Anti-cancer immunotherapy could be used to fight HIV

CRCHUM researchers are exploring a potential therapeutic approach

Researchers at the University of Montreal Hospital Research Centre (CRCHUM) have shown that immunotherapy treatments against cancer could reduce the amount of virus that persists in people on triple therapy. In a study published in the journal *Nature Communications*, they show, in the cells of people living with HIV, how these therapies reveal the virus – until now hidden in the hollows of infected cells – to the immune system.

"We identified the mechanism by which anti-cancer immunotherapy 'awakens' the virus from its hiding places and reduces the size of HIV reservoirs in people on triple therapy. Although most of our experiments have been performed in vitro, our approach could lead to the development of new therapies," stated Nicolas Chomont, a CRCHUM researcher and Université de Montréal professor.

HIV reservoirs are cells and tissue in which the virus persists despite triple therapy. This treatment prevents the infection from developing into acquired immunodeficiency syndrome (AIDS). To survive and replicate, HIV needs to be hosted in a cell. As a rule, it infects CD4+ T lymphocytes, white blood cells responsible for activating the body's defenses against infections.

The virus remains dormant in these cells and builds a reservoir that is controlled, but not eliminated by antiretroviral drugs. The subject of intense study, these reservoir cells are the last hurdle in eradicating the virus and force people living with HIV to take antiretroviral drugs

for the rest of their lives.

In 2016, Rémi Fromentin, a research associate in Nicolas Chomont's laboratory, showed that the cells housing the persistent viruses have specific immunological characteristics: three proteins called PD-1, LAG-3 and TIGIT, that are frequently expressed at their surface. Today these molecules are the target of immunotherapies used to treat cancer. The researchers decided to evaluate the effect of these therapies on HIV reservoirs.

A strategy evaluated in a small number of people with HIV and cancer

"Our results prove that immunotherapies targeting molecules such as PD-1 could reduce the amount of virus persisting in people on triple therapy. One of the next steps would be to combine immunotherapy with molecules that, up to now, have been ineffective in eradicating HIV reservoirs. This combination of immunotherapy and chemical molecules could 'awaken' the virus and help remove the cells infected by HIV," added Chomont.

In this article, Rémi Fromentin and Nicolas Chomont also present data from a patient in Montreal infected with HIV and treated by immunotherapy for a melanoma.

"The size of the patient's HIV reservoirs decreased significantly, which is encouraging. However, we must remain cautious, because this doesn't work with all patients. These treatments also cause considerable side effects," indicated Fromentin. The results of clinical trials currently underway in the United States on patients with cancer and HIV should help guide future research.

Nearly 37 million people around the world live with HIV. Every

day, 5,000 cases are reported to global health authorities.

Source:

https://www.chumontreal.qc.ca/

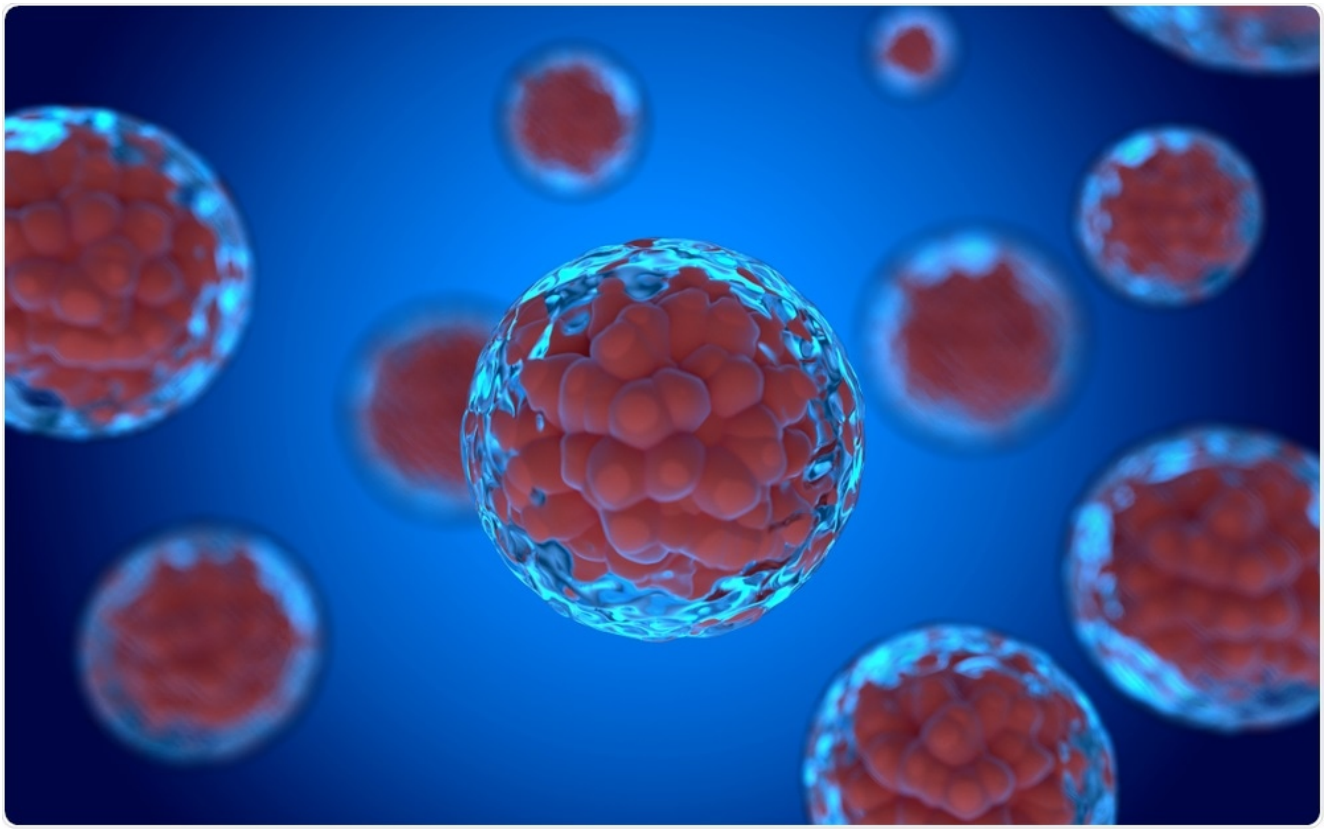
Customized Micropatterning for Improved Physiological Relevance

Sponsored Content by AlveoleFeb 18 2019

News-Medical speaks to Marie-Charlotte Manus from Alvéole, to find out about a new technology called PRIMO that improves the physiological relevance of cells in culture by giving researchers the ability to customize the cellular microenvironment.

What is the cellular microenvironment and how does it influence cellular mechanisms?

The cellular microenvironment is defined as the environment surrounding cells. Like organisms, cells are sensitive to their environment and respond to it. Within an organism (*in vivo*), this microenvironment is highly complex and dynamic, containing other cells with which one cell will interact, various molecules, and a specific stiffness (think of bones compared to the skin for instance), amongst others.



m63085 | Shutterstock

These mechanical and biochemical factors are sensed by the surrounding cells, inducing a response. In addition, the microenvironment can impact cell proliferation, differentiation, and development.

What is micropatterning and how is this technique used by cell biologists?

Micropatterning is an *in vitro* technique which involves creating protein patterns on a substrate, upon which living cells can adhere. This allows researchers to mimic some *in vivo* conditions or to study the intracellular mechanism in a very controlled and reproducible way.

To give you some more precise examples, researchers can force cells to be confined on a specific shape which could mimic the shape it would have adopted in an organism. This technique can

also be used to create lines of molecules on which cells can move and migrate allowing researchers to study and better understand the mechanism involved in this process.

