



Are bioplastics really the wonder alternative to petro plastics?

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Alternatives to petrochemical-based plastics are emerging, made from everything from banana leaves to tomato skins, especially for food packaging.

Abiodegradable textile made from banana leaves has been developed by a Swiss brand and its Taiwanese partners.

GENERIC: Banane, Bananas, Fruits

(Copyright: bhofack2 / Getty Images)

But questions remain about how biodegradable and compostable they are, as well as their impact on the environment.

- What is biosourced plastic? -

Biosourced means made with less petrol, using non-fossil agricultural products such as sugarcane waste, corn, or wheat starch. Primarily used in packaging, these

biosourced plastics account for less than one percent of global plastic production.

But labs around the world are coming up with more and more new plastics derived from tomato skins or banana leaves.

The French chemicals company Arkema, for instance, is pushing PBAT, made from castor oil, which is used to make sports shoes and car interiors.

Bananatex is a biodegradable textile made from banana leaves that has been developed by a Swiss brand and its Taiwanese partners.

However, "biosourced doesn't necessarily have to be 100 percent" from natural materials, warned Christophe Doukhi de Boissoudy, president of the French association for biosourced compostables.

In Europe, the minimum 50 percent requirement to be considered biosourced "will rise to 60 percent in January 2025", he added.

- What is a bioplastic? -

The generic term "bioplastic" can be confusing, as it can mean either biosourced or compostable: the definition varies by country.

But in Europe, the term is clearly defined -- a bioplastic is a polymer that is both biosourced and compostable, either in soil or industrially.

Not all bioplastics completely degrade under natural conditions.

Some, like PLA (polylactic acid), need to be composted industrially at temperatures between 35 and 60 degrees Centigrade (140 degrees Fahrenheit).

One of the most highly developed bioplastics currently used in textiles or for food packaging, PLA was originally fossil-based but is now being made from fermented plant biomass (corn, beet or sugarcane).

"What alarms us is the speed at which China is advancing its legislation to convert its packaging to PLA, aiming to abandon petrochemical plastics, while Europe is stagnating," said Frederic Van Gansberghe, founder of Belgium-based bioplastics company Futerro, which has a factory in China and plans to open one in France in 2026.

- What environmental impact? -

In its "Atlas of Plastic", the Heinrich Boll Foundation estimates that most biosourced plastics are neither completely biodegradable or compostable, and "actually just sidestep the problem".

For Nathalie Gontard, research director at the French National Institute for Agriculture, Food and the Environment, biosourced plastic "has absolutely no benefit" because these polymers don't degrade in natural conditions but instead fragment into micro- and then nano-plastics.

"What matters is biodegradability under natural conditions," she said.

"Biodegradable" is not well-defined, she argued, as some use it for materials that completely degrade in a few months or years, while others refer to much longer periods.

The environmental benefit of biosourced plastic lies in how they reduce the CO2 emissions of the plastics sector. But caution is needed here, experts warn.

"Additional demand for land to grow the raw materials for biosourced plastics can lead to land-use changes or deforestation," the OECD warned, which in turn can increase CO2 emissions.

"By developing bioplastics, we place the burden of manufacturing these materials on agricultural land that should primarily serve to feed the population," insisted Pauline Debrabandere from the NGO Zero Waste.

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Pros And Cons Of Recombinant DNA Technology

By Maria Cook Updated Aug 30, 2022

DNA exists in the cells of all living things. These long chains of amino acids serve as the genetic blueprints for living organisms. DNA controls how they form before birth and which traits they pass on to the next generation. Recombinant DNA exists in a laboratory by combining genetic material from multiple sources. Recombinant DNA technology can create new kinds of living organisms or alter the genetic code of existing organisms. As with most technology, there are great benefits and notable downsides to the use of recombinant DNA technology.

TL;DR (Too Long; Didn't Read)

Recombinant DNA technology, also called "genetic engineering," has many benefits, such as the ability to improve health and improve the quality of food. But there are downsides as well, such as the potential for using personal genetic information without consent.

Pros of Recombinant DNA Technology

Recombinant DNA technology, sometimes referred to as "genetic engineering," can benefit people in several ways. For example, scientists made artificial human insulin with the help of recombinant DNA technology. Diabetic people cannot produce their own insulin, which they need in order to process sugar. Animal insulin is not a suitable replacement, since it causes severe allergic reactions in most people. Thus, scientists used recombinant DNA technology to isolate the gene for human insulin and insert it into plasmids (cellular structures that can replicate independently of chromosomes). These plasmids were then inserted into bacterial cells, which created insulin based on the human genetic code inside of them. The resulting insulin was safe for humans to use. Thus, people with diabetes went from having a life expectancy of around 4 years after diagnosis to having a normal human life expectancy.

Recombinant DNA technology helped improve food production. Fruits and vegetables, which were prone to attacks from pests, now have genetic modifications to be more resistant. Some foods have modifications for longer shelf lives or higher nutritional content. These advancements greatly increased crop yields, which means that more food is available to the public at the end of each growing cycle.

Scientists have been working to improve vaccines and produce new ones using recombinant DNA technology. These "DNA vaccines," which utilize recombinant DNA, are in the testing stages. Most modern vaccines introduce a small "piece" of a disease into the body, so the body can develop ways to fight that particular disease. DNA vaccines would directly introduce the antigen itself and lead to more immediate and permanent immunity. Such vaccines could potentially protect people against diseases such as diabetes and even cancer.

Cons of Recombinant DNA Technology

Most of the downsides of recombinant DNA technology are ethical in nature. Some people feel that recombinant DNA technology goes against the laws of nature, or against their religious beliefs, due to how much control this technology gives humans over the most basic building blocks of life.

Other ethical concerns also exist. Some people worry that if companies can pay scientists to patent, buy and sell genetic material, then genetic material could become an expensive commodity. Such a system might lead to people having their genetic information stolen and used without permission. It may sound odd, but such cases have already happened. In 1951, a scientist used unique cells stolen from a woman named Henrietta Lacks to create an important cell line (the HeLa cell line) which is still used in medical research today. Her family did not know about her involuntary donation until after her death, and never received compensation, but others have profited from the use of HeLa cells.

Many people worry about the safety of modifying food and medicines using recombinant DNA technology. Although genetically modified foods seem safe in multiple studies, it is easy to see why such fears exist.

What might happen if a crop of tomatoes with modified jellyfish genes to make them more robust became common? What would happen to an unsuspecting person, who is allergic to jellyfish, after eating one of these tomatoes? Would the person have a reaction? Some people fear that such questions will not come up until it is too late.

Other people worry that humans may begin tampering too much with their own genetic material and create societal problems. What if people use recombinant DNA technology to live longer, become stronger or handpick certain traits for their offspring? Will societal division swell between genetically modified people and "normal" people? These are questions that scientists and the public will likely continue to consider as humanity moves toward a future where manipulating DNA is easier than ever before.

References

Read More: <https://www.sciencing.com/pros-cons-recombinant-dna-technology-8433972/>

The enigma of the rare genetic mutation that protects against cancer and heart attacks



The endocrinologist Jaime Guevara-Aguirre, left, with Lucho, a Laron Syndrome patient, in El Oro (Ecuador) in 1994. © J. G-A. (EL PAÍS)

The study of Ecuadorian families with a rare disease known as Laron

Syndrome has just shown that [a genetic mutation](#) protects them from cardiovascular diseases. Researchers believe that it is possible to search for a drug or a diet that mimics these beneficial effects in order to combat diseases associated with aging, such as cancer, in the general population.

In 1987, Ecuadorian endocrinologist Jaime Guevara-Aguirre began treating people with Laron Syndrome who lived in isolated towns in the provinces of Loja and El Oro, in the south of the country, near the border with Peru. The disease is characterized by a mutation in the growth hormone receptor gene that causes short stature. People with this condition do not exceed 1.5 meters (4 ft 10 in) in height. The cause is a mutation of a single biochemical letter — a G instead of an A — in the very long sequence of three billion letters that makes up the human genome. In these communities in Ecuador, endogamy is common, which has favored the spread of the syndrome. Even today, the inhabitants of these

municipalities continue to have children without knowing if they will be born with Laron or not. In the family photos, affected parents are seen with their children of about 10 years of age, who are already taller than them.

In a teleconference from Quito, Guevara-Aguirre apologizes ahead of time in case communication is interrupted due to the blackouts that have been afflicting the country, which has been plunged into [a spiral of violence and instability](#). "In 1987 it took two days to get to these towns in my father's 4x4, and to get to some of them you had to walk two or three more hours. It was a very remote area, but the patients were fascinating," recalls Guevara-Aguirre, of San Francisco de Quito University. Since then, he has diagnosed about 100 affected people, approximately a third of all known cases in the world.

After two decades of follow-up, the doctor observed an enigmatic pattern: there was hardly any cancer or diabetes in Laron's carriers, while their apparently healthy relatives suffered from these ailments with the same frequency as the rest of Ecuadorians. The doctor posited that Laron's mutation protects against diseases related to aging. The matter caught the attention of the biochemist Valter Longo, a researcher at the University of Southern California focused on the search for diets capable of stopping chronic diseases.

In 2011 they showed that people affected by Laron produced less IGF-1, a protein essential for childhood growth but which in adults also promotes uncontrolled cancer cell proliferation. In laboratory studies, mice with low levels of this protein live up to 40% longer, suffer fewer tumors, and appear smaller than normal.

In 2017, the pair of researchers published another study that pointed out that this mutation also protects against neurodegenerative ailments. Although very few affected people live beyond the age of 80, among those identified there were no cases [of Alzheimer's](#) or dementia. While many of the relatives without the mutation suffered and died from diseases related to aging, those affected by the syndrome died mainly from accidents or alcoholism, which is very common in these Andean communities.



Ecuadorians with Laron Syndrome together with Guevara-Aguirre (left) and Longo, at USC. © J. G-A. (EL PAÍS)

In their new work, the researchers posit that the Laron mutation also has a protective effect against cardiovascular diseases. They studied 21 men with the syndrome and 23 unaffected relatives. Carriers had lower glucose levels and blood pressure. Despite showing high levels of “bad” LDL cholesterol, they had much fewer arteriosclerosis plaques, according to the study, published in [the specialized journal *Med*](#).

“This is the most important study of all,” Longo emphasizes. “Skeptics maintained that the most common cause of death in these people was heart problems, but we showed that this is not the case.” Many of the patients in the study are overweight or obese and lead a poor lifestyle, with high tobacco and alcohol consumption. “The worst thing is that we see that some of them feel that they can do whatever they want because they are protected, which is obviously not

the case,” highlights the Italian-American biochemist, who has visited these villages in Ecuador “dozens of times.”

Longo highlights that diets that mimic fasting, which he himself has designed, lower IGF-1 levels in the circulation, the supposed cause of the beneficial effects observed both in animals and in people with Laron. Another of the authors of the work, John Kopchick, from the University of Ohio, has shown that several molecules that block the growth hormone receptor slow tumor progression in mice and in human breast cancer cells, and improve the effectiveness of conventional treatments. One of these molecules is Pegvisomant, an already approved drug manufactured by the multinational Pfizer to treat acromegaly, a hormonal imbalance that causes excessive growth of the face and extremities.

The Israeli doctor Zvi Laron discovered the syndrome in 1966 in highly consanguineous Jewish families from Yemen. In 2013, a genetic study pointed out that this mutation probably originates from [Spanish and Portuguese Sephardic Jews](#) who fled the Inquisition in the 15th century and founded small communities in Ecuador, Chile, and Brazil. There are 17 different mutations that cause Laron Syndrome, and one of them reached America, explains the scientist, professor emeritus at Tel Aviv University. In recent years, he has published several studies focused on how to replicate the cancer-protective effects he sees in these patients. The scientist believes that the results seen in Ecuador cannot be generalized. “In our cohort of 76 individuals, who were followed for many years, we have seen that the majority of older and obese patients develop insulin resistance and three men and eight women suffered from diabetes,” but only one of them has the same mutation as the Ecuadorians, he said. His next scientific goal is to calculate how many people actually suffer from this condition around the world. “There are probably more than 500, but in many countries they are never diagnosed,” he notes in a telephone conversation from Tel Aviv.

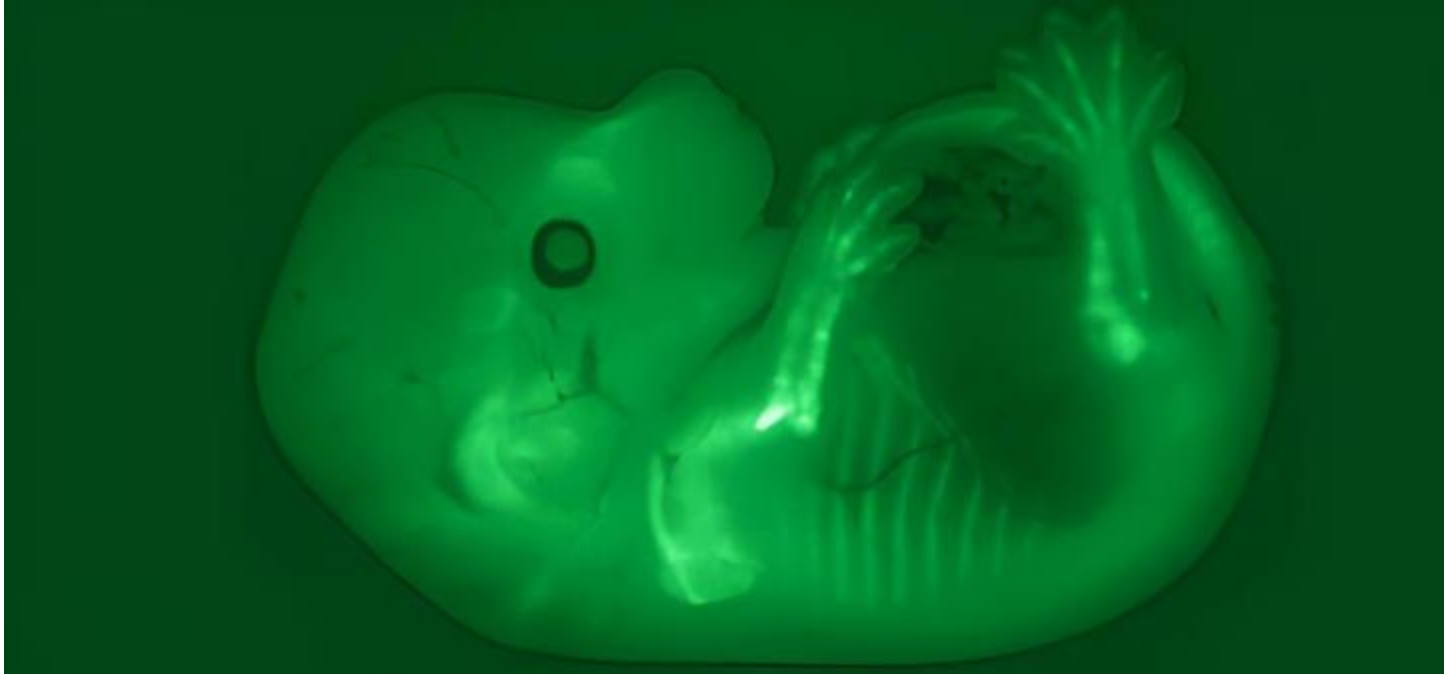
Laron Syndrome is recessive, which means that you have to inherit two mutated copies of the gene, one from the father and one from the mother, to suffer from it. It is possible for one person with the syndrome to have healthy children, and it is also possible for two people without the syndrome to carry the mutation and have children with Laron. “It’s a genetic lottery” that is amplified due to inbreeding, admits Guevara-Aguirre.

This doctor has shown that dwarfism can be treated by administering recombinant IGF-1 protein from an early age. Furthermore, since 1992, he has tried to establish a "massive" genetic diagnosis system that would allow these inhabitants to know if their partners are carriers of the mutation, but this has not yet been done. "It is an easy and cheap intervention, but it has not materialized due to the ignorance of the authorities," he says.

Guevara-Aguirre's goal now is to determine whether carriers of the mutation live longer than their siblings and other relatives. "My feeling is yes, but it has to be proven. The problem is that this area is controlled by the narco-guerrilla," he laments.

Alejandro Martín-Montalvo, a researcher at Spain's National Research Council, collaborated with Longo and Guevara-Aguirre on their study on Laron and cancer in 2011. He considers that "this new work is an advance, as it shows that these people are not predisposed to cardiac failures as was believed until now. In addition, it opens up a possible new line of research on how to transfer these benefits to the general population."

Scientists identify the genetic 'switches' of bone growth



Skeleton of a mouse embryo visible by fluorescence. Credit: Darbellay et al.© Provided by Medical Xpress

Scientists at the UNIGE have identified the genetic sequences that regulate the activity of the genes responsible for bone growth.

In mammals, only 3% of the genome consists of coding genes which, when transcribed into proteins, ensure the biological functions of the organism and the in-utero development of future individuals. But genes do not function alone. They are controlled by other sequences in the genome, called enhancers, which, like switches, activate or deactivate them as required.

A team from the University of Geneva (UNIGE) has identified and located 2,700 enhancers—among millions of non-coding genetic sequences—that precisely regulate the genes responsible for bone growth.

This discovery sheds light on one of the major factors influencing the size of individuals in adulthood, and explains why their failure could be the cause of certain bone malformations. [The results](#) are published in *Nature Communications*.

Tall or short, our height is largely inherited from our parents. Furthermore, many genetic diseases affect bone growth, the exact cause of which often remains unknown. What if an explanation could be found not in the genes themselves, but in other parts of the genome responsible for activating them?

Guillaume Andrey, assistant professor in the Department of Genetic Medicine and Development at the UNIGE Faculty of Medicine and at the Geneva Institute of Genetics and Genomics (IGE3), who led this research, explains, "Short DNA sequences—known as enhancers—give the signal for transcription of DNA into RNA, which is then translated into proteins. While the genes that regulate bone formation and their location in the genome are already well known, it is not the case for the switches that control them."

Fluorescent bones

Andrey and his team have developed an innovative experimental technique, rewarded in 2023 with the Swiss 3R Competence Center Prize, which makes it possible to obtain mouse embryos carrying a precise genetic configuration from murine stem cells.

"In this case, our mouse embryos have fluorescent bones that are visible by imaging, enabling us to isolate the cells of interest to us and analyze how the enhancers work during bone development," explains Fabrice Darbellay, a post-doctoral researcher in Professor Andrey's laboratory and first author of this work.

The team monitored the activity of chromatin, the structure in which DNA is packaged, specifically in fluorescent bone cells. Using markers of gene activation, the scientists were able to identify precisely which regulatory sequences came into action to control the genes responsible for building bone. They then confirmed their discovery by selectively deactivating the enhancers without affecting the coding gene.

"We then observed a loss of activation of the genes in question, which indicates both that we had identified the right switches and that their role is indeed crucial to the proper functioning of the gene," explains Darbellay.

Three-dimensional mapping

Of the 2,700 switches identified in mice, 2,400 are found in humans. "Each chromosome is a long strand of DNA. Like pearls on a necklace, the enhancers and the genes they control form little balls of DNA on the same chromosomal thread. It is this physical proximity that enables them to interact in such a controlled way," explains Andrey.

Variations in the activity of these regions could also explain the differences in size between human beings: the activity of bone cells is indeed linked to the size of bones and therefore of individuals.

Moreover, many bone diseases cannot be explained by a mutation affecting the sequence of a known gene. The answer could be found elsewhere, and more precisely in the non-coding but regulatory regions of the genome.

"There are already a few documented cases where a mutation in the switches rather than in the genes themselves is the cause of bone disease. It is therefore very likely that the number of cases is underestimated, especially when the patients' genes appear normal," the authors explain. And beyond bone disease, failures of these various, as yet little-understood genetic switches could be the cause of many other developmental pathologies.

More information: Fabrice Darbellay et al, Pre-hypertrophic chondrogenic enhancer landscape of limb and axial skeleton development, *Nature Communications* (2024). DOI: [10.1038/s41467-024-49203-2](https://doi.org/10.1038/s41467-024-49203-2)

Provided by University of Geneva

Airborne DNA reveals predictable spatial and seasonal dynamics of fungi



Laboratory technicians at the Konnevesi Research Station of the University of Jyväskylä collect fungal spores from the air. Credit: University of Jyväskylä© Provided by Phys.org

Only a fraction of nature's diversity, or species richness, is still known, especially when it comes to insects and fungi, both of which have millions of species still unknown to science. At the same time, the loss of nature is progressing at an unprecedented rate, and researchers are racing against time to find out the unknown diversity while also coming up with ways to save it.

"Air is a real treasure trove for nature research," says Academy Research Fellow Nerea Abrego from the University of Jyväskylä. "It is full of DNA from plants, fungi, bacteria, insects, mammals and other organisms."

Abrego led a [study](#) published in the journal *Nature* in which DNA sequencing was used to identify fungi from air samples collected around the world. The research produced ground-breaking knowledge about the climatic and evolutionary

factors influencing the occurrence and seasonal variation of both previously known and unknown fungi.

"This knowledge is essential not only to understand where and when different fungal species thrive, but also to predict their fate under the ongoing global change," says Abrego.

Monitoring and prediction of biodiversity loss

Otso Ovaskainen, an Academy Professor at the University of Jyväskylä, was involved in the research project and he is convinced that such new biodiversity sampling techniques will revolutionize biomonitoring and biodiversity forecasts in the coming years. Using DNA as well as image and audio, Ovaskainen is leading a follow-up project in which fungi, insects, mammals, birds, bats, and frogs are studied at hundreds of locations around the world.

"There are more than a million insect species in the samples already collected, which is many more species than have been described by science so far," says Ovaskainen. "The enormous size of the data set makes analysis challenging. We have more than a hundred years of sound, millions of camera trap images, and billions of DNA sequences."

The core activity of Ovaskainen's and Abrego's multidisciplinary research group is the development of statistical modeling, bioinformatics and artificial intelligence methods for using new types of biodiversity data for accurate forecasting.

New information about fungal diseases

Since almost all fungi are at least partially spread through the air, the study included not only boletes and russulas, but also, for example, lichens, bracket fungi, molds and yeasts.

"One particularly interesting subject for further research is a more detailed review of the sequences for fungi that are important to humans," says Abrego. "These include fungal diseases of humans, crops and production animals, as well as fungi

that indicate the progress of the loss of nature and the weakening of natural ecosystem processes."

Abrego is leading a project where air sampling and other new research methods are being piloted as part of the regular Finnish national forest inventory coordinated by the Natural Resources Institute Finland. The goal of this project is to produce comprehensive information about natural diversity, especially about previously poorly known fungi and insects, which can then be used in decision-making processes.

More information: Nerea Abrego et al, Airborne DNA reveals predictable spatial and seasonal dynamics of fungi, *Nature* (2024). DOI: [10.1038/s41586-024-07658-9](https://doi.org/10.1038/s41586-024-07658-9)

Provided by University of Jyväskylä

Scientists trick T-cells to resist aging, find fountain of youth within

The biological fountain of youth

Scientists at Cold Spring Harbor Laboratory worked to genetically engineer T-cells to target and destroy senescent cells. Senescent cells are linked to aging and age-related disorders such as [Alzheimer's](#) disease, obesity, diabetes, and Parkinson's disease. They are cells that are permanently stunted. The process of cellular senescence is important in healthy bodies because it stops the growth and spread of abnormal cells. However, these cells accumulate in organs and tissues over time. This makes it increasingly hard for tissue to regenerate.

Eliminate damaging cells

"Senescent cells are cells in our body that have accumulated a lot of damage and as a result they have stopped doing their normal jobs and instead become very inflammatory," says Assistant Professor Corina Amor Vegas at the Cold Spring Harbor Laboratory and study author. *"The accumulation of these cells in*

tissues is really deleterious because it creates a severe pro-inflammatory microenvironment that prevents the other cells in the tissue from working properly too."

Programing anti-aging cells

So the researchers modified T-cells with the mission to eliminate these senescent cells in mice to test for [anti-aging](#) effects. In particular, they used a drug known as CAR (chimeric antigen receptors) T-cells. The mice in the study experienced lower body weight, better glucose tolerance, boosted metabolism, and more physical activity. There was no tissue damage or toxicity as a result.

One dose for life?

What's even more noteworthy is the longevity of the CAR T-cells. After one dose, young mice retain the anti-aging effects for the rest of their lives. *"T-cells have the ability to develop memory and persist in your body for really long periods, which is very different from a chemical drug,"* says Armor Vegas. *"With CAR T-cells, you have the potential of getting this one treatment, and then that's it. For chronic pathologies, that's a huge advantage. Think about patients who need treatment multiple times per day versus you get an infusion, and then you're good to go for multiple years."*

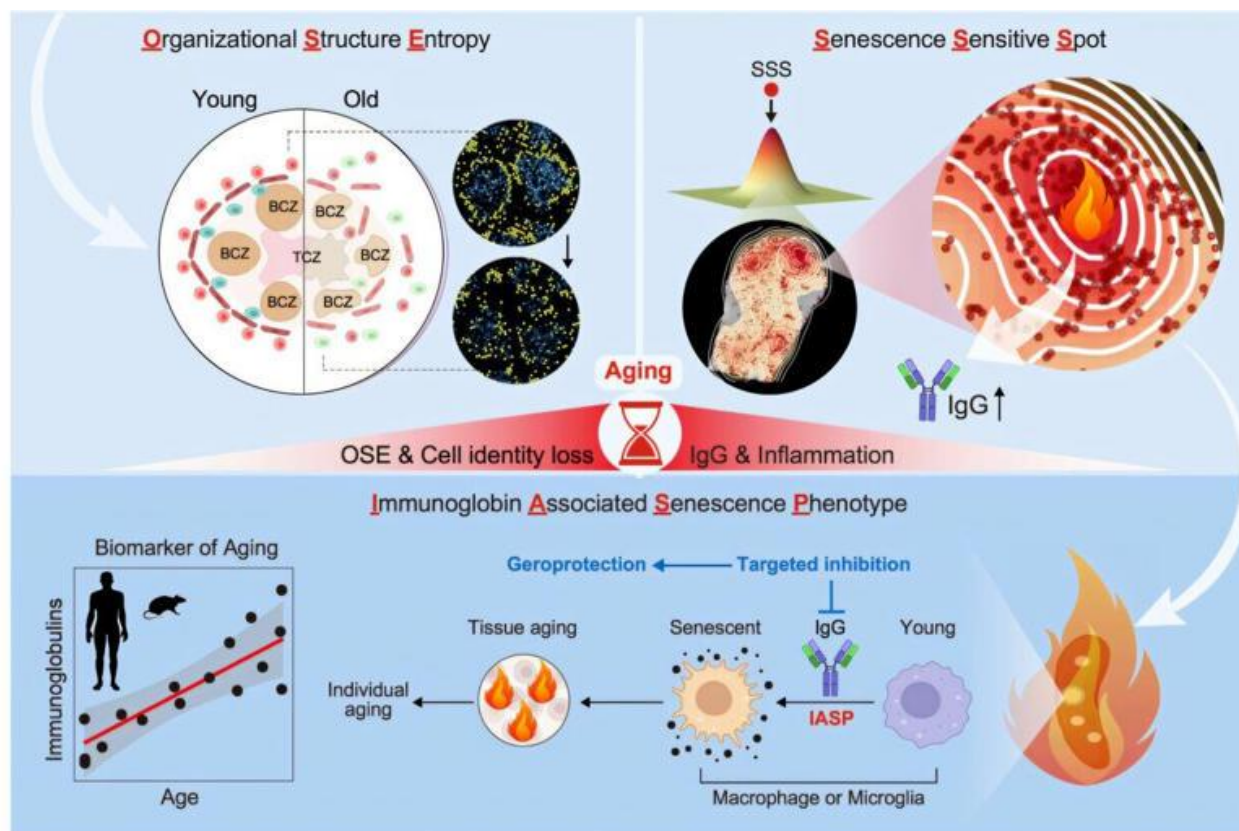
Eliminating senescent cells

There are currently medications that target and eliminate senescent cells, but they need to be taken regularly. Additionally, what's called "senolytic treatment" is new and it's unclear exactly who can benefit from it. It's likely that researchers will need to customize these drugs to target specific issues. Meanwhile, CAR T-cells seem like they have the potential to benefit a person's overall health after one dose-or at least they can benefit a mouse's health.

The future of CAR T-cell anti-aging treatment

In 2017, CAR T-cells received FDA approval as treatment for different kinds of blood cancer. But this study further investigates its medical potential. Armor Vegas and her colleagues are now researching if mice with this treatment would not only live healthier lives but longer ones. There is much to discover before CAR T-cells can be proven to be humanity's fountain of youth.

Unveiling the secrets of aging: Scientists discover dual role of immunoglobulins



A team of scientists from the Chinese Academy of Sciences (CAS) and BGI Research has uncovered the intricate mechanisms by which immunoglobulins

influence the aging process, a finding that might reshape our understanding of aging.

This research, [published](#) in *Cell* on Nov. 4, not only charts a high-precision map of aging across various organs but also reveals the dual-edged sword of immunoglobulins in systemic aging.

The quest for systemic biomarkers and key drivers of aging has been a long-standing puzzle in the field of gerontology. This study, a collaborative effort between Liu Guanghui's team from the Institute of Zoology (IOZ) of CAS, Gu Ying's team from BGI Research, Zhang Weiqi's team from the Beijing Institute of Genomics of CAS, and Qu Jing's team also from IOZ, has provided compelling answers.

By meticulously analyzing millions of spatial spots across nine organs in male mice, the team created high-precision spatial transcriptomic maps. These maps detailed the spatial distribution of more than 70 cell types, offering a vivid picture of aging's spatial characteristics.

The transcriptomic landscape, dubbed Gerontological Geography (GG), exposes the common threads of tissue structural disorder and loss of cellular identity as hallmarks of aging.

"This landscape is a significant step forward, pinpointing the epicenters of aging within multiple organs and uncovering the accumulation of immunoglobulins as a key aging characteristic and driver," said Professor Liu, one of the corresponding authors of the study.

Using the novel method of organizational structure entropy (OSE) analysis, the researchers discovered that increased spatial structural disorder and loss of cellular identity are universal signs of systemic aging, suggesting that spatial structural damage may be a primary cause of organ functional decline during aging.

The team also identified senescence-sensitive spots (SSS), which are structural regions in different tissues more susceptible to aging's effects. They found that areas closer to SSS exhibit higher tissue structural entropy and greater loss of cellular identity, indicating that SSS could be the nucleus of organ aging.

Notably, in immune organs, plasma cells, which are responsible for antibody synthesis, and cells with specific structures and functions, are the main components of the SSS microenvironment. The expression levels of immunoglobulin-related genes in these cells increase around SSS.

The study further discovered that immunoglobulin G (IgG) accumulates in multiple tissues and organs during aging in humans and mice, suggesting that IgG levels could serve as a new biomarker for aging. Moreover, IgG was found to directly induce aging in human and mouse macrophages and microglia, releasing inflammatory factors. Intriguingly, injecting IgG into young mice induced aging in multiple tissues and organs, demonstrating its potent aging effects.

In a promising development, the team developed an intervention strategy using antisense oligonucleotides (ASO) to reduce IgG content in mouse tissues, thereby delaying the aging of multiple organs.

This study is the first to map the spatial transcriptome of pan-organ aging in mammals, revealing tissue structural disorder and loss of cellular identity as key aging hallmarks and precisely locating the core regions and microenvironmental characteristics of aging sensitivity.

The Immunoglobulin-associated Senescence Phenotype (IASP) proposed by the study expands the frontiers of aging science and opens new avenues for delaying aging and preventing related diseases.

More information: Shuai Ma et al, Spatial transcriptomic landscape unveils immunoglobulin-associated senescence as a hallmark of aging, *Cell* (2024). DOI: [10.1016/j.cell.2024.10.019](https://doi.org/10.1016/j.cell.2024.10.019)

Provided by Chinese Academy of Sciences

Cannabis Use Linked to Epigenetic Changes, Study Finds



Using cannabis may cause changes in the human body's epigenome, a study of over 1,000 adults suggests. The [epigenome](#) functions like a set of switches, activating or deactivating genes to change how our bodies function.

"We observed associations between cumulative marijuana use and multiple epigenetic markers across time," [explained](#) epidemiologist Lifang Hou from Northwestern University when the research was published in 2023.

[Cannabis](#) is a [commonly used substance in the United States](#), with 49 percent of people trying it at least once, Hou and a team of US researchers report in their [published paper](#).

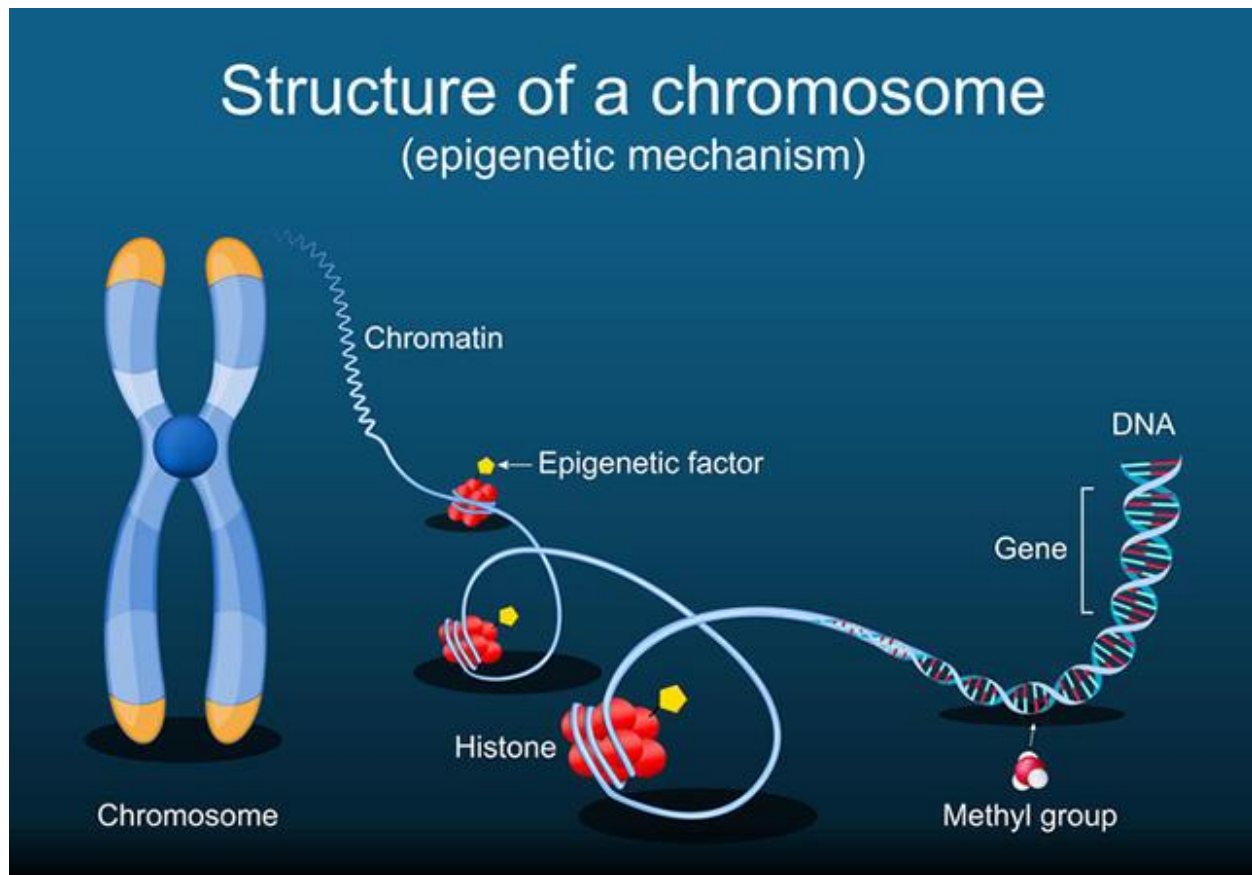
Some US states and [other countries](#) have made cannabis legal, but we still don't fully understand its [effects on our health](#).

The researchers studied around 1,000 adults who had participated in a long-term previous study where they had been asked about their cannabis use over a 20-year period.

Study participants provided blood samples on two occasions during that time, at the 15- and 20-year points. They were aged between 18 and 30 at baseline, or 'year 0'.

Using these blood samples from five years apart, Hou and her team looked at the [epigenetic changes](#), specifically [DNA methylation](#) levels, of people who had used cannabis recently or for a long time.

The addition or removal of [methyl groups](#) from DNA is one of the most studied epigenetic modifications. Without changing the genomic sequence, it changes the activity of genes, because it's harder for cells to read the genome instruction manual with these molecular changes in their way.



When epigenetic factors, which can come from other genes or the environment inside a cell or beyond, recruit a methyl group, it changes the expression of our genes. (ttsz/iStock/Getty Images)

Environmental and lifestyle factors can trigger these methylation changes, which can be [passed onto future generations](#), and blood [biomarkers](#) can provide information about both recent and historical exposures.

"We previously identified associations between marijuana use and the aging process as captured through DNA methylation," Hou [said](#).

"We wanted to further explore whether specific epigenetic factors were associated with marijuana and whether these factors are related to health outcomes."

Environmental and lifestyle factors can trigger methylation changes, which can be passed on to future generations.

The comprehensive data on the participants' cannabis use allowed them to estimate cumulative use over time as well as recent use and compare it with DNA methylation markers in their blood for analysis.

They found numerous DNA methylation markers in the 15-year blood samples, 22 that were associated with recent use, and 31 associated with cumulative cannabis use. In the samples taken at the 20-year point, they identified 132 markers linked to recent use and 16 linked to cumulative use.



The buds of a cannabis plant contain the most cannabinoids. (Esteban López/Unsplash)

"Interestingly, we consistently identified one marker that has previously been associated with tobacco use," Hou [explained](#), "suggesting a potential shared epigenetic regulation between tobacco and marijuana use."

Multiple epigenetic changes associated with cannabis use had previously been linked to things like [cellular proliferation](#), [hormone signaling](#), infections, neurological disorders like [schizophrenia](#) and [bipolar disorder](#), and [substance use disorders](#).

It's important to note that this study doesn't prove that cannabis directly causes these changes or causes health problems.

"This research has provided novel insights into the association between marijuana use and epigenetic factors," [said](#) epidemiologist Drew Nannini from Northwestern University.

"Additional studies are needed to determine whether these associations are consistently observed in different populations. Moreover, studies examining the effect of marijuana on age-related health outcomes may provide further insight into the long-term effect of marijuana on health."

The study has been published in [Molecular Psychiatry](#).

Longevity Breakthrough: New Protein Discovery Could Be the Key to Healthier Aging

New research found that the protein MANF helps cells manage toxic protein clumps, improving cellular health and potentially aiding treatments for age-related diseases like Alzheimer's and Parkinson's.

Researchers at [McMaster University](#) have uncovered a previously unidentified cell-protective role of a protein, potentially paving the way for new treatments for age-related diseases and promoting healthier aging.

The team has found that a class of protective proteins known as MANF plays a role in the process that keep cells efficient and working well.

The findings appear in the journal *Proceedings of the National Academy of Sciences*.

Our cells make proteins and discard them after they perform their jobs. This efficient, continuous maintenance process is known as cellular homeostasis. However, as we age, our cells' ability to keep up declines.

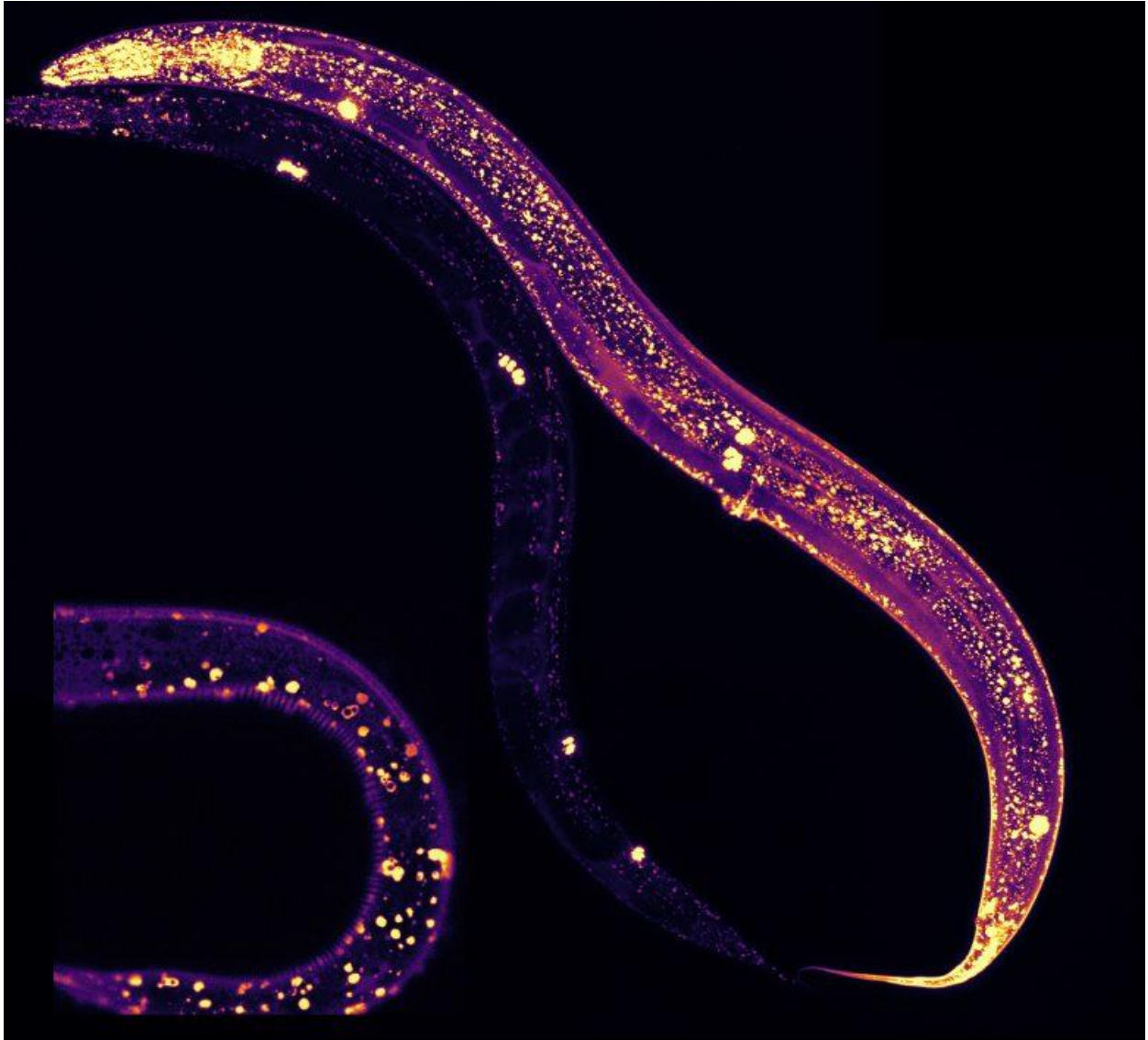
Cells can create proteins incorrectly, and the cleanup process can become faulty or overwhelmed. As a result, proteins can clump together, leading to a harmful buildup that has been linked to such diseases as Alzheimer's and Parkinson's.

