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Alternatives to whole liver transplants for children have become safer, study finds

Findings suggest opportunity to increase organ supply, save lives

In a new Johns Hopkins study of patient and graft survival trends for pediatric liver transplant recipients between 2002 and 2015, researchers found that outcomes for alternatives to whole liver transplantation (WLT), such as splitting a liver for two recipients or using a part of a liver from a living donor, have improved significantly.

A report of the findings, published Jan. 4 in The Journal of Pediatrics, highlights opportunities for an increased organ supply, better use of those organs and the chance to save more lives.

"Our study indicates that while there were initially worse outcomes when a whole liver from a deceased donor was given to two recipients, known as a "split liver transplant," outcomes are now similar to the classic liver transplant, when a whole liver is given to one recipient. Additionally, outcomes when a living donor gives a portion of his or her liver may actually be superior to a whole liver transplant," says Douglas B. Mogul, M.D., M.P.H., assistant professor of pediatrics at the Johns Hopkins University School of Medicine and the study's lead author. Mogul also practices at Johns Hopkins Children's Center.

Currently, donor livers from deceased people are allocated to patients based on the Pediatric End-stage Liver Disease (PELD) or Model for End-stage Liver Disease (MELD) system, which provide a score for potential recipients based on how urgently they need a liver transplant within the next three months. Those with high PELD/MELD scores can be subject to long-term physical and mental impairments, hospitalizations and increased costs until they are sick enough to qualify for a transplant.

Alternatives to WLT, or to taking whole livers from deceased donors, can potentially increase organ supply, shorten wait list times and reduce pre-transplant complications and deaths, according to Mogul. The alternatives include split liver transplantation (SLT), in which a liver is divided up to transplant into two recipients, and living donor liver transplantation (LDLT), in which a portion of a liver from a live donor is used. The liver of such a donor can regenerate its own tissue.

While there has been an emerging consensus that adult recipients of SLT do just as well as recipients of WLT for several years, outcomes among children have been less clear, Mogul says.

To better understand recent outcomes for pediatric liver transplants by transplant type, Mogul and the research team looked at data for liver-only pediatric transplant recipients from the Scientific Registry of Transplant Recipients, a data system that includes information on all donors, wait listed candidates and transplant recipients in the United States.

The research team identified 5,175 pediatric liver-only transplant recipients who received an organ between March 1, 2002, (after implementation of the PELD/MELD system) and Dec. 31, 2015. Of the recipients, 3,428 (60 percent) patients received a WLT, 1,626 (28.5 percent) an SLT and 661 (11.6 percent) an LDLT.

From 2002 to 2009 and 2010 to 2015, 30-day survival for SLT improved (94 to 98 percent), and one-year survival for SLT improved from 89 to 95 percent. One-year survival also improved for LDLT, from 93 percent in 2002 to 2009 to 98 percent in 2010 to 2015.

The researchers found no change in survival rates for WLT at either 30 days or one year. The risk of early death with SLT was 2.14 times higher from 2002 to 2009 compared to WLT, but this risk disappeared in 2010 to 2015. From 2002 to 2009 and 2010 to 2015, the frequency of transplants was similar for WLT (60 percent for both periods), SLT (29 and 28 percent) and LDLT (11 and 12 percent).

SLT and LDLT recipients were more likely to be under 2 years of age and weigh less than 22 pounds. African-Americans were less likely than Caucasians to receive LDLT and more likely to receive WLT. Donor age for all patients receiving an LDLT was 18-50, whereas WLT recipients were more likely to have donors age 0-17. Those undergoing

LDLT were more likely to have private insurance, and those with SLT were more likely to have public insurance.

"A recent report tells us that nearly half of all children that died while on the wait list didn't receive a single offer for an organ. Our findings, which show that overall patient and graft survivals have improved , and that outcomes for alternatives to WLT are comparable, will hopefully influence policy for organ allocation such as greater use of split liver transplantation," says Mogul.

One in 10 children on the wait list die each year, and the cost for a pediatric liver transplant is estimated to be between $150,000 and $250,000, he adds.

Other authors on this paper include Xun Luo, Mary G. Bowring, Eric K. Chow, Allan B. Massie, Kathleen B. Schwarz, Andrew M. Cameron, John F.P. Bridges and Dorry L. Segev of The Johns Hopkins University.

Funding for this study was provided by the Agency for Healthcare Research and Quality (5K08HS023876-02) and the National Institute of Diabetes and Digestive and Kidney Diseases (K23DK101677).

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Twenty-five years of satellite data confirm rising sea levels

Twenty-five years of satellite data prove climate models are correct in predicting that sea levels will rise at an increasing rate.

Tampa, Fla. - In a study published in the journal Proceedings of the National Academy of Sciences, researchers found that since 1993, ocean waters have moved up the shore by almost 1 millimeter per decade. That's on top of the 3 millimeter steady annual increase. This acceleration means we'll gain an additional millimeter per year for each of the coming decades, potentially doubling what would happen to the sea level by 2100 if the rate of increase was constant.

"The acceleration predicted by the models has now been detected directly from the observations. I think this is a game-changer as far as the climate change discussion goes," said co-author Gary Mitchum, PhD, associate dean and professor at the University of South Florida College of Marine Science. "For example, the Tampa Bay area has been identified as one of 10 most vulnerable areas in the world to sea level rise and the increasing rate of rise is of great concern."

Dr. Mitchum is part of a team led by University of Colorado Boulder Professor Steve Nerem, PhD, that used statistical analysis to enhance previous studies based on tide gauge data, which have also suggested acceleration over the last century. However, satellites give a better view of sea level rise, because samples are collected over the open ocean, rather than just along the coastline.

Experts have long said warming temperatures are heating ocean waters and melting ice sheets in Greenland and Antarctica. As it continues, the next generation will experience a far different landscape than it does today.

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Deep-sea fish use hydrothermal vents to incubate eggs

DNA analysis revealed that the egg cases found near the black smoker belong to deep-sea skates.

Some deep-sea skates -- cartilaginous fish related to rays and sharks -- use volcanic heat emitted at hydrothermal vents to incubate their eggs, according to a new study in the journal *Scientific Reports*. Because deep-sea skates have some of the longest egg incubation times, estimated to last more than four years, the researchers believe the fish are using the hot vents to accelerate embryo development. This the first time such behavior has been seen in marine animals.

"Hydrothermal vents are extreme environments, and most animals that live there are highly evolved to live in this environment," said Charles Fisher, Professor and Distinguished Senior Scholar of Biology at Penn State and an author of the paper. "This study is one of the few that demonstrates a direct link between the vent environment and animals that live most of their life elsewhere."

Among the least explored and unique ecosystems, deep-sea hydrothermal fields are regions on the sea floor where hot water emerges after being heated in the ocean crust. In their study, an international team of researchers, led by Pelayo Salinas-de-León of the

Charles Darwin Research Station, used a remotely operated underwater vehicle (ROV) to survey in and around an active hydrothermal field located in the Galapagos archipelago, 28 miles north of Darwin Island. "The first place the ROV landed on the sea floor was on a ridge, in the plume of a nearby hydrothermal vent that we had specifically come to investigate - a black smoker," said Fisher. "When we panned the camera down, we found something we did not expect: These giant egg cases, also known as mermaid purses. And we found several layers of them, indicating that whatever was laying these eggs had been coming back to this spot for many years to lay them. As the dive progressed, we saw more and more of these egg cases and realized that this was not the result of a single animal, but rather a behavior shared by many individuals. "

The researchers found 157 egg cases in the area and collected four with the ROV's robotic arm. DNA analysis revealed that the egg cases belonged to the skate species Bathyraja spinosissima, one of the deepest-living species of skates that is not typically thought to occur near the vents. The majority -- 58 percent -- of the observed egg cases were found within about 65 feet of the chimney-like black smokers, the hottest kind of hydrothermal vents, and over 89 percent had been laid in places where the water was hotter than average. The researchers believe that the warmer temperatures in the area could reduce the typically years-long incubation time of the eggs.

While several species of reptiles and birds lay their eggs in locations that optimize soil temperatures, only two other groups of animals are known to use volcanically heated soils: the modern-day Polynesian megapode -- a rare bird native to Tonga -- and a group of nest-building neosauropod dinosaurs from the Cretaceous Period.

Because of their long lifespan and slow rate of development, deep-water skates may be particularly sensitive to threats to their environment, including fisheries expanding into deeper waters and sea-floor mining. Understanding the development and habitat of the skates is vital for developing effective conservation strategies for this poorly understood species.

"The deep sea is full of surprises," said Fisher. "I've made hundreds of dives, both in person and virtually, to deep sea hydrothermal vents and have never seen anything like this."

In addition to Fisher, the research team includes Pelayo Salinas-de-León and Florencia Cerutti-Pereyra of the Charles Darwin Research Station in Ecuador and the National Geographic Society; Brennan Philips of Harvard University and the University of Rhode Island; David Ebert of the Moss Landing Marine Laboratories, California Academy of Sciences and the South African Institute for Aquatic Biodiversity; Mahmood Shivji and Cassandra Ruck of Nova Southeastern University; and Leigh Marsh of University of Southampton, Waterfront Campus, and the National Oceanography Centre, both in the United Kingdom. This work was funded by the National Oceanic and Atmospheric Administration (NOAA), the Helmsley Charitable Trust, and the Save Our Seas Foundation.

Related video: https://www.youtube.com/watch?v=L5RCgANRXq0

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Tiny fossils, huge slides: Are diatoms the key to Earth's biggest slides?

The biggest landslides on Earth aren't on land, but on the seafloor.

Boulder, Colo., USA: - These mega-slides can move thousands of cubic kilometers of material, and sometimes trigger tsunamis. Yet, remarkably, they occur on nearly flat slopes of less than three degrees. Morelia Urlaub, a marine geoscientist at the Geomar Helmholtz Center for Ocean Research in Kiel, Germany, voices the obvious question: "How can you fail on a slope that is so flat?" Now, Urlaub and colleagues may have discovered the answer. The smoking -- or in this case, oozing -- gun is a layer of siliceous microfossils called diatoms.

The study, published online ahead of print for the Geological Society of America's journal Geology, is the first to identify the weak layer responsible for a submarine mega-slide.

Although the nature of these critical weak layers has been highly debated, studying them has been nearly impossible because they are typically destroyed along with the slides.

Urlaub was compiling ocean drilling data from 1980 when she realized that the core sampled the seafloor just outside the Cap Blanc slide, a

149,000 year-old mega-slide off the coast of northwest Africa. She correlated that data with high resolution seismic reflection data recorded in the same area in 2009. Together, these data revealed diatom-rich layers, up to ten meters thick, that traced directly from the core to the base of slide layers within the mega-slide complex.

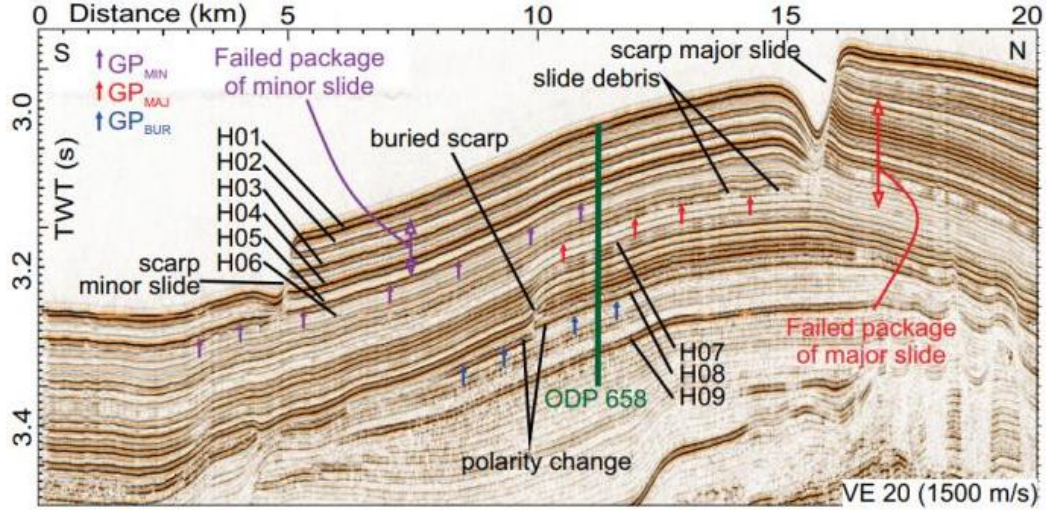

Figure 2. Seismic reflection line GeoB09-040 across the Cap Blanc slide area (offhore northwest Africa) and Ocean Drilling Program (ODP) Site 658 (green vertical line). TWT—two-way traveltime; VE—vertical exaggeration. Colored arrows indicate glide planes corresponding to minor slide (GP_{MIN}, purple), major slide (GP_{MAJ}, red) and buried slide (GP_{BUR}, blue). Nine prominent high-amplitude reflectors are termed H01–H09. See Figure 1 for location of profile, and Data Repository (see footnote 1) for enlarged and uninterpreted version of profile.

This is seismic reflection data. **Morelia Urlaub and colleagues, and Geology.**

What's more, each diatom layer was topped by a layer of clay-rich sediment. That clay is apparently key. "Diatom layers are very compressible and water rich," Urlaub says. As pressure builds, she explains, water would be squeezed from the diatom layer into the clay. Ultimately the clay or the interface between the clay and diatoms fails, sending the sediments above sliding.

At the Cap Blanc slide, the seafloor slopes at just 2.8 degrees. Yet when it broke loose, the slide transported over 30 cubic kilometers of material, and extended at least 35 kilometers. Another submarine mega-slide 8,500 years ago off Norway moved a staggering 3,000 cubic kilometers, causing a damaging tsunami. And some scientists speculate that the 2011 Tohoku tsunami in Japan may have been amplified by a submarine mega-slide.

Although such slides don't occur very often, says Urlaub, their size makes them quite significant. "One-fifth of all tsunamis may be caused by undersea mega-slides," she says. If diatom layers are a major factor, then understanding where paleoclimate conditions may have favored diatom growth might help reveal potential mega-slide sites.

FEATURED ARTICLE

Diatom ooze: Crucial for the generation of submarine megaslides?

M. Urlaub, Jacob Geersen, Sebastian Krastel, and Tilmann Schwenk. Geology: https://doi.org/10.1130/G39892.1.

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Huntington's disease provides new cancer weapon

Scientists harness a super assassin gene for new cancer treatment

CHICAGO --- Patients with Huntington's disease, a fatal genetic illness that causes the breakdown of nerve cells in the brain, have up to 80 percent less cancer than the general population.

Northwestern Medicine scientists have discovered why Huntington's is so toxic to cancer cells and harnessed it for a novel approach to treat cancer, a new study reports.

Huntington's is caused by an over abundance of a certain type of repeating RNA sequences in one gene, huntingtin, present in every cell. The defect that causes the disease also is highly toxic to tumor cells. These repeating sequences -- in the form of so-called small interfering RNAs -- attack genes in the cell that are critical for survival. Nerve cells in the brain are vulnerable to this form of cell death, however, cancer cells appear to be much more susceptible.

"This molecule is a super assassin against all tumor cells," said senior author Marcus Peter, the Tom D. Spies Professor of Cancer Metabolism at Northwestern University Feinberg School of Medicine. "We've never seen anything this powerful."

Huntington's disease deteriorates a person's physical and mental abilities during their prime working years and has no cure.

The study will be published Feb. 12 in the journal EMBO Reports.

