Scientists identify compound with potent antiseizure effects

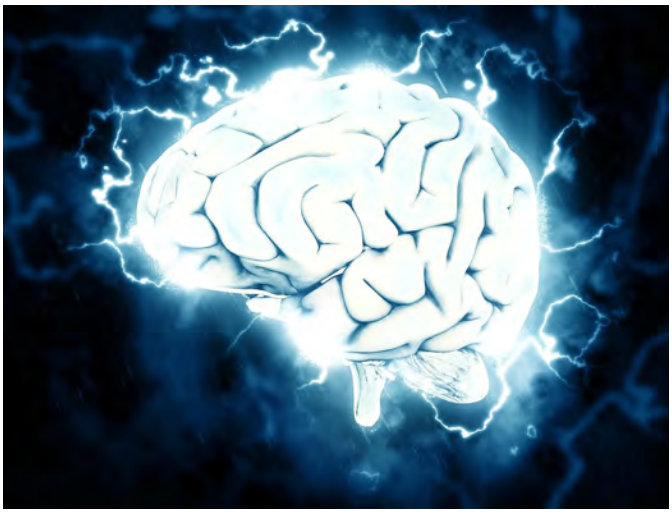
Researchers studying epileptic seizures of the temporal lobe – the most common type of epilepsy – discovered a compound that reduces seizures in the hippocampus, a brain region where many such seizures originate. The compound, known as TC-2153, lessened the severity of seizures in mice.

The scientists report their findings in the journal *Epilepsia.*

"We found that TC-2153 ultimately reduces seizure severity in mice by decreasing the activity of hippocampal neurons," said University of Illinois Urbana-Champaign doctoral candidate Jennifer Walters, who led the research with molecular and integrative physiology professor Hee Jung Chung."In most temporal lobe epilepsy, the seizures start in the medial temporal lobe, which includes the hippocampus," Chung said. "And 60% or more of patients who have medial temporal lobe epilepsy develop drug-resistant seizures, which correlate with the extent of neuronal death and inflammation in the hippocampus."

The hippocampus plays a central role in learning and memory, so anything that damages it can have devastating consequences for the individual, she said. The strength of synaptic communication between neurons and the excitability of individual neurons can affect the likelihood that seizures occur, Chung said.

The finding that TC-2153 lessened the occurrence of seizures was a surprise, the researchers said, because it is known primarily as an inhibitor of a brain-specific protein called STEP that reduces the strength of synaptic communication between neurons. "We hypothesized that seizure activity would increase when we used TC-2153 because STEP inhibition would increase synaptic communication," Walters said. "But we found that it actually reduced seizure severity in both male and female mice."



The female mice responded more to treatment with the compound than the males did. To determine whether TC-2153 interacted with sex hormones, the team repeated the experiment in female mice that had their ovaries removed. "That completely abolished the effect from the TC-2153," Walters said. "Therefore, female sex hormones play a role in its efficacy." This finding may be relevant to sex differences seen in temporal lobe epilepsy, she said.

Follow-up experiments in mouse brains and in neuronal culture revealed a possible mechanism by which TC-2153 decreases seizure severity. The team found that the compound reduced the excitability of individual neurons, suggesting a novel function of STEP, Chung said. "TC-2153 is a STEP inhibitor," she said. "So far, STEP has been known as a negative regulator of neuronal communication but was never implicated in regulating the excitability of individual neurons."

Further studies will explore how TC-2153 works and will test its effects in human neurons, the researchers said.

Anti-malaria drugs may help fight pulmonary disease

A research team at Colorado State University has discovered that drugs used to treat malaria are also effective at treating a pulmonary disease similar to tuberculosis. Their findings were featured in Science Translational Medicine.

The study is a significant development in the fight against infections caused by non-tuberculous mycobacteria, or NTM, which are now more common than tuberculosis in the United States and often attack people who have a weakened immune system or preexisting con-

ditions like chronic obstructive pulmonary disease or cystic fibrosis.

"There are currently very few antibiotics available to treat NTM infections, and some patients fail to respond to any treatment," said Professor Mary Jackson of CSU's Department of Microbiology, Immunology and Pathology, one of the lead authors. "The perspective that antimalarial drugs that already have undergone advanced clinical trials may become part of the arsenal of drugs available to fight these infections could have an immediate impact in the clinic."

The researchers believe that the bacterium is capable of sensing and responding to threats in its environment, such as lowered oxygen levels, oxidative stress and acidic pH, which are our body's natural ways of fighting disease. It does so by activating, among other things, a regulator known as DosRS which controls many essential functions in the bacterium such as its respiration, ability to form biofilms and ability to enter a dormant state when the conditions are not favorable to bacterial multiplication.

They found that in mice, two existing antimalarial drugs were able to prevent DosRS from responding to stresses, meaning that the bacterium struggled to fight off antibiotics and the immune system's natural disease response.

"It blocked the regulator and kept it from doing its job," Jackson explained in a news release by the university. "One of the things the treatment did, in particular, was to lower the bacterium's ability to form biofilms, thereby reducing its ability to resist killing by antibiotics."