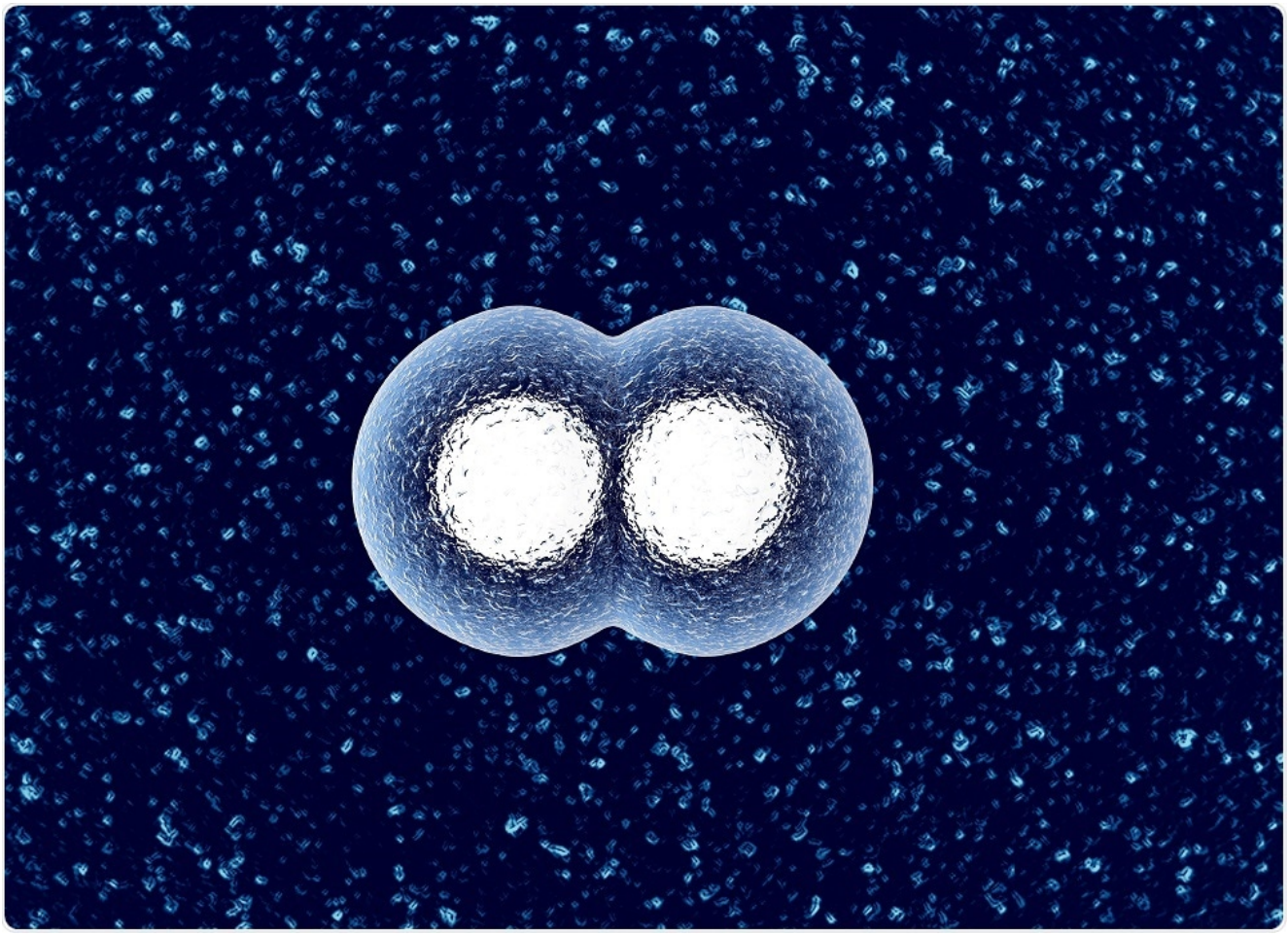
Micropatterning can also allow researchers to isolate and study single cells, but also to place one cell to a specific distance from another cell and see if they interact and how.

Why are current micropatterning techniques considered to be laborious and over complicated?

Actually, it is the optimization of the right protein micropatterns which is a laborious process.

Using current techniques, you would need to create a sort of stencil (called a mask) with specific shapes on it and use this to create your protein micropattern. But, if for some unknown reason, the shape you used doesn’t suit the cells you are studying, you need to create a new protein micropattern and therefore to create a new stencil or order already micropatterned substrates.

It is for this reason that we developed PRIMO, a technology that allows you to draw the shape you want to use and simply project it onto the substrate. The system allows you to create a micropattern within minutes. If you need to use another pattern, you simply draw a new shape and project it.



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Please can you describe the PRIMO micropatterning platform in more detail?

The PRIMO technique is based on LIMAP technology (Light Induced Molecular Adsorption of Proteins) and combines a maskless and contactless photolithography system (PRIMO) controlled by a dedicated piece of software (named “Leonardo”) and a specific photoactivatable reagent (PLPP).

The combined action of UV and PLPP makes it possible to generate, in only a few seconds, any multi-protein pattern on standard cell culture substrates.

A few months ago, we updated our technology so that it now goes further, not only controlling the biochemistry of the

microenvironment but also enabling researchers to control the topography and stiffness of the microenvironment which can have a huge impact on cell behavior and function.

As a photopatterning system, PRIMO can be used for microfabrication to create microstructured substrates and recreate the shape of *in vivo* microenvironments in 3D. The UV projected on a photosensitive material will react with it (polymerization) and stiffened it accordingly to the projected shape.

Why is the physiological relevance of cells in culture important, and how does PRIMO provide this?

Every cell within a living organism is constantly interacting with its environment. This means that if you study them in an environment that is completely different to the one in which they would naturally evolve in “real life” in an organism, you do not know if their behavior is “normal” and representative of *in vivo* conditions. This makes it almost impossible to evaluate the physiological effects of a small molecule.

PRIMO allows scientists to fine-tune the topography, stiffness, and biochemistry of the cell microenvironment, making it possible for researchers to create and work with a controlled reproducible microenvironment. All of this leads to better *in vitro* cell models and reproducible results that are physiologically relevant.

What are the major benefits of this technology, compared to previous

techniques?

The major benefit of PRIMO is the flexibility and versatility that it provides: with one tool, researchers can tune several parameters of the microenvironment simply by drawing the shape they want to create and then visualize and project it thanks to our optical module, PRIMO.

Another huge benefit is that the technique is reproducible. You define precise parameters, size, UV dose for the illumination, location, protein or material used, and the Leonardo software than launches a sequence which you can later replicate.

How is PRIMO advancing research?

PRIMO is the perfect tool to define and quickly optimize experimental conditions. It allows researchers to save time and design experiments they couldn’t have done with other techniques.

As PRIMO allows to control the mechanical and biochemical parameters of the microenvironments, it opens new possibilities for creating relevant physiological and pathological *in vitro* cell models, that mimic *in vivo* conditions for stem cells differentiation, cardiomyocytes contractility or spheroid formation for instance.

Alvéole is known for its innovative approach to laboratory science. What’s next for the company?

We are working on making this technology more automatable so that researchers can save even more time on the experimental steps and more time analyzing the results. Our overall goal is

to accelerate scientific research.

To this end, we launched 2 new products in January:

1. A robot called Nomos which automates the rinsing steps for micropatterning
2. A new form of photo-initiator, PLPP Gel, which accelerates the speed of protein micropatterning up to 30 times compared to our previous photo-initiator.

Where can readers find more information?

About Marie-Charlotte Manus

Marie-Charlotte Manus is the Operational Marketing Manager for Alvéole. She graduated with a Master's Degree in Biology and Marketing from the Rennes 1 University, she completed her training with a placement year in England.

After finishing her studies, she joined the Thalgo cosmetic laboratories, first in communication and then in the training department for national and international distributors. She then managed the international communication and events of an international network.

Marie-Charlotte joined Alvéole in March 2016 and uses her dual competences in Biology and Marketing to develop the company's operational tools.

