Blood cancer gene defect can be treated with existing drugs

A defective gene, normally found in blood cancers, could be treated with drugs already available for cancers with similar gene defects, scientists at Queen's University Belfast and the University of Birmingham have revealed.

The research team, funded mainly by Cancer Research UK and the Medical Research Council, found that tumours with mutations in the SF3B1 gene respond to PARP inhibitors, a type of drug used to treat cancers which have similar mutations in the BRCA1 and BRCA2 genes.

The researchers believe that PARP inhibitors could be used to treat patients with tumours carrying the defective SF3B1 gene. This mutation is most often found in blood cancers, including chronic lymphocytic leukaemia, as well as some rare cancers like uveal melanoma.

SF3B1 Mutations and PARP Inhibitors

Dr Kienan Savage, lead author and Reader at the Patrick G Johnson Centre for Cancer Research at Queen's, said: "Our findings have clinical implications for the treatment of many cancers. We specifically focused on this genetic mutation as it is found in several difficult to treat leukaemias and other cancers, and it affects so many cancer patients. By deepening our understanding of this gene mutation, we have identified new ways of treating these cancers that could improve survival rates."

PARP inhibitors, which include olaparib and rucaparib, are used to treat some patients with ovarian, breast, prostate and pancreatic cancers – usually patients who have inherited a faulty BRCA1 or BRCA2 gene. Around 1 in 400 people have a faulty BRCA1 or BRCA2 gene.

The research, published in *Cancer Research*, a journal of the American Association for Cancer Research, found that the SF3B1 mutation produces similar effects to the faulty BRCA1 gene by damaging DNA, preventing it from being repaired properly, and stopping it from making normal copies of itself. PARP inhibitors target the cell's DNA repair tools by locking them in place on the DNA. This stops DNA repair, causing the cancer cells to die.

The scientists found that cancer cells with the SF3B1 mutation were sensitive to olaparib, the most common PARP inhibitor, some specific chemotherapies and to radiotherapy. The scientists believe that the SF3B1 mutation disrupts the cell's ability to make DNA repair proteins, leaving it vulnerable to drugs which target these proteins.

Promise in Clinical Trials

The SF3B1 mutation occurs in up to 30% of blood cancers called myelodysplastic syndromes, where blood cells don't form properly. They are difficult to treat as they occur predominantly in older patients who may not be considered fit for treatment. The mutation is also common among uveal melanoma or cancers of the eye, which currently have limited treatment options.

"This work will pave the way for clinical trials using PARP inhibitors for the treatment of patients with this commonly associated cancer mutation, allowing a more personalised approach to the treatment of these cancers," Dr Katrina Lappin, from Queen's and first author of the study

The researchers now want to test PARP inhibitors in clinical trials with patients who have the SF3B1 mutation to see if they can stop their cancer from spreading.

Medicines for anxiety and anti-depressants trigger post-surgery delirium

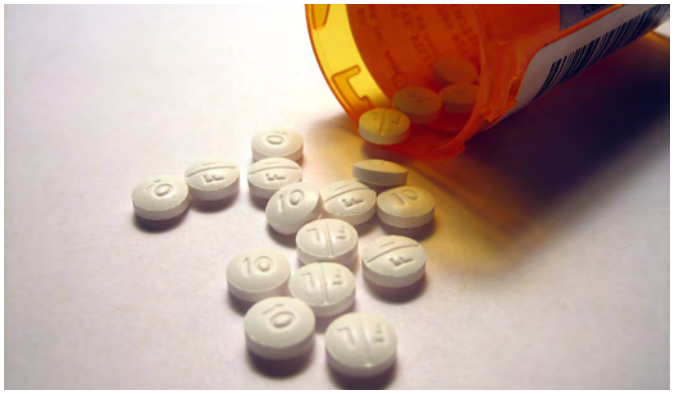
Older people taking a medicine used to treat anxiety and insomnia – nitrazepam – as well as those on antidepressants, are twice as likely to suffer post-operative delirium after hip and knee surgery, a new Australian study has found.

The finding has prompted calls by University of South Australia (UniSA) researchers for older patients to temporarily cease these medications or change to safer alternatives prior to surgery.

In a study published in the journal *Drug Safety*, UniSA scientists scanned data from 10,456 patients aged 65 years and older who had undergone knee or hip surgery in the past 20 years. A quarter of them (2614 people) had experienced delirium after surgery.

