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The President’s Science & Technology Awards (PSTA) are the highest honours bestowed on exceptional research scientists and engineers in Singapore for their excellent achievements in science and technology. These national awards are given annually to recognise and celebrate outstanding and invaluable contributions by individuals or teams to the research and development landscape in Singapore.

CONGRATULATIONS TO THE 2012 PSTA WINNERS

**President’s Science & Technology Medal**

The President’s Science & Technology Medal is awarded to outstanding individuals who have made distinguished, sustained and exceptional contributions and played a strategic role in the development of Singapore through the promotion and management of R&D.

**PSTM 2012 Winner:**
**Professor Dim-Lee Kwong**
*Agency for Science, Technology and Research*

“For his distinguished, sustained and exceptional contributions to Singapore’s science and engineering landscape, particularly in advancing the semiconductor industry through R&D and the forging of strategic research partnerships between industry and public sector agencies”

**President’s Science Award**

The President’s Science Award is presented to research scientists and engineers in Singapore who have made outstanding contributions in basic research leading to the discovery of new knowledge or the pioneering development of scientific or engineering techniques and methods.

**PSA 2012 Winner:**
**Professor Wang Yue**
*Agency for Science, Technology and Research*

“For his ground-breaking discoveries in the biology and virulence of the fungus Candida albicans, a leading cause of serious hospital-acquired infections”

**President’s Technology Award**

The President’s Technology Award gives recognition to research scientists and engineers in Singapore who have made outstanding contributions to research & development resulting in significant new technology or innovative use of established technology.

**PTA 2012 Winner:**
**Professor Dim-Lee Kwong**
*Agency for Science, Technology and Research*

“For the development of a novel flexible endoscopic robotic system that enables intricate surgical procedures to be performed without the need for external incisions”

**PTA 2012 Winners:**
**Professor Ho Khek Yu**
*National University Health System*

**Assoc. Professor Louis Phee**
*National Technological University*

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**RESEARCH HIGHLIGHTS**

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- Editor-in-Chief: Charles Zukoski
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**ON THE COVER**
Research from A*STAR is enabling lithography at the nanoscale through the development of new, higher-contrast techniques [page 71]
The Young Scientist Awards (YSA) recognise young researchers, aged 35 years and below, who are actively engaged in R&D in Singapore, and who have shown great potential to be world-class researchers in their field of expertise. This award is organised by the Singapore National Academy of Science (SNAS) and supported by A*STAR.

Congratulations to the 2012 YSA Winners

Assistant Professor Chen Wei
National University of Singapore
“For his research on interface engineering for molecular, organic and graphene electronics”

Assistant Professor David Lou
National Technological University
“For his research on nanostructured materials for energy and environmental applications”

Dr Joel Yang
Agency for Science, Technology and Research
“For his research on nanolithography and nanoplasmonics”

YSA 2013 Call for Nominations
Nomination forms are available at:
http://www.science.edu.sg/snas
Nominations will close on 30th April 2013
For assistance, please contact the YSA Secretariat at 6790 3854 or email subramaniam.r@nie.edu.sg
The 2012 President’s Science and Technology Awards

Innovative and impactful research takes center stage at Singapore’s prestigious science awards

Widely regarded as the nation’s top scientific honors, the President’s Science and Technology Awards (PSTA) recognize outstanding contributions to research and development that are helping to shape Singapore’s science and engineering landscape. A uniting theme at the 2012 awards, conferred by Tony Tan Keng Yam, president of Singapore, at a ceremony held on 30 October 2012, was the impact on society and the economy associated with each of the award-winning fields of research.

A*STAR scientists were among the award winners this year. Dim-Lee Kwong, executive director of the A*STAR Institute of Microelectronics (IME), was awarded the President’s Science and Technology Medal, and Wang Yue of the A*STAR Institute of Molecular and Cell Biology (IMCB) received the President’s Science Award. In addition, Joel Yang of the A*STAR Institute of Materials Research and Engineering (IMRE) was one of the recipients of the Young Scientist Awards, which celebrate young researchers who demonstrate the potential to be future leaders in their fields.

Congratulating all 2012 PSTA winners, Tan stated: “This year’s winners have all demonstrated the spirit of innovation, admirable passion and commitment, and a relentless pursuit of excellence. All of them have made important discoveries, raised the bar for scientific excellence in Singapore, and made a significant positive impact on Singapore’s economy and society.”

A big win for innovation

Throughout his distinguished career, Kwong has played a prominent role in the development of Singapore’s semiconductor industry. He is credited not only with establishing major partnerships between the IME and more than 50 multinational companies, but also helping to launch large-scale initiatives supporting the emergence of innovative enterprises and technologies such as the 3-D Through-Silicon Via (3D TSV), Micro-Electro-Mechanical-Systems (MEMS) and the Electronic Packaging Research Consortium.

On being awarded the 2012 President’s Science and Technology Medal, Kwong comments: “I am honored to receive this prestigious award. This would not have been possible without the commitment and untiring efforts of every one of us at IME, and our partners in industry. We have worked hard to build up research capabilities for the microelectronics sector and constantly pushed the envelope of scientific excellence and have raised the profile of Singapore’s R&D internationally. I am very gratified to see that the work we do has reaped success and has contributed to the progress of Singapore’s industry, particularly the semiconductor sector.”

Among his many achievements, Kwong is a longstanding advocate of A*STAR’s outreach and educational activities, and has served as an A*STAR Research editorial board member from 2009 to 2011.

As remarkable strides continue to be made in Singapore’s burgeoning technology market, Kwong emphasizes the importance of building strategic collaborative partnerships, noting that the semiconductor industry is “undergoing a major paradigm shift from the fabless/foundry model to integrated fabless manufacturer (IFM) model.” He explains, “Fabless companies are now actively engaging chip equipment and materials suppliers to know what technologies would become available and how they could be implemented. IFM requires holistic path-finding of advanced technology and optimization of packaging-process-design integration. It is all about integration and collaboration.”
Excellence in medical research

The 2012 President’s Science Award was awarded to Yue for his exemplary research on *Candida albicans*, a fungal pathogen that causes life-threatening infections in humans. Wang and his IMCB team’s studies have yielded valuable insights into *C. albicans* development; his laboratory was the first to identify Hgc1 as a master regulator of the transformation of *C. albicans* from a benign to virulent form, and showed that removing Hgc1 significantly reduced the ability of the pathogen to cause infection in mice. Wang’s group also found that Hgc1 works together with a protein called Cdc28 to regulate cellular machines responsible for cell shape formation.

“The impact of this discovery is manifold,” explains Wang. “First, we gained a better understanding of mechanisms underlying *C. albicans* virulence. Second, Hgc1 may be targeted for drug development. And third, we found an excellent model to address the fundamental biological question of how cells attain a certain shape.”

On receiving his award, Wang comments: “It is a great honor for me to be conferred this prestigious award. It is recognition of not only my achievements but also those of all people who have worked with me in the past 15 years. It gives me a strong sense of satisfaction that my studies have made significant contributions towards a better understanding of a major human disease and opened up new opportunities for drug development. This award will certainly serve as a great inspiration and encouragement for me and my group to scale new heights in the future.”

Nanoscience gets the nod

In the Young Scientist Award category, Yang at A*STAR’s IMRE was recognized for his work on nanolithography and nanoplasmonics. Yang and his team have been pushing the boundaries of digital imaging technologies, most recently demonstrating that color images can be produced at an unrivaled resolution of 100,000 dots per inch (dpi). (See Fine prospects for high-resolution printing and Microscopy: A glance from the nanoworld for more details.)

“It is a very special honor to win the Young Scientist Award,” says Yang. “I feel very fortunate and thankful that not only the effort I have put in, but also the efforts of those with whom I’ve worked closely are being recognized.”

Yang refers to the IMRE’s “top-notch research facilities” as a key factor in enabling his team’s cutting-edge work. “The support from IMRE’s management for young scientists to attend and present our work at focused conferences is also important in keeping us abreast of the latest developments in the field,” he says. “On a day-to-day basis, being able to build a group and surround myself with intelligent and passionate peers was crucial in creating an atmosphere where constant discussions generate new ideas and stimulate creativity.”

Slimmer data storage solutions

In recent years, the hard disk drive industry has undergone dramatic change in response to the growing interest in light, portable computing devices — such as notebooks, Ultrabooks and tablets — that are still capable of performing sophisticated tasks without loss of quality and speed. The challenge for developers of data storage technology has been to devise compact, cost-effective solutions for use...
Innovative data storage solutions offer exciting prospects for the technology industry and consumers alike.

At less than five millimeters thick, the A-Drive is one of the world’s slimmest storage devices of its kind.

In a move that promises to boost next-generation storage technologies in Singapore, the A*STAR Data Storage Institute (DSI) has launched a hybrid hard disk drive that, with a thickness of just 5 millimeters, ranks as one of the world’s slimmest storage devices of its kind.

Dubbed the ‘A-Drive’ by its designers, the sleek new device boasts marked advantages on all fronts: increased storage capacity, lower power consumption, and lower manufacturing costs. By offering power consumption reductions of up to 50%, researchers expect the drive to become a leading contender in the quest to offer a cheaper and ultimately greener alternative to solid-state drive (SSD) solutions currently on the market.

**Top-of-the-range technology**

The ever-increasing popularity of smaller and lighter computing devices has driven leading manufacturers to seek out new and innovative ways to provide reliable, high-capacity storage solutions while minimizing cost. One such solution is the hybrid hard disk drive — where the platters and heads of conventional hard disk drives are combined with additional non-volatile memories. Crucially, the non-volatile memory component can cache data for greater efficiency, enabling swifter boot-up times.

Interest in hybrid hard disk drives has heightened due to their potential for integration into the thinnest of notebooks and tablet devices. “In the future, hybrid drives will potentially be a preferred storage device choice for consumers and business owners looking for more compact mobile computing devices,” say the A*STAR researchers who contributed to the A-Drive project. “The A-Drive would be able to address the limitations of the popular, yet expensive, flash-based SSD, as well as the conventional hard disk drive for the consumer and business industry.”

The development of the A-Drive fulfills a long-held vision of the DSI: to produce one of the world’s most compact hybrid hard disk drives within the 2.5-inch form factor used for laptops. “The A-Drive provides a seamless integration of data and storage management and offers top-of-the-line features without incurring high costs,” say the researchers. “With its slim form factor, the A-Drive could fit into Ultrabooks and tablets, and due to its hybrid architecture, it offers a larger storage capacity than SSDs currently used in Ultrabooks, offering the same instant-on capability and with larger storage capacity, while capable of extending battery life by up to 30% as compared to conventional hard disk drives.”

**Unique design**

One of the biggest challenges faced during the design and development of the A-Drive was the reduction in thickness of the hard disk drive from 7 millimeters to just 5 millimeters, without compromising on performance and stability. In order to overcome this major technological hurdle, the researchers incorporated the DSI’s proprietary 4-millimeter-thin axial field motor, which can spin at 5,400 revolutions per minute. The slim spindle motor helps to reduce the friction loss of the bearing, vibration and acoustic noise, leading to lower power consumption and resulting in a more environmentally friendly design. Notably, the axial field motor has been patented, along with thirty other unique designs relating to the A-Drive.

The development of the A-Drive has allowed the DSI to deepen its ties with industry, with key parts being developed in collaboration with some of the world’s leading manufacturers of precision engineered components, including Seiko Instruments Singapore Partnerships Ltd, Miyoshi Precision Ltd and Unisteel Technology Ltd.

To further build upon the advantages of the ultra-thin drive, the researchers note that the DSI is “already working with another sister research institute, the A*STAR Singapore Institute of Manufacturing and Technology, on a helium-sealed...”
Crystal structure of a drug molecule bound to a common cold viral drug target.

Drug discovery is a rapidly evolving discipline, fuelled by recent advances in biotechnology and medicinal chemistry, and forms an essential part of pharmaceutical research. From the identification of new drug targets to the screening of candidate compounds to determine their therapeutic efficacy, the road to drug discovery presents immense challenges to biologists and chemists alike, who share the common goal of developing treatments that will ultimately enter clinical trials in patients.

Given the importance of bringing together basic, clinical and commercial insights for the successful development of new treatments, the field of drug discovery is one that particularly benefits from close interaction between academia and industry. At the A*STAR Experimental Therapeutic Centre (ETC), a unique educational program called the Drug Discovery Course, launched in September 2011, is attracting leading researchers as well as those from the private sector to promote deeper understanding of drug discovery methods and techniques.

The inaugural course in 2011 was attended by 80 participants from A*STAR-affiliated institutions, hospitals, pharmaceutical companies, regulatory bodies and universities in Singapore. The program was carefully structured to offer real-world examples of the methodologies, tools and techniques used in translating biological insights into safe and effective therapeutic agents.

Due to the high level of interest generated by the program content and based on the positive feedback about the quality of the training, the ETC ran the Drug Discovery Course again in September 2012, which was attended by 96 participants, also from diverse backgrounds.

Opening up the world of drug discovery

The A*STAR Experimental Therapeutic Centre strengthens its educational initiative through its popular Drug Discovery Course

Two decades of technological innovation

The year 2012 marks the twentieth anniversary of the establishment of the DSI. Befittingly, the A-Drive project is a milestone achievement in the institute’s intensive efforts to advance innovative research and development (R&D) capabilities for next-generation data storage technologies in Singapore. The official launch of the A-Drive was presided over by S. Iswaran, a minister in the Prime Minister’s Office and Second Minister for Home Affairs and Second Minister for Trade and Industry.

The DSI continues to play an integral role in the growth of the technology sector in Singapore, accelerating R&D in the key areas of data center technologies, non-volatile memories, advanced magnetic recording and bit-patterned media recording, and nanotechnology. Some of the latest examples of the DSI’s work on magnetic recording and modeling research include “Data storage: How magnetic recording heats up” and “Data storage: Going with the grain,” and other advances in computing technologies achieved by the institute’s non-volatile memory coding team were presented in the article “Innovation: Novel coding technique patented by A*STAR researchers”, in 2012.

Sharing his thoughts on the successful launch of the A-Drive, DSI Executive Director Pantelis Alexopoulos states: “Our year-long vision of creating a 5-millimeter-thin hybrid hard drive in 2.5-inch form factor with increased storage capacity and reduced power consumption at a lower cost for manufacturers has become a reality. We have managed to fit an amazing amount of innovation and advanced technology into a thinner, cheaper, and faster design, and we think the consumer and enterprise impact will be significant.”

Alexopoulos adds: “Our capabilities have been the result of collaboration with industry partners around the world. This has enabled the DSI to develop groundbreaking solutions like the ‘A-Drive’. We look forward to future partnerships as we continue to strive towards new innovations that will shape the data storage landscape.”
**High-caliber training**

The Drug Discovery Course broadly consists of twelve modules, with topics including target identification and validation, screening and in vivo drug evaluation, preclinical development, and the procedures involved in drug regulatory submissions. The course also provides a historical overview of drug development, highlighting practical examples of both the successes and pitfalls of generating new medicine candidates. In addition, it covers contemporary issues such as the protection of intellectual property rights in drug discovery and development.

The course draws on the wealth of expertise brought by the guest lecturers and trainers who are involved in putting the program together. The trainers have included members of the ETC and the A*STAR p53 Laboratory, as well as distinguished representatives from Novartis, GlaxoSmithKline, Merck Sharp & Dohme, Aslan Pharmaceuticals, Takeda, Codexis, S*Bio and Singapore’s Health Sciences Authority.

The original idea behind the Drug Discovery Course grew out of the interest expressed by Singapore-based academics in furthering their knowledge of the processes involved in drug discovery, and the program was designed to respond to the needs of both A*STAR researchers and the wider biomedical science community.

The Drug Discovery Course is part of a wider initiative by the ETC to promote interaction and collaboration with industry and encourage community engagement in the ETC’s activities. Situated at Biopolis, Singapore’s premier hub for biomedical research and development, the ETC is well-positioned to continue accelerating drug discovery and developing innovative research tools in collaboration with both academic and industrial partners.

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**Sighting the genetic variants of eye diseases**

*In a world’s first, Singaporean scientists have discovered the genes responsible for cornea blindness, providing valuable information for treatment and prevention of degenerative eye diseases*

In a new study, researchers at A*STAR’s Genome Institute of Singapore (GIS) and the Singapore Eye Research Institute (SERI) successfully identified the genes involved in central corneal thickness (CCT). CCT can result in potentially eye-blinding conditions such as keratoconus, a degenerative disorder in which the cornea changes to a conical shape, and glaucoma, where damage to the optic nerve leads to permanently impaired vision. Uncovering specific genes associated with CCT would therefore be most valuable in assisting eye doctors to promptly diagnose patients with high risk for progression.

The GIS’s collaborator in this study, SERI, is the national institute for ophthalmic and vision research in Singapore. SERI works with local clinical ophthalmic centers and biomedical research institutions, as well as major eye centers and research institutes throughout the world. The international research team, led by Deputy Director of SERI and Head of Glaucoma Service at Singapore National Eye Centre, Tin Aung, consisted of over 50 clinicians, clinician-scientists, research scientists, research staff and statisticians. A meta-analysis of more than 20,000 individuals in European and Asian populations was conducted with 16 new loci — the specific location of a gene on a chromosome — associated with CCT being identified. “It has been a tremendous achievement spanning extensive global efforts, with Singapore playing a major role particularly in SERI’s population-based studies of 10,000 Chinese, Malays and Indians,” explains Aung.

Prior to this extensive global collaborative effort, the Singaporean team achieved considerable success by identifying six distinct genetic loci. Samples were collected from local Chinese, Indians and Malays, as well as Chinese populations in Beijing between 2011 and 2012. However, within the sampled populations, no genes were demonstrated to be associated with common eye diseases, suggesting that most of the CCT-associated loci identified from populations of European descent are shared with Asian populations. The findings prompted the researchers to establish partnerships worldwide in order to expand the scope of study.
As a leading public research agency in Singapore, A*STAR’s mission is to foster world-class scientific research and talent that will transform the country into a vibrant, knowledge-based economy. It aims to achieve this by strategically investing in human, intellectual and industrial capital to support research and development across engineering and the biomedical and physical sciences. In its latest venture, A*STAR has established ‘D3’, a cooperative effort named after the platform’s mission of drug discovery and development. D3 has been launched as a national resource and is jointly funded by A*STAR and Singapore’s National Medical Research Council (NMRC) and National Research Foundation (NRF). The platform’s team of experts will focus on taking projects through the development process from preclinical development candidates (PDCs) to ‘proof-of-concept’ (PoC) studies in humans, with the overall goal of developing treatment modalities for Singaporean patients, generating major economic benefit through licenses and potentially creating new intellectual property.

Alex Matter, the CEO and driving force behind the development of D3, has a clear vision for the platform. “Our mission is to perform translational R&D for biomedical discoveries made in Singapore and elsewhere. If we want to take this seriously we need to build a seamless value chain from biomedical discovery — or even a mere concept — to a clinical application,” he says. “We have crystallized this to say that we want to go from a validated drug target to proof-of-concept in humans, the point at which we have obtained evidence that early clinical endpoints can be attained with the novel medical entity, at tolerated doses, via the proposed mechanism of action.”

Overcoming hurdles
In recent times, large pharmaceutical companies and venture capital investors within the drug discovery and development space have required that the risk of failure be reduced. In the current environment, the drug development process is complicated and lengthy. It may take as long as 10 to 15 years and significant financial investments to bring a new medicine from an initial discovery concept to the market. Consequently, the challenges are considerable. The A*STAR D3 platform has been established to build strong bridges between basic science and clinical research and development.
discovery sector have become more cautious and are typically less willing to invest in early-stage projects. Furthermore, commercial partners prefer to engage in projects where major or risky hurdles have already been overcome. D3 was founded to be a cost-effective and professional development partner able to advance and add value to early-stage projects on a ‘shared-risk, shared-reward’ basis. Fortunately, D3 already has solid human and financial resources in place to take new chemical entities (NCEs) and biologics that have reached the preclinical-development candidate stage through to early development and early clinical trials in humans. Such trials can be initiated via authorization from regulatory authorities, including Singapore’s Health Sciences Authority (HSA) and the US Food and Drug Administration, and are driven by D3 to a PoC stage. Following PoC, D3 licenses the compounds to pharmaceutical or biotechnology companies for further global development and launch.

By working closely with other A*STAR institutes, D3 is building a bridge between basic science and clinical translation. For example, the Experimental Therapeutics Centre (ETC), a sister organization of D3 which shares a similar focus, is a rich source of projects for the platform. D3 also collaborates with other research groups in Singapore, such as the Singapore Clinical Research Institute (SCRI), the Investigational Medicine Units of the Singapore Health Services, the Changi General Hospital and the National University Health System, as well as industry partners.

“D3 looks for projects that are innovative and offer real benefits over existing therapies or address an unmet medical need,” says Louise Sarup, head of the platform’s business development and licensing activities. “Our primary focus is on drugs targeted at oncology indications and infectious diseases. However, the group isn’t limited to these areas and will consider projects in other areas if they are innovative, exciting and D3 can develop them efficiently and effectively using locally available expertise.”

A fortuitous start
In the first half of 2013, D3 will spearhead a project to advance an H1N1 influenza virus-like particle vaccine from preclinical through to clinical development. Jointly developed with the ETC, the Singapore Immunology Network (SIgN), the Duke–NUS Graduate Medical School (Duke–NUS), the DSO National Laboratories and biopharmaceutical company Cyros Biotechnology AG, the project is a successful example of the collaboration between D3 and the ETC. The transition of an oncology small molecule project from the ETC to D3 has also commenced with D3 embarking on early preclinical-development activities. This project, developed to date by the ETC and Duke–NUS, is another example of multiple groups in Singapore working together across the drug development pathway.

“In addition to the development of the influenza vaccine and the oncology small molecule project, our immediate intentions for D3 are to increase the number of projects in our portfolio,” says Sarup. “To do this we are looking at all of the institutes in Singapore, as well as reaching out to our industry contacts and attending scientific and ‘biopartnering’ conferences and meetings.”

The novel products created by D3 are likely to serve both global and regional markets, contributing to overall improvements in human health in addition to boosting industry and the economy in Singapore. By complementing Singapore’s vision to become a global hub for drug discovery and development, the activities of the D3 platform have the potential to generate both high-value jobs for skilled individuals and intellectual property rights from drug or vaccine candidates — pointing to a promising future as D3’s projects take off.
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• Nanomaterials for Energy, Environmental, Chemical and Catalytic Applications

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• Joseph M. DeSimone, University of North Carolina, USA

INVITED SPEAKERS
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The inflammatory response is a double-edged sword — it enables the body to mount a vigorous defense against infection, but can also inflict serious physiological damage if allowed to rampage uncontrolled. Patients experience the worst of both worlds when an infection gives way to sepsis. They undergo an initial strong inflammatory response that subsequently gives way to immunosuppression, wherein immune cells no longer respond to toxic molecules produced by bacteria.

“Sepsis is a major cause of mortality in intensive care units worldwide,” says Subhra Biswas of the A*STAR Singapore Immunology Network, “but no reliable biomarkers or specific drug therapies are available.” This may soon change, thanks to new insights from Biswas and his co-workers. They have revealed how a specific population of immune cells known as monocytes could exacerbate this condition.

“It is believed that these cells play a role in regulating both the inflammatory and immunosuppressive features of sepsis,” explains Biswas. However, there is a variety of monocyte subtypes, each of which manifests a different collection of cell surface proteins that might activate distinct downstream signaling pathways. For this study, Biswas and his co-workers focused on a receptor protein called CD16, which is predominantly expressed on a particular subtype of monocytes. In the blood of patients with sepsis, they found increased numbers of CD16-expressing monocytes.

