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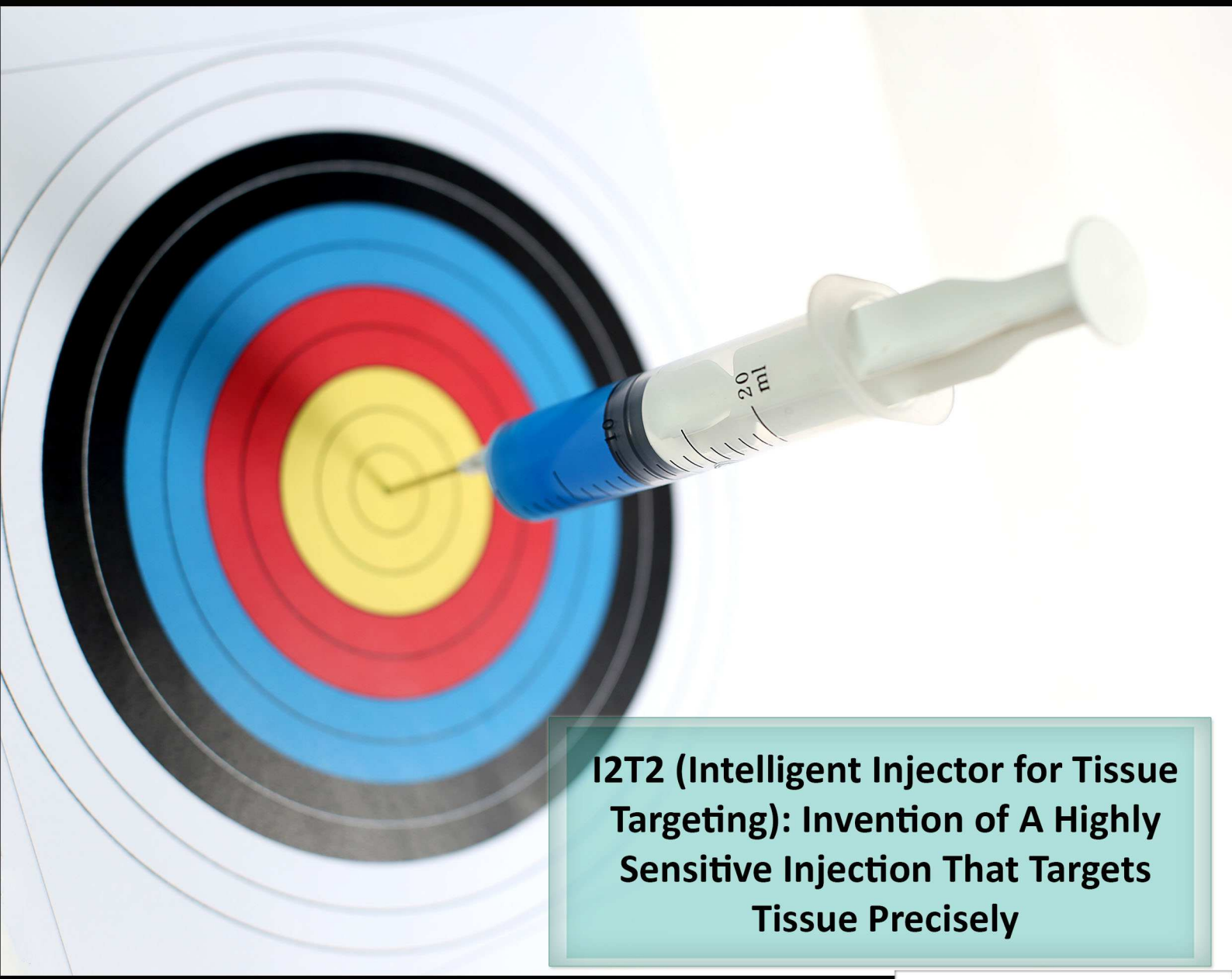

I2T2 (Intelligent Injector for Tissue Targeting): Invention of A Highly Sensitive Injection That Targets Tissue Precisely

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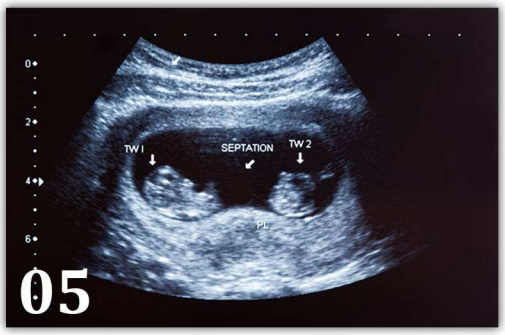

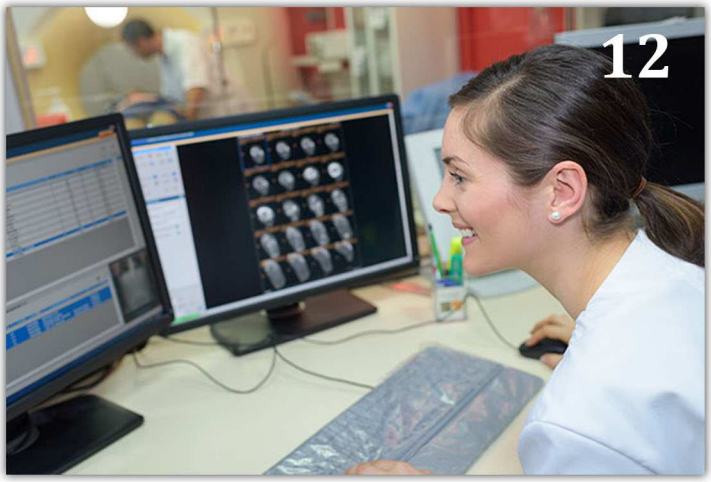

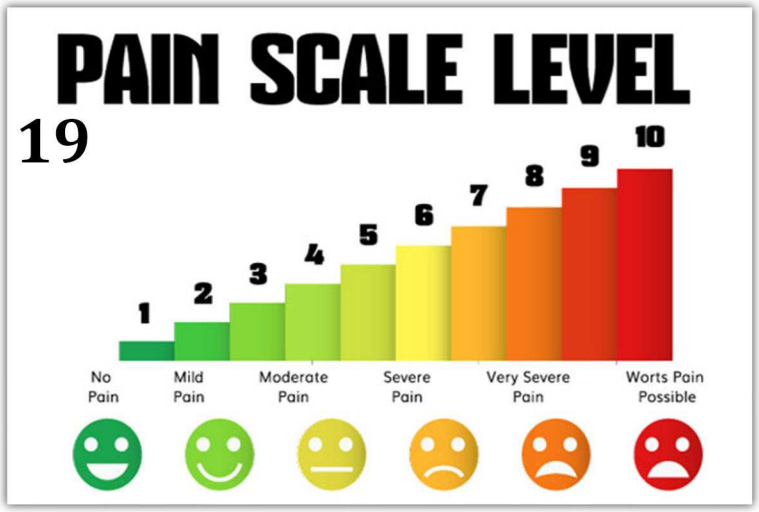

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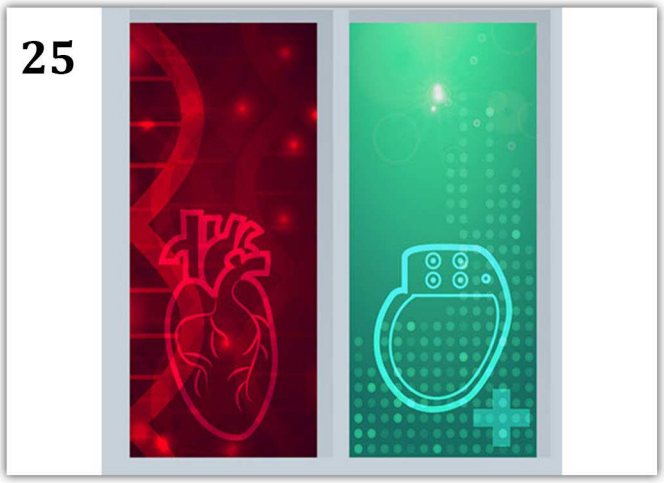

NOTE FROM EDITOR-IN-CHIEF

We are delighted to bring to you nine articles on recent significant research in science which will have a strong impact on mankind including battery-free heart pacemaker, a novel injector for delivering medication, a new electronic tool to predict asthma, treatment for osteoarthritis and many more.

Hope you find them intellectually stimulating!