To test the super assassin molecule in a treatment situation, Peter collaborated with Dr. Shad Thaxton, associate professor of urology at Feinberg, to deliver the molecule in nanoparticles to mice with human ovarian cancer. The treatment significantly reduced the tumor growth with no toxicity to the mice, Peter said. Importantly, the tumors did not develop resistance to this form of cancer treatment.

Peter and Thaxton are now refining the delivery method to increase its efficacy in reaching the tumor. The other challenge for the scientists is figuring out how to stabilize the nanoparticles, so they can be stored.

First and co-corresponding author Andrea Murmann, research assistant professor in medicine at Feinberg, also used the molecule to treat human and mouse ovarian, breast, prostate, liver, brain, lung, skin and colon cancer cell lines. The molecule killed all cancer cells in both species.

The Huntington's cancer weapon was discovered by Murmann, who had worked with Peter on earlier research that identified an ancient kill-switch present in all cells that destroys cancer.

"I thought maybe there is a situation where this kill switch is overactive in certain people, and where it could cause loss of tissues," Murmann said. "These patients would not only have a disease with an RNA component, but they also had to have less cancer."

She started searching for diseases that have a lower rate of cancer and had a suspected contribution of RNA to disease pathology. Huntington's was the most prominent.

When she looked at the repeating sequences in huntingtin, the gene that causes the disease, she saw a similar composition to the earlier kill switch Peter had found. Both were rich in the C and G nucleotides (molecules that form the building blocks of DNA and RNA).

"Toxicity goes together with C and G richness," Murmann said. "Those similarities triggered our curiosity."

In the case of people who have Huntington's, the gene huntingtin has too many repeating sequences of the triplet sequence CAG. The longer the repeating sequence, the earlier they will develop the disease.

"We believe a short-term treatment cancer therapy for a few weeks might be possible, where we could treat a patient to kill the cancer cells without causing the neurological issues that Huntington's patients suffer from," Peter said.

Peter also is co-leader of the Translational Research in Solid Tumors Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Huntington's patients have a lifetime exposure to these toxic RNA sequences, but generally don't develop symptoms of the disease until age 40, he noted.

Every child of a parent with Huntington's has 50/50 chance of carrying the faulty gene. Today, there are approximately 30,000 symptomatic Americans and more than 200,000 at-risk of inheriting the disease.

The research was supported in part by funding from the National Institutes of Health/National Cancer Institute grant R35CA197450 and The Northwestern University Feinberg School of Medicine Developmental Therapeutic Institute.

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Study shows benefits of exercise can outweigh health effects of severe obesity

Fat but Fit? York U research shows you can't judge a person's fitness by weight alone

TORONTO - Can you be fit and healthy even if you're overweight? That's the question researchers at York University's Faculty of Health set out to answer in a new study that shows physical activity may be equally and perhaps even more important than weight for people living with severe obesity.

According to the recent study, led by Jennifer Kuk, associate professor in York University's School of Kinesiology and Health Science, and collaborator Dr. Sean Wharton, MD, medical director of the Wharton Medical Clinic and adjunct professor at York University, individuals with severe obesity who are fit have a similar health profile to those who weigh significantly less than them. The goal of the study was to look at the benefits of cardiorespiratory fitness on cardiovascular health in populations with mild to severe obesity.

The results suggest individuals with even severe obesity, or a BMI greater than 40, can be fit and healthy.

"Obesity is only related with worse health in individuals who were unfit," says Kuk. "We know that once you get beyond a BMI of 40, the risk of cardiovascular conditions increases exponentially so this study shows that having a high fitness level is still beneficial and it really reinforces the importance of fitness."

Kuk says doing 150 minutes of exercise per week, as per physical activity guidelines, generally translates to less than half pound of weight loss. Nevertheless, this amount of exercise can mean dramatic improvements in health for those with severe obesity.

"You really have to disconnect the body weight from the importance of fitness," says Kuk. "You can get fit without losing weight and have health benefits."

Data was gathered from 853 Canadian patients attending Wharton Medical weight management clinics in Southern Ontario. Individuals completed a clinical exam which included fasting blood measures and a maximal treadmill stress test.

The amount of fitness necessary to achieve health benefits was far less than what most individuals would think. The research showed that the greatest health benefits come from avoiding the lowest 20 per cent of fitness levels. This means that 80 per cent of people are fit enough to get health benefits.

In this study, 41% of participants with mild obesity had high fitness levels, while 25 per cent and 11 per cent of the participants with moderate and severe obesity, respectively, had high fitness. Individuals with severe obesity were more likely to have high blood pressure, glucose, and triglycerides if they were in the lowest 20 per cent of fitness levels, but were not more likely to have these issues if they were in the 80 per cent group.

Earlier research has shown that much less physical activity is required to improve health than is needed to lose weight. However, this is some of the first research suggesting that physical activity may be more important for people living with severe obesity.

"In my practice, I see many patients who are looking for different results," says Wharton. "There are some patients that want to significantly improve their health and others that are only looking for an aesthetic goal. When it comes to health, this study reinforces the notion that people don't need to lose weight to be healthy."

T*he Canadian Institutes of Health Research funded study, Association between cardiorespiratory fitness and metabolic risk factors in a population with mild to severe obesity was recently published in BMC Obesity.*

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Obesity associated with longer survival for men with metastatic melanoma

Unexpected result launches search for underlying cause, including hormonal impact

Obese patients with metastatic melanoma who are treated with targeted or immune therapies live significantly longer than those with a normal body mass index (BMI), investigators report in a study published in Lancet Oncology of 1,918 patients in six independent clinical cohorts.

This effect, referred to as the "Obesity Paradox", principally manifested itself in men, said Jennifer McQuade, M.D., lead author and instructor of Melanoma Medical Oncology at The University of Texas MD Anderson Cancer Center.

"Obese men consistently did much better than men with a normal BMI, with nearly a doubling of overall survival," McQuade said. The researchers found no significant differences in survival between women with normal, overweight or obese BMI.

"The question is what underlying mechanism causes this advantage in obese men, and can we take advantage of it to improve outcomes in patients with melanoma?" McQuade said. "One hint may be the interaction between obesity, sex, and outcomes, which has not been detected before in any cancer."

Women with metastatic melanoma have long been known to have better outcomes compared to men, McQuade noted. In this study obesity overcame that survival disadvantage for men, leading researchers to now look at the possible impact of sex hormones in this effect.

Associations don't prove causation, the researcher's note, but point to new areas to study in greater depth.

"The public health message is not that obesity is good. Obesity is a proven risk factor for many diseases," McQuade said. "Even within our metastatic melanoma population, we would not suggest that patients intentionally gain weight. We need to figure out what is driving this paradox and learn how to use this information to benefit all of our patients."

Obesity is a known risk factor for developing 13 types of cancer according to the World Health Organization and is set to overtake smoking as the leading preventable cause of cancer. The relationship between obesity and survival in patients that already have cancer is not as consistent. Recent studies have shown a similar survival benefit for obese patients with colorectal or kidney cancer.

Obesity expected to be disadvantage

The team expected to find obesity to be harmful for melanoma patients, based in part on research that implicates obesity in activation of a cancer-promoting molecular pathway called IGF-1/PI3K/AKT.

They analyzed the association between body mass index (weight divided by height) and progression-free survival (PFS) and overall survival (OS) in six independent cohorts of patients treated with targeted therapy, immunotherapy or chemotherapy in pivotal trials that led to FDA approval of these drugs.

While advantages in PFS and OS emerged in an overall meta-analysis of the entire group, the survival benefit associated with obesity was restricted to men treated with targeted or immunotherapies, where obese men had a 47 percent decreased risk of death compared to men with normal BMI.

Doubling of overall survival in men

Results from 599 patients receiving combination targeted therapy of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) were:

Normal BMI of 18.5-24.9 - median PFS of 9.6 months, OS of 19.8 months

Obese BMI 30 and above - median PFS 15.7 months, OS 33.0 months

A multivariable analysis that included factors such as age, sex, stage, disease burden, certain mutations and prior treatment showed that obesity still improved PFS and OS compared to normal BMI patients.

The team analyzed results by sex and found significant differences only among men.

Normal BMI men - PFS 7.2 months, OS 16.0 months

Obese men - PFS 12.8 months, OS 36.5 months.

By contrast, women, for example, had overall median survival of at least 33 months, regardless of BMI.

A validation cohort of 240 patients treated with vemurafenib (BRAF inhibitor) and cobimetinib (MEK inhibitor) yielded similar results.

For immunotherapy, in a cohort (330 patients) treated with checkpoint inhibitors blocking either the PD1 check point on T cells or its PD-L1 ligand, results again showed no differences among women, but:

Normal BMI men - PFS 2.7 months, OS 14.3 months

Obese men - PFS 7.6 months, OS 26.9 months

A cohort of patients treated with the immune checkpoint inhibitor ipilimumab (207 patients) showed similar results. There was no effect of obesity found among two cohorts (541 patients) treated only with the chemotherapy dacarbazine.

Possible estrogen connection

The researchers are following up to understand biological factors that might provide an advantage to obese male patients. Obesity is associated with increased inflammation, which could improve the effectiveness of checkpoint blockade drugs that unleash an immune response against cancer.

The sex-specificity of the observed differences points to a potential hormonal mediator. Fat (adipose) tissue produces an enzyme called aromatase that converts male hormones called androgens into estrogens, female hormones. Perhaps this happens enough in obese men to help

them clear some type of hurdle toward greater survival, McQuade said. The researchers are collaborating with investigators at the University of Pennsylvania that have found that turning on a very specific type of estrogen receptor on melanoma makes it vulnerable to immunotherapy. The MD Anderson team also is looking at gene expression, mutations and immune profiling to identify potential differences in melanoma in obese and non-obese patients and developing preclinical models.

Co-authors with McQuade and senior author and co-corresponding author Michael Davies, M.D., Ph.D, are Patrick Hwu, M.D., of Melanoma Medical Oncology; Carrie Daniel-MacDougall, Ph.D., of Epidemiology; Kenneth Hess, Ph.D., of Biostatistics; Lauren Haydu, Ph.D., Shenying Fang, M.D., Ph.D., Jennifer Wargo, M.D., Jeffrey Gershenwald, M.D., and Jeffery Lee, M.D., of Surgical Oncology; Christine Spencer of Genomic Medicine; and Meredith McKean, M.D., of Cancer Medicine, all of MD Anderson; and Carmen Mak, Ph.D., Stephen Lane, Dung-Yang Lee, Ph.D., Mathilde Kaper, Tomas Haas, and Jeffery Legos, Ph.D., of Novartis Pharmaceuticals of East Hanover, N.J.; Daniel Wang, M.D., Kathryn Beckermann, M.D., Samuel Rubinstein, M.D., and Douglas Johnson, M.D., of Vanderbilt University Medical Center, Nashville; Rajat Rai, M.D., Matteo Carlino, M.D., Georgina Long, M.D., and Alexander Menzies, M.D., of the Melanoma Institute Australia and the University of Sydney, Sydney, Australia; John Park, M.D., Princess Mary Cancer Centre, Westmead Hospital, Westmead, Australia; Matthew Wongchenko, Isabelle Rooney, M.D., Luna Musib, Ph.D., Nageshwar Budha, Ph.D., Jessie Hsu, Ph.D., Yibing Yan, PH.D., and Edward McKenna, PharmD, of Genentech, San Francisco; Theodore Nowicki, M.D., and Anthoni Ribas, M.D., of the University of California Los Angeles Medical Center; Alexandre Avila, M.D., and Dana Walker, M.D., of Bristol-Myers Squibb, New York; Maneka Puligandla and Sandra Lee, SciD, of Dana-Farber Cancer Institute, Boston; Paul Chapman, M.D., of Memorial Sloan Kettering Cancer Center, New York; Jeffrey Sosman, M.D., of Northwestern University, Chicago; Dirk Schadendorf, M.D., of University Hospital Essen and the German Cancer Consortium, Essen, Germany; Jean-Jacque Grob, M.D., of Hospitalo-Universitaire Timone, Aix Marseille University, Marseille, France; Keith Flaherty, M.D., of Massachesetts General Hospital Cancer Center, Boston; and John Kirkwood, M.D., Hillman University of Pittsburgh Medical Center Cancer Center, Pittsburgh.

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http://on.wsj.com/2F4OxcI

Experimental Drug Promises to Kill the Flu Virus in a Day

Even if drug lives up to claim, it likely won't be available in U.S. until next year at earliest

By Preetika Rana 2018 年 2 月 10 日 21:00 JST

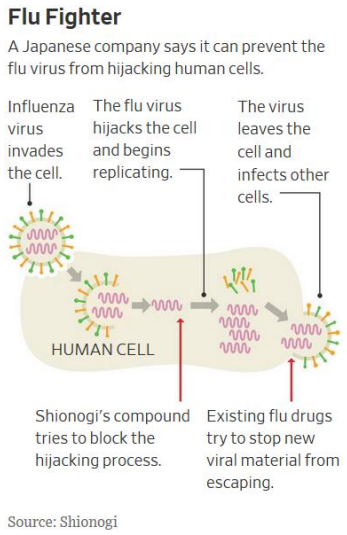
As Americans suffer through the worst influenza outbreak in almost a decade, a Japanese drugmaker says it has developed a pill that can kill the virus within a day. But even if the experimental drug lives up to the claim, it likely won't be available in the U.S. until next year at the earliest.

A late-stage trial on Japanese and American flu patients found that for the people who took the Shionogi 4507 0.68% & Co. compound, the median time taken to wipe out the virus was 24 hours. That is much quicker than any other flu drug on the market, including Roche AG's RHHBY 2.73% Tamiflu, which the trial showed took three times longer to achieve the same result. Quickly killing the virus could reduce its contagious effects, Shionogi said.

Also, Shionogi's experimental drug requires only a single dose, while patients need to take two doses of Tamiflu a day, for five days.

Both Shionogi's compound and Tamiflu take roughly the same amount of time to entirely contain flu symptoms, but Shionogi says its compound provides immediate relief faster.

Scientists at the Japanese company leveraged their work on a blockbuster anti-HIV drug to create the compound, which works differently from existing flu medicines. It blocks the flu virus from hijacking human cellular machinery, Chief Executive Isao Teshirogi said. Switzerland's Roche has acquired the international license to distribute Shionogi's experimental drug.



"The data that we've seen looks very promising," said Martin Howell Friede, who leads the World Health Organization's advisory on vaccines, including for influenza. "This could be a breakthrough in the way that we treat influenza."

Shionogi said Japan's drug regulator is fast-tracking its approval and could approve it for use in Japan as early as March. The regulator declined to comment. Roche and Shionogi say they will apply for U.S. approval this summer and Shionogi doesn't expect a decision until next year.

Other players including Johnson & Johnson , AstraZeneca PLC and a startup backed by Merck & Co. are testing new compounds to treat influenza A, the most common flu strain. Shionogi's candidate is furthest along and it says the compound can also treat B strains that infect humans too.

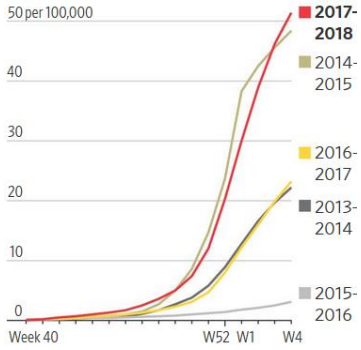
The U.S. has been hit by one of the worst flu epidemics in years, and transmissions are now the most intense since a pandemic in 2009.