Apart from nitrazepam, five medications – commonly prescribed for depression and various anxiety disorders including obsessive-compulsive disorder and post-traumatic stress disorder – were associated with delirium, although not to the same extent. They included mirtazapine, sertraline, venlafaxine, citalopram and fluvoxamine.

Lead researcher Dr Gizat Kassie says in a news release from the university that no link was found between pain-relieving opioids and delirium."Our findings show that some medicine types within the same classes of medicines are riskier than others when it comes to causing delirium after surgery, and the older the patients are, the greater the risk," he says.



Smoking, alcohol use, multiple health conditions, polypharmacy (taking five or more medications), male gender, older age and impaired cognition also put people at risk. Many of these factors can't be altered but we can do something about medications.

"Delirium affects up to 55 per cent of older patients undergoing hip surgery and is associated with an increased risk of death, prolonged hospital stays and cognitive decline. Delirium is costly to manage and puts enormous stress on the healthcare system, health professionals and families," Dr Kassie says.

"In people undergoing elective procedures it should be practical to taper specific medications well in advance. It's important that people are weaned off these riskier drugs well before surgery because abrupt withdrawal can have even worse consequences," Dr Kassie added.

Study finds experimental gene therapy reverses sickle cell disease for years

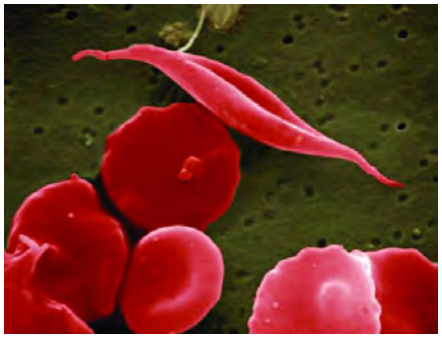
A study of an investigational gene therapy for sickle cell disease has found that a single dose restored blood cells to their normal shape and eliminated the most serious complication of the disease for at least three years in some patients.

Sickle cell disease is caused by mutations in the beta-globin gene, leading to the production of abnormal hemoglobin, the oxygen-carrying molecule in red blood cells.

Four patients at Columbia University Irving Medical Center/ NewYork-Presbyterian participated in the multicenter study, the first to report on such long-term outcomes of a sickle cell gene therapy. The study was published in the *New England Journal of Medicine* with John F. Tisdale, MD, senior investigator at the NIH's National Heart, Lung and Blood Institute, and corresponding author.

The single-dose therapy, tested on 35 adults and adolescents with sickle cell disease, essentially corrected the shape of the patient's red blood cells, but also completely eliminated episodes of severe pain, caused when rigid, crescent-shaped red blood cells clump together and block blood vessels. The painful episodes often result in widespread organ damage. Such episodes are a frequent cause of emergency department visits and hospitalizations and lead to early death.

Normal red blood cells are shaped like donuts, but in sickle cell disease, the abnormal hemo-



globin causes red blood cells to stiffen and adopt a spiky, sickle-like shape. Sickle cell disease can be cured with a donor bone marrow transplant but use of this therapy has the best chance of success in patients who have a closely matched sibling donor, which is only a minority of patients.

With the new gene therapy, called LentiGlobin, blood-forming stem cells are collected from the patient's blood. Harmless lentiviruses are then used to deliver a modified copy of the beta-globin gene into the stem cells. When the cells are later reinfused into the patient, they take up residence in the bone marrow and start making healthy new red blood cells.

In the clinical trial the therapy completely eliminated severe pain crises in the months following infusion (follow-up ranged from 4 to 38 months)—the longest period in which a gene therapy for sickle cell disease has been studied.

One limitation of the gene therapy is that patients must first be treated with high-dose chemotherapy to eliminate old stem cells and make room for the modified stem cells, a process known as conditioning. Chemotherapy can be toxic and is associated with a small risk of cancer. Two patients in the trial developed leukemia, which the researchers suspect was related to the chemotherapy, not to LentiGlobin treatment.

Researchers are currently working on less toxic approaches for conditioning the bone marrow before gene therapy.

A Single blood sample can determine if women are at risk of pre-eclampsia

According to a new study published in *Nature,* involving researchers from King's and Guy's and St Thomas' NHS Foundation Trust, genetic material found in blood samples can predict pregnancy complications such as pre-eclampsia.

Pre-eclampsia effects up to 1 in 12 pregnancies and is a significant cause of maternal morbidity. It is also a cause of a higher risk of cardiovascular disease. Most cases of pre-eclampsia are diagnosed when the mother experiences symptoms in the third trimester.