Umesh Prasad

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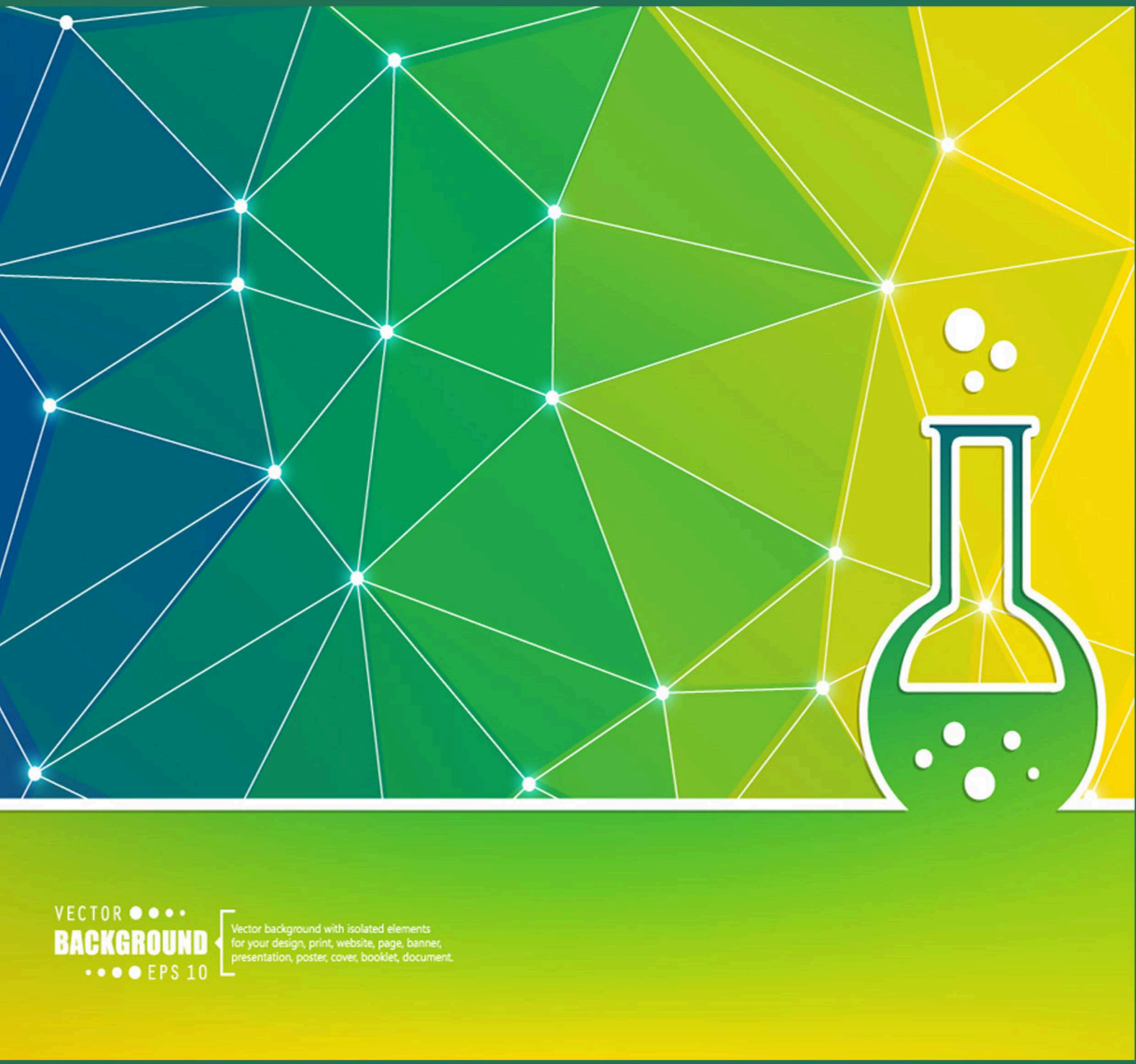
A Virtual Large *Library to Assist Rapid Drug Discovery* and Design

Docking a large virtual docking library to target proteins can assist in rapidly discovering new drugs and therapeutics

To develop new drugs and medications for illnesses, a potential way is to 'screen' a large number of therapeutic molecules and generate 'leads'. Drug discovery is a long and challenging process. To speed up the process of discovering a new drug, drug companies generally use core structures (called scaffolds) of already known drug-like molecules since exploring a new molecule is arduous and expensive.

Structure-based drug discovery approach

Computational modelling followed by virtual or *in silico* docking of chemical compounds onto a target protein is a promising alternative approach to speed up drug discovery and reduce laboratory costs. Molecular docking is now an integral part of computer-aided structure-based drug design. Many software programs like AutoDock and DOCK are available which can autonomously perform docking in high configuration computer systems. The 3-D macromolecular structure of the target receptor is taken from either an experimental method like X-ray crystallography or through in silico homology modeling. ZINC[1,2] is a freely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available open source database of commercially-available 230 million compounds in downloadable 3D format which can be used for molecular docking and virtual screening. Post docking, molecules can be visually analyzed on how well they dock to the receptor protein. This analysis includes their calculated binding energies and their 3D conformations. The interaction between a compound and target protein can provide information about that molecule's pharmacological properties. Computational modelling and docking provide an opportunity to screen large number of molecules before proceeding to wet laboratory, cutting down resources as only one-time computational infrastructure is required to be set up.

Building and utilizing a large library for in silico docking

In a new study[2] published in *Nature*, researchers analyzed structure-based virtual docking of a library containing a staggering 170 million molecules[1]. Millions of diverse drug-like molecules are known to exist but they are inaccessible due to the limitations faced in building molecular libraries. A virtual docking technique can show up false positives called 'decoys' which may be well docked *in silico* but they would be unable to achieve similar result in laboratory testing and may be biologically inactive. To overcome this scenario, researchers focused on molecules which were from well-characterized and understood 130 chemical reactions by utilizing 70,000 different chemical building blocks. The library is very diverse as it represents 10.7 million scaffolds which were not part of any other library. These compounds were simulated on the computer and this contributed to library growth and limited the presence of decoys.

Researchers performed docking experiments using X-ray crystal structures of two receptors, first the D4 dopamine receptor – an important protein belonging to G protein-coupled receptors family which carries out actions of dopamine - brain chemical messenger. D4 receptor is thought to play a central role in cognition and other functions of brain which gets affected during a mental illness. Second, they performed docking on an enzyme AmpC which is a leading cause of resistance of certain antibiotics and is difficult to block. The top 549 molecules from docking of D4 receptor and top 44 from enzyme AmpC was shortlisted, synthesized and tested in the laboratory. Results indicated that several molecules binding strongly and specifically to D4 receptor (while not to D2 and D3 receptors which are closely related to D4). One molecule, a strong binder of AmpC enzyme, was unknown up till now. Docking results were indicative of testing results in bioassay.

The library used in the current study is large and diverse and therefore results were robust and clear confirming that virtual docking with large libraries can predict better and thus outperform multiple studies using smaller libraries. The

Key points

- Computational modelling and docking provide an opportunity to screen large number of molecules before proceeding to wet laboratory, thus cutting down resources.
- Using a large and diverse library against two protein receptors gave robust and clear results, confirming that virtual docking with large libraries can predict better and outperform multiple studies using smaller libraries.
- ZINC is a freely available open source database of commercially-available 230 million compounds in downloadable 3D format which can be used for molecular docking and virtual screening.

compounds used in this study are freely available in ZINC library which is being expanded and is expected to grow to the 1 billion mark by 2020. The process of first discovering a lead and then designing it into a drug remains challenging, but a larger library will provide access to newer chemical compounds which may lead to surprise findings. This study showcases *in silico* computational modelling and docking using powerful libraries as a promising approach to discover new potential therapeutic compounds for different illnesses.

Source
1. Teague Sterling and John J. Irwin 2015, 'ZINC 15 – Ligand Discovery for Everyone', *J. Chem. Inf. Model.*, Vol. 55,
DOI: 10.1021/acs.jcim.5b00559
2. http://zinc15.docking.org/
3. Jiankun Lyu, et al. 2019, 'Ultra-large library docking for discovering new chemotypes', *Nature*, DOI: 10.1038/s41586-019-0917-9