In many infections, sepsis is mediated largely by signaling pathways activated by the Toll-like receptor 4 (TLR4) protein. Biswas and co-workers learned that CD16 activation regulates the effects of TLR4 signaling in monocytes in a manner that may enable sepsis to progress. They observed that stimulation of both CD16 and TLR4 in monocytes led to the increased expression of a number of genes that contribute to inflammation. However, CD16-mediated signals also led to the expression of molecules that inhibit signaling pathways responsible for the initial inflammatory stage of sepsis. “These results indicate the possibility that this pathway acts as a ‘switch’ to tip the function of monocytes over the course of inflammation,” says Biswas.

Although CD16 monocytes seem to be important contributors to sepsis, Biswas points out that their role needs to be further clarified before considering their use as a focus for therapy. “Targeting these cells at the wrong phase of sepsis could lead to problems for patients,” he says. Accordingly, he and his team will continue to chart the role of monocytes throughout sepsis in order to understand how progression might be thwarted.

Some bacterial infections will give rise to immune failure in the form of sepsis, a condition that poses an especially serious mortality risk for hospital patients.

Inappropriate activation of an immune signaling pathway during infection leaves the body vulnerable to sepsis.
Cell biology:

Accelerating cellular assembly lines

*Insights into cellular productivity could boost generation of proteins with valuable research and medical applications*

The immune system generates antibodies to mark threats that need to be eliminated, and these protein complexes bind their targets with remarkable strength and selectivity. Scientists have learned how to generate cell lines that can produce large quantities of specific ‘monoclonal’ antibodies (mAbs) with desirable properties; these mAbs are powerful tools for diagnostics, medicine and biological research.

The selection of suitable cell lines is an important aspect of large-scale production, as these can vary considerably in their individual mAb output. To assist manufacturing facilities in maximizing the generation of these precious molecules, Ying Swan Ho’s team at the A*STAR Bioprocessing Technology Institute in Singapore has identified key features of top-performing cells in mAb-producing cultures.

“By selecting antibodies (blue and yellow) with strong affinity for particular targets, scientists can label or isolate proteins of interest, or even modulate the function of those proteins in living cells.”

The researchers cultivated CHO clones that were either high or low mAb producers, where productivity differed by up to 28-fold. They observed clear differences between the two groups in levels of molecules associated with several key metabolic pathways. For example, high-producer clones contained elevated levels of compounds associated with the electron transport chain, a mechanism that generates the adenosine triphosphate (ATP) molecules that power virtually every cellular process.

As energy and mAb production ramp up, cells also generate large quantities of molecules known as reactive oxygen species, which can inflict serious damage on the cell. This threat can be neutralized by molecules such as reduced glutathione (GSH). Ho and co-workers determined that high producers of mAbs also generated greater amounts of GSH than their low-production counterparts.

These findings offer a more global view into how CHO cells might brace themselves to handle the rigors of large-scale protein synthesis. The researchers now intend to explore the individual contributions of these various metabolic pathways. “This will be done by evaluating the effects of increasing the cellular pools of these metabolites on mAb productivity in different cell lines,” says Ho. With a deeper understanding of the key pathways, scientists should be able to either improve the selection of mAb-producing clones or modify culture conditions to ensure that the cells can work as hard as possible.

Dendritic cells (DCs) — workhorses of the immune system — derived from human embryonic stem cells (hESCs) may provide an economical way of generating off-the-shelf therapeutic vaccines against cancers, according to research led by Jieming Zeng and Shu Wang from the A*STAR Institute of Bioengineering and Nanotechnology, Singapore.

DCs process and present antigens — substances that stimulate immune responses — to other cells of the immune system that will then eliminate pathogenic cells carrying these antigens. This ability makes DCs ideal as vaccines within the body. As such, the US Food and Drug Administration recently approved the first DC-based vaccine for use. DCs sourced from another individual, however, may be attacked by the immune system of a recipient. Consequently, DC-based vaccines have been prepared using cells derived from the recipient’s own body. This is expensive, the supply of cells is limited, and highly variable results have complicated the evaluation of clinical trials.

Using hESCs, however, it is possible to produce a steady supply of DCs in unlimited numbers, under strict quality control. But, since these DCs are still susceptible to immune attack, Zeng, Wang and co-workers enlisted the aid of invariant natural killer T (iNKT) cells. These cells can be stimulated by compounds attached to molecules of the glycoprotein CD1d and used to boost the activity of DCs, thereby enabling them to trigger the immune response before being eliminated.

First the researchers added genes to DCs generated from hESCs to produce extra CD1d. The greater amount of this glycoprotein produced by the cells then triggered an expansion of iNKT cells in the presence of α-galactosylceramide (α-GC), a ligand or compound which binds to iNKT cells. Subsequently, they found that α-GC was unnecessary for inducing an anti-tumor response. This is advantageous because previous studies by others with mice had shown that using α-GC for this purpose can lead to uncontrolled iNKT activation. In fact, the researchers showed that pulsing the modified DCs with melanoma antigen was sufficient to prime immune T cells against melanoma tumor cells. The same strategy worked with DCs derived from human monocytes, a type of white blood cell.

“The ability to generate large amounts of uniform hESC-DCs competent in inducing antitumor immunity indicates that they could be used as an unlimited cell source to produce off-the-shelf DC vaccines, to overcome the drawbacks of using an individual’s own cells,” Wang says. “We are now focusing on developing a simpler process to produce DCs with similar or even better capabilities.”

A repressor protein that blocks differentiation-specific genes helps maintain stem cells’ ability to develop into any cell type

Researchers at the A*STAR Institute of Medical Biology (IMB) have discovered a critical checkpoint protein that controls when human embryonic stem cells (hESCs) begin to differentiate.

The Nodal/Activin signaling pathway is an important regulator of hESC fate. Signaling molecules in this pathway trigger the downstream proteins SMAD2 and SMAD3 to activate a transcription factor known as NANOG, as well as other core pluripotency proteins. These regulatory factors, in turn, ensure that the self-renewing hESCs remain capable of forming all cell types in the embryo and avoid differentiation. When differentiation is triggered, however, the role of this signaling axis changes, and the very same pathway begins to drive the formation of primitive cell types, namely the mesoderm and endoderm.

To explain these contrasting effects of Nodal/Activin signaling, a team led by the IMB’s Ray Dunn explored the role of repressor proteins in the pathway. “We reasoned that one explanation for why hESCs do not differentiate in the presence of Nodal/Activin is the existence of repressor proteins that decorate the regulatory elements of differentiation genes and turn them off,” Dunn explains. “In my lab, we identified one such repressor that fits this bill, [it is] called SNON.”

SNON, an abbreviation of Ski-related oncogene N, is a potent repressor of SMAD2 and SMAD3 and, as Dunn’s team showed, is abundant in undifferentiated hESCs, but only at the promoters of differentiation genes. At the onset of differentiation, SNON is destroyed by the proteasome, the cell’s clean-up machinery for unwanted proteins. SNON levels then drop precipitously (see image), which allows SMAD2 and SMAD3 to cooperate with other transcription factors involved in the determination of cell fate, including FoxA2. This leads to the formation of early mesoderm and endoderm, two of the three primitive germ layers.

“Our research shows that when hESCs begin to differentiate, SNON is targeted for degradation,” says Dunn. This finding is consistent with many studies of cancer cell lines, which, like hESCs, retain the ability for continuous proliferation and also have elevated levels of SNON.

One outstanding question, according to Dunn, remains the identity of the molecules that target SNON for degradation. A protein called ARKADIA is one suspect. ARKADIA is known to regulate SNON stability in a cell type-dependent fashion, but its role in embryonic stem cells remains unclear.

“Follow up experiments in our lab aim to determine whether ARKADIA acts alone or collaborates to degrade SNON in hESCs.”

Cell biology:

Picking out partners

An intracellular labeling technique allows scientists to monitor interactions between proteins in their natural environment

One can often begin to understand a protein’s function by identifying its accomplices in the cell. Accordingly, scientists have developed diverse biochemical assays that essentially allow them to go ‘fishing’ for interaction data — using a purified protein of interest as ‘bait’ to pluck its binding partners from out of a cellular extract.

“BioID has the potential to capture those weak and transient interactions that the other biochemical methods often miss.”

Such assays are not always an option, however; many cellular proteins are very difficult to purify, making it impractical to use them as bait in a binding assay. For example, Kyle Roux of the Sanford Children’s Health Research Center, USA, has encountered persistent difficulties in his efforts to study interactions with proteins that contribute to the envelope surrounding the cellular nucleus. In collaboration with A*STAR researchers Manfred Raida of the Experimental Therapeutics Centre and Brian Burke of the Institute of Molecular Biology, Roux has now developed a promising solution for dealing with such tricky targets. They made use of a mutant variation of BirA, a bacterial enzyme that tags nearby proteins with a molecule called biotin. The mutant, BirA*, is indiscriminate in its labeling. Roux and co-workers predicted that any cellular protein that gets fused to BirA* should permanently mark its interacting partners with biotin. This would make them easy to isolate after the assay is done. Most importantly, these experiments can be done in the milieu of a living cell, making them more ‘natural’ than conventional binding assays.

As a test case, the researchers used lamin A, a nuclear envelope-associated protein that confounds efforts at purification by forming insoluble clumps. Their technique, which they termed BioID, proved highly effective, yielding more than 120 biotin-marked proteins that potentially interacted with lamin A over the course of the 24-hour labeling period. Even fleeting associations can result in BirA* labeling, notes Roux. “BioID has the potential to capture those weak and transient interactions that the other biochemical methods often miss,” he says, but adds that follow-up experimental confirmation will still be required.

The team’s demonstration of BioID also netted at least one previously uncharacterized protein that appears to represent a bona fide nuclear envelope constituent (see image). Roux is confident that this technique could prove a potent tool for mapping interaction networks in structures throughout the cell. “We have already successfully applied BioID to integral membrane proteins,” he says. “We have also used BioID in the mitochondrial matrix and at the nuclear pore complex, and these studies will soon expand to the extracellular space.

Mice have made an immeasurable contribution to medicine and our overall understanding of human disease. This animal model is not without its limitations, however, and scientists are continually learning about important ways in which mouse and human biology differ.

Both human and murine immune systems, for example, function in a similar fashion, but individual subtypes of human immune cells often display characteristics unlike those of their mouse counterparts. These differences make it difficult to directly translate mouse data into medically meaningful results. By identifying parallels between a crucial class of immune cells in mice and humans, a team led by Florent Ginhoux of the A*STAR Singapore Immunology Network has obtained valuable insights that should accelerate this translation.

“Now that we know that this population exists, our aim is to understand how to mobilize it, activate it and to target it with adjuvants and antigens relevant for vaccination.”

Cells known as dendritic cells (DCs) are at the immune frontline, capturing pathogen-derived antigens and training other immune cells known as cytotoxic T cells to recognize them via a process called ‘cross-presentation’. “This is very important, as it is the only way DCs can present tumor-derived antigens or viral antigens without being a tumor cell or directly infected by a virus,” explains Ginhoux. “And, it has important implications for vaccine design, where you want to get a good cytotoxic T cell response.”

A subset of DCs found within the murine skin plays a particularly prominent role in this process, but equivalent cells have not yet been identified in humans. DC subsets that look similar but function differently from each other can be distinguished via distinct combinations of surface proteins that act as a ‘name tag’. Through careful analysis, Ginhoux and his co-workers isolated and characterized a population of skin cells that express high levels of the protein CD141 (see image), which effectively tags this human DC subset.

The researchers determined that these skin DCs indeed possess the cellular machinery needed for cross-presentation. Ginhoux believes they should offer a useful tool for training the immune system to fight disease. “Now that we know that this population exists, our aim is to understand how to mobilize it, activate it and to target it with adjuvants and antigens relevant for vaccination,” he says. In the process of characterizing these cells, the researchers also succeeded in profiling the expression of various ‘name tag’ proteins. From these profiles, they can draw parallels between equivalent DC subsets in mice and humans, building a valuable informational resource for future research. “This will allow clear inferences to be made between mice and humans,” says Ginhoux.

Microbiology: Eavesdropping on bacterial conversations

A signaling receptor that aids bacterial communication may provide a target for reducing virulence without antibiotics

For decades, microbiologists thought that bacteria act individually, unaware of their multitudinous counterparts involved in causing the same infection. In the past two decades, however, they have discovered that many species of bacteria ‘communicate’. In fact, bacteria can signal to each other that their numbers are sufficient to launch a coordinated attack.

Owing to the relative newness of this research area, few of these cell-to-cell signaling systems, known as quorum-sensing, have been described. Now, by working with Burkholderia cenocepacia, an opportunistic pathogen that infects cystic fibrosis patients, a research team led by Lian-Hui Zhang from the A*STAR Institute of Molecular and Cell Biology (IMCB) has described a previously unknown quorum-sensing system that is present in many human bacterial pathogens.

Many types of individual bacterial cells send and receive ‘messages’ via chemical signals called quorum-sensing (QS) molecules. When concentrations of QS molecules reach a threshold, individual bacterial cells simultaneously activate their virulence genes. By identifying the signaling molecules and decoding these communications, researchers may also be able to reduce bacterial virulence by interrupting these conversations. Such treatments could provide an alternative to antibiotics.

For the QS molecule of B. cenocepacia, BDSF, Zhang and his co-workers identified a novel receptor, RpfR. The researchers produced mutant bacteria that lacked either the receptor RpfR, or the capacity to produce the signal BDSF. Both types of mutant bacteria showed decreased motility, produced fewer host-degrading enzymes, and were less able to form biofilms — bacterial aggregates encased in slime — indicating that BDSF and RpfR act together to send and receive the virulence signal.

Zhang and his co-workers also showed that, unlike other QS receptors, RpfR is a multitasking molecule. In other systems, after the receptor binds the QS molecule, it recruits another molecule to perform the next step in the signaling cascade and trigger gene expression. In the quorum-sensing system of B. cenocepacia, however, RpfR binds BDSF, then changes shape and performs the next step itself. Combining the two functions in a single molecule expedites the signaling process, and enables bacteria to adapt very quickly to changing environmental conditions.

The team’s search of known bacterial genomes showed that the system is present in many other pathogenic bacteria, including several groups that produce opportunistic infections in immunocompromised patients. “We would like to design chemical compounds to block the BDSF receptor, to compete with BDSF signals and reduce the virulence and pathogenicity of B. cenocepacia,” says IMCB team member Yinyue Deng.

The antibody response to immune threats is managed by cells known as B lymphocytes. The differentiation and function of B cells are tightly regulated to ensure a prompt response to confirmed dangers, such as viruses or bacteria, and also to prevent the emergence of harmful autoimmune responses that can damage healthy tissues in the body.

Many B cells express a protein called TACI on their surface, but its specific function has remained ambiguous. “Human patients with TACI mutations manifest two seemingly opposing conditions — immunodeficiency as well as autoimmunity,” says Kong-Peng Lam, a researcher at the A*STAR Bioprocessing Technology Institute. By exploring the roots of these contradictory effects, Lam and his team have provided an explanation.

Much of the antibody response is marshaled at sites known as germinal centers (GCs), where so-called ‘follicular helper T (Tfh)’ cells essentially ‘train’ GC B cells to respond to infectious threats. Lam and co-workers examined mice that lack TACI, and found that these mice generated considerably greater numbers of both Tfh and GC B cells. A pathway driven by a signaling protein called BAFF plays a major role in driving GC B cell proliferation; the researchers determined that this pathway is hyperactive in TACI-deficient mice, and proposed a model wherein TACI normally sequesters excess BAFF to limit cellular expansion of GCs.

In spite of the increased GC B cells, TACI-deficient mice generally failed to mount an efficient antibody response against an immune challenge. Upon closer examination, Lam and co-workers found that these animals had fewer plasma cells (see image), the class of B lymphocytes that secretes antibodies, and determined that TACI acts as a ‘survival factor’ that enables these cells to flourish.

Although these two effects would seem to counteract each other, the researchers’ proposed model links these physiological changes with the unusual immune defects observed in human patients. Lam notes that B cell selection in the GC also entails elimination of harmful B cells that recognize host antigens. “Absence of TACI increases the population of GC B cells, and this probably has the follow-on effect of reducing the stringency of the selection process, such that autoimmunity may arise,” he says.

Thus, while the drop in the number of plasma cells would result in overall immunodeficiency, the ‘quality’ of surviving plasma cells would also drop. “The few antibody-secreting cells that manage to survive may be autoreactive,” says Lam, “and this explains the two seemingly opposing conditions that are found in TACI-deficient patients.”
Muscle withering can occur as part of the progression of many diseases, including cancer and muscular dystrophy, as well as during the normal aging process. Cellular organelles known as mitochondria provide energy for muscle contraction, and their fragmentation within muscle cells can lead to muscle wasting. Now, a team of researchers led by Ravi Kambadur at the A*STAR Singapore Institute for Clinical Sciences has identified a key role for mitochondrial E3 ubiquitin protein ligase 1 (Mul1) in mitochondrial fragmentation. Such fragmentation occurs in response to stimuli that cause muscle loss.

Starvation and the use of anti-inflammatory steroid drugs can induce muscle wasting in animals. In cell culture experiments, the researchers found that these same stimuli could cause mitochondrial dysfunction and fragmentation in muscle cells. More specifically, these stimuli increased the expression of the Mul1 protein. In turn, this led to a decrease in the levels of a protein called Mfn2, resulting in the mitochondria breaking apart. Interestingly, normal levels of Mfn2 expression led mitochondria to fuse with one another.

When the researchers over-expressed Mul1 in muscle cells, instead of fusing with other mitochondria, these organelles merged with a cellular compartment called the lysosome in which proteins and organelles are degraded. Exposing muscle cells to starvation or steroids also led to fusion between mitochondria and lysosomes. However, Kambadur and co-workers found that they could block this fusion by silencing the expression of Mul1, effectively preventing degradation of the mitochondria.

Kambadur and his team observed that, in keeping with its known role of marking proteins to be degraded with ubiquitin tags, Mul1 binds and adds ubiquitin groups to Mfn2, leading to Mfn2 degradation. They then showed that once degraded, Mfn2 can no longer drive mitochondrial fusion, which tips the balance such that the mitochondria begin to fragment.

When Mul1 was overexpressed in the muscle of mice, the researchers observed a drop in muscle weight. Upon starvation, mice normally experience muscle loss, but Kambadur and co-workers were able to block this wasting by preventing the increased expression of Mul1 that is normally triggered by starvation. These findings indicate that Mul1 is required for the mitochondrial fragmentation and muscle loss caused by stimuli that normally break down muscle.

Next, the team will focus on determining whether Mul1 also induces muscle wasting in human muscle cells under various nutrition stress conditions. “If it does,” says Kambadur, “the major clinical application, I believe, would be treatment of anorexia that normally leads to heavy muscle wasting.”

Patients with systemic lupus erythematosus (SLE) come under attack by their immune system, producing ‘autoantibodies’ that inflict damage throughout the body. Antibodies normally target foreign proteins, but SLE autoantibodies attack targets contained within the nuclei of host cells, and immunologists have struggled to untangle how this happens.

Research led by Anna-Marie Fairhurst of the A*STAR Singapore Immunology Network has now uncovered valuable insights into early SLE onset. Part of SLE’s complexity arises from the intersecting involvement of multiple genetic factors. Accordingly, one of the primary SLE mouse models that Fairhurst uses contains two clusters of genomic variants, Sle1 and Yaa. Each cluster contains numerous SLE-susceptibility genes.

One of the most interesting genes contained within Yaa is Tlr7, which encodes the TLR7 protein. Fairhurst’s team revealed previously that increased Tlr7 expression is an essential contributor to disease severity in Sle1Yaa mice. TLR7 is a cell-surface receptor that recognizes viral RNA, so it is important for the immune response to infection. However, since TLR7 performs different functions in different immune cell types, its potential contributions to disease are ambiguous. One possibility is that TLR7 hyperactivity establishes a ‘feedback loop’ that drives autoantibody-secreting B cells to overreact to host proteins.

To discern TLR7’s role, Fairhurst and co-workers engineered mice whose cells each contain extra copies of its gene. These mice were asymptomatic. When the researchers crossed these mice with Sle1 mice, their offspring produced antinuclear autoantibodies and exhibited severe abnormalities of the kidney and spleen that are typically seen in Sle1Yaa mice.

Fairhurst and her co-workers designed their mouse strain so that the extra Tlr7 copies could be selectively deleted in certain cells via a targeted genetic recombination mechanism. They anticipated that by normalizing TLR7 levels in B cells, they could largely prevent disease onset in animals that still overexpress this receptor elsewhere. Although the researchers observed the expected strong reduction in anti-RNA autoantibodies in these mice, they were surprised to see only partial mitigation of other SLE symptoms.

This suggests a more complex role for TLR7 in SLE. “TLR7 is required for the initial steps of autoimmunity, meaning autoantibody production,” says Fairhurst, “but the [increased expression] of TLR7 in other cells drives the inflammation that leads to tissue destruction and severe disease.” Accordingly, she and her co-workers are now actively investigating both how TLR7 drives B cells to attack inappropriate targets in early SLE onset and the cell populations in which it acts to accelerate progression.

Developmental biology:
Foundations for a filter

A recently discovered stem cell population could one day provide useful source material for kidney repair

Within every human kidney, millions of filtration units known as nephrons are hard at work clearing metabolic waste products from the blood. Given the dirty work they perform, one might expect that the cells composing the nephrons undergo routine self-replacement, but nephrons retain very limited regenerative capabilities and essentially shut down when those limits are exceeded — a potential prelude to organ failure.

“Identification of stem cells in the kidney is of paramount importance if we are to better understand their contribution to kidney disease and harness their regenerative medicine potential,” says Nick Barker of the A*STAR Institute of Medical Biology, Singapore. Barker’s team has now made important progress towards this goal, identifying cells that appear to be critical progenitors for several structures within the mammalian nephron.

Previous studies have revealed the general cell pool from which these structures emerge, but not the specific cell subsets within that pool that directly contribute to nephron formation. Barker and colleagues were therefore interested in identifying specific proteins that might ‘mark’ such cells. Since his team had recently identified a gene called Lgr5 as a marker for key stem cell pools in several other major organ systems, they attempted to determine whether this same gene may also be relevant in the early stages of kidney formation.

Nephron development begins in the late stages in embryonic development and proceeds until shortly after birth. Barker and co-workers examined patterns of Lgr5 expression during that time-span in mice. This revealed the existence of a stem-like population of Lgr-positive (Lgr5⁺) epithelial cells localized within primitive nephron precursor structures. The researchers subsequently genetically engineered various strains of mice for a series of ‘lineage tracing’ experiments, wherein a cell’s expression of a gene of interest, such as Lgr5, switches on an indicator gene that will also remain active in that cell’s descendants, enabling generation of a visible cellular family tree.

These labeling studies allowed Barker and co-workers to monitor Lgr5⁺ cells as they participated in the formation of nephron tubules during kidney development (see image). “We succeeded in demonstrating that these were indeed multipotent, self-renewing stem cells responsible for generating part of the nephron blood filtration unit,” says Barker.

Barker is hopeful that these recently discovered stem cells might provide valuable seeds for kidney regeneration in the clinic. “We could try and grow new nephrons in the culture dish or expand these stem cells for use in transplantation into damaged kidneys,” he says.