The treatment alone was just as effective at dropping bacterial loads in the lungs as the combination of antibiotics currently used to treat the disease.

The lead authors are now working with doctors at National Jewish Health to administer the drug that proved most effective — OZ439 — to humans, particularly those with cystic fibrosis.

Spinal fluid analysis could speed up diagnosis of breast cancer spread

Analysing cancer DNA in spinal fluid could speed up and improve the diagnosis of breast cancer which has spread to the brain and spinal cord, according to a new pilot study.

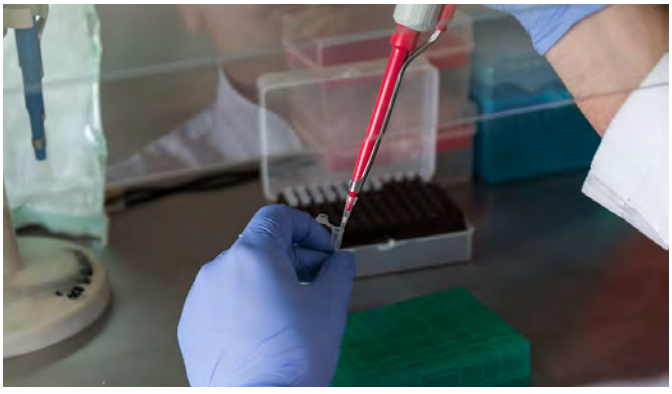
The type of test, known as a liquid biopsy, is more accurate than current methods used to diagnose this type of breast cancer, where it has spread to the lining of the brain and spinal cord.

This method would allow a diagnosis at an earlier stage, when patients are more likely to benefit from treatment.

In the new study, researchers at The Institute of Cancer Research, London, analysed cancer DNA present in samples of spinal fluid from breast cancer patients with suspected leptomeningeal metastasis – where cancer cells have spread to the leptomeninges, a thin layer of tissue that covers the brain and spinal cord. They assessed the ability of liquid biopsies to accurately diagnose and guide treatment of the disease.

Though further research is needed, scientists believe the test could aid the diagnosis of advanced stages of other cancers that commonly spread to the brain, such as lung cancer and melanoma skin cancer, or cancers that originate in the brain, such as glioblastoma.

The study is published in the journal Clinical Cancer Research, and was funded by the Medical Research Council, Breast Cancer Now, and the National Institute



for Health Research Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research (ICR).

The team analysed samples of the spinal fluid of 30 breast cancer patients with suspected leptomeningeal metastasis, and measured the amount of cancer DNA present in the samples. They found that the spinal fluid liquid biopsy correctly diagnosed 100 per cent of positive cases, and correctly refuted diagnosis in all negative cases.

Leptomeningeal metastasis occurs in about five to ten per cent of patients who have breast cancer that has spread to other parts of the body. It has a very poor outcome, with patients only surviving three to four months, on average, after diagnosis.

The standard tests currently used to diagnose lep-

tomeningeal metastasis are lumbar puncture cytology – where spinal fluid is collected from the lower back using a needle and then analysing it under a microscope – and MRI scans. Tumour cells are only correctly detected using cytology in about 50 per cent of cases and MRI findings can be inconclusive.

As a result, patients often have to undergo repeated lumbar punctures for a definitive diagnosis. This invasive procedure can lead to the disease being diagnosed at a late stage, when patients are too unwell to have treatment.

The new liquid biopsy would mean each patient only needing to have one lumbar puncture to reach a definitive diagnosis, allowing a diagnosis far more quickly than through current methods.

Liquid biopsies are normally performed using samples of blood plasma, but as leptomeningeal metastasis occurs in the central nervous system, little to no cancer DNA is found in the blood because the blood brain barrier prevents tumour cells from entering the bloodstream.

In addition to improving diagnosis, the researchers believe that, with further research, this approach could also help measure how well patients respond to chemotherapy, and help clinicians make decisions about individuals' treatment.

Scientists uncover new targets for treating Parkinson's disease

Scientists at La Jolla Institute for Immunology (LJI) have found that people with Parkinson's disease have a clear "genetic signature" of the disease in their memory T cells. The scientists hope that targeting these genes may open the door to new Parkinson's treatments and diagnostics.

"Parkinson's disease is not usually seen as an autoimmune disease," says LJI Research Assistant Professor Cecilia Lindestam Arlehamn, Ph.D. "But all of our work points toward T cells having a role in the disease."

"Now that we can see what these T cells are doing, we think intervening with antibody therapies could have an impact on the disease progression, especially early on, " adds LJI Professor Alessandro Sette, Dr.Biol.Sci., who led the work with Lindestam Arlehamn.

This study was published recently in the journal npj Parkinson's Disease.

Parkinson's progresses as dopamine-producing neurons in the brain die. Unfortunately, scientists have been unable to pinpoint what causes this cell death—though they do have a clue: The doomed neurons contain clumps of a damaged protein called alpha-synuclein.

LJI research suggests these clumps may be the kiss of death for dopamine-producing neurons. Sette and Lindestam Arlehamn recently showed that people with Parkinson's have T cells that target alpha-synuclein early on in Parkinson's disease. Self-reactive T cells can damage the body's own cells, including neurons. In fact, self-reactive T cells are the culprits behind many autoimmune diseases.