■

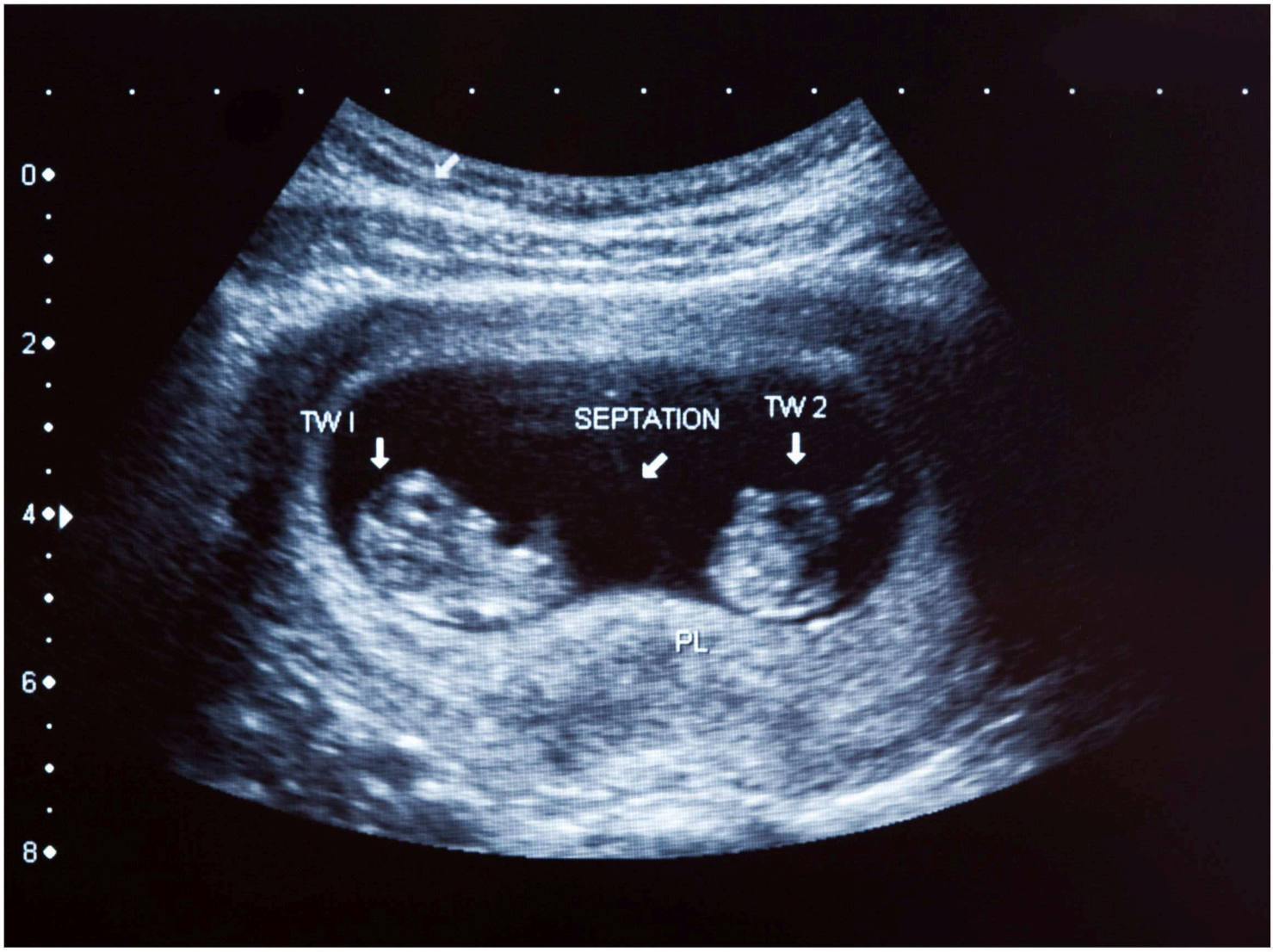
Understanding *Sesquizygotic (Semi-Identical)* Twins: The Second, Previously Unreported Type of *Twinning*

Case study reports first rare semi-identical twins in humans to be identified during pregnancy and only second ever known till now

Identical twins (monozygotic) are conceived when cells from a single egg are fertilized by a single sperm and they divide into two post fertilization. Identical twins are always of the same gender and have identical genetic material or DNA. Fraternal twins (dizygotic) are conceived when two eggs are fertilized by two individual sperms and they develop together so they can be of different sexes. Fraternal twins are as genetically similar as siblings of same parents born at a different time.

Semi-identical twins identified during pregnancy

In a case study published in The *New England Journal of Medicine* researchers at Queensland University of technology, Australia have reported semi-identical twins - a boy and a girl – identified for first time during pregnancy and they are the only second set of such twins known[1]. During the 28-year-old mothers' ultrasound at six weeks, it was indicated that identical twins are expected based upon the presence of a single shared



placenta and positioning of amniotic sacs. Later at her 14 weeks ultrasound in the second trimester, the twins were seen to be a boy and girl which is only possible for fraternal twins and not identical.

Genetic inspection done by amniocentesis showed that the twins shared 100 percent maternal DNA and for most part one twin received paternal DNA from one set of paternal cells and other twin from the other set. However, some mixture happened during early embryonic development revealing that these twins were not ordinary twins but chimeras i.e. they have cells from different genes. Chimeras are composed of different populations of genetically distinct cells and thus are not genetically uniform. The typical chromosome arrangement for boy is 46XY and girl is 46XX but these twins both have an assortment of female XX cells and male XY cells in varied proportions – meaning that some cells in their body were XX and others XY. The boy had XX/XY chimerism ratio of 47:53 and girl had XX/XY chimerism ratio of 90:10. This conveys the potential domination towards male and female development of the respective twin.

How are semi-identical twins conceived

When a sperm penetrates an egg, the egg's membrane changes and thus locks out another

sperm. In this particular pregnancy, mother's egg was fertilized simultaneously by two sperms from the father called as 'dispermic fertilization' in which two sperms penetrate a single egg. A normal embryo has two sets of chromosomes, one each from mother and father. But if such a simultaneous fertilization takes place, three sets of chromosomes are produced instead of two i.e. one from the mother and two from each sperm of the father. Three sets of chromosomes are incompatible with central dogma of life and therefore such a pregnancy caused by double fertilization is not viable and the embryos do not survive and result in abortion. In this particular rare pregnancy, there might have been a possible failure in some mechanism which prevents polyspermy and thus two sperms fertilized an egg producing three sets of chromosomes. Such a sequence of events is termed as 'heterogonic cell division' as previously reported in animals. The third chromosome containing material from just the two sperms cannot grow normally so it did not survive. The remaining two typical cell types combined again and continued to grow before splitting into two embryos - a boy and a girl - thus making the twins 78 percent identical on father's side. The early cells in a zygote are pluripotent meaning that they can develop into any type of cells making development of these cells a possibility.

The twins were 100 percent identical on the mother's side and 78 percent with the father, so this averages out to being 89 percent identical with each other. In scientific terms, semi-identical twins is a third type of characterization, a rare form of twinning which can be called as an intermediate between identical and fraternal twins and similarity wise they are closer to fraternal twins. It is an extraordinarily rare occurrence, the first ever semi-identical twins were reported in USA in 2007[2] in which one twin had ambiguous genetilia. And both these twins also got identical chromosomes from mother but got only half of DNA from father. In the current study no ambiguities were reported. At one-point researchers thought of a probability that perhaps these semi-identical twins were not rare and previously reported fraternal twins might actually be semi-identical. However, analysing twin databases showed no previous occurrence of semi-identical twins. Also, genetic data analysis of 968 fraternal twins and their parents showed no indications of semi-identical twins. Though the twins were born healthy via a caesarean delivery, some health complications were reported as the girl post birth and at the age of three. Such complications are a result of mainly the genetic makeup.

Source

1. Michael T. Gabbett et al. Molecular Support for Heterogonesis Resulting in Sesquizygotic Twinning, *The New England Journal of Medicine*, 2019 DOI: 10.1056/NEJMoa1701313
2. Souter, V.L., Parisi, M.A., Nyholt, D.R. et al. 2007, 'A case of true hermaphroditism reveals an tunusual mechanism of twinning', *Human Genetics*, Vol. 121, DOI: 10.1007/s00439-006-0279-x

I2T2 (Intelligent Injector for Tissue Targeting): *Invention of A Highly* Sensitive Injection That *Targets Tissue Precisely*

A new innovative injector which can deliver medications to difficult locations of the body has been tested in animal models

Needles are the most important tool in medicine as they are indispensable in delivering countless medications inside our body. The syringes and hollow needles of today have been used since decades for extracting fluids and blood from our body and are important for many invasive delicate medical procedures like dialysis. Trying to target specific tissues by using a conventional needle of a syringe is a challenging task and is limited by skill and levels of precision of the medical personnel as this process is mostly guided by their own sense of pressure and touch since every patient's tissue feels different. Though injuries or infections have rarely been reported but sometimes a flu shot can cause extreme pain and muscle damage. No new design has been incorporated into standard needles especially in regards to their accuracy.

Traditional needles are difficult and risky to administer medication to delicate regions of our body example the space at back of our eye. The suprachoroidal space (SCS) located between sclera and choroid in the back of the eye is a very difficult location to target using a conventional


20
ml
10

needle mainly because the needle has to be very precise and it must stop after it has transitioned through the sclera - whose thickness is less than 1 mm – to avoid any damage to retina. This region is considered important for delivery of many medications. Any lapse could cause a serious infection or even blindness. Other challenging areas are peritoneal space in abdomen and tissue between skin and muscles and epidural space around the spinal cord where epidural anesthesia is given during vaginal delivery.

A new pressure-sensitive needle

In a study published in *Nature Biomedical Engineering* researchers from Brigham and Women's Hospital, USA have designed a novel intelligent and highly precise injection for targeting tissues - called the I2T2 (intelligent-injector for tissue-targeting). They aimed to improve tissue-targeting while keeping the design neat, simple and practical. The I2T2 device was created using standard hypodermic needle and other parts of commercially sold syringes and functionally I2T2 consists of slight modifications to the traditional syringe-needle system. It is a sliding needle which can penetrate outer layer of tissue, then it can automatically stop at the interface of two tissue layers and release the syringe content into target area as the user pushes the syringe plunger.

