring that all the generated radiation goes where it is supposed to. This will make the source promising for medical treatments as it could be used to target tumors more precisely and hence minimize damage to surrounding organs and cells, notes Wong.

Perhaps most attractive will be the source’s versatility. The output radiation frequency can be tuned in real time from longer infrared rays to shorter X-rays by modifying various elements of the source, such as the speed of the electrons, the frequency of the graphene plasmons and the conductivity of the graphene. This flexible, compact source is promising as a cost-effective alternative to the high-intensity beams used for fundamental scientific and biomedical research. “Although there is a long way to go to actual realization, this is a very exciting research direction,” says Wong. “Developing an intense X-ray source that can fit on a table or be held in one’s hand would potentially revolutionize many areas of science and technology.” The team next plans to experimentally verify their concept with proof-of-principle trials.

Biotechnology:

SIDLING UP TO NATURAL KILLERS

A TECHNIQUE HAS BEEN DEVELOPED TO GENERATE ANTIBODIES THAT CAN HELP STRENGTHEN NATURAL IMMUNE RESPONSES TO CANCER AND LEUKEMIA

The artificial enhancement of the body’s natural immune defenses is a potential weapon in the battle against diseases such as leukemia. A*STAR researchers are honing methods to boost the interactions between antibodies and natural killer (NK) cells, which will increase the ability of the immune system to attack and destroy cancer cells.

Recombinant therapeutic antibodies are commonly produced in Chinese hamster ovary (CHO) cells and some of these antibodies are used to treat cancer patients by killing cancer cells. It is the job of these antibodies (usually human immunoglobulin G1 or IgG1) to bind to target antigens on cancer cells; the antibody then acts as a bridge to recruit natural killer (NK) cells by binding to its receptor, FcγRIII, on the NK cells, before the NK cells trigger cancer cell death using a mechanism known as antibody-dependent cellular cytotoxicity (ADCC).

It is widely accepted that the removal of the sugar, fucose, from IgG1 antibodies can increase their affinity with FcγRIII, dramatically enhancing ADCC activity.

Now, Zhiwei Song at the A*STAR Bioprocessing Technology Institute and co-workers have successfully created fucose-free IgG1 antibodies by inactivating a key fucose-transporting gene (Slc35cl) in CHO cells. These fucose-free antibodies have the potential to...
be used in therapies to treat breast cancer and leukemia patients.

“Other methods exist to generate fucose-free antibodies, but some simply reduce the level of fucose rather than eliminating it,” explains Song. “Earlier studies investigated the removal of a different gene involved in transferring fucose to IgG1, for example. Our new technique provides a feasible strategy for creating fucose-free antibodies, and cell lines can be produced in less than two months.”

The team faced two main challenges when it came to mutating genes in mammalian cells. Firstly, they needed to create a mutation at the target site on the chromosome; to achieve this they used three different gene editing techniques and compared their effectiveness. Secondly, they had to find a way to quickly and efficiently identify and isolate the cells that carry the mutated genes of interest, and used fluorescent cell-sorting for this purpose.

Although all three gene editing techniques successfully inactivated \(\text{Slc35cl}\) to produce fucose-free antibodies, one method — CRISPR-Cas9 — proved easy and quick compared with the other two. Most importantly, Song and his team found that inactivating \(\text{Slc35cl}\) did not affect cell growth, cell density or antibody productivity.

“Our hope is to collaborate with biotechnology companies to generate anti cancer antibodies on a larger scale in future,” says Song.


Plasmonics:

**TINY GAPS PROVIDE A GOLDEN OPPORTUNITY**

Lining up gold nanoparticles in narrow trenches carved into a gold substrate has enabled A*STAR researchers to greatly enhance an optical effect that doubles the frequency of impinging light\(^1\). This approach could help produce miniature ‘on-chip’ devices that convert the frequency of light.

Nanoparticles of metals, such as gold, act as miniature antennas for light, concentrating the electromagnetic field of incident light. This field intensification could be exploited to boost nonlinear optical effects, which occur only in very strong fields.

One such nonlinear effect is second-harmonic generation (SHG), in which two incoming photons with the same frequency combine to form one photon with twice the frequency. Symmetry considerations, however, preclude SHG from occurring inside a gold structure; it can only occur on a gold surface. This limitation has previously hindered the use of gold nanoparticles for SHG.