The new study may offer a way to stop these T cells in their tracks. The LJI team found that people with Parkinson's disease have memory T cells with a very specific gene signature. Genes associated with targeting alpha-synuclein may very well be causing ongoing inflammation in cases of Parkinson's.

"Identifying these genes may allow doctors to quickly determine which patients have autoimmune T cells and provide a much-needed early diagnostic," says Lindstam Arlehamn in news release.

One important gene expressed in these T cells is LRRK2. This gene is associated with the genetic, or familial, type of Parkinson's disease. Neurons in many people with Parkinson's express LRRK2, but the new study is the first to show this gene expressed in T cells.

But many of the genes expressed in these T cells were completely unexpected and not previously linked to Parkinson's disease. "This finding suggests we found novel targets for potential therapeutics," says Sette.

The scientists found these genes expressed in blood samples collected at LJI's John and Susan Major Center for Clinical Investigation and by study collaborators at UC San Diego, Columbia University Irving Medical Center, and the University of Alabama at Birmingham.

Going forward, Lindestam Arlehamn and her collaborators plan to study post-mortem brain samples. This work will confirm whether the same self-reactive T cells found in blood also target neurons in people with Parkinson's. The team also wants to look for other targets, called antigens, that might be recognized by T cells in individuals with Parkinson's disease.

How good cholesterol in the body may help treat sepsis

Replenishing the body's high-density lipoprotein (HDL) could be an effective treatment for sepsis, according to a new University of Kentucky College of Medicine study published in Science Signaling.

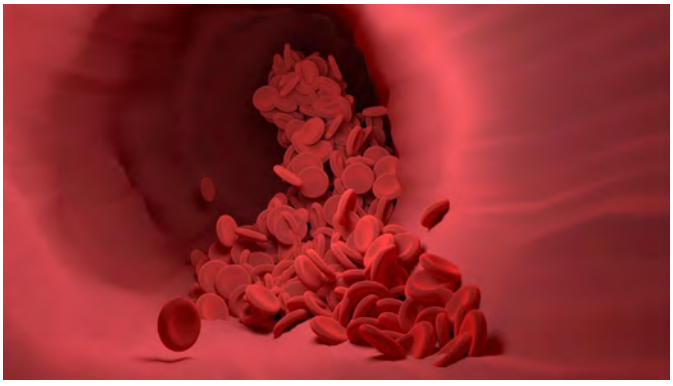
The lab study, led by Xiangan Li, Ph.D., a professor in the Department of Physiology and the Saha Cardiovascular Research Center, found that a synthetic form of HDL provided protection against sepsis in mice.

Sepsis is a life-threatening condition that occurs when an infection triggers a chain reaction throughout the body. Without timely treatment, it can quickly lead to tissue damage, organ failure and death.

HDL cholesterol is known as "good" cholesterol because it helps remove other forms of cholesterol from the bloodstream. Higher levels of HDL are associated with a lower risk for heart disease and stroke, and according to data used in the study, better outcomes for septic patients.

In collaboration with co-investigators at the University of Michigan Hospital Intensive Care Unit, this study showed that septic patients have decreased HDL cholesterol levels compared to nonseptic patients. Additionally, lower levels of HDL correlated with a poorer prognosis for septic patients.

Together with Li's previous studies of HDL deficient mice, these findings suggest a decrease in HDL abundance is a risk factor for sepsis and that increasing HDL abundance may offer a viable therapeutic



strategy against sepsis, according to the study.To test this hypothesis, Li's team treated septic mice with a synthetic HDL treatment called ETC-642 and those receiving it had increased survival rates and better protection against sepsis, including improved kidney function and reduced inflammation.

"Together, these data suggest that HDL treatment could be an effective treatment for patients with sepsis," said Li. "ETC-642 also presents an opportunity for rapid translation to clinical trials."

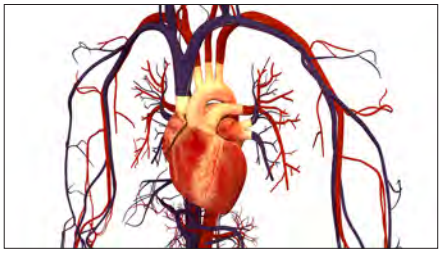
ETC-642 was previously developed to treat cardiovascular disease and has proven to be effective in increasing patient HDL levels in several clinical trials. While additional studies are needed, ETC-642's established clinical manufacturing and human safety make it an ideal candidate to move forward and test its protective ability in septic patients, Li says in a news release from the university.

A breakthrough therapy to lower cholesterol and stabilize plaques associated with heart attack

A novel new therapy has been found to reduce harmful plaque in arteries and change its composition so it is less likely to rupture and cause a heart attack, following a clinical trial led by the Victorian Heart Institute (VHI) at Monash University.

The HUYGENS study treated high-risk patients over a 12-month period and was successful in a number of ways by combining commonly used statins together with a cholesterol-lowering drug called Evolocumab, which is already available to patients.