About Alvéole

Alvéole is a Deep Tech company founded in 2010 by three researchers from the French National Center for Scientific Research (CNRS) collaborating with Quattrocento, a ‘creator of Deep Tech companies in the life sciences field’ allowing academic researchers to transform their inventions into marketed products.

The young company, headed by Romuald Vally, CEO since 2016, has 12 staff, combining multidisciplinary R&D skills with biologists, chemists and physicists. The company’s ambition is to become the benchmark for in vitro cell environment creation tools with more reliable

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Unique gene therapy approach paves new way to tackle rare, inherited diseases

Nonsense mutations are single-letter errors in the genetic code that prematurely halt the production of critical proteins. These unfinished proteins are unable to function normally, and nonsense mutations cause 10-15 percent of all inherited genetic diseases, including Duchenne muscular dystrophy, spinal muscular atrophy, cystic fibrosis and polycystic kidney disease. There is currently no cure or broadly effective treatment for these often devastating conditions that are individually rare but estimated to collectively affect up to 30 million people worldwide.

A new study, led by Christopher Ahern, PhD, at the University

of Iowa Carver College of Medicine, reveals a novel approach and robust technology platform for suppressing nonsense mutations using engineered transfer RNA (tRNA) molecules. The research by Ahern, his UI colleagues, and collaborators at The Wistar Institute in Philadelphia, the Cystic Fibrosis Foundation Therapeutics Lab in Lexington, Mass., and Integrated DNA Technologies Inc. in Coralville, Iowa, shows that modified tRNAs can efficiently and accurately repair nonsense mutations with any amino acid. The findings were published Feb. 18 in *Nature Communications*.

“Because nonsense mutations cause a wide range of severe, life threatening diseases, there is a significant unmet medical need to efficiently repair these stop codons in people having these inherited genetic alterations,” says Ahern, UI professor of molecular physiology and biophysics and a member of the Iowa Neuroscience Institute. “Our unique gene therapy approach takes advantage of the built-in fidelity of the translation process but reengineers tRNAs to turn disease-causing stop signals back into the correct amino acid. Basically, our anticodon engineered tRNA technology turns ‘stops’ into ‘gos’ and hopefully one day may be used to correct defective genetic sequences in people.”

The process of turning genetic code into protein is called translation. Transfer RNAs (tRNAs) match up with the blueprint code of the messenger RNA and deliver the correct amino acid in the correct order to build the protein. The code sequences of the messenger RNA, which dictate the order of amino acids, are called codons. The matching sequence on the tRNAs are called anticodons.

At the end of every protein coding sequence there is a genetic stop signal—a stop codon—that tells the protein production machinery to halt. Nonsense mutations occur when a mistake in the genetic sequence turns an amino acid codon in the middle of the protein into a stop codon.

Ahern and his UI team, including lead study author John Lueck, PhD, who is now at the University of Rochester, systematically tested the engineered tRNA molecules for their ability to repair premature stop codons with each of the 20 natural amino acids. The high-throughput screen efficiently identified multiple potent engineered tRNAs for each amino acid and stop codon type.

To demonstrate that the approach could work in more complex and physiologically relevant systems, Ahern lab members, together with collaborators at the Cystic Fibrosis Foundation Therapeutics (CFFT) lab and the laboratory of David Weiner, PhD, at The Wistar Institute showed that the engineered tRNAs when encoded and formulated for efficient delivery are expressed at high levels and are effective at correcting nonsense mutations in living mouse muscle tissue. Interestingly, the tRNA activity persisted for weeks in the delivered forms, suggesting this sustainable gene therapy approach may have potential for being used in the clinic one day.

Importantly, the team at the CFFT lab under William Skach, MD, showed that the tRNAs were selective in their activity and did not affect normal stop codons that signal the true end of the protein sequence.

And at the UI, Ahern with postdoctoral fellows Lueck and Danny Infield, PhD, and UI professor of pediatrics and cystic fibrosis expert Paul McCray, MD, showed that the approach could correct a CF-causing nonsense mutation and accurately produce a functional CFTR protein.

“What I like about this study is that a number of different labs with different expertise all verified our engineered tRNA technology in a variety of contexts,” Ahern says. “That suggests the approach is robust.”

Although he is excited about the potential for anticodon

engineered tRNAs to tackle diseases caused by nonsense mutations, Ahern notes there are many scientific questions to answer and technical hurdles to overcome to find out if this approach can be translated into human therapies.

“For many diseases caused by nonsense mutations, even correcting a small percent of the mutated protein could be enough to be therapeutic to the patient,” Ahern says. “If this were to work as a human therapy, we would have a way to target every known stop codon disease.”

Activating gene that helps excite neurons reverses depression in male mice

Directly activating a gene important to exciting our excitatory neurons and associated with major depression may help turn around classic symptoms like social isolation and loss of interest, at least for males, scientists report.

They looked in the prefrontal cortex, a brain area involved in complex behaviors like planning, personality and social behavior and known to have an important role in the pathogenesis of major depression, and found that making the SIRT1 gene inactive in excitatory neurons there created symptoms of depression in male mice, they report in the journal *Molecular Psychiatry*.

When, like in real life, stress not direct gene manipulation caused depression, a drug that activated SIRT1, reversed the symptoms in the males, says molecular behavioral neuroscientist Dr. Xin-Yun Lu.

“It has an antidepressant-like effect,” says Lu, the study’s corresponding author, a professor in the Department of Neuroscience and Regenerative Medicine at the Medical College of Georgia at Augusta University and Georgia Research Alliance Eminent Scholar in Translational Neuroscience.

That means drugs that activate SIRT1 and enable the usual high level of activity of these excitatory neurons might one day be an effective therapy for some with major depression, says Lu. Major depression is one of the most common mental disorders in the United States, affecting nearly 7 percent of adults, according to the National Institute of Mental Health.

The firing of excitatory neurons is definitely decreased in depression, and neurons are not communicating as they should. “It’s like they are disconnected,” says Lu. Problems like manic behavior and seizures, on the other hand, indicate excessive firing.

It’s hard to get excited without energy, and another of SIRT1’s known roles in brain cells is regulating cell powerhouses, called mitochondria. The scientists found that at least part of the way knocking out SIRT1 in males impacted the excitability of these normally excited neurons was by reducing the number of cell powerhouses and the expression of genes involved in powerhouse production.

The depressed behaviors they saw as a result are another indicator of SIRT1’s importance in that region to mood regulation and how without it, there is insufficient excitation of neurons. So was the resolution of stress-induced depression in male mice when they activated SIRT1 that had been deactivated by stress, the scientists say.

They note surprise at the lack of impact in female mice since the SIRT1 variant was first identified in a large gene study of depressed women. They suspect physical differences in this front region of the brain, like differences in the numbers of

neurons and synapses between males and females, could help explain the sex differences they found. Lu is already looking to see if she finds similar sex disparities in the hippocampus, another brain region important in depression as well as other conditions like Alzheimer's.

Still, depressed mice and humans act similarly, Lu says, which includes an impaired ability to feel pleasure called anhedonia. So they used the mice's usual high preference for a sweet, sucrose solution, as one way to gauge their depression.

"You give them a choice and they will drink that," she says. "But if you stress them, they won't lose their preference necessarily but it will reduce their interest." Males also forego their normal social nature and instead become loners. They even lose their interest in sex and in sniffing the females' pheromones.

Lu, who is also a pharmacologist, plans to look at existing drugs, including some older drugs never used for depression, to see if any have an impact on SIRT1 like the research drug they used.

Depression is generally considered caused by a combination of genetic and environmental factors. Lu says some individuals likely are born with the SIRT1 variant identified in genome-wide association studies, which predisposes them to depression, although environmental factors must also come into play for depression to happen. She notes that the SIRT1 variant is likely rare and only associated with depression rather than considered causative.

The prefrontal cortex is known to have a role in emotional responses and involved in controlling neurotransmitters, like serotonin, which are key to mood regulation. The severity of depression correlates with the degree of inactivity of that brain region, Lu and her colleagues write.