Now, Joel Yang and Zhaogang Dong of the A*STAR Institute of Materials Research and Engineering and co-workers have solved this problem by producing gold structures in which approximately 8-nanometer-diameter gold nanoparticles coated with an organic compound are squeezed into 12-nanometer-wide trenches. This creates gaps about two nanometers wide on either side of the nanoparticles (see image). These tiny gaps have a dual function - both boosting the field enhancement of the nanoparticles and

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\(\text{FINE}

\[\text{GOLD}\]

\[\text{SUB-5-NANOMETER GAP}\]

Tiny gaps between gold nanoparticles in a trench and the gold substrate greatly enhance frequency doubling of incident light.

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increasing the interaction of light with the gold surface.

The enhancement is stunning. The combination of these two effects augments SHG by more than 4,000 times compared to when the same gold nanoparticles are packed on to a flat gold substrate. “This enhancement in SHG is one of the highest ever reported,” notes Yang.

The team produce the structures in two stages; they used a ‘top-down’ lithography process to create the trenches and then ‘bottom-up’ self-assembly to drop the nanoparticles into the trenches. Importantly, both processes are scalable, so that the structures could potentially be manufactured on a commercially viable scale.

While conventional nonlinear crystals that perform SHG in their interiors still have higher conversion efficiencies, the tiny size of the nanostructures makes them very attractive for realizing SHG on very small scales, including devices that can be integrated into chips. Yang notes that there is much scope for optimization. “There’s plenty of room for improvement, especially for achieving SHG in a miniaturized format,” he says.

The researchers are exploring the use of other materials to achieve even higher SHG enhancements. They are also liaising with a Singapore-based company with a view to commercializing the technique in the future.


Fluid dynamics:
BURSTING THROUGH FOR A BUBBLE SOLUTION

A SIMPLE FLUID DYNAMICS MODEL ACCURATELY PREDICTS HOW BUBBLES IMPACT ON SOLID SURFACES

Bubbles are an essential part of many industrial applications including foam formation, water purification, and oil and gas extraction. To understand the effects of bubbles in these systems, A*STAR researchers have developed a computer model that predicts exactly how they rise through liquids and impact on solid surfaces.

The dynamics of bubbles are surprisingly complex, influenced by processes on micrometer to millimeter length scales, and on timescales ranging from milliseconds up to several seconds. The interface between the air inside a bubble and the surrounding liquid, and the terminal velocity of rising bubbles both change considerably depending on the composition of the liquid.

Then, when a bubble hits a solid surface, the film of liquid that drains off the solid can form complicated shapes that are difficult to predict.

A full solution of this problem would require solving the non linear Navier-Stokes equations — a task that even a supercomputer would take weeks to complete. So, Rogerio Manica at the A*STAR Institute of High Performance Computing and co-workers developed a simpler ‘force balance model’ in which forces such as buoyancy and drag are considered along with lubrication theory to model the draining liquid film.

“We aimed to provide the simplest model to capture the physics.”

“We aimed to provide the simplest model that can capture the physics of the problem,” explains Manica. “In fluid dynamics, more often than not, it is the knowledge of which effects can be neglected and which effects should be included, rather than brute computer power, that determine if a model can represent experimental data accurately.”

They used real data from high-speed camera observations of bubbles to provide some boundary conditions on their simulations and were able to run their simplified model in seconds using a regular desktop computer.

“Our model contains all the major physical ingredients of the system, and in fact
we were surprised by how well it performed when compared to experimental data,” says Manica. “It also has great predictive power, because the parameters are not fitted to any one dataset.”

The team is hopeful that their results will open up possibilities for future research, for example modeling the interaction between bubbles and deformable surfaces. This would include bubbles colliding with the separation boundary between oil and water, a pressing problem for the oil industry. The team will also extend their model to consider oblique impacts of bubbles, and the effects of bubbles sliding along a surface.


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**Materials:**

**FINE-GRAINED MEMORY LOSS**

**NANOCRYSTALLINE SHAPE MEMORY ALLOYS LOSE THEIR MEMORY AS THE CRYSTALLINE GRAINS GET SMALLER**

The ability of shape memory alloys, used as materials for medical stents, to revert to their original shape after an increase in temperature is suppressed at nanometer grain sizes due to effects related to the larger proportion of grain boundaries, according to a mathematical model developed by A*STAR researchers.

This finding helps explain shape memory loss in and increase our understanding of nanocrystalline shape memory materials, which will lead to improvements in the design of such devices.