"If the cells are experiencing stress because this protein aggregation has started, the endoplasmic reticulum, which is where proteins are made and then released, gets the signal to stop making these proteins," explains biology professor Bhagwati Gupta, who supervised the research.

"If it can't correct the problem, the cell will die, which ultimately leads to degeneration of the neurons and then neurodegenerative diseases that we see."

MANF's Role in Cellular Maintenance

Previous studies, including one from McMaster, had shown that MANF protects against increased cellular stress. The team set out to understand how this happens by studying microscopic worms known as *C. elegans*. They created a system to manipulate the amount of MANF in *C. elegans*.



C. elegans examined under a microscope. The yellow and purple dots are the regions where MANF protein is located. Credit: McMaster University

“We could literally see where MANF was expressed in the worms because they are translucent. We could see it in all different tissues. Within these tissues, MANF was present in structures known as lysosomes which are associated with lifespan and protein aggregation,” said Shane Taylor, now a post-doctoral fellow at the University of British Columbia who worked on the project for his PhD while at McMaster.

Activating the Natural Cellular Clean-Up System

The team discovered that MANF plays a key role in the cell’s disposal process by helping to break down the accumulated proteins, keeping cells healthier and clutter-free.

Increasing MANF levels also activates a natural clean-up system within cells, helping them function better for longer.

“Although our research focused on worms, the findings uncover universal processes. MANF is present in all animals, including humans. We are learning fundamental and mechanistic details that could then be tested in higher systems,” said Taylor.

To develop MANF as a potential therapy, researchers want to understand what other players MANF interacts with.

“Discovering MANF’s role in cellular homeostasis suggests that it could be used to develop treatments for diseases that affect the brain and other parts of the body by targeting cellular processes, clearing out these toxic clumps in cells, and maintaining their health,” said Gupta.

“The central idea of aging research is basically can we make the processes better and more efficient. By understanding how MANF works and targeting its function, we could develop new treatments for age-related diseases. We want to live longer and healthier. These kinds of players could help that.”

Reference: “The neurotrophic factor MANF regulates autophagy and lysosome function to promote proteostasis in *Caenorhabditis elegans*” by Shane K. B. Taylor, Jessica H. Hartman and Bhagwati P. Gupta, 17 October 2024, *Proceedings of the National Academy of Sciences*.

DOI: [10.1073/pnas.2403906121](https://doi.org/10.1073/pnas.2403906121)

Could a genetic trait delay Alzheimer’s?

Researchers have discovered a rare genetic trait that could delay the onset of Alzheimer's in people who face an overwhelming risk of developing the mind-robbing disease.

A study published Wednesday in The New England Journal of Medicine reported that 27 people from an extended Colombian family who carried a genetic variant called Christchurch developed Alzheimer's disease several years later than expected. The findings build on early research in 2019 from a unique family predisposed to pass on the disease. The researchers found that a woman who had the same genetic trait delayed the onset of Alzheimer's by about three decades.

Scientists from Mass General Brigham believe the evidence could be used to develop an Alzheimer's drug or medication that replicates the protective effects of the Christchurch genetic variant.

"We have enough evidence, and now the focus should be on trying to leverage this discovery to our therapies," said Dr. Joseph Arboleda-Velasquez, a scientist at Mass General Brigham who co-authored the study. The aim is huge, he said: "How can we learn from the protective effects of Christchurch to develop new therapies that will help everybody?"

Why did researchers focus on a family in Colombia?

The research was isolated to South America where the participants worked with a rare set of data. More than 1,000 members of an extended family in Colombia carry a genetic mutation that puts them at near certain risk of developing early-onset Alzheimer's disease. The symptoms usually begin when the relatives are in their mid-40s. The mutation carriers are part of an extended family of about 6,000 people who live in and around Medellin, Colombia. In the 1980s, a University of Antioquia neurologist, Francisco Lopera, discovered the family [had been afflicted with this inherited mutation](#), passed from generation to generation, for decades. Using advances in genetic testing, doctors identified the inherited mutation that triggered early-onset Alzheimer's in these family members. It was called the Paisa mutation, named after the inhabitants of the region.

What did this study examine?

From 1995 through 2022, researchers from the University of Antioquia in Medellin collected detailed information about the family members who participated in [a series of medical studies](#). The family members underwent medical exams, genetic testing and neuropsychological assessments.

Researchers examined detailed information of family members who carried the Paisa mutation. Researchers knew the Paisa mutation carriers typically developed memory and thinking problems in their mid-40s and typically died more than a decade later.

In 2019, researchers discovered a woman who carried the Paisa mutation and did not experience symptoms of Alzheimer's until she reached her 70s – about three decades later than the symptoms have typically appeared among Paisa mutation

carriers. Genetic testing revealed this woman also had two copies of the Alzheimer's gene APOE3 variant, called the Christchurch variant.

In the study published this week, researchers examined whether Christchurch offered extra protection to people who also have the Paisa mutation. They found 27 people with the Paisa mutation and one copy of the Christchurch variant. Those individuals preserved normal memory and thinking longer than a comparable group who just had the Paisa mutation.

The group that only had Paisa showed signs of disease at a median age of 47, while people who carried Christchurch and Paisa did not exhibit memory and thinking problems until they were 52 - five years later.

Yakeel T. Quiroz, a study co-author and clinical neuropsychologist and neuroimaging researcher at Massachusetts General Hospital, said the research findings "suggest the potential for delaying cognitive decline and dementia in older individuals."

Quiroz added the findings can be used to develop effective treatments to prevent Alzheimer's dementia.

What's next for drug development?

Arboleda-Velasquez, who works as a Harvard Medical School associate professor of ophthalmology, said his laboratory is using these study findings to develop potential antibody drugs to combat Alzheimer's disease.

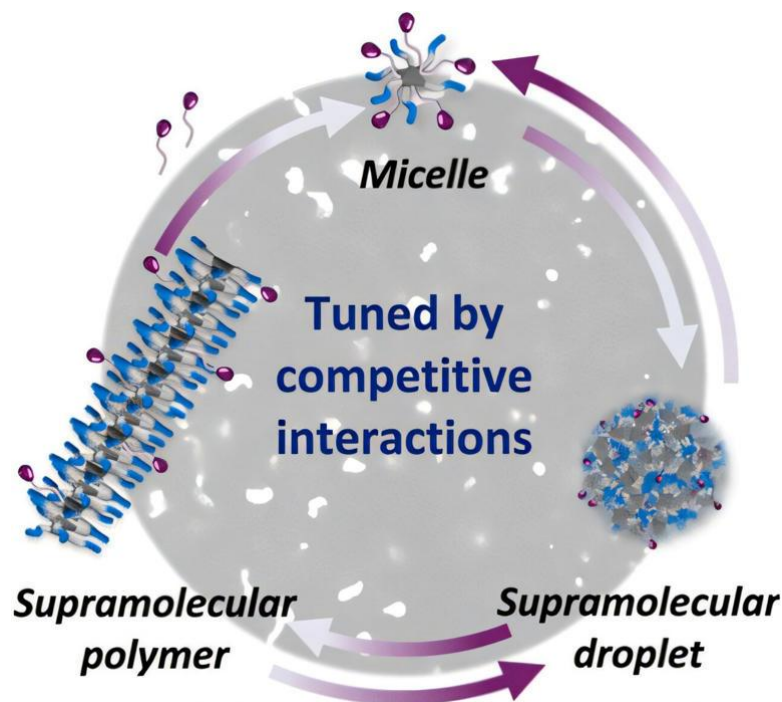
His goal is to begin testing medications in human clinical trials by 2026.

Eric Reiman, executive director at Banner Alzheimer's Institute in Phoenix and a co-author of the study, said the study bolsters the "idea that this rare variant of the major genetic risk factor for Alzheimer's disease plays a protective role in the development of Alzheimer's."

Reiman said further research is needed into the underlying role of APOE on hallmarks of the disease, including beta-amyloid plaques and tau tangles found in Alzheimer's patients.

The Christchurch study "provides further support for the idea of targeting APOE in the treatment and potential prevention of Alzheimer's disease."

Simple model system can break down fibrils to investigate drugs for neurodegenerative diseases



Credit: Journal of the American Chemical Society (2024). DOI: 10.1021/jacs.4c11285

The origin of many diseases such as Alzheimer's or Parkinson's can be found at the molecular level in our body, in other words, in proteins. In a healthy system, these proteins are responsible for numerous physiological functions.

In order to carry out certain tasks, they may also assemble in groups consisting of numerous proteins. Once that job is done, they split up again and go their own ways. However, if larger clusters of a hundred or more proteins form so-called fibrils, which are bundles of long, filament-like accumulations of proteins, the attraction between the proteins is so strong that they can no longer separate from each other.

The resultant plaques can induce a wide variety of disorders. If the fibrils accumulate in the brain, for instance, they can increase intracranial pressure, thus triggering neurodegenerative diseases.

Disintegration of fibrils achieved for the first time

The formation of fibrils is generally an irreversible process, both in the human body and in synthetic systems. Professor Shikha Dhiman of Johannes Gutenberg University Mainz (JGU) in Germany and Professor Lu Su of Leiden University in the Netherlands have recently succeeded in creating a model system in which fibrils can be broken down into their individual components or liquid droplets.

The project also involved two Ph.D. students, Mohit Kumar in Mainz and Heleen Duijs in Leiden. "This is the first model system in which we have succeeded in reversing this process without any chemical reaction," reported Dhiman. The findings are [published](#) in the *Journal of the American Chemical Society*.

Within fibrils, non-covalent bonds—such as hydrogen bridges—link the single units together. These are not particularly robust on their own, but it is the high number of bonds and their order that gives fibrils their superior stability. The researchers thus decided to use a bit of a trick: They added substances that embed themselves in fibrils, creating pocket-like formations that make the fibril structure unstable.

"What we are in effect doing is introducing competing binding partners. These form bonds with single units, the interaction between units becomes redundant, and the fibrils begin to disintegrate," explained Dhiman.

Model system allows for systematic investigations

A particularly interesting feature of the model system is that it allows all parameters that can be modified to be systematically studied one by one. Until recently, researchers had assumed that individual proteins come together to form fibrils. Recently, however, this concept has been disproved. Rather, several

proteins accumulate together with water and salts resulting in liquid droplets, with the proteins arranging themselves on the surface of these droplets. This is a significant intermediate state in the actual formation of fibrils.

In contrast with fibrils, these droplets can undertake normal functions in the body and can even break up to release the proteins again.

"Our model system has been able to map all three states, namely individual single units, liquid droplets, and fibrils," explained Shikha Dhiman, Professor at the JGU Department of Chemistry and senior researcher in the CoM2Life (Communicating Biomaterials: Convergence Center for Life-Like Soft Materials and Biological Systems) research network.

Fundamental basis for the development of innovative therapies

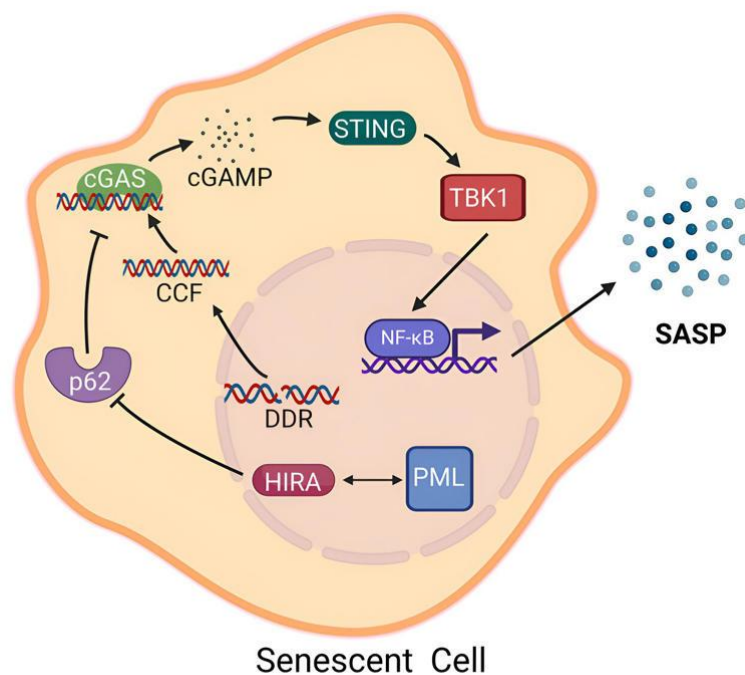
In the long term, the model system will support the development of drugs to treat a range of disorders, particularly neurodegenerative diseases such as Alzheimer's and Parkinson's. Unlike in complex systems such as cells, all parameters of the model system can be readily explored to answer various questions: What causes protein droplets to clump together to form fibrils? How can this process be regulated? How can fibrils be broken down into short fibers?

Once the researchers have resolved these fundamental issues, they can investigate the cellular level—based on large-scale screening of active substances. "The potential in terms of therapeutic applications is enormous," emphasized Lu Su, Assistant Professor at the Leiden Academic Center for Drug Research.

"We expect that drugs developed on the basis of this model will be used for the targeted disintegration of pathological fibrils to alleviate symptoms and improve outcomes for patients."

More information: Heleen Duijs et al, Harnessing Competitive Interactions to Regulate Supramolecular "Micelle-Droplet-Fiber" Transition and Reversibility in

The secret to sleepy cells' control of inflammatory secretions



Credit: *Molecular Cell* (2024). DOI: [10.1016/j.molcel.2024.08.006](https://doi.org/10.1016/j.molcel.2024.08.006)

Scientists at Sanford Burnham Prebys and the La Jolla Institute for Immunology have revealed a new secret regarding senescence, a cellular state similar to sleep that is more likely to affect aged cells. This drowsy condition is known to provide health benefits under certain conditions while also potentially causing collateral damage.

"Senescence is not all bad," said Peter D. Adams, Ph.D., the director of the Cancer Genome and Epigenetics Program at Sanford Burnham Prebys and senior author on the new study. "It is a tumor suppression mechanism that prevents cancer by blocking the proliferation of potentially cancerous cells."

"It is also involved in orchestrating the wound healing response," added Nirmalya Dasgupta, Ph.D., instructor at the La Jolla Institute for Immunology, former postdoctoral associate in Adams' lab and first author on the study. "Through its inflammatory function, it can control tissue repair and wound healing."

However, senescence can be a double-edged sword with age and the immune system's declining efficiency at removing senescent cells. As these sleepy cells accumulate to unhealthy levels, they can stop aging tissues from properly regenerating.

"In addition to no longer growing and proliferating, the other hallmark of senescent cells is that they have this inflammatory program causing them to secrete inflammatory molecules," said Adams.

Too many of these secreted molecules can contribute to chronic inflammation in the body. This pervasive inflammation—called "inflammaging"—has been linked to many age-related diseases, such as rheumatoid arthritis, liver disease, atherosclerosis, muscle wasting (sarcopenia) and cancer.

Adams, Dasgupta and their collaborators have [published](#) results in *Molecular Cell*, describing a new connection between the inflammation caused by senescent cells and a protein involved in the process of winding up six feet of DNA tightly enough to fit into the nuclear center of cells.

The scientists defined how this protein influences the increase in inflammation when our cells slip into a state of slumber. By detailing this process, the authors may have uncovered a new opportunity to find drugs that can promote healthy aging by preventing or reducing chronic inflammation from the collection of too many senescent cells as we get older.

The research team began by modifying cells to deactivate the gene holding the codes for the HIRA protein, one of the histone chaperones responsible for helping to build spools out of histones used to hold DNA like a thread.

They also similarly silenced the gene for promyelocytic leukemia (PML) protein, which—when contained in tiny, dense spheres called nuclear bodies—serves as an anchor and organizing point for many proteins involved in a wide variety of functions, including the replication of complete copies of DNA during cell growth and the transcription of DNA into RNA during the building of new proteins. The scientists then forced the cells to become senescent and compared the modified cells to normal senescent cells.

The absence of HIRA and PML in the modified cells did not reverse the sleepy cells' lack of growth and proliferation. The two proteins did prove to be necessary for the cells to begin emitting the inflammatory molecules that can lead to inflammaging, which is known as senescence-associated secretory phenotype (SASP).

"One school of thought is that we should remove senescent cells to promote healthier aging," said Dasgupta. "An alternative view is that senescence has had a role throughout evolution, so removing it could be harmful. Under this view, reducing the inflammation from SASP may be more helpful and less risky, so learning more about its causes is crucial."

The research team followed up with additional experiments that demonstrated that HIRA had to move to PML nuclear bodies for senescent cells to enter their inflammatory state. The scientists also found that HIRA was essential for activating the pathway of cellular signals considered to be the primary way senescent cells begin oozing out inflammatory molecules.

In addition, the team discovered a new behavior for HIRA within the gel-like cytoplasm that occupies the space in the cell between the membrane and nucleus. HIRA physically interacts with a protein called p62 that was found to reduce the secretion of inflammatory molecules.

"With these results, we've defined a new pathway and new players in the process that kick-starts senescent cells' inflammatory program," said Adams. "This knowledge provides more opportunities to try and find new drugs to inhibit that process."

Adams says that the team will continue this research by collaborating with the team at Sanford Burnham Prebys' Conrad Prebys Center for Chemical Genomics (Prebys Center) to identify small molecules which target the newly defined

pathway. The Prebys Center is a comprehensive center for drug discovery and chemical biology.

In addition to finding new drugs, it may be possible to repurpose existing drugs. Dasgupta said at least four drugs currently in cancer clinical trials may be effective at preventing HIRA from being transported to PML nuclear bodies. This movement by HIRA was found to be needed for senescent cells to secrete inflammatory molecules, marking drugs that can halt HIRA's localization to PML nuclear bodies as candidates for future research into healthy aging treatments.

"Our results also will help accelerate the work of the SenNet Consortium as we continue developing a detailed map of where these senescent cells are and what they look like," notes Adams.

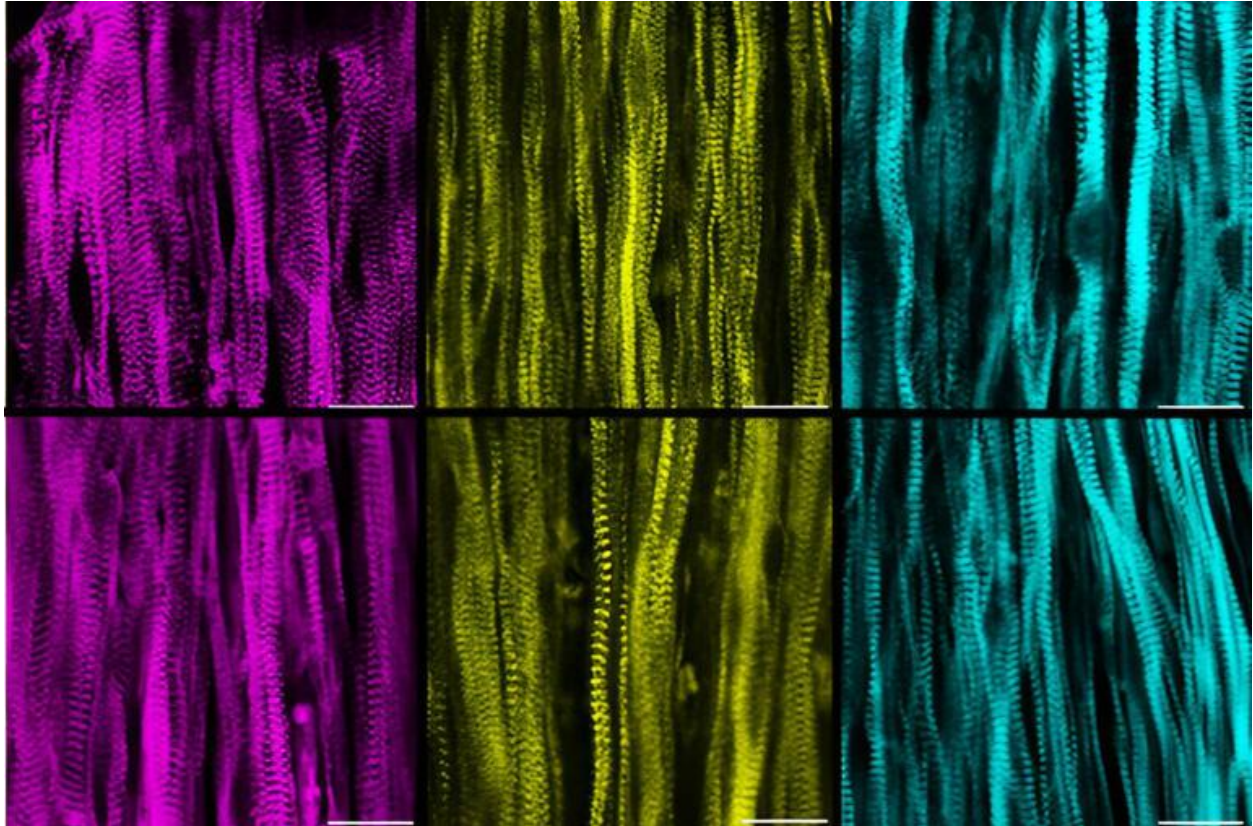
Adams co-directs the San Diego Tissue Mapping Center within the Cellular Senescence Network (SenNet) Consortium, a large network of U.S. labs and research institutions.

"With our partners in the consortium, we want to know what senescent cells look like at the molecular level," said Adams. "We're looking for the gene expression programs and the signaling pathways which are activated in these cells, in different cell types and different tissues. With Nirmalya and the team, now we've uncovered another piece to the larger puzzle we're pulling together. Building a comprehensive map of senescence will enable us to better target senescent cells with treatments to promote healthy aging."

More information: Nirmalya Dasgupta et al, Histone chaperone HIRA, Promyelocytic Leukemia (PML) protein and p62/SQSTM1 coordinate to regulate inflammation during cell senescence., *Molecular Cell* (2024). DOI: [10.1016/j.molcel.2024.08.006](https://doi.org/10.1016/j.molcel.2024.08.006). [www.cell.com/molecular-cell/fulltext/S0092-8674\(24\)00660-9](https://www.cell.com/molecular-cell/fulltext/S0092-8674(24)00660-9) ... 1097-2765(24)00660-9

Provided by Sanford-Burnham Prebys

Lab-grown muscles reveal mysteries of rare muscle diseases



The top row of photos show a microscopic view of healthy muscle fibers stained to reveal a variety of irregularities, while the bottom row shows the same but for muscle fibers afflicted by the disease LGMD2B. Notice any differences? Neither did the experts, revealing that the effects of the disease are not caused by physical malformations within the muscles. Credit: Alastair Khodabukus, Duke University© Provided by Medical Xpress

Biomedical engineers at Duke University have developed a new technique to better understand and test treatments for a group of extremely rare muscle disorders called dysferlinopathy or limb girdle muscular dystrophies 2B (LGMD2B). The approach grows complex, functional 3D muscle tissue from stem cells in the laboratory, creating a platform that replicates patient symptoms and treatment responses.

In their debut study, researchers reveal some of the biological mechanisms underlying the characteristic loss of mobility caused by LGMD2B. They also

demonstrate that a combination of existing treatments may be able to alleviate some of the worst symptoms of the disease.

The [results](#) appear in the journal *Advanced Science*.

LGMD2B affects only about eight people per million around the world. Unlike its more well-known and more common cousin Duchenne muscular dystrophy, the disease affects both men and women, presents later in life—in the late teens or early 20s—and is rarely fatal. However, LGMD2B patients develop severe weakness in the legs and shoulders, typically requiring them to use wheelchairs for the rest of their lives.

Caused by a genetic disorder, LGMD2B stops the body from creating a fully functional form of a protein called dysferlin. There are currently no approved treatments or cures. Part of the reason for this lack of options is the many functions of dysferlin, including sealing holes in muscle membranes, regulating calcium balances required for muscle contraction and controlling cellular metabolism. And for reasons unknown, affected muscles initially accumulate fat within the muscle fibers themselves before degenerating and ultimately being replaced by fat cells.

An array of Petri dishes each housing a platform for growing muscle fibers from stem cells. The Bursac Lab was the first to grow contracting, functional human skeletal muscle in a Petri dish and has been improving its processes ever since to enable studies of muscle strength, metabolism and repair. Credit: Alastair Khodabukus, Duke University© Provided by Medical Xpress

"This phenomenon is very rare even for muscular dystrophies," said Nenad Bursac, professor of biomedical engineering at Duke. "It's a burning question within the community of why that happens."

One of the challenges facing researchers trying to solve these problems is that the mouse model used to approximate LGMD2B shows very mild symptoms compared to patients. Mice with the disease are still able to walk, and it does not present until nearly a year into their two-year long lifespan, making studies of the disease extremely slow.

Dysferlin is expressed in other cell types, and blood levels of metabolic fuels such as cholesterol are also altered in mice and patients. Together, this complicates LGMD2B research by making it difficult to assess what cell types are responsible for the disease and if metabolic changes are due to the loss of dysferlin itself or whole-body effects.

To get around these challenges, Bursac and his research scientist Alastair Khodabukus turned to an engineered muscle platform that they have been developing for nearly a decade. The Bursac Lab was the first to grow contracting, functional human skeletal muscle in a Petri dish and has been improving its processes ever since to enable studies of muscle strength, metabolism and repair. This system allowed them to focus their study on only the effects of dysferlin on skeletal muscle without the complications of other cell types or altered blood metabolite profiles.

In the study, the researchers began with induced pluripotent stem cells (IPSCs) derived from patients living with LGMD supplied by The Jain Foundation, a charity focused on finding a cure for LGMD2B. Using their muscle-growing techniques, the lab matured these stem cells into muscle fibers and ran them through a battery of tests over the course of six weeks.

Like muscles found in patients themselves, the lab-grown versions displayed a wide variety of issues.

"Overall, our model repeated a lot of the clinical manifestations of the disease and observations made in real patients, but it was all done in a Petri dish," said Bursac. "We've been able to gain new insights into the muscle-specific aspects of the disease."

The researchers discovered that the loss in muscle strength was not the result of deficiencies in muscle structure or size, but in its handling of calcium. Muscle contractions are physically caused by reservoirs of calcium in muscle cells being released and binding to muscle proteins. Tests showed that the diseased muscle cells had sprung leaks in their calcium reserves, resulting in less calcium to release and weaker contractions.

The researchers also showed that the lack of dysferlin caused damage to the muscle cells to go unrepaired, and that an inability to burn fatty acids for energy production was at least partially to blame for the accumulation of fat within muscle fibers that has long puzzled the medical community.

"We replicated something seen in patients and showed that it's not due to environmental factors within the body, but issues within the muscle itself," Khodabukus said.

The researchers then tested the effects of two drug candidates to potentially treat the disease that have been identified through mouse models but have not yet been tested in humans. One called dantrolene is supposed to stop calcium from leaking from muscle cells' reservoirs. The second, called vamorolone, was recently approved for use with Duchenne muscular dystrophy patients, although researchers do not fully understand how it works.

Together, the drugs prevented the calcium leak and helped the cell membrane repair itself, restoring much of the muscles' strength. And while they also helped reduce the amount of fat accumulated within the muscles, they did not fully prevent it, nor did they help the muscles efficiently burn fats for fuel.

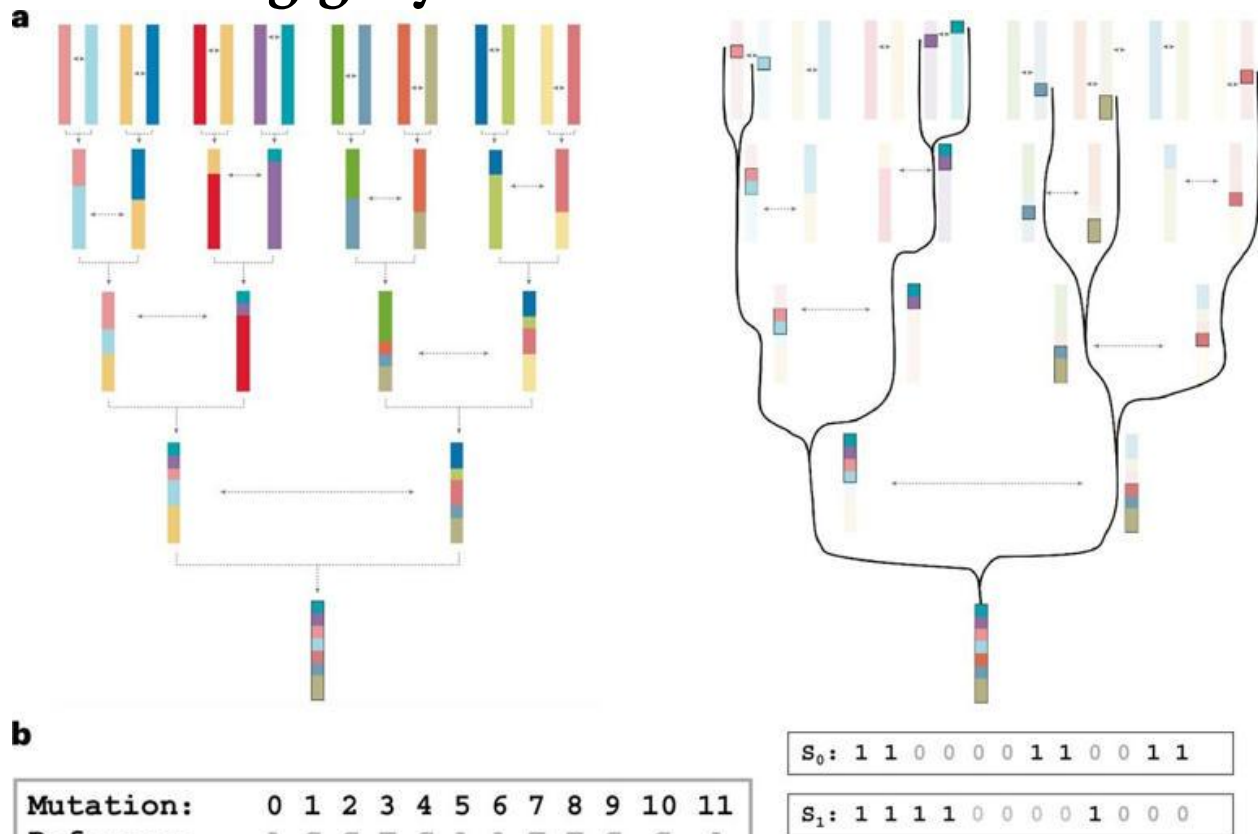
Moving forward, the group is planning to add immune and fat cells to their experiments for greater complexity. They also are looking to further understand disruptions to cellular metabolism and to find new drugs that fully restore all strength, repair and metabolic deficit.

"Right now, we have a basic muscle-only system, which is great to see the effects of the disease within the muscle itself, but what is also important is the crosstalk between immune cells, fat cells and muscle cells," Khodabukus said. "By building out our system more, we'll hopefully be able to fully figure out what is driving the loss of muscle and its replacement by fat in these patients."

More information: Alastair Khodabukus et al, Bioengineered Model of Human LGMD2B Skeletal Muscle Reveals Roles of Intracellular Calcium Overload in Contractile and Metabolic Dysfunction in Dysferlinopathy, *Advanced Science* (2024). DOI: [10.1002/advs.202400188](https://doi.org/10.1002/advs.202400188)

Provided by Duke University

New method compresses terabytes of genomic data into gigabytes



The biological interpretation of the GRG data structure. Credit: Nature Computational Science (2024). DOI: 10.1038/s43588-024-00739-9

Genomic researchers used to be able to store their datasets on a laptop, but with so many whole genomes available now to study, the resulting big datasets must be stored in the cloud—resulting in more expensive, slower and more unwieldy computations.

A new method developed at Cornell provides tools and methodologies to compress hundreds of terabytes of genomic data to gigabytes, once again enabling researchers to store datasets in local computers. Their paper, "Enabling Efficient Analysis of Biobank-Scale Data with Genotype Representation Graphs," [published](#) Dec. 5 in *Nature Computational Science*.

"Even just a few years ago, the data we were studying usually wasn't whole genome sequencing data, which meant only a small fraction of the genomes were being measured, rather than the entire genome. And because of that, the size of the data wasn't so crazy," said April Wei, assistant professor of computational biology in the College of Arts and Sciences.

Raw data size can now run into the petabytes, said co-author Drew DeHaas, computational genetics programmer in the College of Agriculture and Life Sciences.

Wei had always wanted to develop methods to utilize biobank-scale data for doing research because of the richness of the information available, but many of the things she wanted to do weren't possible because of the computational cost and challenge. This inspired her, she said, to tackle the compression problem, which led to the Genotype Representation Graph (GRG) method, which uses graphs to manage the data.

"Graph-based methods have long been used in computer science and other fields to provide a clear framework for solving challenging problems," DeHaas said, but prior to GRG had not been applied to a data compression solution in genomics at the Biobank scale.

Wei, trained as a population geneticist, had deep familiarity with graphs used in population genetics—although GRG is designed quite differently.

"Unlike conventional matrix-based representations, GRG represents genotypes as a graph, where relationships between individuals are captured through shared mutations in their genomes. The GRG data structure not only encodes genotypic information more intuitively and compactly, but also facilitates efficient graph-based computations for advanced analyses," said co-author Ziqing Pan, doctoral student in the field of computational biology.

GRG compresses the data while focusing on scalability and faithfully representing the data, according to Wei.

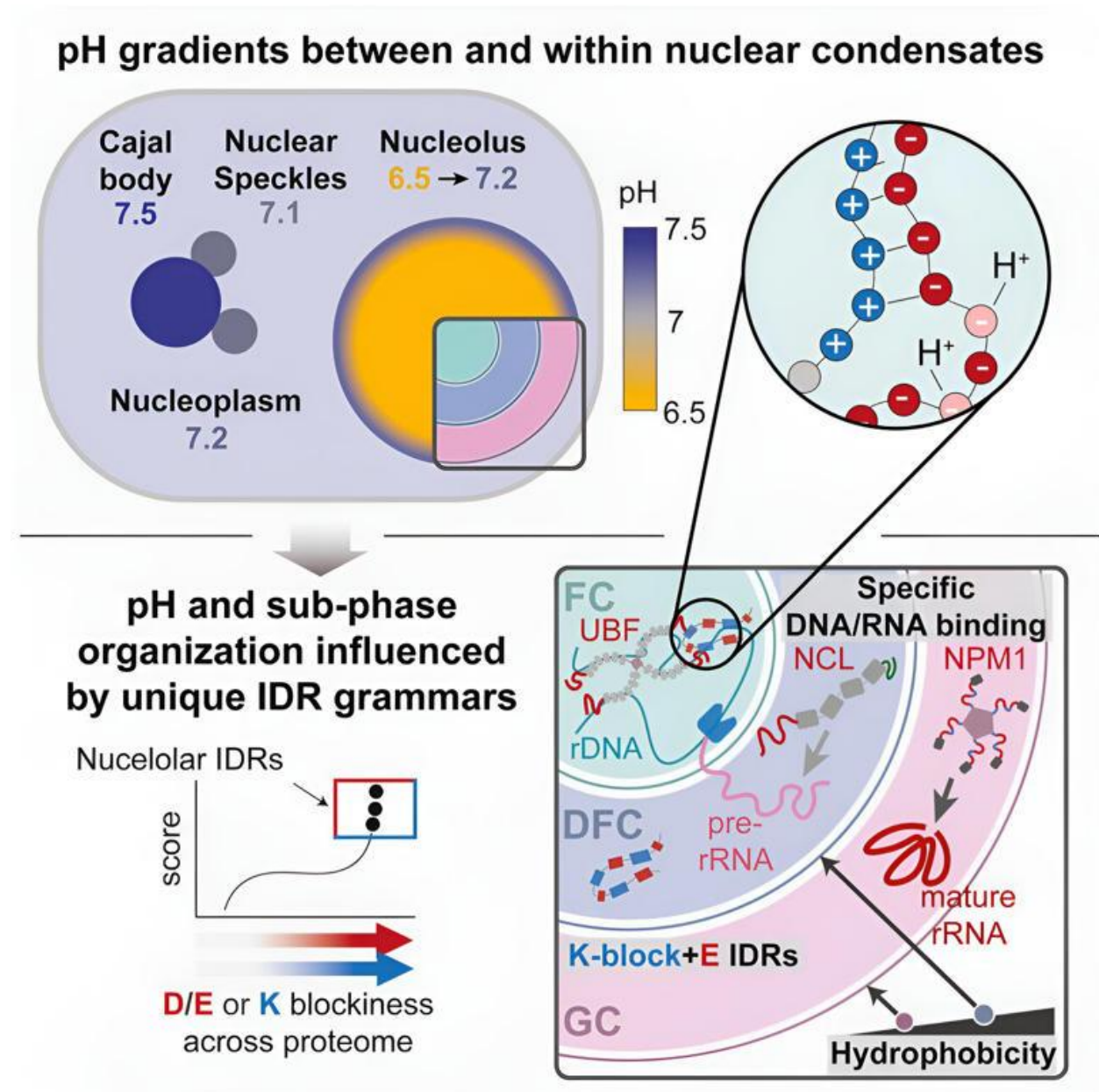
"The great benefit of utilizing graphs for compression is that we can do computations with graphs, without the need to decompress the data," she said. "Also, specific algorithms could be developed to do things that people couldn't do with older formats, so there are potentially more benefits."

Because the GRG enables researchers to analyze the same data more efficiently, it also lowers costs.

More information: Drew DeHaas et al, Enabling efficient analysis of biobank-scale data with genotype representation graphs, *Nature Computational Science* (2024). DOI: [10.1038/s43588-024-00739-9](https://doi.org/10.1038/s43588-024-00739-9)

Provided by Cornell University

Engineers manage a first: Measuring pH in cell condensates



Graphical Abstract. Credit: Cell (2024). DOI: 10.1016/j.cell.2024.02.029© Provided by Phys.org

Scientists trying to understand the physical and chemical properties that govern biomolecular condensates now have a crucial way to measure pH and

other emergent properties of these enigmatic, albeit important, cellular compartments.

Condensates are communities of proteins and nucleic acids. They lack a membrane and come together and fall apart as needed. The nucleolus is a prominent condensate in cells. It serves vital roles in cellular physiology and is the site of ribosome production.

Ribosomes are the multi-protein and RNA assemblies where the genetic code is translated to synthesize proteins. Impairment of ribosome production and other nucleolar dysfunctions lie at the heart of cancers, neurodegeneration, and developmental disorders.

In a first for the condensate field, researchers from the lab of Rohit Pappu, the Gene K. Beare Distinguished Professor of biomedical engineering, and colleagues in the Center for Biomolecular Condensates in the McKelvey School of Engineering at Washington University in St. Louis, figured out how nucleolar sub-structures are assembled.

This organization gives rise to unique pH profiles within nucleoli, which they measured and compared with the pH of nearby non-nucleolar condensates, including nuclear speckles and Cajal bodies.

In the study [published](#) in *Cell*, the authors report that the distinct protein compositions of nucleoli give them an acidic character, whereas nuclear speckles have the same pH as the nucleus, and Cajal bodies are more basic.

Building on spatial proteomics data from the lab of Emma Lundberg, associate professor of bioengineering at Stanford University, and novel algorithms developed by Kiersten Ruff, a staff research scientist at McKelvey, and colleagues in the Pappu lab, the team identified unique "molecular grammars" including the presence of proteins with long acidic tracts as a key defining feature of many nucleolar proteins.

This, the team reasoned, must help carry hydrogen protons into nucleoli (pH is the measurement of the activity of protons).

Condensates are like a gathering of people on a convention floor. There are no walls keeping them in place, just sparkling conversations led by a few key

individuals—the "scaffolds." The community of molecules that come together enables emergent properties in the condensates, like internal pH in nucleoli.

Condensates form via a process that the team now refers to as condensation. This combines phase separation—think demixing of oil and water—and sticky interactions among molecules that like to bind with one another.

"A combination of specific interactions and distinct solubility profiles defines biomolecules. Condensation involves the totality of these interactions, and this gives rise to what is known as emergent properties," said Matthew King, a postdoctoral fellow in the Pappu lab and lead author of the paper.

The new research provides a starting point for understanding how emergent properties, whereby the whole is greater than the sum of its parts, give rise to condensate-specific "physicochemical barcodes," according to King.

Differentials in pH between condensates and the surrounding nucleoplasm generate gradients, and "a pH gradient generates what is known as a proton motive force," King said.

This proton motive force, measured to be -88 mJ per proton, "might be able to facilitate directional movement of RNA and protein molecules, which is a key first step in enabling ribosomal assembly," King added.

Getting chemical probes to the right place in cells and measuring the condensates required technological innovations that included contributions from McKelvey project partners Michael Vahey, assistant professor of biomedical engineering, and Matthew Lew, associate professor of electrical and systems engineering.

According to Pappu, this work "provides an elegant solution to the challenge that many biochemists see for the condensate concept."