The first line of defense is vaccination, although vaccines aren't always effective as sometimes they don't target all the circulating flu strains. Scientists around the world are seeking to develop a super vaccine to prevent all strains of the flu, but any breakthrough remains at least a decade away.

Less research has gone into developing new drugs to treat the flu once people are infected—only a handful of such treatments exist, including Tamiflu. Part of what makes the virus hard to tackle is that it invades human cells and tricks them into producing viral material instead of human proteins. Existing drugs allow the virus to hijack cells, working instead to block the viral material from escaping and infecting other cells. Some still escape, so the drugs slow the rate of infection without immediately containing it.

Feverish Activity

Cumulative flu hospitalization rate for each week since early October for the 2017-2018 season compared with previous seasons



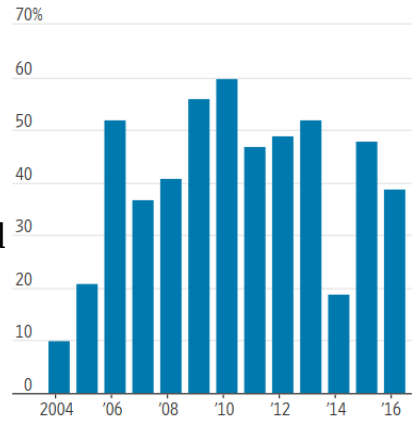
Source: Centers for Disease Control and Prevention

Shionogi scientists began researching a novel flu drug more than a decade ago, shelving almost 2,500 compounds in the process. Then, the 140-year-old Osaka company, which has created blockbuster drugs used to treat HIV and high cholesterol, had a breakthrough.

Shionogi scientists knew from their research that an anti-HIV drug the company had developed with a joint venture of Pfizer Inc. and GlaxoSmithKline Co. worked by blocking a metallic enzyme that HIV uses as a weapon to hijack human cells. They found the flu virus was also exploiting a metallic enzyme.

"So we said, 'why don't we build on our HIV knowledge to find a way to treat the flu?' And we did," said Takeki Uehara, who led the compound's development.

Seasonal flu vaccine effectiveness rate



Note: Dates are for the start of the flu season
Source: Centers for Disease Control and Prevention

A Roche spokesman said the compound proved significantly faster at killing the virus, and that its single-dose requirement was more convenient. He said the compound offered "improved tolerability" for participants over Tamiflu. Shionogi and Roche are in the final stages of conducting a second late-stage global trial.

J&J's drug division, Janssen, last month began late-stage trials involving one anti-flu compound named pimodivir, which blocks a different enzyme that allows the flu virus to multiply inside the human body, said Brian Woodfall, head of Janssen's infectious disease development.

Results from an earlier trial demonstrated that pimodivir "significantly decreased viral load over seven days," a company spokeswoman said. Pimodivir worked better in combination with Tamiflu. J&J will take several years to enroll patients in the trial, the spokeswoman said.

Separately, Janssen is researching a biologic injectable, which AstraZeneca and Merck-backed Visterra Inc. are also developing. These injections act like antidotes, attaching themselves to foreign

invaders, such as viruses, and then disabling them, while leaving healthy cells alone.

AstraZeneca's biologics unit said it is evaluating preliminary results from a mid-stage trial in patients. Future plans depend on the findings. Cambridge, Mass.-based Visterra said it began enrolling hospitalized flu patients in December for a mid-stage trial.

http://bit.ly/2o0Fimi

Clay tablets from the cradle of civilisation provide new insight to the history of medicine

Clay tablets from the Neo-Assyrian Empire's heyday document a man's education to become a doctor

February 12, 2018 by Bo Christensen,

Before the Greeks excelled in science and philosophy, culture was blooming in Mesopotamia, located between the Euphrates River and the Tigris River in present day Iraq.

This region, known as the cradle of civilisation, was the seat of the Neo-Assyrian Empire, which lasted from around 900 to 612 BCE.

Some historians consider the kingdom to be the first true empire in history and many Assyrian kings and cities are described in The Old Testament.

Clay tablets from ancient Mesopotamia provide an entirely new insight to early medical history. **The Trustees of the British Museum**

A Danish Ph.D. student has now analysed clay tablets from the Kingdom's heyday, in which a man called Kisir-Ashur documents his education to become a doctor, and how he combined magical rituals with medical treatments.

Some of the concepts of illness described by Kisir-Ashur and in other, similar texts, were perhaps handed down to the Greeks.

Some of the most detailed sources of ancient medical practices

The clay tablets were largely written by Kisir-Ashur at the end of the seventh century BCE. He is one of the earliest examples of a doctor, or at least something like a doctor, in terms of the level of detail of training and practice.

Researchers have known about the clay tablets for decades, but this is the first time that Kisir-Ashur's writings have been studied together. And they have turned out to be one of the most detailed accounts of ancient medical education and practice ever recorded.

"The sources give a unique insight into how an Assyrian doctor was trained in the art of diagnosing and treating illnesses, and their causes," says Dr. Troels Pank Arbøll from the Department of Cross-Cultural and Regional Studies, University of Copenhagen, Denmark. Arbøll studied the text as part of his Ph.D., which he recently defended.

"It's an insight into some of the earliest examples of what we can describe as science," he says.

Illness in Mesopotamia

The residents of Mesopotamia did not distinguish between what we today call magic and medicine. For them, disease was caused by supernatural forces such as gods and demons.

Treatment typically included identifying the illness according to the power that caused it. Then medical agents were applied to heal the disease and its symptoms, alongside rituals to appease the gods.

Some text, which researchers call "medical," consists of both diagnoses, descriptions of symptoms, prescriptions, incantations, prayers, and rituals.

Disease could be caused by sinful or objectionable behaviour, or it could be the result of witchcraft performed against the patient.

Illness was not the only type of divine punishment. Other examples include economic ruin or social exclusion. These problems were treated on the same level as physical illness by healers like Kisir-Ashur.

You might say that Mesopotamian healers focused a great deal on communicating with the patient about the problems.

New insights in the doctor's training

Kisir-Ashur recorded the treatments that he learned and used during and after his medical training.

He wrote his name, and often the purpose of the text. When you review the material chronologically, it reveals the progression of his training and practice, says Arbøll.

Kisir-Ashur may have learnt his skills by practising on animals and progressed to treating babies when he was close to finishing his studies.

"It's likely he did not treat human adults on his own before he was trained. This shows a relatively clear chronology in his training, where he takes on more and more responsibility," says Arbøll.

Magic and science: hand in hand

The texts reveal that religious or magical rituals were a regular part of treatment.

The title of the text is often translated as "exorcist," which is misleading as Kisir-Ashur was not working exclusively with the expulsion of spirits, says Arbøll.

"He does not work simply with religious rituals, but also with plant-based medical treatments. It is possible that he studied the effects of venom from scorpions and snakes on the human body and that he perhaps tried to draw conclusions based on his observations," says Arbøll.

It was widely assumed that medical treatments for scorpion stings and snakebites had not been recorded before, since they were most often treated by magic.

"Kisir-Ashur observed patients with bites or stings. Perhaps he did this to find out what the toxins had done to the body and from that, try to understand the venom's function," says Arbøll.

Mesopotamian scholarship could have spread to Europe

The ancient Mesopotamians may have believed that some diseases and liquids were connected. This was partly based on the idea that human bile was toxic, says Arbøll.

"At this time, bile is considered similar to a venomous substance. It can regulate certain bodily processes and could be the cause or contribution to the cause of an illness. This idea is reminiscent of the important Greek physician, Hypocrites' theory of humors, where the imbalance of four fluids in the body can be the cause of illness," he says.

"However, the Mesopotamian conception of bile seems to differ from the Greek. Moreover, Hippocrates lived some 200 years after Kisir-Ashur and the fall of the Assyrian Kingdom, so it is far from certain that the idea spread from Mesopotamia to the Greeks. But it would be interesting to investigate," says Arbøll.

"If there are relationships between ancient Mesopotamian medical knowledge and Hippocratic medicine, which I think there are, we must show these connections in text, which is not easy," writes Nils Heeßel, professor at the Philipps-Universität Marburg, Germany, in an email.

"General assumptions on a single doctor's academic focus can hardly be seen as a trace of later medical traditions," he writes.

A snapshot of history

Kisir-Ashur's clay tablets have been preserved for 2,700 years because the city of Ashur, together with Kisir-Ashur's family library were burnt down in the year 614 BCE, during the dissolution of the Neo-Assyrian Empire.

The library was preserved and first excavated by archaeologists at the beginning of the 20th century.

A large number of clay tablets were preserved well enough to be read, and the family library represents one of the most important collections of written sources from the Neo-Assyrian Empire.

People did not write theoretical works in Mesopotamia and the only way scientists can understand Assyrians' thoughts and views of the world is by collecting various sources and combining letters and commentaries on medical treatments.

"Great Piece of Work"

The study provides a micro-history of Kisir-Ashur's experiences in this specific town, at this particular time.

"It's a snapshot of history that is difficult to generalise and it is possible that Kisir-Ashur worked with the material in a slightly different way than other practising healers. Kisir-Ashur copied and recorded mostly pre-existing treatments and you can see that he catalogues knowledge and collects it with a specific goal," says Arbøll.

For Heeßel, this is the most exciting part of the thesis.

"It's a great piece of work and for me this micro-history of the ancient Near East is the most interesting aspect of the thesis. It's never been done before and I'm glad to see this concept used on our limited material in the region," he writes.

Professor Fredrik Norland Hagen, who studies medical history at the University of Copenhagen, Denmark, is similarly enthusiastic.

"The micro-historical perspective allows for a better understanding of how medicine in ancient Mesopotamia was practised and how medical knowledge was transmitted," says Hagen, a professor in Egyptology at the Department of Cross Cultural and Regional Studies. He was not involved in the research.

"He has written a new chapter in Mesopotamian medical history. It is solid work," says Hagen.

http://bit.ly/2Hh8yNO

Antibiotic hunters hit pay dirt

The solution to antibiotic resistance could come from soil.

Paul Biegler reports.

It might come as a surprise to learn that dirt, that canonical cause of infection, is also a megafactory for antibiotics.

Research, published in the journal *Nature Microbiology*, has exploited that facility to produce a new class of antibiotics, dubbed "malacidins", which are not only effective against that bane of modern hospitals, Golden Staph, but could pave the way for exponential increases in the rate of new antibiotic discovery.

Although some antibiotics are fully synthesised in the lab, most have come from the natural world, produced by fungi and bacteria as weapons to fight off other bugs that compete for nature's microbe-sustaining goodies.

Dirt, as anyone with a passing knowledge of infection control understands, is positively teeming with bacteria, for whom killing off rivals is pretty much a full-time job.

The upshot, write the researchers, led by Sean Brady, a chemical biologist at the Rockefeller University in New York, is that "environmental microbes are in a continuous antibiotic arms race that is likely to select for antibiotic variants capable of circumventing existing resistance mechanisms."

That could prove very useful; global deaths from antibiotic-resistant infections are predicted to rise more than tenfold, to 10 million a year, by 2050.

The team took their lead from the action of daptomycin, an antibiotic that uses calcium to disrupt bacterial cell walls, and distinguishes itself as a particularly strong performer against multidrug-resistant bugs.

They used a gene sequencing technique to probe samples, from their more than 2000-strong collection of soils, for antibiotics exhibiting a similar calcium-dependent action. This technique of widely interrogating the so-called "soil metagenome" is still in its infancy, but is replacing traditional culture methods which have fallen by the wayside as rates of new antibiotic discovery dwindled.

The researchers, quite literally, struck pay dirt.

They discovered a previously unknown class of antibiotic that deploys calcium in a novel way against bacterial cell walls. They named it, rather unparsimoniously, *metagenomic acidic lipopeptide antibiotic-cidins* – malacidins to you and me.

Applying malacidin-A to rat wounds infected with Golden Staph (more formally known as methicillin-resistant staphylococcus aureus), a bug whose presence in hospital patients generally presages the arrival of an infectious disease SWAT team, was decisive.

"At 24 and 72 [hours] post infection, malacidin-A treatment resulted in no observed bacterial burdens in the wounds," the researchers report.

There were, however, yet further good tidings.

"Our experimental efforts to induce resistance to malacidin in the laboratory have so far been unsuccessful. Even after 20 days of exposure to sub-lethal levels of malacidin-A, we did not detect any malacidin-resistant S. Aureus," they write.

The discovery brings to mind a homily from Brazilian author Paolo Coelho's novel *The Alchemist*, which, for infectious disease specialists contemplating the prospect of a trove of undiscovered, resistance-proof antibiotics, could well have new meaning.

The treasure, Coelho famously wrote, *is buried beneath your feet*.

http://nyti.ms/2suQMmV

Heart Stents Are Useless for Most Stable Patients. They're Still Widely Used.

Why are so many people agreeing to an expensive procedure — and putting themselves at risk — for a placebo effect?

By Aaron E. Carroll

When my children were little, if they complained about aches and pains, I'd sometimes rub some moisturizer on them and tell them the "cream" would help. It often did. The placebo effect is surprisingly effective.

Moisturizer is cheap, it has almost no side effects, and it got the job done. It was a perfect solution.

Other treatments also have a placebo effect, and make people feel better. Many of these are dangerous, though, and we have to weigh the downsides against that benefit.

Lots of Americans have chest pain because of a lack of blood and oxygen reaching the heart. This is known as angina. For decades, one of the most common ways to treat this was to insert a mesh tube known as a stent into arteries supplying the heart. The stents held the vessels open and increased blood flow to the heart, theoretically fixing the problem.

Cardiologists who inserted these stents found that their patients reported feeling better. They seemed to be healthier. Many believed that these stents prevented heart attacks and maybe even death. Percutaneous coronary intervention, the procedure by which a stent can be placed, became very common.

Then in 2007, a randomized controlled trial was published in The New England Journal of Medicine. The main outcomes of interest were heart attacks and death. Researchers gathered almost 2,300 patients with significant coronary artery disease and proof of reduced blood flow to the heart. They assigned them randomly to a stent with medical therapy or to medical therapy alone.

They followed the patients for years. The result? The stents didn't make a difference beyond medical treatment in preventing these bad outcomes.

This was hard to believe. So more such studies were conducted.

In 2012, the studies were collected in a meta-analysis in JAMA Internal Medicine. Three studies looked at patients who were stable after a heart attack. Five more examined patients who had stable angina or ischemia but had not yet had a heart attack. The meta-analysis showed that stents delivered no benefit over medical therapy for preventing heart attacks or death for patients with stable coronary artery disease.

Still, many cardiologists argued, stents improved patients' pain. It improved their quality of life. Even if we didn't reduce the outcomes that physicians cared about, these so-called patient-centered outcomes mattered, and patients who had stents reported improvements in these domains in studies.

The problem was that it was difficult to know whether the stents were leading to pain relief, or whether it was the placebo effect. The placebo effect is very strong with respect to procedures, after all. What was needed was a trial with a sham control, a procedure that left patients unclear whether they'd had a stent placed.

Many physicians opposed such a study. They argued that the vast experience of cardiologists showed that stents worked, and therefore randomizing some patients not to receive them was unethical. Others argued that exposing patients to a sham procedure was also wrong because it left them subject to potential harm with no benefit. More

skeptical observers might note that some doctors and hospitals were also financially rewarded for performing this procedure.

Regardless, such a trial was done, and the results were published this year.