Researchers took 2500 blood samples from eight prospectively collected cohorts that included multiple ethnicities, nationalities, socioeconomic contexts and geographic locations. They then examined the anonymized cfRNA profiles – signals from the fetus and pregnant mother's tissues – that reflect fetal development and healthy pregnancy progression. This provided a non-invasive window into maternal and fetal health.

In the study, researchers demonstrate the cfRNA signals which deviate from those of a healthy pregnancy. One single blood sample could reliably identify women at risk of developing pre-eclampsia months prior to the presentation of the disease. Using machine learning to analyse tens of thousands of RNA messages from the mother, baby and placenta, an RNA platform called Mirviecan identify 75% of women who go on to develop pre-eclampsia. Researchers hope this test can be widened to investigate other pregnancy complications, such as preterm birth.

'We are now focused on ongoing clinical research to further validate these results and improve the understanding of other pregnancy complications. As a scientist, it was also extremely interesting to see that the molecular signature tells us something about mechanisms associated with health in pregnancy and complications including preeclampsia; such knowledge will aid development of treatment strategies in the future,"Professor Rachel Tribe, Department of Women and Children's Health, the School of Life Course & Population Sciences said in a news release.

Changes in heart shape can predict future sudden cardiac arrest

Medical computing scientists at King's College London have developed a new way to detect early warning signs of sudden cardiac arrest, which involves analyzing the shape of a person's heart with machine learning methods.

The research, published in *EP Europace,* was tested by analyzing MRI images from 156 patients with dilated cardiomyopathy, a deadly heart muscle disease. The patients who later experienced sudden cardiac arrest could be detected by subtle changes to their heart shape,

thought to be signs of worsening disease.

Dr Pablo Lamata, Professor at King's College London School of Biomedical Engineering & Imaging Sciences, who led the research said in a news release, that the new heart shape analysis method has implications for the use of defibrillator implantation therapies.

Data shows that only 50 percent of sudden cardiac arrest cases involve prior symptoms. Many of these patients' lives could be saved with implantable defibrillators if only clinicians knew that they were at risk.

"Given to the right patients, implantable defibrillators prevent cardiac arrest by automatically shocking the heart back into a normal rhythm. However, finding out which patients are actually in need of an implantable defibrillator is a difficult challenge," said Dr Gabriel Balaban, postdoctoral researcher.

The use of defibrillator implantations is controversial. Previous medical studies have shown that for every defibrillator implantation that saves a life, there are about 10-40 that are unnecessary. "With further testing and more patient data, we hope to develop our heart shape analysis method into a practical tool for cardiologists to select the right patients for treatment with implantable defibrillators," Dr Lamata said.

Cardiologists and other researchers only need to upload the borders of the heart, which is anonymous, and safe to share. In return the service provides a 3D shape model and a sudden cardiac arrest risk score, so that the newly developed risk prediction techniques can be further tested by other groups.

The researchers say that the new heart shape analysis could also be used for other diseases because the heart changes shape for other reasons as well, such as hypertension or high blood pressure.

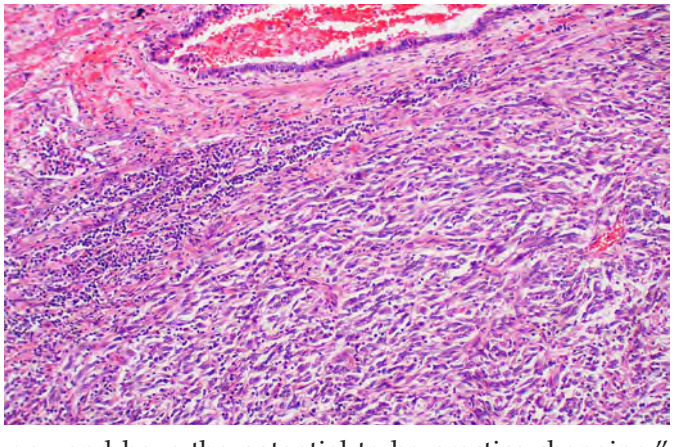
Relatlimab plus nivolumab improves progression-free survival in metastatic melanoma

According to a study published in the New England Journal of Medicine, in patients with untreated, advanced melanoma, the combination of immune checkpoint inhibitors relatlimab and nivolumab doubled the progression-free survival benefit compared to nivolumab alone, with a manageable safety profile.