“Identification of stem cells in the kidney is of paramount importance if we are to better understand their contribution to kidney disease and harness their regenerative medicine potential.”

Chromosomes are capped by long, repetitive DNA sequences called telomeres. These caps prevent genomic damage by insulating against the steady shortening of DNA ends that naturally accompanies replication. Once mature, cells generally stop producing the telomere-building enzyme telomerase and stop dividing when these caps have shortened to a critical length. However, many cancer cells get around this restriction by restoring telomerase production, allowing uncontrolled growth.

Several studies have indicated that telomerase performs functions other than chromosome capping. Research from Vinay Tergaonkar’s team at the A*STAR Institute of Molecular and Cell Biology in Singapore has revealed how NF-κB — another protein abnormally activated in many cancers — not only stimulates release of signals that promote an inflammatory response to help beat back infectious threats, but can also establish physiological conditions that favor cancerous growth if left unchecked. “Chronic inflammation and telomerase reactivation are hallmarks of most human cancers,” says Tergaonkar, “but the mechanism of how enhanced NF-κB and telomerase activities are each sustained in cancers is unknown.”

Their experiments revealed a surprisingly close relationship between these processes. Boosting telomerase activity in cultured human cancer cells enhanced tumorigenesis, but these effects could be countered by forcing cells to produce lower levels of NF-κB. The researchers subsequently demonstrated that telomerase directly enhances NF-κB activity (see image), and found that genetically modified mice lacking telomerase showed a greatly reduced inflammatory response following exposure to bacterial toxins.

Similar effects were apparent when Tergaonkar’s team compared NF-κB activity in telomerase-producing and deficient cells. Since both cell lines exhibited equivalent telomere lengths, these results favor a telomere-independent mode of action. The researchers demonstrated that telomerase binds directly to numerous NF-κB target genes, and actually strengthens NF-κB’s association with several of these genomic sites. For example, telomerase and NF-κB collaboratively stimulate production of the major inflammatory signal interleukin-6 (IL-6). Tergaonkar and co-workers also showed that a chemical inhibitor of telomerase dramatically reduced IL-6 production in a wide variety of leukemia cell lines.

Perhaps most importantly, the gene encoding telomerase is itself a target of NF-κB, creating a ‘vicious circle’ of signaling. “The two pathways fuel each other’s activities,” says Tergaonkar. “These findings hence provide a unifying mechanism for the sustained inflammation seen in a vast majority of cancers, and identify telomerase as a novel regulator of inflammation.” In future efforts, his team will explore how telomerase exerts its gene regulatory effects and seek out potential partner molecules that assist in this process.

Neural stem cells are the precursors of cells in the nervous system. As well as being crucial for early development, they are present throughout life, contributing to flexibility and repair of the nervous system. As such, they can be used to study the brain, and may offer new ways of treating neurological disease.

Current techniques for identifying and labeling live neural stem cells use antibodies to detect specific cell-surface molecules. Small fluorescent molecules, which are commonly used to visualize the locations and movements of molecules and cells, may offer a more convenient and safer alternative.

Young-Tae Chang at the A*STAR Singapore Bioimaging Consortium and co-workers have now identified a fluorescent compound that specifically labels neural stem cells by binding to an intracellular protein. The molecule, named CDr3, was singled out for its selective labeling of neural stem cells after testing thousands of fluorescent compounds from a ‘Diversity Oriented Fluorescence Library’, or DOFL.

“A DOFL is a collection of intrinsically fluorescent low molecular weight compounds which have been synthesized, purified and characterized in our lab,” says co-author Seong-Wook Yun. “We have generated more than 10,000 DOFL compounds so far, each with different chemical and biological properties.”

The researchers narrowed down the number of potentially useful molecules by assessing how strongly they labeled stem cells, and finally determined that CDr3 stained them the most selectively and brightly (see image). They confirmed the specificity of labeling by incubating CDr3 with different cell types and showing that it only stained neural stem cells. Growing stem cells in the presence of CDr3 also showed that it does not affect their survival or division.

A combination of molecular biology techniques revealed that CDr3 labeled the cells by binding to a neural stem cell-specific protein called FABP7. This is found inside the cell, unlike other labeling targets. “Conventionally, live neural stem cells have been identified by detecting cell surface molecules,” explains Yun. “However, these molecules are also highly expressed in other types of cells. FABP7 is a specific intracellular marker of neural stem cells.”

Labeling of neural stem cells with CDr3 not only allowed them to be identified, but also to be separated from other types of cells. According to Yun, this is important for practical applications.

“Detection and isolation of live neural stem cells from heterogeneous cell populations is a key technology, not only for basic research but also for the development of cell-based therapeutics and drug development,” he says.

Organic synthesis:

The sweetest melting pot

A ‘one-pot’ industrial process for manufacturing high yields of an artificial sweetener under mild conditions proves successful

Most industrial manufacturing processes involve the use of many different reagents across multiple reactors — an approach that is costly, laborious, time-consuming and environmentally unfriendly. ‘One-pot’ processes, in contrast, involve putting all the reagents in a single reactor and fine-tuning conditions to achieve maximum yield.

Xylitol, a popular artificial sweetener that contains 40% less calories than white sugar, has traditionally been manufactured from plant matter through a multi-step process under intense heat in a high-pressure hydrogen environment. Guangshun Yi and Yugen Zhang at the A*STAR Institute of Bioengineering and Nanotechnology in Singapore have now developed a technique that produces xylitol in a single reactor. This one-pot technique avoids the need to separate and purify the intermediate chemical compounds, thereby speeding up the process while using less reagent and increasing chemical yield.

The technique also operates under milder conditions than current industrial techniques.

Yi and Zhang’s technique depends on two distinct but equally important steps. The first involves using a strong acid to break some of the chemical bonds in xylan, an organic molecule found in the cell walls of plants, to form an intermediate molecule called xylose. In the second step, a ruthenium catalyst, in the presence of isopropanol, changes xylose into xylitol. The catalyst can be re-used many times throughout the manufacturing process, which makes it cost-effective. Although replacing the standard hydrogen environment with isopropanol does have a small negative environmental impact, the overall process, which avoids multiple steps, is more environmentally friendly than current industrial techniques, according to Zhang.

The researchers’ reaction achieved a maximum yield of 80% at a temperature of 140 °C, which is relatively mild compared with current industrial techniques for producing xylitol. The presence of a strong acid in the first step of the reaction also proved crucial for achieving a high yield; without it, the yield was a mere 5.7%. The maximum yield of 80% was achieved over a reaction time of 3 hours; increasing this time to 8 hours caused very little difference in yield, but extending the reaction time beyond 8 hours reduced the yield.

Yi and Zhang are confident about the prospects of their new technique, particularly given its advantageous properties of a short reaction time, reusable catalyst and relatively low reaction temperature. “We are currently in discussion with a company to develop this technology, and are also in the process of testing and optimizing conditions for real industrial samples,” Zhang says.

One-atom-thick sheets of carbon — known as graphene — have a range of electronic properties that scientists are investigating for potential use in novel devices. Graphene’s optical properties are also garnering attention, which may increase further as a result of research from the A*STAR Institute of Materials Research and Engineering (IMRE). Bing Wang of the IMRE and his co-workers have demonstrated that the interactions of single graphene sheets in certain arrays allow efficient control of light at the nanoscale. Light squeezed between single graphene sheets can propagate more efficiently than along a single sheet. Wang notes this could have important applications in optical-nanofocusing and in superlens imaging of nanoscale objects. In conventional optical instruments, light can be controlled only by structures that are about the same scale as its wavelength, which for optical light is much greater than the thickness of graphene. By utilizing surface plasmons, which are collective movements of electrons at the surface of electrical conductors such as graphene, scientists can focus light to the size of only a few nanometers.

Wang and his co-workers calculated the theoretical propagation of surface plasmons in structures consisting of single-atomic sheets of graphene, separated by an insulating material. For small separations of around 20 nanometers, they found that the surface plasmons in the graphene sheets interacted such that they became ‘coupled’ (see image). This theoretical coupling was very strong, unlike that found in other materials, and greatly influenced the propagation of light between the graphene sheets.

The researchers found, for instance, that optical losses were reduced, so light could propagate for longer distances. In addition, under a particular incoming angle for the light, the study predicted that the refraction of the incoming beam would go in the direction opposite to what is normally observed. Such an unusual negative refraction can lead to remarkable effects such as superlensing, which allows imaging with almost limitless resolution.

As graphene is a semiconductor and not a metal, it offers many more possibilities than most other plasmonic devices, comments the IMRE’s Jing Hua Teng, who led the research. “These graphene sheet arrays may lead to dynamically controllable devices, thanks to the easier tuning of graphene’s properties through external stimuli such as electrical voltages.” Graphene also allows for an efficient coupling of the plasmons to other objects nearby, such as molecules that are adsorbed on its surface. Teng therefore says that the next step is to further explore the interesting physics in graphene array structures and look into their immediate applications.
Optical materials:

Light’s magnetism shows its true colors

Tiny spheres of silicon can control the magnetic side of light, paving the way to novel optical devices

Light is an oscillating wave of electric and magnetic fields. The way the electric field component interplays with the atoms in a material largely determines how light interacts with matter. With visible light, however, the influence of the magnetic component is usually much smaller. Arseniy Kuznetsov at the A*STAR Data Storage Institute, Singapore, and co-workers have now created tiny spheres of silicon that can strongly interact with the magnetic field of visible-wavelength light. These engineered ‘magnetic materials’ enable new ways of controlling light at the nanoscale. Relative permeability is a measure of a substance’s ability to support a magnetic field. Most optical materials have a permeability approximately equal to one. A more diverse choice, however, would open the door to a whole host of novel optical devices. Negative permeability, for example, could be used to create high-resolution lenses and even invisibility cloaks. As no such materials exist in nature, scientists have started to develop metamaterials, which are artificial structures engineered to interact with light in a desired way. Kuznetsov and co-workers have shown that nanoscale engineering provides a way of tuning the magnetic properties of silicon nanoparticles.

The researchers fired a high-intensity laser at a silicon wafer, which blasted off spheres of silicon with diameters between 100 and 200 nanometers. The separation between the spheres was large enough that the researchers could see them individually under an optical microscope. They could also see that the nanoparticles scattered light of all colors in the rainbow, from red to violet.

In a theoretical analysis, Kuznetsov and co-workers showed that the optical response resulted from incoming light generating a circular electric field, or displacement current, in the sphere. This, in turn, supported an oscillating magnetic field in the middle of the particle — a so-called magnetic dipole (see image). “We have experimentally demonstrated that silicon nanoparticles can have strong electric and magnetic dipole resonances in the visible spectrum,” explains Kuznetsov.

“The advantage of our approach is that it is free of energy loss because the modes are not related to real electron currents.”

The properties of the dipole were dependent on the size of the particle, so particles of different sizes scattered light of different colors. The team predicts that more sophisticated fabrication techniques will soon enable greater control over a nanoparticle’s size and shape, thus enabling selective tuning of its optical properties. “Our future research will target possible applications of these nanoparticles and the realization of novel nanodevices for light-on-a-chip integration,” says Kuznetsov.

Computational chemistry:

A faster way to untangle intermolecular interactions

More effective medicines could result from a method that improves simulations of the binding interactions between drugs and their targets

A powerful computational technique used by the pharmaceutical industry to expedite new drug development has just received a performance boost. Chandra Verma and his co-workers at the A*STAR Bioinformatics Institute in Singapore have developed a method for extracting greater information from the simulations that are used to predict how candidate drug molecules will interact with biomolecular targets. The technique could enable drug makers to create highly effective medicines for a broader range of individuals.

Pharmaceutical researchers currently process molecular dynamics simulations using a technique known as ‘MM-PBSA’ free-energy calculations. These calculations predict how tightly a drug candidate will bind to its target protein inside the body. In general, the more tightly a drug binds to its target, the more effective it will be. “MM-PBSA can be used to rapidly assess the relative binding propensities of a series of molecules to a protein to distill out a select few candidates that can then be tested experimentally,” Verma explains. By cutting down on experimental work, companies can save time and money.

Since the MM-PBSA method was first developed in the late 1990s, computer processing power has increased significantly. Researchers can now run simulations that map drug–protein interactions over much longer timeframes. As simulation times have lengthened, the complexity of protein dynamics has become an increasingly important consideration. Proteins are inherently flexible structures with multiple possible conformations, each of which interacts differently with the drug molecule over time. Taking these differences into account provides more reliable results.

Verma and his co-workers’ method for analyzing and reporting the results of MM-PBSA calculations, which they named MM-PBSA_segmentation, separately captures the free energies of binding for multiple protein conformations. MM-PBSA_segmentation is based on an algorithm that can extract the binding behavior of individual protein subpopulations from the overall free-energy calculations. For example, using their method on the well-characterized interaction between the p53 and MDM2, the researchers identified six distinct subpopulations of p53 conformations (see image). They also established each subpopulation’s relative size and hence overall importance.

MM-PBSA_segmentation, which is freely available from the team, expands the range of protein conformations accessible for analysis, Verma says. This ability to examine multiple protein conformations could be particularly important for cancer drug development, for example, where protein targets can become mutated and so change their conformation. As these changes can differ among individuals, Verma and his team are currently investigating whether they can use their technique to develop drugs targeted to individual patients.

Catalysis: Putting cyanide to work

Industrial-scale chemistry could benefit from a robust new catalyst that selectively generates amino acid precursors from cyanide at room temperature

Cyanide exposure can be lethal, but with careful handling, the molecule can be a very useful chemical building block. For example, from cyanide chemists can make life-essential amino acids that are in great demand as food additives and components in pharmaceutical production. The key step in this process is called the asymmetric Strecker reaction. Until now, this reaction has needed complex and costly catalysts, restricting its use to small-scale laboratory research. A new Strecker catalyst more amenable to scale-up is now available, thanks to Abdul Seayad, Balamurugan Ramalingam and their co-workers at the A*STAR Institute of Chemical and Engineering Sciences in Singapore. The catalyst also offers a safer way to handle the cyanide.

“Since only a limited amount of cyanide is present at the reaction zone at any point in time, any unforeseen situation can be easily handled.”

Seayad and Ramalingam made their Strecker catalyst from an inexpensive material based on titanium. It is called the self-supported chiral titanium cluster (SCTC). When warmed in the presence of water, the SCTC precursor assembles into robust solid clusters (see image). The key to its performance in the Strecker reaction is that the surface of each cluster is covered in tiny asymmetric “chiral pockets”, says Seayad. The reactions take place in these pockets, generating molecules that are a trivial chemical step away from amino acids.

Amino acids are chiral: they can exist in either of two mirror-image forms called enantiomers. For many applications — such as pharmaceutical production — chemists need a pure supply of only one enantiomer. Seayad and Ramalingam found that SCTC’s chiral pockets very selectively produce one enantiomer over the other, with a purity — or ‘enantiomeric excess’ — of up to 99%. Unlike previous catalysts, which required temperatures as low as -30 °C to operate effectively, the researchers achieved this selectivity at room temperature.

Stability is a further advantage of SCTC. The catalyst is impervious to air or moisture, and remains stable to 300 °C, making it well suited to use in a continuous flow reactor. The researchers could pack the catalyst into a cartridge and pump through the cyanide and other starting materials, generating amino acids in a steady stream. Safety is another key advantage, says Ramalingam. “Since only a limited amount of cyanide is present at the reaction zone at any point in time, any unforeseen situation can be easily handled,” he explains.

So far, the researchers have used an expensive reagent called TMSCN as their cyanide source. They are currently researching ways to generate SCTC in situ from inexpensive salts. “We will also evaluate the feasibility of up-scaling the reaction under flow conditions,” Seayad says.

Production of biocompatible and super-absorbent materials may become easier, thanks to Anbanandam Parthiban and co-workers at the A*STAR Institute of Chemical and Engineering Sciences. Using a modification to the high-precision technique known as atom transfer radical polymerization (ATRP), which links molecules into long chains, the researchers have developed new compounds that can directly polymerize acidic vinyl monomers, such as acrylic acid. Acrylic acid polymers are water-absorbing materials widely used in diapers and as emulsifying agents for pharmaceuticals and cosmetics.

Previous attempts to use ATRP with polar vinyl monomers, including acrylic acid, were unsuccessful, a failure that some chemists attributed to catalyst ‘poisoning’ by carboxylic acids. Parthiban and his team’s compounds resolve this problem by binding to the catalyst while simultaneously initiating the radical polymerization process. This process prevents poisoning and dramatically reduces metallic waste.

Despite ATRP’s inability to directly produce acrylic acid polymers, it is used in laboratories worldwide; it allows researchers to assemble complex polymers in a step-by-step fashion that gives enormous control over product architectures. The key is using a catalyst that can readily switch between two oxidation states, such as a copper salt, explains Parthiban. The copper catalyst first interacts with an ATRP initiator molecule to activate organic free radicals and an oxidized metal complex. The free radicals then quickly polymerize target monomers, while the metal complex undergoes equilibrium with a dormant, lower oxidation state. With appropriate reaction conditions, chemists can then restart polymerization with new monomers.

Parthiban and co-workers addressed ATRP’s limitation by developing ‘unimolecular ligand–initiator systems’ (ULIS), a series of branched molecules containing multiple binding sites for copper atoms, as well as halogens for activating free radical species. In this approach, the ULIS molecules become part of the polymer chain during the active–dormant cycles instead of remaining isolated. The researchers envisaged that this interconnection would suppress the acidic side-reactions that lead to catalyst poisoning.

Experiments by the researchers proved their theories correct: they could efficiently polymerize acrylic acid and other vinyl monomers using ULIS-promoted ATRP (see image). Surprisingly, they found that these reactions could be achieved using less than 100 parts-per-million concentrations of copper catalyst, a quantity comparable to residues left in conventional ATRP purified polymers.

Parthiban notes that although the ULIS ligands are part of the polymer chain and might be expected to produce high amounts of metal waste, the homogenous nature of intramolecular-based free radical polymerization allows less metal to be used — an important consequence for sustainable chemistry efforts.

“The researchers could efficiently polymerize acrylic acid & other vinyl monomers using ULIS-promoted ATRP.”
Data storage:

Reflections turned upside down

A phase-change material with unexpected optical-reflectivity properties offers fresh perspectives for data storage

Memory is a central component of any computer or mobile device. Digital memories must not only store large amounts of data in a small space — and in a way that it is conveniently written, read and erased — but also meet ever-increasing demands on their size as well as their speed and energy efficiency. Phase-change materials, which switch their physical properties depending on whether they are in their crystalline or non-crystalline form, are being used to meet these requirements. A new kind of phase-change material with interesting features for memory applications — and with unexpected optical characteristics — has now been discovered by Wen Dong Song from the A*STAR Data Storage Institute and co-workers in Singapore.

“These unique characteristics may lead to novel applications in data storage, such as new optical media and solid-state memories.”

Digital data requiring storage in a memory is generated in the form of ones and zeroes. This means that the storage material should be able to switch between two distinct states, one encoding ‘1’ and the other ‘0’. This is typically accomplished by altering either magnetic properties, or, as is the case for phase-change materials, optical or electrical behavior.

Song and his co-workers found that materials made of the chemical elements iron and tellurium can change their property known as optical reflectivity depending on their crystalline state (see image). They demonstrated that the change between the crystalline and the non-crystalline form — and therefore between high and low reflectivity — can be induced simply and reversibly by heating the material, for example, by using a laser pulse. This switchable reflectivity provides a practical way for managing data in a small area. Moreover, the researchers showed that the change between the non-crystalline and crystalline phases can happen extremely fast, within tens of nanoseconds.

“Also, by altering the relative amount of iron and tellurium in the material, the temperature at which the phase change happens can be tuned and therefore adjusted for specific applications,” says Song.

Other researchers have observed related behaviors in other phase-change materials, but Song and his team observed properties that are unique to their system. “To our surprise we found that in its non-crystalline state our material has a higher reflectivity than in its crystalline state,” says Song. Normally, the opposite is true. “We [also] found that our material exhibits not only anomalous optical behavior, but also has anomalous electrical properties,” Song explains. “These unique characteristics may lead to novel applications in data storage, such as new optical media and solid-state memories.” He says that they will explore these anomalies further.

Conversion of water into hydrogen is a fundamental reaction powered by light, but the lack of suitable artificial drivers, or photocatalysts, for this reaction has hampered its commercial development. Platinum-decorated semiconductor nanoparticles are expected to fill this gap; however, production of these tiny particles typically requires high-temperature metal deposition or ultraviolet irradiation techniques in organic solvents. When synthesized in water, as a benign alternative, the particles tend to form clumps during metal deposition. This unwanted agglomeration can now be avoided, thanks to a method developed by a research team at the A*STAR Institute of Materials Research and Engineering in Singapore.

Led by Yinhtai Chan, the team used a thin hydrophilic shell of silica to encapsulate individual semiconductor nanoparticles. According to Chan, this encapsulation is the key difference between his team’s method and previous aqueous-phase systems. These systems make the nanoparticles water-dispersible by replacing hydrophobic organic molecules, which bind the as-synthesized semiconductor, with hydrophilic compounds, or ligands. “Our strategy is certainly more robust than those aggregation-free approaches where ligand loss can take place easily upon changes in the solvent environment,” Chan says.

To produce the metal–semiconductor nanostructures, Chan and his co-workers first coated ultra-small, cadmium-containing, semiconducting tetrapods in silica using a surfactant-based emulsion procedure in water (see image). Easily dispersed and stable in aqueous media, the resulting structures displayed a multilayered silica coating that consisted of a hard, tightly woven outer ‘crust’ enveloping a soft, porous inner layer. By selectively removing this inner layer with an acidic etching agent, the team effectively created a hollow shell around each tetrapod. The water-mediated reduction of a platinum precursor, concomitant with its diffusion across the porous shell, generated metal particles that settled on the tetrapod arms.

More importantly, Chan and his team discovered that the encapsulation enabled unprecedented cation exchange reactions which swapped cadmium ions for silver or palladium ions, yielding new platinum–semiconductor tetrapods. “Those nanostructured metal–semiconductor combinations were not readily achievable by established methods, and certainly not via mild aqueous reaction conditions,” Chan notes. Further assessment revealed the presence of an ultrathin film of platinum sulfide at the metal–semiconductor interface. “This unique film is responsible for preserving the metal framework during the cationic exchange of the underlying semiconductor nanostructure,” he explains.

The team is currently investigating the catalytic properties of their tetrapods. “We believe that their stability and efficient light-harvesting abilities may afford a competitive advantage over other metal–semiconductor nanostructures with respect to photocatalysis,” says Chan.

Catalysis:

Optimizing water splitting

Computer simulations of a metal–sulfide alloy unlock the secrets to designing solar-powered catalysts that generate hydrogen fuel from water

Partnerships can pay off when it comes to converting solar into chemical energy. By modeling a cadmium sulfide (CdS)–zinc sulfide (ZnS) alloy with special computational techniques, a Singapore-based research team has identified the key photocatalytic properties that enable this chemical duo to ‘split’ water molecules into a fuel, hydrogen gas (H₂). The theoretical study was published by Jianwei Zheng from the A*STAR Institute of High Performance Computing and his co-workers.

Chemists had already identified CdS and ZnS semiconductors as promising photocatalysts for water splitting. However, both came with a drawback related to the size of their so-called ‘band gap’ — the energy difference between occupied and unoccupied electronic states that determine photoactivity. While CdS can readily harvest solar energy because of its small band gap, it needs a metal co-catalyst to produce H₂. On the other hand, ZnS requires high-energy ultraviolet light to initiate water splitting owing to its large band gap.