A 2015 study in the journal Nature reported genome-wide

studies of 5,303- Chinese women with major depressive disorder and 5,337 controls identified a variant of the SIRT1 gene as one of two variants associated with the disorder. Those scientists later replicated the finding in males.

Lu notes the magic of finding it in the females in the large human study was likely because of the consistent severity of the disease and the fact that all the women were from a similar region.

Source:

https://www.augusta.edu/mcg/

Science Puzzling Out Differences in Gut Bacteria Around the World

THURSDAY, Feb. 14, 2019 – Scientists say nearly 2,000 previously unknown types of bacteria in the human gut have been identified.

The human gut hosts many species of microbes, collectively referred to as the gut microbiota. Scientists are working to identify the individual species and understand the roles they play in human health.

While investigators are getting closer to completing a list of common microbes in the guts of North Americans and Europeans, there is a significant lack of data from other regions of the world.

Some microbes remain unidentified because of their low numbers in the gut or because they can't survive outside it.

For this study, researchers at the European Molecular Biology Laboratory's European Bioinformatics Institute (EMBL-EBI) and the Wellcome Sanger Institute in England used a number of computational methods to analyze gut bacteria samples from people worldwide and reconstruct the bacteria's genomes.

These methods allow scientists to understand bacteria they cannot yet culture in a lab, according to Rob Finn, a team leader at EMBL-EBI.

"Using metagenomics [the study of genetic material directly from environmental samples] to reconstruct bacterial genomes is a bit like reconstructing hundreds of puzzles after mixing all the pieces together, without knowing what the final image is meant to look like, and after completely removing a few pieces from the mix just to make it that bit harder," he explained in a laboratory news release.

"Researchers are now at a stage where they can use a range of computational tools to complement and sometimes guide lab work, in order to uncover new insights into the human gut," Finn said.

The findings highlight how gut bacteria differ worldwide and the need for samples from around the world, according to the researchers.

"We are seeing a lot of the same bacterial species crop up in the data from European and North American populations," Finn said. "However, the few South American and African datasets we had access to for this study revealed significant diversity

not present in the former populations."

Finn said collecting data from underrepresented populations is essential to getting a comprehensive picture.

Studies like this one are helping researchers create a blueprint of the human gut, said Trevor Lawley, group leader at the Wellcome Sanger Institute.

"In the future [this] could help us understand human health and disease better, and could even guide diagnosis and treatment of gastrointestinal diseases," Lawley said.

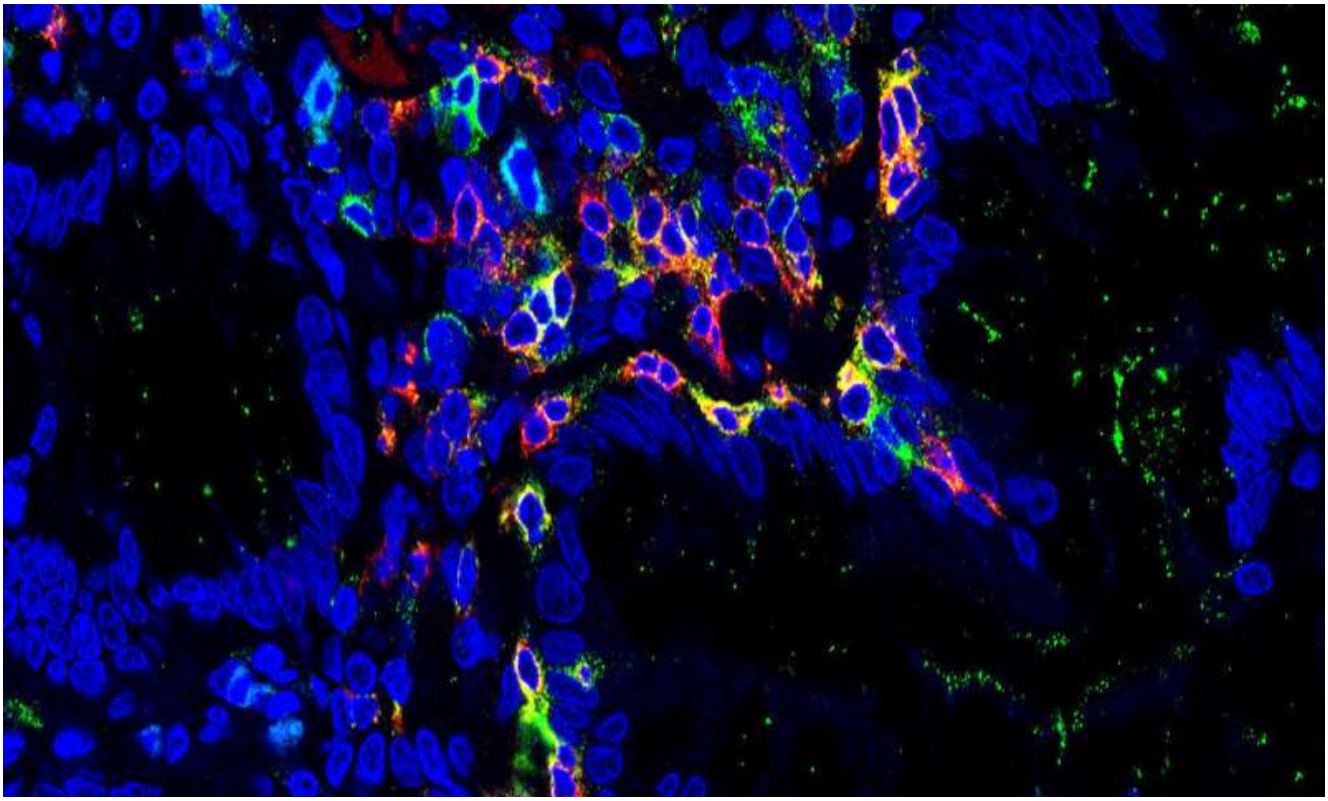
The study findings were published Feb. 11 in the journal *Nature*.

More information

The U.S. National Institutes of Health has more on the human microbiome.

Posted: February 2019

Cells that destroy the intestine



FAU researchers have now discovered that so-called TRM cells (shown in yellow) presumably cause flare-ups in chronic inflammatory diseases such as Morbus Crohn or ulcerative colitis. Credit: Universitätsklinikum Erlangen/Sebastian Zundler

Patients affected by the chronic inflammatory bowel diseases morbus Crohn and ulcerative colitis often suffer from flare-ups, which damage intestinal tissue. Despite advances in treating these diseases with medication, associated chronic inflammation cannot be kept sufficiently in check for a number of patients. Until now, little has been known about what actually causes flare-ups. In a collaboration with researchers from the Netherlands, researchers at Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) have now proven that certain cells in the intestines play a key role in inducing acute inflammatory episodes. This discovery could lead to innovative approaches to treating the diseases in future.

The results of the research have now been published in the journal *Nature Immunology*.

Chronic inflammatory diseases are caused by a complex combination of factors. This eventually leads to

overstimulation of the intestinal immune system, with the resulting inflammation often leading to serious symptoms. The immune system in the intestines includes cells known as tissue resident memory cells, or TRM cells for short. Previously, scientists were unsure of the role these cells play in causing chronic inflammation in the intestines.

The researchers at Universitätsklinikum Erlangen, led by Dr. Sebastian Zundler and Prof. Dr. Markus F. Neurath, have now successfully deciphered these mechanisms. In cooperation with Sanquin Research Institute in the Netherlands, the researchers were able to prove that TRM cells have a highly inflammatory potential and appear to induce flare-ups. The data also suggest that TRM cells regulate the migration and differentiation of other immune cells and therefore play a central role in regulating the immune response. Accordingly, patients with a high proportion of TRM cells in their intestinal lining have a greater risk of suffering from acute inflammatory episodes than those with a lower proportion.