Relatlimab is a novel antibody that blocks lymphocyte-activation gene 3 (LAG-3), an immune checkpoint found on the surface of T cells. LAG-3 is often upregulated in melanoma, as is programmed death-1 (PD-1), the immune checkpoint inhibited by nivolumab.

The clinical trial, conducted by The University of Texas MD Anderson Cancer Center revealed that the median progression-free survival was 10.1 months in the combination arm and 4.6 months in the monotherapy arm. After 12 months' follow-up, progression-free survival rates were 47.7% in the combination arm versus 36% in the monotherapy arm, with a 25% lower risk of disease progression or death in the combination arm.

"The results from this global effort advance the field of immunotherapy by establishing a third class of immune checkpoint inhibitors through the LAG-3 pathway and have the potential to be practice-changing," said lead author Hussein Tawbi, M.D., Ph.D., professor of Melanoma Medical Oncology.



These data represent the first Phase II/III clinical trial results of a third-generation checkpoint inhibitor and the first clinical trial designed to compare combination checkpoint inhibitor therapy versus nivolumab monotherapy in melanoma.

Currently, PD-1 and CTLA-4 inhibitor monotherapy and combination therapy are approved frontline treatment options for metastatic melanoma. The com-

bination therapies benefit more patients than monotherapy, but also greatly affect quality of life, with toxicity rates of more than 50%.

In this study, grade 3 or 4 treatment-related adverse events occurred in 18.9% of patients in the combination arm and 9.7% in the monotherapy arm. The most common grade 3 or 4 events included increased levels of pancreatic and liver enzymes, and fatigue. Investigators determined three deaths in the combination arm and two deaths in the monotherapy arm were treatment-related. Immune-mediated adverse events included hypothyroidism/thyroiditis, rash and colitis. No new safety signals were identified, and patients rated their health-related quality of life similarly across both treatment arms.

"We now have evidence of a clear benefit for combination therapy compared to single-agent PD-1 inhibitors, and we're looking forward to seeing response and overall survival data," Tawbi said. "We're also thinking about the populations that were excluded from this trial, including those with untreated brain metastases and uveal melanoma, so that all patients can have a chance to take advantage of the progress we're making against melanoma."The study was funded by Bristol Myers Squibb (BMS).

Study identifies biomarkers linked to autism risk

A large study by researchers at Columbia University Mailman School of Public Health and the Norwegian National Institute of Public Health has identified molecular signatures of gestational inflammation linked to the risk of developing autism spectrum disorder (ASD). These findings, which provide insights into abnormal brain development, could eventually lead to a test to screen for ASD at birth.

The new research aligns with growing evidence that the risk of ASD is increased by fetal exposure to inflammation. In earlier studies, the researchers linked ASD risk to prenatal exposure to maternal fever, and to influenza infection and herpes virus type 2 infection—two of many potential triggers for maternal inflammation and ASD.

In the new study, which has been published in the journal *Molecular Psychiatry*, researchers analyzed the presence of 60 molecular markers of immune response, including cytokines and growth factors. Blood samples were collected during pregnancy (maternal mid-gestational blood sample) and at birth (cord blood) from 957 children, roughly half of whom were later diagnosed with ASD. The study linked ASD risk to groupings of inflammation-related molecules, with different groupings seen in boys versus girls. Among the most predictive molecules were interleukins like IL1RA and IL4. Four molecules thought to be involved in fetal brain development were also linked to ASD risk in both sexes: TNFα, Serpin E1, VCAM1, and IL1β. Biomarkers collected at birth were only slightly less predictive than those collected during pregnancy.

"Our research suggests a period of vulnerability during gestation when inflammation can interfere

with central nervous system development," says first author Xiaoyu (Jason) Che, PhD, assistant professor of biostatistics in the Center for Infection and Immunity at Columbia Mailman School.

"We found immune signatures in mid-pregnancy blood samples from mothers and in umbilical cord blood from children later diagnosed with autism that correlate with responses to infection, and molecules important for the development of the brain and its blood supply," says study co-first author Mady Hornig, MD, associate professor of epidemiology at Columbia Mailman School.

"Our future research will focus on finding the triggers for inflammation and links between those triggers and genetic susceptibility," says corresponding author W. Ian Lipkin, John Snow Professor of Epidemiology and professor of neurology and pathology.