Researchers gathered patients with severe coronary disease at five sites in Britain, and randomized them to one of two groups. All were given medication according to a protocol for a period of time. Then, the first group of patients received a stent. In the second, patients were kept sedated for at least 15 minutes, but no stent was placed.

Six weeks later, all the patients were tested on a treadmill. Exercise tends to bring out pain in such patients, and monitoring them while they're under stress is a common way to check for angina. At the time of testing, neither the patient nor the cardiologist knew whether a stent had been placed. And, based on the results, they couldn't figure it out even after testing: There was no difference in the outcomes of interest between the intervention and placebo groups.

Stents didn't appear even to relieve pain.

Some caveats: All the patients were treated rigorously with medication before getting their procedures, so many had improved significantly before getting (or not getting) a stent. Some patients in the real world won't stick to the intensive medical therapies, so there may be a benefit from stents for those patients (we don't know). The follow-up was only at six weeks, so longer-term outcomes aren't known. These results also apply only to those with stable angina. There may be more of a place for stents in patients who are sicker, who have disease in more than one blood vessel, or who fail to respond to medical therapy.

But many, if not most patients, probably don't need them. This is hard for patients and physicians to wrap their heads around because, in their experience, patients who got stents got better. They seemed to receive a benefit from the procedure. But that benefit appears to be because of the placebo effect, not any physical change from improved blood flow. The patients in the study felt better from a procedure in the same way that my children did when I rubbed moisturizer on them.

The difference is that while the moisturizer can't really harm, stent placement can. Even in this study, 2 percent of patients had a major bleeding event. Remember that hundreds of thousands of stents are placed every year. Stents are also expensive. They can add at least $10,000 to the cost of therapy.

Stents still have a place in care, but much less of one than we used to think. Yet many physicians as well as patients will still demand them, pointing out that they lead to improvements in some people, even if that improvement is from a placebo effect.

Stents are probably not alone in this respect. It's possible that many procedures aren't better than shams. Although we would never approve a drug without knowing its benefits above a placebo, we don't hold devices to the same standard. As Rita Redberg noted in The New England Journal of Medicine in 2014, only 1 percent of approved medical devices are approved by a process that requires the submission of clinical data, and that data is almost always from one small trial with limited follow-up. Randomized controlled trials are very rare. The placebo effect is not.

There seems to be a strong argument that we should be more conscious of what we are willing to risk, and what we are willing to pay, for a placebo effect. If we don't want to give up the benefit, should we design cheaper, safer fake procedures to achieve the same results? Is that ethical? Is it more unethical than charging people five figures and putting them at risk for serious adverse events?

It surely seems reasonable that stable patients with single-vessel disease should be informed that stents work no better than fake procedures, and no better than medical therapy. Some may still choose a stent. They should at least know what they're paying for.

Aaron E. Carroll is a professor of pediatrics at Indiana University School of Medicine who blogs on health research and policy at The Incidental Economist and makes videos at Healthcare Triage. He is the author of The Bad Food Bible: How and Why to Eat Sinfully. @aaronecarroll

http://go.nature.com/2sxkJD3

Stone Age people laid staked skulls in watery grave

Complex ritual included creation of stone pavement on lake bottom.

Prehistoric residents of what is now Sweden mounted the heads of some of their dead on wooden stakes before consigning them to the waters of a small lake.

Anna Kjellström at Stockholm University and her colleagues recovered two staked skulls and the remains of at least eight other individuals from an expanse of large, closely packed stones on a prehistoric lake bottom.

Ancient people in what is now Sweden mounted human skulls on wooden sticks, perhaps as a funerary display. **Adapted from Fredrik Hallgren/The Cultural Heritage Foundation.**

The people who laid the stones and deposited the remains were hunter-gatherers living 7,500 to 8,000 years ago.

Seven of those left in the lake had suffered blows to the skull well before their deaths. The proportion of damaged to undamaged skulls and the positions of the injuries suggest that the trauma resulted from violence, rather than accidents, the authors say.

http://bit.ly/2HiuQ1N

Medical care for wounded ants

The African Matabele ants (*Megaponera analis*) tend to the wounds of their injured comrades.

And they do so rather successfully: Without such attendance, 80 percent of the injured ants die; after receiving "medical" treatment, only 10 percent succumb to their injuries.

Erik T. Frank, Marten Wehrhan and Karl Eduard Linsenmair from Julius-Maximilians-Universität Würzburg (JMU) in Bavaria, Germany, made this astonishing discovery. Their results have been published in the journal *Proceedings of the Royal Society B*. No other insects are known to dress the wounds of their comrades. The JMU biologists even believe that such behaviour is unique in the entire animal kingdom.

Ants go on high-risk raids

Matabele ants have a high risk of getting injured every day: The insects, which are widely distributed in Sub-Saharan Africa, set out to raid termites two to four times a day.

Proceeding in long files of 200 to 600 animals, they raid termites at their foraging sites, killing many workers and hauling the prey back to their nest where they are ultimately eaten.

A Matabele ant treats the wounds of a mate whose limbs were bitten off during a fight with termite soldiers. **Photo: Erik T. Frank**

However, the ants meet fierce resistance from the well-armoured termite soldiers that are very adept at using their powerful jaws to fend off the attackers. Injury and mortality among the ants occur during such combats.

For example, the ants frequently lose limbs that are bitten off by termite soldiers. When an ant is injured in a fight, it calls its mates for help by excreting a chemical substance which makes them carry their injured comrade back to the nest. Erik T. Frank already described this rescue service in 2017.

But the Würzburg biologists dug deeper: What happens once the injured ants are back in the nest? The ants treat the open wounds of their injured fellows by "licking" them intensively, often for several minutes. "We suppose that they do this to clean the wounds and maybe even apply antimicrobial substances with their saliva to reduce the risk of bacterial or fungal infection," Frank explains.

Severely injured ants are left behind on the battlefield

The team from the JMU Biocentre uncovered more exciting details about the emergency rescue service of the Matabele ants. Badly injured

ants missing five of their six legs, for example, get no help on the battleground.

The decision who is saved and who is left behind is made not by the rescuers but by the injured ants themselves.

Slightly injured ants keep still and even pull in their remaining limbs to facilitate transport. Their badly injured counterparts in contrast struggle and lash out wildly. "They simply don't cooperate with the helpers and are left behind as a result," Frank says. So the hopeless cases make sure that no energy is invested in rescuing them.

Slightly injured ants keep still

When Matabele ants are only slightly injured, they move much more slowly than normal once potential helpers are near. This behaviour probably increases their chances of being noticed by the other ants rushing back to the nest in a column. Or it may be that ants can localize the "save-me-substance" more easily in resting ants.

More questions arise

The new insights give rise to new questions: How do ants recognize where exactly a mate was injured? How do they know when to stop dressing the wounds? Is treatment purely preventive or also therapeutic, after an infection has occurred?

Erik T. Frank will continue to tackle these and other questions at the University of Lausanne in Switzerland where he has been doing postdoc research since February 2018. He recently completed his doctoral thesis at JMU.

http://bit.ly/2F5V2Mb

Sleepless in Japan: How insomnia kills

It is possible that insomnia itself causes many of the conditions that it is seen as a symptom of

Laypeople tend to think that insomnia is usually a symptom of something else, like stress, a bad diet or a sedentary lifestyle, but this may not be true at all. It is possible that insomnia itself causes many of the conditions that it is seen as a symptom of.

Using previous research that shows that insomnia causes a decrease in blood flow in the front dorsal lobe of the brain, and correlates it with depression, the authors of a Japanese study recently published in De Gruyter's open access journal Open Medicine entitled 'Insomnia and depression: Japanese hospital workers questionnaire survey' seeks to establish a link between insomnia and depression.

Depression is a hidden killer. It is a condition that affects people all around the world. Suicide is one of the leading causes of death in Japan. The yearly financial cost to the Japanese economy of depression and suicide is estimated by UPI to be USD 4.1 billion. Middle-aged males, one of the groups that was found to suffer the highest rates of insomnia are also the likeliest to commit suicide.

In March of 2011, over 7000 hospital staff in ten hospitals in the district of Rosai were given a self-administered anonymous questionnaire. The questions included information about the respondent's gender, age, and medical profession, as well as questions about their sleeping history two weeks prior to responding to the survey, as well as detailing their overtime work, and their history of disease and chronic pain. It also asked them to assess their own feelings of depression and fatigue.

The results were alarming. Thirteen percent of men, and nineteen percent of women suffered from insomnia, and the medical profession with the highest rate of insomnia were nurses at twenty percent. For comparison, about ten percent of Americans suffer from chronic insomnia.

Chronic insomnia can lead to depression, and a better understanding of the link between the two conditions could be used to improve treatment, and prevent the condition from worsening while strengthening the world economy.

The hope is a survey will be developed for healthcare professionals (and other high-stress professions) that can identify insomnia before it becomes a problem.

Read the paper, for free, here: DOI: https://doi.org/10.1515/med-2017-0056

http://bit.ly/2CmwRpP

Prehistoric wine discovered in inaccessible caves forces a rethink of ancient Sicilian culture

Discovering traces of wine has big implications for the story archaeologists tell about ancient Sicilians

Author Davide Tanasi[1]

Monte Kronio rises 1,300 feet above the geothermally active landscape of southwestern Sicily. Hidden in its bowels is a labyrinthine system of caves, filled with hot sulfuric vapors. At lower levels, these caves average 99 degrees Fahrenheit and 100 percent humidity. Human sweat cannot evaporate and heat stroke can result in less than 20 minutes of exposure to these underground conditions.

Deep inside Monte Kronio, hot, humid and sulfurous caves held an ancient secret. **Giuseppe Savino, La Venta Esplorazioni Geografiche, CC BY-ND**

Nonetheless, people have been visiting the caves of Monte Kronio since as far back as 8,000 years ago. They've left behind vessels from the Copper Age (early sixth to early third millennium B.C.) as well as various sizes of ceramic storage jars, jugs and basins. In the deepest cavities of the mountain these artifacts sometimes lie with human skeletons.

Archaeologists debate what unknown religious practices these artifacts might be evidence of. Did worshipers sacrifice their lives bringing offerings to placate a mysterious deity who puffed gasses inside Monte Kronio? Or did these people bury high-ranking individuals in that special place, close to what was probably considered a source of magical power?

One of the most puzzling of questions around this prehistoric site has been what those vessels contained. What substance was so precious it might mollify a deity or properly accompany dead chiefs and warriors on their trip to the underworld?

Using tiny samples, scraped from these ancient artifacts, my recent analysis came up with a surprising answer: wine. And that discovery has big implications for the story archaeologists tell about the people who lived in this time and place.

The storage jars and their mysterious contents, left millennia ago in the recesses of Monte Kronio. **Davide Tanasi et al. 2017, CC BY-ND**

Analyzing scraping samples

In November 2012, a team of expert geographers and speleologists ventured once again into the dangerous underground complex of Monte Kronio. They escorted archaeologists from the Superintendence of Agrigento down more than 300 feet to document artifacts and to take samples. The scientists scraped the inner walls of five ceramic vessels, removing about 100 mg (0.0035 ounces) of powder from each.

I led an international team of scholars, which hoped analyzing this dark brown residue could shed some light on what these Copper Age containers from Monte Kronio originally carried. Our plan was to use cutting-edge chemical techniques to characterize the organic residue.

We decided to use three different approaches. Nuclear magnetic resonance spectroscopy (NMR) would be able to tell us the physical and chemical properties of the atoms and molecules present. We turned to scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM/EDX) and the attenuated total reflectance Fourier transform infrared spectroscopy (ATR FT-IR) for the elemental analysis – the chemical characterization of the samples.

These analysis methods are destructive: The sample gets used up when we run the tests. Since we had just that precious 100 mg of powder from each vessel, we needed to be extremely careful as we prepared the

samples. If we messed up the analysis, we couldn't just run it all over again.

We found that four of the five Copper Age large storage jars contained an organic residue. Two contained animal fats and another held plant residues, thanks to what we inferred was a semi-liquid kind of stew partially absorbed by the walls of the jars. But the fourth jar held the greatest surprise: pure grape wine from 5,000 years ago.

Presence of wine implies much more

Initially I did not fully grasp the import of such a discovery. It was only when I vetted the scientific literature on alcoholic beverages in prehistory that I realized the Monte Kronio samples represented the oldest wine known so far for Europe and the Mediterranean region. An incredible surprise, considering that the Southern Anatolia and Transcaucasian region were traditionally believed to be the cradle of grape domestication and early viticulture. At the end of 2017, research similar to ours using Neolithic ceramic samples from Georgia pushed back the discovery of trace of pure grape wine even further, to 6,000-5,800 B.C.

This idea of the "oldest wine" conveyed in news headlines captured the public's attention when we first published our results.

But what the media failed to convey are the tremendous historical implications that such a discovery has for how archaeologists understand Copper Age Sicilian cultures.

From an economic standpoint, the evidence of wine implies that people at this time and place were cultivating grapevines. Viticulture requires specific terrains, climates and irrigation systems. Archaeologists hadn't, up to this point, included all these agricultural strategies in their theories about settlement patterns in these Copper Age Sicilian communities. It looks like researchers need to more deeply consider ways these people might have transformed the landscapes where they lived.

The discovery of wine from this time period has an even bigger impact on what archaeologists thought we knew about commerce and the trade of goods across the whole Mediterranean at this time. For instance, Sicily completely lacks metal ores. But the discovery of little copper artifacts – things like daggers, chisels and pins had been found at several sites – shows that Sicilians somehow developed metallurgy by the Copper Age.

The traditional explanation has been that Sicily engaged in an embryonic commercial relationship with people in the Aegean, especially with the northwestern regions of the Peloponnese. But that doesn't really make a lot of sense because the Sicilian communities didn't have much of anything to offer in exchange for the metals. The lure of wine, though, might have been what brought the Aegeans to Sicily, especially if other settlements hadn't come this far in viticulture yet.

Ultimately, the discovery of wine remnants near gaseous crevices deep inside Monte Kronio adds more support to the hypothesis that the mountain was a sort of prehistoric sanctuary where purification or oracular practices were carried out, taking advantage of the cleansing and intoxicating features of sulfur.

Wine has been known as a magical substance since its appearances in Homeric tales. As red as blood, it had the unique power to bring euphoria and an altered state of consciousness and perception. Mixed with the incredible physical stress due to the hot and humid environment, it's easy to imagine the descent into the darkness of Monte Kronio as a transcendent journey toward the gods. The trek likely ended with death for the weak, maybe with the conviction of immortality for the survivors.

And all of this was written in the grains of 100 milligrams of 6,000-year-old powder.

[1]*Assistant Professor, Department of History and Center for Visualization and Applied Spatial Technologies (CVAST), University of South Florida*

Disclosure statement

Davide Tanasi does not work for, consult, own shares in or receive funding from any company or organisation that would benefit from this article, and has disclosed no relevant affiliations beyond their academic appointment.

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Blood thinners may raise stroke risk in over-65s with kidney disease

Warning that doctors should be more cautious about prescribing anticoagulants to those with chronic kidney disease

People over 65 years old may be increasing their stroke risk by taking anticoagulants for an irregular heartbeat if they also have chronic kidney disease, finds a new study led by UCL, St George's, University of London and the University of Surrey.

Based on their findings, published today in the BMJ, the researchers warn that doctors should be more cautious about prescribing anticoagulants, also known as blood thinners, in this population until more studies can clarify the consequences of doing so.