Prof. Dr. Neurath says, “We believe that our findings are also of relevance for other chronic inflammatory diseases.” In addition, the researchers hope that their discovery will form the basis for treating diseases in future. “Future treatments may well be based on the important role TRM cells have to play in the chronic inflammation of the intestine,” predicts Dr. Sebastian Zundler. “By taking early action, we may be able to suppress the disease or flare-ups of the condition.”

Researchers report inflammation suppression process

More information:
Sebastian Zundler et al, Hobit- and Blimp-1-driven CD4+ tissue-resident memory T cells control chronic intestinal inflammation, *Nature Immunology* (2019). DOI:

10.1038/s41590-018-0298-5

Provided by
University of Erlangen-Nuremberg

On recovery, vulnerability and ritual: An exhibit in white

Matthew Wetschler, MD, was once dead for ten minutes.

In November 2017 while surfing at Ocean Beach in San Francisco, a wave drove him headfirst into the ocean floor, breaking his neck and leaving him partially paralyzed. He would have drowned had another surfer not spotted him and dragged him to shore, where a vacationing nurse helped resuscitate him. He was transported to Zuckerberg San Francisco General Hospital, where he was the first person in the U.S. to receive a post-experimental treatment focused on

maintaining sufficient blood flow within the spinal cord.

That accident and the ensuing months of struggle to ultimately regain movement serve as the inspiration for Wetschler's new exhibit of paintings, *Documenta*, now on display at the School of Medicine's Li Ka Shing Center for Learning and Knowledge (on the first and third floors).

The exhibit documents his recovery, but before you visit (and you should), there are finer points to the story, which I've collected in the notes below. As Wetschler himself noted in our recent conversation, "People want to create an arc of triumph and personal will. That's too simple a narrative."

Exhibit Note 1: **Wetschler is a philosopher.**

Wetschler, who completed residency in emergency medicine at Stanford before the accident, said he was drawn to medicine because of the social and humanist role of the physician. But as an undergraduate, Wetschler majored in philosophy, and the study clearly influences his practice of medicine, his art, and his view of his accident.

"We are in an interesting time," he explained. "The Enlightenment philosophical approach suggested that through empiric (i.e. scientific) observation and rational thought we could understand the world and find the ultimate truth. But we overestimate the impartial nature of our observations. Even if there is a Truth, post-modern philosophy suggests that we cannot reach it. That it is impossible to escape our subjective experience. I fall somewhere in the middle, trying to find truth while recognizing individual limitation. Ultimately, I'm interested in how we as people experience the world, how do we suffer, how do we survive and heal. Medicine offers a front row seat."

Exhibit Note 2: **Wetschler values rituals.**

The death of patients is sadly not an unusual occurrence in

emergency medicine, and the protocol is often to call time of death, begin cleaning the room, and turn to the next patient. But when a patient died early in Wetschler's medical training, a nurse made everyone stop, close the door, turn off the monitors, and observe 60 seconds of silence.

"It was not a religious moment," Wetschler explains, "but rather the secular application of the mechanism of ritual. Taking 60 seconds and ignoring chaos and need of the emergency room and acknowledging that we as providers are doing something very meaningful. We need space to keep intrinsic values, values that are important to us, present and active."

Exhibit Note 3: **The paintings in *Documenta* are all done with white paint.**

Wetschler created all of the works in the *Documenta* exhibit in the past year, and they are directly inspired by his accident and the recovery process. They are also exclusively a product of ritual. Wetschler, who still experiences loss of fine-motor coordination in his hands, began each piece with a ritual of repetition that used positioning and stress to create weakness in his hands and arms. Then he painted.

What arrived on the canvas was a direct product of that physical vulnerability (see exhibit note 5) in brush strokes and movement. Wetschler views the ritual itself as the art, and said he felt color would detract from the viewer's comprehension of the ritual.

The location of the exhibition in the School of Medicine also becomes part of the viewer experience.

"There is something cyclical about showing [at Stanford University School of Medicine]. This is an expression of my own healing in the place I learned to become a healer. It becomes a statement of how that is an active process for all of us. Sometimes we are the healer, and sometimes we need to be healed."

Exhibit Note 4: **Pay close attention to the painting called "Reentry."**

The first time Wetschler returned to the site of his accident, he brought a canvas but he did not start painting immediately. Instead, he drew a large circle in the sand, walked the 200-foot perimeter as a ritual, then went into the frigid ocean. He repeated this circle-walk and ocean dip 13 times to induce hypothermia and weakness, but surprisingly, he found his final laps were his strongest. He then hurled his body, sand and all, onto a paint-covered canvas. This work is the result.

Exhibit Note 5: **We are all vulnerable, and that makes us strong.**

After a year of recovery, Wetschler is finally returning to the practice of emergency medicine at the end of February. While he feels his accident may influence his compassion for his patients, more than anything he believes he's gained a deeper understanding of how vulnerable humans are, and how acknowledging this provides true strength. He adds:

> *My accident was a manifestation of an individual encountering the chaos of world and his own frailty. We aren't in control. Things can change at any moment. In emergency medicine, we are exposed to people's vulnerabilities. That requires a certain constitution to face every day and still remain emotionally whole…*
>
> *The antidote is adopting the perspective that crazy things can happen, and we will always rise to the challenge. Hopefully I'm living proof that even if we break ourselves in some way, we can still move forward. Within us is a deep well of capacity we underestimate. There is strength in acknowledging vulnerability and still persisting.*

Photo by Susan Coppa

Scientific Duo Gets Back To Basics To Make Childbirth Safer

Kristin Myers, a mechanical engineer, and Dr. Joy Vink, an OB-GYN, both at Columbia University, have learned that cervical tissue is a complicated mix of material.

COPD patients need more support when understanding new chest symptoms

People with Chronic Obstructive Pulmonary Disease (COPD) need more support when understanding and acting on new chest symptoms, a study in the journal *Psycho-Oncology* reports.

During this unique study, led by the University of Glasgow and University of Surrey, researchers investigated how the experience of COPD, influences how individuals understand new or changing chest symptoms and their decision to seek help from medical professionals.

COPD is the name for a group of lung conditions, including emphysema and chronic bronchitis, which cause breathing difficulties. Incidence of lung cancer is four-times higher in those with COPD compared to the general population and

patients often confuse early signs of the devastating disease with a deterioration of their existing condition and do not seek medical advice.

Interviewing 40 participants with COPD, researchers discovered that none of the participants were aware that having the condition put them at increased risk of developing lung cancer. Due to a lack of knowledge and support, participants often attributed chest symptoms to external factors such as the weather or illness.

Researchers found that some participants did not seek medical advice following the development of symptoms as they were keen to ‘not make a fuss’ and believed that poor health was something to be accepted when diagnosed with the condition. A stigma associated with continued smoking was also identified by researchers, as participants were found to be reluctant in seeking help as they felt the doctor would blame their symptoms on smoking.

Participants also spoke about barriers in accessing care, which included scheduling appointments outside of usual working hours and difficulties in getting to the GP’s surgery, when symptoms present themselves.

Early diagnosis of lung cancer is vital to improving survival. Figures from Cancer Research UK reveal that when diagnosed at its earliest stage, almost 6 in 10 people with lung cancer will survive their disease for five years or more, compared with almost 5 in 100 people when diagnosed at a later stage.

Dr Katie Robb, Senior Lecturer at the University of Glasgow, said: “Healthcare professionals need to do more to educate those with COPD about their increased risk of developing lung cancer and be more vigilant when a patient with the illness presents changing symptoms.”

Dr Katriina Whitaker, Reader in Cancer Care at the University of Surrey, said: “Early diagnosis of lung cancer is vital in

improving survival rates, we need those with COPD to go to the doctor as a matter of course when they notice a change in their symptoms and not be concerned about wasting the doctor's time."