Cellular reactions require specificity. Every biochemical reaction must take place in the right place, at the right time, and must involve specific sets of proteins and nucleic acids.

"Condensates were often criticized as being non-specific blobs," Pappu said.

Thanks to this new research, those blobs clearly have specific physiochemical properties.

"We now have evidence that distinct compositional biases of condensates generate distinct physicochemical environments, and this might provide the basis for biochemical specificity," Pappu noted.

More information: Matthew R. King et al, Macromolecular condensation organizes nucleolar sub-phases to set up a pH gradient, *Cell* (2024). DOI: [10.1016/j.cell.2024.02.029](https://doi.org/10.1016/j.cell.2024.02.029)

Provided by Washington University in St. Louis

DECEMBER 16, 2024

Study finds brain enzyme inhibition reduces obesity in mice

Endocannabinoids in the brain play a key role in food intake and energy use. Modulating the action of these molecules could help fight obesity, say researchers at Université de Montréal's affiliated hospital research center (CRCHUM).

For years, Université de Montréal medical professor Stephanie Fulton and her team have been unraveling the mechanisms in the human nervous system that control people's need to eat and to engage in [physical activity](#), and how their metabolism affects their mood.

Their latest discovery, [published](#) in *Nature Communications*, takes that knowledge a step further.

In their study, first co-authors David Lau, an Université de Montréal doctoral student, and Stephanie Tobin, a former postdoctoral fellow, show that body-weight control in mice is strongly modulated by neurons in the [nucleus accumbens](#), a region of the brain that's rich in endocannabinoids and that helps regulate food reward and physical activity.

In the brain, the enzyme ABHD6 degrades a key endocannabinoid molecule known as 2-arachidonoylglycerol (2-AG).

With the discovery in 2016 that whole-body inhibition of ABHD6 reduced body weight and protected against diabetes—a finding made by the team of Marc Prentki, a researcher at the

CRCHUM—the question arose as to what this enzyme does in the brain to affect appetite and body weight.

"We expected that increasing 2-AG levels would stimulate [food intake](#) by increasing cannabinoid signaling, but paradoxically found that when we deleted the gene encoding ABHD6 in the nucleus accumbens in mice, there was less motivation for food and greater interest in physical activity," said Fulton.

"The mice chose to spend more time on a running wheel as compared to the [control group](#) which became obese and lethargic."

By injecting a targeted ABHD6 inhibitor into the brains of mice, her team was able to completely protect them from [weight gain](#) and obesity.

Can have opposite effects

The ability to target specific neuronal pathways in the brain to control weight is crucial for scientists today. Depending on the area of the brain targeted, inhibiting ABHD6 can have opposite effects.

In 2016, Fulton and her CRCHUM colleague Thierry Alquier showed that blocking ABHD6 in certain hypothalamic neurons made mice resistant to weight loss.

In the current study, however, the authors show that brain-wide inhibition of this molecule has a net effect of diminishing weight gain on a high-fat diet.

No signs of anxiety

"In our study, we also show that mice in which the gene encoding ABHD6 has been inhibited do not show signs of anxiety and depressive behavior," said Fulton.

This is important given that Rimonabant, a [weight-loss](#) drug that targeted [cannabinoid receptors](#) in the central nervous system, was withdrawn from the market in the late 2000s after people taking the drug reported strong side effects: depression and suicidal tendencies.

Fulton's team's latest work helps pave the way for therapies to fight obesity and metabolic disorders such as type 2 diabetes, the scientists believe.

While ABHD6 drug inhibitors are being screened, it remains to be seen whether the mechanisms targeted by the researchers in [mice](#) will be the same in humans.

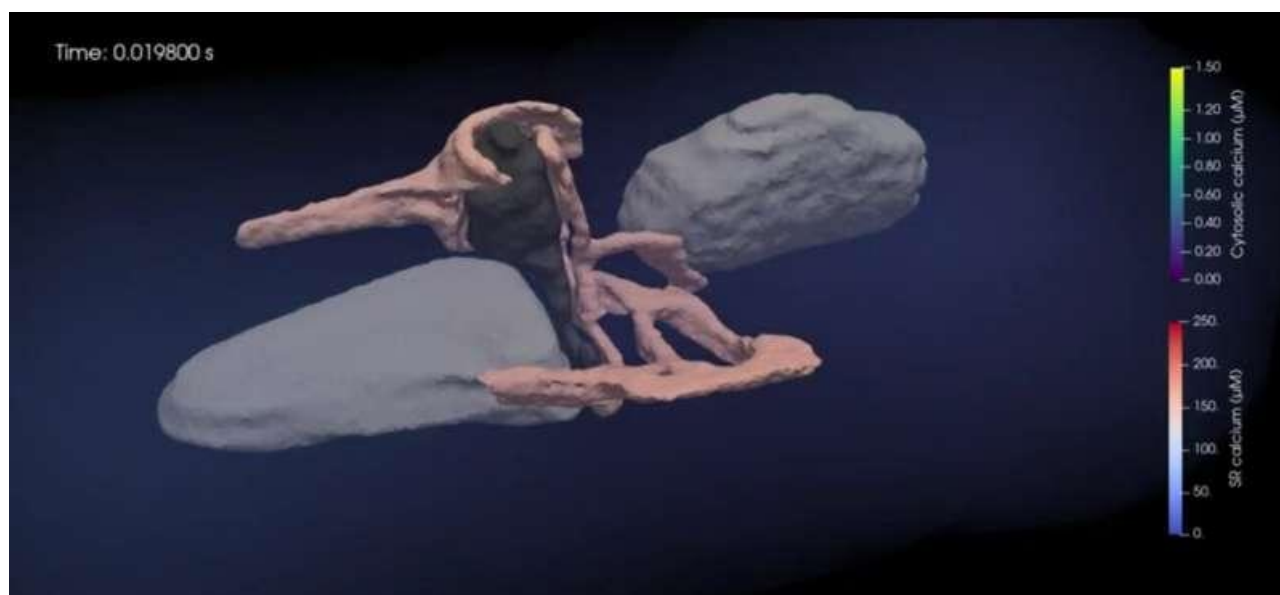
More information: ABHD6 loss-of-function in mesoaccumbens postsynaptic but not presynaptic neurons prevents diet-induced obesity in male mice, *Nature Communications* (2024). DOI: [10.1038/s41467-024-54819-5](https://doi.org/10.1038/s41467-024-54819-5)

DECEMBER 19, 2024

[Editors' notes](#)

New software unlocks secrets of cell signaling, showing realistic simulations

by [University of California - San Diego](#)



Credit: Department of Pharmacology at UC San Diego School of Medicine and the Department of Mechanical and Aerospace Engineering at UC San Diego Jacobs School of Engineering.

Researchers at University of California San Diego have developed and tested a new software package, called Spatial Modeling Algorithms for Reactions and Transport (SMART), that can realistically simulate cell-signaling networks—the complex systems of molecular interactions that allow cells to respond to diverse cues from their environment.

Cell-signaling networks involve many distinct steps and are also greatly influenced by the complex, three-dimensional shapes of cells and subcellular components, making them difficult to simulate with existing tools. SMART offers a solution to this problem, which could help accelerate research in fields across the life sciences, such as [systems biology](#), pharmacology and [biomedical engineering](#).

The researchers successfully tested the new software in biological systems at several different scales, from cell signaling in response to adhesive cues, to calcium release events

in subcellular regions of neurons and [cardiac muscle cells](#), to the production of ATP (the energy currency in cells) within a detailed representation of a single mitochondrion.

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This video shows a simulation created with SMART that showcases the calcium release dynamics within heart cells. This process is essential for heart muscles to contract. Credit: Emmet Francis, Ph.D., an American Society for Engineering Education postdoctoral fellow in the research group supervised by Professor Padmini Rangamani, Ph.D., both affiliated with the Department of Pharmacology at UC San Diego School of Medicine and the Department of Mechanical and Aerospace Engineering at UC San Diego Jacobs School of Engineering.

By providing a flexible, accurate and efficient tool for modeling cell-signaling networks, SMART paves the way for more detailed simulations to advance our understanding of cellular behavior and drive the development of new treatments for human diseases.

The study, published in [Nature Computational Science](#), was led by Emmet Francis, Ph.D., an American Society for Engineering Education postdoctoral fellow in the research group supervised by Professor Padmini Rangamani, Ph.D., both affiliated with the Department of Pharmacology at UC San Diego School of Medicine and the Department of Mechanical and Aerospace Engineering at UC San Diego Jacobs School of Engineering. The initial version of this software was written by Justin Laughlin, Ph.D., a former graduate student in Rangamani's group.

SMART is part of an ongoing collaboration with a research team led by Marie Rognes, Ph.D., at Simula Research Laboratory in Oslo, Norway.

More information: *Nature Computational Science* (2024). DOI: [10.1038/s43588-024-00745-x](https://doi.org/10.1038/s43588-024-00745-x). www.nature.com/articles/s43588-024-00745-x

Journal information: [Nature Computational Science](#)

Provided by [University of California - San Diego](#)

[Making cell modeling more realistic](#)

DECEMBER 19, 2024

Evolutionary study reveals toxic reach of disease-causing bacteria across plant kingdom

by [John Innes Centre](#)



Spores of *Ceratopteris richardii*, the model fern used in the study. Credit: Phil Carella
The capacity of bacteria to spread disease across the plant kingdom may be much more widespread than previously suspected, according to new analysis.

John Innes Centre researchers took a comparative evolutionary approach, using the diversity of *Pseudomonas syringae* bacteria, to determine how this pathogen infects distantly related plants.

In experiments, researchers in the team of Dr. Phil Carella, group leader, analyzed the toxin syringomycin produced by the most widely infectious *P. syringae* strains, and compared its effect on both non-flowering and flowering plants.

The results showed that syringomycin was toxic in non-flowering plants (represented in this study by model species of a liverwort and fern), causing tissue death and activation of stress-related genes.

These effects were even more important for infections in non-flowering plants compared to flowering plants, which was surprising as much of our current understanding of how pathogenic (disease causing) bacteria manipulate plant hosts is centered on flowering plants which include some of our major crops.

By featuring non-flowering species, this [study](#), which appears in *Cell Host & Microbe*, adds to a growing body of research that shows how bacterial pathogens carry the potential to colonize distantly related plants.

"Each of the [plant species](#) used in this study has a different life history since they last shared a [common ancestor](#) 500 million years ago. However, a single group of pathogens can infect each of them using a common set of pathogenicity factors," said Dr. Carella.

"Our results demonstrate that pathogen virulence may be more general across plants than previously believed."

The researchers hypothesize that *P.syringae* virulence is centered on fundamental processes shared among the Plant Kingdom. In this case, the toxin syringomycin likely interferes with cell membranes across each of the diverse plants tested.

Sometimes non-flowering plants are considered less sophisticated than their flowering relatives which arrived later in [evolutionary history](#), but this study emphasizes the importance of analyzing the whole of the plant world to understand fundamental mechanisms and processes which could be applied to defending food crops against disease.

"Overall, our research shows that diverse plants can reveal useful knowledge about plant-pathogen interactions in general, which is informative for research on crop diseases. We don't eat liverworts, but they can teach us a lot about the core virulence mechanisms of important pathogens," observes Dr. Carella.

The next step for this research is to explore the role the toxin plays in promoting the spread of bacteria, and how it cooperates with bacterial effector proteins to cause disease. Another interesting research question to explore is why some *P.syringae* populations do not carry the toxin.

The group will also expand the diversity of plants used in the experiments to search for those that are resistant to bacterial pathogens.

More information: A necrotizing toxin enables *Pseudomonas syringae* infection across evolutionarily divergent plants, *Cell Host & Microbe* (2024). DOI: [10.1016/j.chom.2024.11.014](https://doi.org/10.1016/j.chom.2024.11.014). www.cell.com/cell-host-microbe ... 1931-3128(24)00445-1

Journal information: *Cell Host & Microbe*

Provided by [John Innes Centre](#)

Scientists develop game-changing method to grow crops using 'built-in' fertilizer: 'We're learning what genes ... are needed'



Reducing pollution from fertilizer further benefits human health.

In a win for crucial cereal crops, researchers have developed a way to allow the plants to convert nitrogen gas from the air to fertilizer to help them grow, as [reported](#) by Interesting Engineering.

The method, which aims to place a series of a minimum of seven genes into the crops' mitochondria and chloroplasts, allows cereal crops, such as [corn](#) and [rice](#), to achieve nitrogen fixation through sunlight without applying fertilizer.

Nearly 100 years ago, the [Haber-Bosch](#) process led to an enormous increase in global food production by revolutionizing the conversion of nitrogen in the atmosphere to a form that allowed for the production of fertilizer on an industrial scale.

However, despite the mass production of the product, IE explained that many areas, like sub-Saharan Africa, are still unable to get it due to a lack of infrastructure. This area, and others like it, have [high food scarcity](#), an issue that is growing as [extreme weather](#) further threatens the crops they can grow.

Ironically, while the Haber-Bosch process has prevented mass starvation, it also has a large carbon footprint. While it allows crops to be mass produced, it also contributes to Earth's overheating, the effects of which are threatening [staple products](#).

Utah State University biochemist Lance Seefeldt told the publication that almost 2% of the world's well of [dirty energy](#) is used to produce fertilizer. Not only does this harm the environment, but the fertilizer itself is also damaging, with [toxic runoff](#) wreaking havoc on water ecosystems.

To help highly struggling areas and the overall [global food supply](#), which is at risk due to the effects of rising global temperatures, Seefeldt and USU Senior Scientist Zhi-Yong Yang have collaborated on a project with colleagues in Spain and the United States for the past five years to [reengineer the biology](#) of cereal crops.

At first, they narrowed the number of genes needed for nitrogen fixation to nine but were later surprised to find they could eliminate some they initially considered critical.

"The goal is to place genes into the crops' mitochondria and chloroplasts, enabling them to generate sufficient energy to drive nitrogen fixation," Yang told IE. "This is a pretty cool piece of evidence. Essentially, these staple caloric crops — rice, corn, and potatoes — could have built-in fertilizer."

"Piece by piece, we're learning what genes and what combination of genes are needed to achieve nitrogen fixation in different cells," Seefeldt said. "Instead of just one horn playing, we're trying to get the whole orchestra to play together."

Aside from providing a solution to end food scarcity in less-developed and less-accessible areas, by eliminating the need for toxic fertilizer for a large subset of crops, the process plays a major role in helping to clean up the food and agriculture industries. Reducing [pollution from fertilizer](#) further benefits human health.

The process brings out-of-this-world benefits, too. IE reported that Seefeldt and USU colleague Bruce Bugbee have collaborated on [NASA-funded efforts](#) to investigate how to sustain human life on long-duration space missions, including trips to Mars.

Bioengineers propose revolutionary new method for grow-in-the-dark food: 'Becoming increasingly vital to ... support a growing population'



Bioengineers propose revolutionary new method for grow-in-the-dark food: 'Becoming increasingly vital to ... support a growing population'

Bioengineers have proposed using an innovative method to grow food called "electro agriculture," a [technology](#) that enables food to grow in the dark and massively reduces energy use.

As Interesting Engineering [reported](#), our rapidly changing climate is making it harder to grow crops efficiently, necessitating technological adaptations to bridge the gap. Traditional agriculture requires tons of resources, such as land,

water, and fertilizer, which are under enormous pressure as the population grows.

That's why bioengineers came up with the idea to [grow food indoors](#) in the dark to improve efficiency. The IE report [explained](#) the process would mimic photosynthesis in plants using a solar-powered chemical reaction between carbon dioxide and water, producing acetate. Genetically engineered plants would then utilize the acetate for energy rather than sunlight, resulting in an efficiency rate four times higher than photosynthesis.

Under normal climate conditions, photosynthesis would be efficient enough to provide food for everyone, even though only 1% of sunlight is transformed into chemical energy. But with rising demand, it's crucial to [harness technology](#) so we have plenty of food for the future.

"Since electro-agriculture is not dependent on climate conditions and offers greater efficiency than traditional farming, it could serve as a valuable method for producing supplemental food when necessary," senior author Feng Jiao told IE.

"With global [climate change](#) affecting agriculture, innovative food production technologies are becoming increasingly vital to stabilize food markets and support a growing population."

[Watch now: Expert reveals one message that marketers keep getting wrong](#)

If the electro agriculture method is made commercially available, it could reduce land needed for agriculture by a whopping 94%, the researchers explained in a [news release](#).

Agriculture is a major contributor to our overheating planet, accounting for roughly 10% of total U.S. pollution, per [Resources for the Future](#). Growing food in vertical indoor farms powered by solar power would help reduce heat-trapping gases and free up land for conservation or other purposes.

The key to achieving success with this method is getting the plants to eat acetate instead of consuming sunlight for energy. While bioengineers are still working on reconfiguring plants to eat acetate, we can look to mushrooms, algae, and yeast

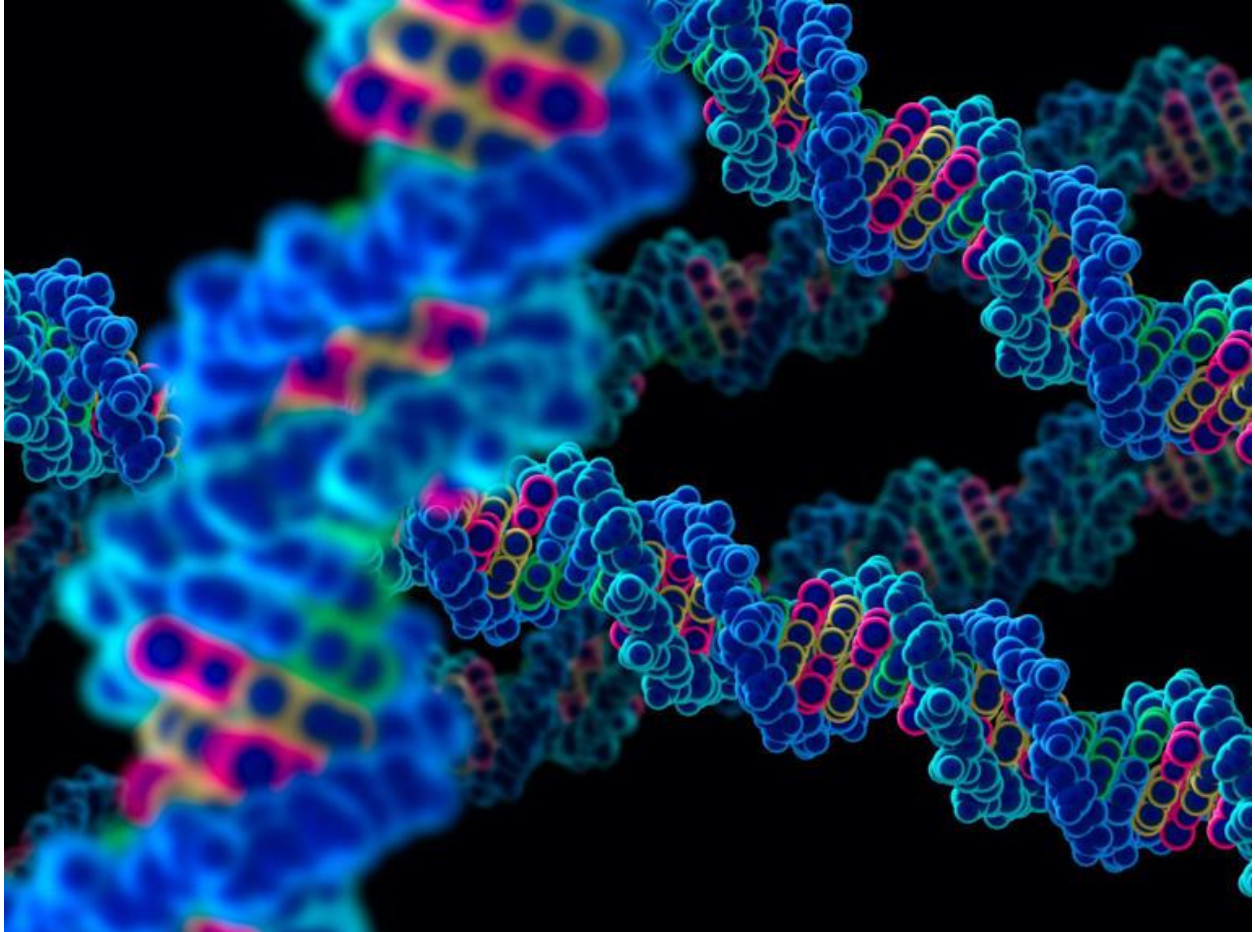
for encouragement since they already rely on acetate for energy. This means that with more research, the technology to grow other crops using this process could be available on a mass scale sooner than we think.

The team is currently working on growing lettuce and tomatoes using electro agriculture, but it hopes to produce other nutritious foods, such as cassava, sweet potatoes, and grains in the future.

"We have successfully produced mushrooms entirely from acetate derived from CO₂. These mushrooms look and taste just like traditional mushrooms, with no noticeable differences. Other food products are still under development, but they are expected to have a similar taste to conventional options," Jiao [told IE](#).

[Vertical ocean farms](#) that produce oysters and clams, and [indoor farms that grow fruits and veggies](#), are becoming an increasingly popular way to bolster our food supplies. One way we can make a difference is by [eating more plants and less meat](#) for our health and the planet.

Researchers solve the mystery of 50,000 DNA "knots" in the human genome



Scientists have mapped 50,000 i-motifs in the human genome, uncovering their regulatory roles and potential applications in disease treatment and diagnostics. (CREDIT: National Institutes of Health)© The Brighter Side of News

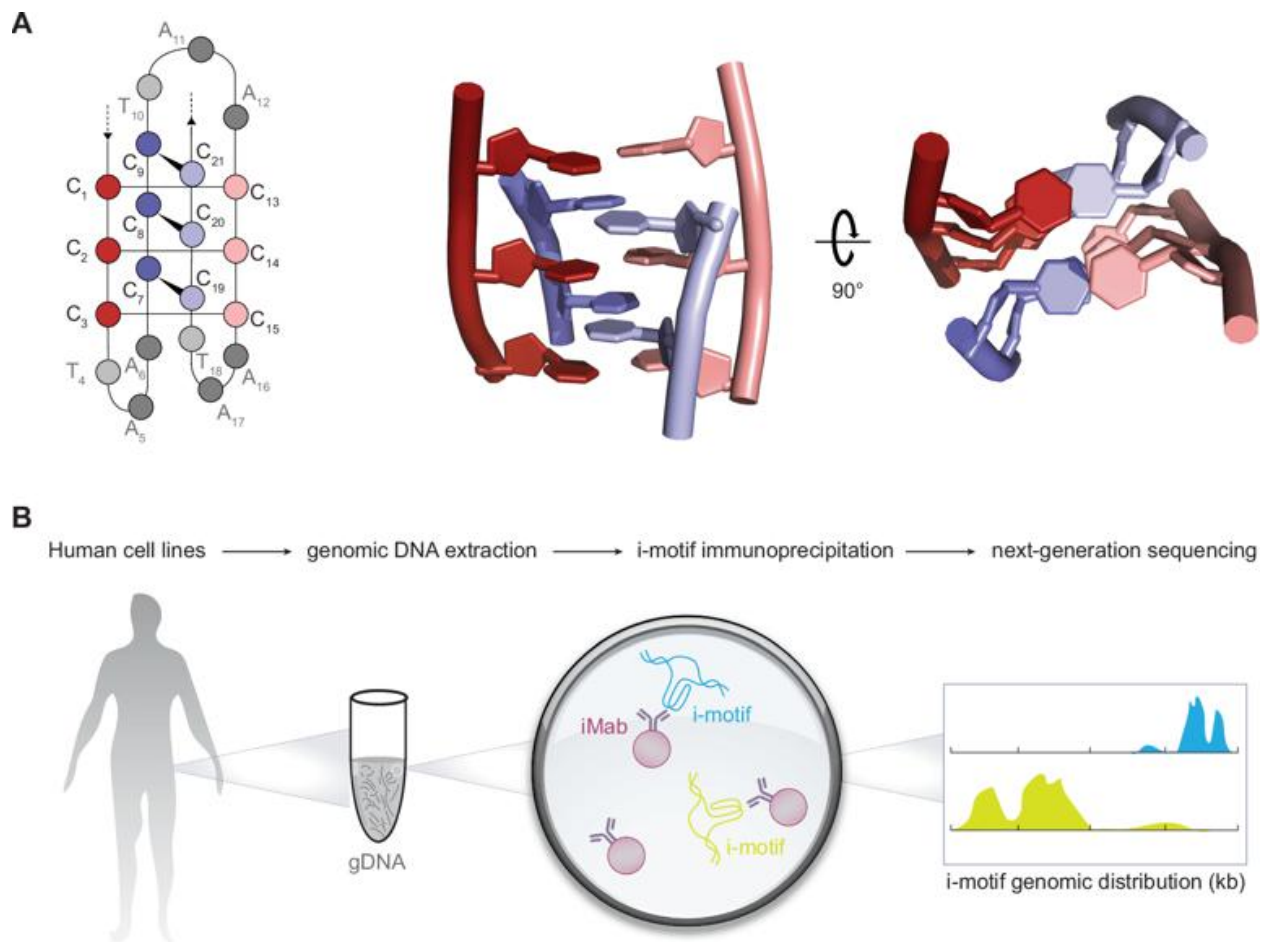
DNA's iconic double helix has long been the symbol of life's blueprint. However, the [human genome](#) conceals far more complexity. Among these mysteries are i-motifs, unusual knot-like DNA structures formed when cytosine-rich sequences fold into a four-stranded, twisted configuration.

Recent research has illuminated the prevalence and potential significance of i-motifs in human cells, shedding light on their possible role in gene regulation and disease.

Mapping i-Motifs in the Genome

A groundbreaking study by researchers at the [Garvan Institute of Medical Research](#) has revealed the presence of more than 50,000 i-motifs across the human genome. This comprehensive mapping, published in [The EMBO Journal](#), represents a major advance in understanding these mysterious structures.

Using a specially developed antibody capable of identifying and binding to i-motifs, researchers pinpointed their locations in three distinct human cell types.



Identification of iM structures in human genomic DNA. (CREDIT: The Embo Journal)© The Brighter Side of News

Professor Daniel Christ, the study's senior author, highlights the significance of these findings. "This study confirms that i-motifs are not just laboratory curiosities but widespread structures that likely play key roles in genomic function," he says.

The discovery underscores how integral these formations may be to [cellular](#) processes, including gene regulation and cell cycle activity.

Unlike the canonical double helix, i-motifs form under specific conditions. They emerge when cytosine bases on the same DNA strand pair with each other, creating a unique structural feature.

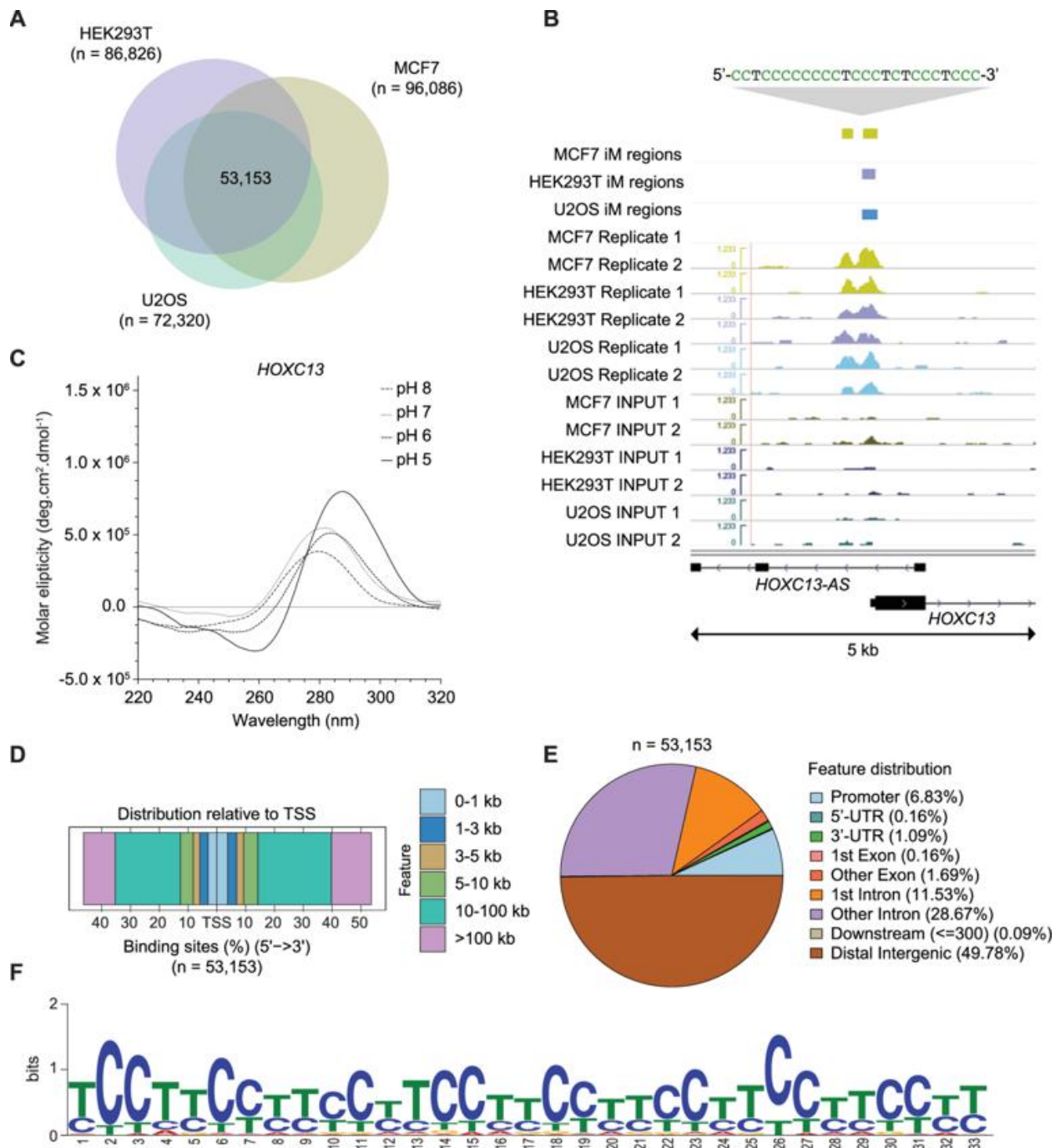
Initially, scientists questioned their relevance due to their apparent dependence on [acidic conditions](#) for formation. However, subsequent research demonstrated that i-motifs could exist at physiological pH levels, especially under conditions like molecular crowding and DNA superhelicity.

The latest study found that i-motifs are not randomly distributed. Instead, they are concentrated in genomic regions critical for regulating [gene activity](#). These areas include promoter regions of genes that are active during specific cell cycle phases.

“We discovered that i-motifs are associated with genes highly active during certain times in the cell cycle, suggesting they play a dynamic regulatory role,” explains Cristian David Peña Martinez, the study’s first author.

Intriguingly, i-motifs were also identified in the promoter regions of oncogenes, including the notoriously “undruggable” MYC oncogene. This discovery opens new avenues for targeting genes linked to cancer and other diseases.

The potential applications of i-motif research extend beyond understanding [DNA structure](#). Their association with regulatory regions linked to disease highlights their promise as therapeutic and diagnostic targets.



iM structures are detectable and broadly distributed across human genomic DNA. (CREDIT: The Embo Journal)© The Brighter Side of News

Associate Professor Sarah Kummerfeld, a co-author of the study, underscores this potential. "The widespread presence of i-motifs near 'holy grail' sequences involved in hard-to-treat cancers opens up possibilities for innovative diagnostic and therapeutic approaches," she says.

Designing drugs to target i-motifs could provide a novel way to influence gene expression, expanding options for treating diseases like [cancer](#).

While the discovery of i-motifs marks a significant milestone, their full biological implications remain a subject of ongoing investigation. Advanced techniques, such as high-affinity i-motif immunoprecipitation followed by sequencing, have enabled researchers to map these structures and explore their genomic distribution. These tools have shown that i-motifs are prevalent in genes upregulated during the G0/G1 [cell cycle](#) phases.

"This study exemplifies how fundamental research and [technological innovation](#) can converge to make paradigm-shifting discoveries," says Professor Christ. The ability to map i-motifs and identify their roles in gene activity provides a foundational resource for future studies.

Researchers aim to unravel their structural and molecular functions further, paving the way for breakthroughs in understanding genome architecture and function.

The journey to decode i-motifs continues, offering exciting opportunities to address fundamental questions about DNA's hidden complexity.

As research progresses, these unique structures may hold the key to unlocking new treatments and diagnostics for [diseases](#) that have long eluded effective solutions.

Researchers discover how DNA impacts reproductive health and life expectancy

Human reproduction is influenced by a complex interplay of biology, genetics, and socioeconomic factors. Over the past few decades, substantial changes have occurred in reproductive trends across high-income countries.

People...

Genetic research reveals how DNA impacts fertility, menopause timing, and health outcomes. (CREDIT: CC BY-SA 4.0)

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[Human reproduction](#) is influenced by a complex interplay of biology, genetics, and socioeconomic factors. Over the past few decades, substantial changes have occurred in reproductive trends across high-income countries.

People are now delaying childbirth, often having their first child at or after age 30. Fertility declines as people get older, and birth intervals between children have lengthened, with some parents having additional children past age 40.

At the same time, [lifetime infertility](#) is rising. Globally, around 17.5% of people experience infertility, meaning one in six couples struggle to conceive. Childlessness is increasing as well, driven both by voluntary decisions and involuntary infertility.

For example, 20% of women born in 1965 remained childless by the end of their reproductive years. In Japan, this figure rose to 28% for women born a decade later. Finnish men face similar challenges; one-third of those born between 1969 and 1971 had no children by age 40. Economic pressures, shifting gender roles, and limited access to childcare are among the key drivers of these changes.

However, alongside these social and economic factors, genetic research reveals new insights into fertility and reproductive health. Recent studies show that nearly 50% of infertility cases can be traced to genetic causes. Genetic traits influence when menstruation begins, when menopause occurs, and how many children people are likely to have.

Researchers from the [University of Oxford](#) and the [University of Iceland](#) analyzed genetic data from 159 studies, identifying 37 genes tied to reproductive traits. Their findings highlight the profound link between DNA, fertility, and broader health outcomes.

One of the most significant discoveries is the role of the *FSHB* gene. This gene regulates follicle-stimulating hormone, which controls menstruation and menopause. *FSHB* is associated with 11 different reproductive traits, including the timing of puberty and

fertility decline. The gene's influence doesn't stop there; it connects reproductive health to conditions such as obesity, hormone-sensitive cancers, and even psychiatric traits. Lead author Professor Melinda Mills from the [Leverhulme Centre for Demographic Science](#) emphasized the importance of understanding these genetic factors, particularly as more people delay parenthood. "Our study brings together research on the genetics of reproduction to reveal common genes across traits and insights beyond fertility," she explained. "These are inherently linked to health, BMI, obesity, and other key outcomes."

Scientists recreate mouse from reprogrammed stem cells

Researchers use ancient genes from single-celled organisms to create mouse stem cells, uncovering a billion-year evolutionary link.

The emergence of multicellular life roughly 700 million years ago was a pivotal event that shaped the evolution of [life on Earth](#).

Key to this transformation was the development of stem cells, which possess the unique ability to either replicate themselves or differentiate into specialized cell types. These pluripotent stem cells play a foundational role in forming the complex structures and functions of multicellular organisms, including humans.

Stem cells fall into categories based on their potential. Pluripotent stem cells can become any cell type within the body, while multipotent stem cells are more limited, specializing in certain lineages. For instance, [neural stem cells](#) differentiate into neurons, astrocytes, and oligodendrocytes.

In vertebrates, pluripotent stem cells only exist during early embryonic stages, driven by specific transcription factors (TFs) like Sox2 and Oct4. These "pioneer" TFs are crucial, binding tightly to DNA even when it is wrapped in nucleosomes, and directing gene activity necessary for stem cell function.

Sox2 and Oct4 are central players in maintaining pluripotency. Without them, [stem cells](#) lose their capacity for self-renewal and differentiation. This partnership is essential during early embryonic development and in laboratory settings, such as in the generation of induced pluripotent stem cells (iPSCs).

These cells, created by reprogramming differentiated cells, rely on a cocktail of factors, including Sox2 and Oct4, to regain their pluripotent state.

Research has long held that Sox and POU family genes, like Oct4, emerged uniquely within the animal kingdom. However, a groundbreaking study published in [Nature Communications](#) challenges this view, suggesting these genes predate multicellular animals.

Dr. Alex de Mendoza of [Queen Mary University of London](#), along with colleagues from [The University of Hong Kong](#), achieved a scientific milestone by using genetic tools from choanoflagellates—unicellular relatives of animals—to reprogram mouse cells into pluripotent stem cells.

Super-fast DNA-based computer can run 100 billion parallel algorithms

In the ever-evolving world of computer technology, the fusion of biology and electronics is driving groundbreaking research.



In the ever-evolving world of computer technology, the fusion of biology and electronics is driving groundbreaking research. (CREDIT: Creative Commons)

In the ever-evolving world of computer technology, the fusion of biology and electronics is driving groundbreaking research.

At the center of this revolution is a liquid computer that can run over an astounding 100 billion different circuits, using DNA strands as its main component. This transformative approach might soon play a pivotal role in diagnosing diseases within living cells.

In the ever-evolving world of computer technology, the fusion of biology and electronics is driving groundbreaking research. (CREDIT: Creative Commons)

In the ever-evolving world of computer technology, the fusion of biology and electronics is driving groundbreaking research.

At the center of this revolution is a liquid computer that can run over an astounding 100 billion different circuits, using DNA strands as its main component. This transformative approach might soon play a pivotal role in diagnosing diseases within living cells. In a conventional computer, when you key in a command, it signals electrons to travel through a designated path on a silicon chip. This specific electron path configuration represents different mathematical operations. Consequently, introducing more functions to computer chips necessitates adding more of these paths.

Rather than relying on traditional wiring, the researchers investigated the potential of DNA. They strategized how to merge short segments of DNA to craft larger structures, which could operate as circuit components. These structures could act as the wiring itself or function to guide the wiring, ensuring stable molecular connections. The practical application involved filling tubes with DNA strands and a buffer fluid, then allowing the strands to connect, forming more complex molecules through chemical reactions. The team incorporated fluorescence markers into all the molecules, enabling monitoring of the circuit's activity based on the glowing of its parts.

DNA-based Programmable Arrays (DPGA)

The fundamental building blocks of this innovative computer are termed DNA-based programmable arrays (DPGA). With each DPGA designed to support over 100 billion unique circuits, researchers can customize its function by adding specific short molecules.

Schematic workflow of DPGA programming. (CREDIT: Nature)

In one of their notable experiments, the team linked three DPGAs, composed of about 500 DNA strands, creating a circuit capable of solving quadratic equations. In another experiment, they developed a circuit designed for calculating square roots. Inputs were added through specific molecules, which then interacted with the circuit's molecules in a manner comparable to electrons traveling through wires.

The circuit's output was identified in the molecules resulting from the final reaction. These molecules' fluorescent glow provided the means for the researchers to decode the results.

Nonlinear KIRC classification using integrated DPGAs. (CREDIT: Nature)

A Beacon of Hope in Medical Diagnostics

Beyond mere mathematical calculations, the research's most promising application lies in medical diagnostics. Using similar techniques, the team crafted a DPGA capable of differentiating between various small RNA molecules, particularly identifying those associated with a specific renal cancer.

This experiment epitomizes the ultimate goal of the DPGA technology. DNA's inherent compatibility with biological systems positions it as a potential tool for "intelligent diagnostics of different kinds of diseases," according to Dr. Wang. The diagnostic devices based on DPGA technology promise unparalleled parallel processing capabilities and energy efficiency.

DPGA reconfiguration for multitask operation. (CREDIT: Nature)

Looking Ahead

While the technology remains in its nascent stage, the potential implications are vast. As the realm of DNA computing expands, we could soon witness revolutionary advancements in medical diagnostics. Imagine a future where doctors can detect diseases seamlessly by merely analyzing the glow of molecules in our body fluids, or even from within our cells. With pioneers like Dr. Wang and his team at the helm, such a future may not be far off.

Dr. Wang optimistically stated, "DPGA-based diagnostic devices would be highly parallel and energy efficient." As science pushes the boundaries of possibility, it's clear that the intersection of biology and technology offers a hopeful path forward, promising transformative benefits for healthcare and beyond.

Breakthrough unlocks the secret of virgin birth: Implications for the future of reproduction

University of Cambridge scientists have identified and triggered a genetic mechanism that allows virgin birth, known as "parthenogenesis".

One strain of this fly reproduces only through virgin birth. (CREDIT: Jose Casal and Peter Lawrence)

In a groundbreaking discovery, scientists from the [University of Cambridge](#) have identified and triggered a genetic mechanism that allows virgin birth, known as "parthenogenesis", in the fruit fly *Drosophila melanogaster* – a creature that typically reproduces sexually. This newly acquired capability, once activated, can be inherited by subsequent generations, revealing potential profound implications for evolutionary biology and agriculture.

One strain of this fly reproduces only through virgin birth. (CREDIT: Jose Casal and Peter Lawrence)

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While the potential for parthenogenesis existed, the occurrence rate remained low. In their laboratory experiments, only a mere 1-2% of the second generation of genetically altered female flies exhibited the capability for virgin birth. Interestingly, these births transpired exclusively in the absence of male flies. When potential mates were available, females opted for conventional reproductive methods.

The ability to switch to a virgin birth could act as an evolutionary buffer. In situations where finding a mate becomes improbable, parthenogenesis can serve as a critical survival mechanism, ensuring the continuity of a species.

The findings, which are now available in the esteemed [journal Current Biology](#), were the culmination of meticulous research that spanned over six years and involved the examination of over 220,000 virgin fruit flies.