Research sheds light on heart disease risk reduction in patients with diabetes

Researchers at the Rajiv Gandhi Centre for Biotechnology (RGCB) have identified Cyclophilin A, a protein which is a known player in several human diseases, as a potential drug target for reducing risk of heart disease in patients with diabetes.

Heart attacks result from rupture of cholesterol plaque deposited on walls of arteries. A tear or rupture in the plaque would activate a repairing mechanism resulting in a blood clot. Such clots can completely block blood flow to the heart muscle and cause a heart attack.

"Patients with diabetes mellitus have increased risk of vascular disease and are prone to ruptures. Our research has shown that Cyclophilin A plays a major role in increasing the risk," said Dr. Surya Ramachandran, a program scientist with the cardiovascular diseases and Diabetes Biology lab, RGCB. Inhibitors of Cyclophilin A would have potential use in reducing the vulnerability to heart attacks due to plaque rupture, she said, adding: "It is also being developed as a clinical serological marker of detecting

vascular inflammation in patients with diabetes."

RGCB Director Prof. Chandrabhas Narayana said the research findings with regard to the role played by Cyclophilin will provide a better understanding of the molecular mechanisms underlying cardiovascular diseases. "It will help in risk detection and development of novel pharmacological therapies," he pointed out.

The findings of the research were recently published in *Cells*, an international, peer-reviewed, open access, journal of cell biology."The protein Cyclophilin A impairs the process of prompt and efficient clearance of cells that have been programmed to die, resulting in rapid progression of plaque formation in patients with Type 2 diabetes mellitus," said Dr. Ramachandran, explaining the science behind their research. The clearance of dead cells and debris is critical for inflammation resolution in patients with cardiovascular risks.

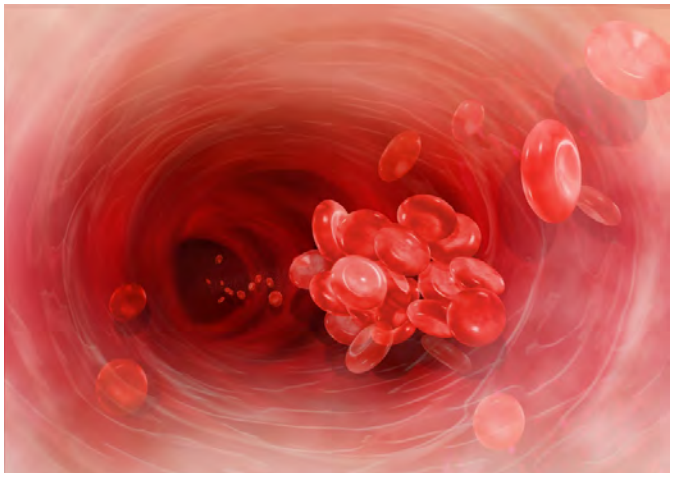
Just like leaves that fall off a tree when they die, cells in human body are also programmed for death and the process is known as apoptosis, derived from a Latin word which means 'to fall off', she said. As in the case of every death, the dead cells need to be taken to their graves. The dying cells express 'eat-me' signals on their surface to attract macrophages, a type of white blood cell that removes dead cells. Cyclophilin A can induce programmed cell death of macrophages, which interferes with the natural process of burying of dead cells

Globally, drug research on cyclophilin inhibitors and clinical trials have confirmed their treatment utility in cancer, viral infections and neurodegeneration."Our research findings are significant since it can lead to reduction of the risk of heart disease in patients with diabetes," Dr Ramachandran said.

Blood clot-busting nanocapsules could reduce existing treatment's side effects

Imperial College, London researchers have designed drug delivery nanocapsules that could reduce the side effects of a major blood clot dissolving drug. Tested on human blood in the lab, the selective nanocapsules could reduce the side effects of a major blood clot dissolving drug, which include bleeding on the brain. If confirmed with animal tests, the nanocapsules could also make the drug more effective at lower doses.

Blood clots, also known as thrombi, are a key cause of strokes and heart attacks which are leading causes of death and ill-health worldwide. They can be treated with a clot dissolving drug called tissue plasminogen activator (tPA) which disrupts clots to clear the blocked blood vessel and re-establish blood flow.



However, tPA can cause life-threatening off-target bleeding and lasts only a few minutes in circulation, so often requires repeated doses, which further increases the risk of bleeding. Consequently, it is only used for a minority of potentially eligible patients.