Using a new imaging method,



researchers were able to view a change in the biology or composition of the harmful plaque in the arteries following treatment, not only reducing its size but changing it from hot to cold, rendering it effectively scar tissue and stable.

The degree to which this was successful was also directly related to how much the patient's bad cholesterol was lowered.

Lowering cholesterol is an important strategy in helping mitigate risk factors, but the new therapy was highly effective in reducing cholesterol ratios down to 0.7mmol/L, which is lower than the current clinical guidelines of less than or equal to 1.8 mmol/L suggested in the first instance.

The study has now been published in the Journal of the American College of Cardiology: *Cardiovascular Imaging.*

Plaque consists of cholesterol,

fatty substances, waste products, calcium and the clot-making substance fibrin. It typically builds up on artery walls over many years and can clog or damage your arteries, which limits or stops blood flow to your heart muscle.

Professor Stephen Nicholls, Director of Monash University's Victorian Heart Institute and HUYGENS trial lead, says the trial tells clinicians that they need to work as hard as they can to keep cholesterol down as low as they can and maintain it.

"It is important after a heart attack to lower cholesterol as much as possible and with this new therapy, we can reduce it to an extent we haven't seen before while also stabilising plaque, making it less likely to burst. This is a new frontier in therapy," Professor Nicholls said.

He adds: "If you've had a heart attack, you are twice as likely to die prematurely compared to the general population. These findings show that plaque reduction and stabilisation was doubled for high-risk patients who had already experienced a heart attack, making it effective for those who need it most."

Shortness of breath predicts worse survival than chest pain for heart attack patients

Just 76% of heart attack patients with dyspnoea or fatigue as their main symptom are alive at one year compared to 94% of those with chest pain as the predominant feature. That's the finding of research presented at the ESC Acute CardioVascular Care 2022, a scientific congress of the European Society of Cardiology (ESC).

"Dyspnoea and extreme tiredness were more common heart attack symptoms in women, older people and patients with other conditions such as high blood pressure, diabetes, kidney disease and lung disease," said study author Dr. Paulo Medeiros of Braga Hospital, Portugal. "While our study did not show that these symptoms cause poorer outcome, they were warning signs of greater risk."

Chest pain is the hallmark presentation of myocardial infarction but other complaints such as shortness of breath, upper abdominal or neck pain, or transient loss of consciousness (blackouts) may be the reason to attend the emergency department. This study investigated which patients tend to present with atypical complaints and whether these symptoms result in the same consequences as chest pain.

The study focused on non-ST-elevation myocardial infarction (NSTEMI), a type of heart attack in which an artery supplying blood to the heart becomes partially blocked. The study included 4,726 patients aged 18 years and older admitted with NSTEMI between October 2010 and September 2019.

The average age of study participants was 68 years and 71% were men. Patients were divided into three groups according to their main symptom at presentation. Chest pain was the most common presenting symptom (4,313 patients; 91%), followed by dyspnoea/fatigue (332 patients; 7%) and syncope (81 patients; 2%).

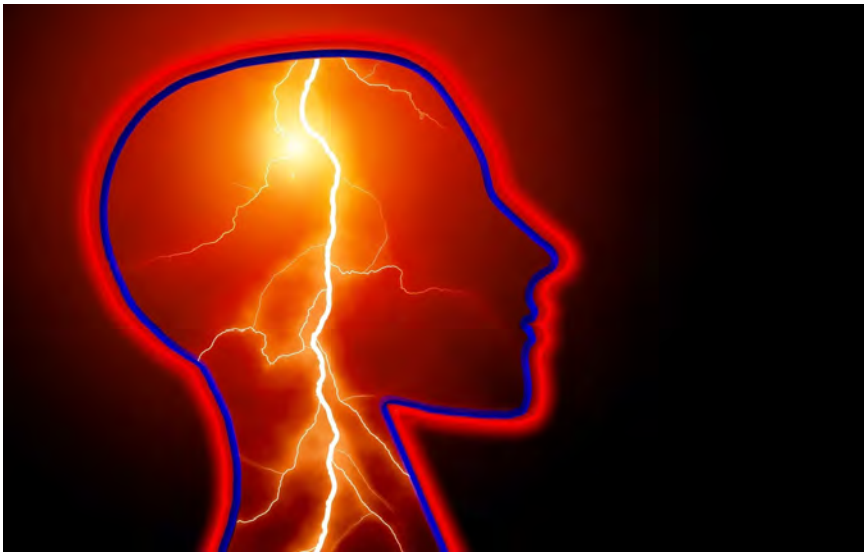
The researchers compared rates of survival between the three groups at one year. At one year after the heart attack, 76% of patients in the dyspnoea/fatigue group were alive compared with 94% of the chest pain group and 92% of the syncope group. During the year after their heart attack, 76% of patients in the dyspnoea/fatigue group avoided being hospitalised for a cardiovascular reason compared with 85% of the chest pain group and 83% of the syncope group.

Dr. Medeiros said: "Patients presenting with shortness of breath or fatigue had a worse prognosis than those with chest pain. They were less likely to be alive one year after their heart attack and also less likely to stay out of hospital for heart problems during that 12-month period."