"Chronic kidney disease is common among older people, and one in three people affected also have atrial fibrillation, commonly called an irregular heartbeat - and for that, they typically get prescribed blood thinners to reduce their risk of stroke. We found that in this particular group, their medication seems to do the opposite of its intended effect," said the study's first author, Dr Shankar Kumar (UCL Centre for Medical Imaging).

The researchers estimate that close to half a million people over 65 in the UK have both chronic kidney disease and atrial fibrillation.

"People with chronic kidney disease tend to have numerous severe complications, including cardiovascular illnesses. As their blood clots more but they also bleed more easily, it is extremely difficult to strike a balance between different treatments," said senior author Professor John Camm, professor of clinical cardiology at St George's, University of London.

"As we found a paradoxical reduced mortality rate alongside increased rates of stroke and major bleeding, this is clearly a very complex area. We strongly call for randomised controlled studies to test the clinical value and safety of anticoagulant drug therapy for people with both atrial fibrillation and chronic kidney disease," said Dr Kumar.

In the population-based, retrospective cohort study, the researchers used a Royal College of General Practitioners database to identify 4848 people over 65 with chronic kidney disease and newly diagnosed atrial fibrillation, half of whom were on anticoagulants and half were not. The participants were monitored for a median of 506 days.

Over the study period, participants who were taking anticoagulants were 2.6 times as likely as those not on anticoagulants to have a stroke, and 2.4 times as likely to have a haemorrhage. The crude rates for ischaemic stroke (the most common type) were 4.6 per 100 person years for those on anticoagulants, and 1.5 for those not on blood thinners (in other words, if the participants were followed for exactly one year, there would be an estimated total of 4.6 ischaemic strokes per 100 people in the blood thinner group and 1.5 ischaemic strokes per 100 people not on blood thinners).

Mortality in the anticoagulant group was slightly lower; the researchers speculate it may have been due to a reduced risk of fatal strokes or heart attacks, but they say that more research is needed.

"Our work shows the power of big data in providing real world evidence to study important clinical scenarios. Until more data is available, general practitioners, nephrologists and cardiologists need to weigh up the risks and benefits of giving an anticoagulant and make a decision together with their patient," said co-author Professor David Goldsmith (Guy's and St Thomas' NHS Foundation Trust and St George's, University of London).

The study was conducted by researchers at UCL, St George's, University of London, the University of Surrey, Guys and St Thomas' Hospitals NHS Foundation Trust and NYU School of Medicine, USA.

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Poor fitness linked to weaker brain fiber, higher dementia risk

Scientists have more evidence that exercise improves brain health and could be a lifesaving ingredient that prevents Alzheimer's disease.

DALLAS – In particular, a new study from UT Southwestern's O'Donnell Brain Institute suggests that the lower the fitness level, the faster the deterioration of vital nerve fibers in the brain. This deterioration results in cognitive decline, including memory issues characteristic of dementia patients.

"This research supports the hypothesis that improving people's fitness may improve their brain health and slow down the aging process," said Dr. Kan Ding, a neurologist from the Peter O'Donnell Jr. Brain Institute who authored the study.

White matter

The study published in the *Journal of Alzheimer's Disease* focused on a type of brain tissue called white matter, which is comprised of millions of bundles of nerve fibers used by neurons to communicate across the brain.

Dr. Ding's team enrolled older patients at high risk to develop Alzheimer's disease who have early signs of memory loss, or mild cognitive impairment (MCI). The researchers determined that lower fitness levels were associated with weaker white matter, which in turn correlated with lower brain function.

Distinctive tactics

Unlike previous studies that relied on study participants to assess their own fitness, the new research objectively measured cardiorespiratory fitness with a scientific formula called maximal oxygen uptake. Scientists also used brain imaging to measure the functionality of each patient's white matter.

Patients were then given memory and other cognitive tests to measure brain function, allowing scientists to establish strong correlations between exercise, brain health, and cognition.

Lingering mysteries

The study adds to a growing body of evidence pointing to a simple yet crucial mandate for human health: Exercise regularly.

However, the study leaves plenty of unanswered questions about how fitness and Alzheimer's disease are intertwined. For instance, what fitness level is needed to notably reduce the risk of dementia? Is it too late to intervene when patients begin showing symptoms?

Some of these topics are already being researched through a five-year national clinical trial led by the O'Donnell Brain Institute.

The trial, which includes six medical centers across the country, aims to determine whether regular aerobic exercise and taking specific medications to reduce high blood pressure and cholesterol levels can help preserve brain function. It involves more than 600 older adults at high risk to develop Alzheimer's disease.

"Evidence suggests that what is bad for your heart is bad for your brain. We need studies like this to find out how the two are intertwined and hopefully find the right formula to help prevent Alzheimer's disease," said Dr. Rong Zhang of UT Southwestern, who oversees the clinical trial and is Director of the Cerebrovascular Laboratory in the Institute for Exercise and Environmental Medicine at Texas Health Presbyterian Hospital Dallas, where the Dallas arm of the study is being carried out.

Prior findings

The research builds upon prior investigations linking healthy lifestyles to better brain function, including a 2013 study from Dr. Zhang's team that found neuronal messages are more efficiently relayed in the brains of older adults who exercise.

In addition, other teams at the O'Donnell Brain Institute are designing tests for the early detection of patients who will develop dementia, and seeking methods to slow or stop the spread of toxic proteins associated with the disease such as beta-amyloid and tau, which are blamed for destroying certain groups of neurons in the brain.

"A lot of work remains to better understand and treat dementia," said Dr. Ding, Assistant Professor of Neurology & Neurotherapeutics. "But, eventually, the hope is that our studies will convince people to exercise more."

About the study

The study was supported in part by the National Institutes of Health and the American Heart Association. It included collaborations with staff at the Institute for Exercise and

Environmental Medicine and UT Southwestern's Alzheimer's Disease Center. Dr. Zhang is Professor of Neurology & Neurotherapeutics and Internal Medicine at UT Southwestern.

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Living human tracheas

Case Western Reserve University researchers engineer natural windpipe replacement alternative to synthetic scaffolding now being used

Biomedical engineers at Case Western Reserve University are growing tracheas by coaxing cells to form three distinct tissue types after assembling them into a tube structure-without relying on scaffolding strategies currently being investigated by other groups.

Successful trials and further research and development could someday allow surgeons the option of replacing damaged or faulty trachea with a fully functional natural-tissue trachea in both adults and children, said Eben Alsberg, professor in Biomedical Engineering and Orthopaedic Surgery and director of the Alsberg Stem Cell & Engineered Novel Therapeutics (ASCENT) Lab at Case Western Reserve University.

"The unique approach we are taking to this problem of trachea damage or loss is forming tissue modules using a patient's cells and assembling them like childhood toy Legos into a more complex tissue," said Alsberg, who is leading the research.

This step toward building living windpipe structures from self-assembled modules is explained in detail in the most recent issue of Advanced Science.

Co-authors include: Marsha Rolle, an associate professor of biomedical engineering from Worcester Polytechnic Institute in Worcester, Massachusetts; Hannah Strobel, a WPI graduate student; Calvin Cotton, a professor of pediatrics and physiology and biophysics at Case Western Reserve; and nine researchers from Alsberg's lab, including co-first authors Anna Dikina and Daniel Alt.

The research was supported by a $1.9 million grant from the National Institutes of Health's National Institute of Biomedical Imaging and Bioengineering.

The problem

The trachea, commonly called the windpipe, is the airway between the voice box and the lungs.

Patients may need a rebuilt trachea because of tumor resection or an injury that results in tracheal stenosis, a narrowing or constricting of the windpipe, which inhibits breathing.

Damage to or loss of trachea tissue can be life-threatening or lead to a significantly reduced quality of life, Alsberg said.

Doctors have limited solutions for patients with damaged tracheas.

If a portion of the trachea is damaged, for example, they can only surgically join the ends if less than half of the trachea is damaged in adults or less than 30 percent in children.

Other procedures, such as implanting a stent or simply clearing away tissue obstructing the airway, offer only short-term relief as the repaired tube tends to close off again after about a year.

Recent tissue-engineering approaches using synthetic or natural materials as scaffolding for cells have been met with challenges.

Difficulties have included uniformly seeding cells on the scaffolding, recreating the multiple different tissue types found in the native trachea, tailoring the scaffolding degradation rate to equal the rate of new tissue formation, and recreating important contacts between cells because of the intervening scaffold.

Improving upon current treatments

The trachea engineering strategy now being pursued at Case Western Reserve, however, wouldn't have those problems because it doesn't rely on a separate scaffold structure, Alsberg said.

According to Alsberg's research, a new trachea replacement must do three critical things to function properly:

maintain rigidity to prevent airway collapse when the patient breathes;

contain immunoprotective respiratory epithelium, the tissue lining the respiratory tract, which moistens and protects the airway and functions as a barrier to potential pathogens and foreign particles;

and integrate with the host vasculature, or system of blood vessels, to support epithelium viability.

The self-assembling rings developed by the Alsberg and Rolle labs meet all three of those requirements because they can fuse together to form tubes of both cartilage and "prevascular" tissue types.

Prevascular refers to tissues potentially ready to participate in the formation of blood vessels, though not yet functional in that way.

The cartilage rings are formed by aggregating marrow-derived-stem cells in ring-shaped wells.

Polymer microspheres containing a protein that induces the stem cells to become "chondrocytes," or cells that form cartilage, are also incorporated into the cell aggregates.

Rolle said it is the combining of those two things-the self-assembled tissue ring modules and the polymer microspheres-that "makes it possible to create the complex multi-tissue structure that makes up the trachea."

The prevascular rings are comprised of both these marrow-derived stem cells and endothelial cells, the thin layer of cells that line the interior of blood vessels.

The researchers then coat the tubes with epithelial cells to form multi-tissue constructs that satisfy all of those requirements: cartilage provides rigidity, epithelium serves the role of immunoprotection and the vascular network would ultimately permit blood flow to feed and integrate the new trachea tissue.

Using this method, Alsberg, Rolle and their team have been able to engineer highly elastic "neo-tracheas" of various sizes, including tissues similar to human trachea.

When these tracheas were implanted under the skin in mice, there was evidence the prevascular structures could join up with the host vascular supply.

"The hope is that a surgeon could implant the tissue tube into the body and it will grow and incorporate into the existing tissue," Alsberg said. "We're excited about this approach, as it may have broad applicability to bottom-up engineering of many other complex tissues and organs."

http://bit.ly/2ExtuhC

Cardiac macrophages found to contribute to a currently untreatable type of heart failure

Mass. General team's findings could lead to new treatment for impaired relaxation of heart muscle

A team of Massachusetts General Hospital (MGH) investigators has discovered, for the first time, that the immune cells called macrophages contribute to a type of heart failure for which there currently is no effective treatment. In their report published in the February issue of the *Journal of Experimental Medicine*, the MGH team describes finding how macrophage activity leads to the development of heart failure with preserved ejection fraction (HFpEF) in mouse models of the condition, which accounts for around half of all human heart failure cases.

"We show that macrophages - white blood cells primarily known for removing cellular debris, pathogens and other unwanted materials - are actively involved in the development of HFpEF," says Maarten Hulsmans, PhD, a research fellow in the MGH Center for Systems Biology and lead author of the paper. "These findings put macrophages on the map when it comes to HFpEF therapy and open up previously unexplored treatment options."

The concept of heart failure traditionally referred to a loss of the organ's pumping capacity, which is called systolic heart failure. But in HFpEF the heart retains the ability to pump or eject blood into the circulation. What is compromised is the ability of the heart muscle to relax and allow blood to flow into the left ventricle, reducing the amount of blood available to pump into the aorta. Symptoms of HFpEF are similar to those of heart failure in general, but since factors contributing to the condition are not well understood, it has been difficult to find promising therapies.

Interactions among cells within the heart - including macrophages - are essential to normal cardiac function but can also contribute to problems. For example, after the heart muscle is damaged by a heart attack, macrophages induce the cells called fibroblasts to generate the

connective tissues that help reinforce damaged tissue. But excessive fibroblast activation can lead to the distortion and stiffening of tissues, further reducing cardiac function.

To explore a potential role for macrophages in HFpEF, the MGH team examined cardiac macrophages in two mouse models that develop the sort of diastolic dysfunction - impaired relaxation of the heart muscle - that characterizes HFpEF.

Those animals were found to have increased macrophage density in the left ventricle and exhibited elevated levels of a factor called IL-10, which is known to contribute to fibroblast activation. Deletion of IL-10 from cardiac macrophages in one model, in which the development of hypertension is induced, prevented the upregulation of macrophages and reduced the numbers and activation of cardiac fibroblasts.

Levels of cardiac macrophages were also elevated in tissue biopsies from human patients with HFpEF, as were levels of circulating monocytes, which are precursors of macrophages.

"Not only were numbers of inflammatory cardiac macrophages increased in both the mice and in humans with HFpEF, but their characteristics and functions were also different from those in a healthy heart," says Hulsmans.

"Through their participation in the remodeling of heart tissue, these macrophages increase the production of extracellular matrix, which reduces diastolic relaxation. Our findings regarding the cell-specific knockout of IL-10 are the first to support the contribution of macrophages to HFpEF."

Senior author Mathias Nahrendorf, MD, PhD , of the Center for Systems Biology, adds, "Heart muscle cells and fibroblasts have been considered the major contributors to HFpEF. Our identification of the central involvement of macrophages should give us a new focus for drug development. And since macrophages naturally take up materials for disposal, inducing them to ingest drugs carried in by nanoparticles could limit their contributions to the development of HFpEF." Nahrendorf is a professor of Radiology at Harvard Medical School.

Additional co-authors of the Journal of Experimental Medicine paper include Anthony Rosenzweig, MD, MGH Cardiovascular Research Unit and Division of Cardiology; Filip Swirski, PhD, MGH Center for Systems Biology, and Flora Sam, MD, Boston University School of Medicine. Support for the study includes National Institutes of Health grants 5T32076136-12, HL122987, HL135886, TR000901, HL117153, HL117829, HL125428, and HL096576.

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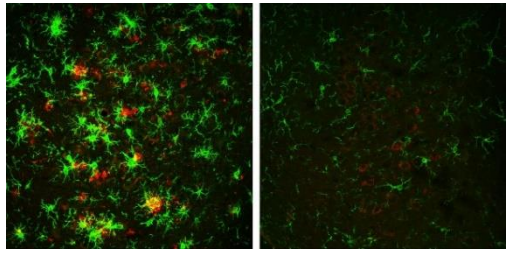
Researchers successfully reverse Alzheimer's disease in mouse model

Gradually depleting BACE1 completely reverses the formation of amyloid plaques in the brains of mice with Alzheimer's disease

A team of researchers from the Cleveland Clinic Lerner Research Institute have found that gradually depleting an enzyme called BACE1 completely reverses the formation of amyloid plaques in the brains of mice with Alzheimer's disease, thereby improving the animals' cognitive function.

The study, which will be published February 14 in the Journal of Experimental Medicine, raises hopes that drugs targeting this enzyme will be able to successfully treat Alzheimer's disease in humans.



The brain of a 10-month-old mouse with Alzheimer's disease (left) is full of amyloid plaques (red) surrounded by activated microglial cells (green). But these hallmarks of Alzheimer's disease are reversed in animals that have gradually lost the BACE1 enzyme (right). **Hu et al., 2018**

One of the earliest events in Alzheimer's disease is an abnormal buildup of beta-amyloid peptide, which can form large, amyloid plaques in the brain and disrupt the function of neuronal synapses. Also known as beta-secretase, BACE1 helps produce beta-amyloid peptide by cleaving amyloid precursor protein (APP). Drugs that inhibit BACE1 are therefore being developed as potential Alzheimer's disease treatments but, because BACE1 controls many important processes by cleaving proteins other than APP, these drugs could have serious side effects.