Researchers have identified the genes that are switched on, or switched off, when these flies reproduce without fathers. (CREDIT: Jose Casal and Peter Lawrence)

The investigative team began by sequencing the genomes of two strains of the fruit fly species *Drosophila mercatorum*. While one strain depended on males for reproduction, the other exclusively employed virgin birth. Through a careful comparison of the genomic structures, the team identified genes that were activated or deactivated when the flies underwent fatherless reproduction.

Armed with potential gene candidates responsible for parthenogenesis in *Drosophila mercatorum*, the scientists then tried to replicate the same genetic configurations in the commonly studied fruit fly, *Drosophila melanogaster*. The results were groundbreaking: for the first time, the *Drosophila melanogaster* exhibited the ability for virgin birth.

Dr Alexis Sperling in the laboratory (CREDIT: University of Cambridge/PA)

The success of this research is highly attributed to the choice of using the *Drosophila melanogaster* species. Known as the archetypal organism for genetic studies for over a century, the fruit fly's genetic landscape is well-charted, which made this genetic manipulation feasible. Dr. Sperling emphasized that achieving similar results in other animals would have been exponentially more challenging.

The ramifications of this discovery extend beyond the confines of mere academic interest. Dr. Sperling, who has since transitioned to the Cambridge Crop Science Centre, is eager to delve into the increasing prevalence of parthenogenesis in insect pests. "If there's continued selection pressure for virgin births in insect pests, which there seems to be, it will eventually lead to them reproducing only in this way. It could become a real problem for agriculture because females produce only females, so their ability to spread doubles," warned Sperling.

Dr Alexis Sperling in the laboratory (CREDIT: University of Cambridge/PA)

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problem for agriculture because females produce only females, so their ability to spread doubles,” warned Sperling.

This discovery has shed light on an astonishing and under-explored facet of reproductive biology. As science continues to delve into the enigmatic world of parthenogenesis, we may be on the brink of rewriting evolutionary paradigms and redefining agricultural practices in the future.

The Virus That Could’ve Ended Us is Now Saving Lives, Thanks to AI

Viruses are nature’s master engineers, capable of **encapsulating** and delivering **genetic material** with remarkable precision. These natural systems have long been a source of inspiration for scientists seeking to revolutionize gene therapy. Yet, replicating the intricate functionality of viral protein shells—known as **capsids**—has proven challenging. Artificial **nanocages**, modeled after viruses, have fallen short due to limited capacity and lack of complexity.

Now, a collaboration between **Professor Sangmin Lee** from **POSTECH** and **2024 Nobel Chemistry Laureate Professor David Baker** from the **University of Washington** has transformed this field. Their groundbreaking research, published in *Nature* on December 18, uses **artificial intelligence (AI)** to mimic and enhance viral structures, offering a new frontier in therapeutic delivery.

The Power of AI in Redefining Protein Design

Traditional gene therapy vectors, such as **adeno-associated viruses (AAVs)**, are limited by their small genetic payload capacity. To overcome this, the research team turned to **AI-driven computational design**, reimagining nanocages in tetrahedral, octahedral, and icosahedral shapes.

The standout is the **icosahedral nanocage**, with a diameter of 75 nanometers and the capacity to hold three times more genetic material than AAVs. By incorporating subtle asymmetries found in natural viruses, these AI-designed nanostructures achieve levels of functionality previously unattainable with traditional methods.

Key Features of Ai-Designed Nanocages:

- **Geometries:** Tetrahedral, octahedral, and icosahedral shapes.
- **Size:** Up to 75 nanometers in diameter.
- **Capacity:** Holds three times more genetic material than traditional AAVs.
- **Complexity:** Includes six distinct protein-protein interfaces.
- **Precision:** Symmetry confirmed via electron microscopy.

Precision Meets Performance: Testing the Nanocages

The AI-designed nanocages aren't just efficient—they're transformative. Electron microscopy validated the accuracy of these designs, and functional experiments proved their ability to deliver [therapeutic genes directly to target cells](#). This combination of precision and performance redefines what's possible in medical biotechnology.

Potential Applications:

- Gene therapy for genetic disorders.
- Development of next-generation vaccines.
- Precision-targeted drug delivery.

These multifunctional nanocages challenge the status quo, offering a platform for breakthroughs that go beyond current limitations.

Collaboration at the Forefront of Innovation

This achievement highlights the value of interdisciplinary collaboration. **Professor Lee**, who spent nearly three years working in **Professor Baker's** lab before joining POSTECH, brought a unique perspective to this partnership. Supported by

funding from the **Ministry of Science and ICT of Korea** and the **Howard Hughes Medical Institute (HHMI)**, the research exemplifies how global collaboration can drive scientific breakthroughs.

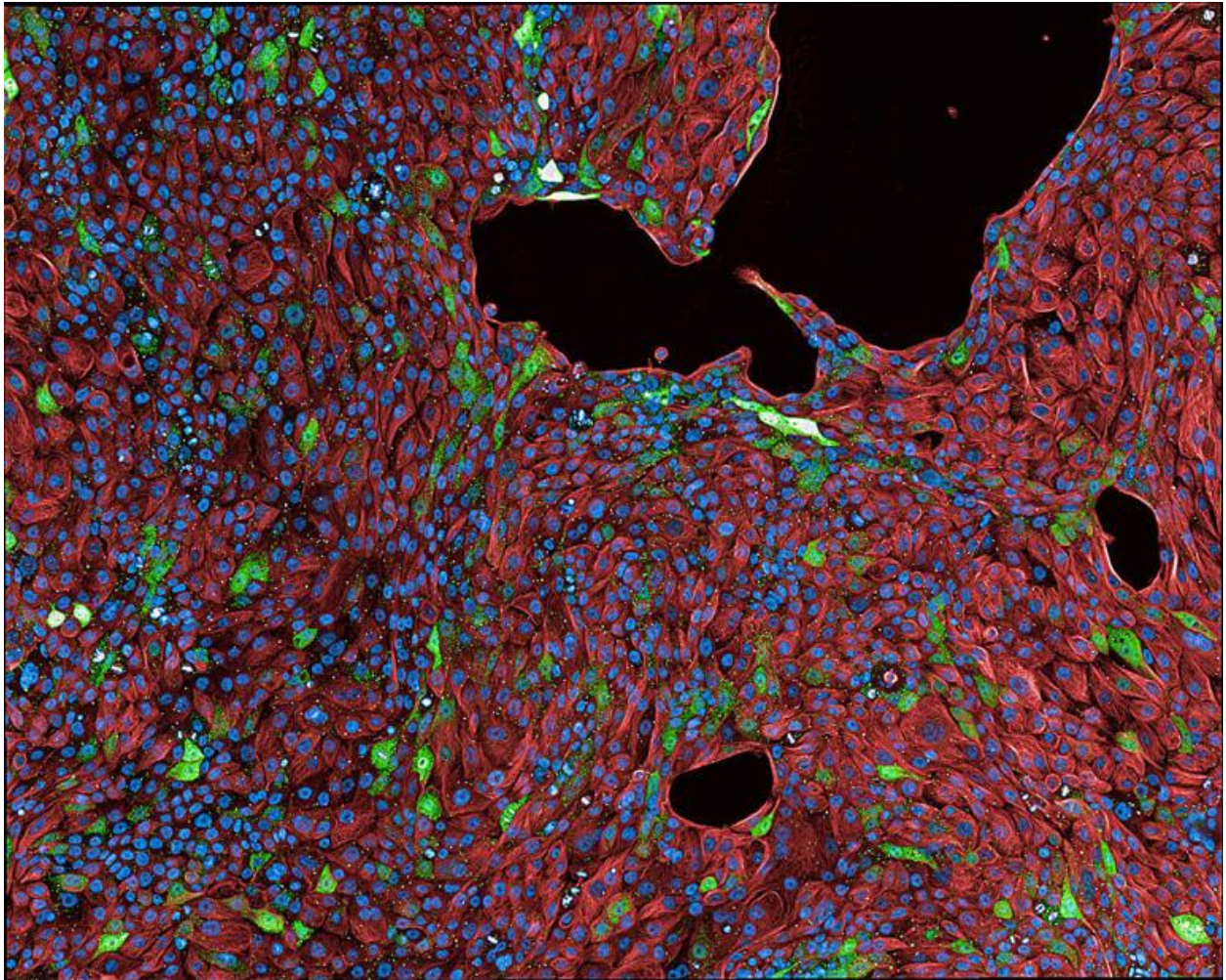
Contributions to the Research:

Reimagining the Future of Medicine

"Advancements in AI have opened the door to a new era where we can design and assemble artificial proteins to meet humanity's needs," said **Professor Lee**. These AI-designed nanocages represent a leap beyond mimicking nature—they redefine it. Their potential spans far beyond gene therapy, promising innovations in **next-generation vaccines**, targeted drug delivery, and beyond.

This research is more than a milestone; it's a bold statement that challenges conventional thinking. By leveraging the power of AI, scientists are not just learning from nature—they're improving upon it, ushering in a new era of precision medicine. The question now is not whether AI can reshape biotechnology, but how far it can take us.

Using computer-engineered DNA to study cell identities



The LSD algorithm spotlights actively responding lung cells (green). Credit: Matthias Schmitt, Gargiulo Lab, Max Delbrück Center© Provided by Phys.org

All the cells in our body have the same genetic code, and yet they can differ in their identities, functions and disease states. Telling one cell apart from another in a simple manner, in real time, would prove invaluable for scientists trying to understand inflammation, infections or cancers.

Now, scientists at Germany's Max Delbrück Center for Molecular Medicine have created an algorithm that can design such tools that reveal the identity and state of cells using segments of DNA called "synthetic locus control regions" (sLCRs). They can be used in a variety of biological systems. The findings, by a team led by

Dr. Gaetano Gargiulo, head of the Molecular Oncology Lab, are [reported](#) in *Nature Communications*.

"This algorithm enables us to create precise DNA tools for marking and studying cells, offering new insights into cellular behaviors," says Gargiulo, senior author of the study. "We hope this research opens doors to a more straightforward and scalable way of understanding and manipulating cells."

This effort began when Dr. Carlos Company, a former graduate student at the Gargiulo lab and co-first author of the study, started to invest energy into automating the design of the DNA tools and making it accessible to other scientists. He coded an algorithm to generate tools to help researchers understand basic cellular processes as well as disease processes such as cancers, inflammation and infections.

"This tool allows researchers to examine the way cells transform from one type to another. It is particularly innovative because it compiles all the crucial instructions that direct these changes into a simple synthetic DNA sequence. In turn, this simplifies studying complex cellular behaviors in important areas like cancer research and human development," says Company.

Algorithm to make a tailored DNA tool

The computer program is named "logical design of synthetic cis-regulatory DNA" (LSD). The researchers input the known genes and transcription factors associated with the specific cell states they want to study, and the program uses this to identify DNA segments (promoters and enhancers) controlling the activity in the cell of interest. This information is sufficient to discover functional sequences, and scientists do not have to know the precise genetic or molecular reason behind a cell's behavior; they just have to construct the sLCR.

The program looks within the genomes of either humans or mouse to find places where transcription factors are highly likely to bind, says Yuliia Dramaretska, a graduate student at the Gargiulo lab and co-first author. It generates a list of 150-basepair long sequences that are relevant, and that likely act as the active promoters and enhancers for the condition being studied.

"It's not giving a random list of those regions, obviously," she says. "The algorithm is actually ranking them and finding the segments that will most efficiently represent the phenotype you want to study."

Like a lamp inside the cells

Scientists can then make a tool called a synthetic locus control region (sLCR), which includes the generated sequence followed by a DNA segment encoding a fluorescent protein.

"The sLCRs are like an automated lamp that you can put inside of the cells. This lamp switches on only under the conditions you want to study," says Dr. Michela Serresi, a researcher at the Gargiulo lab and co-first author. The color of the "lamp" can be varied to match different states of interest, so that scientists can look under a fluorescence microscope and immediately know the state of each cell from its color. "We can follow with our eyes the color in a petri dish when we give a treatment," Serresi says.

The scientists have validated the utility of the computer program by using it to screen for drugs in SARS-CoV-2 infected cells, as published last year in *Science Advances*. They also used it to find mechanisms implicated in brain cancers called glioblastomas, where no single treatment works.

"In order to find treatment combinations that work for specific cell states in glioblastomas, you not only need to understand what defines these cell states, but you also need to see them as they arise," says Dr. Matthias Jürgen Schmitt, the researcher at the Gargiulo lab and co-first author, who used the tools in the lab to showcase their value.

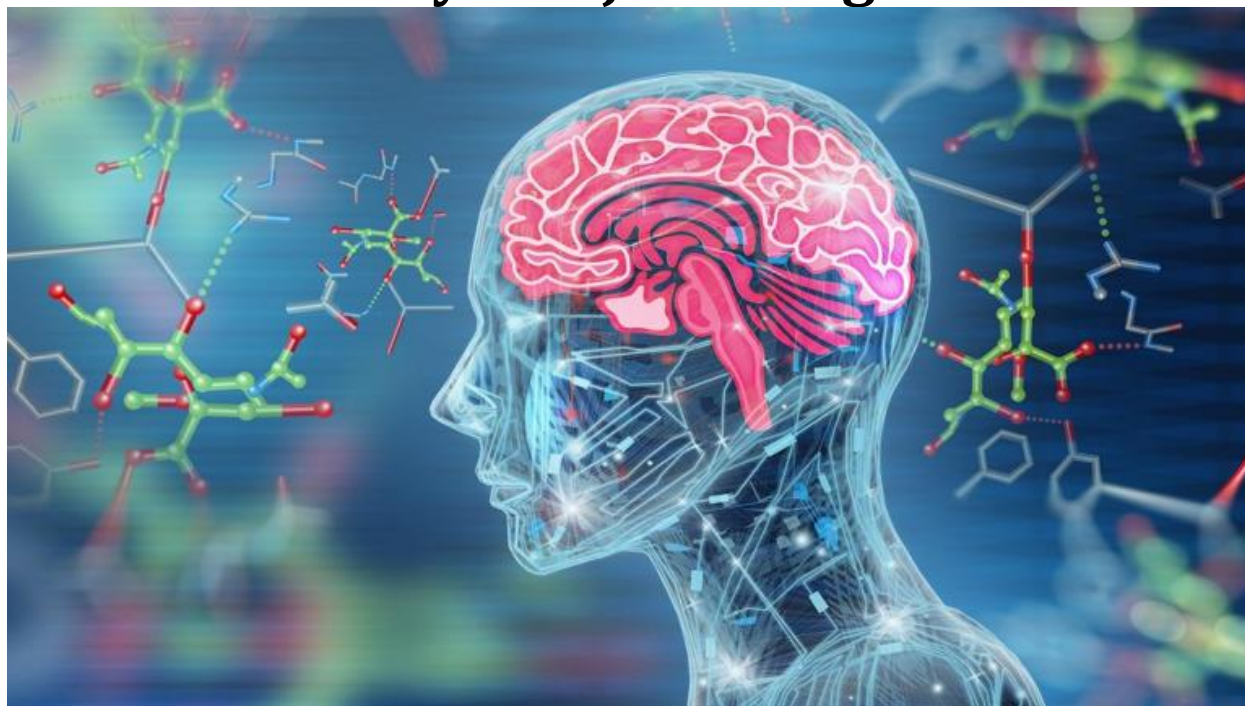
Now, imagine immune cells engineered in the lab as a gene therapy to kill a type of cancer. When infused into the patient, not all these cells will work as intended. Some will be potent and while others may be in a dysfunctional state. The Gargiulo lab will be using this system to study the behavior of these delicate anti-cancer cell-based therapeutics during manufacturing.

"With the right collaborations, this method holds potential for advancing treatments in areas like cancer, viral infections, and immunotherapies," Gargiulo says.

More information: Carlos Company et al, Logical design of synthetic cis-regulatory DNA for genetic tracing of cell identities and state changes, *Nature Communications* (2024). DOI: [10.1038/s41467-024-45069-6](https://doi.org/10.1038/s41467-024-45069-6)

Provided by Max Delbrück Center for Molecular Medicine

Aging 'hotspot' found in brain, researchers say: 'Major changes'



The brain plays a big part in the [aging process](#), and scientists think they've pinpointed the specific cells that control it.

In a study of mice, researchers at the Allen Institute identified certain cells that showed "major changes" with age, particularly in one specific "hotspot," according to a press release.

Mice were chosen because their brains share "many similarities" to [human brains](#).

The researchers used RNA sequencing and brain-mapping tools to analyze more than 1.2 million brain cells from young mice (2 months old) and older mice (18 months old).

The 18-month-old mice are roughly equivalent to a "late middle-aged human," the researchers indicated.

The researchers grouped the cells into 847 different types and also identified nearly [2,500 genes](#) that changed with aging, according to Zeng.

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WARDING OFF DEMENTIA MEANS MORE READING, PRAYING AND LISTENING TO MUSIC: STUDY

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Mice (not pictured) were chosen because their brains share "many similarities" to human brains, the researchers said.
iStock© iStock

The cells that were linked to aging showed an increase in inflammation and a decrease in "neuronal function."

"Changes in these genes point to deteriorated neuronal structure and function in many neuronal and glial cell types, as well as increased immune response and inflammation in the brain's immune and vascular (blood vessel) cell types," Zeng detailed.

The cells that experienced the biggest changes were the ones in the hypothalamus, the part of the brain that is linked to food intake, energy balance and metabolism, the researchers noted.

This suggests that this area is a "hotspot for aging," Zeng noted, and that there could be a connection between diet, [lifestyle factors](#), brain aging and risk of age-related cognitive disorders.

"The findings from the study reinforce the notion that maintaining a [healthy lifestyle](#), promoting a healthy metabolic state, and reducing inflammation in the

body and brain could slow down or delay the aging process and reduce the risks of aging-associated brain diseases," he said.

The hope is that this discovery could lead to new age-related therapies to improve the function of these cells and help prevent neurodegenerative diseases, according to the researchers.

"Aging is the most important risk factor for many brain diseases," Zeng noted.

"Our study provides a highly detailed genetic map for which brain cell types may be most affected by aging and suggests new gene and cell targets for developing new treatments for aging-related brain diseases."

The study did have some limitations, the authors acknowledged.

"The main limitation of our study is that the findings are correlational," Zeng said.

Inflammation plays a role in chronic age-related diseases such as Alzheimer's, a neurologist noted. AP Images© AP Images

"We don't know yet if the gene expression changes observed in specific cell types are causal to brain aging. Our study lays the groundwork by providing a detailed genetic map and cell targets."

Zeng called for [future studies](#) to investigate the cells' roles in aging and determine whether the reversal of the changes could delay the aging process.

Dr. Earnest Lee Murray, a [board-certified neurologist](#) at Jackson-Madison County General Hospital in Jackson, Tennessee, commented that the new research adds to existing evidence supporting the role of diet in human brain health.

The detailed "brain roadmap" will be very beneficial for future research into aging and possible therapeutics, according to Murray, who was not involved in the study.

The detailed "brain roadmap" discovered in the study will be very beneficial for future research into aging and possible therapeutics, experts agree. iStock© iStock

It's been known for some time that inflammation plays a role in chronic age-related diseases [such as Alzheimer's](#), the neurologist noted.

"More and more evidence is pointing to the fact many chronic diseases can be prevented, and it often comes down to [diet and exercise](#)," he told Fox News Digital. "Altering diet to exclude processed foods and initiating some habits such as intermittent fasting have been shown to reduce this cellular inflammation that appears to be leading to so many diseases."

Original article source: [Aging 'hotspot' found in brain, researchers say: 'Major changes'](#)

5 major Alzheimer's discoveries scientists made in 2024

The Alzheimer's Association shares some of its most significant dementia findings

Published December 27, 2024

[Drug shows promise in treating Alzheimer's](#)

Gillian Turner reports how BAN2401 might help slow the mental decline of Alzheimer's patients.

With an estimated 6.9 million Americans aged 65 and older currently living with [Alzheimer's disease](#), the road to a cure seems long and uncertain.

But as the year comes to a close, experts are reflecting on some of the hopeful advances in diagnosis, treatment and risk management that have been made in 2024.

The Alzheimer's Association — a Chicago-based nonprofit committed to [Alzheimer's research](#), care and support — shared its top five significant discoveries from the year.

DEMENTIA REPORT REVEALS 'SHOCKING' SIGNS AT AGE 60 THAT YOU'LL DEVELOP THE DISEASE BY AGE 80

1. Third new Alzheimer's drug is approved

2024 saw a new drug enter the dementia landscape, as the U.S. Food and Drug Administration (FDA) approved Kisunla (donanemab) in July.

This was the third new approval since 2021.



The Alzheimer's Association — a Chicago-based nonprofit committed to Alzheimer's research, care and support — shared its top five significant discoveries from the year. (iStock)

Kisunla, which is made by Eli Lilly, is designed to "slow progression and change the underlying course of the disease," according to the Association's press release.

The [once-monthly injection](#) is intended for adults with early symptomatic Alzheimer's disease.

This is the first medication to target amyloid plaques — the proteins that build up in the brains of Alzheimer's patients, often impairing memory and cognitive function — with evidence to support stopping therapy when amyloid plaques are removed, a company release stated.

'HIDDEN' FAT COULD PREDICT ALZHEIMER'S DISEASE UP TO 20 YEARS BEFORE SYMPTOMS, RESEARCH FINDS

"This is real progress," said Alzheimer's Association President and CEO Dr. Joanne Pike in a statement shared with Fox News Digital at the time.

"[This FDA] approval allows people more options and greater opportunity to have more time. Having multiple treatment options is the kind of advancement we've all been waiting for."

2. Blood tests could improve speed and accuracy of diagnosis

Research this year has helped move Alzheimer's blood tests closer to being used in [physicians' offices](#).

Studies have shown that blood tests can achieve a higher accuracy of diagnosis, which could help fast-track patients' access to clinical trials and treatments, according to the Alzheimer's Association.

"This is real progress."

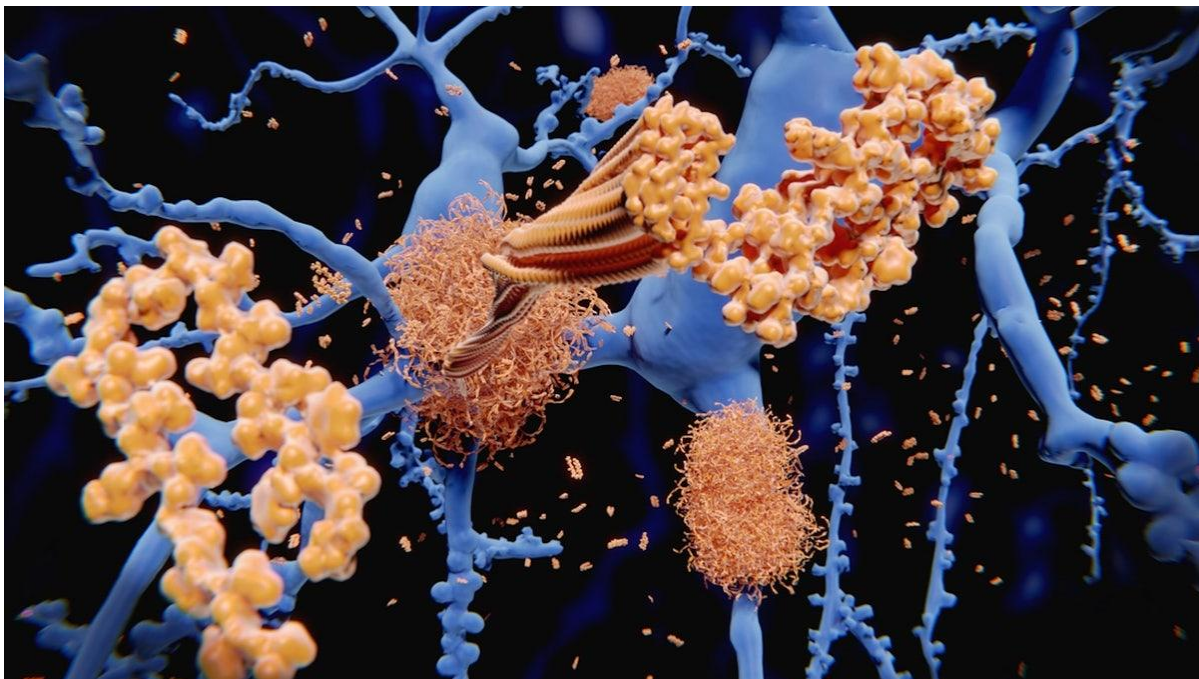
"Blood tests for Alzheimer's are demonstrating in research that they could significantly improve a clinician's accuracy and confidence, provide greater accessibility and a reason for more communication," the same source stated.

In one study reported this year, a specific blood test was around 90% accurate in identifying Alzheimer's in patients with cognitive symptoms seen in [primary care](#) and at specialized memory care clinics, per the Association.

3. Individuals and caregivers want more support post-diagnosis

People who are newly diagnosed with Alzheimer's and their caregivers need more support in navigating the health care system.

That's according to a 2024 Alzheimer's Association survey, which found that 97% of dementia caregivers expressed a desire for those support systems.



2024 saw the approval of the first medication to target amyloid plaques, the proteins that build up in the brains of Alzheimer's patients and often impair memory and cognitive function. (iStock)

A majority of dementia caregivers (70%) also noted that "coordination of care is stressful."

To help address this, the Centers for Medicare & Medicaid Services in July 2024 launched an eight-year pilot program in dementia care management, called the Guiding an Improved Dementia Experience (GUIDE) model.

DEMENTIA RISK COULD BE LINKED TO WALKING SPEED, STUDY SUGGESTS

The program aims to work with [health care systems](#) to provide supportive services to people living with dementia and their caregivers, with a focus on helping patients remain in their homes and communities, according to the Alzheimer's Association.

4. Wildfire smoke raises risk of dementia

Air pollution has been linked to an increased risk of dementia, according to 2024 research.

The 10-year study, which was presented during the Alzheimer's Association International Conference in Philadelphia in July, found that wildfire smoke can be "particularly hazardous" for [brain health](#).

A 2024 Alzheimer's Association survey found that 97% of dementia caregivers expressed a desire for those support systems. (iStock)

The research included more than 1.2 million people in southern California, an area that experiences frequent wildfire activity.

Air pollution produced by wildfires could be more hazardous to health because it is produced at higher temperatures, contains a greater concentration of toxic chemicals, and is smaller in diameter than other sources, the Alzheimer's Association stated.

5. Alzheimer's causes physical changes in the brain

In June 2024, scientists and clinicians published research that showed physical changes that happen in the brain due to Alzheimer's disease. "Defining diseases by the biology has long been standard in many areas of medicine — including cancer, [heart disease](#) and diabetes," the Alzheimer's Association wrote.

In June 2024, scientists and clinicians published research that showed physical changes that happen in the brain due to Alzheimer's disease. (iStock)

"The new publication defines Alzheimer's as a biological process that begins with brain changes before people exhibit memory and thinking problems."

These brain changes were found to come ahead of the typical outward symptoms, such as memory loss, confusion, disorientation and trouble with planning or organizing.

Warding off dementia means more reading, praying and listening to music: study

Downtime decisions may have profound health impacts, say researchers

Published January 1, 2025

[Could being bilingual help prevent dementia?](#)

Fox News medical contributor Dr. Nicole Saphier joins 'Fox & Friends Weekend' to weigh in on a new report that being bilingual could help people ward off dementia.

For long-term brain health, [older adults](#) might want to carefully consider how they spend their downtime, according to a new study. Researchers from the University of South Australia assessed the 24-hour activity patterns of nearly 400 people over age 60. When it comes to brain health, the study found that the context or type of activity individuals engage in matters, news agency SWNS reported.

DEMENTIA REPORT REVEALS 'SHOCKING' SIGNS AT AGE 60 THAT YOU'LL DEVELOP THE DISEASE BY AGE 80

Some sedentary behaviors are better for [cognitive function](#) than others, according to the findings, which were published in The Journal of Gerontology Series A. Mentally stimulating behaviors, [such as reading](#), listening to music, praying, crafting and playing a musical instrument — as well as social behaviors like chatting with others — are beneficial for memory and thinking abilities, the study noted.

Mentally stimulating behaviors such as reading, listening to music, praying, crafting and playing a musical instrument are beneficial for memory and thinking abilities, a new study noted. (iStock)

The research team referred to the "valuable insights" that could help reduce instances of cognitive impairment. More passive activities, like playing video games or watching TV, do not offer the same benefits as reading, [praying and other activities](#), they noted. More than 55 million people around the globe have dementia, according to estimates from the World Health Organization. Another 10 million new cases are diagnosed each year. Dr. Maddison Mellow, researcher at the University of South Australia, said that not all sedentary behaviors are equal when it comes to memory and cognitive health.

"The context of an activity alters how it relates to cognitive function, with different activities providing varying levels of cognitive stimulation and social engagement." (iStock)

"In this research," she said, "we found that the context of an activity alters how it relates to cognitive function, with different activities providing varying levels of cognitive stimulation and social engagement." She said that scientists "already know that physical activity is a strong protector against dementia risk, and this

should be prioritized if you're trying to [improve your brain health](#)," as SWNS reported.

"Even small, 5-minute time swaps can help."

"But until now, we hadn't directly explored whether we can benefit our brain health by swapping one sedentary activity for another." She went on, "And while the 'move more, sit less' message certainly holds true for cardiometabolic and brain health, our research shows that a more nuanced approach is needed when it comes to thinking about the link between sedentary behaviors and cognitive function." It's wise to "prioritize movement that's enjoyable and gets [the heart rate](#) up," she also said. And "even small, 5-minute time swaps can help."

"A more nuanced approach is needed when it comes to thinking about the link between sedentary behaviors and cognitive function." (iStock)

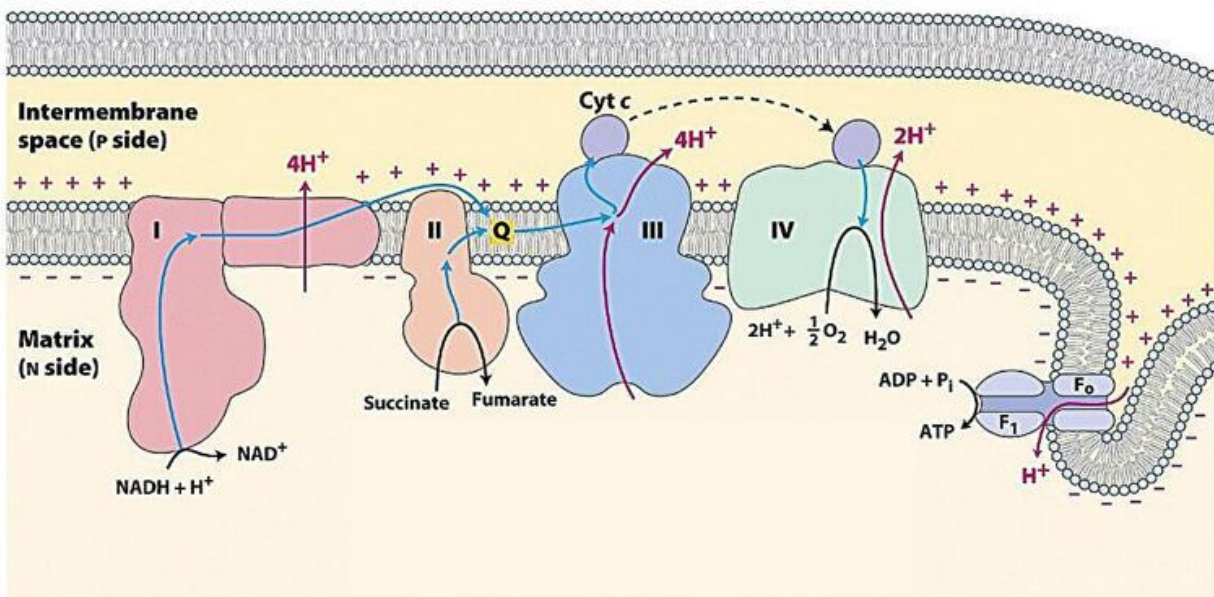
A recent study published by the RAND Corporation in California also identified several major predictors occurring around age 60 that could likely lead to cognitive impairment and dementia in individuals [by age 80](#), as Fox News Digital previously reported. Researchers evaluated 181 potential risk factors, including demographics, socioeconomic status, lifestyle and health behaviors, health history, psycho-social factors and more. The list of predictors, according to RAND, included "never exercising" and "low engagement in hobbies."

The study results suggested that "[maintaining good physical](#) and mental health is beneficial not just to staying in shape, but also to staying sharp and delaying cognitive decline," study co-author Peter Hudomiet, a RAND economist in California, told Fox News Digital.

Creating a simplified form of life: Scientists build modules for a synthetic cell

Producing ATP in mitochondria

>100 proteins

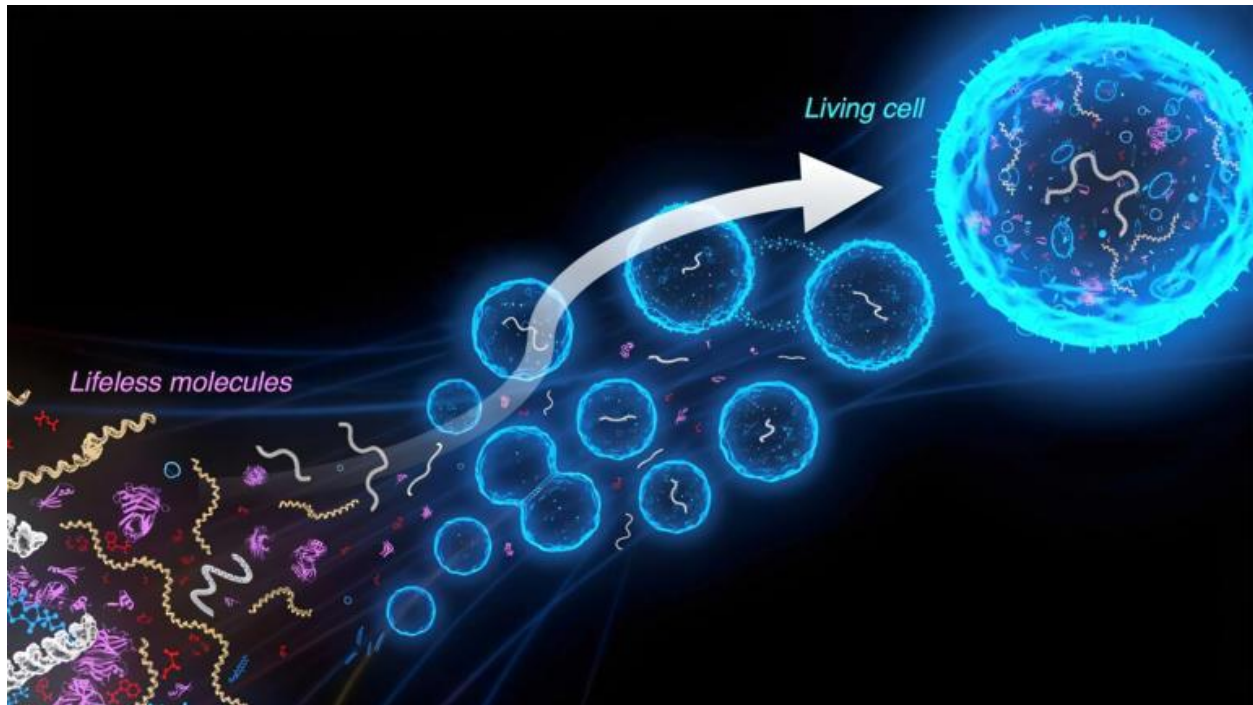


Producing ATP in functional analogs of mitochondria and enabling cross-feeding

5 proteins

The production of ATP in a mitochondrion, requiring > 100 proteins, and the synthetic vesicles producing ATP, with only 5 proteins. Credit: University of Groningen, Poolman lab

It is one of the most fundamental questions in science: how can lifeless molecules come together to form a living cell? Bert Poolman, Professor of Biochemistry at the University of Groningen, has been working on this problem for over 20 years. He aims to understand life by trying to reconstruct it; he is building simplified artificial versions of biological systems that can be used as components for a synthetic cell.



A simplified synthetic equivalent of a cell would be like a blueprint for life. Credit: EVOLF project

Poolman has published two papers in [Nature Nanotechnology](#) and [Nature Communications](#). In the first paper, he describes a system for energy conversion and cross-feeding of products of this reaction between synthetic cells, while he describes a system for concentrating and converting nutrients in cells in the second paper.

Six Dutch research institutes are collaborating in the consortium [BaSyc](#) (Building a Synthetic Cell) to build the elements needed for a synthetic cell. Poolman's group has been working on energy conversion.

The real-life equivalents he aims to replicate are mitochondria, the 'energy factories' of the cell. These use the molecule ADP to produce ATP, which is the standard 'fuel' that cells require to function. When ATP is converted back into ADP, the energy is released and used to drive other processes.

Artificial energy factories

"Instead of the hundreds of components of mitochondria, our system for energy conversion uses just five," says Poolman. "We set out to simplify it as much as possible." This may sound odd, as evolution has done a great job of producing functional systems.

"However, evolution is a one-way street, it builds on existing components and this often makes the outcome very complex," explains Poolman. An artificial replica, on the other hand, can be designed with a specific outcome in mind.

The five components were placed inside vesicles, tiny cell-like sacs, that can absorb ADP as well as the amino acid arginine from the surrounding fluid. The arginine is 'burned' (deaminated) and thus provides the energy to produce ATP, which is secreted from the vesicle.

"Of course, the simplification comes at a price: we can only use arginine as the energy source, while cells use all kinds of different molecules, such as amino acids, fats, and sugars."

Next, the Poolman group designed a second vesicle that is able to absorb the secreted ATP and use it to drive an energy-consuming reaction. The energy is provided by turning ATP back into ADP, which is then secreted and can be absorbed by the first vesicle, closing the loop.

Such a cycle of ATP production and use is the foundation of metabolism in every living cell and drives the 'machinery' for energy-consuming reactions such as growth, cell division, protein synthesis, DNA replication, and more.

An artificial pumping system

The second module that Poolman created was a bit different: a vesicle in which a chemical process causes the interior to build up a negative charge and, in doing so, form an electrical potential, similar to that of an electronic circuit. The electrical potential is used to couple charge movement to the accumulation of nutrients inside the vesicle, which is carried out by transporters.

These proteins in the membrane of the vesicle work a bit like a water wheel: positively charged protons 'flow' through it from outside the vesicle to the negatively charged interior. This flow drives the transporter, which in this case imports a sugar molecule, lactose. Again, this is a very common process in living cells, requiring many components that Poolman and his team mimicked with just two components.

When he submitted a paper describing this system, a reviewer asked if he couldn't do something with the lactose that is being transported, as cells use

nutrients like this to produce useful building blocks. Poolman took up the challenge and added three more enzymes to the system, which oxidized the sugar and enabled production of the coenzyme NADH.

But what about the synthetic cell?

Having a simplified synthetic equivalent of two key features of life is fascinating, but many more steps need to be integrated to form an autonomously growing and dividing synthetic cell. "The next step we want to take is adding our metabolic energy producing systems to a synthetic cell division system created by colleagues," says Poolman.

The BaSyc program is entering its final years; funding for a new program has recently been secured.

This [EVOLF](#) project is set to run for another 10 years and aims to find out how many more lifeless modules can come together and create living cells.

"Ultimately, this would give us a blueprint for life, something that is currently lacking in biology," concludes Poolman. "This may eventually have all kinds of applications, but will also help us to better understand what life is."

More information: Laura Heinen et al, Synthetic syntrophy for adenine nucleotide cross-feeding between metabolically active nanoreactors, *Nature Nanotechnology* (2024). DOI: [10.1038/s41565-024-01811-1](https://doi.org/10.1038/s41565-024-01811-1)

Miyer F. Patiño-Ruiz et al, Chemiosmotic nutrient transport in synthetic cells powered by electrogenic antiport coupled to decarboxylation, *Nature Communications* (2024). DOI: [10.1038/s41467-024-52085-z](https://doi.org/10.1038/s41467-024-52085-z)

Provided by University of Groningen

Scientists discover new blood group system, ending 50-year-old mystery

Researchers have solved a 50-year-old mystery by discovering a new blood group system called MAL.

Scientists from NHS Blood and Transplant (Bristol), the International Blood Group Reference Laboratory (IBGRL), and the University of Bristol identified the genetic basis of the previously mysterious AnWj blood group antigen.

This breakthrough will help identify and treat patients who lack this rare blood group.

While some people can temporarily lose this antigen due to illness, the inherited absence of AnWj is extremely rare and has only been found in a few individuals worldwide. Thanks to this discovery, it will now be easier to identify others with this condition.

Blood group systems like ABO and Rh are well-known, but blood is more complex and matching across the other groups can be lifesaving. There are many other important blood group markers. Mismatches in rare groups like AnWj can cause severe transfusion reactions.

This research enables better testing to detect individuals with this rare blood type, reducing the risk of complications.

The AnWj antigen was first discovered in 1972, but its genetic origin remained unknown until now. [Published in the journal Blood](#), the research reveals that AnWj is carried on a protein called Mal.

Over 99.9% of people have the AnWj antigen because they produce full-length MAL protein on their red blood cells. In contrast, AnWj-negative individuals lack this protein due to deletions in the MAL gene.

The study found that most people who are AnWj-negative have underlying health issues, such as blood disorders or certain cancers, that suppress the expression of the antigen.

Only a few individuals are genetically AnWj-negative, including a family of Arab-Israeli descent.

Researchers used whole exome sequencing, a technique that examines the protein-coding regions of DNA, to identify the deletions in the MAL gene responsible for the absence of AnWj.