Dr. Medeiros explained "Shortness of breath was more common among patients that died during the year after their heart attack. However, when considering all of the studied variables, the type of presenting symptom was not an independent predictor of mortality, meaning that we cannot specifically state that shortness of breath was the reason for the worse outcome. Poorer survival may be due to other factors in those patients, such as reduced heart pump function."

He concluded: "This study highlights the need to consider a diagnosis of myocardial infarction even when the primary complaint is not chest pain. This may be particularly important for women and older patients where diagnosis could be delayed and result in worse outcomes. In addition to the classic heart attack symptom of chest pain, pressure, or heaviness radiating to one or both arms, the neck or jaw, people should seek urgent medical help if they experience prolonged shortness of breath."

Higher triglycerides may elevate risk of second stroke: Study



Stroke can have many causes. An atherothrombotic stroke is caused by a clot that forms from plaques that build up within blood vessels in the brain. A new study suggests that people who have this type of stroke who also have higher levels of triglycerides, a type of fat, in their blood may have a higher risk of having another stroke or other cardiovascular problems one year later, compared to people who had a stroke but have lower triglyceride levels.

The research is published in the online issue of *Neurology*, the medical journal of the *American Academy of Neurology*. The study found an association even when people were taking statin drugs meant to lower triglycerides and protect against heart attack and stroke.

Statin Medication

"Our study suggests that for people who had atherothrombotic stroke, having elevated levels of triglycerides in their blood is a risk factor for having another stroke or other cardiovascular problems in the future, and we found that to be true even if the person is on statin therapy," said study author Takao Hoshino, MD, of the Tokyo Women's Medical University in Japan. "The good news is that statin medications are just one therapy for high triglycerides—diet and exercise can also be effective ways to reduce the levels in your blood at little or no cost."

High triglyceride level - Higher risk of death

The study looked at 870 people who had a stroke or transient ischemic attack. Researchers followed up with the participants one year later to find out if there was an association between high triglyceride levels and having another stroke, acute coronary syndrome, which is any condition caused by a sudden reduction of blood flow to the heart, or death due to vascular causes. Researchers found that people who had high triglyceride levels had a 21% greater risk of death, stroke or heart condition one year, compared to 10% greater risk for those with lower levels.

When researchers looked specifically at people who had another stroke after an atherothrombotic stroke, they found that 14 out of 114 people with normal triglyceride levels, or 12%, had one during the study, compared to 33 out of 217 people, or 16%, of those with elevated levels.

For acute coronary syndrome, one out of 114 people, or 0.9%, with normal triglyceride levels developed the heart condition one year after an atherothrombotic stroke, compared to five out of 60, or 8%, of those with elevated levels.Hoshino notes the study did not find an association between higher triglyceride levels and future cardiovascular problems in people who had a different type of stroke called cardioembolic stroke.

"More research is needed, but for people who have had an atherothrombotic stroke, triglyceride levels may emerge as a key target for preventing future strokes and other cardiovascular problems," Hoshino says in a news release by The American Academy of Neurology. "Statin therapy is still an effective treatment for people with high triglyceride levels, but our study highlights how important it is to look at all the tools a person can use to lower their triglycerides, including diet modifications, exercise and taking omega-3 fatty acids."

Lithium may lower risk of developing dementia

Researchers have identified a link which suggests that lithium could decrease the risk of developing dementia. The researchers, from the University of Cambridge, conducted a retrospective analysis of the health records of nearly 30,000 patients from Cambridgeshire and Peterborough NHS Foundation Trust.

Their findings, reported in the journal *PLoS Medicine*, support the possibility that lithium could be a preventative treatment for dementia, and could be progressed to large randomised controlled trials.

The analysis suggested that patients who received lithium were less likely to develop dementia than those who did not, although the overall number of patients who received lithium was small.

Dr Shanquan Chen from Cambridge's Department of Psychiatry, the paper's first author says, "It's been estimated that de-

laying the onset of dementia by just five years could reduce its prevalence and economic impact by as much as 40 percent."

Lithium is a mood stabiliser usually prescribed for conditions such as bipolar affective disorder and depression. "Bipolar disorder and depression are considered to put people at increased risk of dementia, so we had to make sure to account for this in our analysis," said Chen.

Chen and his colleagues analysed data from patients who accessed mental health services from Cambridgeshire and Peterborough NHS Foundation Trust between 2005 and 2019. Of the 29,618 patients in the study cohort, 548 patients had been treated with lithium and 29,070 had not. Their mean age was just under 74 years, and approximately 40% of patients were male.

For the group that had received lithium, 53, or 9.7%, were diagnosed with dementia. For the group that had not received lithium, 3,244, or 11.2%, were diagnosed with dementia.

After controlling for factors such as smoking, other medications, and other physical and mental illnesses, lithium use was associated with a lower risk of dementia, both for short and long-term users. However, since the overall number of patients receiving lithium was small and this was an observational study, larger clinical trials would be needed to establish lithium as a potential treatment for dementia.