“Shape memory alloys are commonly used as materials for medical stents because of their interesting shape memory and mechanical properties, and also in other biomedical and engineering applications,” says lead researcher, Rajeev Ahluwalia, from the A*STAR Institute of High Performance Computing.

Shape memory refers to the ability of a material to return to its original form, usually by heating, after relatively large degrees of deformation. This shape recovery occurs because atoms in the crystalline structure of the material change their relative arrangements when there is a decrease in temperature, and return to their original sites upon reheating. This type of ‘martensitic’ transformation can be extremely useful in various applications, but experimentally it has been found that this transformation is suppressed as the constituent crystal grains approach nanoscale dimensions. This potentially reduces the applicability of shape memory alloys at small scales.

Ahluwalia and his team developed a mathematical model for martensitic transformation that successfully reproduces experimentally observed suppression of the transformation in these materials (see image).

“Our model shows that this suppression of the martensitic transformation can be attributed to grain boundary effects,” explains Ahluwalia. “Grain boundaries can impose an energy penalty during transformation, suppressing the transformation locally at grain boundaries, and leading to complete suppression of transformation in small grains below a critical grain size.”

While showing that the temperature induced transformation is suppressed in the nanograin regime, the team’s findings also explained the reduction in ‘mechanical hysteresis’ — the difference in how a material deforms under a given force depending on whether it is loading or unloading — as the grain size decreases. This implies reduced energy loss and reduced mechanical fatigue — desirable properties that can be obtained by decreasing the grain size.

“Understanding the cause behind these interesting behaviors at small grain sizes gives us a means of designing material microstructures to have desirable properties,” says Ahluwalia.

Ethnicity affects the links between vitamin D levels and high blood-sugar levels in pregnant women and the likelihood of them undergoing emergency Cesarean deliveries, shows research in Singapore.

The findings come from a large scale ongoing study of mothers and infants before and after birth, called ‘Growing Up in Singapore Towards healthy Outcomes (GUSTO)’ — a collaboration of Singapore’s National University Health System (NUHS), KK Women’s and Children’s Hospital (KKH) and the A*STAR Singapore Institute for Clinical Sciences.

The GUSTO study is unique in its ability to compare participants from the three major ethnic groups of Singapore — Chinese, Malay and Indian. This enables researchers to explore the influences of ethnicity on several aspects of maternal and infant nutrition and health.

Blood levels of vitamin D and of glucose were measured in 940 women between weeks 26 and 28 gestation. Of these, 388 women had some level of vitamin D inadequacy, which was particularly prevalent among the women of Malay and Indian origin. Vitamin D status was associated most significantly with higher fasting blood glucose levels, and therefore a greater risk of metabolic conditions, in Malay women. For emergency Cesarean section, an intervention often required due to poor muscle performance and uterine contractions, the risk was most significantly increased in Chinese and Indian women.

Although more intensive follow-up study is needed, these findings suggest that the guidance and clinical intervention offered to pregnant women may need to be refined to take greater account of ethnic differences.

“Our evidence also suggests health professionals should monitor vitamin D status in pregnancy, or at least screen those at risk of inadequate vitamin D,” says Mary Chong of A*STAR.

Chong is also concerned about the relatively widespread vitamin D inadequacy

Nutrition:

VITAMIN D IN PREGNANCY

THE SIGNIFICANCE OF VITAMIN D LEVELS IN PREGNANT WOMEN MAY DEPEND ON THEIR ETHNIC ORIGIN
A new route has been identified, through which cell surface receptors can reach the cell nucleus and potentially control gene expression. The discovery by A*STAR researchers could open the door to a new class of drugs to fight cancer and other diseases.

Human cells are separated from their environment by an impermeable membrane, but material is able to enter cells for signaling, nutrition and a wide variety of other functions. In the case of large molecules, cells surround them with an area of their outer membrane which then buds off into internal compartments called endosomes in a process called endocytosis. The molecular cargo can then be recycled, broken down in an organelle called an endolysosome, or taken to a cellular processing machine called the Golgi apparatus.

Frederic Bard’s group at A*STAR’s Institute of Molecular and Cell Biology has been studying how toxins target cells by exploiting this third route via the Golgi apparatus. Frederic Bard’s group at A*STAR’s Institute of Molecular and Cell Biology has been studying how toxins target cells by exploiting this third route via the Golgi apparatus.

An electron microscopy image of a nuclear enveloped-associated endosome (circular object, top left hand quadrant) in close apposition with the nuclear envelope (darker grey line).