Recently chemists had overcome these problems by alloying CdS and ZnS together into a ‘solid solution’: a physical state where Zn ions are distributed homogenously inside the crystal lattice of CdS. Altering the proportion of ZnS in these alloys enables production of photocatalysts with tunable responses to visible light and high H₂ evolution rates in water. Improving the design of a Cd–ZnS solid solution is difficult, because its underlying mechanism is poorly understood.

As a workaround, Zheng and his co-workers used a technique known as ‘special quasi-random structures’ (SQS) to mimic a completely random alloy with a series of small, periodic models. After carefully working to correlate experimental random hexagonal crystals with their SQS approximations, they calculated the electronic properties of the Cd–ZnS solid solution using hybrid density functional theory — a computational method that gives accurate descriptions of band gaps.

When the researchers gradually increased the Zn content of their model alloy, they saw that the band gap deviated from a linear combination of the two components. This effect, known as band ‘bowing’, arises from volume deformations within the Cd–ZnS solid solution and is an essential parameter for predicting catalytic solar H₂ production.

Further calculations revealed that the alloy’s high catalytic activity stemmed from obvious elevation of the position of unoccupied electronic states, and a subtle change in the position of occupied electronic states, as the amount of Zn increased. But to retain strong light harvesting capabilities and to avoid premature corrosion, the team proposes an equal ratio of ZnS to CdS for optimal photocatalytic water splitting.

A thin film made of graphene and a charge-inducing polymer shows promise as a replacement for transparent electrical conductors in displays

The hunt is on for a replacement for indium tin oxide (ITO) that is currently used as a transparent conductor in display screens. Flatscreen televisions, computers and mobile phone displays all require transparent electrical conductors to connect embedded electrical devices without obstructing back illumination. Indium tin oxide (ITO) is currently used for this purpose, but it is expensive and fragile. A low-cost alternative, based on a composite film made of graphene and a ferroelectric polymer, is now available thanks to an international research team, including researchers from the A*STAR Institute of Materials Research and Engineering (IMRE) in Singapore.

Graphene is transparent since it consists only of a single layer of carbon atoms. “Graphene can show a high electrical conductivity and is also stronger and much more flexible than indium tin oxide, and thus could even be used for foldable displays and thin solar cells,” explains Guangxin Ni, a PhD candidate in the research team. Although very thin, graphene’s single layer of carbon atoms forms strong, tough bonds that explain its good mechanical and electrical properties. In its pristine state, however, graphene’s electrical conductance is low because it has very few free electrons that can carry an electrical current. Injection of electrical charges, usually by applying an electrical voltage, can increase conductivity; however, this is undesirable in consumer devices because it uses electrical power.

Nl and his co-workers’ thin film offers a more permanent solution. They combined graphene with a ferroelectric polymer, which has a constant electrical charge on its surface. They grew the graphene on a copper foil by evaporating organic precursor molecules, and then deposited the polymer on top as a thin film from solution. When brought in close contact, the electrical field from the polymer induced electrical charges in graphene. This increased graphene’s electrical conductivity by a factor of 12.

The advantage of this approach is that this charge donation is extremely long lasting, indefinitely in theory, and does neither damage to the material nor substantially compromises the high optical transparency of graphene, notes team member Kui Yao from IMRE. Moreover, the fabrication process is very scalable and suitable for industrial applications.

Before developing commercial applications, even higher conductivities are desirable: the conductivity of ITO is still about 20% better than the hybrid graphene-ferroelectric polymer. Nevertheless, the research team is striving to overcome this barrier and even double the conductivity of the films by optimizing and enhancing the design and fabrication of these graphene/polymer devices. If successful, the team will greatly enhance the commercial potential of this transparent conductor, and bring the broad commercial application of graphene a step closer.

**Drug manufacture: Going green with iron**

**Safe and inexpensive iron catalysts provide a ‘greener’ alternative to typical pharmaceutical production methods**

More than one-quarter of all known pharmaceuticals contain the chemical group known as amides: carboxylic acid derivatives derived from ammonia or amines. Most methods for synthesizing amides, however, are inefficient and use hazardous reagents. New work from Anqi Chen and co-workers at the A*STAR Institute of Chemical and Engineering Sciences in Singapore promises to make amide chemistry more economical and sustainable than before. The team has uncovered a way to convert aldehydes and amine salts into amides using iron(II) sulfate — a harmless, inexpensive substance as the catalyst to perform this transformation efficiently and with little waste.

Nontoxic and cheap catalysts with sufficient chemical activity for amide transformation are hard to find. To identify an efficient and inexpensive catalyst, the team screened a range of iron compounds and discovered that iron(II) sulfate (see image), a supplement for anemia that costs less than a dollar per kilogram, has strong potential to catalyze amide formation from aldehydes with amine salts.

Apart from the environmentally benign iron catalyst, the transformation uses an inexpensive oxidant known as tert-butyl hydroperoxide and very cheap calcium carbonate, the main composition of limestone, as a base. By combining these inexpensive ingredients together, the researchers achieved excellent amide yields under conditions convenient for both laboratory and industrial operations.

Further experiments revealed the versatility of this amide synthesis. A range of amine salts and aldehydes with different structural and electronic features could be transformed into amides with good-to-excellent yields. Importantly, salts derived from natural amino acids such as valine and proline also underwent oxidative amidation without disrupting their chirality or ‘handedness’ — a critical structural phenomenon for drug molecules and peptides.

The team demonstrated the potential of this iron-catalyzed amidation for drug manufacturing by synthesizing the antiarrhythmic drug N-acetylprocainamide in a one-step procedure that is more efficient than previous multiple-step routes. "This environmentally benign method has significant advantages over conventional techniques," says Chen, "and we intend to identify pharmaceutical targets where this promising method could bring about significant cost-savings and improved sustainability."

Nanomaterials:
Bringing crystals into line

The temperature-controlled alignment of tiny crystals could help harness their collective properties for nanotechnology applications

The unique magnetic properties of cobalt phosphide nanowires stand them in good stead as future components of high-performance devices. Unlike bulk materials, these ultrasmall elongated crystals consist of single-domain structures that account for their superparamagnetism — a temperature-induced magnetism that arises in a magnetic field. To maintain and fully exploit this behavior, scientists must generate materials composed of precisely positioned and oriented building blocks. Such superstructures are now available, thanks to the development of a method that uses temperature changes to align individual nanowires. Ming-Yong Han from the A*STAR Institute of Materials Research and Engineering, Singapore, led the research1.

Current nanocrystal self-assembly approaches involve depositing a crystal suspension on a solid surface, and then slowly evaporating the solvent. Theoretically, the evaporation enhances the relatively weak attraction forces that exist between the nanocrystals, forcing them to align. However, high degrees of alignment of anisotropic structures — those exhibiting direction-dependent physical properties — remain difficult to achieve.

“We took a distinct pathway from the slow evaporation approach,” says Han. His team’s strategy followed similar principles to those used in chemical synthesis. First, they reacted a cobalt derivative with the phosphide precursor trioctylphosphine (TOP) at high temperature. This produced TOP-coated nanowires. Next, they stored the solution in which the nanowires formed at various temperatures. These storage, or ‘aging’, temperatures produced larger, well-defined superstructures with different alignments.

Washing the nanowires without the latter step resulted in random arrangements or small assemblies (see image). After cooling and aging the reaction mixture at room temperature for two hours, the team observed superstructures composed of nearly one million vertically standing nanowires. In this arrangement, each nanowire was surrounded by six others in a honeycomb pattern. When cooled to room temperature and then refrigerated, the reaction mixture produced extended sheets of nanowires aligned side-by-side horizontally.

The superstructures resisted any high temperature, ultrasound, or organic solvent treatment, indicative of strong cohesive forces between the nanowires. Further investigations revealed that, during the self-assembly, the TOP molecules continually adsorbed and desorbed from the nanowires, bringing them in close contact. This caused irreversible chemical bonds to form between the nanocrystals, facilitating and enhancing their alignment.

The team is currently testing the performance of the superstructures against that of the randomly oriented nanowires to explore their potential use as sensors or electrical components called inductors. “We are also trying to extend this methodology to self-assemble other systems, with a hope to establish a more universal method for aligning anisotropic nanocrystals,” adds Han.

A computational study of human hair provides insights into the structure of its poorly understood outer surface

Human hair is a complex, multi-layered material, the composition of which is only partly established. Hair fibers are sheathed in a thin protective coating called the epicuticle, but despite its industrial importance — the epicuticle is the first surface with which hair products interact — the exact structure of this layer is unknown. Now, a theoretical model of epicuticle structure developed at the A*STAR Institute of High Performance Computing (IHPC) has revealed the likely composition and properties of hair’s outer surface. The model, developed by Daniel Cheong and his co-workers at IHPC, is already helping to resolve apparent discrepancies over epicuticle structure.

Previous experimental research has shown that hair’s outermost surface consists of a thin monolayer of fatty acid molecules called 18-MEA, which stand on end like the bristles on a brush. According to Cheong, one study suggested that these molecules attach to the surface around 1 nanometer apart. “Although this distance is frequently cited, it has never been corroborated, as it is very difficult to measure this value experimentally,” says Cheong.

To examine the 18-MEA separation distance further, Cheong and his co-workers constructed simplified computational models of the hair surface. They then looked for the separation distance that gave the most energetically stable structure. “Surprisingly, our simulation results indicated that the separation distance between the fatty acids should be around 0.5–0.65 nanometers,” says Cheong.

One possible explanation for this apparent disagreement with earlier work could be that bound 18-MEA molecules are indeed spaced 1 nanometer apart; but extra, unbound lipids may pack the space in between to generate the more stable structure, Cheong suggests.

This theory could also resolve apparently conflicting results regarding experimental measurements of the fatty acid layer’s thickness, which have ranged from 1.3 nanometers to 2.6 nanometers. The team’s model shows that the more tightly the fatty acids are packed, the more upright they stand, which makes the epicuticle appear thicker (see image). Cheong suggests that, in studies where this layer was found to be only 1.3 nanometers thick, the free lipids may have been lost, partly collapsing the fatty acid structure. Tellingly, his model predicts that for fatty acids spaced 1 nanometer apart, the layer would appear 1.3 nanometers deep.

“When this simple model, we can also study the interactions between small molecules and the hair surface,” Cheong explains. “This would be important in understanding how potential active ingredients in hair products will behave at the hair surface.”

Biochemical engineering:

Waste not, want not

A simple fermentation treatment can convert a by-product of biofuel production into a valuable chemical feedstock for a wide range of biomedical products.

Powered by sunlight, microalgae are tiny biofuel generators that soak up carbon dioxide to produce energy-rich lipids, which are showing promise as a potential source of clean energy. Maximizing lipid production is the focus of many research efforts, but the material remaining after lipid extraction has caught the attention of Md. Mahabubur Rahman Talukder and his co-workers at the A*STAR Institute of Chemical and Engineering Sciences. Currently, this ‘lipid-depleted biomass’ is either burned for energy, or simply discarded as a waste product. Talukder and his team have developed a process that turns this material into a valuable chemical feedstock.

The researchers have pioneered a two-step biochemical process that converts lipid-depleted biomass into lactic acid. This substance is in increasing demand as a feedstock for polylactic acid (PLA), a biopolymer with numerous medical applications, ranging from surgical sutures to orthopedic implants. The high cost of raw materials used in the manufacture of lactic acid currently limits PLA use. Thus, producing an alternative source from algal lipid-extraction waste is proving attractive. Generating two valuable products from the algae, specifically the microalgae Nannochloropsis salina, would spread the costs of microalgae production, making the biofuel more cost-competitive with conventional fuels.

To produce both lipid and lactic acid from N. salina, Talukder and his co-workers first subjected the microalgae to an acid hydrolysis pre-treatment step. This process broke down the organisms’ polysaccharide-based cell walls into simple sugars, while releasing the lipid for extraction. The researchers also systematically examined different acid concentrations, reaction times and temperatures. They identified that treatment for 1 hour at 120 °C maximizes sugar and lipid production.

When Talukder and his co-workers extracted the lipid at this point, the lipid-depleted biomass, now rich in sugars, remained. They converted this material into lactic acid by fermentation. The team then added the bacterium Lactobacillus pentosus, which consumed the sugars over a 48-hour period, to generate the lactic acid.

The researchers found that, to maximize lactic acid production, they first had to remove metal ions from the mixture. Microalgae harvesting typically involves an iron chloride treatment, but the residual iron appeared to inhibit fermentation. “One of the next steps in our research will be to develop a chemical-free microalgae harvesting method so that fermentation will not be negatively affected,” Talukder says.

The researchers are also screening different bacterial strains for higher lactic acid productivity, and developing their current two-step process into a single-step operation.

Fluid mechanics:
Bubble impacts caught on film

High-speed cameras reveal the complex physics at work as air meets water and glass

When a bubble of air rising through water hits a sheet of glass, it doesn’t simply stop — it squishes, rebounds, and rises again, before slowly moving to the barrier. This seemingly simple process actually involves some knotty fluid mechanics. An international research team, including researchers at the A*STAR Institute of High Performance Computing, and Nanyang Technological University, Singapore, has now unpicked this physical process.

The researchers used a fine capillary to blow air bubbles 0.5 to 1.5 millimeters wide into a glass of de-ionized water. The bubbles rose 5 millimeters before hitting a glass cover, all under the watchful eye of a high-speed camera. Meanwhile, a laser beam shining from above illuminated the contact points between glass, water and the bubble, creating a changing interference pattern that was captured by a second camera running at up to 54,000 frames per second (see image).

A bubble typically took about 17 milliseconds to impact, bounce and return to the glass slide. But a film of water remained between them; it took a further 250 milliseconds for that to drain away before the bubble’s air came into direct contact with the glass. “The film drains slowly because the process is controlled by viscosity and surface tension,” says team member Rogerio Manica. “Eventually, this layer breaks and a three-phase contact line — water, glass and air — forms, with a region on the glass surface that is not wet.” This ‘dewetting’ stage is about 100 times faster than the film drainage process.

The researchers found that a simple mathematical model, called lubrication theory, could accurately describe the film drainage measured in the experiments. “We thus understand the fluid mechanics now in very great detail,” says Manica. “Many industrially relevant processes use impacting bubbles, including wastewater cleaning and mineral extraction,” he says, adding that simulations of these processes can now be improved by incorporating the team’s bubble model.

Other researchers had studied the behavior of much smaller bubbles when rising at very slow speeds. They found that the bubbles settled on to the cover without bouncing, thus skipping the most complex parts of the process.

Manica notes that their experiments also demonstrated the utility of synchronizing cameras to study two very different length scales — the side view is measured in millimeters, while the interferometry camera captures features thousands of times smaller. The researchers are now investigating how rising bubbles behave if the water contains small amounts of other materials, such as surfactants.

Research Highlights

GENETICS & DISEASE
Cancer biology: Keeping bad company

Certain mutations cause a cancer-preventing protein to interfere with cellular pathways and actively drive cancer progression

The p53 tumor suppressor protein manages DNA repair mechanisms in response to genetic damage and kills off precancerous cells before they multiply. The loss of p53 due to mutation greatly increases risk of tumorigenesis. Even worse, however, are the various 'missense' mutations that change the amino acid sequence of p53: they warp its function to promote rather than prevent cancer.

"Mutated forms of p53 are found in 50% of human cancers," says Jayantha Gunaratne of the A*STAR Institute of Molecular and Cell Biology. "We hypothesized that mutant p53 proteins interact with selected proteins that do not bind to wild-type p53 to promote processes involved in cancer progression." To test this theory, Gunaratne teamed up with colleagues including David Lane, chief scientist of A*STAR and one of the initial discoverers of p53, to hunt for binding partners that specifically interact with the common p53R273H mutant.

The researchers used stable isotopes to label all the proteins in cultured cells expressing either wild-type p53 or p53R273H. Then they used a technique called mass spectrometry that enabled them to accurately catalogue the subset of proteins associated with either p53 variant. "We captured at least 15 protein binding partners specific to the p53R273H mutant," says Gunaratne. Among the most immediately interesting was a protein called nardilysin (NRD1), which is associated with the invasive growth and migratory behavior observed in aggressive cancers.

After determining that NRD1 exclusively binds p53R273H but not to other p53 mutants, Gunaratne and co-workers proceeded to explore how it specifically collaborates with this variant. By selectively reducing the expression of NRD1 in cultured cancer cells, they learned that this protein is a critical component of the invasive behavior manifested by p53R273H-expressing cells in response to a particular chemical trigger, a cellular signal called heparin-binding epidermal growth factor-like growth factor (HB-EGF). This HB-EGF-oriented invasion appears to occur via a cellular mechanism distinct from those that direct cell movement in response to other growth factors, indicating a novel biological process involving both p53R273H and NRD1 that needs further elucidation.

Abnormal production of HB-EGF manifests in a broad array of cancers. Gunaratne and co-workers are intrigued by the possibility that NRD1 might therefore represent a critical factor involved in tumor spread. "This study indicates that molecules that modulate NRD1 or other p53 mutant-specific protein partners could offer an exciting and defined therapeutic approach to reduce cancer metastasis," says Gunaratne.

Malignant glioma is generally a death sentence for patients. These tumors, which arise from non-neuronal cells within the brain, grow quickly and aggressively, and contain a core population of glioma stem cells (GSCs) that are largely invulnerable to the weapons typically brought to bear against other cancers. “GSCs display resistance to radiation due to increased activation of DNA damage repair pathways, and also possess intrinsic resistance mechanisms against chemotherapy-induced cell death,” explains Prabha Sampath of the A*STAR Institute of Medical Biology.

New work from Sampath and her co-workers has revealed a potential vulnerability in GSCs that might give glioma patients a fighting chance. Her team studies microRNAs, tiny RNA molecules that do not encode protein; instead, they govern the production of proteins encoded by other genes. This research has a direct bearing on glioma progression. “MicroRNA-mediated translational control is known to be a major factor in brain tumor pathology,” explains Sampath.

She and her colleagues obtained GSCs from five patients with malignant glioma, and examined how their expression levels of known microRNAs differed relative to normal neural stem cells (NSCs). This revealed that GSCs produce markedly higher levels of the microRNA miR-138; importantly, miR-138 levels dropped when the researchers chemically forced the GSCs to ‘mature’ into differentiated brain cells, supporting a role for this RNA in uncontrolled tumor growth.

Treatment with ‘antimiR-138’, a molecule that selectively blocks the function of miR-138, killed cultured GSCs but had no effect on normal NSCs. Closer examination revealed that the inactivation of this microRNA prevented GSCs from undergoing cell division, and instead caused these cells to undergo a cellular ‘self-destruct’ program.

Subsequent transplantation experiments indicated that this approach might also yield therapeutic fruit: mice that received implants of human GSCs promptly developed aggressive gliomas, but inactivation of miR-138 was sufficient to prevent tumorigenesis. Finally, the researchers demonstrated that elevated miR-138 expression may be predictive of disease recurrence in patients with glioblastoma multiforme (GBM), a typical malignant glioma.

Having established this previously unrecognized role for miR-138 in ensuring GSC survival, Sampath is interested in examining whether this microRNA also contributes to progression and post-therapeutic recurrence of other brain cancers. Even if its influence is limited to a handful of cancers, the clinical impact of these findings could prove very significant. “We are currently performing tumor regression experiments and developing specific vectors for delivery of antimiR-138, with a vision to exploit this further as a novel therapy for treating malignant gliomas,” she says.

The Wip1 protein is important for survival, but mutations that inactivate it carry some surprising features. "A lack of Wip1 results in an excessive immune reaction to infectious organisms, in some cases killing the host," explains Dmitry Bulavin of the A*STAR Institute of Molecular and Cell Biology, Singapore. He also notes, however, that mice lacking Wip1 are considerably less prone to certain cancers. Now, research from Bulavin and his co-workers has revealed that Wip1-deficient animals also exhibit improved fat metabolism and cardiovascular health.

"We never suspected that autophagy could be part of tumor resistance in Wip1-deficient mice."

Wip1 is a phosphatase, an enzyme that specializes in the targeted removal of phosphate chemical groups that modulate function of proteins such as Atm and p53. Both of these proteins regulate pathways that ameliorate potentially cancer-causing genetic damage, but have also been linked to cardiovascular health.

To investigate whether Wip1 also regulates lipid processing, Bulavin’s team generated mice that were deficient in both Wip1 and apolipoprotein E (apoE), a protein involved in cholesterol trafficking. Mice without apoE are vulnerable to atherosclerosis, a narrowing and hardening of the arterial walls resulting from excessive accumulation of cholesterol-laden low-density lipoprotein (LDL) particles. Wip1-deficiency mitigated this effect, and mice lacking both proteins had lower body weight and greatly reduced tendency to develop atherosclerosis relative to mice lacking only apoE.

The vascular damage associated with atherosclerosis is initiated when immune cells known as macrophages begin to consume oxidized LDL particles, and gradually transform into lipid-loaded ‘foam cells’. Bulavin and co-workers found that macrophages from Wip1-deficient mice are far more resistant to becoming foam cells, and that this transformation is dependent on Wip1-mediated inhibition of Atm. "Removal of just a single copy of the Atm gene resulted in a striking reversal of the suppression of obesity and atherosclerosis seen in Wip1-deficient mice," says Bulavin.

Closer investigation revealed that the actions of Wip1 on Atm cause macrophages to pump out cholesterol rather than hoard it. This requires the cells to physically liberate cholesterol molecules from lipid droplets; Wip1 promotes this by stimulating a mechanism called ‘autophagy’, wherein lipid droplets are absorbed into cellular compartments, known as lysosomes, and broken down enzymatically.

The finding highlights a promising target pathway for drugs addressing cardiovascular health, but also reveals a novel function of Wip1 that may prove relevant for cancer research. "We never suspected that autophagy could be part of tumor resistance in Wip1-deficient mice," says Bulavin, "and we are now checking whether we can integrate this with other mechanisms of tumor resistance."

Lipid droplets, labeled with the dye ‘Oil red O’, accumulate in normal macrophages exposed to oxidized LDL (top) as they transform into artery-damaging foam cells. However, macrophages that lack the gene encoding Wip1 (bottom) rapidly eliminate cholesterol and show little lipid accumulation.

A digital representation of the human papillomavirus.

Depending on the strain, or genotype, of the human papillomavirus (HPV) (see image), the lesions it causes can range from relatively benign to cancer causing. Differentiating between lesions caused by low-risk and high-risk viral genotypes, however, is difficult. Françoise Thierry at the A*STAR Institute of Medical Biology in Singapore and co-workers have now identified proteins that could be used as reliable, sensitive markers to diagnose infections with high-risk types of HPV.

Commonly known as an inducer of genital warts, HPV is transmitted by sexual contact. Of the approximately 100 HPV genotypes known, a few, including HPV-18, have a high likelihood of leading to cervical or anal cancer. If pre-cancerous lesions are identified in their early stages, they can usually be removed using simple surgical procedures, with a very good prognosis.

“We would like to find out whether or not they are involved in the oncogenic potential of HPV-18 compared to other high-risk HPV genotypes which do not express E2^E4.”

The marker proteins identified by Thierry and colleagues, called E2^E4, are natural fusions between two known HPV proteins, E2 and E4. When Thierry and her co-workers discovered the fusion proteins, they were investigating the activity of the HPV-18 E2 protein, using cells engineered to express the E2 protein only.