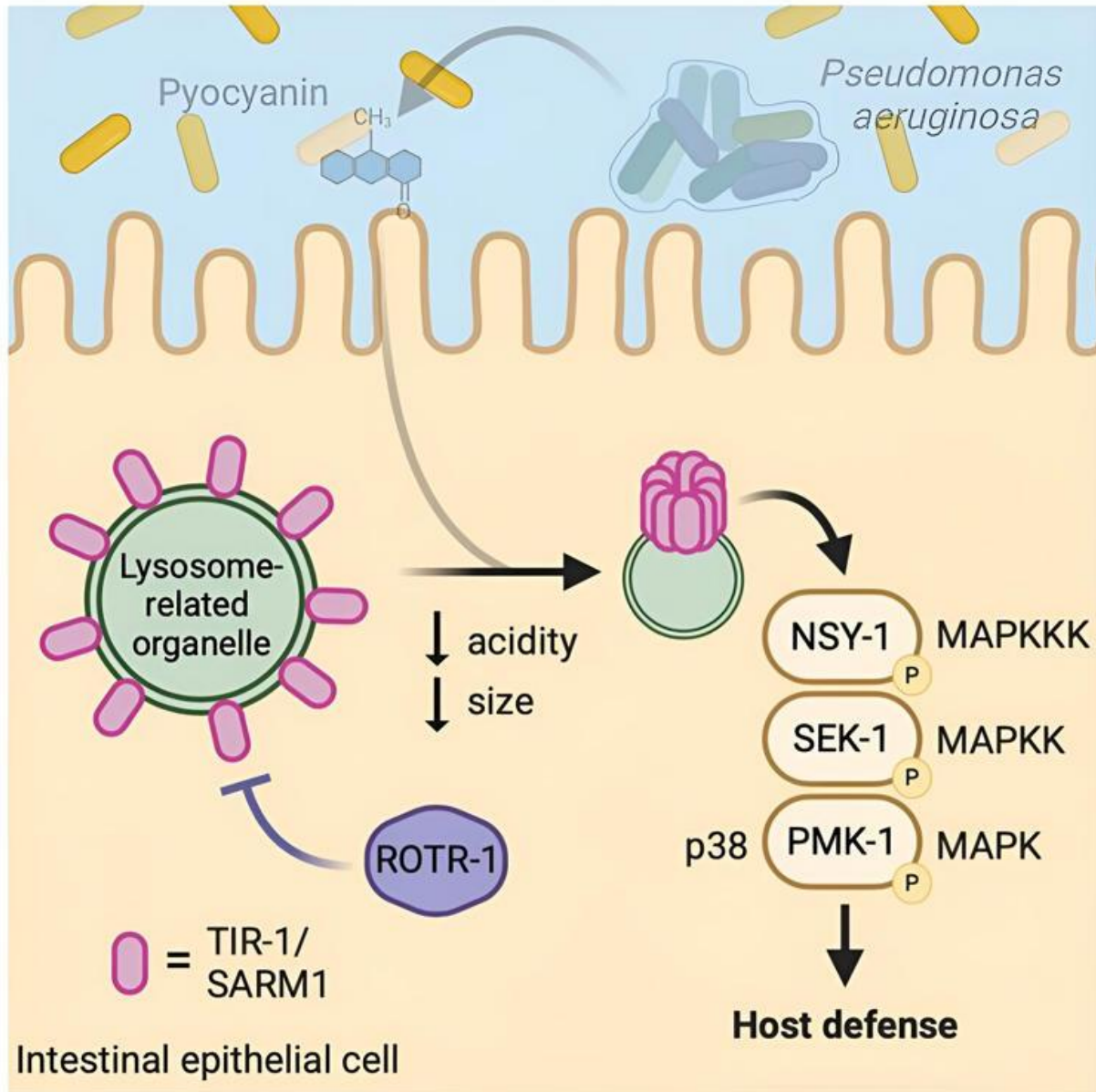
They confirmed their findings by reintroducing a normal MAL gene into cells, which restored the antigen.

Senior Research Scientist Louise Tilley from IBGRL called this discovery a significant milestone after two decades of effort, highlighting the importance of teamwork and advanced genetic tools.

Ash Teye from the University of Bristol emphasised how gene manipulation techniques played a crucial role in solving this long-standing puzzle.

The discovery of the MAL blood group system is a step forward in improving care for patients with rare blood types and paves the way for better diagnostic tools and treatment options in the future.

Research reveals mechanism of effector-triggered immunity



Graphical abstract. Credit: Cell Reports (2024). DOI: 10.1016/j.celrep.2024.114674

A pair of studies examining immune response in *C. elegans* reveal broad implications for understanding pathogen detection in higher animals and the evolutionary origins of immunity itself.

The research, co-authored by MD/Ph.D. student Samantha "Sammy" Tse-Kang and Read Pukkila-Worley, MD, professor of medicine, uncovered a mechanism of effector-triggered immunity in animals, in which host cells detect infection by sensing the harmful effects of a pathogen rather than simply the presence of a dangerous microbe.

The new research details the mechanism of an immune regulator whose role in pathogen sensing is conserved across all organisms.

The papers, which were published simultaneously in the journals *Immunity* and *Cell Reports*, examine a type of immune regulator called SARM, which is required for immune defenses in plants and bacteria. It was not previously known whether these proteins have a role in pathogen sensing in animals.

Tse-Kang and her colleagues showed that the SARM homolog in *C. elegans* is specifically expressed on a cellular compartment in intestinal cells that enables it to respond to pathogen-induced damage to the host and activate protective immune defenses.

Tse-Kang said the two papers began with a single question: "What regulates the immune response in *C. elegans*?"

"These companion papers started from an unbiased genetic screen, and it was not always clear where these stories were progressing. As we went along, we realized that we were thinking about two separate mechanisms, one that activated the host immune response during infection and another that prevented damaging inflammation by restraining the same pathway," Dr. Pukkila-Worley said.

"Sammy was essential to this recognition and the execution of the incredibly detailed and challenging experiments."

"Our studies show that *C. elegans* intestinal epithelial cells can identify not only the presence of infectious pathogens, but a pathogen that's actively causing disease, by sensing what we call 'patterns of pathogenesis,'" Tse-Kang said. "We think this will open up avenues for similar studies in higher order mammals such as mice and humans."

Tse-Kang and Pukkila-Worley credit the contribution of their former lab member, Nick Peterson, MD, Ph.D. In 2023, Dr. Peterson published a [paper](#) in *Immunity* characterizing a different pattern of pathogenesis in *C. elegans*. He and his colleagues showed that a metabolite derived from a pathogen is sensed in the host to indicate the toxic potential of an invading pathogen.

Fiachra Humphries, Ph.D., assistant professor of medicine; Khursheed A. Whani, instructor in medicine; MD/Ph.D. student Amanda Page; and Peterson, are co-authors with Tse-Kang and Pukkila-Worley on the paper published in *Immunity* identifying TIR-1 as a guard protein in an effector-triggered immune response.

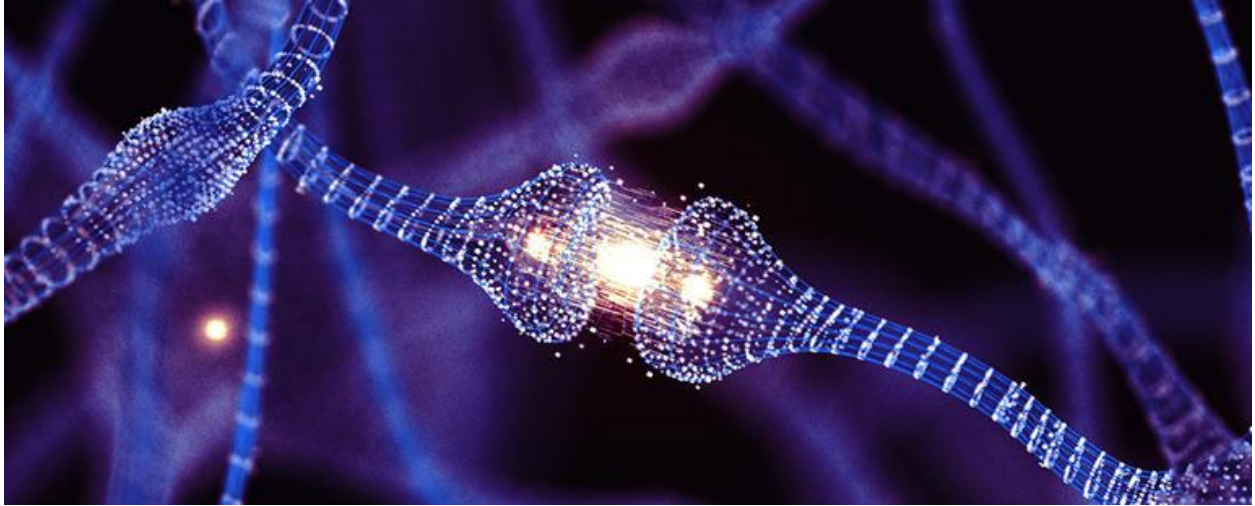
"Some of this was luck, and you need a little bit of luck in science. The rest of it was the result of wonderful conversations in the lab, bouncing ideas off each other. These stories could not have been possible without everyone else involved. It was a team effort," Tse-Kang said.

More information: Samantha Y. Tse-Kang et al, Intestinal immunity in *C. elegans* is activated by pathogen effector-triggered aggregation of the guard protein TIR-1 on lysosome-related organelles, *Immunity* (2024). DOI: [10.1016/j.immuni.2024.08.013](https://doi.org/10.1016/j.immuni.2024.08.013)

Samantha Y. Tse-Kang et al, Lysosome-related organelle integrity suppresses TIR-1 aggregation to restrain toxic propagation of p38 innate immunity, *Cell Reports* (2024). DOI: [10.1016/j.celrep.2024.114674](https://doi.org/10.1016/j.celrep.2024.114674)

Provided by University of Massachusetts Medical School

Study Reveals Key Alzheimer's Pathway – And Blocking It Reverses Symptoms in Mice

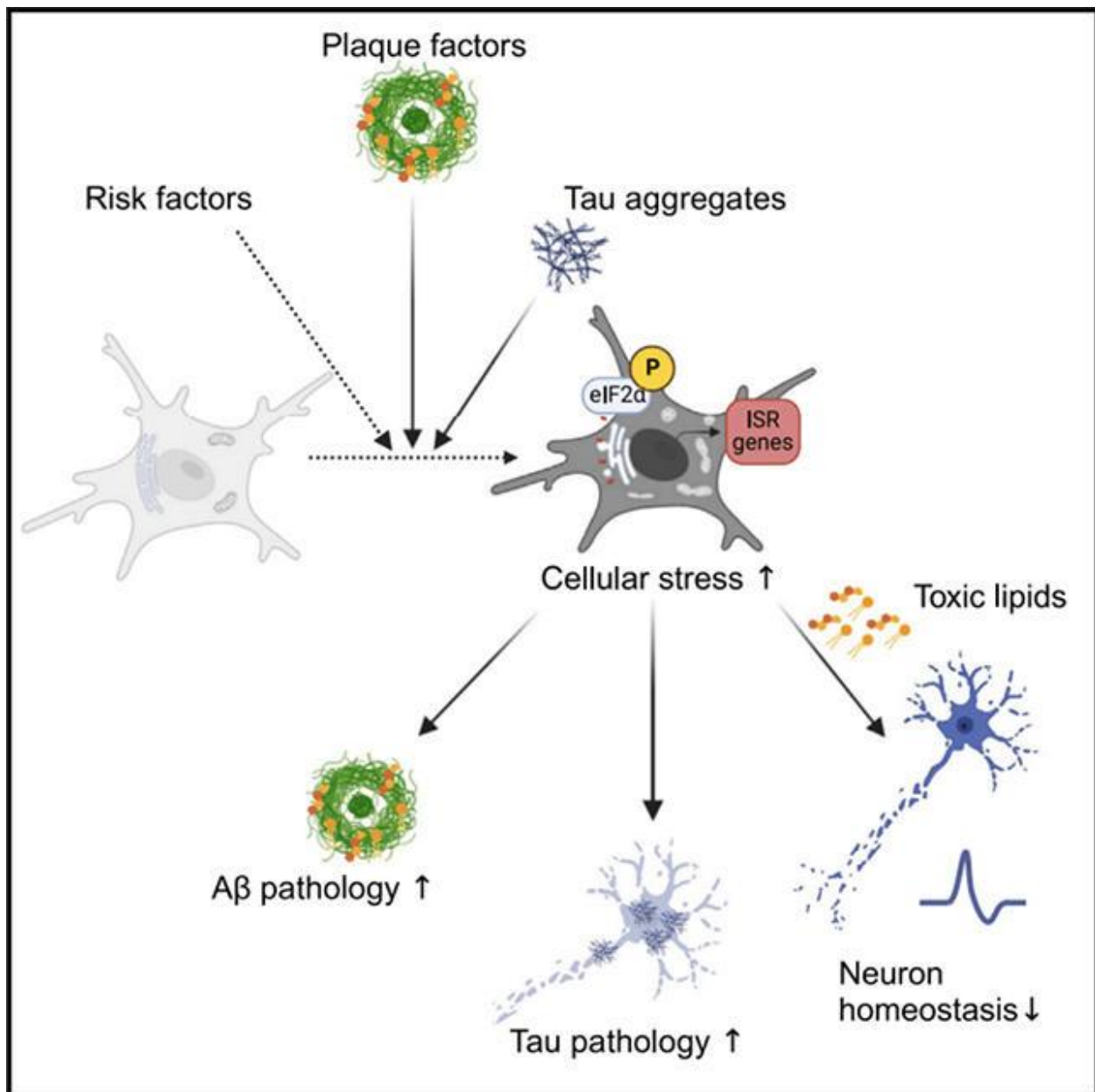


Neuron links

A sequence of stress signals among specialized clean-up cells in the brain could at last reveal why some immune responses can cause significant nerve degeneration that results in the loss of memory, judgement, and awareness behind [Alzheimer's](#) disease.

Blocking this pathway in mouse brains modeled on Alzheimer's prevented damage to their synapse connections and reduced the buildup of potentially toxic [tau proteins](#) – both hallmarks of the condition.

The researchers, led by a team from the City University of New York (CUNY), believe this pathway – called the integrated stress response (ISR) – causes brain immune cells called [microglia](#) to go 'dark' and start damaging rather than benefiting the brain.



he researchers looked at the effects of stress on microglia cells. (Flury et al., Neuron , 2024)

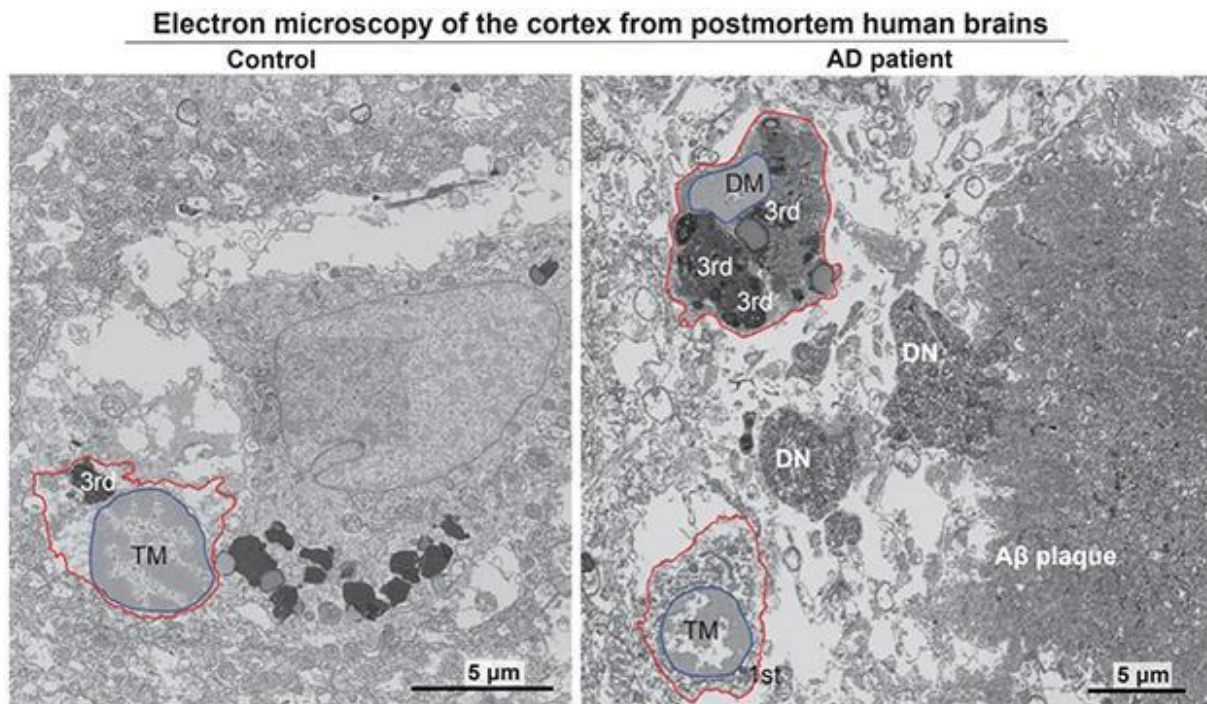
"We set out to answer what are the harmful microglia in Alzheimer's disease and how can we therapeutically target them," [says](#) CUNY neuroscientist Pinar Ayata.

"We pinpointed a novel neurodegenerative microglia phenotype in Alzheimer's disease characterized by a stress-related signaling pathway."

Haywire immune cells have previously [been linked](#) to Alzheimer's, prompting the team to use an [electron scanning process](#) to identify the buildup of dark microglia in human brains affected by Alzheimer's.

Finding around twice as many stressed microglia in brains with the condition compared with healthy brains, the researchers went on to show how the ISR pathway was causing dark microglia to release harmful lipids into the brain's tissues.

It was these damaging fats that caused the damage to [synapses](#) and neuron communication seen in Alzheimer's.



Brain scans were used to identify dark microglia. (Flury et al., Neuron , 2024)

As is often the case with Alzheimer's research, a better understanding of how the disease operates can also give scientists more ideas for [how to treat it](#). If treatments that block ISR can work safely and effectively in humans, the method could potentially slow the chaos that Alzheimer's causes in our own brain.

"These findings reveal a critical link between cellular stress and the neurotoxic effects of microglia in Alzheimer's disease," [says](#) molecular biologist Anna Flury from CUNY.

"Targeting this pathway may open up new avenues for treatment by either halting the toxic lipid production or preventing the activation of harmful microglial phenotypes."

The team behind this study found that the [misfolded protein malfunctions](#) that often drive dementia could be triggering the ISR to begin with, meaning that these signals are both a result of Alzheimer's and a reason for its further progression.

Further studies should make this relationship clearer, now that we have a better idea of how the ISR pathway and dark microglia act in the brain – and from there, hopefully, new approaches to therapies.

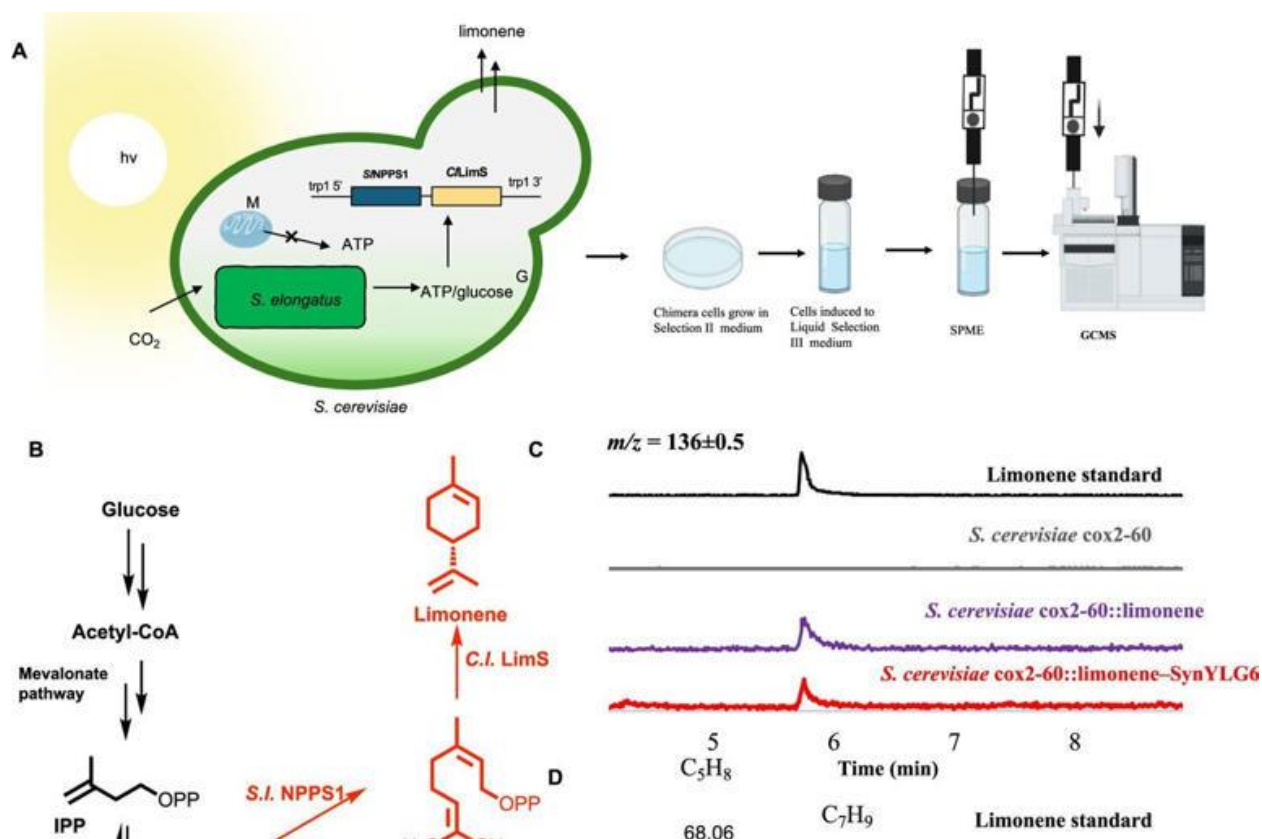
"Such treatments could significantly slow or even reverse the progression of Alzheimer's disease, offering hope to millions of patients and their families," [says](#) neuroscientist Leen Aljayousi, from CUNY.

The research has been published in [Neuron](#).

Scientists use evolution to bioengineer new pathways to sustainable energy and pharmaceuticals

Inspired by the evolution of some of the earliest lifeforms, University of Illinois professor Angad Mehta, left, Yang-Le Gao and Bidhan De led a proof-of-concept study verifying that natural metabolic processes within cyanobacteria-yeast hybrids can be bioengineered to produce important hydrocarbons and pharmaceutical precursors. Credit: Michelle Hassel

Using evolution as a guiding principle, researchers have successfully engineered bacteria-yeast hybrids to perform photosynthetic carbon assimilation, generate cellular energy and support yeast growth without traditional carbon feedstocks like glucose or glycerol. By engineering photosynthetic cyanobacteria to live symbiotically inside yeast cells, the bacteria-yeast hybrids can produce important hydrocarbons, paving new biotechnical pathways to non-petroleum-based energy, other synthetic biology applications and the experimental study of evolution.



Directed endosymbiosis for biosynthesis of a monoterpene. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-49585-3

"All cells that have a nucleus also house a variety of organelles—such as mitochondria and chloroplasts—which perform specific functions and contain their own DNA," said University of Illinois Urbana-Champaign chemistry professor Angad Mehta, who led the all-Illinois research team. "Researchers had long theorized that complex life forms got their start when one of these types of cells fused with another in a process called endosymbiosis."

In a [previous study](#), Mehta's team showed that lab-generated cyanobacteria-yeast chimeras, or endosymbionts, can supply photosynthetically generated ATP to the yeast but don't provide sugars. In the new study, the team engineered cyanobacteria to break down sugars and secrete glucose, then combined them with yeast cells to create chimeras that can grow in the presence of CO₂, using the sugar and energy produced by the bacteria.

The new study findings are [published](#) in the journal *Nature Communications*.

Armed with the ability to engineer a non-photosynthetic organism into a photosynthetic, chimeric life form, the team focused their research on

determining how these chimeras could be used to bioengineer new metabolic pathways capable of producing valuable products like limonene, a simple hydrocarbon compound found in citrus fruits, under photosynthetic conditions.

"Limonene is a relatively simple but important molecule with a large market," said Mehta, who is also affiliated with the Carl R. Woese Institute for Genomic Biology. "This proof-of-concept study shows us that we can engineer pathways in our hybrids to photosynthetically produce limonene, which belongs to a class of molecules called terpenoids, which are also precursors to many high-value compounds such as fuels, anticancer and antimalarial drugs."

Mehta said that their goals for this line of research are to determine if their method can produce more complex compounds, like fuels and pharmaceuticals, and if so, work on scaling up the process to be marketable.

"I think it would be incredible to get to the point where we could assure that every bit of carbon in a high-value compound comes from CO₂," Mehta said. "This could be one way to recycle CO₂ waste in the future."

The team also said that in their quest to understand and perfect endosymbiotic systems to advance biotechnology, they will also answer many fundamental evolutionary questions along the way.

"This will happen whether we intend it or not," Mehta said. "We are always keeping an eye on how our work can answer some of the mysteries behind how life evolved. In my view, the best way to engineer endosymbiotic systems will be by recreating the evolution process in the lab. Finding answers to some of biology's biggest questions will come naturally."

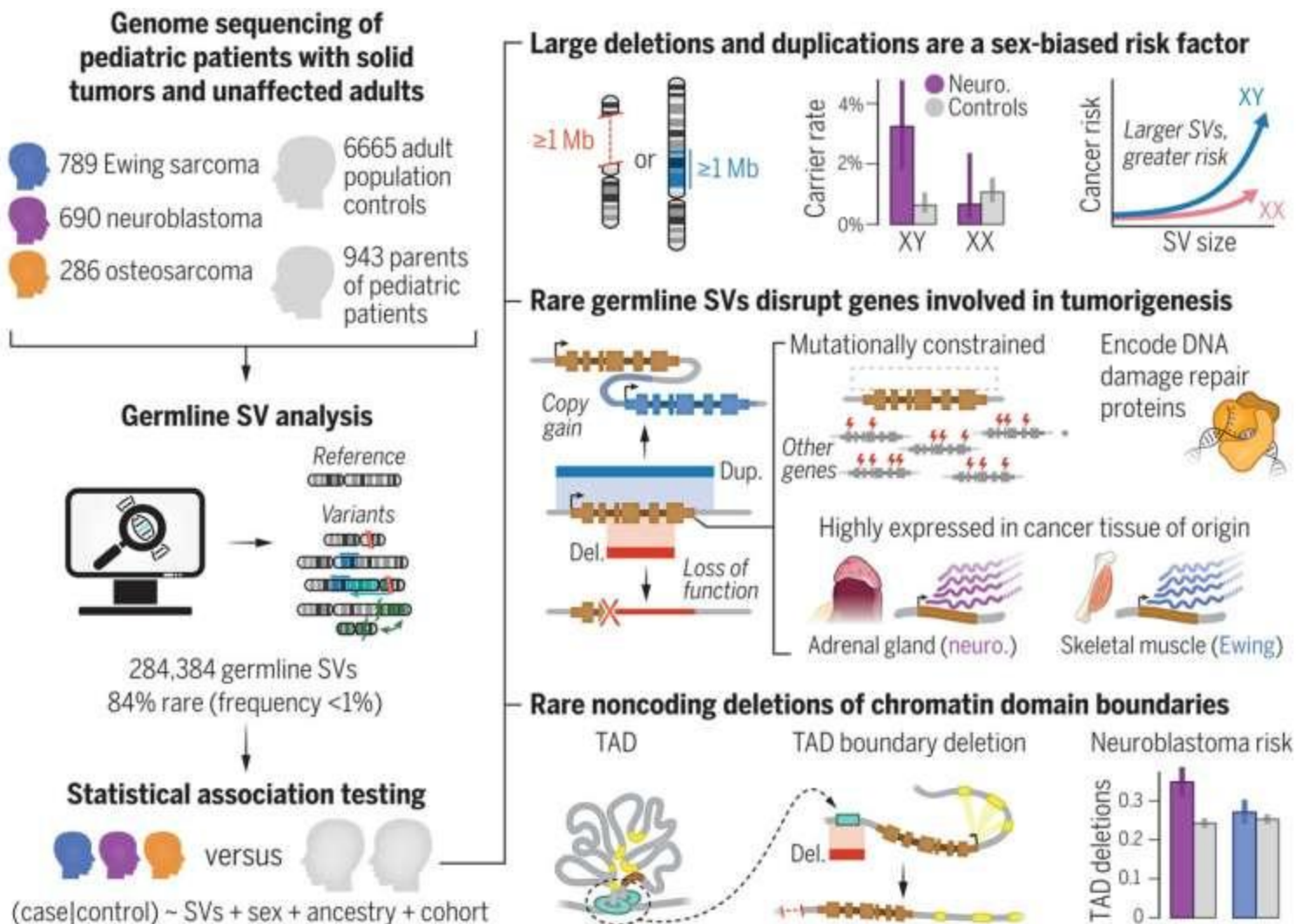
Illinois researchers Yang-le Gao, Jason Cournoyer, Bidhan De, Catherine Wallace, Alexander Ulanov and Michael La Frano also participated in this study.

More information: Yang-le Gao et al, Introducing carbon assimilation in yeasts using photosynthetic directed endosymbiosis, *Nature Communications* (2024). DOI: [10.1038/s41467-024-49585-3](https://doi.org/10.1038/s41467-024-49585-3)

Provided by University of Illinois at Urbana-Champaign

Childhood cancer genome study reveals hidden variants

by Justin Jackson , Medical Xpress



Rare germline SVs are risk factors for pediatric solid tumors. Credit: Science (2025). DOI: 10.1126/science.adq0071

Researchers at Dana-Farber Cancer Institute collaborated with multiple institutions to pinpoint rare germline structural variants as risk factors for non-blood-related cancers in

children, including tumors in various organs. Findings indicate that structural variations in both coding and noncoding regions of the genome contribute to childhood cancers such as neuroblastoma, Ewing sarcoma, and osteosarcoma.

Solid tumors constitute about one-third of new childhood cancer diagnoses worldwide. Prior studies have focused on the genetic drivers of these tumors but have lacked comparable insight into the earliest [germline](#) risk factors. Recognized predisposition genes currently account for only 10 to 15% of childhood cancer cases, leaving most heritable factors uncharacterized.

Early identification of pathogenic genetic alterations in children is vital. Genetic screenings that account for structural variants have not yet been widely implemented, limiting the understanding of contributors to early tumorigenesis and slowing the rate at which research might develop targeted treatment interventions.

In the study, "Rare germline structural variants increase risk for pediatric [solid tumors](#)," [published](#) in *Science*, researchers analyzed high-coverage germline whole-genome sequencing data from 1,765 patients with neuroblastoma, Ewing sarcoma, or osteosarcoma, plus 943 unaffected parents and 6,665 unrelated adult controls, looking for hidden causal gene variants.

The GATK-SV pipeline was used to detect large deletions, duplications, inversions, translocations, and more complex rearrangements. A category-wide association framework was applied to systematically assess coding and noncoding structural variants in patient genomes relative to controls.

Researchers identified 84 extensive chromosomal abnormalities. These ultra-rare deletions or duplications exceeding 1 million nucleotides were observed far more often in male [pediatric patients](#) and were linked to a substantially higher risk for childhood cancer compared with adult controls.

Intriguingly, abnormalities were predominantly (82%) inherited from unaffected parents. Most did not overlap known cancer-related genes or established pathogenic loci, suggesting an indirect elevation of cancer risk where the specific gene variant is only one part of the disease mechanism.

Rates of de novo germline variations were not substantially elevated in pediatric patients compared with adult controls but were distinguished by larger average size and greater disruption of protein-coding regions.

Complex structural rearrangements were notable in critical gene sets linked to DNA damage repair, mutational constraint, and tissue-specific expression. Events predicted to alter chromatin domain boundaries were strongly associated with neuroblastoma risk.

With a current scientific consensus of a 350% increased risk of childhood cancer if it has occurred elsewhere in the family, only 10–15% of cases can be attributed to known pathogenic inherited variants.

Estimates based on the findings suggest that rare germline structural variants may explain up to 5.6% of heritability in certain child tumors. The study authors suggest the findings support the integration of germline SVs into [clinical practice](#) and research efforts related to pediatric solid tumor predisposition.

A [perspective article](#) on the study, "Inherited genome instability: Germline [structural variants](#) are a risk factor for pediatric extracranial solid tumors," also published in *Science*, suggests that a mechanism to consider is the overall instability of the genome in children.

Childhood tumors often harbor defects in DNA damage repair pathway genes, consistent with inherited genomic traits predisposed to higher mutation rates.

In the pediatric environment, where [cell proliferation](#) is naturally heightened for growth and development, cancer formation can be accelerated. Consequently, children may require fewer overall mutations than adults to drive tumorigenesis.

During critical growth periods, more active cell division occurs, which could accelerate the acquisition of mutations that can go unrepaired. Perhaps worse, non-pathogenic rare variants may be repaired incorrectly, leading to pathology.

Misrepair due to a faulty repair pathway can be worse because a mutation only happens once (and then replicates onward from a [single cell](#)), whereas a misrepair can occur continually in many progenitor cells, leading to more widespread replication.

Based on the study's findings, it may be time to consider the use of therapies that inhibit DNA damage repair pathways as a targeted approach against pediatric extracranial solid tumors.

More information: Riaz Gillani et al, Rare germline structural variants increase risk for pediatric solid tumors, *Science* (2025). DOI: [10.1126/science.adq0071](https://doi.org/10.1126/science.adq0071)

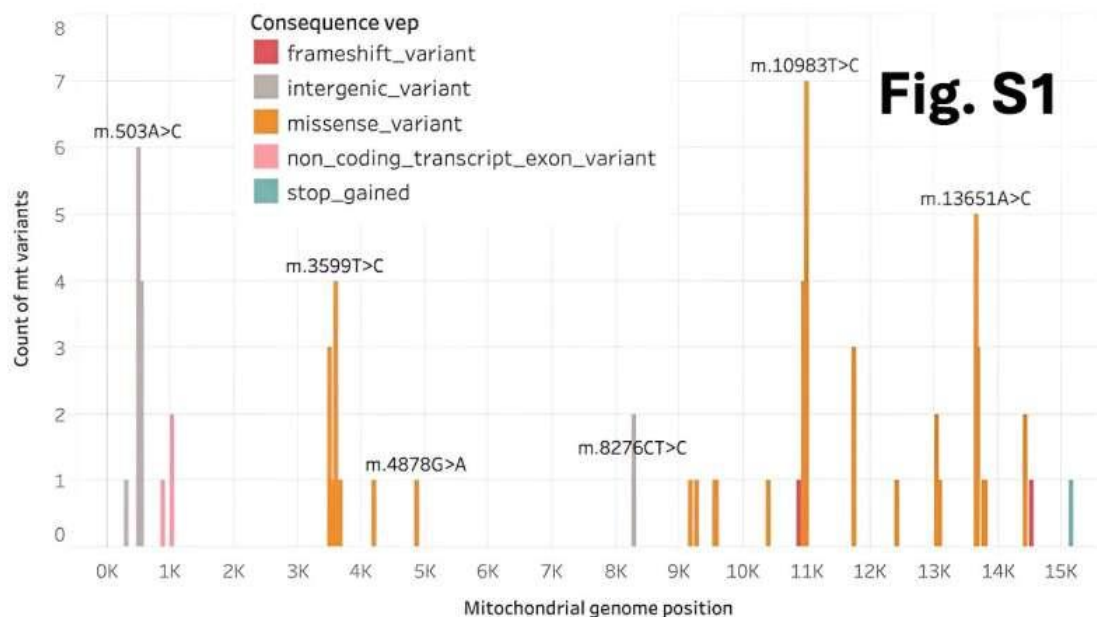
Jayne Y. Hehir-Kwa et al, Inherited genome instability, *Science* (2025). DOI: [10.1126/science.adu6125](https://doi.org/10.1126/science.adu6125)

Journal information: [Science](#)

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Team finds new potential causes of rare and lethal bone cancer

by [Children's Hospital Los Angeles](#)



Credit: *Molecular Cancer Research* (2024). DOI: 10.1158/1541-7786.MCR-23-0741

Little is known about the genetics and biology of chordoma, a rare and aggressive bone tumor. Chordomas occur in approximately one in a million people in the U.S. a year and 5% of these are in children. These tumors can arise anywhere along the spine in adults. However, in children, these tumors occur mostly at the base of the skull, making complete surgical removal challenging or impossible. Any tumor remnants are treated with high doses of radiation—which can cause significant damage to the developing brain.

A team of researchers led by Xiaowu Gai, Ph.D. and Jaclyn Biegel, Ph.D., FACMG, at the Center for Personalized Medicine at Children's Hospital Los Angeles, has published a [genomic study](#) that uncovered two classes of genetic causes for chordoma in children by conducting some genomic detective work. The findings are [published](#) in the journal *Molecular Cancer Research*.

"Finding the causes driving the different subtypes of chordoma could lead to the development of better treatment strategies for children," says Katrina O'Halloran, MD, MS, pediatric neuro-oncologist and first author of the study.

"Prior studies have been conducted primarily in adults and we know that children's tumors can present and behave differently." For example, pediatric solid tumors are more likely to be driven by underlying germline changes—alterations that can be passed on to future generations—that increase the risk for cancer.

A few genetic clues

Previous chordoma studies revealed the primary genetic defect in one subtype of the disease, poorly differentiated pediatric chordoma, is the loss of SMARCB1, a gene that encodes a key member of the SWI/SNF chromatin remodeling complex, which is a group of proteins that associate to remodel the way DNA is packaged within the cell.

While there have been additional genetic risk factors and somatic (acquired) mutations identified in tumors from other subtypes, there was no common biological mechanism connecting all these variants. Moreover, prior genomic studies of chordoma focused only on the nuclear DNA genome, neglecting the mitochondrial DNA genome entirely.

Looking beyond the nuclear DNA genome and nuclear-encoded genes

The CHLA research team had previously identified and published strong causal and contributory roles of mitochondrial DNA variants in a variety of pediatric cancers.

In the present study, they performed dual-genome investigation by sequencing the coding regions (exons) of all genes in the nuclear DNA genome, as well as the entire mitochondrial DNA genome, of 29 chordoma [tumor](#) samples from 23 [pediatric patients](#). Because of the rarity of chordoma, these samples were contributed by six different academic medical centers across the nation.

To determine whether their findings were unique to pediatric chordoma, co-first author Hesamedin Hakimjavadi, Ph.D., clinical bioinformatics scientist at CHLA, analyzed the whole-genome sequencing datasets of 93 chordomas and their matched normal tissues derived from a group of 80 adult skull-base chordoma patients.

Aberrant indels and haywire mitochondria

Tumors from five of the 23 pediatric chordoma patients (22%) were shown to carry short inframe insertions and deletions (indels) in the ARID1B gene. The same mutations were found in the normal tissue from one of the five patients. Computational studies demonstrated a strong likelihood that they were of germline origin in the remaining patients, implicating them as risk factors for pediatric chordoma.

A significant fraction of the adult chordoma patients (5%) carried comparable inherited ARID1B indels. While this was a lower number than that of pediatric chordoma patients, it

was still significantly higher than reported in the general population. The ARID1B gene encodes a member of the SWI/SNF complex, similar to SMARCB1.

"These findings implicate a common disease pathway in different subtypes of chordoma that may alter gene expression through defects in the SWI/SNF chromatin remodeling complex," says Dr. Jaclyn Biegel, Director of the Center for Personalized Medicine and a senior author of the study.

The research team also discovered a significant number of mitochondrial DNA (mtDNA) mutations in the pediatric chordoma samples. These mutations were especially enriched in NADH (Mitochondrial Complex 1 genes). Analysis of the data from the adult chordoma cohort revealed similar mtDNA alterations in Complex 1 genes.

"This study implicates a potential interplay of chromatin remodeling and mitochondrial metabolism in chordoma genesis," says Dr. Gai, Director of Bioinformatics, Center for Personalized Medicine, and senior study author.

"It will therefore be extremely interesting to understand how this may drive the growth of these tumors. Unraveling this could be the crucial first step for developing more targeted and effective therapies for chordoma in both pediatric and adult patients."

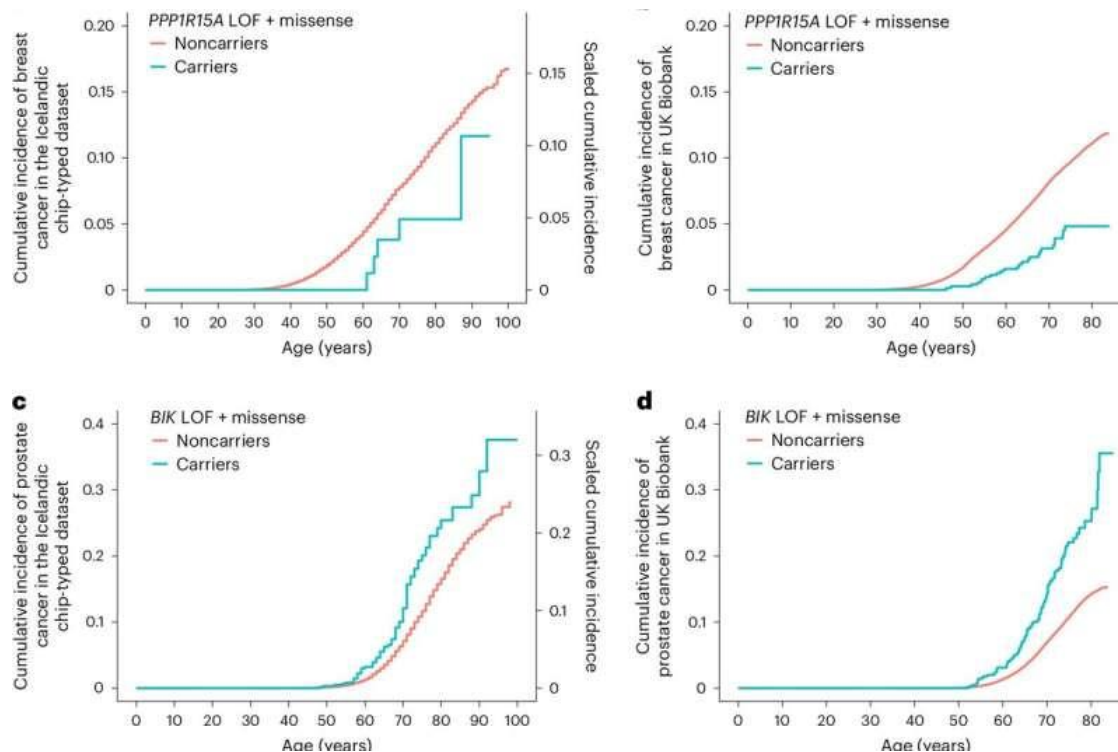
More information: Katrina O'Halloran et al, Pediatric Chordoma: A Tale of Two Genomes, *Molecular Cancer Research* (2024). DOI: [10.1158/1541-7786.MCR-23-0741](https://doi.org/10.1158/1541-7786.MCR-23-0741)

Journal information: [Molecular Cancer Research](#)

Provided by [Children's Hospital Los Angeles](#)

Scientists identify six novel genes linked to cancer risk

by deCODE genetics



Cumulative incidence of cancer among carriers and noncarriers. Credit: *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01966-6.