Mice completely lacking BACE1 suffer severe neurodevelopmental defects. To investigate whether inhibiting BACE1 in adults might be

less harmful, Riqiang Yan and colleagues generated mice that gradually lose this enzyme as they grow older. These mice developed normally and appeared to remain perfectly healthy over time.

The researchers then bred these rodents with mice that start to develop amyloid plaques and Alzheimer's disease when they are 75 days old. The resulting offspring also formed plaques at this age, even though their BACE1 levels were approximately 50% lower than normal. Remarkably, however, the plaques began to disappear as the mice continued to age and lose BACE1 activity, until, at 10 months old, the mice had no plaques in their brains at all.

"To our knowledge, this is the first observation of such a dramatic reversal of amyloid deposition in any study of Alzheimer's disease mouse models," says Yan, who will be moving to become chair of the department of neuroscience at the University of Connecticut this spring.

Decreasing BACE1 activity also resulted in lower beta-amyloid peptide levels and reversed other hallmarks of Alzheimer's disease, such as the activation of microglial cells and the formation of abnormal neuronal processes.

Loss of BACE1 also improved the learning and memory of mice with Alzheimer's disease. However, when the researchers made electrophysiological recordings of neurons from these animals, they found that depletion of BACE1 only partially restored synaptic function, suggesting that BACE1 may be required for optimal synaptic activity and cognition.

"Our study provides genetic evidence that preformed amyloid deposition can be completely reversed after sequential and increased deletion of BACE1 in the adult," says Yan. "Our data show that BACE1 inhibitors have the potential to treat Alzheimer's disease patients without unwanted toxicity. Future studies should develop strategies to minimize the synaptic impairments arising from significant inhibition of BACE1 to achieve maximal and optimal benefits for Alzheimer's patients."

Hu et al., 2018. J. Exp. Med. http://jem.rupress.org/cgi/doi/10.1084/jem.20171831?PR

http://bit.ly/2HoY0wl

China confirms first human case of H7N4 bird flu

Hong Kong is warning travellers to avoid any contact with poultry in China after a woman was confirmed with the first human case of the H7N4 strain of bird flu

China has confirmed the first human case of H7N4 bird flu, prompting Hong Kong to issue a health warning for those travelling to the mainland during the busy Lunar New Year holiday.

The strain was identified in a 68-year-old woman from the eastern province of Jiangsu who was admitted to hospital after falling ill on December 25 but had since recovered, according to China's National Health and Family Planning Commission.

"She had contact with live poultry before the onset of symptoms," Hong Kong's Centre for Health Protection said late Wednesday after being informed of the case by Chinese authorities, who said the virus genes were of avian origin.

The world's first human cases of bird flu were reported in Hong Kong in 1997, when six people were killed by the H5N1 strain of the virus. Hundreds more have died worldwide in subsequent outbreaks, especially of highly-virulent strains like H7N9.

The semi-autonomous southern Chinese city is a high-risk area for the spread of communicable diseases because of its high population density and busy regional and international transport links.

"Travellers to the mainland or other affected areas must avoid visiting wet markets, live poultry markets or farms," the Centre for Health Protection warned after the H7N4 strain was reported by China.

Authorities in China and Hong Kong did not provide further details on the H7N4 strain found in the woman, such as its virulence. An outbreak of this type of bird flu hit chickens in New South Wales, Australia, in 1997, according to World Health Organization records.

Hong Kong authorities are already battling a deadly flu outbreak, and were forced to shut down kindergartens and primary schools early for the Chinese New Year break.

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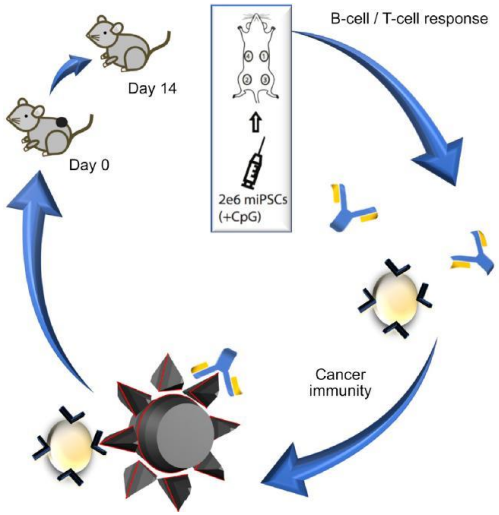
Stem cell vaccine immunizes lab mice against multiple cancers

Injecting mice with inactivated induced pluripotent stem cells launched a strong immune response against breast, lung, and skin cancers

Stanford University researchers report that injecting mice with inactivated induced pluripotent stem cells (iPSCs) launched a strong immune response against breast, lung, and skin cancers. The vaccine also prevented relapses in animals that had tumors removed. The work appears in the journal Cell Stem Cell on Feb. 15.



This visual abstract depicts how cancer immunity against multiple types of cancer can be achieved using an easily generable iPSC-based cancer vaccine. This immunity is based on overlapping epitopes between iPSCs and cancer cells and can also be achieved by reactivating the immune system as an adjuvant.
Kooreman and Kim et al./Cell Stem Cell

iPSCs are generated from adult cells genetically reprogrammed to mimic embryonic stem cells' ability to become any type of cell in the body.

In the study, 75 mice received versions of the iPSC vaccine created from iPSCs that have been inactivated by irradiation. Within four weeks, 70 percent of the vaccinated mice fully rejected newly introduced breast cancer cells, while the remaining 30 percent had significantly smaller tumors. The effectiveness of the iPSC vaccine was also validated for lung and skin cancers.

Lead author Joseph C. Wu at Stanford's Cardiovascular Institute and Institute for Stem Cell Biology and Regenerative Medicine and colleagues found that a large amount of the antigens present on iPSCs are also present on cancer cells. When lab mice were vaccinated with iPSCs, their immune systems built an immune response to the antigens on the iPSCs. Because of key similarities between the iPSCs and cancer cells, the animals simultaneously built an immune response against cancer.

The iPSCs seemed to "prime their immune systems to eradicate tumor cells," Wu says.

To be effective, anti-cancer vaccines must introduce one or more antigens into the body that activate T cells or produce antibodies capable of recognizing and binding to antigens on the surfaces of cancer cells.

One of the biggest challenges for cancer immunotherapies is the limited number of antigens that can be presented to the immune system at a given time. The Stanford study uses an animal's own cells to create an iPSC-based cancer vaccine that simultaneously targets multiple tumor antigens. Using whole iPSCs eliminates the need to identify the most optimal antigen to target in a particular type of cancer.

"We present the immune system with a larger number of tumor antigens found in iPSCs, which makes our approach less susceptible to immune evasion by cancer cells," Wu says. The researchers also combined iPSCs with an immunity booster--a snippet of bacterial DNA called CpG that has been deemed safe in human trials. Stanford oncologist and study co-author Ronald Levy previously found CpG to be a potent tumor-fighting agent.

In the future, a patient's skin or blood cells may be re-programmed into iPSCs and administered as an anti-cancer vaccine or as a follow-up booster after surgery, chemotherapy, or radiation therapy.

"What surprised us most was the effectiveness of the iPSC vaccine in re-activating the immune system to target cancer," Wu says. "This approach may have clinical potential to prevent tumor recurrence or target distant metastases."

This work was supported by the California Institute of Regenerative Medicine (CIRM) and the National Institutes of Health (NIH).

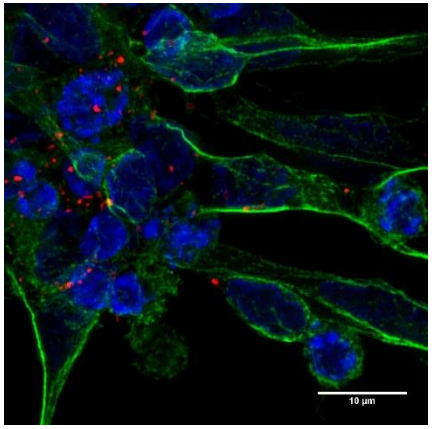
Cell Stem Cell, Kooreman and Kim et al.: "Autologous iPSC-Based Vaccines Elicit Anti-tumor Responses In Vivo" http://www.cell.com/cell-stem-cell/fulltext/S1934-5909(18)30016-X

http://bit.ly/2syxYTM

New stem-cell based stroke treatment repairs damaged brain tissue

Human clinical trials could begin as early as next year

Athens, Ga. - A team of researchers at the University of Georgia's Regenerative Bioscience Center and ArunA Biomedical, a UGA startup company, have developed a new treatment for stroke that reduces brain damage and accelerates the brain's natural healing tendencies in animal models. They published their findings in the journal *Translational Stroke Research*.



Exosomes, shown as small red punctate clusters, are taken up by neurons, shown as green cell extensions surrounding a blue nucleus. **Credit: UGA**

The research team led by UGA professor Steven Stice and Nasrul Hoda of Augusta University created a treatment called AB126 using extracellular vesicles (EV), fluid-filled structures known as exosomes, which are generated from human neural stem cells.

Fully able to cloak itself within the bloodstream, this type of regenerative EV therapy appears to be the most promising in overcoming the limitations of many cell therapies-with the ability for exosomes to carry and deliver multiple doses-as well as the ability to store and administer treatment. Small in size, the tiny tubular shape of an exosome allows EV therapy to cross barriers that cells cannot.

"This is truly exciting evidence, because exosomes provide a stealth-like characteristic, invisible even to the body's own defenses," said Stice, Georgia Research Alliance Eminent Scholar and D.W. Brooks Distinguished Professor in the College of Agricultural and Environmental Sciences. "When packaged with therapeutics, these treatments can actually change cell progression and improve functional recovery."

Following the administration of AB126, the researchers used MRI scans to measure brain atrophy rates in preclinical, age-matched stroke models, which showed an approximately 35 percent decrease in the size of injury and 50 percent reduction in brain tissue loss - something not observed acutely in previous studies of exosome treatment for stroke.

Outside of rodents, the results were replicated by Franklin West, associate professor of animal and dairy science, and fellow RBC members using a porcine model of stroke-the only one of its kind in the U.S.

Based on these pre-clinical results, ArunA Biomedical plans to begin human studies in 2019, said Stice, who is also chief scientific officer of ArunA Biomedical.

"Until now, we had very little evidence specific to neural exosome treatment and the ability to improve motor function," said Stice. "Just days after stroke, we saw better mobility, improved balance and measurable behavioral benefits in treated animal models."

Named as part of the 'stroke belt' region, Georgia continues to exceed the national average in stroke deaths, which is the third leading cause of death in the U.S., with more than 140,000 Americans dying each year, according to the Centers for Disease Control and Prevention.

ArunA recently unveiled advances to the company's proprietary neural cell platform for the production of exosome manufacturing. Today, ArunA's manufacturing process positions the company to produce AB126 exosomes at a scale to meet early clinical demand. The company has plans to expand this initiative beyond stroke for preclinical studies in epilepsy, traumatic brain and spinal cord injuries later this year.

Researchers also plan to leverage collaborations with other institutions through the National Science Foundation Engineering Research Center for Cell Manufacturing Technologies, based at the Georgia Institute of Technology and supported by $20 million in NSF funding.

Stice, the UGA lead for CMaT, and industry partners like ArunA Biomedical, will develop tools and technologies for the consistent and

low-cost production of high-quality living therapeutic cells that could revolutionize treatment for stroke, cancer, heart disease and other disorders.

The study, "Human Neural Stem Cell Extracellular Vesicles Improve Tissue and Functional Recovery in the Murine Thromboembolic Stroke Model," is available at https://link.springer.com/content/pdf/10.1007%2Fs12975-017-0599-2.pdf

Funding was supported by ArunA Biomedical, Inc., and R.L.S. was partially supported by the Science and Technology Center Emergent Behaviors of Integrated Cellular Systems (EBICS) Grant No. CBET-0939511.

http://bit.ly/2EMCpPJ

Fast-acting, readily available gas may mitigate blast-induced brain injury

The inert gas has been used for the first time to try and reduce the impact of traumatic brain injuries (TBI) caused by blasts such as those in conflict zones and terror attacks.

Traumatic brain injuries are frequently caused by blunt force trauma, but there has been an increase in TBIs caused by blasts (bTBIs). Blast TBI is one on the most common injuries experienced by soldiers in recent conflicts, and is dubbed a 'signature injury' of the conflicts in Iraq and Afghanistan. Civilians exposed to industrial accidents or terrorist attacks are also at risk.

Unlike blunt force trauma, where damage/injury is usually localised to one area of the brain, blasts create a shockwave that affects the whole brain - causing widespread damage. This can cause anxiety, depression, and problems with cognition, memory and sleep.

Previously, Dr Robert Dickinson and colleagues from Imperial College London showed that xenon gas helped limit brain damage and improve long term neurological outcomes in mice which had suffered blunt force brain injury.

Now, the same research group has found for the first time that xenon can also limit blast-induced brain injury from developing in mouse brain tissue exposed to a blast shockwave, in a study published in the Journal of Neurotrauma.

In this study, the researchers from Imperial's Department of Surgery and Cancer and the Royal British Legion Centre for Blast Injury Studies, applied xenon to slices of mouse brain tissue after exposing them to blast shockwaves that emulated those produced by improvised explosive devices (IEDs).

By using a dye that highlights damaged brain cells, they were able to monitor injury development in the slices up to three days after blast exposure. They compared slices given xenon treatment starting one hour after exposure to blast shockwaves, with slices exposed to blast without xenon treatment.

They then assessed injury development at 24, 48 and 72 hours after blast exposure, and found that the slices treated with xenon suffered significantly less blast-induced injury than the untreated control slices. The blast-injured slices treated with xenon were not significantly different to uninjured slices at 24 hours and 72 hours after injury, indicating that xenon prevented injury from developing.

Xenon reaches the brain within a few minutes after inhalation, so if these preliminary results translate to humans it could be a viable treatment option after blasts occur. Lead author Dr Rita Campos-Pires from Imperial said: "One of the most insidious aspects of TBI in general, and it is believed bTBI also, is that the damage can continue to grow long after the initial injury. The secondary injury can be many times worse than the primary injury, so our goal is to stop the damage from spreading as early as possible."

Xenon is used in hospitals as a general anaesthetic, so it is already known to be safe in humans. The authors say more research is needed before clinical trials in bTBI patients, but that their results are a positive step in this direction.

Dr Dickinson said: "Blast TBI has not been as widely studied as other types of brain trauma, but is now becoming recognised as a specific injury that can result in debilitating symptoms. Our discovery that xenon reduces blast-induced injury in mouse brain tissue is very encouraging, and will prompt further research in this area."

There is currently no standard treatment for bTBI. The authors say this preliminary research may be a first step before exploring xenon's benefits in humans who suffer bTBI. The next stage will be to test xenon in live rodents exposed to similar conditions.

The research was funded by the Royal Centre for Defence Medicine, the Royal British Legion Centre for Blast Injury Studies, the Medical Research Council and the Fundação para a Ciência e a Tecnologia, Portugal.

http://bit.ly/2HrnGbA

Infection outbreaks at hospitals could be reduced by copper-coated uniforms

Doctors, nurses and healthcare professionals could soon be wearing uniforms brushed with tiny copper nanoparticles to reduce the spread of bacterial infections and viruses, such as Escherichia coli (E. coli), at hospitals.