The I2T2 consists of a pushing plunger, a needle plunger, a mechanical stop, fluid and a movable needle. The needle is mounted on the needle-plunger which is a sliding support that allows precise movement along the axis of the syringe barrel. First, the needle tip is inserted into the tissue at shallow depth, but just sufficiently to avoid any flow of fluid through the needle. This stage is called 'pre-insertion'. The syringe barrel prevents unwarranted penetration and needle plunger mechanical lock prevents undesired backward motion of the needle. During the second stage called 'tissue penetration', internal fluid gets pressurized by pushing the plunger. The driving forces which act on the needle (that enable forward motion of the needle) overcome the opposing forces (that oppose needle motion) and advance the needle deeper inside the tissue while the syringe barrel stays immobile. These forces play a critical role in controlling the needle's motion and also its automatic stopping. When the needle tip enters the desired target space, fluid starts to exit so as to reduce the internal pressure which will then lower the driving force below than opposing force and this will subsequently stop the needle at the cavity interface. During this third stage called 'targeted delivery' the syringe fluid gets delivered into the cavity having lower resistance as the user pushes the plunger in a single continuous motion. The needle's position is now affixed at the tissue-cavity interface. Since every biological tissue in our body has a different density, an integrated sensor in this intelligent injector senses loss-of-resistance as it moves through softer tissue or a cavity and then automatically stops its motion when the

Key points

- A novel intelligent and highly precise injection for targeting tissues - called the I2T2 has been designed which has a neat, simple and practical design.
- The pressure-sensitive injection automatically detects any changes in resistance – particularly loss of resistance in softer tissues or cavity - so as to safely and accurately deliver medication.
- The main advantage of I2T2 injector over traditional needles is that it displays higher level of precision and it does not rely on skills of the operating personnel.

needle tip penetrates tissue offering lower resistance.

The I2T2 was tested in extracted tissue samples and three animal models including sheep to evaluate its delivery accuracy into suprachoroidal, epidural and peritoneal spaces. The injection automatically detects any changes in resistance so as to safely and accurately deliver medication in preclinical tests. The injector decides instantly allowing for improved tissue targeting and minimal overshoot into any unwanted location past the target tissue which could cause injury. The study is to be extended to human preclinical testing and then to trials in the next 2-3 years to evaluate injector's utility and safety.

I2T2 preserves equivalent simplicity and cost-effectiveness of standard syringe-needles. The main advantage of I2T2 injector is that it displays higher level of precision and it does not rely on skills of the operating personnel as the injector can sense loss of resistance when it encounters a softer tissue or a cavity and then it stops advancing the needle and starts delivering its cargo of therapeutic agent into the target space. The syringe's plunger device is a simple mechanical system and does not require additional electronics. The I2T2 injector technology is a new platform to achieve better tissue targeting in different and difficult locations in the body. The needle is simple and easy to manufacture with low costs. No additional technique or training was required to operate it. Such a versatile, sensitive, cost-effective and user-friendly technology could be promising for multiple clinical applications.

Source

Girish D. Chitnis, et al. 2019, 'A resistance-sensing mechanical injector for the precise delivery of liquids to target tissue', *Nature Biomedical Engineering*, DOI: 10.1038/s41551-019-0350-2 ■

Mobile Telephony in *Combination with Internet-Connected* Diagnostic Devices Offers Novel *Ways to Diagnose, Track and* Control Diseases

Studies show how existing smartphone technology can be used to predict and control infectious and non-infectious diseases

The demand and popularity of smartphones is on the rise worldwide as it is an excellent way to connect. Smartphones are being used for every little to important tasks on a daily basis as the world is adopting them in an impressive manner. Since smartphones are being used in more or less every domain of our lives, it is only evident that it will be critical in healthcare system in the future. 'mHealth', the application of mobile devices to healthcare is promising and smartphones are already used to improve a patient's access to advice, information and treatment.

SMS campaign for diabetes

A study[1] published in *BMJ Innovations* has evaluated the impact of an awareness SMS (Short Message Service) campaign for diabetes. The 'Be He@lthy, Be Mobile' initiative started in 2012 aimed to develop, establish and scale-up prevention and management of disease using mobile phones. Since then it has been launched in 1o countries worldwide. In this trial, a regular awareness SMS campaign focused at people who had voluntarily signed up for free 'mDiabete' programme. The participations for this programme increased significantly from 2014 till 2017. In this study conducted in Senegal, participants received a series of SMSs over the course of 3 months to which they responded with either of the three options - 'interested in diabetes', 'have diabetes' or 'work as a healthcare professional'. The efficacy of the SMS campaign was assessed by comparing two centres - one which received

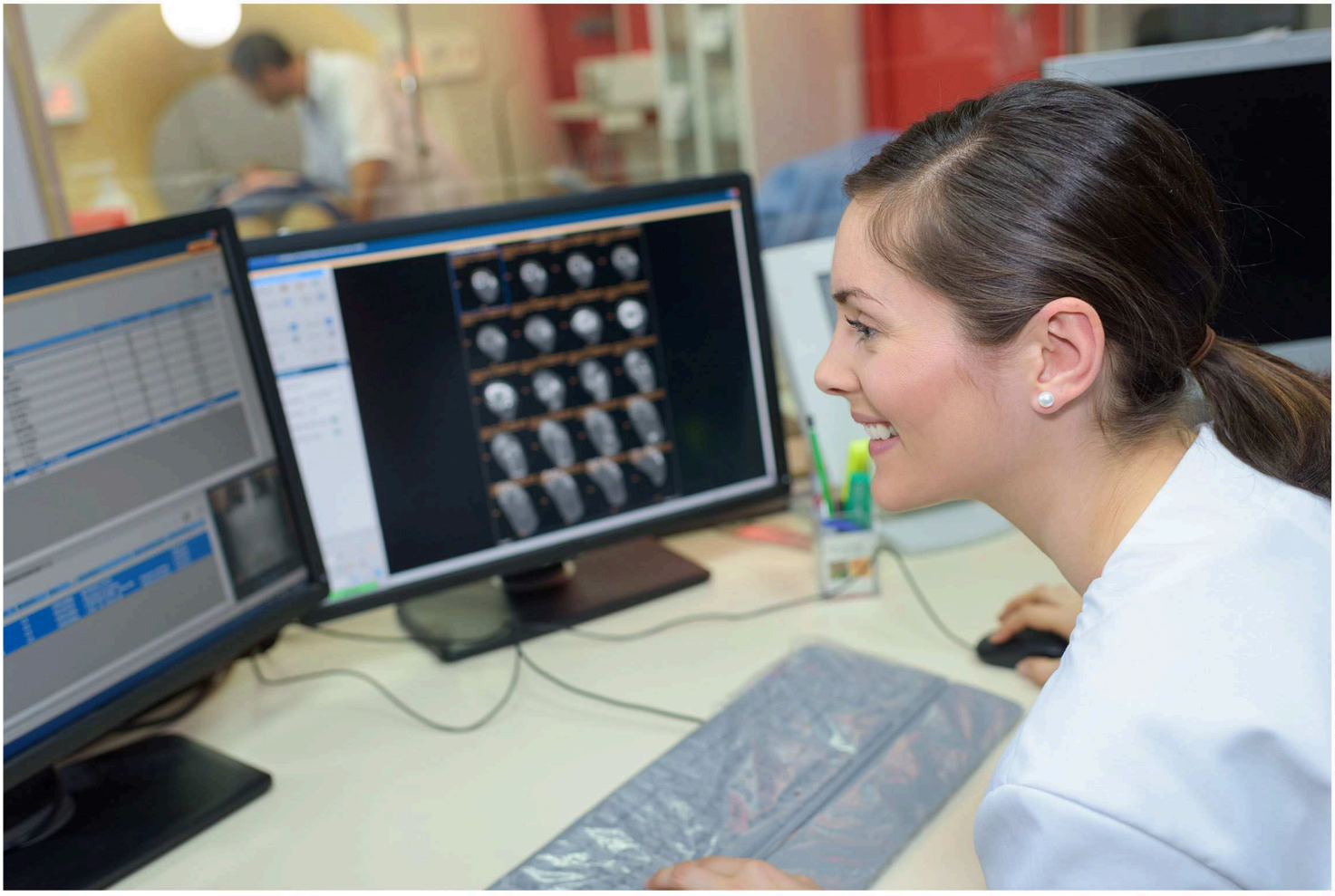
the campaign and second which did not receive - marked as centre S and centre P respectively. Alongside usual diabetes care was provided at medical centres.

The SMSs were sent to centre S from 0 to 3 months and to centre P from centre 3 to 6 months and HbA1c was measured at both these centres using same assays. The HbA1c test, called haemoglobin A1c is a crucial blood test which indicates how well diabetes is being controlled in a patient. Results showed important difference between change in HbA1c from 1 to 3 months of the campaign and HbA1c further evolved in centres S and P from month 3 till 6. The Hb1Ac change from month 0 till 3 was better in centre S compared to P. Thus, by sending diabetes education messages via SMS there was an improvement in glycaemic control in type 2 diabetes patients. This effect was consistently seen at both centres and it even improved during the 3 months once SMSs were stopped.