The results were repeatedly ‘contaminated’ by E4 protein. Sequencing the HPV-18 E2 gene transcripts revealed the source of the E4 sequences: the gene includes triggers to make the E4 protein and attach it to the E2 protein. The DNA for the E4 gene is embedded within the DNA for the E2 gene, just ‘shifted’ over by one DNA base — akin to starting to read the word ‘intermittent’, and finding the word ‘mitten’ at the sixth letter. Thus, cells infected with HPV-18 automatically produce E2^E4 along with E2.

Knowing that a protein unique to HPV-18 could be clinically useful, the researchers checked the DNA sequences of other HPV types and found that they could not produce the fusion protein. “Since E2^E4 transcripts (and proteins) are specific to HPV-18, they could be used to unambiguously detect the presence and expression of this particular HPV genotype in early stage lesions,” Thierry explains.

What makes the protein useful as a marker may have even broader clinical implications. Because the proteins are specifically expressed in only a few high-risk HPV types, the researchers suspect they may not only mark but also contribute to these genotypes’ virulence. “We would like to find out whether or not they are involved in the oncogenic potential of HPV-18 compared to other high-risk HPV genotypes which do not express E2^E4,” says Thierry.

Cardiovascular disease:
The mechanics of prosthetic heart valves

Computer simulations of blood flow through mechanical heart valves could pave the way for more individualized prosthetics

Every year, over 300,000 heart valve replacement operations are performed worldwide. Diseased valves are often replaced with mechanical heart valves (MHVs), which cannot yet be designed to suit each patient’s specific needs. Complications such as blood clots can occur, which can require patients to take blood-thinning medication.

The researchers focused on the blood flow dynamics in a prosthetic valve known as a bileaflet MHV. This type of MHV contains two mobile leaflets, or gates, which are held in place by hinges. The leaflets open and close in response to blood flow pressures through the valve. Little is known about the effect that the hinged leaflets have on blood dynamics, although such designs are suspected of causing blood clots.

The computer model developed by Nguyen and his team simulates pressure flows through bileaflet MHVs by representing blood vessels as a computational mesh, where calculations are performed for individual blocks of the mesh. Their crucial advance was in enabling this mesh to move and evolve in response to the leaflet movements.

The researchers validated their computer model through laboratory experiments with a full 3D reproduction of the heart’s circulation system. Particle imaging equipment allowed them to visualize the fluid dynamics under different scenarios including pulsatile flow, which follows the pattern of a typical cardiac cycle.

“We obtained good agreement between our computer simulations and the experiments in terms of the magnitude and velocity of blood flow through the leaflets,” states Nguyen. The researchers also found that leaflet hinges might play a vital role in clotting, because individual hinges have different tolerances that can disrupt normal blood flow and cause stress in the vein walls.

This research is a first crucial step in understanding the impact of MHVs on blood flow. “Ultimately we hope to provide doctors with a tool to evaluate blood flow dynamics and other related aspects in patients with newly implanted valves,” says Nguyen.

To investigate why such complications occur, Vinh-Tan Nguyen at A*STAR’s Institute of High Performance Computing, Singapore, together with scientists at the National University of Singapore and institutions across the USA, have developed a new computer model to simulate the dynamics of blood flow through MHVs.

“The current practice for heart valve replacement in patients is a one-size-fits-all approach where a patient is implanted with the best-fit valve available on the market,” explains Nguyen. “The valves are well designed for general physiological conditions, but may not be suitable for each individual’s particular heart condition.”

“Ultimately we hope to provide doctors with a tool to evaluate blood flow dynamics and other related aspects in patients with newly implanted valves.”

Patients with DMD lack the protein dystrophin, which causes muscles to deteriorate and break down, leading to progressive difficulty with walking and general mobility.

New design guidelines from researchers in Singapore simplify the development of targeted therapies for muscular dystrophy and other diseases

The dystrophin protein offers critical support to muscle fibers. Mutations affecting dystrophin’s expression cause the muscle-wasting disease muscular dystrophy. In Duchenne muscular dystrophy (DMD), these mutations take the form of small sequence changes that make much of the dystrophin gene (DMD) untranslatable, yielding nonfunctional protein or no protein at all.

Therapies based on a strategy known as ‘exon skipping’ could undo the damage from these mutations. Development of such treatments is set to accelerate, thanks to research by a team led by Keng Boon Wee of the A*STAR Institute of High Performance Computing and Zacharias Pramono of the National Skin Centre in Singapore.

Proteins are translated from messenger RNA transcripts of genes; however, only certain RNA regions — known as exons — actually encode protein, and these are enzymatically spliced together prior to translation. Several clinical studies have demonstrated that small ‘antisense oligonucleotide’ (AON) molecules that bind mutated DMD exons can induce elimination of those defective exons during splicing, yielding shorter but largely functional versions of dystrophin.

“We are cautiously optimistic that AON-induced exon skipping could be the first effective therapy for DMD patients,” says Wee.

Unfortunately, DMD arises from many different mutations, and targeted AON design remains a time-consuming, trial-and-error process. To address this challenge, Wee and Pramono sought to define the characteristics of AONs that efficiently promote exon-skipping. They used computational analysis to zoom in on exonic sequences that coordinate splicing. They also identified regions of suitable length within dystrophin RNA transcripts that span these sequences and would be accessible to AONs in living cells.

The researchers thus derived a set of guidelines enabling them to effectively design AONs that targeted nine different exons affected in DMD patients. For each exon, at least one AON proved capable of boosting dystrophin expression to clinically relevant thresholds in cultured muscle cells (see image). “Our proposed set of factors resulted in a reasonable success rate of designing efficient AONs — 61% versus 38% using semi-empirical methods,” says Wee. Clinical studies have already demonstrated the promise of efficient exon skipping in treating DMD patients.

Wee notes that other diseases arising from abnormal RNA processing could also benefit from this approach. However, his team is also exploring this method as a general strategy to abort production of disease-causing proteins in cancer and other conditions.

“In contrast to small-molecule inhibitor drugs that can target only about 10% of the human genome, this approach could downregulate most human genes,” Wee says.

Cancer biology: Modeling cancer on the fly

A study of fruit fly genes reveals how molecules cooperate to induce tumor formation

Cancer biologists have known for decades that even the most potent cancer-causing genes do not act alone. Yet, identifying which combinations of genetic changes can cause a tumor to form and disease to progress remains a challenge. “The hope is that by understanding these combinations, it will be possible to design therapeutic strategies tailored to the genetic changes in different cancers,” says Stephen Cohen of the A*STAR Institute of Molecular and Cell Biology (IMCB) and the National University of Singapore.

Sequencing the genomes of tumors from cancer patients is one approach to identifying cancer-causing mutations. The number of mutations can be so large, however, that researchers are left wondering which mutations are cancer ‘drivers’ and which are innocuous ‘passengers’, Cohen notes.

Taking an alternative approach, Cohen and his team in Singapore succeeded in identifying cancer-causing genes in the fruit fly, Drosophila melanogaster, based on function. The team set out to find genes that cooperate with known cancer drivers that promote tumor formation.

They began with a gene linked to breast and lung cancer, epidermal growth factor receptor (EGFR). Team member Hector Herranz developed a fly model in which activation of EGFR caused tissue overgrowth, but these overgrowths did not progress to form tumors. He then screened for secondary genetic changes that would enhance the ability of EGFR to produce tumors. Herranz found that co-expression of a microRNA called bantam with EGFR produced tumors that spread through the body and killed the fly.

As regulatory genes that produce small RNA molecules, microRNAs typically reduce the expression of other genes, decreasing their ability to produce proteins. The team therefore searched for a target of the microRNA whose absence increased the tumor-forming potential of EGFR. Team member Xin Hong was able to locate it: a gene known as Soc36E. In the team’s fly model, Soc36E behaved like a tumor suppressor: the deletion of Soc36E enhanced EGFR-induced tumor formation.

Hong then identified the corresponding human gene as SOCS5. He found that it also behaved as a tumor suppressor; SOCS5 cooperated with EGFR in an experimental model of human cancer.

Studies on human SOCS5 are ongoing, Cohen explains, but early indications point to a breast cancer link. Further work by the team will determine whether SOCS5 could be a useful biomarker.

Cerebral malaria: Pinpointing a potential therapeutic target

Identification of the subtype of immune cells that is crucial to the onset of cerebral malaria provides a therapeutic starting point

An excessive response of the immune system to malarial infection can lead to serious complications, such as cerebral malaria. While the mechanism causing the onset of cerebral malaria is unclear, immunologists think that contributing factors include cells of the immune system and the inflammation that they cause. Laurent Renia and co-workers at the A*STAR Singapore Immunology Network and collaborators from Nanyang Technological University, Singapore, have now singled out one subtype of immune cells that is key to the onset of this often fatal disease.

The researchers used an established mouse model of the disease, called experimental cerebral malaria. Accumulation of CD8+ T cells, immune cells that destroy infected or damaged cells, is one known contributing factor in this model. Dendritic cells (see image), another type of immune cell, are important in activating certain types of T cells and are also known to be involved in experimental cerebral malaria.

“One dendritic cells are essential for the development of the immune response in particular T cells,” explains Renia. “These cells express different markers and are present in many tissues like the spleen. It was previously shown that splenic dendritic cells are important for experimental cerebral malaria to develop.”

In the earlier work, dendritic cells were modified so that they could be selectively destroyed. A marker that all dendritic cells express, called CD11c, was targeted with a diphtheria toxin receptor, allowing them to be killed using this toxin. The targeted destruction of dendritic cells prevented experimental cerebral malaria. However, this method did not discriminate between the several subtypes of dendritic cells that express CD11c, so the exact dendritic cell type responsible remained elusive.

Renia and his co-workers used a similar approach in this study, but targeted a marker called Clec9A with the diphtheria toxin receptor. Clec9A is expressed by one subtype of dendritic cells only. The subtype, called CD11c<sup>hi</sup>CD8<sup>+</sup>, is a candidate in experimental cerebral malaria because its cells are involved in activating CD8<sup>+</sup> T cells.

“Dendritic cells are essential to CD8<sup>+</sup> T cell development and thus to experimental cerebral malaria,” says Renia.

“Dendritic cells from human blood are integral parts of the immune system.

Infectious disease experts have long thought that children, teenagers and young adults who are chronically infected with the hepatitis B virus (HBV) lack the immune cells needed to fight this pathogen. As such, physicians currently withhold therapeutic interventions from younger patients until they have reached an advanced age — typically around 30 years old — at which time the immune system is thought to have ‘awakened’ to the virus.

Yet, contrary to the conventional medical wisdom, new research from the A*STAR Singapore Institute for Clinical Sciences (SICS) indicates that there is no such inherent age-associated period of so-called ‘immune tolerance’ to HBV. In fact, older people with chronic hepatitis B seem to have a weaker immune response, represented by weaker antiviral T-cell repertoires, than younger individuals infected with the virus.

“These findings can have major implications for the clinical management of chronic hepatitis B infections,” says the SICS’s Antonio Bertoletti, who led the research. “It might be better to start treatment early, as young people have a less compromised HBV-specific immune response, and [because] functional recovery of HBV-specific T cells is associated with successful control of the infection.”

Scientists from Bertoletti’s laboratory, together with clinical collaborators in the UK, isolated T cells from 44 people with chronic HBV infections between the ages of 10 and 30, the majority of whom were of Asian descent. Around 75% of the world’s 400 million people with chronic hepatitis B can be found within the region of Asia.

They compared the immune-cell samples to those from healthy age-matched controls, and showed that young patients infected with HBV expressed increased levels of virus-associated T cells, and these T cells displayed the ability to expand and produce pro-inflammatory signaling molecules known as cytokines, which are involved in antiviral responses. Furthermore, these HBV-specific T cells became more dysfunctional with age, the authors found, suggesting that the longer a patient is left untreated, the less effective the immune system becomes at clearing the virus.

The study upends the idea that immune recognition of HBV is somehow averted in certain individuals, thus indicating that all patients, regardless of age, could be suitable for treatment. It also highlights the inadequacy of measuring biomarkers of liver inflammation — the current proxy for immune activity in people with chronic hepatitis B infections. Such indicators are typically absent in young patients despite the study’s suggestion of the presence of active T-cell responses to the virus.

Cancer biology: Lifting the brakes on breast cancer growth

A protein that represses a critical checkpoint protein for cellular growth helps drive tumor development

One of the hallmarks of cancer is unchecked cellular growth. Fortunately, our cells contain a number of tumor suppressor proteins, including the cell cycle regulator p21, to keep cell growth in check. The protection conferred by p21, however, can be overridden by an overactive histone-modifying enzyme called PRMT6. This protein represses p21 expression, thereby promoting tumor growth and preventing senescence in breast cancer cells, A*STAR scientists have found.

Elevated expression levels of PRMT6 had been reported in a number of cancer types, including breast, cervix, bladder, prostate and lung cancer. However, the protein’s role in malignant growth had not been well established. To elucidate PRMT6’s function, cancer biologist Ernesto Guccione and his co-workers at the A*STAR Institute of Molecular and Cell Biology in Singapore turned to breast cancer cell lines in which PRMT6 is overexpressed when compared with normal tissue (see image). The researchers used chromatin immunoprecipitation assays, which can determine whether a given protein binds to a specific genomic sequence, and showed that PRMT6 binds directly at the promoter region of the p21 gene.

Depleting PRMT6 led to p21 induction, resulting in growth arrest. Importantly, this effect did not rely on p53, a master tumor suppressor that also interacts with p21. “Our data proves that by targeting PRMT6 we can re-activate the expression of the tumor suppressor p21 in cancer cells, which would lead to cell cycle arrest and would prevent tumor formation,” says Guccione.

“We believe p21 is just one of many targets that are controlled directly by PRMT6.”

Chemists have developed a number of drugs that block PRMT6. However, many of these compounds also inhibit other members of the protein arginine methyltransferase (PRMT) family, resulting in intolerable side effects because of the broad-sweeping nature of these agents on cell physiology. Thus, “it would be very useful to find new inhibitors to specifically target PRMT6 activity,” notes Guccione. Researchers in the United States recently discovered two compounds that specifically inhibit PRMT1. Meanwhile, the hunt for selective PRMT6-blockers continues.

Adding further weight to Guccione’s team’s findings, two research groups working in Europe independently confirmed that the p21 gene is a target of PRMT6 in human bone cancer cell lines. Intriguingly, one group found that p16 is also directly regulated by PRMT6, while the other linked p27 expression to PRMT6 activity. As a follow up, Guccione and his colleagues are now searching for other tumor suppressors affected by PRMT6. “We believe p21 is just one of many targets that are controlled directly by PRMT6,” he says.

Cilia, microscopic whip-like organelles that protrude from the surface of many cell types, are almost ubiquitous. They are present in all eukaryotes — organisms whose cells have a nucleus — and have diversified to perform a huge variety of functions, from making cells mobile to sensing light. In vertebrates, nearly every cell in the body has some form of cilia. It has now been shown that the development of cilia — in even the most evolutionarily ancient animals — is controlled by the same gene, FoxJ1. The finding is the result of research from an international team led by Sudipto Roy of the A*STAR Institute of Molecular and Cell Biology (IMCB).

"We are systematically studying the functions of these genes in cilia and their contribution to ciliopathies."

Biologists knew that FoxJ1 is essential for cilia formation in vertebrates, but little about how cilia develop in other organisms. Roy’s team searched for similar genes in over 200 diverse groups of organisms, including algae, fungi, amoebas, plants, insects and sea urchins. They found FoxJ1 present only in animals and fungi — groups which originated long ago — indicating that FoxJ1 may be nearly a billion years old.

The function of a gene can change over the course of evolutionary time, so it is possible that FoxJ1 homologs in lower animals do not control cilia development. Using two complementary methods, Roy’s group tested this possibility. First, they ‘knocked down,’ or silenced, FoxJ1 in a simple animal often used to study cilia: the flatworm, Schmidtea mediterranea. As predicted, cilia development was strongly impaired (see image).

The researchers then took FoxJ1 genes from primitive animals and expressed them in the zebrafish, a common model of animal development. FoxJ1 switched on the same genes as would the zebrafish’s FoxJ1 homolog. These two lines of evidence indicate that control of cilia development has changed little over hundreds of millions of years; the same gene regulates the process in both humans and the earliest animals to evolve.

Cilia perform a wide range of functions in humans, and studying their development may help in the treatment of diseases, Roy notes. “Motile cilia that line our respiratory passages beat to clear mucus that entraps pathogens and pollutants that we breathe in, and immotile primary cilia function as hubs for a number of signaling pathways,” he explains. “Dysfunctional cilia lead to a number of diseases that are collectively called ciliopathies.”

Roy’s team recently identified a large collection of genes that are activated by FoxJ1 during cilia formation. “We are systematically studying the functions of these genes in cilia and their contribution to ciliopathies,” he says.
Glaucoma is the leading cause of irreversible blindness in the world. A form known as primary open angle glaucoma (POAG) predominantly affects Europeans and Africans, whereas primary closed angle glaucoma (PACG) mostly affects Asians. Despite the high levels of blindness caused by PACG in Asian countries, scientists lacked the information that could confirm the disease’s genetic basis and provide a starting point to tackle the problem.

An international research team, including Chiea-Chuen Khor at the A*STAR Genome Institute of Singapore and Eranga Vithana and Tin Aung from the Singapore Eye Research Institute, has now identified three genetic variants that make individuals susceptible to PACG1.

Glaucoma results from damage to the optic nerve that is caused by reduced drainage of fluid in the eye. In POAG, fluid flows correctly in the eye, but cannot drain because there is damage to the trabecular meshwork — the structure that is responsible for the drainage. In PACG, the gap through which fluid flows from the back to the front of the eye is closed, preventing it from reaching the trabecular meshwork (see image).

Khor and co-workers enrolled patients with PACG from multiple countries, including Singapore, Hong Kong, China, India, Malaysia, Vietnam, Saudi Arabia and the UK. The researchers compared these patients’ DNA sequences with those of healthy controls to identify specific genetic characteristics that were consistently over-represented in the patients. They performed the process in two stages; to test the results from the first stage, they repeated the analysis with a second, independent set of patients.

In total, Khor and co-workers compared 3,771 patients with 18,551 controls. The analysis revealed three genetic variants strongly associated with PACG, implicating three genes in the disease: PLEKHA7, COL11A1 and PCMTD1.

“This is the first time that heritable determinants underlying PACG have been robustly discovered,” says Khor. “Many clinicians suspected a genetic cause, but were unable to prove it. We have definitively identified three genes that are important.” Khor also points out that it makes sense for these genes to be involved: “The genes identified, in particular PLEKHA7 and COL11A1, are strongly expressed in eye tissue at the suspected site of pathology.”

Identification of genetic variants that make patients susceptible to PACG provides researchers with a foundation upon which to develop ways of tackling the disease. For example, susceptibility to PACG could be assessed by genetic analysis, providing a predictive test, and this work could lead to the identification of drug targets.

Researchers in Singapore have succeeded in tracking, for the first time, the molecular changes caused by type 2 diabetes that affect how the body handles glucose production in the liver. In a series of experiments in mice, the researchers introduced a form of the compound pyruvate that incorporated specially treated carbon nuclei. This allowed the researchers to follow the processing of the compound using magnetic resonance spectroscopy (MRS). In this way, the team, led by Phillip Lee of the Singapore Bioimaging Consortium, showed that the enzyme pyruvate carboxylase plays a key role in the development of diabetes.

Diabetes is a consequence of the dysfunction of insulin, a hormone that stimulates cellular uptake of glucose from the blood. This process is closely linked to the production of glucose in the liver. Since the 1980s, limited study of the molecular details of glucose production has been possible using MRS to track organic compounds incorporating the rarer type of natural carbon known as carbon-13. Recently a ‘hyperpolarized’ form of carbon-13 — vastly easier to detect using MRS — has become available.

Lee and his co-workers injected hyperpolarized carbon-13-labeled pyruvate into a strain of mice in which type-2 diabetes can be induced simply by changing the diet from normal to high fat. Using MRS, they then traced over time, in both normal and diabetic mice, the compounds into which the hyperpolarized carbon nuclei became incorporated, and in what proportions. Their results provide evidence not only of which biochemical pathways are active, but also which are dominant in normal and diabetic mice.

By comparing the two groups of mice, they were able to show distinct changes in the liver metabolism of diabetic mice over time, particularly the importance of the biochemical pathway dependent on the enzyme pyruvate carboxylase in the development of diabetes. When the researchers gave the mice drugs typically used to treat diabetes, their technique detected the metabolic changes resulting from the therapy.

“This technology could be used to screen for metabolic disorders associated with other conditions such as heart failure, cancers and brain diseases,” Lee says. “We are extending our work to investigate metabolic aberrations in the diabetic heart, and to understand the therapeutic effects of anti-diabetic drugs on cardiac function.”
Research Highlights

PHYSICAL & LIFE SCIENCE TECHNOLOGIES
**Microelectronics:**

**A tougher seal for rugged environments**

An aluminum–germanium alloy forges a tough, hermetic seal for electronics in extreme environments

Sensors used in harsh conditions, such as deep-sea oil wells, must withstand extreme temperatures and pressures for hundreds of hours without failing. Vivek Chidambaram and co-workers at the A*STAR Institute of Microelectronics, Singapore, have investigated two metal alloys that could give micro-electromechanical system (MEMS) sensors better protection in the toughest environments.

“Cost effectiveness, better thermo-mechanical properties, and its eutectic microstructure makes it an attractive alternative.”

Typical MEMS sensors measure temperature, pressure or vibration, and they are hermetically sealed inside a strong metal casing to prevent air or moisture degrading the sensors’ electronics. Chidambaram’s team wanted to find cheaper, more durable alternatives to the metal solders, such as gold–tin or copper–tin, which are typically used to seal the case. They tested a 70:30 aluminum–germanium mixture, which has a melting point of about 420 °C. This temperature — the eutectic point — is much lower than that for either metal on its own. Unlike most conventional packaging materials, aluminum and germanium are compatible with the processes used to manufacture the MEMS. Using the aluminum–germanium sealant should make MEMS manufacturing easier and cheaper, and could also improve the device’s performance, says Chidambaram.

The researchers built a stack of 4 alternating wafers of aluminum and germanium, each less than a micrometer thick, and heated the sandwich under pressure to about 400 °C for 2 hours. Although the wafers did not liquefy, this “thermal aging process facilitated bonding prior to melting,” explains Chidambaram. Raising the temperature to 475 °C for another 2 hours fully melted the mixture, which then formed a strong seal after cooling — a process known as transient liquid-phase bonding.

Next, the researchers used acoustic microscopy, scanning electron microscopy and X-ray spectroscopy to reveal any voids or other defects in the seals. They found that the thermal aging process improved the quality of the seal. Tests showed that it was strong enough to withstand a shear of 46 megapascals — similar to the pressure exerted by almost half a ton per square centimeter — and was impermeable to water. The material lost little of its strength after being exposed to 300 °C for hundreds of hours.

Chidambaram and his team also tested a platinum–indium seal — which has the highest re-melting point (894 °C) of all the solders being considered for these applications — but it lost its strength after long durations at 300 °C, leaving the aluminum–germanium mixture in pole position as a better seal for MEMS. “Cost effectiveness, better thermo-mechanical properties, and its eutectic microstructure makes it an attractive alternative,” says Chidambaram.

Early detection of soft-tissue diseases, such as breast cancer, typically requires invasive biopsies. Now, a new self-assembled nanoparticle developed by Bin Liu at the A*STAR Institute of Materials Research and Engineering and co-workers may soon make biopsies obsolete. The team’s material significantly enhances the safety of two-photon microscopy (TPM) — a technique that uses fluorescent probes to generate three-dimensional pictures of cancer cell structures in living tissue.