Now, researchers at Imperial College London have found that by encasing tPA in newly designed tiny capsules, it can be targeted more specifically to harmful blood clots with an increased circulation time. They designed the nanocapsules to attach to activated platelets present in thrombi, release the tPA payload and dissolve clots.

Lead author Dr Rongjun Chen of Imperial's Department of Chemical Engineering said: "tPA has a narrow window between the desired effect and side effects, so we have wrapped it in a package that extends this therapeutic window and minimises the required dose. Our results are exciting but animal and clinical studies are required for validation."

Blood clots are made of blood cells called platelets which link together when activated. These platelets are held together with proteins called fibrinogen which bind to activated platelets and form 'bridges' between them. The new nanocapsule, called tPA-cRGD-PEG-NV, mimics fibrinogen so that it seeks out clots within blood vessels.

The researchers tested this on healthy human blood under both static conditions, where still blood was tested in Petri dishes and physiological flow conditions in a simulated blood vessel. To test flow conditions, they designed a computer model to simulate how the encapsulated tPA might act in circulating blood. They found that the nanocapsules were highly selective in binding to activated platelets and that the time it took to dissolve clots was similar to that with unencapsulated tPA.

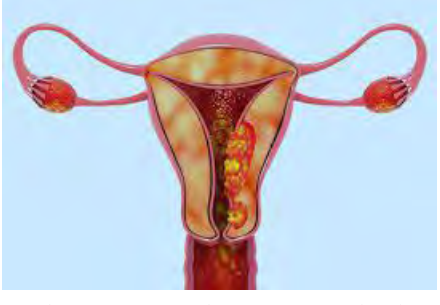
The findings are published in *Science Advances.*

Immunotherapy drug shows promise for treating advanced endometrial cancer

A cancer immunotherapy drug currently approved by the U.S. Food and Drug Administration (FDA) to treat several forms of cancer is also effective for treating aggressive forms of endometrial (uterine) cancer, according to results from an international phase II clinical trial led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

Pembrolizumab is a cancer immunotherapy that works by inhibiting certain cellular receptors that prevents the immune system from recognizing and destroying cancer cells. The FDA has approved the drug for treating several other cancers, including melanoma, lung, head/neck, cervical and stomach cancer.

For the study, researchers enrolled 90 women diagnosed with recurrent or advanced endometrial cancer to determine whether the drug pembrolizumab could be used to effectively treat this subset of patients with MMR deficient (dMMR) or MSI-high tumors. The study included patients treated at 38 hospitals in 15 countries.



In this study, researchers showed that 48% of advanced endometrial cancer patients experienced a complete or partial response. Two-thirds of these patients also had a response that lasted more than three years. Additionally, two-thirds of all patients in the study had a clinical response.

"These findings suggest a long-term benefit to patients. Even the potential for curative intent is now possible in patients with recurrent or metastatic uterine cancer," said David O'Malley, MD, lead author of the study and a gynecologic oncologist at the OSUCCC – James.

Previous research suggests that up to 31% of patients with endometrial cancer have DNA structure changes known as microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR). In a group of patients (approximately 2%), these are inherited mutations (passed down through families, clinically known as Lynch syndrome) in one of the mismatch repair (MMR) genes. Dr. O'Malley notes that the mutation is usually present in the tumor and not a genetic mutation.

Clinical trials to evaluate if pembrolizumab for the treatment of earlier stage disease are currently underway. The international research team reported its findings in the *Journal of Clinical Oncology.*

Study reveals how ovarian cancer begins in high-risk women

Stem cell scientists have revealed the origins of a common ovarian cancer by modeling fallopian tube tissues, allowing them to characterize how a genetic mutation puts women at high risk for this cancer. The created tissues, known as organoids, hold potential for predicting which individuals will develop ovarian cancer years or even decades in advance, allowing for early detection and prevention strategies.

While the lifetime risk of developing ovarian cancer is less than 2% for the general female population, the estimated risk for women who carry a mutation in the so-called BRCA-1 gene is between 35% and 70%, according to the American Cancer Society.

Faced with such steep odds, some women with BRCA-1 mutations choose to have their breasts or ovaries and fallopian tubes surgically removed even though they may never develop cancers in these tissues. The new study findings, published in *Cell Reports*, could help physicians pinpoint which of these women are most likely to develop ovarian cancer in the future—and which are not—and pursue new ways to block the process or treat the cancer.