<https://www.nature.com/articles/s41588-024-01966-6>

Scientists at deCODE genetics/Amgen, and their collaborators have discovered six novel genes with rare germline variants that associate with cancer risk. The findings are published today in *Nature Genetics* under the title "Gene-based burden tests of rare germline variants identify six cancer susceptibility genes."

A subset of cancers arises in individuals who are born with rare sequence variants that significantly alter their cancer risk. The discovery of such variants, like those in the BRCA1- and BRCA2 genes, has led to improved early cancer detection and the development of targeted therapies, ultimately reducing the cancer burden and improving prognosis of those carrying these mutations.

In this study, the scientists analyzed three large genetic datasets from individuals of European descent, including 130,991 cancer patients and 733,486 controls.

Through a gene-based burden association analysis across 22 different cancer types, they found four novel genes associated with a risk of developing cancer; the pro-apoptotic BIK for [prostate cancer](#), the autophagy involved ATG12 for [colorectal cancer](#), TG for [thyroid cancer](#), and CMTR2 for both lung cancer and cutaneous melanoma.

The relative increase in cancer risk conferred by these variants was substantial (90%–295%), but it should be noted that the design of the study does not allow accurate assessment of absolute lifetime [cancer risk](#).

Additionally, the researchers found the first genes with rare variants that are associated with a decreased risk of cancer. Specifically, loss of AURKB was found to protect against any cancer type, and loss of PPP1R15A was associated with a 53% lower risk of breast cancer. This suggests that inhibition of PPP1R15A may be a therapeutic option for breast cancer.

The study revealed new insight into the biological mechanisms involved in cancer predisposition that will hopefully lead to better screening and treatment strategies.

More information: Erna V. Ivarsdottir et al, Gene-based burden test yields rare germline variants in six novel cancer genes, *Nature Genetics* (2024). DOI: [10.1038/s41588-024-01966-6](https://doi.org/10.1038/s41588-024-01966-6). www.nature.com/articles/s41588-024-01966-6

Journal information: [Nature Genetics](#)

Provided by deCODE genetics

JANUARY 2, 2025

Detecting disease with a single molecule: Nanopore-based sensors could transform diagnostics

by Jules Bernstein, [University of California - Riverside](#)

The sensor, a glass tube that is melted at the tip to form a sharp needle-like structure, is dipped into a fluid containing molecules. Credit: Kevin Freedman/ImageFX/UCR
UC Riverside scientists have developed a nanopore-based tool that could help diagnose illnesses much faster and with greater precision than current tests allow, by capturing signals from individual molecules.

Since the molecules scientists want to detect—generally certain DNA or protein molecules—are roughly one-billionth of a meter wide, the [electrical signals](#) they produce are very small and require specialized detection instruments.

"Right now, you need millions of molecules to detect diseases. We're showing that it's possible to get useful data from just a [single molecule](#)," said Kevin Freedman, assistant professor of bioengineering at UCR and lead author of a paper about the tool [appearing](#) in *Nature Nanotechnology*. "This level of sensitivity could make a real difference in disease diagnostics."

Freedman's lab aims to build electronic detectors that behave like neurons in the brain and can retain memories: specifically, memories of which molecules previously passed through the sensor. To do this, the UCR scientists developed a new circuit model that accounts for small changes to the sensor's behavior.

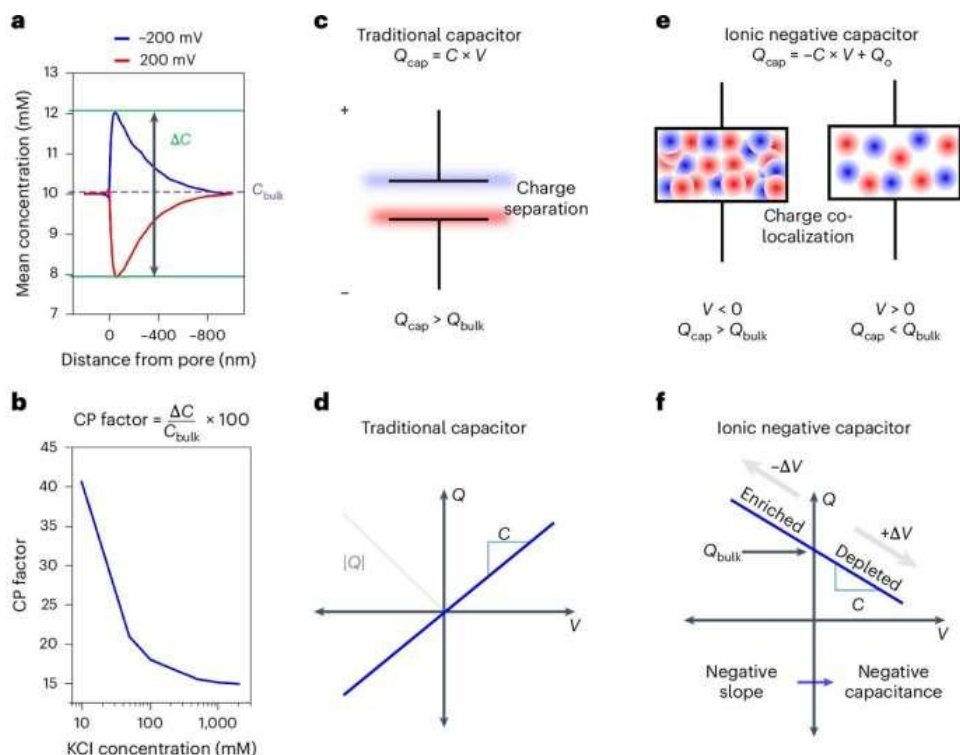
At the core of their circuit is a nanopore—a tiny opening through which molecules pass one at a time. Biological samples are loaded into the circuit along with salts, which dissociate into ions.

If protein or DNA molecules from the sample pass through the pore, this reduces the flow of ions that can pass.

"Our detector measures the reduction in flow caused by a protein or bit of DNA passing through and blocking the passage of ions," Freedman said.

To analyze the electrical signals generated by the ions, Freedman suggests, the system needs to account for the likelihood that some molecules may not be detected as they pass through the nanopore. What distinguishes this discovery is that the nanopore is not just a sensor but itself acts as a filter, reducing background noise from other molecules in a sample that could obscure critical signals.

Traditional sensors require external filters to remove unwanted signals, and these filters can accidentally remove valuable information from the samples. Freedman's approach ensures that each molecule's signal is preserved, boosting accuracy for diagnostic applications.



CP and charge storage model. **a**, Mean concentration of ions inside a nanopipette under +200 mV and -200 mV as obtained through numerically solving the Poisson–Nernst–Planck and Navier–Stokes equations. Bulk ionic concentration used in the simulation was 10 mM and ionic properties were that of K^+ and Cl^- . The surface charge on the pore was -10 mC m^{-2} . **b**, CP factor as a function of ionic concentration as predicted by numerical simulations. **c,d**, Schematic of a traditional capacitor in which charge is separated in space and can discharge during a voltage change. **e,f**, Schematic of an ionic negative capacitor in which charge is co-localized but can still discharge with a voltage change. The negative slope of the Q versus V curve is a characteristic of negative capacitance. Credit: *Nature Nanotechnology* (2025). DOI: 10.1038/s41565-024-01829-5

Freedman envisions the device being used to develop a small, portable diagnostic kit—no larger than a USB drive—that could detect infections in the earliest stages. While today's tests may not register infections for several days after exposure, nanopore sensors could detect infections within 24 to 48 hours. This capability would provide a significant advantage for fast-spreading diseases, enabling earlier intervention and treatment.

"Nanopores offer a way to catch infections sooner—before symptoms appear and before the disease spreads," Freedman said. "This kind of tool could make early diagnosis much more practical for both viral infections and chronic conditions."

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In addition to diagnostics, the device holds promise for advancing [protein research](#). Proteins perform essential roles in cells, and even slight changes in their structure can affect health. Current diagnostic tools struggle to tell the difference between healthy and disease-causing

proteins because of their similarities. The nanopore device, however, can measure subtle differences between individual proteins, which could help doctors design more personalized treatments.

The research also brings scientists closer to achieving single-molecule protein sequencing, a long-sought goal in biology. While DNA sequencing reveals genetic instructions, protein sequencing provides insight into how those instructions are expressed and modified in real time. This deeper understanding could lead to earlier detection of diseases and more precise therapies tailored to each patient.

"There's a lot of momentum toward developing protein sequencing because it will give us insights we can't get from DNA alone," Freedman said. "Nanopores allow us to study proteins in ways that weren't possible before."

Nanopores are the focus of an effort in which Freedman's team will attempt to sequence single proteins. This work builds on his previous research on refining the use of nanopores for sensing molecules, viruses, and other nanoscale entities. He sees these advances as a sign of how molecular diagnostics and biological research may shift in the future.

"There's still a lot to learn about the molecules driving health and disease," Freedman said. "This tool moves us one step closer to personalized medicine."

Freedman expects that [nanopore](#) technology will soon become a standard feature in both research and health care tools. As the devices become more affordable and accessible, they could find a place in everyday diagnostic kits used at home or in clinics.

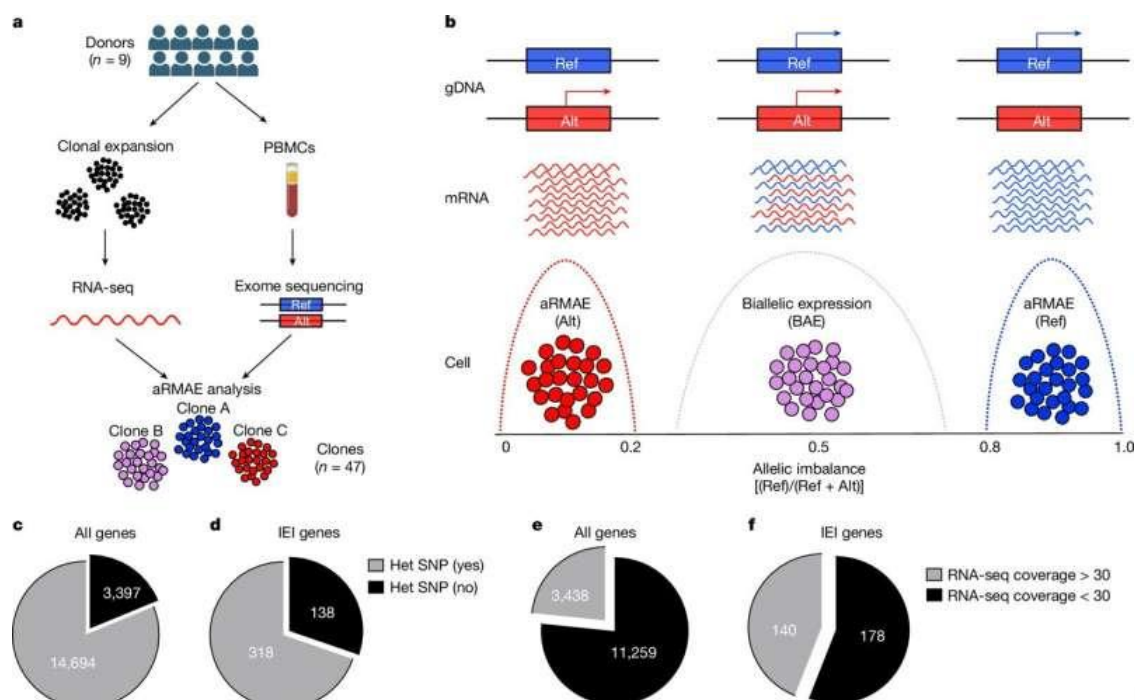
"I'm confident that nanopores will become part of everyday life," Freedman said. "This discovery could change how we'll use them moving forward."

More information: Nasim Farajpour et al, Negative memory capacitance and ionic filtering effects in asymmetric nanopores, *Nature Nanotechnology* (2025). DOI: [10.1038/s41565-024-01829-5](https://doi.org/10.1038/s41565-024-01829-5)

Journal information: [Nature Nanotechnology](#)
Provided by [University of California - Riverside](#)

Genetic bias in cells: Why some genes favor mom or dad, and what it means for disease outcomes

by Alan Dove, [Columbia University Irving Medical Center](#)



Ex vivo
clonally expanded primary T cells used for detection of aRMAE. Credit: *Nature* (2025). DOI: 10.1038/s41586-024-08346-4

New work by Columbia researchers has turned a textbook principle of genetics on its head and revealed why some people who carry disease-causing genes experience no symptoms.

Every biology student learns that each cell in our body (except sperm and eggs) contains two copies of each gene, one from each parent, and each copy plays an equal part in the cell.

The new study shows that some cells are often biased when it comes to some genes and inactivate one parent's copy, a phenomenon that was discovered about a decade ago but wasn't known to influence disease outcomes, as the new study reveals.

The Columbia researchers looked at certain immune cells of ordinary people to get an estimate of the phenomenon and found that these cells had inactivated the maternal or paternal copy of a gene for 1 out of every 20 genes utilized by the cell.

"This is suggesting that there is more plasticity in our DNA than we thought before," says study leader Dusan Bogunovic, professor of pediatric immunology at Columbia University Vagelos College of Physicians and Surgeons.

"So in some cells in your body, every 20th gene can be a little bit more mom, a little bit less dad, or vice versa. And to make things even more complicated, this can be different in [white blood cells](#) than in the kidney cells, and it can perhaps change with time."

These results were [published](#) Jan. 1 in the journal *Nature*.

The new study explains a longstanding puzzle in medicine: Why do some people who've inherited a disease-causing mutation experience fewer symptoms than others with the same mutation?

"In many diseases, we'll see that 90% of people who carry a mutation are sick, but 10% who carry the mutation don't get sick at all," says Bogunovic, a scientist who studies children with rare immunological disorders at Columbia University Irving Medical Center.

Enlisting an international team of collaborators, the researchers looked at several families with different genetic disorders affecting their immune systems. In each case, the disease-causing copy was more likely to be active in sick patients and suppressed in healthy relatives who had inherited the same genes.

"There was some speculation that this bias toward one copy or the other could explain wide differences in the severity of a genetic disease, but no experimental evidence existed until now," Bogunovic says.

Though the current work looked only at [immune cells](#), Bogunovic says the selective bias for the maternal or paternal copy of a gene affected more than just immune-related genes. "We don't see a preference for immune genes or any other class of genes, so we think this phenomenon can explain the wide variability in disease severity we see with many other genetic conditions," he says, adding "this could be just the tip of the iceberg."

The phenomenon could help explain diseases with flares, like lupus, diseases that emerge following environmental triggers, and may play a role in cancer.

The future of treatments for genetic diseases

The study's findings point to an entirely new paradigm for diagnosing and perhaps even treating inherited diseases.

The investigators propose expanding the standard characterization of [genetic diseases](#) to include patients' "transcriptotypes," their gene activity patterns, in addition to their genotypes.

"This changes the paradigm of testing beyond your DNA to your RNA, which as we've shown in our study, is not equal in all cell types and can change over time," says Bogunovic.

If researchers can identify the mechanisms behind selective gene inactivation, they may also be able to treat genetic diseases in a new way, by switching a patient's gene expression pattern to suppress the undesirable copy.

While emphasizing that such strategies are still far from clinical use, Bogunovic is optimistic. "At least in cell culture in the lab we can do it, so manipulation in that way is something that could turn somebody's genetic disease into non-disease, assuming we are successful."

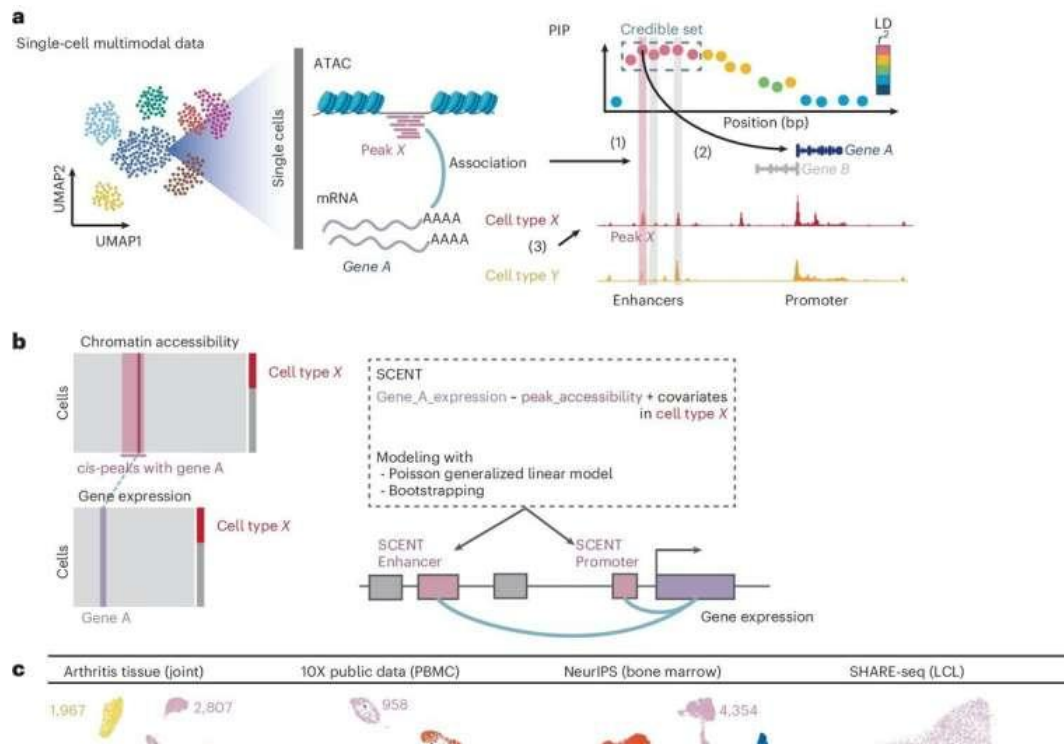
More information: O'Jay Stewart et al, Monoallelic expression can govern penetrance of inborn errors of immunity, *Nature* (2025). DOI: [10.1038/s41586-024-08346-4](https://doi.org/10.1038/s41586-024-08346-4)

Journal information: [Nature](#)

Provided by [Columbia University Irving Medical Center](#)

Researchers develop statistical method for genetic mapping of autoimmune diseases

by Brigham and Women's Hospital



Schematic overview of SCENT and SCENT enhancer–gene pairs across nine single-cell multimodal datasets. **a**, SCENT identifies (1) active *cis*-regulatory regions and (2) their target genes in (3) a specific cell type. Those SCENT results can be used to define likely causal variants, genes and cell types for GWAS loci. **b**, SCENT models association between chromatin accessibility from ATAC–seq and gene expression from RNA–seq across individual cells in a given cell type. **c**, Nine single-cell datasets on which we applied SCENT to create 23 cell-type-specific enhancer–gene maps. The cells in each dataset are described in UMAP embeddings from RNA–seq, colored by cell types ($n_{\text{cells}} > 500$) and annotated by cell numbers. Credit: *Nature Genetics* (2024). DOI: 10.1038/s41588-024-01682-1

Genetic studies of diseases map segments of the genome driving disease. But to understand how those changes contribute to disease progression, it is important to understand how they may alter gene regulation of disease genes in cell populations assumed to be driving disease.

"Enhancer-gene maps" link genomic regulatory regions to genes and are essential for understanding disease. But constructing them poses challenges due to limitations in current experimental methods, that make it difficult to apply the technique to rare [cell populations](#) and genes that only regulate specific cell types.

Researchers from Brigham and Women's Hospital, a founding member of the Mass General Brigham health care system, have developed a statistical method called SCENT (single-cell enhancer target gene mapping). This method uses multimodal single-cell data to establish links between regulatory elements and genes, allowing them to pinpoint probable causal gene loci for both common and rare diseases. These insights might assist the development of treatments for various conditions.

The research team applied SCENT to nine multimodal single-cell datasets representing various human tissues, including immune, neuronal, and pituitary cells, aiming to understand the intricacies of DNA regulation in each specific cell type.

With these data, they developed 23 distinct gene-enhancer maps to investigate genetic variants and expression patterns associated with 1,143 diseases and traits. Notably, they discovered that, for [immune diseases](#), crucial insights emerged not only from immune cells but also from cells within the affected tissues themselves.

"For most [autoimmune diseases](#), people assume that we need a general map of immune cells. But we find that the enhancer-gene maps of immune cells are different in affected disease tissues," said Soumya Raychaudhuri, MD, Ph.D., of Brigham's Division of Rheumatology, Immunology, and Inflammation. We demonstrate how such a map can be used to interpret [genetic data](#) from [rheumatoid arthritis](#) and other autoimmune diseases."

The study is [published](#) in the journal *Nature Genetics*.

More information: Saori Sakaue et al, Tissue-specific enhancer–gene maps from multimodal single-cell data identify causal disease alleles, *Nature Genetics* (2024). DOI: [10.1038/s41588-024-01682-1](https://doi.org/10.1038/s41588-024-01682-1)

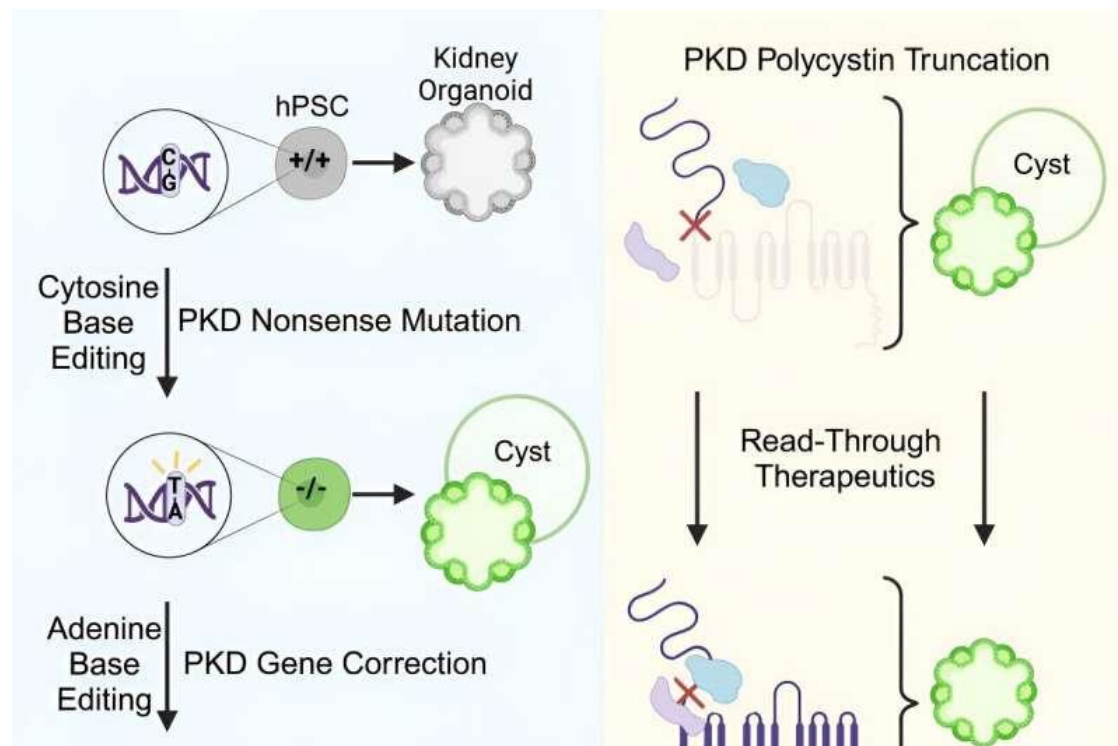
Journal information: [Nature Genetics](#)

Provided by [Brigham and Women's Hospital](#)

APRIL 4, 2024

Scientists discover potential treatment approaches for polycystic kidney disease

by [National Institutes of Health](#)



Credit: *Cell Stem Cell* (2024). DOI: 10.1016/j.stem.2024.03.005

Researchers have shown that dangerous cysts, which form over time in polycystic kidney disease (PKD), can be prevented by a single normal copy of a defective gene. This means the potential exists that scientists could one day tailor a gene therapy to treat the disease. They also discovered that a type of drug, known as a glycoside, can sidestep the effects of the defective gene in PKD. The discoveries could set the stage for new therapeutic approaches to treating PKD, which affects millions worldwide.

The study is [published](#) in *Cell Stem Cell*.

Scientists used gene editing and 3D human cell models known as organoids to study the genetics of PKD, which is a life-threatening, inherited kidney disorder in which a gene defect causes microscopic tubes in the kidneys to expand like water balloons, forming cysts over decades. The cysts can crowd out healthy tissue, leading to kidney function problems

and [kidney failure](#). Most people with PKD are born with one healthy gene copy and one defective gene copy in their cells.

"Human PKD has been so difficult to study because cysts take years and decades to form," said senior study author Benjamin Freedman, Ph.D., at the University of Washington, Seattle. "This new platform finally gives us a model to study the genetics of the disease and hopefully start to provide answers to the millions affected by this disease."

To better understand the genetic reasons cysts form in PKD, Freedman and his colleagues sought to determine whether 3D human mini-kidney organoids with one normal gene copy and one defective copy would form cysts. They grew organoids, which can mimic features of an organ's structure and function, from induced [pluripotent stem cells](#), which can become any kind of cell in the body.

To generate organoids containing clinically relevant mutations, the researchers used a gene editing technique called base editing to create mutations in certain locations on the PKD1 and PKD2 genes in human stem cells. They focused on four types of mutations in these genes that are known to cause PKD by disrupting the production of polycystin protein. Disruptions in two types of the protein—polycystin-1 and polycystin-2—are associated with the most severe forms of PKD.

They then compared cells with two gene copy mutations in organoids to cells with only one gene copy mutation. In some cases, they also used gene editing to correct mutations in one of the two gene copies to see how this affected cyst formation. They found organoids with two defective gene copies always produced cysts and those that carried one good gene copy and one bad copy did not form cysts.

"We didn't know if having a gene mutation in only one gene copy is enough to cause PKD, or if a second factor, such as another mutation or [acute kidney injury](#) was necessary," Freedman said. "It's unclear what such a trigger would look like, and until now, we haven't had a good experimental model for human PKD."

According to Freedman, the cells with one healthy gene copy make only half the normal amount of polycystin-1 or polycystin-2, but that was sufficient to prevent cysts from developing. He added that the results suggest the need for a second trigger and that preventing that second hit might be able to prevent the disease.

The organoid models also provided the first opportunity to study the effectiveness of a class of drugs known as eukaryotic ribosomal selective glycoside on PKD cyst formation.

"These compounds will only work on single base pair mutations, which are commonly seen in PKD patients," explained Freedman. "They wouldn't be expected to work on any mouse models and didn't work in our previous [organoid](#) models of PKD. We needed to create that type of mutation in an experimental model to test the drugs."

Freedman's team found that the drugs could restore the ability of genes to make polycystin, increasing the levels of polycystin-1 to 50% and preventing cysts from forming. Even after cysts had formed, adding the drugs slowed their growth.

Freedman suggested that a next step would be to test existing glycoside drugs in patients. Researchers also could explore the use of [gene therapy](#) as a treatment for PKD.

More information: Courtney E. Vishy et al, Genetics of cystogenesis in base-edited human organoids reveal therapeutic strategies for polycystic kidney disease, *Cell Stem Cell* (2024). DOI: [10.1016/j.stem.2024.03.005](https://doi.org/10.1016/j.stem.2024.03.005)

Journal information: [Cell Stem Cell](#)

Provided by [National Institutes of Health](#)

JULY 4, 2024

[Editors' notes](#)

Scientists discover new T cells and genes related to immune disorders

by [RIKEN](#)

A newly developed method called ReapTEC allowed the discovery of thousands of active bidirectional enhancers. Further analysis of GWAS data revealed that various immune-mediated diseases, like multiple sclerosis and rheumatoid arthritis, are related to genetic variations within these enhancers. Credit: RIKEN

Researchers led by Yasuhiro Murakawa at the RIKEN Center for Integrative Medical Sciences (IMS) and Kyoto University in Japan and IFOM ETS in Italy have discovered several rare types of helper T cells that are associated with immune disorders such as multiple sclerosis, rheumatoid arthritis, and even asthma.

[Published](#) in *Science*, the discoveries were made possible by a newly developed technology they call ReapTEC, which identified genetic enhancers in rare T cell subtypes that are linked to specific [immune disorders](#). The new T cell atlas is publicly available and should help in the development of new drug therapies for immune-mediated diseases.

Helper T cells are a kind of white blood cell that make up a large part of the immune system. They recognize pathogens and regulate the immune response. Many immune-mediated diseases are caused by abnormal T cell function. In [autoimmune diseases](#) like multiple sclerosis, they mistakenly attack parts of the body as if they were pathogens.

In the case of allergies, T cells overreact to harmless substances in the environment like pollen. We know of several common T cells, but recent studies have shown that rare and specialized types of T cells exist, and they might be related to immune-mediated diseases.

Within all cells, including T cells, there are regions of DNA called "enhancers." This DNA does not code for proteins. Instead, it codes for small pieces of RNA, and enhances the expression of other genes. Variations in T cell enhancer DNA therefore lead to differences in gene expression, and this can affect how T cells function. Some enhancers are bidirectional, which means that both strands of the DNA are used as templates for enhancer RNA.

The researchers from several different laboratories at RIKEN IMS, as well as colleagues at other institutes, teamed up to develop the new ReapTEC technology and look for connections between bidirectional T cell enhancers and immune diseases.

After analyzing about a million human T cells, they found several groups of rare T cell types, accounting for less than 5% of the total. Applying ReapTEC to these cells identified almost 63,000 active bidirectional enhancers. To determine whether any of these enhancers are related to immune diseases, they turned to [genome-wide association studies](#) (GWAS), which have reported numerous genetic variants, called single-nucleotide polymorphisms, that are related to various immune diseases.

When the researchers combined the GWAS data with the results of their ReapTEC analysis, they found that genetic variants for immune-mediated diseases were often located within the bidirectional enhancer DNA of the rare T cells that they had identified. In contrast, genetic variants for neurological diseases did not show a similar pattern, meaning that the bidirectional enhancers in these rare T cells are related specifically to immune-mediated diseases.

Going even deeper into the data, the researchers were able to show that individual enhancers in certain rare T cells are related to specific immune diseases. Overall, among the 63,000 bidirectional enhancers, they were able to identify 606 that included single-nucleotide polymorphisms related to 18 immune-mediated diseases.

Lastly, the researchers were able to identify some of the genes that are the targets of these disease-related enhancers. For example, when they activated an enhancer that contained a genetic variant related to inflammatory bowel disease, the resulting enhancer RNA triggered upregulation of the IL7R gene.

"In the short-term, we have developed a new genomics method that can be used by researchers around the world," says Murakawa. "Using this method, we discovered new types of helper T cells as well as genes related to immune disorders. We hope that this knowledge will lead to a better understanding of the genetic mechanisms underlying human immune-mediated diseases."

In the long-term, the researchers believe follow-up experiments will be able to identify new molecules that can be used to treat immune-mediated diseases.

More information: Akiko Oguchi et al, An atlas of transcribed enhancers across helper T cell diversity for decoding human diseases, *Science* (2024). DOI:

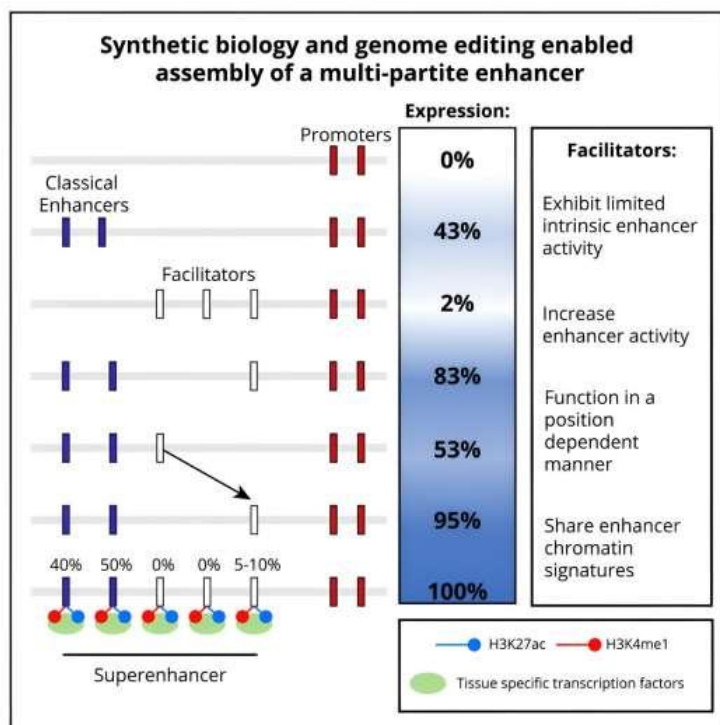
[10.1126/science.add8394](https://doi.org/10.1126/science.add8394). www.science.org/doi/10.1126/science.add8394

Journal information: [Science](#)

DECEMBER 14, 2023

Researchers define new class of regulatory element in DNA

by [University of Oxford](#)



Graphical Abstract. Credit: *Cell* (2023). DOI: [10.1016/j.cell.2023.11.030](https://doi.org/10.1016/j.cell.2023.11.030)

Researchers at the MRC Weatherall Institute of Molecular Medicine's Laboratory of Gene Regulation, led by Professor Doug Higgs and Dr. Mira Kassouf, have published a study in the journal [Cell](#), in which they reveal another piece of the puzzle of how the code in our DNA is read.

In this study, the authors introduce the concept of "facilitators," a newly identified type of non-coding DNA that can help to drive gene expression.

All of the [cells](#) in your body contain the same DNA. However, these cells are able to develop into over 200 different types and make up a variety of different specialized tissues such as the skin, the blood, and the brain.

DNA contains stretches of code called 'genes,' which specify the features of each cell, and yet these genes only account for approximately 2% of all DNA in the cell. The remaining 98% of DNA has been shown to include [regulatory elements](#) that are able to influence the expression of nearby genes and, therefore, control how a cell develops.

One type of regulatory element in DNA is enhancers, which sit in between genes and are needed to switch genes on and off in different combinations, at different times, and at different levels. Despite being discovered over 40 years ago, how enhancers work is still not fully understood. More recently, "super-enhancers" have also been identified, which are composed of teams of individual regulatory elements that work together to drive very high levels of [gene expression](#).

It was previously thought that the individual elements of these super-enhancers might each carry out the same role. However, the authors of this study found that these elements actually have distinct roles and are able to work together to make the super-enhancer greater than the sum of its parts.

In particular, this study identified a new kind of regulatory element, which the authors have named "facilitators." These facilitators do not have any intrinsic enhancer activity but are able to help the classical enhancers do their job more effectively.

In this paper, researchers used a mouse α -globin super-enhancer as a model system to study the individual roles of its five constituent elements. Previous studies have suggested that this super-enhancer was composed of two classical enhancers and three inactive elements. Using a synthetic biology approach, in collaboration with Jef Boeke's laboratory (NYU Langone Health), researchers rebuilt the mouse super-enhancer from the bottom up and tested a wide variety of different combinations of the individual elements.

This way, they were able to show that these 'inactive' elements were really facilitators. The authors also reviewed past analyses of other super-enhancers and found evidence that these facilitators could be a common feature of super-enhancers.

Lead author Dr. Mira Kassouf said, "In addition to the other known fundamental regulatory elements ([enhancers](#), promoters, and insulators), our new observations have identified a new type of regulatory element called a facilitator. As for the original three elements, it is likely that identifying facilitators and understanding how they work will provide new insights into the mechanisms by which [genes](#) are normally switched on and off and how this goes awry in human genetic disease."

More information: Joseph W. Blayney et al, Super-enhancers include classical enhancers and facilitators to fully activate gene expression, *Cell* (2023). DOI: [10.1016/j.cell.2023.11.030](https://doi.org/10.1016/j.cell.2023.11.030)

Journal information: *Cell*
Provided by [University of Oxford](#)

A ‘Holy Grail’ of Science Is Getting Closer

The human cell is a miserable thing to study. Tens of trillions of them exist in the body, forming an enormous and intricate network that governs every disease and metabolic process. Each cell in that circuit is itself the product of an equally dense and complex interplay among genes, proteins, and other bits of profoundly small biological machinery.

Our understanding of this world is hazy and constantly in flux. As recently as a few years ago, scientists thought there were only a few hundred distinct cell types, but new technologies have revealed [thousands](#) (and that’s just the [start](#)). Experimenting in this microscopic realm can be a kind of guesswork; even success is frequently confounding. Ozempic-style drugs were thought to act on the gut, for example, but might turn out to be [brain drugs](#), and Viagra was initially developed to treat cardiovascular disease.

Speeding up cellular research could yield tremendous things for humanity—new medicines and vaccines, cancer treatments, even just a deeper understanding of the elemental processes that shape our lives. And it’s beginning to happen. Scientists are now designing computer programs that may unlock the ability to simulate human cells, giving researchers the ability to predict the effect of a drug, mutation, virus, or any other change in the body, and in turn making physical experiments more targeted and likelier to succeed. Inspired by large language models such as ChatGPT, the hope is that generative AI can “decode the language of biology and then speak the language of biology,” Eric Xing, a computer scientist at Carnegie Mellon University and the president of Mohamed bin Zayed University of Artificial Intelligence, in the United Arab Emirates, told me.

Much as a chatbot can discern style and perhaps even meaning from huge volumes of written language, which it then uses to construct humanlike prose, AI could in theory be trained on huge quantities of biological data to extract key information about cells or even entire organisms. This would allow researchers to

create virtual models of the many, many cells within the body—and act upon them. “It’s the holy grail of biology,” Emma Lundberg, a cell biologist at Stanford, told me. “People have been dreaming about it for years and years and years.”

These grandiose claims—about so ambiguous and controversial a technology as generative AI, no less—may sound awfully similar to self-serving prophecies from tech executives: OpenAI’s Sam Altman, Google DeepMind’s Demis Hassabis, and Anthropic’s Dario Amodei have all declared that their AI products will soon revolutionize medicine.

If generative AI does make good on such visions, however, the result may look something like the virtual cell that Xing, Lundberg, and others have been working toward. (Last month, they published a [perspective](#) in *Cell* on the subject. Xing has taken the idea a step further, co-authoring several papers about the possibility that such virtual cells could be combined into an “AI-driven digital organism”—a simulation of an entire being.) Even in these early days—scientists told me that this approach, if it proves workable, may take 10 or 100 years to fully realize—it’s a demonstration that the technology’s ultimate good may come not from chatbots, but from something much more ambitious.

Efforts to create a virtual cell did not begin with the arrival of large language models. The first modern attempts, back in the [1990s](#), involved writing equations and code to describe every molecule and interaction. This approach yielded some success, and the first whole-cell model, of a bacteria species, was eventually [published](#) in 2012. But it hasn’t worked for human cells, which are more complicated—scientists lack a deep enough understanding to imagine or write all of the necessary equations, Lundberg said.

The issue is not that there isn’t any relevant information. Over the past 20 years, new technologies have produced a trove of genetic-sequence and microscope data related to human cells. The problem is that the corpus is so large and complex that no human could possibly make total sense of it. But generative AI, which works by extracting patterns from huge amounts of data with minimal human instructions, just might. “We’re at this tipping point” for AI in biology, Eran Segal, a computational biologist at the Weizmann Institute of Science and a collaborator of Xing’s, told me. “All the stars aligned, and we have all the different components: the data, the compute, the modeling.”

Scientists have already begun using generative AI in a growing number of disciplines. For instance, by analyzing years of meteorological records or quantum-physics measurements, an AI model might reliably predict the approach of major storms or how subatomic particles behave, even if scientists can't say *why* the predictions are accurate. The ability to explain is being replaced by the ability to predict, human discovery supplanted by algorithmic faith. This may seem counterintuitive (if scientists can't explain something, do they really understand it?) and even terrifying (what if a black-box algorithm trusted to predict floods misses one?). But so far, the approach has yielded significant results.

[Read: [Science is becoming less human](#)]

"The big turning point in the space was six years ago," Ziv Bar-Joseph, a computational biologist at Carnegie Mellon University and the head of research and development and computational sciences at Sanofi, told me. In 2018—before the generative-AI boom—Google DeepMind released AlphaFold, an AI algorithm that functionally "solved" a long-standing problem in molecular biology: how to discern the three-dimensional structure of a protein from the list of amino acids it is made of. Doing so for a single protein used to take a human years of experimenting, but in 2022, just four years after its initial release, AlphaFold predicted the structure of 200 million of them, nearly every protein known to science. The program is already advancing drug discovery and fundamental biological research, which won its creators a [Nobel Prize](#) this past fall.

The program's success inspired researchers to design so-called foundation models for other building blocks of biology, such as DNA and RNA. Inspired by how chatbots predict the next word in a sentence, many of these foundation models are trained to predict what comes next in a biological sequence, such as the next set of As, Ts, Gs, and Cs that make up a strand of DNA, or the next amino acid in a protein. Generative AI's value extends beyond straightforward prediction, however. As they analyze text, chatbots develop abstract mathematical maps of language based on the relationships between words. They assign words and sentences coordinates on those maps, known as "embeddings": In one famous [example](#), the distance between the embeddings of *queen* and *king* is the same as that between *woman* and *man*, suggesting that the program developed some internal notion of gender roles and royalty. Basic, if

flawed, capacities for mathematics, logical reasoning, and persuasion seem to emerge from this word prediction.