Material scientists at The University of Manchester, working in collaboration with universities in China, have created a 'durable and washable, concrete-like' composite material made from antibacterial copper nanoparticles.

They have also developed a way of binding the composite to wearable materials such as cotton and polyester, which has proved a stumbling block for scientists in the past.

Bacterial infection is a major issue in hospitals across the UK and has been rising due to its spread on surfaces and clothing. E. coli infections alone killed more than 5,500 NHS patients in 2015 and Government estimates put the cost of such infections to the NHS at £2.3 billion this year alone.

Precious metals, such as gold and silver, have excellent antibacterial and antimicrobial properties, but their commercial use in textiles is prohibitive due to extremely high costs. That means copper is the material of choice for researchers as it has very similar antibacterial properties to gold and silver but is much cheaper.

That's why material chemists are focussing their attentions on exploring the possibility of using copper as the ultimate antimicrobial agent.

However, prior to this breakthrough, techniques for binding copper to materials like cotton for medical and antimicrobial textile production had limitations.

Now, using a process called 'Polymer Surface Grafting', the research team has tethered copper nanoparticles to cotton and polyester using a polymer brush, creating a strong chemical bond.

The researchers say it is this bond which has led to excellent washable properties and durability. These developments could finally see copper-covered uniforms and textiles commercialised in the future.

Lead author, Dr Xuqing Liu, from the School of Materials, said: "Now that our composite materials present excellent antibacterial properties and durability, it has huge potential for modern medical and healthcare applications."

The researchers tested their copper nanoparticles on cotton as it is used more widely than any other natural fibre and polyester as it is a typical polymeric, manmade material. Each material was brushed with the tiny copper nanoparticles which measure between 1-100 nanometres (nm). 100nm is the equivalent to just 0.0001 millimetres (mm).

The team found their cotton and polyester coated-copper fabrics showed excellent antibacterial resistance against Staphylococcus aureus (S. aureus) and E. coli, even after being washed 30 times.

When compared with the traditional process of copper coating the polymer brush technique developed at the University is far more effective.

Dr Liu said: "These results are very positive and some companies are already showing interest in developing this technology. We hope we can commercialise the advanced technology within a couple of years. We have now started to work on reducing cost and making the process even simpler."

Reference, "Durable and Washable Antibacterial Copper Nanoparticles Bridged by Surface Grafting Polymer Brushes on Cotton and Polymeric Materials," Journal of Nanomaterials, Xuqing Liu. doi:10.1155/2018/6546193. vol. 2018, Article ID 6546193, 2018.

http://bit.ly/2BCMHQL

Not being aware of memory problems predicts onset of Alzheimer's disease

New research could provide clinicians with insights regarding clinical progression to dementia

Doctors who work with individuals at risk of developing dementia have long suspected that patients who do not realize they experience memory problems are at greater risk of seeing their condition worsen in a short time frame, a suspicion that now has been confirmed by a team of McGill University clinician scientists.

Some brain conditions can interfere with a patient's ability to understand they have a medical problem, a neurological disorder known as anosognosia often associated with Alzheimer's disease. In a study published today in *Neurology*, Dr. Pedro Rosa-Neto's team from McGill's Translational Neuroimaging Laboratory shows that individuals who experience this lack of awareness present a nearly threefold increase in likelihood of developing dementia within two years.

Joseph Therriault, a master's student in McGill's Integrated Program in Neuroscience and lead author of the paper drew on data available through the Alzheimer's Disease Neuroimaging Initiative (ADNI), a global research effort in which participating patients agree to complete a variety of imaging and clinical assessments.

Therriault analysed 450 patients who experienced mild memory deficits, but were still capable of taking care of themselves, who had been asked to rate their cognitive abilities. Close relatives of the patient also filled out the similar surveys. When a patient reported having no cognitive problems but the family member reported significant difficulties, he was considered to have poor awareness of illness.

Anosognosia is linked to Alzheimer's disease pathophysiology

Researchers then compared the poor awareness group to the ones showing no awareness problems and found that those suffering from anosognosia had impaired brain metabolic function and higher rates of amyloid deposition, a protein known to accumulate in the brains of Alzheimer's disease patients.

A follow up two years later showed that patients who were unaware of their memory problems were more likely to have developed dementia, even when taking into account other factors like genetic risk, age, gender and education. The increased progression to dementia was mirrored by increased brain metabolic dysfunction in regions vulnerable to Alzheimer's disease.

The finding provides crucial evidence about the importance of consulting with the patient's close family members during clinical visits.

"This has practical applications for clinicians: people with mild memory complaints should have an assessment that takes into account information gathered from reliable informants, such as family members or close friends," says Dr. Serge Gauthier, co-senior author of the paper and Professor of Neurology & Neurosurgery, Psychiatry and Medicine at McGill.

"This study could provide clinicians with insights regarding clinical progression to dementia," adds Dr. Rosa-Neto, co-senior author of the study and clinician scientist and director of the McGill Center for Studies in Aging, a research center affiliated with the Montreal West Island IUHSSC. The scientists are now taking this research further by exploring how awareness of illness changes across the full spectrum of Alzheimer's disease, and how these changes are related to critical Alzheimer's biomarkers.

This study was supported by the Canadian Institutes of Health Research, the Alan Tiffin Foundation, the Alzheimer's Association, the Fonds de Recherche du Québec-Santé, and the Centre for Studies on Prevention of AD.

«?Anosognosia predicts default mode network hypometabolism and clinical progression to dementia?», by J. Therriault et al., was published in Neurology.

http://bit.ly/2GqEe1R

Researchers find existing drug effective at preventing onset of type 1 diabetes

Common blood pressure medication blocks molecule that can trigger the disease

AURORA, Colo. - A drug commonly used to control high blood pressure may also help prevent the onset of type 1 diabetes in up to 60 percent of those at risk for the disease, according to researchers at the University of Colorado Anschutz Medical Campus and the University of Florida in Gainesville. The study was published online this week in the Journal of Clinical Investigation. "This is the first personalized treatment for type 1 diabetes prevention," said Aaron Michels, MD, a researcher at the Barbara Davis Center for Childhood Diabetes and associate professor of medicine at CU Anschutz. "We made this discovery using a supercomputer, on the lab bench, in mice and in humans."

The drug, methyldopa, has been used for over 50 years to treat high blood pressure in pregnant women and children. It is on the World Health Organization's list of essential drugs. But like many drugs used for one condition, Michels and his colleagues found it useful for something totally unrelated.

Some 60 percent of people at risk of getting type 1 diabetes possess the DQ8 molecule which significantly increases the chance of getting the disease. The researchers believed that if they could block specifically the DQ8 molecule they could also block the onset of the disease.

"All drugs have off-target effects. If you take too much acetaminophen you can hurt your liver," Michels said. "We took every FDA approved small molecule drug and analyzed HLA-DQ8 binding through a supercomputer. We searched a thousand orientations for each drug to identify those that would fit within the DQ8 molecule binding groove."

After running thousands of drugs through the supercomputer, they found that methyldopa not only blocked DQ8, but it didn't harm the immune function of other cells like many immunosuppressant drugs do.

The research spanned 10 years and its efficacy was shown in mice and in 20 type 1 diabetes patients who took part in a clinical trial at the Barbara Davis Center for Childhood Diabetes at the University of Colorado School of Medicine.

"We can now predict with almost 100 percent accuracy who is likely to get type 1 diabetes," Michels said. "The goal with this drug is to delay or prevent the onset of the disease among those at risk." The drug is taken orally, three times a day.

Michels and fellow researcher David Ostrov, PhD, hope this same approach of blocking specific molecules can be used in other diseases.

"This study has significant implications for treatment of diabetes and also other autoimmune diseases," said Ostrov, associate professor at the University of Florida College of Medicine's Center for NeuroGenetics. "This study suggests that the same approach may be adapted to prevent autoimmune diseases such as rheumatoid arthritis, coeliac disease, multiple sclerosis, systemic lupus erythematosus and others."

The next step will be a larger clinical trial sponsored by the National Institutes of Health in spring. "With this drug, we can potentially prevent up to 60 percent of type 1 diabetes in those at risk for the disease," Michels said. "This is very significant development."

The other authors of the study include: Aimon Alkanani of the Barbara Davis Center at CU Anschutz; Kristen McDaniel of the Barbara Davis Center; David Ostrov of the University of Florida in Gainesville; Stephanie Case of the Barbara Davis Center; Erin Baschal of the Barbara Davis Center; Laura Pyle of the Barbara Davis Center and Colorado School of Public Health; Sam Ellis of the Barbara Davis Center and Dept. of Clinical Pharmacy at CU Anschutz; Bernadette Pollinger at the Novartis Institutes for Biomedical Research in Basel, Switzerland; Katherine Seidl at Novartis; Viral Shah at the Barbara Davis Center; Satish Garg at the Barbara Davis Center; Mark Atkinson at the University of Florida and Peter Gottlieb at the Barbara Davis Center.

http://bit.ly/2sBWGCF

First Documented Case of Transgender Mother Breastfeeding

Doctors report that a regimen of hormones, an antiemetic drug, and pumping gave the woman enough milk production to feed her baby exclusively breastmilk for six weeks.

By Kerry Grens | February 15, 2018

Two New York physicians report that, for the first time, a transgender woman has been able to breastfeed her child, and did so for six weeks. The 30-year-old patient of theirs took hormones and an anti-nausea medication for three months, after which she was producing eight ounces of milk per day, the doctors reported in Transgender Health this

January. Two weeks later, her partner gave birth and the baby's growth and development progressed well during six weeks of exclusive breastfeeding from the transgender mom, after which the parents began supplementing with formula.

"There have been self-reported cases online of transgender women trying DIY regiments to induce breastfeeding, but this is the first case of induced functional lactation in the academic literature," one of the doctors, Tamar Reisman of Mount Sinai hospital, tells The Guardian.

Boston Medical Center's Joshua Safer, who did not treat the mom, tells New Scientist that transgender women tend to have "good breast development," and that it's not surprising this individual would be able to produce milk with the tissue. "This is very special. It will be very important for the many transgender women who want to breastfeed but do not feel they have the opportunity to do so."

http://nyti.ms/2GnQKiK

The Flu Vaccine Is Working Better Than Expected, C.D.C. Finds

This year's vaccine is about 25 percent effective against the H3N2 strain of flu that is causing most illnesses and deaths

By DONALD G. McNEIL Jr. FEB. 15, 2018

The flu vaccine is more effective than expected, federal health officials said on Thursday at a special news conference held to discuss the dangerous flu season, which is expected to kill more than 50,000 Americans.

This year's vaccine is about 25 percent effective against the H3N2 strain of flu that is causing most illnesses and deaths, said Dr. Anne Schuchat, acting director of the Centers for Disease Control and Prevention. In a bigger surprise, the vaccine is about 51 percent effective in children, according to the C.D.C.'s preliminary analysis.

In Australia, the same vaccine was rated about 10 percent effective overall against H3N2, and a recent Canadian analysis found it to be about 17 percent effective there. (The C.D.C.'s final analysis will not be ready until the flu season ends in late spring.)

Dr. Schuchat and Alex M. Azar II, the new secretary of health and human services who led the news conference, also pointed to a C.D.C. study published Monday in the journal Pediatrics showing that two-thirds of the 675 children and teenagers who died of flu between 2010 and 2016 had not gotten the vaccine the year they died.

"Go get a flu shot!" Mr. Azar said loudly as he ended his portion of the news conference. "Do it for yourself, your family and your community!" He, his wife and his children had all had flu shots, he said, and so had President Trump.

The vaccine is 39 percent effective overall, Mr. Azar said, and 59 percent effective in children. He compared the vaccine to seatbelts.

"Imagine if we could cut our chances of being in a car crash by 39 percent, or our child's by 59 percent," he said. The comparison was only partly correct but very apt. The figures refer to the effectiveness of the vaccine against all circulating strains, including H1N1 and B strains, which have only barely begun to appear this year.

But seatbelts are a telling analogy for flu shots. Studies done since the 1970s have shown them to be only about 40 percent protective against preventing *any* injury in a crash.

But they are highly protective against death; that is, when crashes are so severe that some occupants are killed while others live, it is almost always the ones not wearing belts who die.

Likewise, studies like the C.D.C.'s suggest that flu shots do a better job of preventing death than preventing sniffles and aches.

Mr. Azar's news conference, at H.H.S. headquarters, was brief and unusual. It was held midafternoon on only a few hours' notice. It was televised, but no questions were taken from outside the room.

The event ended with a large panel of experts awaiting questions. Only one was asked: whether administration officials wished they had done anything differently about flu this year.

Dr. Schuchat replied by describing problems that vaccine makers face. She did not address a bigger issue of concern to the C.D.C.: Only about

40 percent of Americans get flu shots each year by the time the season begins in November, and that number has been going down, not up.

The Trump administration and its top health officials have been criticized for showing little public leadership as the flu season became more dangerous. The news conference appeared to be an attempt to remedy that.

Mr. Azar was followed at the podium by Dr. Schuchat and Dr. Jerome Adams, the surgeon general, both in naval uniforms. They were referred to on the podium as “admirals” — which is correct, because they hold ranks in the Public Health Service Commissioned Corps, although the use of their military titles in medical settings is somewhat unusual.

Also on the dais were Dr. Anthony S. Fauci, director of the National Institute for Allergy and Infectious Diseases; Dr. Scott Gottlieb, commissioner of the Food and Drug Administration; and Dr. Robert P. Kadlec, assistant secretary for preparedness and response at H.H.S.

But they had little to say because the session ended abruptly.

http://bit.ly/2o899JU

Drug that treats psoriasis also reduces aortic vascular inflammation

Penn-led randomized trial shows 19 percent improvement over placebo group

PHILADELPHIA - An antibody used to treat the skin disease psoriasis is also effective at reducing aortic inflammation, a key marker of future risk of major cardiovascular events. Researchers from the Perelman School of Medicine at the University of Pennsylvania, in collaboration with the National Heart, Lung, and Blood Institute, led a randomized, double-blind, placebo-controlled study and found patients who took the drug ustekinumab had a 19 percent improvement in aortic inflammation, as measured and confirmed by imaging, when compared to the placebo group. Joel M. Gelfand, MD MSCE, a professor of Dermatology and Epidemiology at Penn and the study's first author, will present the findings at the 2018 American Academy of Dermatology Annual Meeting in San Diego tomorrow.

Psoriasis is a chronic inflammatory disease that causes skin cells to multiply faster than normal resulting in raised, red patches covered by silvery scales. It occurs most commonly on the scalp, knees, and elbows but can appear anywhere on the body including the face, genitals, nails, and other places. In moderate to severe cases, it carries an increased risk of heart attack, stroke, and premature death, a finding established by Gelfand in a 2006 landmark study. The National Psoriasis Foundation estimates psoriasis affects about 7.5 million Americans.

Ustekinumab, sold under the name Stelara, is approved by the U.S. Food and Drug Administration to treat psoriasis, psoriatic arthritis, and Crohn's Disease. Researchers wanted to know if the benefits of the drug go beyond clearing the skin.

"The type of inflammation we see in psoriasis is similar to what we see in atherosclerosis - a type of heart disease that involves the build-up of fats, cholesterol, and inflammatory cells in the artery walls," Gelfand said. "Since ustekinumab blocks the specific pathways involved in in both skin and cardiovascular inflammation, we wanted to test whether it can improve aortic vascular inflammation."