Although TPM provides deep access to cell tissue without significant photo-damage, finding suitable substances to act as light-emitting probes is challenging. ‘Quantum dots’ made from nanoscale aggregates of elements such as cadmium and selenium are excellent cell-structure illuminators, thanks to their bright and stable fluorescence. However, their inherent toxicity restricts many possible biological applications.

Liu and her team therefore turned to conjugated organic molecules to produce less toxic dyes for TPM. While such small organic molecules are normally unable to absorb sufficient amounts of laser light to initiate fluorescence imaging, the team resolved this problem by synthesizing a star-shaped material known as a dendrimer. Consisting of a central triphenyl amine core and three ‘arms’ made from extended conjugated chains, this unique geometry can induce much larger cross sections that can absorb two photons better than isolated fluorescent dyes.

To ensure biocompatibility between the star-shaped dendrimer and cell tissue, the researchers had to employ a chemical trick. Inspired by the versatile binding behavior of chitosan, a natural polysaccharide, the team used a mild bromide–thiol reaction to attach several glucose–amine sugar rings to the dendrimer’s arms. According to Liu, this process lowered the cytotoxicity of the dye and enabled them to functionalize it with folic acid ligands that target the surfaces of a breast cancer cell line known as MCF-7.

The team’s experiments showed that the dendritic dye self-assembled into dispersed nanoparticles when submerged in water — a form that increases two-photon-absorption cross sections and provides a high yield of laser-induced fluorescence. When they incubated these nanoparticles into the MCF-7 cells, subsequent TPM imaging revealed a bright fluorescence localized inside the cancer cell cytoplasm (see image).

This data indicates that specific binding occurs between the dendritic dye and folate receptors on the MCF-7 surface. Cell viabilities close to 100% at dye concentrations used for imaging studies confirm that this strategy is a safe and promising way to increase the use of TPM imaging. “We are keen to expand the current in vitro imaging to in vivo applications,” notes Liu.

Antibiotics:
The plastic approach

Our antibiotic armory is set to benefit from the development of short-chain synthetic polymers with potent efficacy against multidrug-resistant microbes

As pathogenic bacteria overcome our current arsenal of antibiotic drugs, new antimicrobial therapies with fresh modes of action are needed. A set of antimicrobials based on synthetic polymers is a promising approach. These experimental therapeutics are highly effective at killing multi-drug-resistant pathogenic bacterial cells, but they have a low selectivity for their target over host tissues and are toxic to red blood cells. Now, an alternative approach to polymer design that overcomes this toxicity, while retaining the high efficacy against pathogens, has been developed by a team led by Yugen Zhang at the A*STAR Institute of Bioengineering and Nanotechnology.

“"We intend to investigate various applications of these compounds, including their potential as a preservative for cosmetics.”"

Although antibiotic drugs based on these natural peptides would be expensive to produce, polymer-based mimics should be low-cost, says Zhang. These synthetic structures copy the ‘amphiphilic’ structure of the natural peptides: they consist of alternating polar and non-polar subunits. The charged, polar units not only help the polymer to penetrate the pathogen’s cell membrane, they can also disrupt host cells.

In a bid to tune the toxicity of the polymer drugs to avoid killing non-microbial cells, Zhang and his co-workers abandoned the long-chain polymer design. They reasoned that they could improve selectivity by shortening the synthetic chain length, while retaining its highly efficient amphiphilic structure. The short-chain drugs that the researchers produced are known as oligomers.

In tests against a range of drug-resistant pathogenic bacteria and yeast species, the researchers confirmed that the amphiphilic oligomers retained their broad-spectrum killing action. Electron microscope images showed that, within a few hours of treatment, multiple oligomer strands had penetrated the pathogens’ cell walls, causing them to rupture (see image). Crucially, however, even at high concentrations, these oligomers had minimal effect on red blood cells.

Having demonstrated in principle that oligomers can improve target selectivity of antimicrobials based on synthetic polymers, Zhang and co-workers plan to refine the idea by further modifying the oligomers’ structures. They believe this will further improve their antimicrobial properties. Other applications besides medical uses are also possible, according to Zhang. “"We intend to investigate various applications of these compounds, including their potential as a preservative for cosmetics.”"

Biofuels: Metabolic roadmap for sustainable energy

Ethanol from plants may become cheaper, thanks to insights into the metabolism of a fungus used in fermentation

Efficient industrial fermentation of the plant sugar called xylose is critical to the cost-effective production of biofuels and other chemicals. However, most microorganisms cannot ferment xylose; and industrial microbiologists have yet to expose the secrets behind the extraordinary success of the current microbial champion of xylose fermentation, the fungus Scheffersomyces stipitis.

Publication of the genomic sequence of S. stipitis five years ago was but the first step towards this elusive goal. Rajagopalan Srinivasan and his co-workers at the A*STAR Institute of Chemical and Engineering Sciences, Singapore, have taken a critical next step by reconciling the annotated DNA sequence of S. stipitis with its biochemistry and physiology. The more holistic view of the metabolism of S. stipitis that emerges from their model suggests rational approaches to both improve the unique metabolic capabilities of S. stipitis and transfer these to other industrially important microbes. “If successful, such initiatives would substantially improve the efficiency with which energy could be extracted from agricultural and forest residues,” explains Srinivasan.

“Refinement of our metabolic model will help metabolic engineers to propose other testable strategies to increase the efficiency of xylose fermentation in S. stipitis and other industrial microbes.”

Rational engineering of more efficient xylose metabolism has been hindered by the complexity of the metabolic network: mRNA abundance, protein abundance, and metabolite-regulated protein activity all contribute to the regulation of metabolism. Perturbation of the metabolic network by modifying the expression of just one or a few genes usually has only minimal effects and often has unanticipated negative consequences.

To identify the most promising approaches to optimize xylose fermentation, Srinivasan and his co-workers combined information from the annotated genome sequence, pathway databases, and published studies with their own data, which they collected by determining the macromolecular composition of S. stipitis cells under various growth conditions. They used all of this information to generate a mathematical model that represents the relationships between 814 genes, 971 metabolites and 1,371 reactions.

In silico analysis of the model predicted that xylose-driven growth of S. stipitis is restrained by a limited capacity to regenerate a nucleotide cofactor when the oxygen supply is limited. The researchers validated this prediction experimentally and proposed specific strategies to overcome the bottleneck. The model also provided insights into the roles of super-complexes in channeling the flow of electrons during mitochondrial respiration.

Incorporation of thermodynamic constraints, enzyme kinetic information, and high-throughput transcriptomic, proteomic and metabolomic data will enhance the predictive capacity of the model. “Refinement of our metabolic model will help metabolic engineers to propose other testable strategies to increase the efficiency of xylose fermentation in S. stipitis and other industrial microbes,” Srinivasan says.

Exactly how memories are stored and accessed in the brain is unclear. Neuroscientists, however, do know that a primitive structure buried in the center of the brain, called the hippocampus, is a pivotal region of memory formation. Here, changes in the strengths of connections between neurons, which are called synapses, are the basis for memory formation. Networks of neurons linking up in the hippocampus are likely to encode specific memories.

Since direct tests cannot be performed in the brain, experimental evidence for this process of memory formation is difficult to obtain but mathematical and computational models can provide insight. To this end, Eng Yeow Cheu and co-workers at the A*STAR Institute for Infocomm Research, Singapore, have developed a model that sheds light on the exact synaptic conditions required in memory formation.

Their work builds on a previously proposed model of auto-associative memory, a process whereby a memory is retrieved or completed after partial activation of its constituent neural network (see image). The earlier model proposed that neural networks encoding short-term memories are activated at specific points during oscillations of brain activity. Changes in the strengths of synapses, and therefore the abilities of neurons in the network to activate each other, lead to an auto-associative long-term memory.

Cheu and his team then adapted a mathematical model that describes the activity of a single neuron to incorporate specific characteristics of cells in the hippocampus, including their inhibitory activity. This allowed them to model neural networks in the hippocampus that encode short-term memories. They showed that for successful formation of auto-associative memories, the strength of synapses needs to be within a certain range: if synapses become too strong, the associated neurons are activated at the wrong time and networks become muddled, destroying the memories. If they are not strong enough, however, activation of some neurons in the network is not enough to activate the rest, and memory retrieval fails.

As well as providing insight into how memories may be stored and retrieved in the brain, Cheu thinks this work also has practical applications. “This study has significant implications in the construction of artificial cognitive computers in the future,” he says. “It helps with developing artificial cognitive memory, in which memory sequences can be retrieved by the presentation of a partial query.” According to Cheu, one can compare it to a single image being used to retrieve a sequence of images from a video clip.

Computational neuroscience:

Memory-making is all about the connection

A model that shows how connections in the brain must change to form memories could help to develop artificial cognitive computers

Signal processing:

Look-up tables to shoulder the processing load

Advanced mathematical algorithms are essential for processing electronic signals within computers and embedded processors. Scientists and engineers are constantly refining and redesigning their algorithms to obtain higher throughput of information on ever smaller devices that consume less power.

Now, Pramod Kumar Meher of the A*STAR Institute for Infocomm Research in Singapore and co-workers at Central South University in Changsha, China, have developed an efficient new method to implement an important step in signal processing, called the discrete cosine transform (DCT). Their method could lead to devices that occupy smaller areas, provide higher throughput of information, and consume less power than existing devices.

The DCT is commonly used for the compression of digital video and audio such as MPEG files (see image). Similar to the better-known Fourier transform, the DCT involves expressing a series of data points as a sum of their product with cosine functions.

Several algorithms and software architectures already exist for computing so-called ‘power-of-two-length DCTs’. But, those DCTs are not suitable for all applications. The prime-length DCT is an alternative to the power-of-two-length DCT that has the potential to be more efficient for implementation in hardware, Meher notes.

Meher and his co-workers have focused on computing the DCT of different lengths of practical interest using specialized digital circuits that occupy less area on a silicon chip and use less power, but run at adequate speed. They not only derived a more efficient algorithm for DCT, but also derived new architecture — based on the ‘distributed arithmetic’ approach — for implementing the algorithm in integrated circuit chips.

Meher and co-workers made use of a theorem that inter-relates the transforms with cyclic convolution of two finite duration sequences. By using look-up tables, this convolution, and thereafter the prime-length DCT, could be performed quickly and accurately.

The team also described a new, efficient algorithm for decomposing the DCT — in mathematics, this means rewriting the problem in terms of a combination of simpler quantities. In addition to reducing the required size of read-only memory (ROM), the researchers found that overall their algorithm significantly reduced the computation time.

“We found that the proposed design involves significantly less area and it yields higher throughput with less power consumption than the corresponding existing designs,” says Meher. “The structure we propose is highly regular, modular and therefore suitable for Very Large Scale Integration realization.”

Graphene: A patterned template for molecular packing

Simulations of atomic-scale processes show how to trap and pack molecules in patterned graphene sheets that may have molecular storage applications.

Graphene’s versatile electronic, chemical and mechanical properties have placed it center stage in physical sciences research, with attention currently focused on its potential applications. Computational experts are contributing unique insights by investigating graphene-based structures in silico. By exploring the structure and properties of graphene — graphene that is hydrogenated on one side — a research team from Singapore and the USA has provided a potential template for packing molecules. These structures could be useful for trapping molecules for energy storage or biological applications.

“Our graphene-based structures provide a potential template for packing other molecules, such as hydrogen and methanol molecules, which could be used in energy applications.”

Led by Chilla Damodara Reddy of the A*STAR Institute of High Performance Computing, Singapore, the research team computationally constructed a large square graphene sheet with hydrogen atoms covalently bonded above every other carbon atom to form a graphone domain. Depending on the size of the domain, the graphene regions distorted into three distinct three-dimensional architectures. Small domains morphed into a cap shape, while larger domains resulted in interfacing graphene and graphone segments curving in opposite directions with the center of the graphene patch remaining flat. A third, intermediate, morphology showed undulations both at the graphene/graphone interface and in the center of the hydrogenated graphene. A 5% lattice mismatch between graphene and graphone caused the three-dimensional distortions.

All of the structures were stable well above room temperature. Reddy and co-workers also observed so-called ‘energy wells’ in the graphene domains, which they tested to determine whether or not they could trap molecules. They used fullerenes as their model molecules.

The researchers designed materials with graphene domains a suitable distance apart and of appropriate diameter to optimize the trapping of multiple molecules within the energy wells. They also proposed a minimum spacing between the domains to prevent instability between trapped molecules of neighboring domains.

Reddy and his co-workers extended the work to explore the possibility of trapping multiple fullerenes within one graphene domain. They showed that a domain with a diameter of 2 nanometers could trap three fullerenes in a triangular array, while one with a diameter of 4 nanometers could trap twelve molecules in different undulations of the graphene domain (see image). These structures were also stable at room temperature; although at very high temperatures — above 700 kelvin — the molecules could escape the confines of the energy well.

“Our graphene-based structures provide a potential template for packing other molecules, such as hydrogen and methanol molecules, which could be used in energy applications,” say the researchers. They could also trap proteins and DNA for use in biological applications.

Catheters play a crucial role in hospital care, particularly in the transport of intravenous fluids and medication. Typically, they are made of flexible low-toxicity silicon rubber that is, unfortunately, prone to colonization by bacteria or other microbes. Once settled, the microbes form a biofilm that provides resistance to antimicrobial agents and the body’s immune response. These biofilms are the leading cause of potentially lethal healthcare-related infections. To prevent this build-up, or fouling, a team led by Yi-Yan Yang from the A*STAR Institute of Bioengineering and Nanotechnology (IBN) has developed a simple and effective method to modify the rubber surface of catheter tubing.

Existing approaches against microbial adhesion use antibiotics or silver to coat the catheter surface. However, overuse of antibiotics can lead to bacterial resistance and the silver coating can be toxic to blood, limiting the clinical implementation of these methods. “Moreover, the ‘burst release’ of these antibiotics and silver affects their efficacy,” says Yang.

Yang and her co-workers therefore adopted an alternative approach: they altered the silicon rubber using antimicrobial and antifouling copolymers consisting of a polyethylene glycol (PEG) polymer linked to a strand of polycarbonate polymer. The polycarbonate strand was composed of positively charged hydrophilic and hydrophobic units, or monomers. Adopting a cleverly low-effort strategy, the team modified the rubber surface with a reactive substance known as dopamine, and then simply dipped the pre-coated surface in a solution containing the polymer precursors to anchor the copolymer chains.

The researchers determined the antibacterial and antifouling performance of the coatings by incubating the multidrug-resistant Staphylococcus aureus Gram-positive bacteria with the treated rubber. All coatings exhibited antifouling properties thanks to their flexible and bulky PEG portions, which prevented microbial cells from approaching the rubber surface. Furthermore, only coatings that contained hydrophobic monomers in the positively charged polycarbonate killed bacteria in solution. This highlights the importance of these monomers, which may insert into bacterial membranes and thereby enhance the interaction between polymer and bacteria.

Noting that very few red blood cells ruptured upon contact with the coatings, Yang says that there was no blood protein adsorption or platelet adhesion on the treated surface — proof of the excellent blood compatibility of the polymers. Yang and her team recently optimized the polymer compositions to also fight Gram-negative bacteria. “We plan to expand these technologies to other coating applications, such as to contact lenses and to implant coatings, to prevent biofilm formation,” she adds.

By treating catheter surfaces with a polymer coating, life-threatening microbial infections may soon become a problem of the past.
As demand escalates for ever-faster and more efficient and reliable data storage, researchers turn to next-generation non-volatile memory technology

Internet, computing and networking technologies are now integral to many people’s lives, generating ever-increasing amounts of digital information. Data storage experts estimate that by 2020, 35 zettabytes — $35 \times 10^{21}$ bytes — of digital information will require storage that is safe, reliable and above all, quickly accessible.

“Storage is the most likely issue to inhibit the capability and performance of a computing system,” explains Yong Khai Leong at the A*STAR Data Storage Institute. “Current hard disk drives consume significant energy and release a lot of heat.”

Most of the processing work in a computer is performed by random-access memory (RAM), which can access any part of its memory very quickly. However, this comes at a cost — information in RAM is not stored when the computer is off — so storage devices using non-volatile memory (NVM), such as read-only memory (ROM) and flash memory associated with magnetic hard disks, are used for long-term storage.

Yong and co-workers reviewed existing data center storage systems, and suggested ways to incorporate next-generation NVM, which can do the job of RAM as well as providing storage, into future data centers. They focused on the importance of scalable, affordable storage systems, and the need for devices that can quickly read files and metadata. Examples of metadata include the keywords stored alongside every webpage for the benefit of internet search engines.

Data centers already use alternatives to hard disks such as solid-state drives (SSDs) that use less power than magnetic hard disks. However, SSDs are expensive and still slower than RAM. “We propose a new storage architecture incorporating next-generation NVM technology in a hybrid form with magnetic disk drive technology,” explains Yong. “This NVM has a longer life span than SSDs, and is quicker at reading metadata.”

A conventional magnetic disk drive in hybrid with next-generation NVM can spin less quickly because the task of reading data is sent through the NVM first. As a result, less energy is consumed. Also, while the NVM is searching through files, the disk drive is free to carry out maintenance tasks such as file backups, reducing the potential for data loss.

Yong notes that future systems will need intelligent algorithms — software that knows which data tasks to prioritize in the NVM at different times according to user demand.

A*STAR is leading the global search for data storage solutions, with a three-year research program in place. “We are taking a holistic approach in investigating the optimal ways to integrate these new emerging memory technologies into current systems and data centers,” Yong says.

A sharp look beneath the surface

A new image-reconstruction method yields clear images of subsurface features in biological specimens and technological components

Optical coherence tomography (OCT) is a popular imaging modality for obtaining three-dimensional, micrometer-resolution pictures of structures that lie beneath the surface of, for example, the human eye or silicon wafers used in the computer industry. The technique could now become even more powerful, thanks to work led by Hon Luen Seck from the Singapore Institute of Manufacturing Technology at A*STAR. The team has found a way to eliminate one of the main noise sources that otherwise blur these images.

The OCT method works by splitting a light beam into two separate rays. One ray penetrates the sample and partially scatters from features beneath its surface. A fraction of the incident light therefore returns to its origin. This reflected light then interferes with the other ray — known as the ‘reference beam’ — that travelled entirely outside the sample and was reflected from a mirror. The position of the mirror determines which layer of the sample is imaged. By moving the mirror, researchers can obtain information about different parts of the sample.

“We plan to explore now the application of the technique to the imaging of printed electronics devices and micro-fluidics devices.”

The method has proved very successful for biological and technological applications. It is, however, plagued by one problem: light returning from the sample not only interferes with the reference beam, but also with other light fields reflected by the sample. “This adds ambiguities when interpreting the image,” says Seck. The method developed by the researchers reliably removes this so-called ‘autocorrelation noise’.

Seck and co-workers liken the process of light scattering from the sample to the passage of light through a particular kind of filter. There are physical constraints on how this filter may look. By putting this additional information into the reconstruction process, the researchers demonstrated that they could almost entirely delete autocorrelation noise from the images (see image). The technique has been developed for OCT, but is not limited to it. “The approach can be adapted to other image-formation processes,” explains Seck.

The team’s method works particularly well with sparse samples, which sport relatively few features. This is the case, for instance, in biological specimens and in layered electronics. “We plan to explore now the application of the technique to the imaging of printed electronics devices and micro-fluidics devices,” says Seck. Moreover, the researchers are working to make the reconstruction algorithm faster: “At the moment, our method is not able to achieve instantaneous reconstruction as required for real-time applications where an area scan is required, but we expect that with ongoing research the computational demand will decrease.”

Wireless networks:

Mobile devices keep track

A more sensitive technique for determining user position could lead to improved location-based mobile services

Many mobile-phone applications (apps) use spatial positioning technology to present their user with location-specific information such as directions to nearby amenities. By simultaneously predicting the location of the mobile-user and the data access points, or hotspots, improved accuracy of positioning is now available, thanks to an international research team including Sinno Jialin Pan from the A*STAR Institute for Infocomm Research. Software developers expect that such improvements will enable a whole new class of apps that can react to small changes in position.

“We also want to find ways to make use of the estimated locations to provide more useful information, such as location-based advertising.”

Traditionally, device position was determined by the Global Positioning System (GPS) that uses satellites to triangulate approximate location, but its accuracy falters when the mobile device is indoors. An alternative approach is to use the ‘received signal strength’ (RSS) from local transmitters. Attenuation of radio waves by walls can limit accuracy; and, it is difficult to predict signals in complex, obstacle-filled environments.

Palm oil extraction annually produces approximately 13 million tons of waste plant matter. Some of this by-product, known as empty fruit bunch (EFB), is currently incinerated to produce heat and electricity to run palm oil mills, but it is now on the path to a sweeter use. By adapting and optimizing an established technique to convert sugarcane bagasse and corn stover to the useful sugar xylose, a research team in Singapore, led by Jin Chuan Wu from the A*STAR Institute of Chemical and Engineering Sciences, has experimentally extracted high yields of xylose from EFB.

EFB contains xylan, which is a carbohydrate made up of units of xylose. Xylan is very susceptible to being broken down to these individual sugar molecules in the presence of mild acid. Known as hydrolysis, this process is not widely applied to EFB — despite its well-established use for converting sugarcane bagasse and corn stover — because of difficulties in making it cost effective. The key to Wu and his team’s success was the combination of acids they selected for hydrolyzing EFB: sulfuric (H₂SO₄) and phosphoric (H₃PO₄) acids. “The combined use of H₂SO₄ and H₃PO₄ has a synergistic effect in improving sugar yields,” explains Wu.

Since the elements sulfur and phosphorus are essential for the fermentation of xylose using microbes, the researchers’ combination of acids will play a fundamental role in the further conversion of xylose into other useful chemicals, such as the sugar substitute xylitol, lactic acid and ethanol. After hydrolysis and neutralization, these acid components can be used directly in a microbial fermentation. Hydrolysis requires the levels of these elements to be low, with higher levels being detrimental. In previous EFB hydrolysis techniques, higher concentrations of acids were used, but the levels of sulfur and phosphorous were too high for the microbial fermentation stage.

After discerning the right combination of mild acids, Wu and his team used computer modeling followed by supporting experiments to find the optimal conditions for hydrolysis. They obtained xylose yields of 80–90%. The conditions they optimized included the concentrations of the two acids, the reaction temperature, the dilution of the solution and the size of the EFB particles.

“Next, we will convert the sugars into lactic acids by microbial fermentation using lactic acid bacteria,” explains Wu. This lactic acid will be used for producing polylactic acid: a renewable and completely biodegradable biopolymer, that he says is stable at high temperatures and has broad applications.

Microelectronics:

Miniaturized sensors hold up under pressure

Implantable medical devices may soon improve thanks to new developments in miniaturized pressure sensors

Applications as diverse as oil-well drilling and robot-driven surgery are driving demand for improved micro-electromechanical system (MEMS) pressure sensors. As they are made smaller, however, simultaneously achieving high sensor stability and sensitivity becomes progressively more difficult. A research team from Singapore and South Korea has now overcome this technical challenge by producing a miniaturized sensor that couples a key component — a stable diaphragm — with sensitive silicon nanowires.

In principle, the design of a miniaturized pressure sensor is straightforward: create a pressure-deformable diaphragm and then embed a piezoresistor made from a material in which pressure causes a change in electrical resistance, such as a silicon nanowire. In practice, however, problems including difficulties with circuit design and fatally fragile components often plague development of a commercially useful sensor.