"We created these fallopian organoids using cells from women with BRCA-1 mutations who had ovarian cancer," explained Clive Svendsen, PhD, executive director of the Cedars-Sinai Board of Governors Regenerative Medicine Institute in a news release.

The research team generated induced pluripotent stem cells (IPSCs), which can produce any type of cell. They started with blood samples taken from

two groups of women: young ovarian cancer patients who had the BRCA-1 mutation and a control group of healthy women. Investigators then used the iPSCs to produce organoids modeling the lining of fallopian tubes and compared the organoids in the two groups.

"We were surprised to find multiple cellular pathologies consistent with cancer development only in the organoids from the BRCA-1 patients," said Nur Yucer, PhD, project scientist in Svendsen's lab and first author of the Cell Reports study. "Organoids derived from women with the most aggressive ovarian cancer displayed the most severe organoid pathology."

Besides showing how ovarian cancer is "seeded" in the fallopian tubes of women with mutated BRCA-1, the organoid technology potentially can be used to determine if a drug might work against the disease in an individual, Svendsen said. Each organoid carries the genes of the person who provided the blood sample, making it a "twin" of that person's own fallopian tube linings. Multiple drugs can be tested on the organoids without exposing the patient to them.

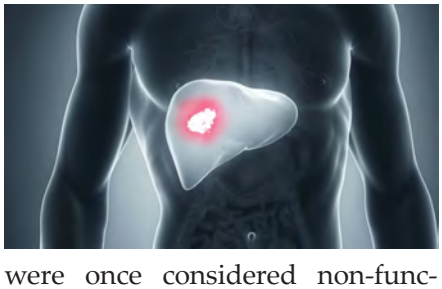
Novel pathways responsible for liver cancer revealed

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. HCC occurs most often in people with chronic liver diseases such as hepatitis B, which is one of the main causes of HCC (particularly in Asia). While surgery, liver transplantation, or radiological intervention may be a viable option for early-stage disease, prognosis for advanced stage HCC remains bleak, with most patients eventually dying within 20 months after diagnosis.

A team of researchers at the Cancer Science Institute of Singapore (CSI Singapore), led by Professor Daniel Tenen and Assistant Professor Yvonne Tay, embarked on a novel study that identified new pathways that are responsible for HCC.

Pseudogenes

The CSI Singapore team focused on pseudogenes. Pseudogenes describe the class of genes that involve genomic sequences that are similar to other genes but are defective, often due to mutations. Pseudogenes



were once considered non-functional evolutionary relics due to their lack of coding potential, but recently, these ncRNAs have recently been linked to patient prognoses and cancer subtypes. Despite the potential clinical importance of pseudogenes, only a handful of

more than 12,000 pseudogenes in humans have been characterised in cancers to date. In this study, Asst Prof Tay and her team established a previously unrecognised role for pseudogenes.

Role of pseudogenes in cancers

The oncogene SALL4 is known to cause HCC and it contains eight pseudogenes. Since many pseudogenes are actively copied or 'transcribed' into new cells, they postulated that pseudogenes could be involved in DNA methylation - a process where a chemical methyl group (CH3) is added to the DNA strand itself. This can affect how genes are expressed – sometimes DNA methylation can repress gene expression, which is exactly what the CSI Singapore team had found.

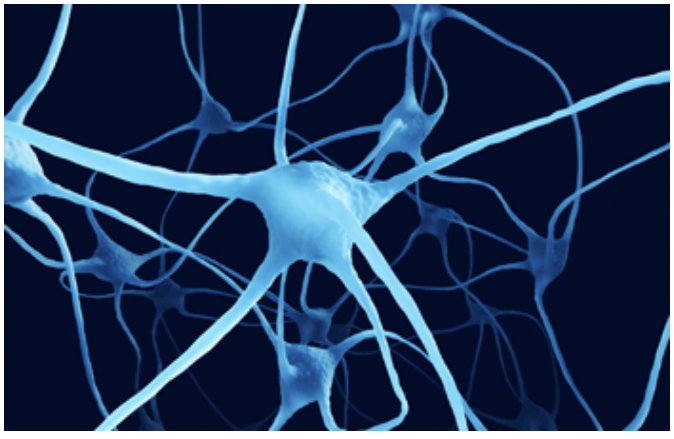
Asst Prof Tay explained in a University release, "We found that as methylation of SALL4 increased, its expression decreased, suggesting the therapeutic potential of using DNA methylation as a regulatory mechanism to suppress the expression of SALL4 in HCC. With this interesting discovery, we decided to take a step further to investigate the correlation between methylation of a specific region in SALL4 and SALL4 expression."