Genetic Link between endometriosis and ovarian cancer

University of Queensland researchers have demonstrated a genetic link between endometriosis and ovarian cancer subtypes enabling them to identify potential drug targets for therapy and increasing the understanding of both diseases.

Previous studies have shown that endometriosis sufferers have a slightly increased risk of developing epithelial ovarian cancer.

Dr Sally Mortlock and Professor Grant Montgomery from UQ's Institute for Molecular Bioscience carried out a large genetic study to identify a genetic basis for this risk with a view to better understand the biological overlap between these reproductive disorders."More information about how they develop, their associated risk factors, and the pathways shared between endometriosis and different types of ovarian cancer has been needed," Dr Mortlock said.

"Our research shows that individuals carrying certain genetic markers that predispose them to having endometriosis also have a higher risk of certain epithe-

lial ovarian cancer subtypes, namely clear cell and endometrioid ovarian cancer."

Dr Mortlock said that although the diseases are genetically linked, the risk of ovarian cancer for those with endometriosis is not substantially increased. "Overall, studies have estimated that 1 in 76 women are at risk of developing ovarian cancer in their life-

time and having endometriosis increases this slightly to 1 in 55, so the overall risk is still very low," she said. The study found genes that could be drug targets to treat both endometriosis and epithelial ovarian cancer in the future.

"We explored specific areas of DNA that increase the risk of both diseases and identified genes in ovary and uterus tissue that could be targets for therapy and may be valuable to understand the link between the disorders and to disrupt biological pathways initiating cancer."

The researchers combined large datasets comparing the genomes of 15,000 people with endometriosis and 25,000 with ovarian cancer to find an overlap in risk factors between the two diseases.

The study was published in *Cell Reports Medicine.*

Losing weight may not increase chances of pregnancy, says new study

Women who are obese and struggling to become pregnant are often advised to lose weight, but a new study finds there are no fertility benefits from weight loss.

A randomized study of 379 women with obesity and unexplained infertility found that intensive lifestyle changes that shed pounds led to no better chances of pregnancy and healthy births than simply increasing physical activity without weight loss.

"We have known for decades that obese women often have difficulty getting pregnant," said researcher Daniel J. Haisenleder, PhD, of the School of Medicine's Center for Research in Reproduction. "For this reason, many physicians advise weight loss prior to conception. However, there are few studies that have addressed the issue comparing a healthy lifestyle – i.e., exercise – vs. exercise plus weight loss."

The FIT-PLESE study, conducted at nine academic medical centers across the country, divided participants into two groups: Half the women dieted intensely using meal replacements, medications and increased physical activity. The other half simply increased their physical activity without trying to lose weight. After completing the programs, both groups received three rounds of standard infertility treatments.

Women in the weight-loss program ended up losing, on average, 7% of their body weight, while participants in the exercise-only group typically maintained their weights. But, in the end, there were no significant differences between the two groups in terms of the frequency of healthy births. In total, 23 of the 188 women who completed the 16-week intensive weight-loss program ended up giving birth; among the 191 who completed the exercise-only program, 29 gave birth.

The intensive dieting program did offer health benefits for the women who completed it, however. In addition to dropping pounds, they saw a major decrease in metabolic syndrome, a cluster of conditions that increase the risk for

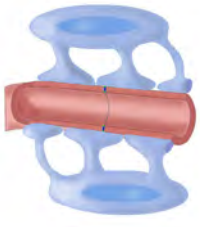
serious health problems such as diabetes, stroke and heart disease.

Based on their findings, Haisenleder and his collaborators conclude that the weight-loss program did not make women more fertile or improve birth outcomes compared with simply exercising. They note the health benefits of weight loss may not translate into better odds of getting pregnant.

"Weight loss improved metabolic health in these subjects. Unfortunately, the changes seen did not improve fertility," Haisenleder said. "Infertility within this population remains an important health issue, and will require further studies to address the problem in the future."The researchers have published their findings in the scientific

Scientists unlock mysteries of the Blood-brain Barrier

This delicate environment in the brain is protected by 400 miles of specialized vasculature designed to limit which substances come into contact with the brain. This blood-brain barrier is essential for protecting the organ from toxins



and pathogens. But in the context of neurological disease, the barrier "becomes your worst enemy," says Anne Eichmann, PhD, Ensign Professor of Medicine (Cardiology) and professor of cellular and molecular physiology, as it also blocks

the passage of therapeutic drugs.

For years, it has been the goal of neuroscientists and vascular biologists alike to find the magic bullet for temporarily opening and resealing the barrier for drug administration. Now, Eichmann's team has developed an antibody as a tool for opening the blood-brain barrier for a couple of hours at a time, allowing for the delivery of drugs to a diseased brain. The team published its findings in *Nature Communications.*

The development and maintenance of the blood-brain barrier are dependent on what is called the Wnt signaling pathway, which regulates a number of crucial cellular processes. Eichmann's team sought to figure out whether this pathway could be modulated to open the barrier "on-demand."