By combining and optimizing three forms of silicon, the research team, which included Liang Lou at the A*STAR Institute of Microelectronics in Singapore, was able to develop an MEMS pressure sensor that is operationally robust, and shows promise for use in robotic surgery.

Since the diaphragm must transfer small pressure changes to the piezoresistor while maintaining resistance to deformation and breakage, material selection is crucial. Lou and his co-workers considered using silicon dioxide for its excellent pressure sensitivity. However, this useful property is countered by a strong tendency to buckle and twist even without pressure. Their solution was to use a double layer of silicon dioxide — with piezoresistive silicon nanowires embedded in between — topped by a stabilizing layer of silicon nitride (see image).

By etching down the silicon nitride and varying the thickness and treatment of the silicon nanowires, the team found an optimum combination. The final sensor resisted deformation and mechanical breakage while still providing the linear change in electrical output upon pressure that is desired for sensitive medical instrumentation.

"The high internal stress of silicon nitride improves the diaphragm structure with good flatness, a large measurement range and waterproof properties," says Lou. "Our work provides a pioneering demonstration that integrating silicon nanowires into a multi-layer diaphragm allows us to scale down the sensor without losing high sensitivity."

The team’s main target now is to realize an implantable miniaturized medical device, according to Lou. Despite this goal being reliant on advances in circuitry research and extensive testing prior to use in humans, the sensor not only shows great promise but also points the way to future silicon nanowire-based sensor design.

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Induced pluripotent stem (iPS) cells have the potential to form any cell type in the body, providing a powerful tool for drug discovery and regenerative medicine. Yet coaxing these cells to reliably take on a specific fate in the laboratory has proven challenging on a large scale. Now, a team of A*STAR stem cell researchers has developed a cell differentiation protocol in which iPS cells are propagated and expanded in a three-dimensional (3D) bioreactor to efficiently create neural progenitor cells.

"Such a method will be a boon for the nascent cell-therapy and drug-screening industry, as it will be able to produce vast amounts of cells for transplantation and drug discovery in a reproducible manner," says Steve Oh at the A*STAR Bioprocessing Technology Institute in Singapore, who led the research.

Oh and his co-workers started with a so-called ‘microcarrier’ platform that they had previously developed for culturing human embryonic stem cells on the surface of small solid particles in a 3D suspension system. They optimized the technology for human iPS cells, demonstrating that protein-coated cylindrical microcarriers in stirred vessels, known as spinner flasks, coupled with twice-daily culture medium exchange, can support 20-fold expansion of reprogrammed stem cells. This yield was higher than any other reported system for growing batches of such cells.

"The 2D approach is manually laborious, gives one-tenth of the yields and is variable from lab to lab,” says Oh. “Microcarrier-based cultures provide larger surface areas for cell growth and more of them can be added to the system to increase the aggregate sizes and yields.”

Oh and his team also coaxed the neural progenitors to further differentiate into many different types of brain cells, including neurons, oligodendrocytes and astrocytes — the three primary neural lineages. In the future, notes Oh, such neurons could be used to treat Parkinson’s disease, for example; and, oligodendrocytes could be transplanted to overcome spinal cord injuries.

Information technology:

Improving the health of machines

A novel adaptive management system boosts the efficiency of wireless sensor networks that monitor surrounding environments

Electronic engineers in Singapore have developed and successfully tested a management system that increases the efficiency of wireless sensor networks for monitoring machine health. The new system, known as an adaptive classification system (ACS), reduces the power consumption of individual sensors and increases their lifespan, while also decreasing network traffic and data storage requirements.

The ACS also achieves more robust results in terms of diagnosis of machine problems and prognosis of performance. “Other applications include monitoring patient health, disaster monitoring systems, such as fire alarms, and environmental monitoring for chemical plant accidents, air and water quality,” says Minh Nhut Nguyen of the A*STAR Institute for Infocomm Research, who led the research team.

Wireless sensors are now so inexpensive and flexible that their application in monitoring systems is widespread. Because of the environments in which they are deployed, sensors increasingly require their own portable power source, typically a battery, which means they have a limited lifespan (see image). Any way of reducing the amount of power the sensors draw would increase their lifespan, decrease the need to replace them and therefore reduce costs, Nguyen explains.

Reducing sensor sampling rates to a practical minimum is one way to lower power consumption; this can be achieved by halting monitoring when a machine is not operating. Typically, a machine functioning smoothly demands a lower and coarser sampling rate than one that needs attention. Nguyen and his co-workers therefore developed their ACS along these lines. Importantly, it incorporates an adaptive system of nested sensors. Some of the ACS sensors sample particular parameters at a low rate to provide data for a model whose purpose is simply to trigger more intensive sampling of other sensors when a potential problem is detected.

In addition, the system utilizes a set of models that is geared to sensors sampling at a particular rate. The ACS also integrates several different methods of classifying whether particular data patterns are of concern such that they require higher levels of sampling. Decisions are therefore made on the basis of multiple classifications. This not only increases the robustness of the system, but also means that it can be trained to detect problems using a minimal amount of data.

Nguyen and his team tested the ACS using a machinery fault simulator, a machine in which key components, such as bearings, could be replaced by faulty or worn ones. Encouragingly, on average the ACS outperformed current models in these tests.

Battery life limits the lifespan and utility of wireless sensors, such as those used in handheld vibration sensors to detect irregular noises in industrial machinery.

A method that boosts the contrast of high-resolution optical images has the potential to enable lithography at the nanoscale

When looking to produce the tiny semiconductor components used in electronic devices, photolithography is the process of choice. It not only provides high-resolution images, but also allows high-throughput production. However, as miniaturization of electronic circuits advances unceasingly, traditional photolithography hits both fundamental and cost limits. Now, a new photolithographic technique that will produce features smaller than those possible today is on the horizon.

This development is thanks to an international research team led by Jing Hua Teng and Hong Liu from the A*STAR Institute of Materials Research and Engineering, Singapore, which included co-workers from the A*STAR Data Storage Institute, Singapore.

In traditional photolithography, light is used to write, for example, the layout of an electronic circuit onto a substrate coated with a light-sensitive material. The assembly is then chemically processed in a way that makes the desired pattern appear on the final component. The minimum size of the features that can be produced with this method is given by the optical diffraction limit: the resolution that can be obtained in optical images cannot be higher than about half of the wavelength of the light used. This limit is typically on the order of several hundreds of nanometers. And, with a view to further miniaturization of electronic components, it constitutes a genuine roadblock, explains Teng.

Physicists have proposed several methods to beat the diffraction limit, including the use of so-called superlenses. The resolution of superlens images exceeds the diffraction limit; however, these images tend to suffer from poor contrast, and this has limited their usefulness for lithography.

Teng and his co-workers demonstrated that they could produce superlens images with a resolution below 50 nanometers and a contrast sufficient for photolithographic purposes. The trick was to carefully control the surface of the lens, which consists of a thin silver film. “A smooth surface ensures that very little light is lost due to scattering,” explains Teng. Through careful optimization of the fabrication process, he and his team succeeded in producing silver superlenses with imperfections that were less than 2 nanometers in height.

The team’s next goal is to optimize the lithography process and the materials involved to meet the high-throughput requirements for industry-scale applications. The result should be a versatile tool for optical lithography in the nano-regime. “Superlens lithography is a promising technology for next-generation optical nanolithography for the semiconductor industry, but also for bioengineering and data storage,” says Liu.

The recently developed ability to measure physical changes in silicon when processed into microelectronic devices could improve fabrication techniques for even smaller circuits

Thinner semiconductor wafers to house electronic circuits are needed so that more computing power can be packed into ever-smaller electrical products. Thinning, however, makes the wafers brittle and prone to warping or breaking. A technique for measuring the stress in those chips during production is now available, thanks to developmental work led by Xiaowu Zhang at the A*STAR Institute of Microelectronics, Singapore. The resulting information could enable miniature but robust semiconductor devices.

The conversion from bare wafer to useful device can be an arduous one for a sheet of silicon, particularly when it is only a few millimeters thick. Fabrication processes can involve bombarding the wafer with a beam of ions, dipping it in corrosive acids to etch tiny structures, exposing it to plasmas for cleaning, or coating it in layers of hot metal to create electrical contacts. Then, the wafer must be fixed into a package.

Zhang and his co-workers designed and built stress sensors directly onto a silicon wafer to monitor the strain that such packaging exerts. They took advantage of the piezoresistive effect in silicon — when a force is applied to a silicon wafer, it pushes atoms closer together. In turn, the change in atom distribution alters the way an electrical current passes through the material, which can be measured as a change in resistance.

Each stress sensor consisted of 16 resistors (see image). Since the piezoresistive properties of silicon are well known, Zhang and his co-workers could simply convert the changes in resistance to a corresponding change in stress.

By equally distributing 17 such sensors on the sample surface, the researchers monitored the stress in a silicon wafer during a number of common packaging processes. These included coating the wafer in a thin film and attaching a small bump of solder. They also embedded the sensors into a plastic test board, which they dropped repeatedly. Zhang and co-workers also developed a data acquisition system that could monitor the stresses during this impact test.

“Semiconductors are a multibillion-dollar industry,” explains Zhang. “This stress data should enable the design of novel packaging technologies and reduce the chance of device damage during processing and during daily use and accidents, such as dropping the device.”

Evaluating the stresses on a device wafer during other processes, including a technique known as ‘through-silicon via’, in which electrical connections are passed all the way through the wafer, will be the next step in the team’s research, says Zhang.
Semiconductor interfaces:

Big opportunities for tiny insulators

A new theoretical model enables accurate predictions of dipoles at oxide interfaces (left, electron microscopy image) using the classical property of electronegativity (right). The scale shows how two elements with different relative electronegativities align at an interface.

Advances in miniaturization have made electronic devices cheaper and more powerful, but these procedures also create new challenges for materials scientists. For example, traditional silicon dioxide insulators used in field-effect transistors begin to leak small amounts of current at nanoscale dimensions. To combat this problem, researchers have developed insulators called ‘high-k dielectrics’ that link heavier elements, such as hafnium or zirconium, into insulating oxide films with exceptional charge-isolating capabilities.

Integrating high-k dielectrics into circuits, however, creates a different manufacturing problem. Localized electric fields known as charged dipoles can form at insulator–semiconductor interfaces and generate unwanted voltages that impact device performance. Sing Yang Chiam from the A*STAR Institute of Materials Research and Engineering in Singapore and co-workers have now developed a model that can identify interface dipole problems before they appear — a finding that promises to help end the ‘trial-and-error’ design issues typical.

Currently, materials scientists employ extensive quantum mechanical calculations to determine whether or not new high-k dielectrics will have interface dipoles. Chiam and co-workers investigated a more intuitive approach: they linked the appearance of interface dipoles to the classical property of electronegativity, a number that relates an element’s electron-attracting power to its position in the periodic table.

Scientists have previously avoided estimating dipoles with electronegativity values because, in many cases, they predict incorrect electric field polarities. To resolve this discrepancy, Chiam and co-workers correlated theoretical electronegativity with experimental ‘charge neutrality levels’ — electronic energies required to counterbalance dipoles on insulator interfaces. After measuring the charge neutrality on several different high-k dielectrics with X-ray and ultraviolet radiation (see image), the team plotted this data against electronegativity. They discovered that a simple linear equation connected the two parameters.

Further manipulation of this equation revealed it could also predict a so-called ‘dipole neutrality point’ (DNP) where interfacial dipoles flip polarity. Armed with this new theoretical tool, the researchers investigated both well-known and novel high-k dielectric/semiconductor interfaces. They found that the DNP concept provided accurate predictions of dipole polarity and strength: the offset voltages needed to turn on a high-k dielectric field-effect transistor closely matched values generated from the electronegativity values.

Chiam notes that the straightforwardness of this model should make it exceptionally practical for scientific discovery. “This is the simplest method to find dipoles at material interfaces before starting experiments,” he says. “Our model can predict what kinds of bulk or interface modifications are needed to offset dipole values — a significant time saving over traditional approaches.”

Just as gardeners can use ‘growth lamps’ to stimulate plant growth, materials scientists can now promote uniform growth of decahedron-shaped silver nanoparticles while they are in solution. These ten-faced solids, only tens of nanometers in size (see image), could enhance bio-imaging and biosensing techniques. The new photo-assisted method for use during crystal growth was developed by Xia Yu of the Singapore Institute of Manufacturing Technology and collaborators in Hong Kong and Singapore.

Yu and her co-workers based their method on a phenomenon known as localized surface plasmons, which are synchronous movements of electrons that occur, for example, at metal–air interfaces. Using plasmons at the surface of silver nanoparticles, the researchers succeeded in specifically growing these particles to be decahedron-shaped and uniform in size. Their idea was based on antecedent work, which showed that crystal growth of decahedral silver nanoparticles can be aided by white-light illumination.

The researchers targeted the plasmons more specifically: rather than use white light, which contains wavelengths across the visible spectrum, they used light with a relatively narrow spectrum, tailored to the frequency of the localized surface plasmons. Yu and co-workers tested a range of light-emitting diodes (LEDs) of different wavelengths and found that illumination with narrow-band light sources did indeed help to grow uniform silver nanodecahedrons. “Also, when precursor solutions containing very small seed particles are irradiated with light of different wavelengths, we can form silver nanoparticles of other shapes,” says Yu.

During the photo-assisted growth process, particles of varying sizes formed initially, but in the course of several hours they reached a uniform size. Some of the silver nanodecahedrons grow initially to a relatively large size. Although these particles are unstable, they are useful, according to Yu. “The silver atoms on their surface etch away and then serve as a source of silver atoms for smaller nanodecahedrons,” she explains. “This dynamic process stabilizes after prolonged irradiation and finally we have uniform silver nanodecahedrons.”

Yu and her co-workers are now exploring practical uses for their particles. “Silver nanodecahedrons strongly enhance electrical fields when they are illuminated with light,” she notes. This can be used, for example, to detect trace amount of molecules on a solid surface. Composite materials incorporating the team’s particles could also be applied to bio-imaging and biosensing techniques, where the interaction of light with these materials could help to visualize, for example, anatomical structures, or to detect tiny amounts of molecules.

Manufacturing:

Chip-free ceramics

Rethinking the process used to machine industrially important ceramics could reduce damaging cracks and chips

Ceramics are hard, chemically inert and can withstand high temperatures. These attributes make them ideal structural components in engines, high-performance disk brakes and medical implants. However, as ceramics are also brittle, using conventional tools — such as drills — to machine them is difficult. Instead, manufacturers rely on ultrasonic machining, in which a ‘hammer’ rapidly vibrates up and down. This process pushes slurry, which contains fine and abrasive grit, into the material and causes chipping.

Research by G. C. Lim and co-workers at the A*STAR Institute of Manufacturing Technology, Singapore, has now improved understanding of how this abrading process creates cracks in a ceramic, making it less durable for applications. The team’s findings could inspire new approaches to machining ceramics, a key element in Singapore’s rapidly growing manufacturing sector.

Ultrasonic machining is known to leave cracks at the entrance and exit of a drilled hole, and a rough surface within the hole (see image). Often, these defects are visible only under a microscope; nonetheless, they make the hole and surrounding material more susceptible to wear and tear. “Imperfections act as initiating locations, where cracks and fractures occur and propagate more easily than other places, resulting in early failure of the component,” says Lim.

The researchers studied crack formation by drilling holes of between 0.7 and 3.0 millimeters in diameter into plates made of three industrially important ceramics: silicon carbide, zirconia and alumina. They recorded images of the cracks and chips along the inner sides of the holes with a microscope and then used diagrams to model the way force is transferred from the hammering tool to the grit, and from the grit into the ceramic.

Lim and his colleagues found that as the grit removes material — by making tiny pits or rubbing against the walls — it creates cracks, which can be up to four times longer than the grit particles and extend out radially from the hole. The team concluded that these cracks are inherent to the way ultrasonic machining works, which means the number of cracks can be reduced by using smaller grit particles but never entirely eliminated.

Lim says they are now in a better position to optimize the drilling process. Since the smallest grit particles yield the smoothest holes but make drilling take longer, Lim recommends a two-step process: quickly drill a slightly smaller hole than needed with a large grit size, and then use a smaller grit size to make the final hole with a smooth finish.

Data storage: Going with the grain

Reducing information stored in magnetic thin films to the physical size of single grains could improve computer hard drives

Despite the increasing competition from alternative technologies such as solid-state drives, magnetic disks remain an important data-storage technology. They are not only reliable and inexpensive, but their storage density has potential for even further improvement. One method under current investigation is storing each data bit in a single magnetic grain of the thin film of the recording medium, rather than in several grains as in conventional hard drives. Storage in single grains only would increase stability and reduce the magnetic fields required to write bits.

By modeling write processes in hard disks, Melissa Chua and her co-workers at the A*STAR Data Storage Institute, Singapore, have demonstrated how this is possible in practice. “The hope is that such a grain-based magnetic recording can extend storage densities by an order of magnitude, to achieve ten terabits per square inch,” she says.

Thin magnetic films for data storage coat the top layer of plastic films in hard-disk drives and consist of many neighboring nanometer-sized grains. As storage density of magnetic films has increased over the years, the surface area used for storage per bit is now comparable to the size of these grains.

Achieving single-grain storage requires a solid understanding of the write processes. Two theoretical models are available to describe these processes. One is an analytical model that uses a simplified description of the magnetic fields within the grains and within the write head of the hard disk. This model achieves fast and easy-to-implement modeling of the recording process, Chua notes.

The second model is a statistical approach that uses tabulated values of parameters that detail the magnetic orientation switching process when information is written to the hard disk. These parameters are derived from detailed simulations of the magnetic fields in the grains and from the computer hard drive write head. From these, the researchers produced a probability for a grain to switch under given circumstances. This detailed approach is more accurate, but also more time intensive than the analytical approach.

Chua and her co-workers successfully applied both models to the grain-based storage process. They simulated the switching of single grains with both methods and then compared their individual performance. By adjusting relevant process parameters for both models, they achieved good agreement between them. Having shown the suitability of both models, choosing which model to use depends on specifics, such as the desired accuracy. Either way, Chua says, “Both models enable the system-level testing of future magnetic recording technologies.”

Semiconductors have revolutionized computing because of their efficient control over the flow of electrical currents on a single chip, which has led to devices such as the transistor. Working towards a similar tunable functionality for light, researchers from the A*STAR Institute of High Performance Computing (IHPC), Singapore, have shown how graphene could be used to control light at the nanometer scale, advancing the concept of photonic circuits on chips.

Graphene, which is made from a single layer of carbon atoms, has excellent electronic properties; some of these are also useful in photonic applications. Usually, only metals are able to confine light to the order of a few nanometers, which is much smaller than the wavelength of the light. At the surface of metals, collective oscillations of electrons, so-called ‘surface plasmons’, act as powerful antennae that confine light to very small spaces. Graphene, with its high electrical conductivity, shows similar behavior to metals so can also be used for plasmon-based applications, explains Choon How Gan of IHPC, who led the research.

Gan and co-workers studied theoretically and computationally how surface plasmons travel along sheets of graphene. Even though graphene is a poorer conductor than a metal, so plasmon propagation losses are higher, it has several key advantages, says team member Hong Son Chu. “The key advantage that makes graphene an excellent platform for plasmonic devices is its large tunability that cannot be seen in the usual noble metals,” he explains. “This tunability can be achieved in different ways, using electric or magnetic fields, optical triggers and temperature.”

The team’s calculations indicated that surface plasmons propagating along a sheet of graphene would be much more confined to a small space than they would traveling along a gold surface (see image). However, the team also showed that surface plasmons would travel far better between two sheets of graphene brought into close contact. Furthermore, by adjusting design parameters such as the separation between the sheets, as well as their electrical conductivity, much better control over surface plasmon properties is possible.

In the future, Gan and his co-workers plan to investigate these properties for applications. “We will explore the potential of graphene plasmonic devices also for the terahertz and mid-infrared regime,” he explains. “In this spectral range, graphene plasmonic structures could be promising for applications such as molecular sensing, as photodetectors, or for optical devices that can switch and modulate light.”

Nanoparticles can be potent catalysts. Bimetallic nano-alloys of platinum and palladium, for example, can help to generate hydrogen fuel by promoting the electrochemical breakdown of water. Identifying the most active nano-alloy for such a task, however, remains a challenge; catalytic performance relates directly to particle structure, and experiments to establish the atomic arrangement of such small particles are difficult to perform. Predicting stable nano-alloy structures is now possible using a computational approach developed by Teck Leong Tan at the A*STAR Institute of High Performance Computing and his co-workers. Their technique can also identify ways in which the nanoparticle’s atomic structure could be tuned to improve catalytic performance.

The challenge with calculating nano-alloy structure and properties from first principles is the computational processing power it requires, says Tan. For their study, he and his co-workers considered a 55-atom nano-alloy particle, each site in the structure filled by either a palladium or a platinum atom. “There are millions of possible alloy configurations, so it would be computationally intractable to do a direct search using first-principles calculations,” Tan explains.

To make the process manageable, the researchers conceptually broke the nanoparticle down into small geometric subunits, or clusters. From first principle calculations on a set of around 100 different alloy structures, each consisting of 30 or so clusters, they generated a reliable model of alloy behavior using an approach called cluster expansion. From this model, they calculated whole-nanoparticle properties. “The model is used to rapidly search through the huge configuration space for low-energy states,” says Tan. These low-energy states represent the stable alloy configurations that should exist experimentally (see image).

Using their calculated stable structures, Tan and his co-workers then predicted how different atomic conformations affect a particle’s performance as a catalyst. As a model reaction, the researchers examined the hydrogen evolution reaction, the electrochemical generation of hydrogen gas. The results suggest that particle catalytic activity will increase as more palladium is added, because this alloy improves hydrogen binding at various adsorption sites on the nanoparticle surface — useful information for guiding the synthesis of new nanocatalysts.

The approach should be widely applicable for nanoparticle research, notes Tan. “The cluster expansion method can generally be applied to any alloy systems where structures and stabilities are of interest,” he says. Tan next plans to investigate the impact of molecules adsorbed onto a catalyst’s surface. “The presence of adsorbed molecules often leads to changes in alloy structures, thereby altering catalytic performance,” he says.

Data storage: Good things come in small packages

Nanoscale engineering of materials that come in two different guises could lead to faster, smaller and more stable electronic memories

Phase-change random-access memory (PCRAM) is one of the most promising approaches to universal memory. Previous research has shown that adding nitrogen to GST, creating NGST, makes a more stable material, but also slows the phase-change process.

Wang and her co-workers showed, however, that both high speed and high stability are possible simultaneously. They experimentally demonstrated that phase change in NGST became much faster by scaling down physically. “We developed a dual-scaling technique to reduce both the overall material volume and the size of the individual grains that make up NGST,” she explains.

When the researchers deposited small-grain NGST into the pores of a thin film of silicon dioxide, they found that phase change in 20-nanometer-wide structures containing 5 nanometer grains was as much as 17 times faster than devices created in 200-nanometer pores. This increase in speed is because the mechanism that drives phase change is fundamentally different for smaller grains that are in smaller cells, owing to their higher surface-area-to-volume ratio.

“In principle, this method is applicable to all types of phase-change materials,” says Wang. “So, appropriate choice of device structure and phase-change material opens new opportunities for optimizing memory device performance.”