The team used CRISPR technology, which allowed them to target and block gene-specific DNA methylation. They found that some SALL4 pseudogenes cause hypomethylation (the absence of CH3 methyl groups) in the CpG region. This hypomethylation (reduction of the methylation) profile in the region – leads to an increased expression of the SALL4 gene with enhanced associated cellular growth. "Hence, blocking the pathways leading to the hypomethylation of the SALL4 locus could have valuable therapeutic effects on HCC patients with elevated SALL4 levels," said first author Dr Kwon Junsu, who is a Research Fellow at CSI Singapore.

"Moving forward, we plan to monitor the activity of pseudogenes that increase the expression of genes known to cause cancer through demethylation (i.e. the reduction of methyl groups). The study has published in *Science Advances*.

An AI model to help discover causes of motor neuron disease

Scientists have developed a new machine learning model for the discovery of genetic risk factors for diseases such as Motor Neuron Disease (MND). Designed by researchers from the University of Sheffield and the Stanford University School of Medicine in the US, the machine learning tool, named RefMap, has already been utilised by the team to discover 690 risk genes for motor neuron disease, many of which are new discoveries.



One of the genes highlighted as a new MND gene, called KANK1, has been shown by the team to produce neurotoxicity in human neurons very similar to that observed in the brains of patients. Although at an early stage, this is potentially a new target for the design of new drugs.

Dr Johnathan Cooper-Knock, from the University of Sheffield's Neuroscience Institute, said, "This new tool will help us to understand and profile the genetic basis of MND. Using this model we have already seen a dramatic increase in the number of risk genes for MND, from approximately 15 to 690.

"Each new risk gene discovered is a potential target for the development of new treatments for MND and could also pave the way for genetic testing for families to work out their risk of disease."The 690 new genes identified by the tool lead to a five-fold increase in discovered heritability, a measure which describes how much of the disease is due to a variation in genetic factors.

"The tool identifies risk genes by integrating genetic and epigenetic data. It is a generic tool and we are applying it to more diseases in the lab," Sai Zhang, PhD, instructor of genetics at the Stanford University School of Medicine said.

Michael Snyder, PhD, professor and chair of the department of genetics at the Stanford School of Medicine and also the corresponding author of this work added: "By doing machine learning for genome analysis, we are discovering more hidden genes for human complex diseases such as MND, which will eventually power personalised treatment and intervention."

Steroids reduce risk for serious renal events in IgA Nephropathy

According to a new study, oral steroids can help reduce the risk of major kidney outcomes for patients with immunoglobulin A (IgA) nephropathy.

IgA also known as Berger's disease, is a kidney disease that occurs when an antibody called immunoglobulin A (IgA) builds up in the kidneys, which could result in local inflammation that, over time, can hamper the kidneys' ability to filter waste from the blood. While no cure exists for it, certain medications can slow the course of the disease.

The findings from a randomized clinical trial called Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING study) that involved 503 subjects revealed that those who received oral methylprednisolone saw a 47% risk reduction for a composite kidney outcome -- defined as a 40% eGFR decline or kidney failure resulting in dialysis, transplantation, or kidney disease-related death, according to VladoPerkovic, MBBS, PhD, of the University of New South Wales in Sydney.

At the start of the trial, participants received a dose of oral methylprednisolone between 0.6-0.8 mg/kg/day, capped at a maximum dose of 48 mg/day for 2 months, and were subsequently weaned by 8 mg/day/month. Participants had an average age of 38 years, with less than 40% of the subjects being female. Being a multicenter, multicountry study, more than 75% of participants were Chinese, with another 13% South Asian. Only 5% of the total cohort was not Asian. The average BMI was 25 and about half the study cohort also had hypertension.

Medpage Today reported that as far as the effect on kidney failure is concerned, those on steroids saw a 41% risk reduction. Furthermore, those on the steroid regimen saw 1% drop in the risk for progression to end-stage kidney disease, during a 4.2-year follow-up period. Those on the steroid regimen also saw a risk reduction in most of the other secondary outcomes, including a 30%, 40%, or 50% eGFR reduction.

However, patients on methylprednisolone saw a higher rate of serious adverse events (AE), largely driven by hospitalization for severe infection, largely driven by hospitalization for severe infection. There were four deaths in the methylprednisolone group and none in the placebo group; however, these differences were not statistically significant.