Rigorous research

When Kevin Boyé, PhD, a postdoctoral associate at Yale and first author of the study, joined Eichmann's lab in 2017, he chose to study a molecule known as Unc5B, an endothelial membrane receptor expressed in the endothelial cells of capillaries. He found that if he knocked out this receptor in mice, they died early in their embryonic development because their vasculature failed to form properly, indicating that it was an important molecule in vascular development. He also discovered that a protein known as Claudin5—which is important for creating the tight junctions between the endothelial cells of the blood-brain barrier—was also significantly reduced. This made the team realize that the receptor could be important in maintaining this barrier.

There was previously no known link between Unc5B and the Wnt signaling pathway. Through this new study, the team figured out that the Unc5B receptor controls the pathway, functioning as an upstream regulator.

Boyé then went a step further and took the receptor out in adult mice with an already established blood-brain barrier, and found that the barrier remained open in the absence of the receptor. Next, he wanted to determine which ligands—which bind to receptors and send signals between or inside cells—were responsible for the barrier effect. He discovered that one ligand, Netrin-1, also caused a blood-barrier defect when it was removed.

Next, the team developed an antibody that could block Netrin-1 from binding to its receptor. Upon injecting the antibody, the team was able disrupt the Wnt signaling pathway, causing the blood-brain barrier to open temporarily on demand.

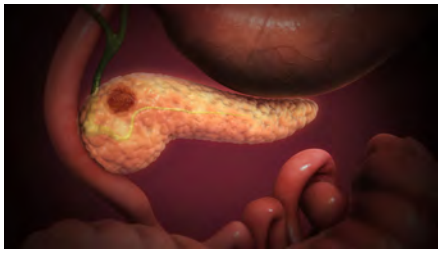
Applications in Alzheimer's, MS, brain tumors and more

Because the blood-brain barrier blocks entry to all but a tiny subset of small molecules, neurological conditions such as Alzheimer's, multiple sclerosis, brain tumors, and depression are exceedingly difficult to treat. Having control over the barrier will be helpful for future drug delivery ventures. The team has not yet identified any potential complications, but plans to evaluate the efficacy and potential toxicity of the antibody in later research.

Scientists discover molecule that kills pancreatic cancer cells

A research team led by scientists at Roswell Park Comprehensive Cancer Center has discovered a molecule that inhibits the growth and metastasis of pancreatic cancer cells through the iron metabolism pathway. Their findings, recently published in *Molecular Cancer Therapeutics*, pave the way toward the development of a new drug candidate for the treatment of pancreatic cancer.

The molecule, MMRi62, targets iron metabolism to kill cancer cells and the harmful proteins that encourage their growth and spread, suggesting that further development and refinement of this compound could lead to a new type of pancreatic cancer therapy.



"MMRi62 causes degradation of an iron-storage protein called FTH1, as well as a protein that is mutated in PDAC, resulting inhibition of metastasis and ferroptosis, a form of cell death triggered by free cellular iron," says Xinjiang Wang, PhD, Associate Professor in the Department of Pharmacology and Therapeutics at Roswell Park in a press relase.

Pancreatic ductal adenocarcinoma (PDAC) cells are predisposed to ferroptosis, a recently identified type of cell death triggered by iron that has become a focal point of cancer research. The identification of novel agents that activate ferroptosis represents a new area of potential therapies for PDAC, an aggressive and largely incurable disease that accounts for 90% of all types of pancreatic cancer.

A unique feature of PDAC are

mutations in the KRAS and TP53 genes, which drive the disease and make tumors resistant to chemotherapy. Because drugs and treatments targeting these mutations are not yet available, therapeutic options for patients with PDAC are limited, and the disease has a 5-year survival rate of only 12%.

"We showed through this study that in a preclinical model, MMRi62 is capable of inducing ferroptosis in PDAC cells harboring either KRAS or TP53 mutations, which in turn inhibited tumor growth and prevented metastasis of tumors to distant organs," adds Dr. Wang. "Although no ferroptosis-inducing agents are currently available, our hope is that our discovery will lead to promising new MMRi62-based treatments for recalcitrant cancers such as PDAC."

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Using 3D matrix ultrasound to accurately identify cardiovascular injury in healthy persons

A new imaging technique for real 3D vascular ultrasound could become a key tool in strategies aimed at preventing cardiovascular disease in apparently healthy persons, complementing traditional risk parameters such as cholesterol and high blood pressure. The new results, published in JACC: Cardiovascular Imaging, show that real 3D vascular ultrasound is reliable, accurate, and faster than previous methods for the assessment of plaque volume in the carotid and femoral arteries.

The burden, or quantity, of atherosclerosis in the carotid and femoral arteries is a well-established marker of cardiovascular risk and is highlighted as a key parameter in international clinical practice guidelines and expert consensus documents. There is therefore a recognized need for better and easy-to-use methods for measuring plaque burden that can be used as population screening tools.

According to a press release, the new imaging method was first validated and implemented in a study of almost 200 healthy participants with an intermediate cardiovascular risk from the Athero

Brain: Head-to-Heart study, led by Dr. Valentín Fuster, Director General of the Centro Nacional de Investigaciones Cardiovasculares (CNIC). The method has now been incorporated into the PESA-CNIC-SANTANDER study, also led by Dr. Fuster, where it is being used to assess more than 4000 healthy individuals over a 9-year follow-up.