There are misconceptions that living in a tropical country like Singapore means the risk of vitamin D deficiency or inadequacy is low,” says Chong. “Our data reveals that this is not true.” Chong points out that many people in Singapore tend to stay indoors to avoid the humid and hot weather, limiting sunlight exposure. There is also only a limited range of local foods that are fortified with vitamin D.

and EGF receptors in the nucleus, and revealed the same two genes were responsible for allowing them to penetrate the nucleus envelope.

Bard believes his findings help explain previous reports of receptors normally seen on cell surfaces accumulating within nuclei. “Before our work, there was no clear mechanism for how this could occur,” he says.

The research could also have important medical applications, notably in the field of cancer therapy. Some cancer drugs work by targeting EGF receptors. However when tumors develop resistance to these therapies, EGF receptors have been reported to accumulate within their cell nuclei.

Greater understanding of how EGF receptors and other proteins can reach the cell nucleus could help researchers develop new therapies that turn genes on or off to fight cancers and other diseases.


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Stem cells:

**BETTER BURN THERAPY ON THE HORIZON**

**ISOLATING THE CELLS RESPONSIBLE FOR HEALTHY SKIN GRAFTS COULD OPTIMIZE A DECADES-OLD BURN THERAPY**

Better treatment for burn victims could follow the discovery of a new marker that can selectively isolate stem cells from a skin sample. This technique, developed by a Singaporean research collaboration, could produce more robust, higher-quality grafts for patients who sustain severe burns, potentially improving treatment for more than 11 million people worldwide each year.

Transplanted skin grafts are used to temporarily cover the large burnt regions of patients’ bodies, protecting them from infection and dehydration. This buys time for doctors to ‘culture’ the patients’ own skin cells in the lab, growing cultured grafts that can permanently replace the donor skin. Pioneered by physician Howard Green in the 1970s, this technique has greatly reduced burn-related mortality.

“Since Howard Green, there has been no technology for skin replacement that surpasses cultured skin grafts,” says Alvin Chua from the Burns Unit at Singapore General Hospital.

To build an improved cultured skin graft, a team led by doctors from Singapore General Hospital and including research colleagues at A*STAR looked to optimize the cell culture step.

“Cultured grafts are usually very fragile,” says Birgit Lane from the A*STAR Institute of Medical Biology. Researchers sought to ‘enrich’ and fortify the grafts by including more stem cells, a cell type with potent tissue repair capability. They needed a cellular marker to identify skin stem cells: a protein usually tasked with evicting foreign chemicals from cells, ATP-binding-cassette G2 (ABCG2), fitted the bill.

Promisingly, “ABCG2 is a cell-surface marker, so we can isolate live cells using a cell-sorting technology,” says Dongrui Ma, the paper’s lead author. Often, stem cell markers cannot target live cells, which limits their clinical applications.

Next they tested human cultured skin, grafted on to mice lacking immune function. ABCG2-positive cultured cells formed thicker and healthier grafts than mixed ABCG2-positive and -negative cells. By contrast, grafts created from ABCG2-negative cells were thin, fragile, and failed to form a healthy outer skin layer.

“IF THIS MOLECULE CAN ALSO ISOLATE THE MELANOCYTE STEM CELLS, IT WOULD BE VERY USEFUL.”

Excitingly, the results also hinted that ABCG2 identifies skin pigmentation stem cells, called melanocytes. “If this molecule can also isolate the melanocyte stem cells, it would be very useful,” says Ma, as melanocytes are...
usually destroyed by deep burns. Restoring them could facilitate a graft that blends better with the patient’s existing skin.

Chua sees great promise for cultured stem cell application in the clinic, but warns that cost could be a barrier to widespread use. He hopes that future research will further improve graft quality, while also speeding production and saving cost. “For severe burn patients, time is of the essence.”


Electronics:

WIRELESS-POWERED NETWORK GETS ITS FAIR SHARE

CALCULATIONS REVEAL HOW SENSORS MUST TAKE TURNS TO HARVEST POWER EFFICIENTLY FROM A DATA HUB

Algorithms that describe the most efficient ways to transmit data and power between wireless sensors and a central hub could help develop large networks of smart devices.

Interconnected wireless devices are increasingly common. For example, smart home appliances can transmit or receive data so that users can remotely control heating or lighting, while remote sensor networks can help gather environmental data such as water quality or air pollution. This burgeoning ‘Internet of Things’ could see billions of sensors deployed across cities, homes, offices and factories.