Jodie Moffat, Head of Early Diagnosis at Cancer Research UK, said: "It's vital patients and their doctors stay alert to signs of cancer to ensure that any potential cancer is diagnosed as soon as possible. Symptoms of other diseases can mask cancer signs, so it's important patients know what to look out for. Changes to existing conditions, as well as new symptoms, should be checked out by a GP, and GPs need to be ready to consider cancer as an option."

Source:

https://www.surrey.ac.uk/news/more-needs-be-done-raise-awareness-lung-cancer-risk-people-copd

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Using light-based method for production of pharmaceutical molecules

Photoelectrochemical (PEC) cells are widely studied for the conversion of solar energy into chemical fuels. They use photocathodes and photoanodes to "split" water into hydrogen and oxygen respectively. PEC cells can work under mild conditions with light, which makes them also suitable for other catalyzing reactions that turn organic molecules into high added-value chemicals, like those used to develop drugs.

However, PEC cells have rarely been used in organic synthesis

so far, except in some recent conceptual attempts that have tested only a handful of simple substrates. Overall, PEC cells remain largely unexplored for broad-scope synthetic methodologies of functional organic molecules.

They could nevertheless prove most helpful in one of the most appealing synthetic methods for pharmaceuticals and agrochemicals, called “direct amination”. It involves adding an amine group to an organic molecule without pre-activating the molecule by an additional processing step.

Direct amination normally requires high temperatures, and also needs what is known as a “directing group” – a chemical unit that fixes the reaction site but has no other functions, and which often has to be removed before using the new compound in applications.

Now, the labs of Xile Hu and Michael Grätzel at EPFL’s Institute of chemical sciences and engineering (ISIC) have developed a new method for aminating arenes – hydrocarbons with a ring in their structure – without the need for a directing group.

“Our method is operationally simple and can be used to synthesize a broad range of nitrogen-containing heterocycles relevant to drug discovery,” writes Lei Zhang, the lead author of the study. Proving the point, the researchers used their method to make several pharmaceutical molecules, including derivatives of the muscle relaxant metaxalone and the antimicrobial benzethonium chloride.

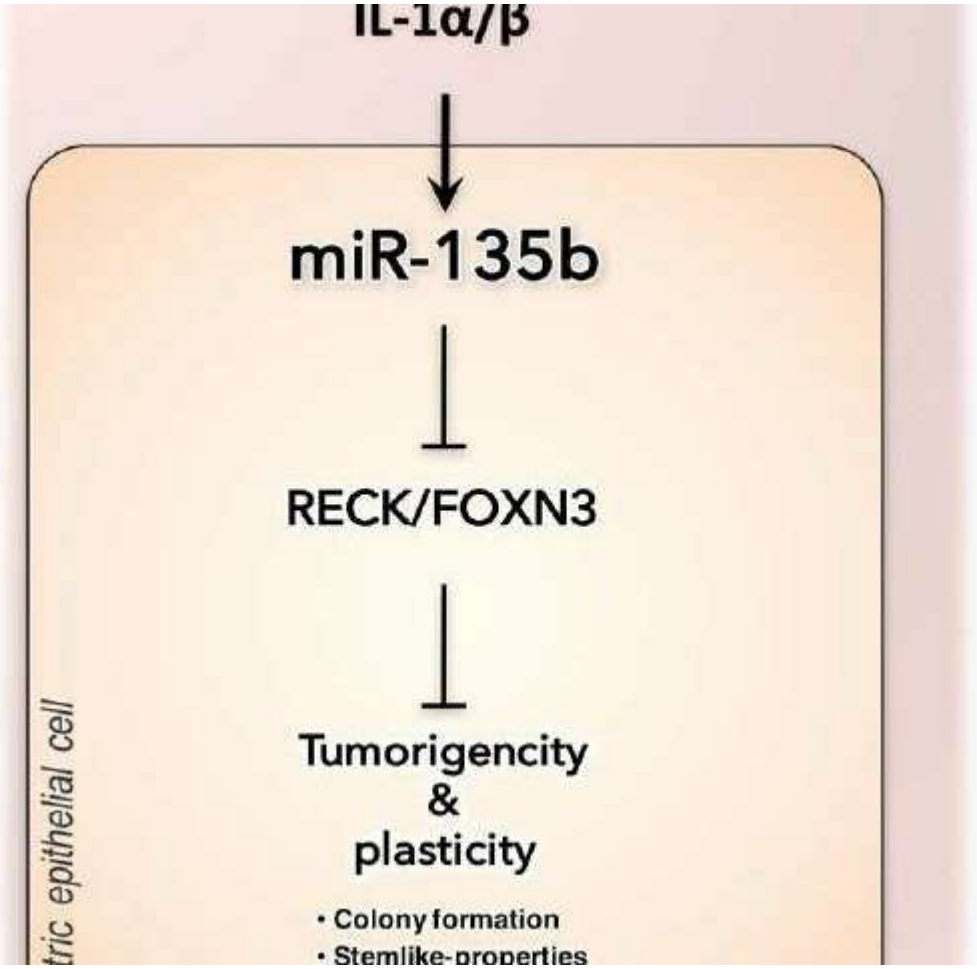
Based on a PEC cell, the method catalyzes the reaction with light and the low-cost, Earth-abundant semiconductor hematite. “Pioneering studies in Michael Grätzel’s lab have yielded robust hematite samples that are efficient for water splitting, but hematite has never been used to catalyze organic synthesis,” says Hu.

In the current study, hematite was found to work well for

direct amination under visible light, while its high stability promises a long lifetime as a working catalyst. And because it harvests light, the photoelectrocatalysis used here consumes less energy than direct electrocatalysis.

“This is an important demonstration of principle for using PEC cells for the production of high added-value chemicals and pharmaceuticals,” says Hu. “The work merges two traditionally separated fields, namely photoelectrochemistry and organic synthesis. There are plenty of untapped opportunities for this approach, and we are excited to further explore these opportunities.”

Scientists find link between inflammation and cancer



The series of molecular steps linking inflammation and cancer, as shown in in the gastric epithelial cells. Inflammatory molecules IL-1α/β, lead to enhancement of MIR135B. This is turn activates FOXN3 and RECK genes, that lead to tumour like properties in cells. Credit: Kanazawa University

Severe inflammation in tissues is often associated with the occurrence of cancer. The mechanism linking both these conditions is not clearly understood. Furthermore, inflamed and cancerous tissues contain a heterogenous mix of damaged and protective cells. This makes it very difficult to isolate the primary damaged cells and study them further. Researchers at Kanazawa University have recently developed a technique to make this possible.

The team used a method of isolating preferred cells from the site of damage, called as laser microdissection (LMD). This involved employing a laser beam to focus on and pick out a specific set of cells. LMD was subsequently applied to understand how gastritis (inflammation of the stomach) can

lead to gastric cancer.

The stomach lining comprises mainly epithelial cells. Epithelial cells were therefore isolated from the damaged lining of mice suffering from either gastritis, or inflammation-associated gastric cancer. It was seen that in both these instances, miR-I35B, a gene modulator, was increased to the same extent; much higher than levels observed in healthy mice. Interestingly, miR-I35B levels were already quite high at early stages of cancer—they did not seem to change much as the cancer advanced. This observation was confirmed in human patient samples too.

To then understand what spikes the levels of miR-I35B, the researchers used different chemical triggers of inflammation. They found that IL-1α and IL-1β, two specific inflammatory cytokines present in the body, were responsible for driving this increase. miR-I35B changes were thus closely connected to an inflammatory response. The exact link between miR-I35B and the development of cancer, however, remained a mystery. Using established cancer cell lines, the research group then showed that a miR-I35B mimicking agent led the cells to attach firmly, proliferate and migrate; very much like cancer cells in the body.