The SMS approach is valuable for low-and-middle income low-resourced countries where otherwise it is challenging to provide information and motivation to patients of diabetes as illiteracy is a major hurdle. SMS approach is also cost-effective for therapeutic education as one SMS costs only GBP 0.05 in Senegal and the campaign costs GBP 2.5 per person. Text messaging can be useful where medical resources are scarce and facilitating useful exchange between diabetes patients and health personnel can mitigate risk of diabetes-related complication.

Smartphones technology for infectious diseases in sub-Saharan Africa

A review[2] published in *Nature* led by Imperial College London shows how healthcare workers in



low-income countries, example in sub-Saharan Africa, could utilize smartphones for diagnosing, tracking and controlling infectious diseases. Even in such countries the use of smartphones is on the rise and has reached 51 percent at the end of 2016. Authors aimed to understand how smartphone technology can be effectively utilized for healthcare in rural areas which do not have sufficient clinics. The smartphones could help people to get tested, access their test results and receive support in their own home rather than a medical centre. Such an arrangement makes people feel easy and comfortable to look after their health especially in remote rural regions which are located far from clinics. Infectious disease like HIV/AIDS is considered a stigma in many societies in low-income countries and therefore people feel ashamed of attending a public clinic to get themselves tested.

Established mobile technologies like SMS and calls can connect patients directly to healthcare workers. Many smartphones have in built sensors which can assist in diagnosis, such as heart rate monitor. A smartphone also has a camera and microphone (via speaker) which can be used to analyse images and sounds like breathing. Simple testing technology could be attached to smartphones using USB or by wireless method. A person could collect a sample easily - example via pinprick for blood - the results would be scanned using mobile apps and then sent to local clinics to be uploaded to a central online database from where a patient could access it from a smartphone rather than visiting the clinic. Further, virtual follow-up appointments could be made using smartphones. Using this alternate methodology rates of disease testing can certainly rise and with just the existing infrastructure. The master database hosting test results from a region can give us details of prevailing symptoms which can help to devise better treatments. It can also warn us of any likely future outbreaks.

The approach is however challenging as the authors state that embracement of technological advances can improve access to testing but around 35 percent of world's total population doesn't have access to mobile phones. Also, safety and hygiene can get compromised at a patient's home compared to the sterile environment of a clinic in which a trained healthcare worker performs the task. In building up a database of patient's information privacy and confidentiality of data will be of utmost importance. The local people in rural areas first need to gain confidence and faith is the technology which can motivate them to trust it for their health-related needs.

These two studies present new methods of developing mobile-based health intervention strategies and tools which can address challenges faced in low-income and middle-income low-resources settings.

Source

1. Christopher S. Wood et al. 2019, 'Taking connected mobile-health diagnostics of infectious diseases to the field', *Nature*, Vol. 566, DOI: 10.1038/s41586-019-0956-2
2. Matthieu Wargny et al. 2019, 'SMS-based intervention in type 2 diabetes: clinical trial in Senegal', *BMJ Innovations*, Vol. 4, no. 3, DOI: 10.1136/bmjinnov-2018-000278 ■

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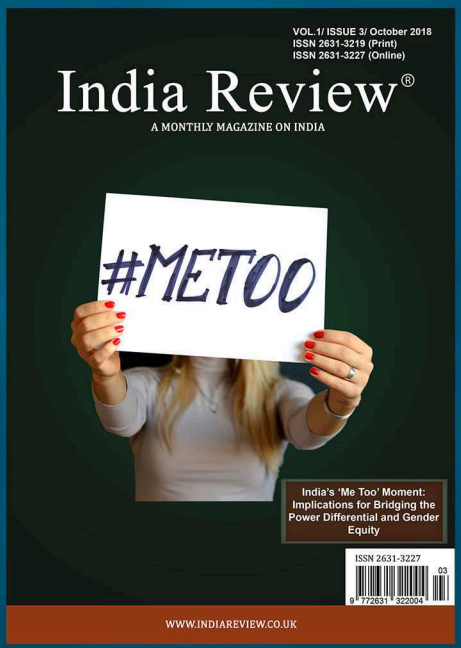

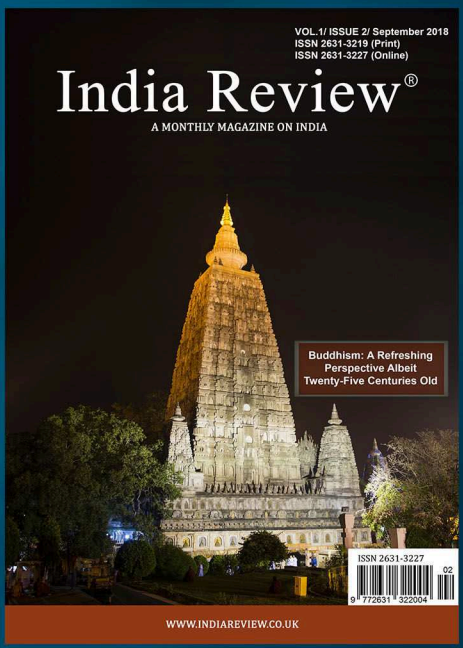

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PARS: A Better Tool to Predict *Asthma Among Children*

Computer-based tool has been created and tested in for predicting asthma in young children

Asthma affects more than 300 million people worldwide and is among the most common chronic diseases putting a high burden on costs. Asthma is a complex disease in which inflammation occurs in airways which then prevents transfer of enough oxygen to the lungs leading to symptoms like constant coughing, shortness of breath and tightness in the chest. Asthma care via therapies is well established but good primary care for asthma is limited by lack of personnel, knowledge, training, resources etc. The global costs of asthma care are estimated to run in billions of pounds annually.

Pediatric Asthma Risk Score (PARS): a tool to predict asthma in young children

In a study published in *Journal of Allergy and Clinical Immunology,* scientists at Cincinnati Children's Hospital Medical Center USA have designed and evaluated a personalized quantitative decision tool called Pediatric Asthma Risk Score (PARS) which can accurately predict asthma development in young children1. It consists of criterion like demographic data and clinical factors of patients unlike established tools.

PARS tool was designed by utilizing data/

factors which predicted asthma development from Cincinnati Childhood Allergy and Air Pollution cohort study. This study comprised of around 800 infants of whom at least one parent had at least one symptom of allergy. The children were clinically examined every year at the ages 1, 2, 3, 4 and 7 for onset of allergic disease using skin testing. Researchers checked for 15 aeroallergens (airborne) and food allergens including cat, mold, cow's milk, eggs and cockroach. A total of 589 children were tested for asthma development at 7 years of age and diagnosed by using standard measurement of lung function like spirometric tests. 16 percent of these children had asthma and their parents were queried to understand various risk factors which might have contributed to it. Variables which predicted asthma using PARS were wheezing, sensitization to 2 or more food and/or airborne allergens and African American race. These children had at least one parent with asthma and they also had other ailments like eczema and allergic rhinitis at a young age.

In comparison to the gold standard Asthma Predictive Score (API) developed and used since 2000, 43 percent more children were marked by PARS score as ranging from mild to moderate risk of asthma as API only provides only a 'yes' or a 'no' for the risk. Children with high risk factors were predicted similar by both these tools. It is critical to identify children with mild or moderate risk as they immediately need and can respond better to asthma prevention strategies with early intervention at a very young age. This can be helpful in alleviating asthma before complications begin.

The new model of PARS was 11 percent more sensitive and also more precise than gold standard API for predicting asthma in early life. The results were confirmed in another study conducted in United Kingdom which did not include African-Americans. PARS is a more robust, valid and generalized tool, plus it is a less invasive method compared to 30 established models. Predicting mild to moderate asthma in children as young as 1-2 years can have a major impact on controlling this disease. PARS is easy to implement and this study includes a PARS sheet containing the decision tool and clinical interpretations. PARS also has a web application2 and apps are available for smartphones.

Key points

- A personalized quantitative decision tool called Paediatric Asthma Risk Score (PARS) has been designed and evaluated which can accurately predict asthma development in young children.
- PARS was able to mark high risk and also mild to moderate risk of asthma in young children.
- PARS was 11 percent more sensitive and more precise than gold standard API (Asthma Predictive Score).

Source
1. Jocelyn M. 2019, 'A Pediatric Asthma Risk Score to better predict asthma development in young children', *Journal of Allergy and Clinical Immunology*, DOI: 10.1016/j.jaci.2018.09.037
2. https://pars.research.cchmc.org. ■

A First Ever Prototype *'Blood Test' Which* Can Objectively Measure *the Severity of Pain*

A novel blood test for pain has been developed which can help to provide objective treatments based on severity of pain.

A physician assesses a patient's pain sensation subjectively since it is generally determined by patient's self-reporting or clinical examination. The main cause of opioid epidemic in several countries is the over-prescription of pain-relieving drugs leading to addiction of these medications. The over subscription happens because of unavailability of methods to objectively measure pain. Effective communication of 'level of pain' is hardly ever achieved in a clinical setting especially for children and elderly. The pain medications were continuously subscribed for all levels of pain and this has created a big problem. Untreated pain can affect quality of life thus getting tailored treatment for pain is the need of the hour.