But many sensors rely on battery power, which can limit their use. “To change the batteries after a few years of deployment would be problematic,” explains Chin Keong Ho of the A*STAR Institute for Infocomm Research. “The sensors might be dispersed throughout a city, and in certain locations, it could be impractical or dangerous to change batteries.”

One alternative is to build a wireless-powered communication network (WPCN), containing sensors that can harvest energy from the radio waves transmitted by the central hub.

Supercapacitors offer a promising way to store this energy, because they are smaller, and charge more quickly, than rechargeable batteries. They can also function through many years of charge-discharge cycles with no loss of performance. However, supercapacitors cannot store energy for long periods, because they tend to self-discharge. This means the sensor may not retain power to transmit data if it only communicates with the hub every few weeks.

Ho and colleagues have now developed a strategy to solve this problem. They calculated the best ways to schedule transmissions around a network of sensors fitted with supercapacitors, so that each sensor was sure to have the energy it needed to send its data back to the hub.

First, they aimed to maximize the total amount of data and power that could be transmitted in a given time, and developed an algorithm that described the optimal solution. “The optimal algorithm we developed performs substantially better than the conventional method,” says Ho.

The researchers also developed a second algorithm to minimize the total charging and transmission time needed to communicate once with every sensor in the network. This algorithm also accounts for differences in the quality of the communication link between different sensors.

In the future, these algorithms should help to design more efficient WPCNs, and the team is now testing them on wireless power prototypes in the lab.

Genetics:

SOME ‘ESSENTIAL’ GENES MORE ESSENTIAL THAN OTHERS

THE ABILITY OF CELLS TO ADAPT TO THE LOSS OF SOME GENES PREVIOUSLY THOUGHT VITAL FOR SURVIVAL CHALLENGES THE CONCEPT OF GENE ESSENTIALITY

Yeast cells can survive even when missing certain ‘essential’ genes, A*STAR researchers have found. This surprising discovery has major ramifications for understanding how cells adapt to challenging situations and for overcoming the problem of drug resistance.

Until now, an essential gene has been defined as one that is critical for a cell’s survival. Knock out an essential gene in a cell and the cell will die. This textbook definition underpins many treatments: drugs are developed to block essential genes in cancer cells and pathogenic microbes, thereby killing these dangerous cells.

Now, Giulia Rancati, Norman Pavelka and co-workers at the A*STAR Institute of Medical Biology and Singapore Immunology Network have shown that the picture is not as clear cut. They found that, given time, yeast cells can undergo evolutionary processes that allow them to adapt to the absence of certain genes previously considered essential.

This means that there are three categories of genes: non evolvable essential genes, non essential genes and a sliding scale of genes lying between these two extremes, which the team dubbed evolvable essential genes. “Our study shows that some essential genes are more essential than others,” explains Rancati.

The researchers performed a multistage investigation on yeast cells from which they had knocked out one of about 1,000 genes that were considered essential. During these experiments, cells were cultured for several days to give them time to evolve to the loss of the gene. Of the about 1,000 genes investigated, 88 were identified as being evolvable essential.

The discovery has evoked a wide range of reactions from the genetics community. “So far we’ve faced responses spanning the whole spectrum from ‘Of course, we see that happening all the time!’ to ‘That can’t be right. You must have made a mistake!’” says Rancati.

It also has profound implications for drug discovery and development. Drug companies frequently sink billions of dollars into developing a promising drug candidate, only to discover several years later that it is useless because resistance can occur. But now, by targeting true essential genes rather than evolvable essential genes, they face much greater chances of finding a drug for which resistance does not develop.

The team intends to bring these results progressively closer to home. “The next big thing will be to bring these studies to mammalian systems,” says Rancati. “We are already planning to do a genome-wide screen to test the evolvability of human cells from which essential genes have been deleted.”

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

A*STAR actively nurtures public-sector research and development in biomedical sciences, physical sciences and engineering, and spurs growth in Singapore’s key economic clusters by providing human, intellectual and industrial capital to our partners in industry and the healthcare sector.

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Data Storage Institute (DSI)
Experimental Therapeutics Centre (ETC)
Genome Institute of Singapore (GIS)
Institute of Bioengineering and Nanotechnology (IBN)
Institute of Chemical and Engineering Sciences (ICES)
Institute of High Performance Computing (IHPC)
Institute for Infocomm Research (I2R)
Institute of Materials Research and Engineering (IMRE)
Institute of Medical Biology (IMB)
Institute of Microelectronics (IME)
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