Since miR-I35B is a type of microRNA, or gene modulating agent, what genes did it target to bring about these actions? A series of gene-analysis studies on the mice suggested a list of implicated genes. Two such candidates, namely, FOXN3 and RECK, were found to be severely inhibited by miR-135B. In the healthy state, FOXN3 and RECK are known to suppress tumour formation. Inhibition of these genes led to increased cell migration, which is a prime feature of cancer cells. FOXN3 and RECK are likely the primary mediators of miR-135B-induced gastric cancer.

This study highlighted a complex mechanism driving inflammation, its close relative cancer, and elucidated how

one molecule is involved in both. “The association of miR-135b with gastritis and early-stage gastric carcinogenesis suggest miR-135b may find utility in the development of diagnostic tools for the early detection of gastric abnormalities”, suggest the authors. This detailed understanding of the miR-135B network also paves the way for developing strategies to fight such conditions.

Loss of tight junction protein promotes development of precancerous cells

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More information:
Tae-Su Han et al, Interleukin 1 Upregulates MicroRNA 135b to Promote Inflammation-associated Gastric Carcinogenesis in Mice, *Gastroenterology* (2018). DOI: 10.1053/j.gastro.2018.11.059

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The High Cost Of Sex: Insurers Often Don’t Pay For Drugs To Treat Problems

For some older people, the joy of sex may be tempered by financial concerns: Can they afford the medications they need to improve their experience between the sheets?

Medicare and many private insurers don’t cover drugs that are prescribed to treat problems people have engaging in sex. Recent developments, including the approval of generic versions of popular drugs Viagra and Cialis, help consumers afford the treatments. Still, for many people, paying for pricey medications may be their only option.

At 68, like many postmenopausal women, Kris Wieland, of Plano, Texas, experiences vaginal dryness that can make intercourse painful. Her symptoms are amplified by Sjogren’s syndrome, an immune system disorder that typically causes dry eyes and mouth, and can affect other tissues.

Before Wieland became eligible for Medicare, her gynecologist prescribed Vagifem, a suppository that replenishes vaginal estrogen, a hormone that declines during menopause. That enabled her to have sex without pain. Her husband’s employer plan covered the medication, and her copayment was about $100 every other month.

However, after she enrolled in Medicare, her Part D plan denied coverage for the drug.

“I find it very discriminatory that they will not pay for any medication that will enable you to have sexual activity,” Wieland said. She plans to appeal.

Under the law, drugs used to treat erectile or sexual dysfunction are excluded from Part D coverage unless they are used as part of a treatment approved by the Food and Drug Administration for a different condition. Private insurers often take a similar approach, reasoning that drugs to treat sexual dysfunction are lifestyle-related rather than medically necessary, according to Brian Marcotte, CEO of the National Business Group on Health, which represents large employers.

So, for example, Medicare may pay if someone is prescribed sildenafil, the generic name for Viagra and another branded drug called Revatio, to treat pulmonary arterial hypertension, a type of high blood pressure in the lungs. But it typically won't cover the same drug if prescribed for erectile dysfunction.

Women like Kris Wieland may encounter a similar problem. A variety of creams, suppositories and hormonal rings increase vaginal estrogen after menopause so that women can have intercourse without pain. But drugs that are prescribed to address that problem haven't generally been covered by Medicare.

Sexual-medicine experts say such exclusions are unreasonable.

"Sexual dysfunction is not just a lifestyle issue," said Sheryl Kingsberg, a clinical psychologist who is the chief of behavioral medicine at University Hospitals MacDonald Women's Hospital in Cleveland. She is the immediate past president of the North American Menopause Society, an organization for professionals who treat women with these problems. "For women, this is about postmenopausal symptoms."

Relief may be in sight for some women. Last spring, the federal Centers for Medicare & Medicaid Services sent guidance to Part D plans that they could cover drugs to treat moderate to severe "dyspareunia," or painful intercourse, caused by menopause. Plans aren't required to offer this coverage, but they may do so, according to CMS officials.

The North American Menopause Society applauded the change.

"Dyspareunia is a medical symptom associated with the loss of estrogen," said Kingsberg. "They had associated it with sexual

dysfunction, but it’s a menopause-related issue.”
For men who suffer from erectile dysfunction, treatment can confer both physical and emotional benefits, according to experts in sexual health.
“In my clinical work, I see a lot of older couples,” said Sandra Lindholm, a clinical psychologist and sex therapist who is also a nurse practitioner in Walnut Creek, Calif. “They are very interested in sex, and they feel like they’re able to embrace their erotic lives. But there may be medical issues that need to be addressed.”
Roughly 40 percent of men over age 40 have difficulty getting or maintaining an erection, studies show, and the problem increases with age. A similar percentage of postmenopausal women experience genitourinary syndrome of menopause, a term used to describe a host of symptoms related to declining levels of estrogen, including vaginal dryness, itching, soreness and pain during intercourse, as well as increased risk of urinary tract infections.
Low sexual desire is another common complaint among women and men. A drug called Addyi was approved in 2015 to treat low sexual desire disorder in premenopausal women. But many insurers don’t cover it.
Unfortunately, medications that treat these conditions may cost people hundreds of dollars a month if their insurance doesn’t pick up any of the tab. A 10-tablet prescription for Viagra in a typical 50-milligram dose may cost more than $600, for example, while the price of eight Vagifem tablets may exceed $200, according to GoodRx, a website that publishes current drug prices and discounts.
In recent years, much more affordable generic versions of some of these medications have gone on the market.
Generic versions of Viagra and Cialis, another popular erectile dysfunction drug, may be available for just a few dollars a pill.
“I never write a prescription for Viagra anymore,” said Dr. Elizabeth Kavaler, a urogynecologist at Lenox Hill Hospital in New York City. “These generics are inexpensive solutions for

men.”
There are generic versions of some women’s products as well, including yuvafem vaginal inserts and estradiol vaginal cream. But even those generic options are often relatively pricey. Some patients can’t afford $100 for a tube of generic estradiol vaginal cream, said Dr. Mary Jane Minkin, a clinical professor of obstetrics, gynecology and reproductive medicine at Yale University School of Medicine.
“I’ve asked, ‘Did you try any of the creams?’ And they say they used up the sample I gave them. But they didn’t buy the prescription because it was too expensive.”

Hearing impairment associated with accelerated cognitive decline with age

Hearing impairment is a common consequence of advancing age. Almost three-quarters of U.S. adults age 70 and older suffer from some degree of hearing loss. One unanswered question has been to what degree hearing impairment intersects with and influences age-related cognitive decline.

In a new study, researchers at University of California San Diego School of Medicine report that hearing impairment is associated with accelerated cognitive decline with age, though the impact of mild hearing loss may be lessened by higher

education.

The findings are published in the February 12, 2019 issue of the *Journal of Gerontology: Series A Medical Sciences*.

A team of scientists, led by senior author Linda K. McEvoy, PhD, professor in the departments of Radiology and Family Medicine and Public Health, tracked 1,164 participants (mean age 73.5 years, 64 percent women) in the longitudinal Rancho Bernardo Study of Healthy Aging for up to 24 years. All had undergone assessments for hearing acuity and cognitive function between the years 1992 to 1996 and had up to five subsequent cognitive assessments at approximately four-year intervals. None used a hearing aid.

The researchers found that almost half of the participants had mild hearing impairment, with 16.8 percent suffering moderate-to-severe hearing loss. Those with more serious hearing impairment showed worse performance at the initial visit on a pair of commonly used cognitive assessment tests: the Mini-Mental State Exam (MMSE) and the Trail-Making Test, Part B. Hearing impairment was associated with greater decline in performance on these tests over time, both for those with mild hearing impairment and those with more severe hearing impairment.

However, the association of mild hearing impairment with rate of cognitive decline was modified by education. Mild hearing impairment was associated with steeper decline among study participants without a college education, but not among those with higher education. Moderate-to-severe hearing impairment was associated with steeper MMSE decline regardless of education level.

“We surmise that higher education may provide sufficient cognitive reserve to counter the effects of mild hearing loss, but not enough to overcome effects of more severe hearing impairment,” said McEvoy.