Many AI researchers believe that the basic understanding reflected in these embeddings is what allows chatbots to effectively predict words in a sentence. This same idea could be of use in biological foundation models as well. For instance, to accurately predict a sequence of nucleotides or amino acids, an algorithm might need to develop internal, statistical approximations of how those nucleotides or amino acids interact with one another, and even how they function in a cell or an organism.

Although these biological embeddings—essentially a long list of numbers—are on their own meaningless to people, the numbers can be fed into other, simpler algorithms that extract latent “meaning” from them. The embeddings from a model designed to understand the structure of DNA, for instance, could be fed into another program that predicts DNA function, cell type, or the effect of genetic mutations. Instead of having a separate program for every DNA- or protein-related task, a foundation model can address many at once, and [several such programs](#) have been published over the past two years.

Take scGPT, for example. This program was designed to predict bits of RNA in a cell, but it has succeeded in predicting cell type, the effects of genetic alterations, and more. “It turns out by just predicting next gene tokens, scGPT is able to really understand the basic concept of what is a cell,” Bo Wang, one of the programs’ creators and a biologist at the University of Toronto, told me. The latest version of AlphaFold, published last year, has exhibited far more general capabilities—it can predict the structure of biological molecules other than proteins as well as how they interact. Ideally, the technology will make experiments more efficient and targeted by systematically exploring hypotheses, allowing scientists to physically test only the most promising or curiosity-inducing. Wang, a co-author on the *Cell* perspective, hopes to build even more general foundation models for cellular biology.

The language of biology, if such a thing exists, is far more complicated than any human tongue. All the components and layers of a cell affect one another, and scientists hope that composing various foundation models creates something greater than the sum of their parts—like combining an engine, a hull, landing gear, and other parts into an airplane. “Eventually it’s going to all come together

into one big model,” Stephen Quake, the head of science at the Chan Zuckerberg Initiative (CZI) and a lead author of the virtual-cell perspective, told me. (CZI—a philanthropic organization focused on scientific advancement that was co-founded by Priscilla Chan and her husband, Mark Zuckerberg—has been central in many of these recent efforts; in March, it held a workshop focused on AI in cellular biology that led to the publication of the perspective in *Cell*, and last month, the group [announced](#) a new set of resources dedicated to virtual-cell research, which includes several AI models focused on cell biology.)

In other words, the idea is that algorithms designed for DNA, RNA, gene expression, protein interactions, cellular organization, and so on might constitute a virtual cell if put together in the right way. “How we get there is a little unclear right now, but I’m confident it will,” Quake said. But not everyone shares his enthusiasm.

Across contexts, generative AI has a persistent problem: Researchers and enthusiasts see a lot of potential that may not always work out in practice. The LLM-inspired approach of predicting genes, amino acids, or other such biological elements in a sequence, as if human cells and bodies were sentences and libraries, is in its “very early days,” Quake said. Xing likened his and similar virtual-cell research to having a “GPT-1” moment, referencing an early proof-of-concept program that eventually led to ChatGPT.

Although using deep-learning algorithms to analyze huge amounts of data is promising, the quest for more and more universal solutions struck some researchers I spoke with as well-intentioned but unrealistic. The foundation-model approach in Xing’s AI-driven digital organisms, for instance, suggests “a little too much faith in the AI methods,” Steven Salzberg, a biomedical engineer at Johns Hopkins University, told me. He’s skeptical that such generalist programs will be more useful than bespoke AI models such as AlphaFold, which are tailored to concrete, well-defined biological problems such as protein folding. Predicting genes in a sequence didn’t strike Salzberg as an obviously useful biological goal. In other words, perhaps there is no unifying language of biology—in which case no embedding can capture every relevant bit of biological information.

[Read: [We’re entering uncharted territory for math](#)]

More important than AlphaFold’s approach, perhaps, was that it reliably and resoundingly beat other, state-of-the-art protein-folding algorithms. But for now,

“the jury is still out on these cell-based models,” Bar-Joseph, the CMU biologist, said. Researchers have to prove how well their simulations work. “Experiment is the ultimate arbiter of truth,” Quake told me—if a foundation model predicts the shape of a protein, the degree of a gene’s expression, or the effects of a mutation, but actual experiments produce confounding results, the model needs reworking.

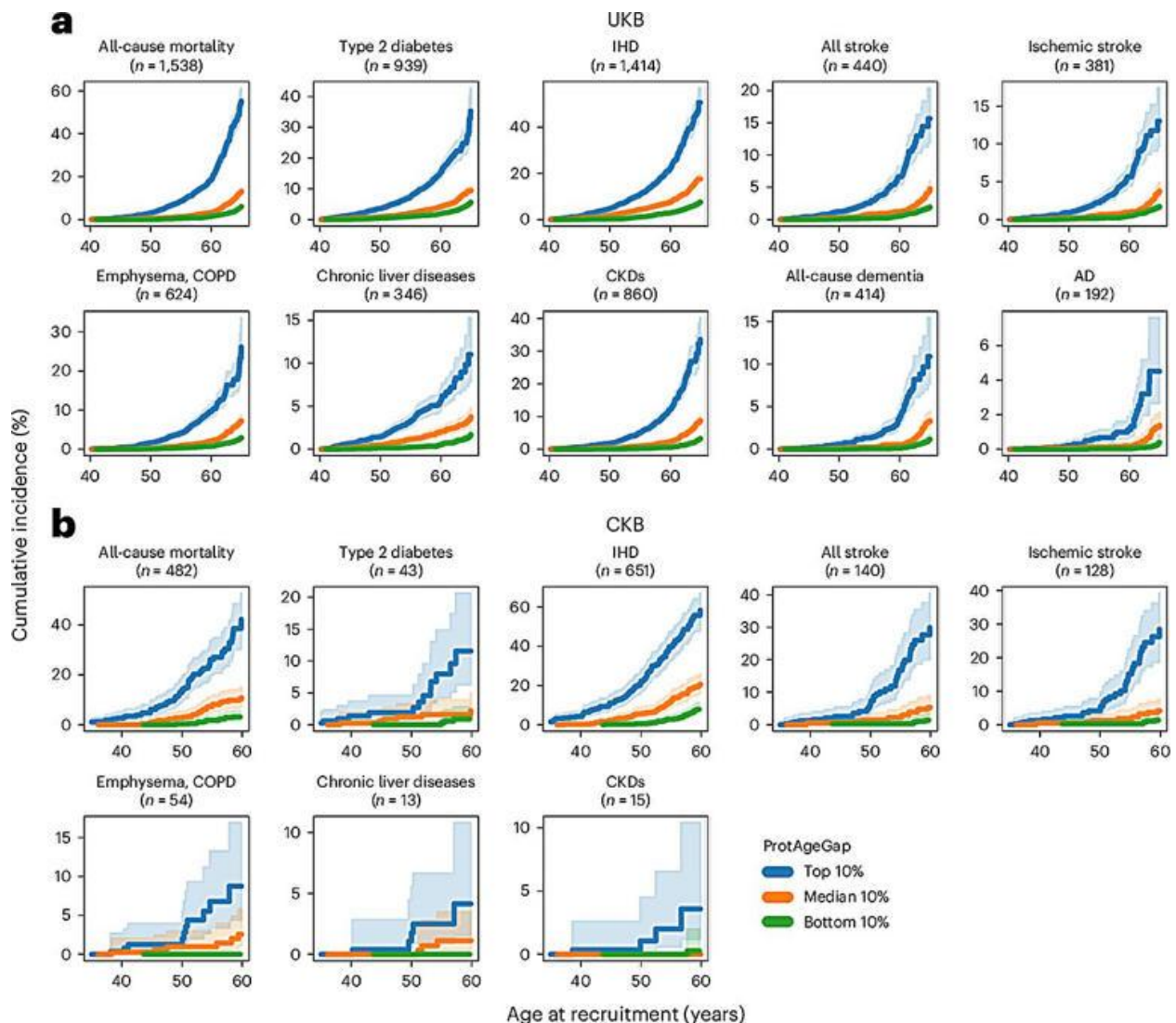
Even with working foundation models, the jump from individual programs to combining them into full-fledged cells is a big one. Scientists haven’t figured out all of the necessary models, let alone how to assemble them. “I haven’t seen a good application where all these different models come together,” Bar-Joseph said, though he is optimistic. And although there are a lot of data for researchers to begin with, they will need to collect far more moving forward. “The key challenge is still data,” Wang said. For example, many of today’s premier cellular data sets don’t capture change over time, which is a part of every biological process, and might not be applicable to specific scientific problems, such as predicting the effects of a new drug on a rare disease. Right now, the field isn’t entirely sure which data to collect next. “We have sequence data; we have image data,” Lundberg said. “But do we really know which data to generate to reach the virtual cell? I don’t really think we do.”

In the near term, the way forward might not be foundation models that “understand” DNA or cells in the abstract, but instead programs tailored to specific queries. Just as there isn’t one human language, there may not be a unified language of biology, either. “More than a universal system, the first step will be in developing a large number of AI systems that solve specific problems,” Andrea Califano, a computational biologist at Columbia and the president of the Chan Zuckerberg Biohub New York, and another co-author of the *Cell* perspective, told me. Even if such a language of biology exists, aiming for something so universal could also be so difficult as to waste resources when simpler, targeted programs would more immediately advance research and improve patients’ lives.

Scientists are trying anyway. Every level of ambition in the quest to bring the AI revolution to cell biology—whether modeling of entire organisms, single cells, or single processes within a cell—emerges from the same hope: to let virtual simulations, rather than physical experiments, lead the way. Experiments may always be the arbiters of truth, but computer programs will determine which

experiments to carry out, and inform how to set them up. At some point, humans may no longer be making discoveries so much as verifying the work of algorithms—constructing biological laboratories to confirm the prophecies of silicon.

Proteins carried in the blood offer new insights into aging and age-related disease risk



Proteomics age clock stratifies people into divergent age-specific mortality and disease risk trajectories. Credit: Nature Medicine (2024). DOI: 10.1038/s41591-024-03170-9

Chronological age is the most important factor determining risk of disease and death in adults. However, life expectancy can vary considerably among individuals with similar chronological age.

In this study, the researchers used data from 51,408 participants across three large population studies to develop the most powerful clock to date that captures biological age and predicts the risk of premature death and numerous diseases. They analyzed nearly 3,000 proteins in blood samples from participants in the UK Biobank study to develop a machine learning model that uses 204 proteins to estimate a person's biological age.

The study, "[Proteomic aging signatures predict disease risk and mortality across diverse populations](#)," is published in *Nature Medicine*.

This protein-based biological age model was also shown to be able to accurately estimate the biological age of participants in the other two studies, the China Kadoorie Biobank, and FinnGen (based in Finland), who have a very different genetic makeup and lifestyles compared with people living in the UK.

The researchers compared the participants' chronological age with their biological age based on blood proteins to calculate the "protein age gap" as a biological indicator of how fast a person is aging. Within UK Biobank, they could link the protein age gap to a wide range of health outcomes to see if it could reliably predict age-related physical and mental well-being, risk of disease and death.

Key findings:

- The protein age gap was shown to differ by up to 12 years between two people with the same chronological age;
- A person's protein age gap is associated with changes in aging and physical/mental well-being, including physical frailty, handgrip strength, renal function, bone density, cognitive function, and telomere length (a marker of aging that can be measured based on your DNA);
- The protein age gap was shown to be able to accurately predict those at high and low risk of premature death and 18 major diseases, including dementia, heart disease, liver and kidney diseases, and various cancers;

- The protein-based biological age clock was able to reveal major pathways that are the key players in aging and risk of multimorbidity (having two or more conditions simultaneously).

The study provides the largest and most comprehensive evidence to date demonstrating that the protein age gap is associated with numerous age-related diseases and premature death, which represents an unprecedentedly powerful instrument compared to previous biological age clocks. The clock also sheds light on the proteins that are driving the risk of multimorbidity, which together with aging already imposes a major pressure on the NHS and global health services.

Professor Cornelia van Duijn, St Cross Professor of Epidemiology at Oxford Population Health and senior author who has led the team, said, "This is the most powerful biological aging clock developed to date that outperforms all previous clocks in identifying those who age faster and experience more ill-health from aging. The number of diseases the protein-based age clock has been able to accurately predict is unprecedented."

Many of the previous studies on biological age have been conducted but none have reached the breadth and depth of the present study, spanning populations with different genetic ancestry and geographic backgrounds and predicting a wide a range of age-related disorders and premature death.

Dr. Austin Argentieri, lead author on the paper at Oxford Population Health and Research Fellow at Massachusetts General Hospital and the Broad Institute of MIT and Harvard, said, "Developing robust protein-based aging clocks that predict future risk of many diseases and generalize to diverse population groups is a key step in developing effective preventative health strategies that can be used to monitor risk of age-related diseases.

"As technology develops and the cost of proteomic analysis drops, this will further support the development of precision medicine approaches that can be put to widespread use to help people live longer and more healthily."

Professor Zhengming Chen, Richard Peto Professor of Epidemiology at Oxford Population Health, UK Principal Investigator for the China Kadoorie Biobank study, and one of the senior co-authors on the paper, said, "Having been tested and validated in diverse populations, the protein-based age clock can be considered for rapid clinical translations in different populations to inform

lifestyle interventions (such as smoking cessation, weight loss), routine health check-up schemes, and clinical trials."

Chronological age simply tells the passage of time rather than the aging of our body's functions. For some people, their biological 'clock' is ticking faster than others and they age faster. Others may age more slowly than expected based on their chronological age. This may be due to differences in their genetic makeup, lifestyles, and living environments.

In order to gain better insight into who is aging more quickly or more slowly, researchers have previously developed biological age clocks using various biological and clinical indicators.

In the future, protein-based biological age clocks could be used to study the relationships between genetics and environment and the impact that these relationships have on aging, in turn delivering key insights into how we age and our likelihood of developing disease across our lifespan.

More information: Proteomic aging signatures predict disease risk and mortality across diverse populations, *Nature Medicine* (2024). DOI: [10.1038/s41591-024-03170-9](https://doi.org/10.1038/s41591-024-03170-9)

Provided by University of Oxford

Breakthrough research reveals how new genes evolve

Discover how fish antifreeze proteins evolved through convergent pathways, offering groundbreaking insights into genetic innovation and adaptation. (CREDIT: CC BY-SA 4.0)© The Brighter Side of News

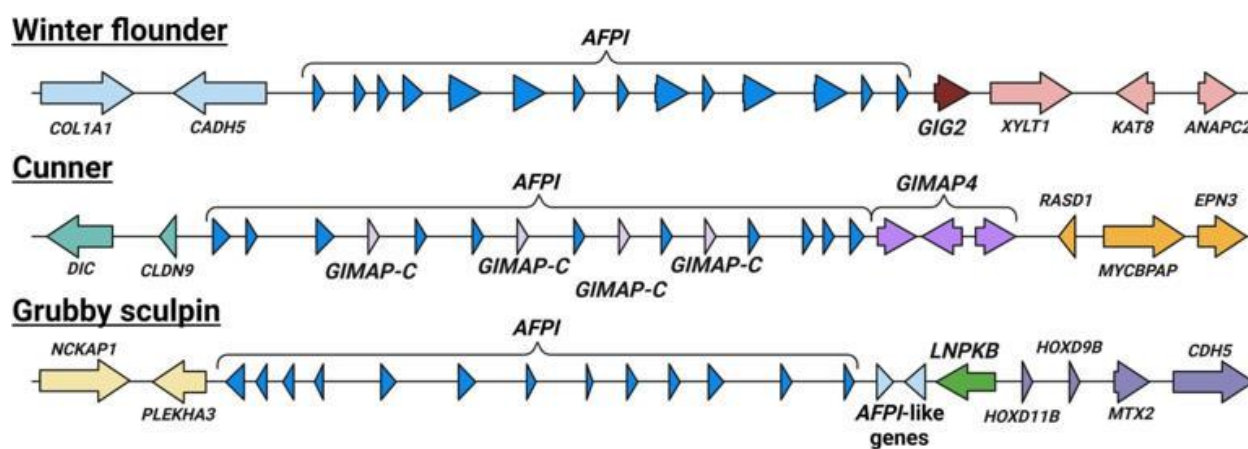
The evolution of life is marked by the emergence of novel traits, driven by the birth of new [genes](#). This process of genetic innovation underpins adaptation, shaping the survival and success of species. Understanding how these new genes originate and evolve remains one of biology's greatest challenges. A recent study on fish antifreeze proteins provides critical insights into the intricate mechanisms driving this phenomenon.

In the icy waters of the polar regions, some fish species have developed a remarkable adaptation: antifreeze proteins (AFPs). These proteins bind to ice crystals in the blood and body fluids, halting their growth and preventing

freezing. This adaptation ensures survival in sub-zero temperatures, exemplifying how environmental pressures shape evolutionary innovations.

Fish AFPs are found across multiple polar and subpolar lineages, including codfishes and notothenioids. Despite differences in structure, all types of AFPs—from antifreeze glycoproteins (AFGP) to AFP types I, II, and III—serve the same [life-saving](#) function. This makes them a prime example of convergent evolution, where unrelated species develop similar traits independently.

Over the past two decades, researchers have made significant strides in uncovering the origins of AFPs. A groundbreaking study on AFGPs in northern codfishes demonstrated the “de novo” formation of new genes from previously noncoding DNA. This process supports the “proto-ORF” model, which proposes that open reading frames (ORFs) acquire regulatory elements to become functional genes.



Genomic loci of AFPI and the neighboring genes in the three focal AFPI-bearing species from separate lineages. Arrows and triangles represent genes in their respective directions. The size of the arrows is not proportional to the actual length of the genes. (CREDIT: Molecular Biology and Evolution)© The Brighter Side of News

In Antarctic notothenioids, the evolution of AFGPs highlights a different pathway. Here, parts of an unrelated trypsinogen gene were co-opted, while a novel coding region evolved from a previously noncoding intron. This partial de novo origination underscores the versatility of [evolutionary mechanisms](#).

Type III AFPs in zoarcid fishes offer another fascinating case. These proteins evolved from a cytoplasmic enzyme through a process called “Escape from Adaptive Conflict” (EAC), where a single protein adapted to serve multiple roles before specializing in one function. In starry flounders, AFP type I arose from a

viral resistance gene, GIG2, showing how genes with unrelated functions can be repurposed.

Among AFPs, type I stands out for its broad distribution across unrelated northern marine fish species, including flounders, sculpins, snailfish, and cunner. These fish belong to different taxonomic orders that diverged over 100 million years ago. Despite this phylogenetic distance, their type I AFPs share striking structural and functional similarities, pointing to a polyphyletic origin.

Recent studies employed advanced genomic tools to explore type I AFP evolution. Researchers sequenced the genomes of winter flounder, grubby sculpin, and cunner, alongside related species. They discovered that each lineage's AFP gene arose from distinct genetic precursors. This finding reveals a remarkable case of convergent evolution at both the functional and [protein sequence](#) levels.

The genomic analyses showed that each lineage independently developed a new coding region for ice-binding proteins while repurposing fragments of ancestral genes for regulatory functions. This "partial de novo" origination bridges the gap between traditional models of [gene duplication](#) and the emergence of entirely new genes.

The study also introduced new conceptual models to explain the diversity of gene evolution. The "Innovation-Amplification-Divergence" model posits that novel functions can arise before gene duplication.

Similarly, the "Duplication-Degeneration-Divergence" model highlights how degenerated pseudogenes—genes that lost their original function—can evolve into entirely new genes. These models emphasize the dynamic nature of the genome, where even nonfunctional or "junk" DNA can be a source of innovation.

Another intriguing mechanism, the "Gene Fission" model, describes how sibling genes arising from duplication can independently degenerate and redevelop distinct functional domains. These insights shed light on the molecular intricacies of new gene formation and adaptation under extreme [environmental pressures](#).

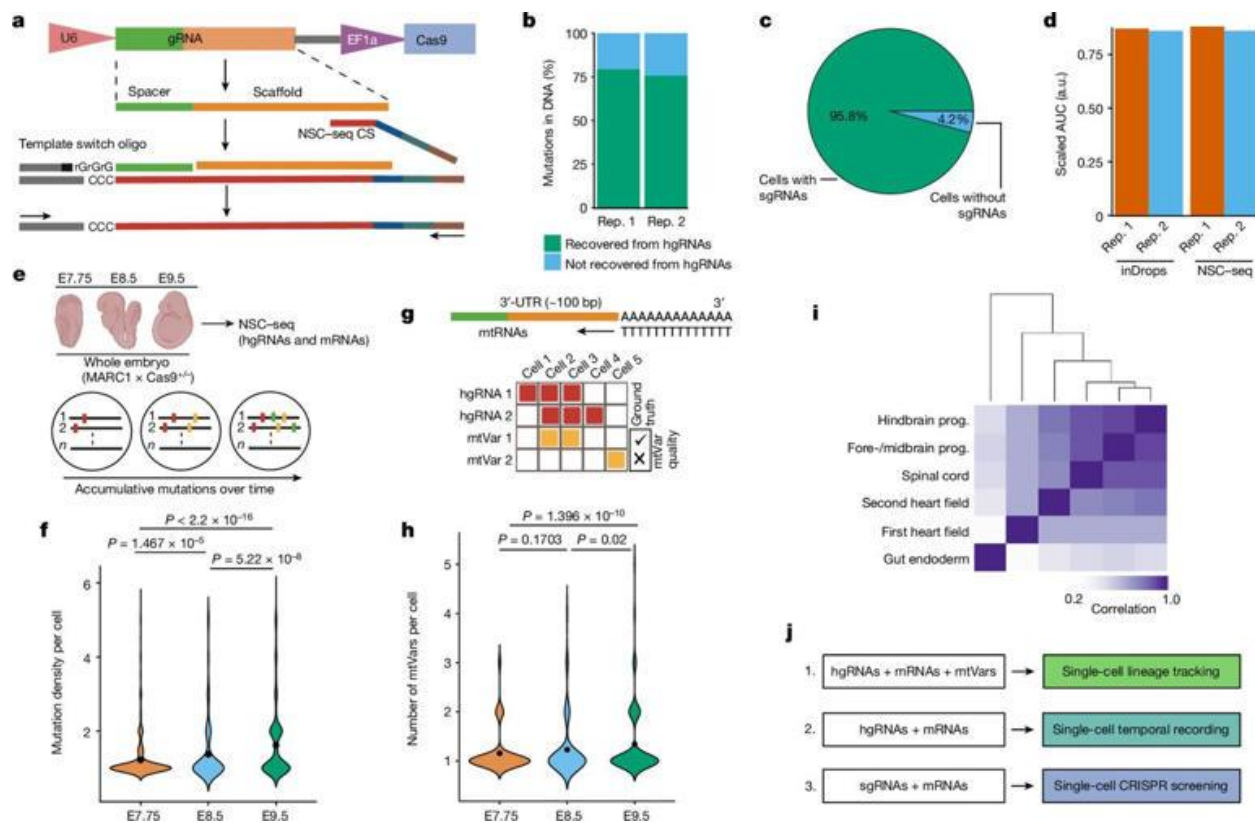
The evolution of fish AFPs offers a rare opportunity to study the birth of new genes in real time. The ability to trace these proteins' origins across unrelated species highlights the adaptability of the genome to environmental challenges.

The study also underscores the importance of integrating ecological and molecular perspectives to understand evolutionary processes.

By uncovering the diverse pathways leading to similar outcomes, this research challenges the notion of linear evolutionary trajectories. Instead, it presents a complex, branching picture of innovation, where nature's toolkit is repurposed time and again to meet the demands of survival.

This work, published in [Molecular Biology and Evolution](#), represents a significant step forward in our understanding of molecular evolution. It provides a comprehensive framework for exploring how new genes emerge and evolve, paving the way for future studies on genetic adaptation and resilience.

Determining precise timing of cellular growth to understand the origins of cancer



Optimization of a multipurpose, single-cell capture platform. Credit: Nature (2024). DOI: 10.1038/s41586-024-07954-4

Cancers are diseases of abnormal cellular growth, and although many are treatable or even curable, their origins are not necessarily clear. Understanding the precise timing of cellular events—as cells transition from normal to cancerous conditions—is key to uncovering new treatments or diagnostic opportunities.

Scientists from Vanderbilt University, led by Mirazul Islam, a graduate student mentored by Professor of Cell and Developmental Biology Ken Lau and Professor of Medicine Robert Coffey, have laid the groundwork for understanding and predicting the natural transition between precancers and cancer. They showed that colorectal cancer is likely to arise from multiple normal cells in the intestinal epithelium, not just from a single cell.

This work lays the foundation for how this approach could be extended to record other aspects of cell activity, such as the timing of when signaling events occur.

"We hope that adding a temporal axis enables a fundamental understanding of tissue development and disease," Lau said.

Although only a low percentage of precancers progress to cancer, the only current predictor of colorectal cancer progression is the size of polyps—small clumps of cells that can become cancerous—in the colon. The researchers have developed a precise molecular "clock" that records the timing of cellular events at a single-cell resolution. This work, [published](#) in the journal *Nature*, helps decipher the origin of colorectal cancer.

Prior to Islam and Lau's work, researchers had used naturally occurring genetic alterations in cancers to track when cell changes occur, but the authors find that although "they provide only inferences of chronological order or clonality," they are not precise enough.

To fill the current gap in knowledge, Islam used a CRISPR platform to create a "genetic barcoding" approach that records the timing of cellular events and clonality in vivo. He tested this approach in both a mouse model and a patient cell-derived model.

Using the strong patient resources at the Vanderbilt University Medical Center—as well as the Human Tumor Atlas Network—the team collected one of the largest multi-omic atlasing datasets on human sporadic polyps to date and

revealed that colorectal cancer originates from independent mutational events occurring in multiple healthy cells.

The team posits that cancers transition from having genetically distinct cells (polyclonal composition) in the early precancer stage to genetically identical cells (monoclonal composition) in advanced stages. Understanding this process will help develop better predictors of the progression from precancer to cancer.

"Mirazul drove this entire project, from conception through execution," Coffey said. "But we couldn't have done this without our collaborators, particularly Mark Magnuson and Qi Liu." Magnuson, Louise B. McGavock Professor and professor of molecular physiology and biophysics, provided expertise in developmental biology. Liu, professor of biostatistics, and her group provided bioinformatics support.

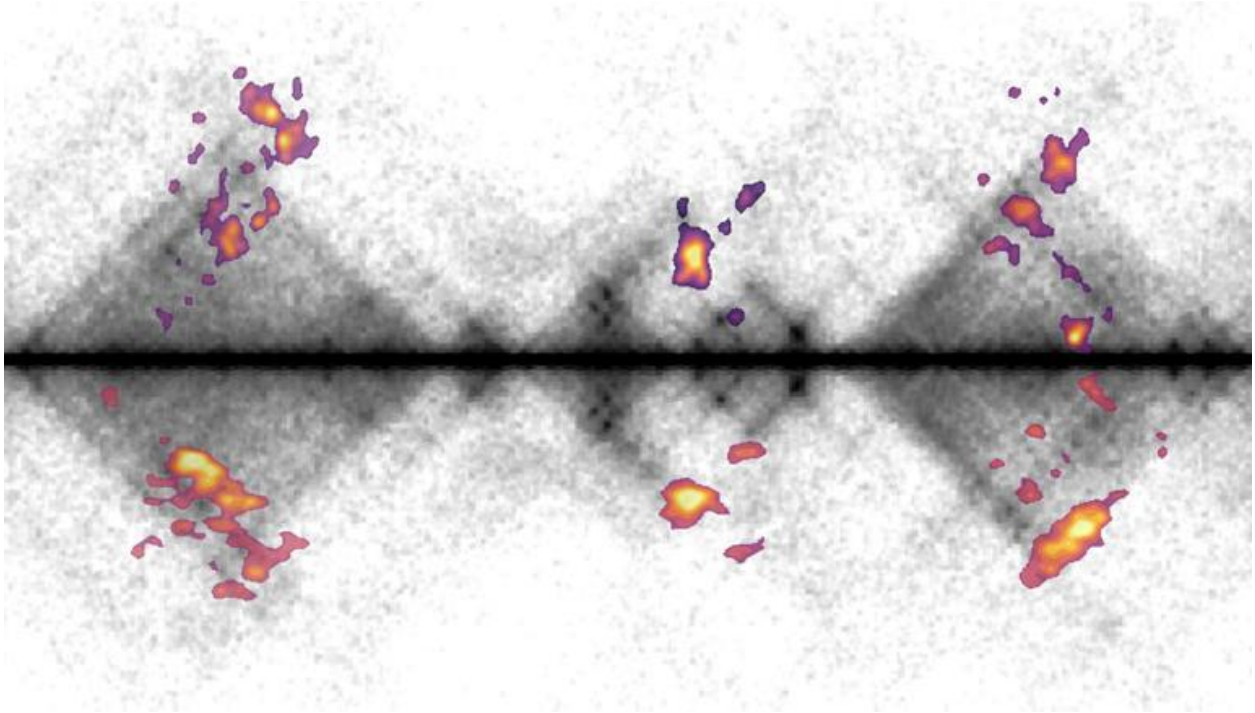
Lau already has an eye toward the future.

"We are applying this approach to understand the clonal dynamics in regeneration by identifying new cell populations with stem cell potential," he said.

More information: Mirazul Islam et al, Temporal recording of mammalian development and precancer, *Nature* (2024). DOI: [10.1038/s41586-024-07954-4](https://doi.org/10.1038/s41586-024-07954-4)

Provided by Vanderbilt University

DNA repair by cooperation between proteins: A look inside the cell's repair hub

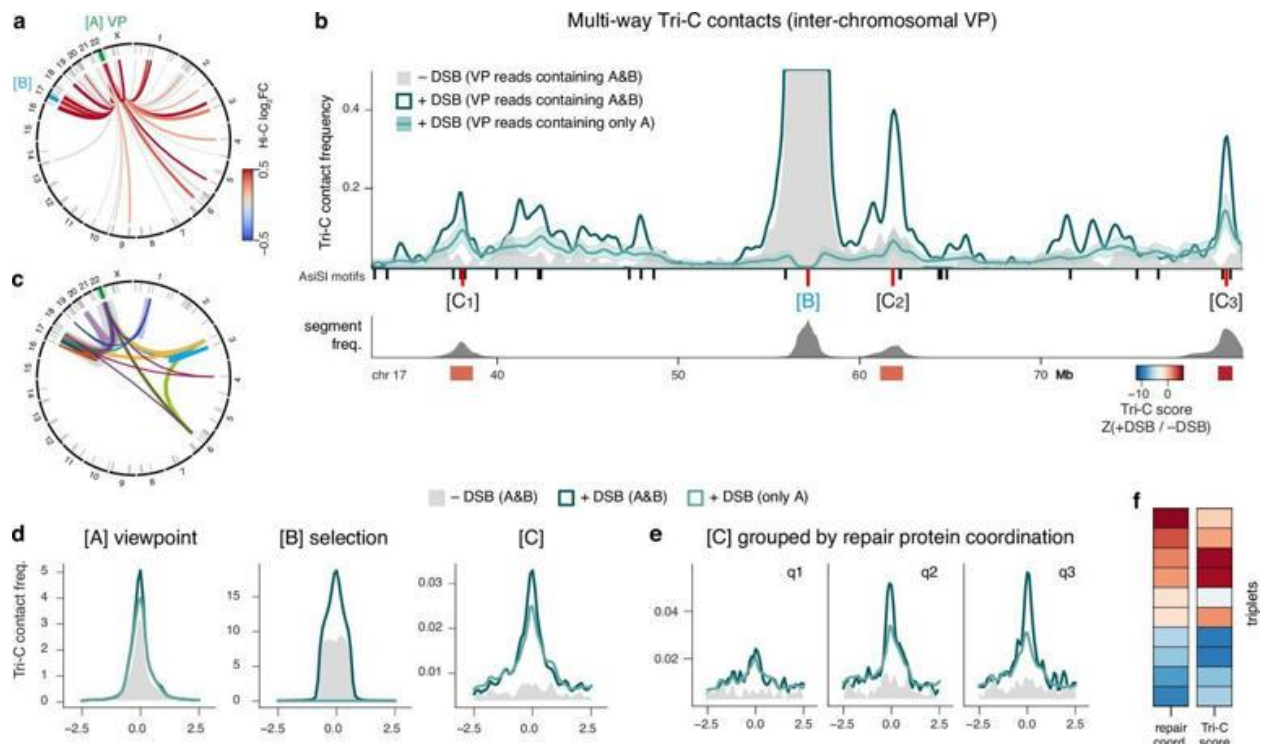


DNA repair domains (colored) projected onto DNA contact maps (gray). Credit: Kim de Luca, Hubrecht Institute

New research from the Kind Group at the Hubrecht Institute sheds light on how cells repair damaged DNA. For the first time, the team has mapped the activity of repair proteins in individual human cells.

The study demonstrates how these proteins collaborate in so-called "hubs" to repair DNA damage. This knowledge offers opportunities to improve cancer therapies and other treatments where DNA repair is essential. The researchers [published](#) their findings in *Nature Communications* on November 21.

DNA is the molecule that carries our genetic information. It can be damaged by normal cellular processes as well as external factors such as UV radiation and chemicals. Such damage can lead to breaks in the DNA strand. If DNA damage is not properly repaired, mutations can occur, which may result in diseases like cancer. Cells use repair systems to fix this damage, with specialized proteins locating and binding to the damaged regions.



Damage-specific three-way contacts identified by Tri-C. Credit: Nature Communications (2024). DOI: 10.1038/s41467-024-54159-4

The body has various mechanisms to repair DNA, but the process can differ from cell to cell. This makes it important to study DNA repair in individual cells.

"Finding breaks in DNA is an enormous challenge," explains first author Kim de Luca. "We don't know exactly where the damage occurs or why some areas are harder to repair. Our approach allowed us to answer these questions."

Using advanced techniques, the researchers mapped where repair proteins attach to DNA. "Previous studies looked at an average picture of multiple cells," De Luca explains. "By studying individual cells, we discovered unique and sometimes rare ways in which DNA damage is repaired."

The findings also revealed that DNA can be repaired by cooperation between repair proteins. These proteins organize themselves into "hubs," where multiple damaged DNA regions come together. These hubs are similar to "repair cafés," where people gather to fix broken items.

"Such a central place makes the process more efficient," says De Luca. "A hub can involve as many as six different breaks that are being repaired in a coordinated way."

The results of this study could contribute to better treatments for diseases involving DNA damage, such as cancer and genetic disorders. By understanding more about how cells repair DNA breaks, researchers can target specific DNA repair mechanisms.

"With precise knowledge of DNA repair, we can design new treatments that are both more effective and less harmful," says De Luca.

More information: Kim L. de Luca et al, Genome-wide profiling of DNA repair proteins in single cells, *Nature Communications* (2024). DOI: [10.1038/s41467-024-54159-4](https://doi.org/10.1038/s41467-024-54159-4)

Provided by Hubrecht Institute

Genetic diseases: How scientists are working to make DNA repair (almost) a piece of cake

I have always been fascinated by genetics, a branch of biology that helps explain everything from the striking resemblance between different members of a family to the fact that strawberry plants are frost-resistant. It's an impressive field!

I also have a personal connection to genetics. Growing up, I learned that members of my family had a form of [muscular dystrophy](#) called dysferlinopathy. I watched as my mother gradually lost the ability to climb stairs and had to use a cane, then a walker, and finally a wheelchair to get around. Her leg muscles were less and less able to repair themselves and became weaker with time.

My parents explained to me that all these changes were due to the error of a single letter among the billions of letters in a long DNA sequence. This error prevents the production of the protein [responsible for repairing arm and leg muscles](#).

Today, I am a doctoral research student in molecular medicine. I study the treatment of hereditary diseases in order to be able to help families like my own. In this article, I will demystify hereditary diseases and show what research is being carried out to treat them.

A piece of cake? Not quite

Let's start by imagining DNA as a recipe book. Each gene represents a different recipe. The page with the chocolate cake recipe has a nice picture, but there is some information missing. The recipe says to preheat the oven and measure the flour, but the rest of the page is torn. So it is impossible to make the cake. We go ahead and serve our meal made from all the other recipes, but there is no chocolate cake even though this is a particularly important part of the meal.

The same is true for hereditary diseases. In this case, the body can make all the proteins it needs except one. In dysferlinopathy, which affects my family, the missing recipe is the protein that repairs the muscles of the arms and legs. Each hereditary disease has its own damaged page in its recipe book.

To be precise, an error in the DNA is called a mutation. There are different types of mutations. Some are caused by adding letters, like adding an ingredient to the recipe. This addition could lead to a delicious chocolate cake with strawberries, or to a cake that is no longer edible because we added motor oil to it.

Other mutations are caused by the removal (or elimination) of one or more letters (or ingredients), or by substitutions that replace one letter with another. All of these modifications can lead to favorable or non-impactful changes, such as the appearance of the first blue eyes in evolution, or the ability to breathe outside of water. But these modifications can also bring about unfavorable results, such as a hereditary disease or cancer.

Repairing DNA

From a young age, I understood that my mother was sick due to the error of a gene, but that I would not develop the disease because my father did not have the same error. This is called a recessive disease, since there must be an error in the gene of each of the two parents in order for the disease to manifest. Other hereditary diseases are dominant, meaning that a mutation in the DNA passed down from just one parent is enough to impair the production of a protein.

As part of my research, I look at the DNA sequence of each dysferlinopathy patient to see where the error is.

To try to correct it, I use [Prime editing](#), a technique which makes it possible to cut the DNA near the mutation and rewrite the sequence correctly. Prime editing is a

version of [CRISPR-Cas9](#), a technique that allows DNA to be cut at a particular location.

Prime editing uses a protein called Cas9, which occurs naturally in bacteria. This protein allows bacteria to destroy the DNA sequences of viruses that could infect them. The mission of the Cas9 protein is to recognize a sequence and cut it.

When we use Cas9 in our human cells, we attach it to another protein, which rewrites the DNA sequence based on a template. In other words, we give the cell an error-free sequence so that it can go ahead and manufacture the protein on its own. It's a bit like recovering the original page of the recipe book so you can finally serve the chocolate cake.

A step in the right direction

So why aren't we hearing about Prime editing, when it could be used to treat a variety of diseases? Because the technology is not yet fully developed. At the moment we are able to repair DNA directly in cells in the laboratory, but we lack the means to deliver the two large proteins (Cas9 and the one that rewrites) to the cells to be treated (for example, to the center of the affected muscles).

In other words, we have found the chocolate cake recipe, but it's written on a page that is too large to fit in an email or put in an envelope. Many laboratories, including mine, are looking for an efficient and safe vehicle that will be able to deliver these proteins.

A new era in genetic engineering: Researchers present single tool with multiple gene editing functions

Sherry Gao, Tyler Daniel (pictured) and their co-authors developed a new tool that can simultaneously and independently edit multiple genes and regulate their expression. Credit: Bella Ciervo

Influential inventions often combine existing tools in new ways. The iPhone, for instance, amalgamated the telephone, web browser and camera, among many other devices.

The same is now possible in gene editing. Rather than employ separate tools for editing genes and regulating their expression, these distinct goals can now be combined into a single tool that can simultaneously and independently address different genetic diseases in the same cell.

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Forever Chemicals in the Brain? New Study Exposes Silent Invasion

BY UNIVERSITY AT BUFFALO JANUARY 12, 2025 [2 COMMENTS](#) 6 MINS READ

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PFAS, known as “forever chemicals,” persist in the brain and alter gene expression, potentially causing neurotoxicity. A University at Buffalo study identified 11 genes consistently affected by PFAS, offering insight into their impact and guiding safer alternatives.

University at Buffalo researchers reveal molecular insights into the neurotoxic effects of PFAS.

Per- and polyfluorinated alkyl substances (PFAS), often referred to as “forever chemicals,” are known for their persistence in water, soil, and even the human brain.

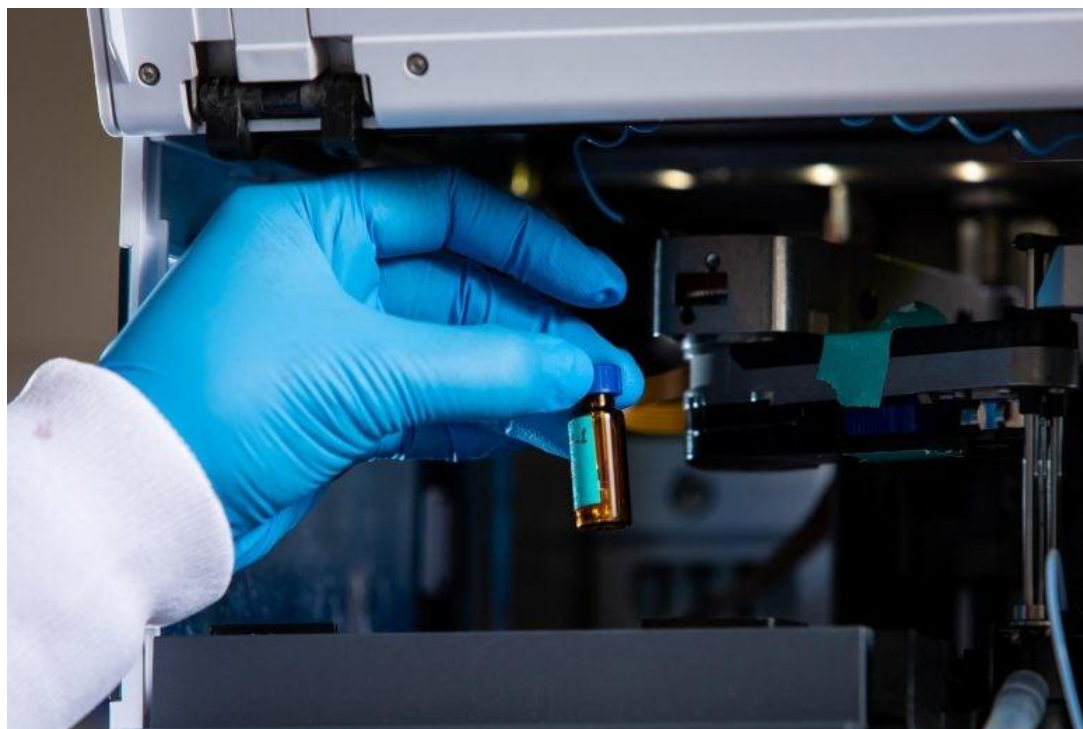
Their ability to cross the blood-brain barrier and accumulate in brain tissue raises significant concerns, yet the mechanisms underlying their neurotoxic effects remain poorly understood.