Psoriasis patients were randomly divided into two groups, with 21 patients in the placebo group and 22 patients receiving the treatment. The primary outcome was aortic inflammation, as measured by 18-FDG-PET/CT scans - an imaging technique that reveals inflammation in the aorta. The imaging was performed before treatment and at 12 weeks. The treatment group saw a 6.6 percent decrease in aortic inflammation, while the placebo group saw a 12 percent increase, meaning the drug is responsible for a 19 percent improvement relative to untreated patients. As expected, ustekinumab also resulted in a dramatic improvement in skin inflammation as well, with 77 percent of treated patients achieving a 75 percent or better improvement in psoriasis activity, compared to just 10.5 percent in the placebo group. Both findings were highly statistically significant (p?0.001).

The results are consistent with a previous, smaller uncontrolled trial of ustekinumab, but they are in direct contrast to two large trials using a different drug called adalimumab, which is sold as Humira.

"This is the first placebo-controlled trial of a biologic drug to show a benefit in aortic inflammation, a key marker of cardiovascular disease," Gelfand said. "The effect is similar to what we would expect if we put the patient on a statin."

Gelfand, who conducted the study in collaboration with Nehal N. Mehta, MD MSCE, Chief of the Section of Inflammation and Cardiometabolic Diseases at the National Heart, Lung, and Blood Institute, confirmed their results by having a second, separate lab independently evaluate imaging data. "This study represents promise that this treatment may reduce the risk of heart attack and stroke in the future. It's an encouraging finding," Gelfand said.

The trial is ongoing, and Gelfand says his team will evaluate these patients at a longer follow up to see if the effects are sustainable and if patients continue to improve.

The study was supported by Janssen Scientific Affairs, LLC, which manufactures ustekinumab. Additional support came from the National Institutes of Health (K24-AR064310, Z01-HL006193-003).

Editor's note: Gelfand is a consultant and has received honoraria from Janssen Biologics, which is owned by the same parent company as the maker of the drug.

http://bit.ly/2FcSxYz

Even without the clean power plan, US can achieve Paris Agreement emissions reductions

CMU researchers point out that there are many paths to compliance

Carnegie Mellon University researchers have calculated that the U.S. can meet--or even beat--the near-term carbon dioxide emission reductions required by the United Nations Paris Agreement, despite the Trump Administration's withdrawal of the Clean Power Plan (CPP).

Published in an *Environmental Science & Technology* viewpoint, the CMU team used data from U.S. Energy Information Administration's 2017 Annual Energy Outlook to examine projected power sector carbon dioxide emissions to determine if the CPP emission targets for 2020, 2025 and 2030 can still be met. They found that emissions declined from 2.7 billion tons to an estimated 1.9 billion tons and revealed a strong link to natural gas prices as being a driving market force. The decrease puts U.S. emissions reduction at the CPP's planned 2025 target this year.

"The U.S. has already come quite far in reducing carbon dioxide emissions. The biggest driver of lower carbon dioxide emissions has been declining natural gas prices, which has allowed the industry to replace coal-fired power plants economically with cleaner natural gas power plants--and without a costly regulatory mandate," said Jeffrey J. Anderson, a doctoral candidate in the Department of Engineering and Public Policy.

Additional actions are needed to assure longer-term compliance with Paris Agreement objectives--and to safeguard against the impact of a rise in natural gas prices. For example, regulatory and legislative focuses should be on maintaining the trajectory that the market forces have created to sustain the current transition period into the intermediate future. To meet longer-term and deeper de-carbonization goals, there will be a need for proactive regulatory activity. In addition, incentivizing low or zero carbon dioxide-emitting sources, improving energy efficiency and encouraging repowering and retrofitting options are other important avenues to de-carbonizing the power sector.

"Our work shows that the U.S. power sector could meet the Paris Agreement goals even without the Clean Power Plan, and that the path to compliance can be a collection of politically feasible, minimally invasive actions--if we plan ahead and start now," said David Rode, a recent Ph.D. graduate from the Department of Social and Decision Sciences.

In addition to Anderson and Rode, Paul Fischbeck, professor of social and decision sciences and engineering and public policy, and Haibo Zhai, associate research professor of engineering and public policy, worked on this research and article.

Read the viewpoint: https://pubs.acs.org/doi/10.1021/acs.est.8b00407

http://bit.ly/2Fd5rpx

First Blood Test for Concussion Approved by FDA

The diagnostic measures two proteins indicative of brain injury.

By Kerry Grens | February 16, 2018

This week (February 14), the US Food and Drug Administration (FDA) approved the first blood-based screening test for concussions. The diagnostic, which measures the abundance of the proteins UCH-L1 and GFAP, can help identify which patients should be sent for a CT scan to confirm any brain damage. “This is going to change the testing paradigm for suspected cases of concussion,” Tara Rabin, a spokesperson for the FDA, tells The New York Times.

In the approval announcement, the FDA stated that the test accurately predicted the presence of “intracranial lesions” 97 percent of the time, and appropriately indicated that there were none 99 percent of the time. In doing so, the screen could avoid CT scans for one-third of people who have a possible mild traumatic brain injury.

“It doesn’t replace CT in all cases,” Jay Alberts, director of the Cleveland Clinic Concussion Center, tells NBC News. “The reason you do those scans is to rule out a clinically important brain injury, which would need surgery. . . . But in 99 percent of concussions you do not need a CT scan because they’re not clinically important, meaning there’s not an immediate need for surgery.”

The FDA says the test could be used for the general population, and will be especially helpful to the military.

http://bit.ly/2sEKjG0

Japanese researchers develop ultrathin, highly elastic skin display

Device displays electrocardiogram recorded by skin sensor, holds promise for home healthcare applications

A new ultrathin, elastic display that fits snugly on the skin can show the moving waveform of an electrocardiogram recorded by a breathable, on-skin electrode sensor. Combined with a wireless communication module, this integrated biomedical sensor system - called "skin electronics" - can transmit biometric data to the cloud.

This latest research by a Japanese academic-industrial collaboration, led by Professor Takao Someya at the University of Tokyo's Graduate School of Engineering, is slated for a news briefing and talk at the AAAS Annual Meeting in Austin, Texas on February 17th.

Thanks to advances in semiconductor technology, wearable devices can now monitor health by first measuring vital signs or taking an electrocardiogram, and then transmitting the data wirelessly to a smartphone. The readings or electrocardiogram waveforms can be displayed on the screen in real time, or sent to either the cloud or a memory device where the information is stored.

The newly-developed skin electronics system aims to go a step further by enhancing information accessibility for people such as the elderly or the infirm, who tend to have difficulty operating and obtaining data from existing devices and interfaces. It promises to help ease the strain on home healthcare systems in aging societies through continuous, non-invasive health monitoring and self-care at home.

The new integrated system combines a flexible, deformable display with a lightweight sensor composed of a breathable nanomesh electrode and wireless communication module. Medical data measured by the sensor, such as an electrocardiogram, can either be sent wirelessly to a smartphone for viewing or to the cloud for storage. In the latest research, the display showed a moving electrocardiogram waveform that was stored in memory.

The skin display, developed by a collaboration between researchers at the University of Tokyo's Graduate School of Engineering and Dai Nippon Printing (DNP), a leading Japanese printing company, consists of a 16 x 24 array of micro LEDs and stretchable wiring mounted on a rubber sheet.

"Our skin display exhibits simple graphics with motion," says Someya. "Because it is made from thin and soft materials, it can be deformed freely."

The display is stretchable by as much as 45 percent of its original length. It is far more resistant to the wear and tear of stretching than previous wearable displays. It is built on a novel structure that minimizes the stress resulting from stretching on the juncture of hard materials, such as the micro LEDs, and soft materials, like the elastic wiring - a leading cause of damage for other models.

It is the first stretchable display to achieve superior durability and stability in air, such that not a single pixel failed in the matrix-type display while attached snugly onto the skin and continuously subjected to the stretching and contracting motion of the body.

The nanomesh skin sensor can be worn on the skin continuously for a week without causing any inflammation. Although this sensor, developed in an earlier study, was capable of measuring temperature, pressure and myoelectricity (the electrical properties of muscle), it successfully recorded an electrocardiogram for the first time in the latest research.

The researchers applied tried-and-true methods used in the mass production of electronics - specifically, screen printing the silver wiring and mounting the micro LEDs on the rubber sheet with a chip mounter and solder paste commonly used in manufacturing printed circuit boards. Applying these methods will likely accelerate the commercialization of the display and help keep down future production costs.

DNP is looking to bring the integrated skin display to market within the next three years by improving the reliability of the stretchable devices through optimizing its structure, enhancing the production process for high integration, and overcoming technical challenges such as large-area coverage.

"The current aging society requires user-friendly wearable sensors for monitoring patient vitals in order to reduce the burden on patients and family members providing nursing care," says Someya. "Our system could serve as one of the long-awaited solutions to fulfill this need, which will ultimately lead to improving the quality of life for many."

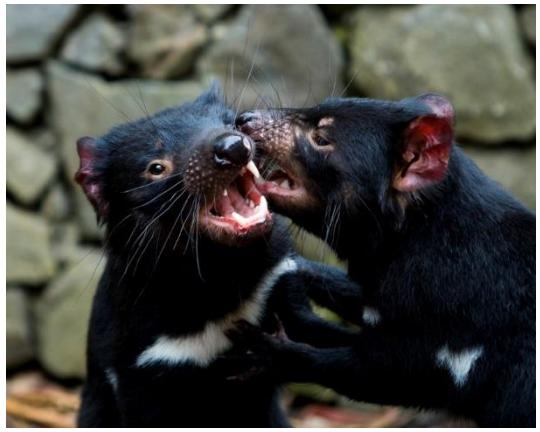
Event: *2018 AAAS Annual Meeting Symposium, Austin, Texas, February 17, 2018*
News briefing: 11:00 a.m.
Scientific Session: "Biomedical Sensors: Advances in Health Monitoring and Disease Treatment," 3:30 - 5:00 p.m.
Talk: "Continuous Health-Monitoring With Ultraflexible On-Skin Sensors," 3:30 - 4:00 p.m. (part of above Scientific Session symposium)
Collaborating Institution: *Dai Nippon Printing Co., Ltd.*

http://bit.ly/2EPvpBK

Faced with extinction, the devils fight back

Research finds clues that Tasmanian devils are adapting to the cancer that threatens their existence.

Andrew P Street reports.



In a very welcome piece of good news about Tasmanian devils (*Sarcophilus harrisii*), new University of Tasmania research on the contagious facial tumour disease currently afflicting wild populations seems to indicate that the marsupials are evolving to live with the cancer, according to a new paper in the journal *Bioessays*.

Tasmanian devils, locked in an evolutionary arms race with a killer cancer.
Dave Walsh / VW Pics / UIG via Getty Images

The researchers looked at animals at risk of catching transmissible cancer, known as devil facial tumour disease (DFTD), which has been driving the species toward possible extinction over the past two decades, and found unexpected signs of immunity, including elevated levels of certain immune system molecules which reduce their likelihood of getting the disease.

"Active immune responses to DFTD and even tumour regression have recently been observed in several animals, showing a very promising sign that could be exploited for the management of the species," says

lead author Beata Ujvari from Deakin University's School of Life and Environmental Sciences in Melbourne, Australia.

The researchers say the adaptations made by the devils in response to the disease can be described as an "evolutionary arms-race between malignant cells and their hosts".

"All the evidence suggests that devils have the capacity to adapt to this transmissible cancer at genetic and phenotypic levels," explains co-author Rodrigo Hamede, from the University of Tasmania. "We have been observing natural selection in action, and this has happened in a very short amount of time."

Part of the devil's arsenal is promiscuity: since individuals mate with multiple partners they maintain a diverse genetic pool which in turn increases the chances of responding to DFTD.

However, while the devils have been evolving, so has the disease. A second strain, DFT2, was described three years ago and future mutations seem inevitable. However, the threat of the species' imminent extinction in the wild appears to have been paused – for now, at least.

http://bit.ly/2GqMXkG

Blood and urine tests developed to indicate autism in children

Test believed to be the first of its kind

Link found between autism and damage to proteins in blood plasma

Could lead to earlier diagnosis of the condition

New tests which can indicate autism in children have been developed by researchers at the University of Warwick.

The academic team who conducted the international research believe that their new blood and urine tests which search for damage to proteins are the first of their kind.

The tests could lead to earlier detection of autism spectrum disorders (ASD) and consequently children with autism could be given appropriate treatment much earlier in their lives.

ASDs are defined as developmental disorders mainly affecting social interaction and they can include a wide spectrum of behavioural problems. These include speech disturbances, repetitive and/or compulsive behaviour, hyperactivity, anxiety, and difficulty to adapt to new environments, some with or without cognitive impairment. Since there is a wide range of ASD symptoms diagnosis can be difficult and uncertain, particularly at the early stages of development.

The paper "Advanced glycation endproducts, dityrosine, and arginine transporter dysfunction in autism -- a source of biomarkers for clinical diagnosis" has been published in Molecular Autism. The team was led by Dr Naila Rabbani, Reader of Experimental Systems Biology at the University of Warwick who said: "Our discovery could lead to earlier diagnosis and intervention."

"We hope the tests will also reveal new causative factors. With further testing we may reveal specific plasma and urinary profiles or "fingerprints" of compounds with damaging modifications. This may help us improve the diagnosis of ASD and point the way to new causes of ASD."

The team which is based at the University's Warwick Medical School involves academics at the University of Warwick's Warwick Systems Biology group, the University of Birmingham, the University of Bologna, the Institute of Neurological Sciences, Bologna, and the Don Carlo Gnocchi Foundation ONLUS. They found a link between ASD and damage to proteins in blood plasma by oxidation and glycation - processes where reactive oxygen species (ROS) and sugar molecules spontaneously modify proteins. They found the most reliable of the tests they developed was examining protein in blood plasma where, when tested, children with ASD were found to have higher levels of the oxidation marker dityrosine (DT) and certain sugar-modified compounds called "advanced glycation endproducts" (AGEs).

Genetic causes have been found in 30-35% of cases of ASD and the remaining 65-70% of cases are thought to be caused by a combination of environmental factors, multiple mutations, and rare genetic variants. However the research team also believe that the new tests could reveal yet to be identified causes of ASD.

The team's research also confirmed the previously held belief that mutations of amino acid transporters are a genetic variant associated with ASD. The Warwick team worked with collaborators at the University of Bologna, Italy, who recruited locally 38 children who were diagnosed as having with ASD (29 boys and nine girls) and a control group of 31 healthy children (23 boys and eight girls) between the ages of five and 12. Blood and urine samples were taken from the children for analysis.

The Warwick team discovered that there were chemical differences between the two groups. Working with a further collaborator at the University of Birmingham, the changes in multiple compounds were combined together using artificial intelligence algorithms techniques to develop a mathematical equation or "algorithm" to distinguish between ASD and healthy controls. The outcome was a diagnostic test better than any method currently available.

The next steps are to repeat the study with further groups of children to confirm the good diagnostic performance and to assess if the test can identify ASD at very early stages, indicate how the ASD is likely to develop further to more severe disease and assess if treatments are working.

Title: Advanced glycation endproducts, dityrosine, and arginine transporter dysfunction in autism--a source of biomarkers for clinical diagnosis

Published in: Molecular Autism DOI 10.1186/s13229-017-0183-3