Identifying biomarkers for pain

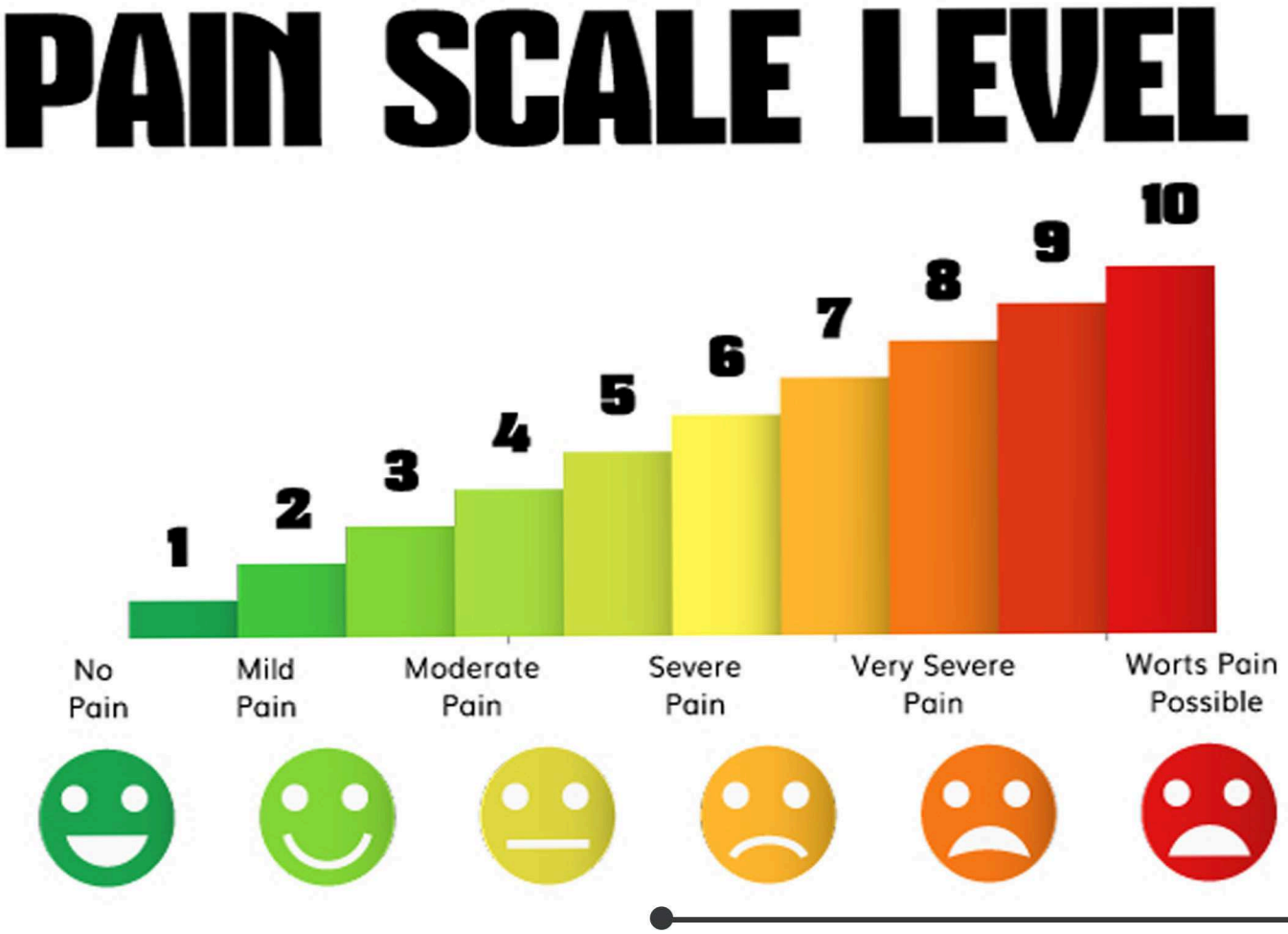
In a breakthrough study published in *Nature* journal *Molecular Psychiatry,* a first ever prototype blood test has been developed by Indiana University School of Medicine, USA which can objectively if not completely quantitively measure severity of a patient's pain with better accuracy. Researchers enrolled

hundreds of participants who were psychiatric patients – a high risk group for pain disorders with increased sensation and perception of pain. Researchers identified gene expression biomarkers in the blood (like a signature or fingerprint which is unique) which could objectively determine severity of one's pain. These biomarkers were molecules that can reflect severity of a disease, for example glucose in blood is a biomarker for diabetes. Some of the biomarkers like MFAP3 had no previous evidence of being involved in pain while many others were targets of existing drugs.

Predicting natural drugs

Researchers used bioinformatics drug repurposing analysis to match pain biomarkers with existing non-addictive drugs, medications and natural compounds profile in a prescription database. Analysis suggested possible lead compounds which would normalize the pain signature. These compounds included both antidepressants as well as natural compound like Vitamin B6 and Vitamin B12. The shortlisted compounds were mostly non-opioid drug or compound. The pain biomarkers can also predict when a patient would next feel pain and is likely to visit the clinic. Some biomarkers were seen as universal and some were specific to a gender.

This information from a simple blood test is helpful to evaluate if a patient is suffering from chronic long-term pain. Treatment can



be provided objectively and quantifiably especially for headache, fibromyalgia etc. For any therapeutic treatment the goal is to find the right drug which has minimal side effects. This study is a first step towards precision medicine for pain i.e. a personalized tailored treatment and it could change the way pain is treated by medical care.

Source

A.B. Niculescu et al 2019, 'Towards precision medicine for pain: diagnostic biomarkers and repurposed drugs, *Molecular Psychiatry*, DOI: 10.1038/s41380-018-0345-5

Identification *of Neuro-Immune Axis:* Good Sleep Protects *Against the Risk of* Heart Diseases

New study in mice shows that getting enough sleep every night could provide protection from cardiovascular diseases

Getting enough sleep is a general advice given by doctors as it is associated with maintaining good health. When someone gets adequate sleep, they feel energized and fresh to start their day and lack of enough sleep increases risk of illnesses. Lack of sleep is now a health problem affecting people of all ages and gender. Many studies have been conducted on animals and humans to understand benefits of sleep. Sleep is thought to play an important role in our immunity, memory, learning etc. Sufficient sleep is also considered important to maintain our cardiovascular health by controlling risk of clogged arteries which can lead to heart attack or stroke. Cardiovascular diseases are the leading cause of deaths worldwide. 85 percent of cardiovascular deaths occur due to heart attack or stroke. Conditions like hypertension or diabetes increase risk of cardiovascular diseases. People who have or are at risk of cardiovascular diseases require early detection and management to keep adverse events at bay. Many cardiovascular diseases are preventable by lifestyle changes like healthy diet, exercise, avoiding tobacco and alcohol.

Association between sleep and cardiovascular diseases in mice

Arteries - our blood vessels - transport oxygen and nutrients from our heart to rest of the body. When our arteries become narrow because of plaque build-up (fatty acids deposits), the condition is called atherosclerosis (or hardening of the arteries) making arteries more prone to rupture. A new study published in *Nature* aimed to understand the association between sleep or rather lack of sleep and cardiovascular diseases via exploring a new pathway for atherosclerosis. Researchers have described a mechanism that lack of enough sleep can escalate production of inflammatory white blood cells (WBCs) which are the biggest contributors towards a person developing atherosclerosis as they contribute towards plaque growth. In the experiment, mice were genetically engineered to develop atherosclerosis as these animals were genetically prone to artery plaque. Mice were subjected to constant interruptions in their sleep through noise or discomfort every 2 minutes during their necessary 12-hour sleep interval. As a result, these sleep-deprived mice who underwent 12 weeks of disturbed sleep developed bigger arterial plaques and also higher number of inflammatory cells like monocytes and neutrophils compared to mice who had normal sleep. Plaque build-up led to atherosclerosis in their blood vessels. Also, there was two-fold increase in production of immune cells in bone marrow giving rise to more WBCs. No changes were seen in

Researchers also identified a hormone in brain called hypocretin which is known to regulate sleep and wakefulness since it is seen in high levels when animals or humans are awake. This hormone, produced by signalling molecule hypothalamus, was found to regulate production of WBCs in bone marrow by interacting with neutrophil progenitors. Neutrophils induce monocyte production by releasing a protein called CSF-1. The mice who were lacking the gene for this protein confirmed that hormone hypocretin controls CSF-1 expression, production of monocytes and development of plaque in arteries. The levels of this hormone were significantly reduced in sleep-deprived mice which led to increased CSF-1 production by neutrophils, increased monocytes and thus advanced atherosclerosis. Therefore, hypocretin hormone is an important inflammatory mediator seen to play a critical role in protection from cardiovascular diseases.