The CNIC researchers partnered with Philips Ultrasound and Philips research Paris-Medisys to develop a new probe and software for real 3D ultrasound to facilitate exploration of the carotid and femoral arteries and speed up quantification of atherosclerotic plaque volume. As Dr. Fuster explained, "it is clear that traditional clinical evaluations based on measurements of cholesterol, blood pressure, blood glucose, and lifestyle habits cannot, on their own, accurately determine accumulated damage in the cardiovascular system, and without this crucial information we cannot take appropriate decisions to prevent acute events such as myocardial infarction or stroke."

The key to personalized prevention and treatment strategies, added Dr. Fuster, "is the ability to detect and quantify an individual's accumulated cardiovascular damage, or atherosclerotic burden, using non-invasive imaging techniques."

The newly validated 3D vascular probe incorporates 3D matrix technology, which underpins the most advanced 3D ultrasound techniques. In addition to demonstrating the accuracy of 3D matrix ultrasound, the study demonstrates that the new technique takes just half the time needed by previous methods to obtain all the information required for the definition of carotid and femoral plaque burden, essential information for correct patient management.

Higher doses of antibiotics needed to eliminate bacterial infections

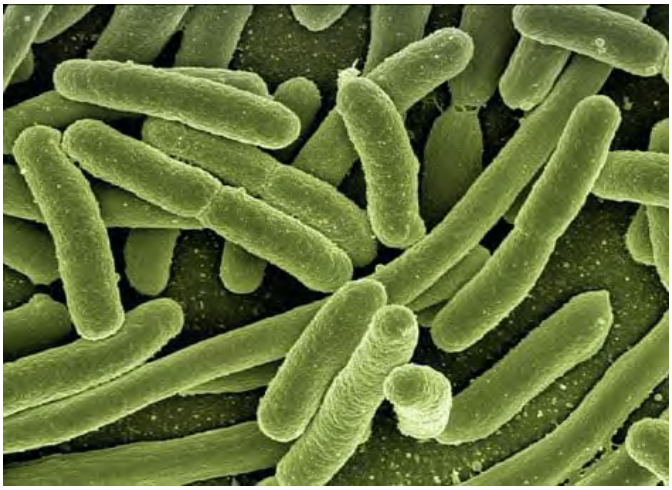
A study has found that much higher doses of antibiotics are needed to eliminate a bacterial infection of the airways when other microbes are present. It helps explain why respiratory infections often persist in people with lung diseases such as cystic fibrosis despite treatment.

In the study, published in The ISME Journal, researchers say that even a low level of one type of mi-

crobe in the airways can have a profound effect on the way other microbes respond to antibiotics.

Chronic bacterial infections such as those in the human airways are very difficult to cure using antibiotics. Although these types of infection are often associated with a single pathogenic species, the infection site is frequently co-colonised by a number of other microbes, most of which are not usually pathogenic in their own right.

Treatment options usually revolve around targeting the pathogen, and take little account of the cohabiting species. However, these treatments often fail to resolve the infection. Until now scientists have had little insight into why this is.



Developing an artificial model with mixture of microbes

To get their results the team developed a simplified model of the human airways, containing artificial sputum ('phlegm') designed to chemically resemble the real phlegm coughed up during an infection, packed with bacteria.The model allowed them to grow a mixture of different microbes, including pathogens, in a stable way for weeks at a time. The three microbes used in the experiment were the bacteria Pseudomonas aeruginosa and Staphylococcus aureus, and the fungus *Candida albicans* – a combination commonly present in the airways of people with cystic fibrosis.The researchers treated this microbial mix with an antibiotic called colistin, which is very effective in killing Pseudomonas aeruginosa. But when the other pathogens were present alongside Pseudomonas aeruginosa, the antibiotic didn't work.

According to a news release from the University of Cambridge, the same effect happened when the microbial mix was treated with fusidic acid – an antibiotic that specifically targets *Staphylococcus aureus*, and with fluconazole - an antibiotic that specifically targets *Candida albicans*.The researchers found that significantly higher doses of each antibiotic were needed to kill bacteria when it was part of poly-microbial infection, compared to when no other pathogens were present.

Tailoring dosage after considering microbial diversity

The results highlight the need to consider the interaction between different species of microbe when treating infections with antibiotics - and to adjust dosage accordingly.

Poly-microbial infections are common in the airways of people with cystic fibrosis. Despite treatment with strong doses of antibiotics, these infections often persist long-term. Chronic infections of the airways in people with asthma and chronic obstructive pulmonary disorder (COPD) are also often poly-microbial.

By looking at the genetic code of the Pseudomonas bacteria in their lab-grown mix, the researchers were able to pinpoint specific mutations that give rise to this antibiotic resistance. The mutations were found to arise more frequently when other pathogens were also present.

Comparison with the genetic code of 800 samples of Pseudomonas from around the world revealed that these mutations have also occurred in human patients who had been infected with Pseudomonas and treated with colistin.