Data storage:

A fast and loose approach improves memory

An unconventional design for a nanoscale memory device uses a freely moving mechanical shuttle to improve performance

A loose and rattling part in your cell phone is generally a cause for concern. Like most other electronic devices, your phone works by moving electrons through fixed circuit pathways. If electrons are not sufficiently contained within these pathways, the efficiency and speed of a device decrease. However, as the miniature components inside electronic devices shrink with each generation, electrons become harder to contain. Now, a research team led by Vincent Pott at the A*STAR Institute of Microelectronics, Singapore, has designed a memory device using a loose and moving part that actually enhances performance. The loose part is a tiny metal disk, or shuttle, about 300 nanometers thick and 2 micrometers long, and lies inside a roughly cylindrical metal cage. Because the shuttle is so small, gravity has little effect on it. Instead, the forces of adhesion between the shuttle and its metal cage determine its position. When stuck to the top of its cage, the shuttle completes an electrical circuit between two electrodes, causing current to flow. When it is at the bottom of the cage, the circuit is broken and no current flows. The shuttle can be moved from top to bottom by applying a voltage to a third electrode, known as a gate, underneath the cage.

Pott and co-workers suggested using this binary positioning to encode digital information. They predicted that the forces of adhesion would keep the shuttle in place even when the power is off, allowing the memory device to retain information for long periods of time. In fact, the researchers found that high temperature — one of the classic causes of electronic memory loss — should actually increase the duration of data retention by softening the metal that makes up the shuttle memory’s disk and cage, thereby strengthening adhesion. The ability to operate in hot environments is a key requirement for military and aerospace applications. The untethered shuttle also takes up less area than other designs and is not expected to suffer from mechanical fatigue because it avoids the use of components that need to bend or flex — such as the cantilevers used in competing mechanical memory approaches. In a simulation, Pott and co-workers found that the shuttle memory should be able to switch at speeds in excess of 1 megahertz.

The next steps, the researchers say, include designing arrays of the devices and analyzing fabrication parameters in detail. If all goes well, their novel device could compete head-to-head with the industry-standard FLASH memory.

Video analysis:

Detecting text every which way

Software that detects and extracts text from within video frames, making it searchable, is set to make a vast resource even more valuable

As video recording technology improves in performance and falls in price, ever-more events are being captured within video files. If all of this footage could be searched effectively, it would represent an invaluable information repository. One option to help catalogue large video databases is to extract text, such as street signs or building names, from the background of each recording. Now, a method that automates this process has been developed by a research team at the National University of Singapore, which also included Shijian Lu at the A*STAR Institute for Infocomm Research¹.

Previous research into automated text detection within images has focused mostly on document analysis. Recognizing background text within the complex scenes typically captured by video is a much greater challenge: it can come in any shape or size, be partly occluded by other objects, or be oriented in any direction.

The multi-step method for automating text recognition developed by Lu and co-workers overcomes these challenges, particularly the difficulties associated with multi-oriented text. Their method first processes video frames using ‘masks’ that enhance the contrast between text and background. The researchers developed a process to combine the output of two known masks to enhance text pixels without generating image noise. From the contrast-enhanced image, their method then searches for characters of text using an algorithm called a Bayesian classifier, which employs probabilistic models to detect the edges of each text character.

Even after identifying all characters in an image, a key challenge remains, explains Lu. The software must detect how each character relates to its neighbors to form lines of text — which might run in any orientation within the captured scene. Lu and his co-workers overcame this problem using a so-called ‘boundary growing’ approach. The software starts with one character and then scans its surroundings for nearby characters, growing the text box until the end of the line of text is found. Finally, the software eliminates false-positive results by checking that identified ‘text boxes’ conform to certain geometric rules.

Tests using sample video frames confirmed that the new method is the best yet at identifying video text, especially for text not oriented horizontally within the image, says Lu. However, there is still room for refinement, such as adapting the method to identify text not written in straight lines. “Document analysis methods achieve more than 90% character recognition,” Lu adds. “The current state-of-the-art for video text is around 67–75%. There is a demand for improved accuracy.”

Deconstructed nanosensors light the way forward

A flexible design approach for nanosensors that overcomes practicality and reliability issues is now available

Metal nanostructures can act as tiny antennae to control light since they can focus and guide light on the smallest of scales. The optical properties of these antennae depend strongly on their size and shape, making it difficult to predict which shape to choose for a desired optical effect without relying on complex theoretical calculations. Mohsen Rahmani and co-workers at the A*STAR Data Storage Institute, Singapore, and Imperial College London, UK, have now developed a method that allows for the practical and reliable design of these nano-antennae. Their method is based on new understanding of the optical resonance properties of a few standardized building blocks of the antennae that arise from plasmons — the collective movements of electrons at their surface. “Our novel understanding captures aspects of device design that extend well beyond known optical interference mechanisms and significantly advances our understanding of the plasmonic resonance spectrum. This could bring about new applications,” explains Rahmani.

Some of the most useful properties of plasmonic antennae arise when the metal nanostructures are brought within close proximity to each other. This leads to interference effects near their surface that cause sharp spectral features, known as Fano resonances. Any changes near the nanostructures, such as the introduction of a few molecules or fluctuations in temperature, can impact the sensitive Fano resonances. These changes can be detected and used for sensing applications.

Typically, researchers iteratively use computer models of nanostructures to optimize the design of plasmonic antennae. Rahmani and co-workers simplified the approach by using standardized subunits of nanoparticles called plasmonic oligomers (see image). For example, they deconstructed a cross-shaped structure, consisting of five dots, into two different subunits — one with three dots in a line and one with four outer dots. They then determined the plasmonic resonance of an entire array simply by combining those subunits.

By modeling the properties of the oligomers and comparing their results with measurements of optical spectra, Rahmani observed a systematic dependence of the optical resonances on individual subunits. The team’s findings suggest that the optical properties of various plasmonic antennae can be designed easily from just a few basic building blocks.

“The possible combinations are almost endless and these structures could find many applications,” says Rahmani. These range from nanoscale lasers and optical switches for telecommunications to biosensing. “We are now going to develop these oligomers as nanosensing platforms for detecting the adsorption of chemical molecules and protein monolayers.”

Plasmon resonances on the surface of metal nanoparticles embedded in stained glass can produce remarkable color variations.
Photonics: Pushing the limits of broadband

Development of an ultrafast photodetector that shows promise for integration with silicon chips could lead to increased fiber optical broadband speeds

Photodiodes, or photodetectors, are key components of fiber-optical broadband networks: they convert light to electrical signals. The inability to efficiently fabricate these detectors directly onto silicon chips has hindered faster broadband speeds thus far. Using thin films of germanium and silicon, a research team at the A*STAR Institute of Microelectronics has developed an ultrafast photodetector that may overcome this problem.1 This detector can be deposited on a chip using a cost-efficient thin-film deposition, or ‘growth’, process that is compatible with electronic components, according to Ning Duan from the team. The realization of such detectors is a key step towards processing fiber-optical signals on a silicon chip.

Duan and his co-workers developed their photodetector — known as an avalanche photodiode — using one of the fastest photodetector designs available. The device is made from semiconductors that operate under an applied electrical field at high voltage. In this field, arriving light excites electrons. They gain so much energy that it leads to an ‘avalanche’ of electrons, which can be easily detected. Since silicon is not suitable for infrared light detection, the related element germanium is typically used instead.

Duan and his co-workers succeeded in depositing germanium thin films on silicon by developing a so-called epitaxial process. During the deposition of the silicon and germanium layers, electrical conductivity was enhanced by selectively implanting into the films atoms from other elements such as arsenic and boron. The deposition worked at only a few hundred degrees Celsius, which is low enough to be compatible with industrial silicon fabrication techniques.

The detectors fabricated from these structures (see image) are designed for operation at wavelengths of around 1,550 nanometers, which is the spectral region used in telecommunications. Compared to a normal germanium photodetector, the avalanche design has enhanced the detected signal by a factor of 30. The gain-bandwidth product, which characterizes both the detector enhancement as well as operation speed, is as high as 310 gigahertz. This level is twice that of the traditional avalanche photodetectors based on compound semiconductors such as gallium–arsenide.

Further research is needed so that these detectors can be integrated with other electronic components on the same chip. A transimpedance amplifier, which converts electrical current from the photodetector into an electrical voltage, is an important component still lacking on the chips, says Duan. “We are working on transimpedance amplifiers that can match the performance of these photodiodes in order to achieve a good overall sensitivity of the circuits.”

Nanoparticles: Making gold economical for sensing

Gold nanocluster arrays developed at A*STAR are well suited for commercial applications of a high-performance sensing technique

Cancer, food pathogens and biosecurity threats can all be detected using a sensing technique called surface enhanced Raman spectroscopy (SERS). To meet ever-increasing demands in sensitivity, however, signals from molecules of these agents require massive enhancement, and current SERS sensors require optimization. An A*STAR-led research team recently fabricated a remarkably regular array of closely packed gold nanoparticle clusters that will improve SERS sensors.

“\textit{It was surprising to reliably attain feature separations of less than 10 nanometers, at high yield, across macroscopic areas using simple processes such as coating and adsorption.}”

So-called ‘Raman scattering’ occurs when molecules scatter at wavelengths not present in the incident light. These molecules can be detected with SERS sensors by bringing them into contact with a nanostructured metal surface, illuminated by a laser at a particular wavelength. An ideal sensor surface should have: dense packing of metal nanostructures, commonly gold or silver, to intensify Raman scattering; a regular arrangement to produce repeatable signal levels; economical construction; and robustness to sustain sensing performance over time.

Few of the many existing approaches succeed in all categories. However, Fung Ling Yap and Sivashankar Krishnamoorthy at the A*STAR Institute of Materials Research and Engineering, Singapore, and co-workers produced closely packed nanocluster arrays of gold that incorporate the most desirable aspects for fabrication and sensing. In addition to flat surfaces, they also succeeded in coating fiber-optic tips with similarly dense nanocluster arrays (see image), which is a particularly promising development for remote-sensing applications, such as hazardous waste monitoring.

The researchers self-assembled their arrays by using surfaces coated with self-formed polymer nanoparticles, to which smaller gold nanoparticles spontaneously attached to form clusters. “It was surprising to reliably attain feature separations of less than 10 nanometers, at high yield, across macroscopic areas using simple processes such as coating and adsorption,” notes Krishnamoorthy.

By varying the size and density of the polymer features, Krishnamoorthy, Yap and co-workers tuned the cluster size and density to maximize SERS enhancements. Their technique is also efficient: less than 10 milligrams of the polymer and 100 milligrams of gold nanoparticles are needed to coat an entire 100 millimeter diameter wafer, or approximately 200 fiber tips. Both the polymer and the nanoparticles can be mass-produced at low cost. By virtue of being entirely ‘self-assembled’, the technique does not require specialized equipment or a custom-built clean room, so it is well suited to low-cost commercial implementation.

“We have filed patent applications for the work in Singapore, the USA and China,” says Krishnamoorthy. “The arrays are close to commercial exploitation as disposable sensor chips for use in portable SERS sensors, in collaboration with industry.”

Schematic of the nanocluster SERS substrate in planar chip and fiber-optic configurations. The dome shape of the gold nanoclusters reflects the shape of the hemispherical polymer nanostructures on the underlying surface. The red/green clusters represent the molecules being analyzed. The arrays are densely packed and regularly spaced (inset: electron micrograph of the arrays).

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Random-access memory (RAM) is a fast electronic device used in computers to temporarily store data. Traditional RAM is based on the flow of electrical current for data processing. To make RAM faster, more energy efficient and capable of storing more information in a smaller volume, hardware developers are investigating RAM based on magnetic fields. Miniaturization of these devices, however, is hampered by thermal instabilities. Hao Meng and his co-workers at the A*STAR Data Storage Institute have now shown how electric fields can help to circumvent this instability in tiny magnetic memories, as well as reduce operating power. “This means more information can be stored in a single chip at a cheaper price,” says Meng.

“Such devices could improve the data transfer rate; that is, how fast you can copy your files from one device to another.”

Meng and his team investigated a type of memory that incorporates so-called ‘magnetic tunnel junctions’ (MTJs). Other researchers have previously observed electric-field induced improvements in MTJs, but only in fairly large devices — about 7 micrometers across. Large structures limit the writing speed and suffer from poor compatibility with other electronic components. Meng and his team demonstrated that the concept is also applicable to smaller and faster MTJs that can be integrated more easily.

MTJs are an ideal building block for magnetic memories because of their simplicity and large output signal. In general, they consist of just two magnetic layers separated by a thin insulating barrier (see image). A current passing through the device writes the binary information by controlling the direction of the magnetization in one of the magnetic layers. This process stores information as either a ‘one’ or a ‘zero’, depending on whether the induced magnetization is parallel or antiparallel to the magnetization of the second magnetic layer. A measurement of the resistance across the intermediate barrier can then read out the information as it is needed.

The researchers are working to make MTJs smaller so that they can squeeze in more information. However, smaller devices require larger current densities to switch the magnetization: this leads to heating and makes them less efficient. As a workaround, Meng and his co-workers applied just 0.2 volts across electrodes attached to each side of a 150-nanometer MTJ made of CoFeB-MgO. This reduced the magnetic field required to switch the magnetization by as much as 30% which, in turn, decreased the writing current density. A voltage applied across a magnetic tunnel junction increases the device’s energy efficiency, thus enabling smaller devices — potentially as small as 5 nanometers — for higher density data storage.

“Such devices could improve the data transfer rate; that is, how fast you can copy your files from one device to another,” says Meng.

Data storage:

How magnetic recording heats up

Characterization of the thermal processes involved in heat-assisted magnetic recording paves the way for commercial devices

Most electronic data is stored on magnetic hard drives that spin at many thousands of revolutions per minute. To keep pace with ever-growing storage demand, however, achieving greater storage capacities by simply increasing the size of disks is infeasible. The required spinning speed would put immense physical strain on the components, particularly on the writing ‘head’ — a small needle-like object used to write data at particular points on the disk (see image).

An alternative technology, heat-assisted magnetic recording (HAMR), is now a significant step closer to commercial realization, thanks to the efforts of Baoxi Xu and his co-workers at the A*STAR Data Storage Institute, Singapore¹. In a system using HAMR, laser light is emitted from a diode on the write head to locally heat the disk during data writing. This technique has the potential to increase a standard disk’s recording density by as much as two orders of magnitude. However, the additional heat can cause components such as the write head to destabilize and fall out of alignment.

“By studying the temperature increase of the head, the thermal effects on the disk and the thermal response of the lubricant in HAMR, Xu and his co-workers discovered how to maximize the recording density of the medium. They began by establishing the three major heat sources present in the device: the laser diode, the optical transducer, which concentrates the incident light into a nanometer-sized spot, and the write pole, which performs the physical recording.

They found that the temperature of the transducer depends on both its size and distance from the write pole — both of which can be easily controlled in a commercial device. They also found that the temperature rise in the HAMR head does not significantly inhibit the performance of the laser diode, which is important.

Xu and his team’s results showed that the recording density of the medium can be maximized by reducing the number of layers through which the heat energy must pass before it can dissipate. This will be of prime importance for achieving the required high-density data storage goals of commercial devices. This study therefore represents an important breakthrough in our understanding of HAMR, and will be essential in bringing this technology closer to commercial fruition.

“Our work indicates the seriousness of the problems in the HAMR head, which gives a reference for HAMR design, and also provides a direction for improving thermal structures for high-density HAMR recording.”

Scanning tunneling microscopy (STM) is routinely employed by physicists and chemists to capture atomic-scale images of molecules on surfaces. Now, an international team led by Christian Joachim and co-workers from the A*STAR Institute of Materials Research and Engineering has taken STM a step further: using it to identify the quantum states within ‘super benzene’ compounds using STM conductance measurements. Their results provide a roadmap for developing new types of quantum computers based on information localized inside molecular bonds.

“Each measured resonance corresponds to a quantum state of the system, and can be used to transfer information through a simple energy shift. This operation could also fulfill some logic functions.”

To gain access to the quantum states of hexabenzocoronene (HBC) — a flat aromatic molecule made of interlocked benzene rings — the researchers deposited it onto a gold substrate. According to team member We-Hyo Soe, the weak electronic interaction between HBC and gold is crucial to measuring the system’s ‘differential conductance’ — an instantaneous rate of current charge with voltage that can be directly linked to electron densities within certain quantum states.

After cooling to near-absolute zero temperatures, the team maneuvered its STM tip to a fixed location above the HBC target. Then, they scanned for differential conductance resonance signals at particular voltages. After detecting these voltages, they mapped out the electron density around the entire HBC framework using STM. This technique provided real-space pictures of the compound’s molecular orbitals — quantized states that control chemical bonding.

When Joachim and co-workers tried mapping a molecule containing two HBC units, a dimer, they noticed something puzzling. They detected two quantum states from STM measurements taken near the dimer’s middle, but only one state when they moved the STM tip to the dimer’s edge (see image). To understand why, the researchers collaborated with theoreticians who used high-level quantum mechanics calculations to identify which molecular orbitals best reproduced the experimental maps.

Traditional theory suggests that STM differential conductance signals can be assigned to single, unique molecular orbitals. The researchers’ calculations, however, show that this view is flawed. Instead, they found that observed quantum states contained mixtures of several molecular orbitals, with the exact ratio dependent upon the position of the ultra-sharp STM tip.

Soe notes that these findings could have a big impact in the field of quantum computing. “Each measured resonance corresponds to a quantum state of the system, and can be used to transfer information through a simple energy shift. This operation could also fulfill some logic functions.” However, he adds that advanced, many-body theories will be necessary to identify the exact composition and nature of molecular orbitals due to the location-dependent tip effect.

Spintronics is a form of signal processing similar to that used in traditional electronics, but it takes advantage of a property of electrons known as spin. Spin is often visualized as an arrow about which the electron rotates, much like a top spinning around its axis. Generating a stream of electrons in which these ‘arrows’ are all parallel — a so-called spin-polarized current (see image) — is the foundation upon which spintronics is based. Imperfections in a material, however, can easily destroy polarization. Simply applying an oscillating voltage across the device could help to maintain a spin-polarized current even in the presence of impurities, according to theoretical research by Seng Ghee Tan at the A*STAR Data Storage Institute, Singapore, and co-workers.

“However, by increasing the frequency, we see an increasingly asymmetrical pattern of oscillation in favor of positive polarization,” explains Tan. “We call this a gradual process of rectification.”

Tan and his colleagues considered a two-dimensional electron gas: a system in which the electrons can move only in one plane. When a spin-polarized current flows through such a material, the spins interact with the electron’s motion through an effect known as Rashba spin–orbit coupling. This makes the spins start to ‘wobble’ or precess: at first they point upwards but then point downwards, and this reduces the total spin polarization to zero.

“We want to prolong the life span of a spin current in the channel by controlling the strength of the Rashba coupling,” says Tan. To this end, he and his team investigated a device, known as a spin-current rectifier, that lets a spin current flow with one particular polarization — upwards only, for example.

The researchers developed a simple mathematical equation that predicts the behavior of the spin current as an alternating voltage is applied across the device. Their model shows that when the frequency of the voltage is zero, the spin polarization goes back and forth as expected. “However, by increasing the frequency, we see an increasingly asymmetrical pattern of oscillation in favor of positive polarization,” explains Tan. “We call this a gradual process of rectification.”

Their approach can even suppress precessional motion entirely. When the external modulation frequency is much faster than the natural precessional frequency of the spins, known as the Larmor frequency, the spins have no time to change direction so remain pointing upwards. Consequently, the system maintains a spin-polarized current.

Once spin currents can be sustained, spintronics will have all the potential of electronics with the additional advantage of an extra degree of control. The spin-current rectifier investigated by Tan and his co-workers could therefore become a vital component in this future technology.
Photonics:

On track for downsizing

The ability to miniaturize photonics devices to sizes compatible with computer chips inches closer

Optical communications, or photonics, technology has failed to match the miniaturization of electronic components, mainly because of fundamental laws of classical optics. The smallest photonic devices are limited to sizes of at least a micrometer. Researchers from the A*STAR Institute of Microelectronics (IME) in Singapore have now realized a device design that beats such size restrictions and can be easily integrated into a silicon chip.

Using so-called ‘plasmonic techniques’, the researchers, led by Shiyang Zhu at the IME, demonstrated optical resonator structures, which allow a beam of light to circulate in a closed path, that can be used as on–off switches for light. The device is based on plasmonic effects that guide the light along the surface of the metal. "The performance of our devices is comparable to the best reported results for related plasmonic resonators," says Zhu.

Conventional optical instruments, such as lenses, modify light as it passes through them. Plasmonic structures, however, act more like antennae that amplify light as it moves along their surface. The closeness of the wire and the circle is critical for efficient device operation. When light of a specific wavelength, which is determined by the dimensions of the circle, passes through the wire, some of it can leak into the circle where it becomes trapped. Light can only pass through the structure if it does not match the resonance wavelength of the circle.

The wavelength at which this resonance occurs is very sensitive to parameters such as temperature. In the future, this sensitivity in the circuits could be harnessed for use as switches that control how light passes through the wire, says Zhu. “The next step is to design and demonstrate active plasmonic devices, such as thermo-optic switchers and high-speed electro-optic modulators.”

Plasmonic features are typically created using metals such as gold or silver. However, integrating these noble metals with silicon chips is not only expensive, but also requires techniques that are incompatible with established silicon processing techniques.

As a workaround, Zhu and co-workers used copper to generate the desired plasmonic effects. Copper is widely used as electronic wires in silicon computer chips, and it has an established track record in the computer industry. The researchers built their plasmonic resonator devices from two copper structures that guide light along them — a long wire adjacent to a circle (see image). The smallest width of the copper circuit is only about 180 nanometers, which is much smaller than conventional light guides.

The ability to miniaturize photonics devices to sizes compatible with computer chips inches closer

Optical fibers are rapidly replacing electrical wires as the primary medium for sending digital information over long distances. Without suffering from interference, pulses of light traveling along these thin strands of glass can carry more data than electrical signals. However, getting light into fibers can be difficult, and this inefficiency limits the total strength of the optical signal received at the far end. The solution may be a fiber structure that was recently proposed by Xia Yu at the A*STAR Singapore Institute of Manufacturing Technology and co-workers which uses a metal core to reduce these aptly named insertion losses. “Our compact fiber-based coupler device is able to couple with light more efficiently and faster than conventional devices,” says Yu.

Yu and her team based the design of their device on a new type of photonic-crystal fiber (PCF). PCFs include spaces in the glass that run along the entire length of the fiber. When examined in cross-section (see image), these ‘air holes’ have a honeycomb-like arrangement. Reflection of the incoming light at the numerous air–glass interfaces confines the light to the center of the fiber.

In a theoretical modeling study, Yu and co-workers showed that the addition of a metal wire through the center of the fiber improved device efficiency. The incoming light couples to the electrons in the metal wire, and this forms matter–light hybrid particles called surface plasmons, Yu explains.

The researchers simulated the optical confinement of infrared light in a structure with air holes 2 micrometers in diameter. They then divided the light-carrying core of the fiber with a silver wire. Their calculations indicated that the best design has a hole-to-hole distance of 4 micrometers: it enabled a coupling efficiency of nearly 82%.

Another important way to characterize fiber performance is to determine the distance light must travel along the structure before it couples properly with the fiber — the shorter the better. Compared with conventional designs, this metal-core approach enabled a one order of magnitude reduction in this coupling length.

Such a device could be used as an optical switch or to combine or separate optical signals at different wavelengths — a procedure called multiplexing — which is vital for maximizing the amount of information optical signals can carry.

“The next step is to fabricate the device,” says Yu. “The structure can be easily realized by replacing the center air hole with a metal wire during fiber production, or by pumping molten metal into the center air hole post fabrication.”

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