This study will need to be extended in humans (because mice and human sleep patterns may not be identical) before hypocretin can be used therapeutically. It is possible that sleep is directly responsible for regulation of inflammatory cells in bone marrow and for the overall health of our blood vessels. Lack of enough sleep affects this control of inflammatory cells production which can lead to higher inflammation and more heart illnesses. It may happen even if other risk factors like obesity and hypertension are controlled. Understanding underlying mechanisms of how sleep affects human health can help to devise new therapies.

Source

McAlpine CS et al. 2019, 'Sleep modulates haematopoiesis and protects against atherosclerosis', *Nature*, Vol. 566, DOI: 10.1038/s41586-019-0948-2

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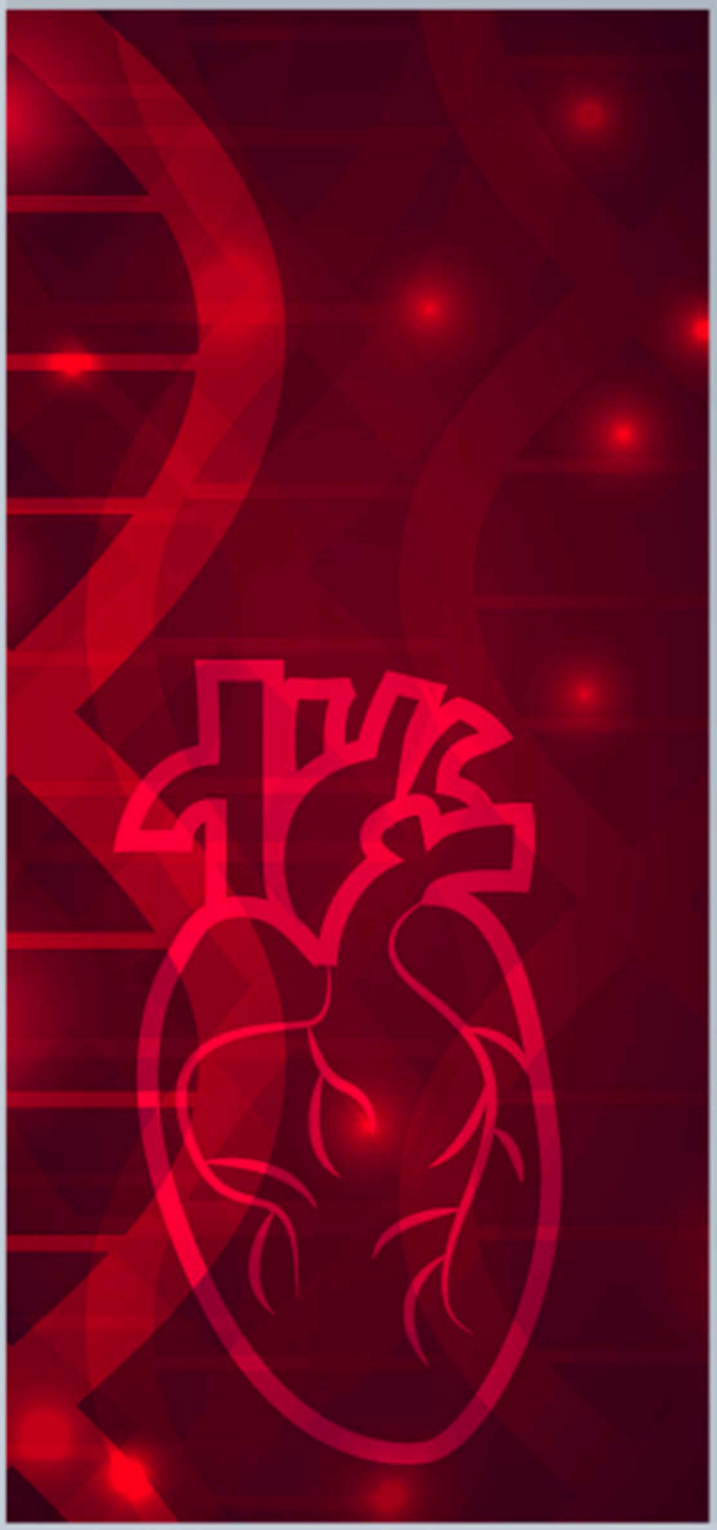
A Battery less *Cardiac Pacemaker* Powered by Natural *Heartbeat*

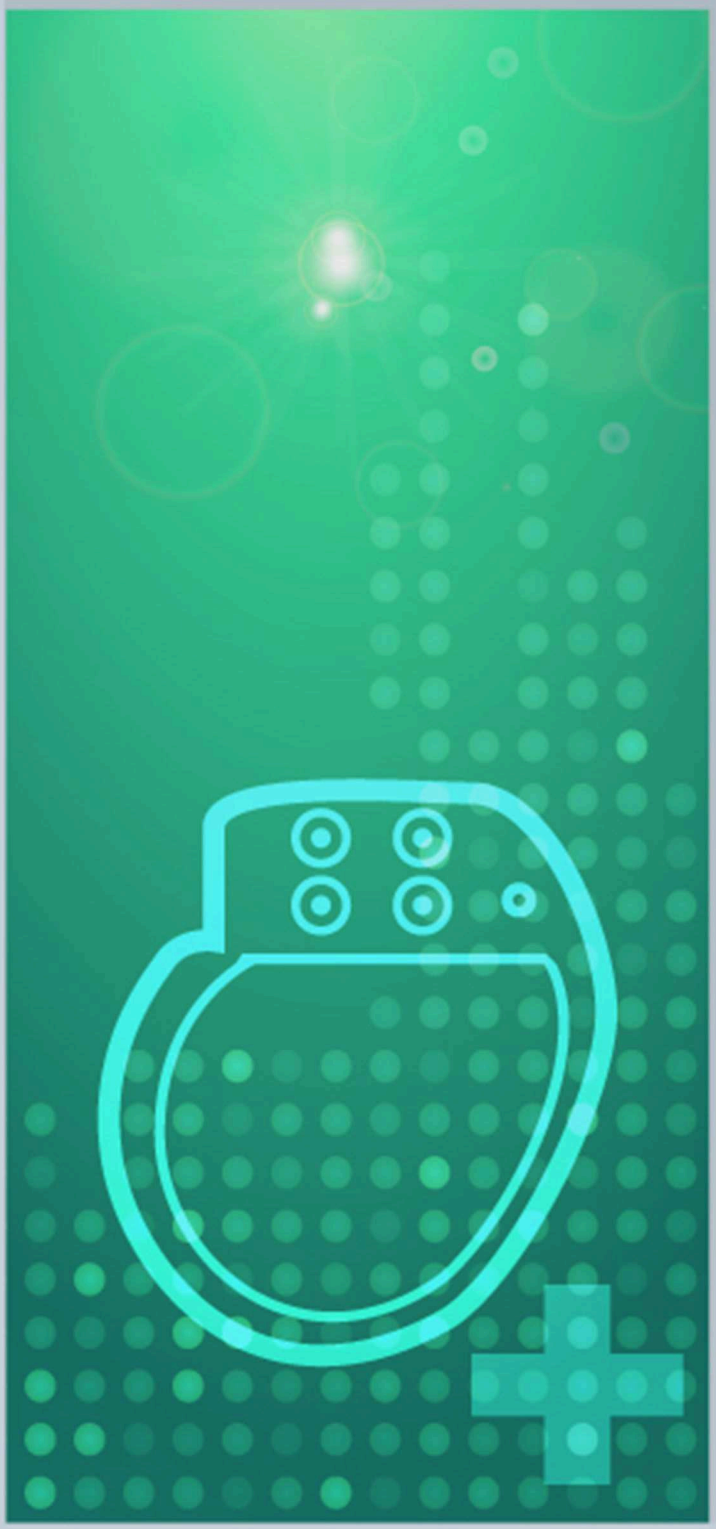
Study shows for the first time an innovative self-powered heart pacemaker tested successfully in pigs

Our heart maintains a pace through its internal pacemaker called sinus mode located in the upper right chamber. This internal pacemaker releases electrical electrical charge 60-100 times in a minute and this energy carries out contractions in heart muscles which allow our heart to pump blood throughout our body. As we age or get an illness, this internal pacemaker is unable to keep the heart beating properly. Irregular heartbeat is also caused by a condition called arrythmia which slows down one's heart's normal rate. To substitute for this loss, a traditional heart pacemaker – a battery-operated electronic device - can be surgically implanted inside a patient to regularize heartbeat and keep the heart beating steadily.

A traditional heart pacemaker

The device consists of a battery-powered pulse generator which is implanted under the skin near the collar bone. It also has insulated wires which connect the device to the heart. The electronic circuit generates electric signals which are delivered to the heart via electrodes. The pacemaker is a life-saving device; however, one significant limitation of current pacemaker is that they need to be replaced at any time between 5 to 12 years of first when they are fitted because of battery's limited life. The implantation can only





be done via an invasive surgery using local anaesthesia which itself is challenging as a patient's chest cavity needs to be opened. Surgery is not only expensive but it also increases patient's risk of complication, infections or even bleeding. Another type of tiny pacemaker has been designed which can be implanted via a catheter avoiding surgery but it is still undergoing testing.