Degree of social engagement did not affect the association of hearing impairment with cognitive decline. “This was a somewhat unexpected finding” said first author Ali Alattar. “Others have postulated that cognitive deficits related to hearing impairment may arise from social isolation, but in our study, participants who had hearing impairment were as socially engaged as those without hearing loss.”

The findings, said the authors, emphasize the need for physicians to be aware that older patients with hearing impairments are at greater risk for cognitive decline. They also emphasized the importance of preventing hearing loss at all ages, since hearing impairment is rarely reversible. One important way to protect hearing, they said, is to minimize loud noise exposure since this is the largest modifiable risk factor for hearing impairment.

Researchers identify multiple genetic variants associated with body fat distribution

A new breakthrough from the Genetic Investigation of Anthropometric Traits consortium, which includes many public health researchers from the University of North Carolina at Chapel Hill, identifies multiple genetic variants associated with how the body regulates and distributes body-fat tissue. The new findings broaden the understanding of how genes can predispose certain individuals to obesity.

The GIANT Consortium is a major international collaboration of more than 275 scientists that seeks to identify genetic sites that affect human body size and shape, including height and

measures of obesity.

Kari E. North, professor of epidemiology at the University of North Carolina at Chapel Hill Gillings School of Global Public Health, is joint lead author of the new study, “Protein-Coding Variants Implicate Novel Genes Related to Lipid Homeostasis 1 Contributing to Body Fat Distribution,” published February 18 in *Nature Genetics*.

Other co-authors from the UNC Gillings School include assistant professor Kristin Young, assistant professor Misa Graff, and postdoctoral fellow Heather Highland, all in the UNC Gillings School’s department of epidemiology.

Identifying the genetic variants associated with obesity is central to developing targeted interventions that can reduce the risk of chronic illnesses, such as hypertension, type 2 diabetes, and heart disease, to which obesity contributes in significant ways. Genome-wide association studies previously identified 49 loci, or positions along a chromosome where the related genetic variants are located, that predispose individuals to a higher waist-to-hip ratio, which is a way to assess body-fat distribution. Lower values of WHR are associated with lower incidence of these diseases.

In this study, with a specific focus on coding variation, the team found 24 coding loci – 15 common and nine rare – along the chromosomes of individuals that predispose to higher WHR. Further analysis revealed pathways and gene sets that influenced not only metabolism but also the regulation of body fat tissue, bone growth and adiponectin, a hormone that controls glucose levels and breaks down fat.

The team also performed functional studies across other organisms and identified two genes that were associated with a significant increase in triglyceride levels and body fat across species.

“For the first time, we were able to examine, on a large

scale, how low-frequency and rare variants influence body fat distribution," said Kari E. North. "These variants are rarer in the population, but the effects they have on individuals are much larger, possibly making them more clinically relevant."

Another major finding from this study is the importance of lipid metabolism to bodyfat distribution, which could lead to a better understanding of how obesity causes downstream diseases such as Type 2 diabetes and cardiovascular disease.

"A better understanding of the genetic underpinnings of body fat distribution may lead to better treatments for obesity and the cascade of downstream diseases obesity also impacts, for example type 2 diabetes and heart disease" North said.

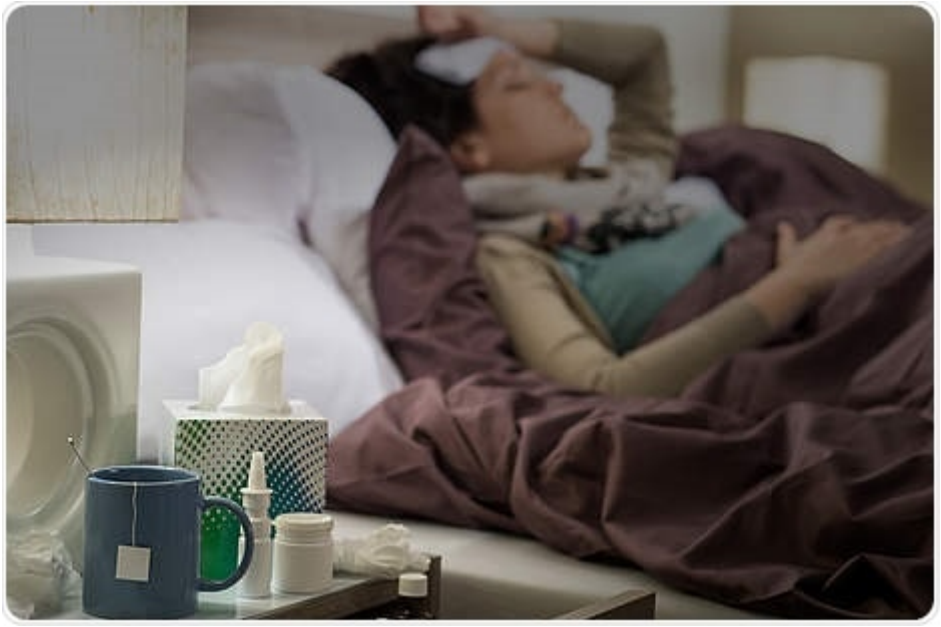
Influenza and common cold are completely different diseases, study shows

Feb 19 2019

International study shows a lack of public knowledge on the subject

There is a lack of information about the difference between influenza, "real" flu, and the common cold. Most people struggle to distinguish between these two diseases and this often leads to irritation and the perpetuation of myths. Similar misconceptions were found in all three countries. This was the finding from a recent international study conducted in Belgium, Croatia and Austria under the supervision of Kathryn

Hoffmann from MedUni Vienna's Division of General and Family Medicine.



> *Influenza and the common cold are completely different things. The clearly delineated influenza viruses cause a potentially serious illness. The common cold, on the other hand, is caused by hundreds of different infectious viruses. In the vast majority of cases, the progression and symptoms of the illness are much more benign. Contrary to popular belief, the common cold can never turn into real flu."*
>
> *Kathryn Hoffmann, MedUni Vienna's Division of General and Family Medicine*

It is easy to distinguish between the two diseases, particularly in the early stages. Whereas influenza comes on suddenly with limb pain and fever in people who, a few hours earlier, felt absolutely fine, a common cold usually starts with a sore throat, a blocked nose and a cough and comes on more gradually. Body temperature rises much more gradually.

Says Hoffmann:

> *However, our study shows that, if fever is one of the symptoms, people immediately think of 'real' flu."*

This is also the reason why many people who have been vaccinated against flu and still develop fever and flu-like symptoms, believe that the vaccine doesn't work. "They become sceptical of vaccinations, even though they are only suffering from a common cold – which, unfortunately you can still get, even though you have had the flu jab," explains the MedUni Vienna expert.

It is therefore always advisable to be vaccinated against seasonal influenza, which, in serious cases, can prove lethal. A study carried out for the Vienna region in 2013, under the supervision of Theresia Popow-Kraupp from MedUni Vienna's Center for Virology, revealed that, in Vienna alone, around 300 people die during a seasonal flu outbreak as a consequence of the illness, which can often last two or three weeks.

However, even though one can protect oneself from influenza by having the vaccination (the relevant seasonal vaccine is between 60 – 95% reliable), one has no protection against infectious common cold viruses.

Hoffmann explains:

> *At some point the viral threshold that our immune system can withstand is exceeded and then we develop a cold. However, we can raise this threshold by healthy lifestyle habits that strengthen the immune system or by scrupulous hand hygiene."*

Even the term "cold" is not really accurate – it is not yet clear whether one is more likely to succumb to a virus, if one gets cold. Whatever the case, the critical factor is contact with the viral pathogens.

However, – in contrast to "real" flu – people usually recover from a common cold in about five days, so long as they rest and look after themselves.

Source:

https://www.meduniwien.ac.at/web/en/about-us/news/detailsite/2019/news-im-februar-2019/influenza-and-the-common-cold-two-different-diseases/