Key points

- A novel small cardiac pacemaker device has been designed which can be powered from energy of one's own heartbeat.
- The pacemaker is based on an ideal symbiotic relationship between one's heart and the device.
- The device has been successfully tested in pigs and is going to be tested for safety and efficacy in humans.

Researchers have been focusing on building cardiac pacemakers which could alternatively use natural energy from a person's own heartbeat instead of battery. Theoretically, such a pacemaker would not need to be replaced once it is implanted inside a patient. Plutonium-powered pacemakers have been manufactured many decades earlier. Experimental design of new pacemakers has faced several limitations so far - like rigid design structure which limits its power and complications with miniaturization.

An innovative battery less pacemaker with a unique design

In a new study published in ACS Nano researchers from National Key Laboratory for Science and Technology, Shanghai, China set out to design a novel small pacemaker device which can be powered from energy of one's own heartbeat and they successfully tested this device in pigs. The new device can be tucked under the heart rather than near the collar bone as with conventional pacemakers. The pacemaker is based on an ideal symbiotic relationship between one's heart and the device.

The design of this new pacemaker was initiated by first making a small flexible plastic frame. This frame was bonded with piezoelectric layers which upon being bent generate energy. This part, called energy 'harvester' was placed on a chip. The device was implanted in pigs and it was observed that the animals' own heartbeat could alter (bend) the shape of the frame thereby generating enough energy (power) equivalent to a battery-powered pacemaker. The device's flexible plastic frame allows it to capture more energy from the heart compared to traditional pacemakers which have hard cases.

Since humans have a physiology very similar to pigs, this pacemaker could work well in humans too. Researchers point out some technical issues which will need to be addressed, example the device comprises of three separate technologies –energy harvester, pacemaker chip and wires – which need to be integrated into one device. Further testing in animals and then in humans can confirm the device's long-term stability. Such a device if successful will require invasive surgery only once reducing patient's risk of complications. One major limitation of this new device could be that doctors may not be able to remotely monitor patients as in the case of battery-operated pacemakers.

Source
Ning Li et al. 2019, 'Direct Powering a Real Cardiac Pacemaker by Natural Energy of a Heartbeat', *ACS Nano*,
DOI: 10.1021/acsnano.8b08567

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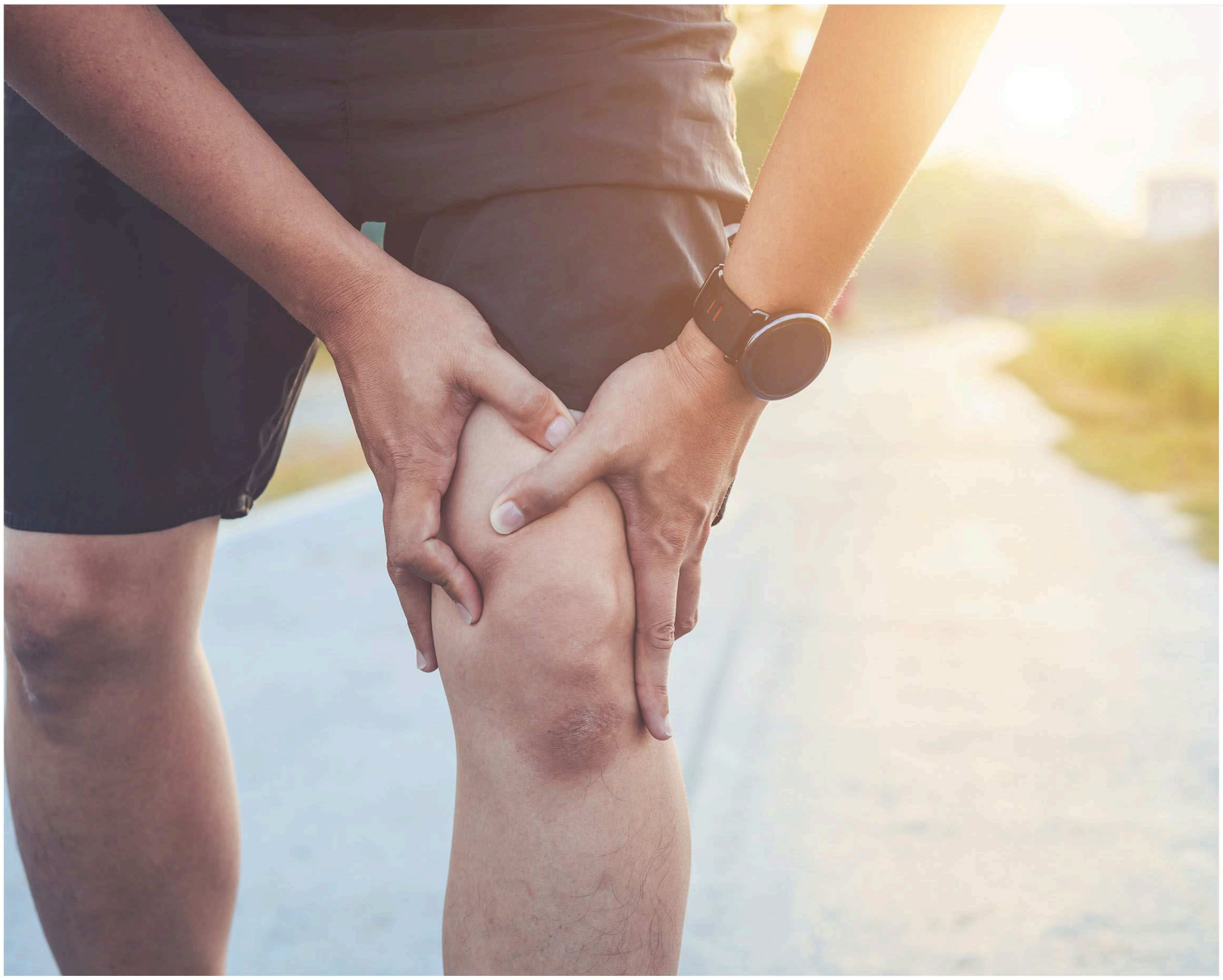
A Potential Method *to Treat Osteoarthritis* by Nano-Engineered *System for Delivery* of Protein Therapeutics

Researchers have created 2-dimensional mineral nanoparticles to deliver treatment in the body for cartilage regeneration

Osteoarthritis is a degenerative disease which affects 630 million people worldwide which is almost 15 percent of the entire population on the planet. In osteoarthritis, cartilage in our bone starts breaking down and this can damage the underlying bone causing pain and stiffness, especially in knee, hip and thumb joints. The incidence of this condition increases as we age. Treatments for osteoarthritis include medications, physiotherapy, occupational therapy targeted mainly to relieve pain symptoms. To treat this condition entirely, damaged joint tissues need to be repaired. This repair is complicated and challenging as cartilage tissue in the bone is difficult to regenerate. As the world's population is ageing, new effective treatments for osteoarthritis are immediately needed.

Growth factors protein

A possible treatment of osteoarthritis involves design and delivery of protein therapeutics i.e. proteins engineered in laboratory for therapeutic use. Protein therapeutics have had a major impact on many diseases in recent decades. One such class of proteins is called growth factors which are



soluble secreted proteins. Our body is capable of self-healing and this process can be enhanced by artificial application of growth factors to improve processes involved in self-healing. However, most of the known growth factors break down rapidly and thus very high dosage is needed to achieve a therapeutic effect. Studies have shown adverse effects of high dosage like inflammation and uncontrolled tissue formation. The application of growth factors is also very limited mainly due to lack of efficient delivery systems or biomaterial carriers. Growth factors along with efficient biomaterial delivery systems are critical in regenerative medicine involving tissue repair and regeneration.

A new treatment for osteoarthritis based upon nanosilicates

Researchers at Texas A&M University, USA aimed to develop a novel treatment for cartilage regeneration by designing two-dimensional (2D) mineral nanoparticles which could be used to deliver growth factors. These nanoparticles (or nanosilicates) possess two key characteristics - high surface area and dual charge - which allow easier attachment of growth factors. Nanosilicates show higher binding efficacy to growth factors without affecting the protein's 3D conformation or its biological function. They allow longer sustained delivery (more than 30 days) of growth factors to human mesenchymal stem cells which are

then used in regeneration of cartilage by inducing enhanced differentiation of stem cells towards cartilage. Enhanced differentiation confirms high activity of the released protein and that also at 10-fold lower concentration compared to current therapies which use much higher dose.

This study published in *ACS Applied Materials & Interfaces* shows a nanoengineered system – a nanoclay-based platform in which nanosilicates can be used as a delivery vehicle to enable sustained delivery of protein therapeutics for treating osteoarthritis. Such a biomaterial-based delivery system could ensure efficient treatment of osteoarthritis by reducing overall costs and minimizing negative side effects. This novel platform of delivery can boost current orthopaedic regeneration strategies and make an impact on regenerative medicine.

Source

Lauren M. Cross et al 2019, 'Sustained and Prolonged Delivery of Protein Therapeutics from Two-Dimensional Nanosilicates', *ACS Applied Materials & Interfaces,* Vol. 11,
DOI: 10.1021/acsami.8b17733

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