A recent study conducted by researchers at the [University at Buffalo](#) has pinpointed 11 genes that may play a crucial role in unraveling how the brain responds to these widely used, environmentally persistent chemicals.

These genes, some involved in processes vital for neuronal health, were found to be consistently affected by PFAS exposure, either expressing more or less, regardless of the type of PFAS compounds tested. For example, all compounds caused a gene key for neuronal cell survival to express less, and another gene linked to neuronal cell death to express more.

“Our findings indicate these genes may be markers to detect and monitor PFAS-induced neurotoxicity in the future,” says lead co-corresponding author G. Ekin Atilla-Gokcumen, PhD, Dr. Marjorie E. Winkler Distinguished Professor in the Department of Chemistry, within the UB College of Arts and Sciences.

Still, the study, published in *ACS Chemical Neuroscience*, found hundreds more genes whose expression changed in different directions based on the compound tested. Plus, there was no correlation between the level at which PFAS accumulates in a cell and the extent to which it causes differential gene expression.



A study led by the labs of University at Buffalo chemistry professors G. Ekin Atilla-Gokcumen and Diana Aga has uncovered some molecular clues about the neurotoxic effects of per- and

polyfluorinated alkyl substances, better known as forever chemicals. Credit: Meredith Forrest Kulwicki/University at Buffalo

Taken together, this suggests that distinct molecular structures within each type of PFAS drives changes in gene expression.

“PFAS, despite sharing certain chemical characteristics, come in different shapes and sizes, leading to variability in their biological effects. Thus, knowledge on how our own biology reacts to the different types of PFAS is of major biomedical relevance,” says the study’s other co-corresponding author, Diana Aga, PhD, SUNY Distinguished Professor and Henry M. Woodburn Chair in the Department of Chemistry, and director of the UB RENEW Institute.

“Depending on their chain length or headgroup, PFAS can have very different effects on cells,” Atilla-Gokcumen adds. “We should not be viewing them as one large class of compounds, but really as compounds that we need to investigate individually.”

Other authors include Omer Gokcumen, PhD, professor in the Department of Biological Sciences. The study was supported by the U.S. Environmental Protection Agency (EPA).

Ups and downs of gene expression

PFAS aren’t immediately toxic. We’re exposed to them practically every day, including through drinking water and food packaging, and don’t notice.

“Therefore, researchers need to find points of assessment further upstream in the cellular process than just whether a cell lives or dies,” Atilla-Gokcumen says.

The team decided to focus on how PFAS affects the gene expression of neuronal-like cells, as well as how PFAS affects lipids, which are molecules that help make up the cell membrane, among other important functions. Exposure to different PFAS for 24 hours resulted in modest but distinct changes in lipids, and over 700 genes to express differently.

Of the six types of PFAS tested, perfluorooctanoic acid (PFOA) — once commonly used in nonstick pans and recently deemed hazardous by the EPA — was by far the most impactful. Despite its small uptake, PFOA altered the expression of almost 600 genes — no other compound altered more than 147. Specifically, PFOA decreased the expression of genes involved in synaptic growth and neural function.

Altogether, the six compounds caused changes in biological pathways involved in hypoxia signaling, oxidative stress, protein synthesis and amino acid metabolism, all of which are crucial for neuronal function and development.

Eleven of the genes were found to express the same way, either more or less, to all six compounds. One of the genes that was consistently downregulated was mesencephalic astrocyte derived neurotrophic factor, which is important for the survival of neuronal cells and has been shown to reverse symptoms of neurodegenerative diseases in rats. One of the genes consistently upregulated was thioredoxin interacting protein, which has been linked to neuronal cell death.

“Each of these 11 genes exhibited consistent regulation across all PFAS that we tested. This uniform response suggests that they may serve as promising markers for assessing PFAS exposure, but further research is needed to know how these genes respond to other types of PFAS,” Atilla-Gokcumen says.

Identifying the least-worst options

As harmful as PFAS can be, the reality is that good substitutes have yet to be found.

The compounds can perhaps be replaced in applications like food packaging, but their effectiveness in firefighting and semiconductor manufacturing, for example, may need to continue long term.

That’s why studies like this are crucial, Atilla-Gokcumen says. The varied reaction most genes had to different compounds, as well as the lack of correlation between PFAS uptake into cells and the extent of gene change expression they cause, underscores just how unique each of these compounds are.

“If we understand why some PFAS are more harmful than others, we can prioritize phasing out the worst offenders while seeking safer substitutes. For example, alternatives like short-chain PFAS are being explored, as they tend to persist less in the environment and accumulate less in biological systems. However, their reduced persistence may come at the cost of effectiveness in certain applications, and there are concerns about potential unknown health effects that require further investigation. Further research is needed to ensure these substitutes are genuinely safer and effective for specific applications,” Atilla-Gokcumen explains. “This research is a major step towards achieving this goal.”

Reference: “Investigating the Mechanism of Neurotoxic Effects of PFAS in Differentiated Neuronal Cells through Transcriptomics and Lipidomics Analysis” by Logan Running, Judith R. Cristobal, Charikleia Karageorgiou, Michelle Camdzic, John Michael N. Aguilar, Omer Gokcumen, Diana S. Aga and G. Ekin Atilla-Gokcumen, 27 November 2024, *ACS Chemical Neuroscience*.

DOI: [10.1021/acscchemneuro.4c00652](https://doi.org/10.1021/acscchemneuro.4c00652)

The study was funded by the Environmental Protection Agency.

Tracking the metabolic origins of cancer from a mosaic of cells

This image shows a mosaic of wild-type and mutated cells (white nuclei) in the skin stem cell layer with different redox ratios that evolve over time—captured by multi-photon imaging. Credit: Yale University

Yale researchers are sifting through a mosaic of cells in a living animal—both normal cells and mutated cells—to better understand how cancer grabs a foothold. But they're starting by studying tolerance.

Most biological organisms, including humans, accumulate cancer-causing mutations in their tissues. Many of these mutated cells, however, are tolerated by the body and therefore never develop into full-blown disease.

But why? What distinguishes the tolerated cells, or the body's response to them, from cells that advance into cancers that grow?

Using mouse models, a team led by the Yale labs of Valentina Greco and Rachel Perry looked at two types of mutations in stem cells in the skin. They tracked the "competition" between normal stem cells and each of the mutated cells over time.

What the researchers discovered is that for tolerated mutations, the body's first reaction is an immediate "redox" response, in which a cell experiences a rapid drop in its redox ratio—a chemical reaction that indicates more oxidation in the cells. It acts as a readout of changes in the way cells metabolize (or break down) glucose.

"We saw that metabolism responds very quickly to cancer mutations in the skin stem cell layer," said Anupama Hemalatha, a former associate research scientist in Greco's lab in the Yale School of Medicine's Department of Genetics and first author of a [new study](#) published in *Nature Cell Biology*. Hemalatha recently accepted a faculty position at the Friedrich Miescher Institute for Biomedical Research in Switzerland.

"Using our imaging technique, called multiphoton imaging, we capture these early changes in the mutated cell's metabolism in the skin of a live mouse and track it through time," Hemalatha added.

But the lowered redox itself was a big surprise, the researchers said.

There are two key pathways of glucose metabolism: glycolysis and oxidation. Glycolysis can be considered akin to chopping down a tree and cutting it into several large pieces, whereas oxidation equates to burning the tree in a bonfire, generating energy.

Typically, while cancer cells are rabid users of glucose via the glycolytic pathway, they use less oxidation than healthy cells, because they prefer to divert glycolytic products toward building new cells. This is a phenomenon known as the Warburg effect.

"What we discovered was almost the opposite of the Warburg effect," said Perry, who is an associate professor of endocrinology and of cellular and molecular physiology. "The mutation that persisted in the skin increased the metabolism of glucose through both the glycolytic and oxidative pathways, whereas the mutation that was eliminated increased glucose oxidation despite reduced glycolysis."

The researchers then continued tracking the progress of the two "tolerated" mutations, one that is typically removed from skin over time and another that remains in the skin but does not lead to disease.

The mutation that is normally eliminated from skin maintained its lower redox ratio, compared with neighboring healthy cells, they found. The mutation that remained in the skin saw its redox ratio increase, "flattening out" in comparison with neighboring, healthy cells, said Greco, the Carolyn Walch Slayman Professor of Genetics and of cell biology and dermatology and a Howard Hughes Medical Institute Investigator.

As a final step in their investigation, the researchers treated the animals with mutated cells with the drug Metformin to inhibit the early redox and metabolic changes. The treatment caused a reversal of each mutation's behavior in the tissue. Mutated cells that had been expanding halted their expansion; mutated cells that were being eliminated from the skin were no longer able to be eliminated efficiently.

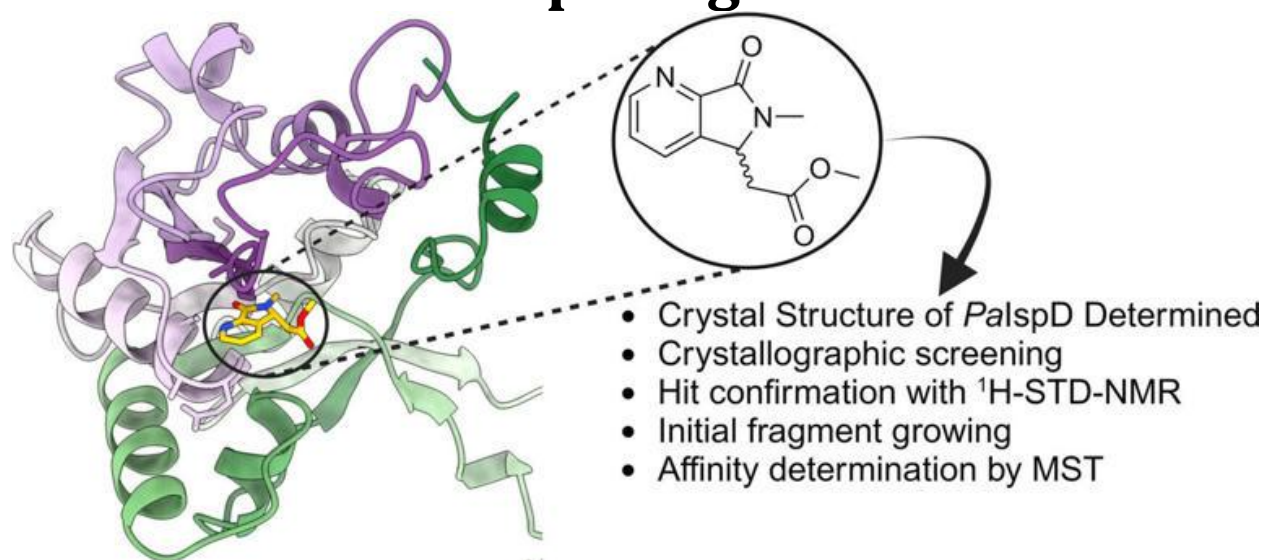
"The implication is that the outcome of cell competition is dependent upon the early metabolic responses initiated by the cancer-causing mutations in the skin stem cells," Hemalatha said. "If these metabolic changes didn't happen, then many of the downstream changes would not happen."

The researchers plan to expand their investigation into instances where cell mutations are not tolerated by neighboring cells to learn whether a similar redox response persists.

More information: Anupama Hemalatha et al, Metabolic rewiring in skin epidermis drives tolerance to oncogenic mutations, *Nature Cell Biology* (2025). DOI: [10.1038/s41556-024-01574-w](https://doi.org/10.1038/s41556-024-01574-w)

Provided by Yale University

Drug candidates target metabolic pathway in bacteria while sparing human cells



Credit: Angewandte Chemie International Edition (2024). DOI: [10.1002/anie.202414615](https://doi.org/10.1002/anie.202414615)

Antibiotics are a double-edged sword—they should be as toxic as possible to pathogenic bacteria while being harmless to the cells of the human body. An international research team led by the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) has now developed drug candidates that achieve precisely that. HIPS is a site of the Helmholtz Center for Infection Research (HZI) in collaboration with Saarland University.

The new molecules target a metabolic pathway that only occurs in bacterial cells, thus sparing human cells. The team [published](#) its results in the journal *Angewandte Chemie International Edition*.

Bacterial cells differ fundamentally in their structure from animal and human cells. For example, bacteria have a rigid cell wall, whereas human cells are surrounded only by a simple membrane. If a pharmaceutical agent targets cell wall construction, only bacterial cells are affected. This principle is an important basis for the development of antibiotics, since these should only act on the disease-causing bacteria, but not humans themselves.

In their search for new active ingredients, a research team led by HIPS department head Prof. Anna Hirsch has now taken a closer look at a less obvious difference between bacteria and humans that has not yet been pharmaceutically exploited: the so-called methylerythritol phosphate pathway, or MEP pathway for short.

The MEP pathway is an essential part of the energy metabolism of several bacteria, including the hospital germ *Pseudomonas aeruginosa*. If the MEP pathway in bacteria is blocked, for example by a drug, the bacteria can no longer produce a number of vital natural products and subsequently die. Human cells do not have the MEP pathway and would therefore not be affected by a respective drug.

In the search for such an active substance, Hirsch's team together with the group of Franck Borel (University of Grenoble) has analyzed the individual steps of the MEP in great detail. Their focus was on the enzyme IspD, which is responsible for the third step in the MEP Pathway. The researchers were able to solve the crystal structure of IspD from *P. aeruginosa* for the first time, thus gaining deep insights into its structural composition.

With the help of the information obtained, the team was able to investigate how a specific chemical fragment binds to the enzyme. This so-called complex structure has enabled the design of optimized derivatives that make even better use of the binding pocket and thus bind more strongly to the enzyme.

"The fragments we synthesized bind excellently to their target protein IspD, and their other pharmaceutical properties also offer a promising basis for the

development of new active ingredients," says Eleonora Diamanti, project manager of the consortium and now assistant professor at University of Bologna.

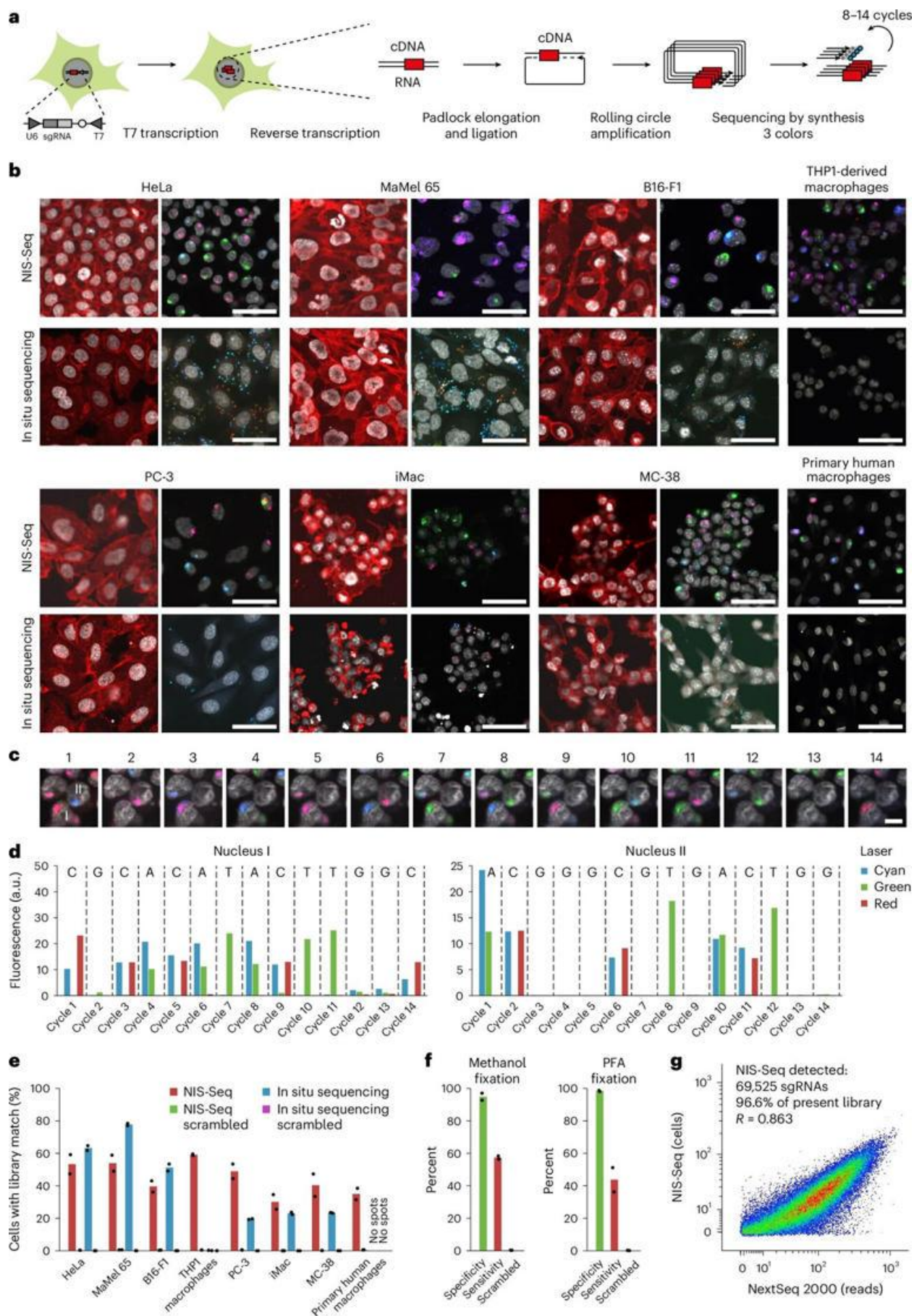
Hirsch, who also holds a professorship in medicinal chemistry at Saarland University, says, "What makes the newly developed molecules so special is that they target IspD, a protein that is not addressed by any drug currently on the market. This is the only way to ensure that a potential new antibiotic will also be effective against pathogens that have already become resistant to most conventional drugs."

Hirsch and her team are currently working on the further development of the new molecules. To this end, they are planning to collaborate closely with the planned excellence cluster nextAID³, in which unexplored targets such as IspD will also play an important role. The next steps include efficacy studies in bacteria and the optimization of efficacy and other pharmaceutical parameters.

More information: Daan Willocx et al, Fragment Discovery by X-Ray Crystallographic Screening Targeting the CTP Binding Site of *Pseudomonas Aeruginosa* IspD, *Angewandte Chemie International Edition* (2024). DOI: [10.1002/anie.202414615](https://doi.org/10.1002/anie.202414615)

Provided by Helmholtz Association of German Research Centres

CRISPR screening method uses colored nuclei to reveal key genes



NIS-Seq enables optical barcode identification in nucleated cells. Credit: Nature Biotechnology (2024). DOI: 10.1038/s41587-024-02516-5

The identification of genes involved in diseases is one of the major challenges of biomedical research. Researchers at the University of Bonn and the University Hospital Bonn (UKB) have developed a method that makes their identification much easier and faster: they light up genome sequences in the cell nucleus.

In contrast to complex screenings using established methods, the NIS-Seq method can be used to investigate the genetic determinants of almost any biological process in human cells. The study has now been [published](#) in *Nature Biotechnology*.

Humans have about 20,000 genes. They determine how our body functions, how we develop and how cells multiply. "Certain genes are responsible for vital immune responses, for example, but are also involved in life-threatening inflammatory processes," says Prof. Dr. Jonathan Schmid-Burgk, research group leader at the Institute of Clinical Chemistry and Clinical Pharmacology at the UKB and member of the Immunosensation2 Cluster of Excellence at the University of Bonn. "Our research interest is to identify these genes in order to better treat diseases."

Conventional methods: High effort and limited spectrum

CRISPR screening methods can be used to systematically examine genes for their function in cells. "CRISPR is used to switch off a random gene in each cell," explains Schmid-Burgk. "We then enrich the cells in which a specific biological process is altered, and identify the genes switched off."

This procedure is quite complex: for each process studied, a method to enrich relevant cells has to be established, e.g., using cell sorting machines. Another weak point: CRISPR screening does not work well in every cell type—human immune cells in particular often do not survive the multi-stage process.

New method: Simple detection of colored cell nuclei with a microscope

The researchers from Bonn have now developed an optical CRISPR screening method that allows identification of important genes much more easily and quickly: Nuclear In-Situ Sequencing, or NIS-Seq for short. "CRISPR is also used here," explains Caroline Fandrey, a doctoral student in Prof. Schmid-Burgk's research group and first author of the study. "However, we can observe almost any biological process in cells while they are still alive in order to identify the key genes involved."

The researchers use a trick to do this: in addition to the CRISPR sequence, they introduce a so-called phage promoter into the cellular genome, which amplifies the CRISPR sequences and makes them visible by using different colors. Colorful confetti can be detected in each nucleus using conventional fluorescence microscopes to reveal which gene has been switched off.

Less than 100 cells uncover a relevant gene

"With NIS-Seq, we currently need around a week to identify a relevant gene," says Marius Jentzsch, also a doctoral student of Prof. Schmid-Burgk and first author of the paper. "For a conventional CRISPR screen, it often takes months to precisely separate the cells according to their function."

Another advantage of the new method is that it works in almost all cells, even in particularly small or inactive cells—provided they have a cell nucleus. In the study, the researchers successfully analyzed eight cell types from two species. Schmid-Burgk says, "We are convinced that our method will become a standard tool for the identification of genetic key players in cellular processes."

More information: Caroline I. Fandrey et al, NIS-Seq enables cell-type-agnostic optical perturbation screening, *Nature Biotechnology* (2024). DOI: [10.1038/s41587-024-02516-5](https://doi.org/10.1038/s41587-024-02516-5)

Provided by University of Bonn

1st-of-its-kind database reveals how DNA mutations 'destabilize' proteins, triggering genetic disease

Scientists have created a mega-database revealing how half a million different DNA mutations generate errors in proteins in humans. The researchers hope that the database will be used to develop new, personalized drugs that directly reverse the mutations' effects.

The human genome carries instructions for [at least 20,000 proteins](#), which are essential [for nearly all physiological processes](#). Each building block of a protein — called an amino acid — is key to its function, and thus, swapping around the amino acids can essentially break a protein. "Missense" mutations — changes in a [DNA](#) sequence that swap one amino acid for another — in [nearly 5,000 human proteins](#) are known to cause genetic diseases, such as [Huntington's disease](#) and [cystic fibrosis](#).

However, in many cases, it's not entirely clear how these mutations affect the structure and function of proteins and thus cause disease. Without this understanding, it is tricky to develop targeted treatments for genetic disorders without altering the genome itself, according to the authors of a new study published Jan. 8 in the journal [Nature](#).

"Depending on what is happening to the protein, if you were to design a drug to try to fix the disease, then the approach would be completely different depending on the individual mutation that you are considering," [Antoni Beltran](#), lead study author and a postdoctoral researcher at the Centre for Genomic Regulation in Spain, told Live Science.

Related: [2024 Nobel Prize in chemistry awarded to scientists who revealed a 'completely new world of protein structures'](#)

To tackle this issue, Beltran and colleagues created an enormous database that catalogs the effect of more than 500,000 missense mutations on the stability of 522 protein "domains," meaning the regions of proteins that are key to their function. They call the database a human "domainome," and they built it by

systematically triggering mutations in proteins in the lab. They then transferred the mutants into yeast cells and monitored the effects.

In the new study, the team especially homed in on 621 missense mutations from the database that were already known to cause diseases in humans. They found that 60% of these mutations made affected proteins less stable. Unstable proteins are [more likely to misfold or denature](#); like origami, proteins must be folded a particular way to reach their intended form. Misfolded proteins can accumulate within cells, potentially causing damage, or simply [be degraded](#) by the body, leaving the cells unable to function.



The team who created the database hope that it will one day be used to develop personalized treatments for genetic diseases (Image credit: nicolas_ via Getty Images)

For instance, the inherited form of cataracts — an eye disease that clouds the lens of the [eye](#) — is triggered by mutations in genes for [beta-crystallin](#) proteins, which normally maintain the lens's transparency. In the new study, Beltran and colleagues discovered that 72% of these mutations destabilize the crystallin proteins, increasing the odds that they clump together and form cloudy areas in the lens.

Rather than causing instability, some missense mutations led to different changes in proteins. For example, some of the mutations behind [Rett syndrome](#), a rare

neurodevelopmental disorder, prevent a specific protein from binding to DNA. This process would normally enable the protein to turn genes on and off in the brain, but in the syndrome, this goes awry.

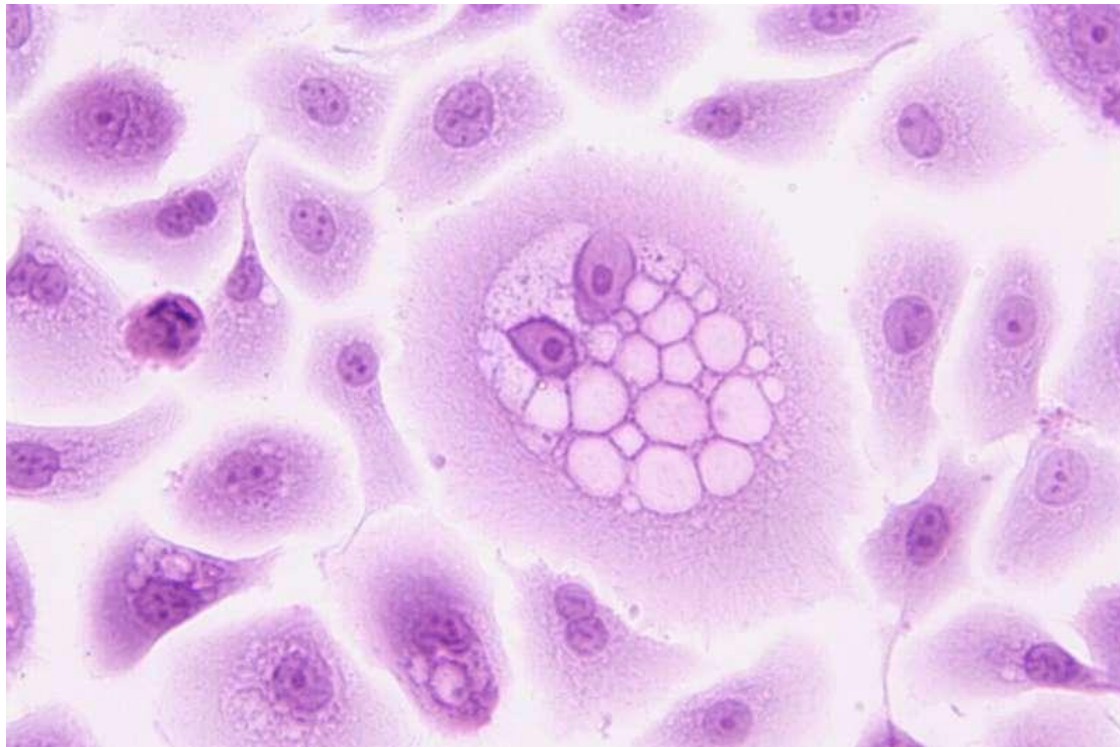
Although the first and biggest database of its kind, so far, it covers only 2.5% of known human proteins, so more work is needed to expand it, Beltran acknowledged. More research will also be needed to determine if the effects seen in isolated domains also show up in full-size proteins.

The team's ultimate goal is to build a database that's useful for predicting the effect of any mutation on protein stability, Beltran said. Such a tool could theoretically enable scientists to develop better drugs for genetic diseases that target the faults in proteins that drive the conditions.

JANUARY 8, 2025

Computational biologists develop AI that predicts inner workings of cells

by [Columbia University Irving Medical Center](#)



Credit:

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Using a new artificial intelligence method, researchers at Columbia University Vagelos College of Physicians and Surgeons can accurately predict the activity of genes within any human cell, essentially revealing the cell's inner mechanisms. The system, [described](#) in *Nature*, could transform the way scientists work to understand everything from cancer to genetic diseases.

"Predictive generalizable computational models allow to uncover biological processes in a fast and accurate way. These methods can effectively conduct large-scale computational experiments, boosting and guiding traditional experimental approaches," says Raul Rabadan, professor of systems biology and senior author of the new paper.

Traditional research methods in biology are good at revealing how cells perform their jobs or react to disturbances. But they cannot make predictions about how cells work or how cells will react to change, like a cancer-causing mutation.

"Having the ability to accurately predict a cell's activities would transform our understanding of fundamental [biological processes](#)," Rabadan says. "It would turn biology from a science that describes seemingly random processes into one that can predict the underlying systems that govern cell behavior."

In recent years, the accumulation of massive amounts of data from cells and more powerful AI models are starting to transform biology into a more predictive science. The 2024 Nobel Prize in Chemistry was awarded to researchers for their groundbreaking work in using AI to predict protein structures. But the use of AI methods to predict the activities of genes and proteins inside cells has proven more difficult.

New AI method predicts gene expression in any cell

In the new study, Rabadan and his colleagues tried to use AI to predict which genes are active within specific cells. Such information about gene expression can tell researchers the identity of the cell and how the cell performs its functions.

"Previous models have been trained on data in particular cell types, usually [cancer cell lines](#) or something else that has little resemblance to normal cells," Rabadan says. Xi Fu, a graduate student in Rabadan's lab, decided to take a different approach, training a machine learning model on gene expression data from millions of cells obtained from normal human tissues. The inputs consisted of genome sequences and data showing which parts of the genome are accessible and expressed.

The overall approach resembles the way ChatGPT and other popular "foundation" models work. These systems use a set of training data to identify underlying rules, the grammar of language, and then apply those inferred rules to new situations.

"Here it's exactly the same thing: we learn the grammar in many different cellular states, and then we go into a particular condition—it can be a diseased [cell type] or it can be a normal cell type—and we can try to see how well we predict patterns from this information," says Rabadan.

Fu and Rabadan soon enlisted a team of collaborators, including co-first authors Alejandro Buendia, now a Stanford Ph.D. student formerly in the Rabadan lab, and Shentong Mo of Carnegie Mellon, to train and test the new model.

After training on data from more than 1.3 million human cells, the system became accurate enough to predict [gene expression](#) in cell types it had never seen, yielding results that agreed closely with experimental data.

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New AI methods reveal drivers of a pediatric cancer

Next, the investigators showed the power of their AI system when they asked it to uncover still-hidden biology of diseased cells, in this case, an inherited form of pediatric leukemia.

"These kids inherit a gene that is mutated, and it was unclear exactly what it is these mutations are doing," says Rabadan, who also co-directs the cancer genomics and epigenomics research program at Columbia's Herbert Irving Comprehensive Cancer Center.

With AI, the researchers predicted that the mutations disrupt the interaction between two different transcription factors that determine the fate of leukemic cells. Laboratory experiments confirmed AI's prediction. Understanding the effect of these mutations uncovers specific mechanisms that drive this disease.

AI could reveal 'dark matter' in genome

The new computational methods should also allow researchers to start exploring the role of genome's "dark matter"—a term borrowed from cosmology that refers to the vast majority of the genome, which does not encode known genes—in cancer and other diseases.

"The vast majority of mutations found in cancer patients are in so-called dark regions of the genome. These mutations do not affect the function of a protein and have remained mostly unexplored," says Rabadan. "The idea is that using these models, we can look at mutations and illuminate that part of the genome."

Rabadan is working with researchers at Columbia and other universities, exploring different cancers, from brain to blood cancers, learning the grammar of regulation in normal cells, and how cells change in the process of cancer development.

The work also opens new avenues for understanding many diseases beyond cancer and potentially identifying targets for new treatments. By presenting novel mutations to the computer model, researchers can now gain deep insights and predictions about exactly how those mutations affect a cell.

Coming on the heels of other recent advances in artificial intelligence for biology, Rabadan sees the work as part of a major trend: "It's really a new era in biology that is extremely exciting; transforming biology into a predictive science."

More information: Raul Rabadan et al, A foundation model of transcription across human cell types, *Nature* (2025). DOI: [10.1038/s41586-024-08391-z](https://doi.org/10.1038/s41586-024-08391-z). www.nature.com/articles/s41586-024-08391-z

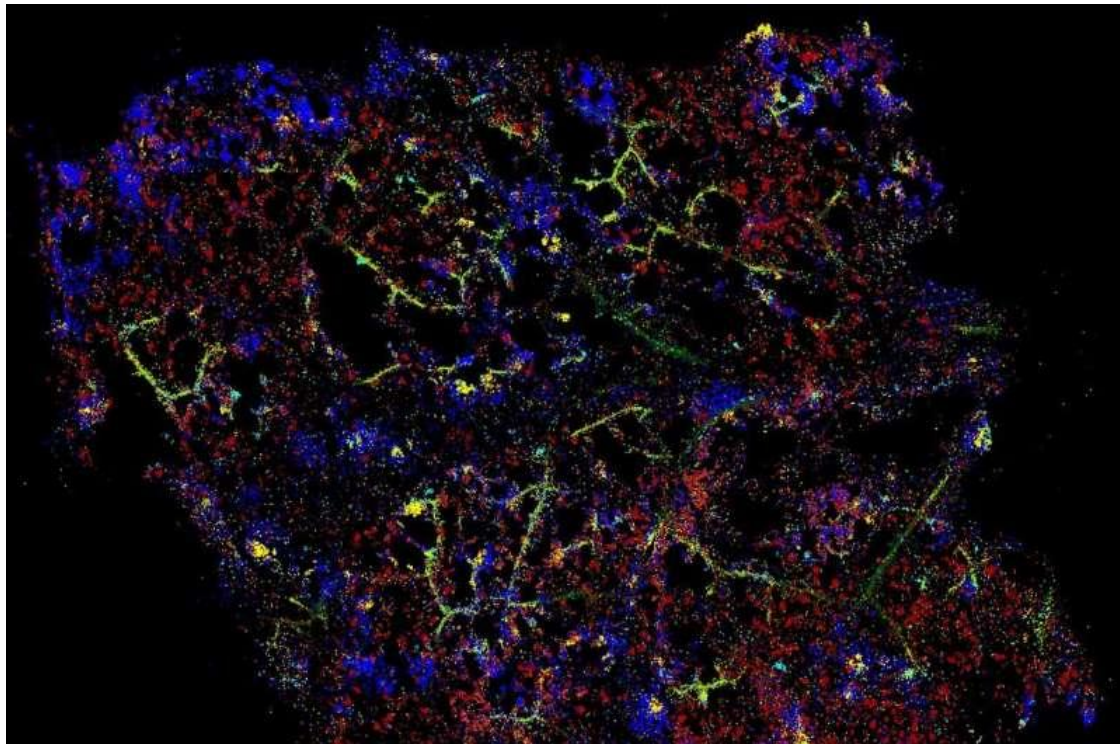
Journal information: *Nature*

Provided by [Columbia University Irving Medical Center](#)

JANUARY 8, 2025

Plant cells gain immune capabilities when it's time to fight disease, scientists discover

by [Salk Institute](#)



Gene expression visualized in a section of a pathogen-infected plant leaf. Credit: Salk Institute
Human bodies defend themselves using a diverse population of immune cells that circulate from one organ to another, responding to everything from cuts to colds to cancer. But plants don't have this luxury.

Because plant cells are immobile, each individual cell is forced to manage its own immunity in addition to its many other responsibilities, like turning sunlight into energy or using that energy to grow. How these multitasking cells accomplish it all—detecting threats, communicating those threats, and responding effectively—has remained unclear.

Research from Salk Institute scientists reveals how plant cells switch roles to protect themselves against pathogens. When a threat is encountered, the cells enter a specialized immune state and temporarily become PRimary IMmunE Responder (PRIMER) cells—a new cell population that acts as a hub to initiate the [immune response](#).

The researchers also discovered that PRIMER cells are surrounded by another population of cells they call bystander cells, which seem to be important for transmitting the immune response throughout the plant.

The findings, [published](#) in *Nature* on January 8, 2025, bring researchers closer to understanding the plant immune system—an increasingly important task amid the growing threats of antimicrobial resistance and [climate change](#), which both escalate the spread of infectious disease.

"In nature, [plants](#) are constantly being attacked and require a well-functioning immune system," says Professor Joseph Ecker, senior author of the study, Salk International Council Chair in Genetics, and Howard Hughes Medical Institute investigator.

"But plants don't have mobile, specialized [immune cells](#) like we do—they must come up with an entirely different system where every cell can respond to immune attacks without sacrificing their other duties. Until now, we weren't quite sure how plants were accomplishing this."

Plants encounter a wide range of pathogens, like bacteria that sneak in through leaf surface pores or fungi that directly invade plant "skin" cells. Since plant cells are stationary, when they encounter any of these pathogens, they become singularly responsible for responding and alerting nearby cells.

Another interesting side effect of immobile cells is the fact that different pathogens may enter a plant at different locations and times, leading to varying immune response stages occurring simultaneously across the plant.

With factors like timing, location, response state, and more all at play, an infected plant is a complicated organism to understand. To tackle this, the Salk team turned to two sophisticated cell profiling techniques called time-resolved single-cell multiomics and spatial transcriptomics. By pairing the two, the team was able to capture the plant immune response in each cell with unprecedented spatiotemporal resolution.

"Discovering these rare PRIMER cells and their surrounding bystander cells is a huge insight into how plant cells communicate to survive the many external threats they face day-to-day," says first author Tatsuya Nobori, a former postdoctoral researcher in Ecker's lab and current group leader at The Sainsbury Laboratory in the United Kingdom.

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The team introduced bacterial pathogens to the leaves of *Arabidopsis thaliana*—a flowering weed in the mustard family commonly used as a model in research. They then analyzed the plant's response to comprehensively identify each cell's state upon infection. In doing so, they discovered a novel immune response state, which they called PRIMER, that emerged in cells at specific immune hotspots.

The PRIMER cells expressed a new transcription factor—a type of protein that regulates [gene expression](#)—called GT-3a, which is likely an important upstream alarm for alerting other cells to an active plant immune response.

Additionally, the cells surrounding these PRIMER cells proved equally important. Dubbed "bystander cells," the cells immediately neighboring PRIMER cells were expressing genes that enable long-distance cell-to-cell communication.

The researchers plan to elucidate this relationship in future research, but for the time being, they suspect the interactions between PRIMER and bystander cells are key to propagating the immune response across the leaf.

This new spatiotemporal, cell-specific insight into the plant immune response is [already available as a reference database](#) for researchers worldwide. As pathogens continue to evolve and spread amid climate-related environmental changes and rising antibiotic resistance, the database offers an important springboard for preserving a future filled with healthy plants and crops.

"There is a lot of interest and demand for detailed cell atlases these days, so we're excited to create a new one that is publicly available for other researchers to use," says Ecker.

"Our atlas could lead to many new discoveries about how individual plant cells respond to environmental stressors, which will be crucial for creating more climate-resilient crops."

Other authors include Joseph Nery of Salk; Alexander Monell of Salk and UC San Diego; Travis Lee of Salk and Howard Hughes Medical Institute; Yuka Sakata, Shoma Shirahama, and Akira Mine of the University of Kyoto in Japan.

More information: Joseph Ecker, A rare PRIMER cell state in plant immunity, *Nature* (2025). DOI: [10.1038/s41586-024-08383-z](https://doi.org/10.1038/s41586-024-08383-z). www.nature.com/articles/s41586-024-08383-z

Journal information: [Nature](#)
Provided by [Salk Institute](#)

What we eat affects our health—and can alter how our genes function

by [Stanford University Medical Center](#)



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Fiber is well known to be an important part of a healthy diet, yet less than 10% of Americans eat the minimum recommended amount. A study from Stanford Medicine might finally convince us to fill our plates with beans, nuts, cruciferous veggies, avocados and other fiber-rich foods.

The research, published in *Nature Metabolism* on Jan. 9 identified the direct epigenetic effects of two common byproducts of fiber digestion and found that some of the alterations in gene expression had anti-cancer actions.

When we eat fiber, the gut microbiome produces short-chain fatty acids. These compounds are more than just an energy source for us: they have long been suspected to indirectly affect gene function. The researchers traced how the two most common short-chain fatty

acids in our gut, propionate and butyrate, altered [gene expression](#) in healthy human cells, in treated and untreated human colon cancer cells, and in mouse intestines.

They found direct epigenetic changes at [specific genes](#) that regulate [cell proliferation](#) and differentiation, along with apoptosis, or pre-programmed cell death processes—all of which are important for disrupting or controlling the unchecked cell growth that underlies cancer.

"We found a direct link between eating fiber and modulation of gene function that has anti-cancer effects, and we think this is likely a global mechanism because the short-chain fatty acids that result from fiber digestion can travel all over the body," said Michael Snyder, Ph.D., Stanford W. Ascherman, MD, FACS Professor in Genetics.

"It is generally the case that people's diet is very fiber poor, and that means their microbiome is not being fed properly and cannot make as many short-chain [fatty acids](#) as it should. This is not doing our health any favors."

Given the [worrying rates](#) of colon cancer in younger adults, the study findings could also spur conversation and research about the possible synergistic effects of diet and [cancer treatment](#).

"By identifying the gene targets of these important molecules, we can understand how fiber exerts its beneficial effects and what goes wrong during cancer," Snyder added.

More information: Short-chain fatty acid metabolites propionate and butyrate are unique epigenetic regulatory elements linking diet, metabolism and gene expression, *Nature Metabolism* (2025). DOI: [10.1038/s42255-024-01191-9](https://doi.org/10.1038/s42255-024-01191-9)

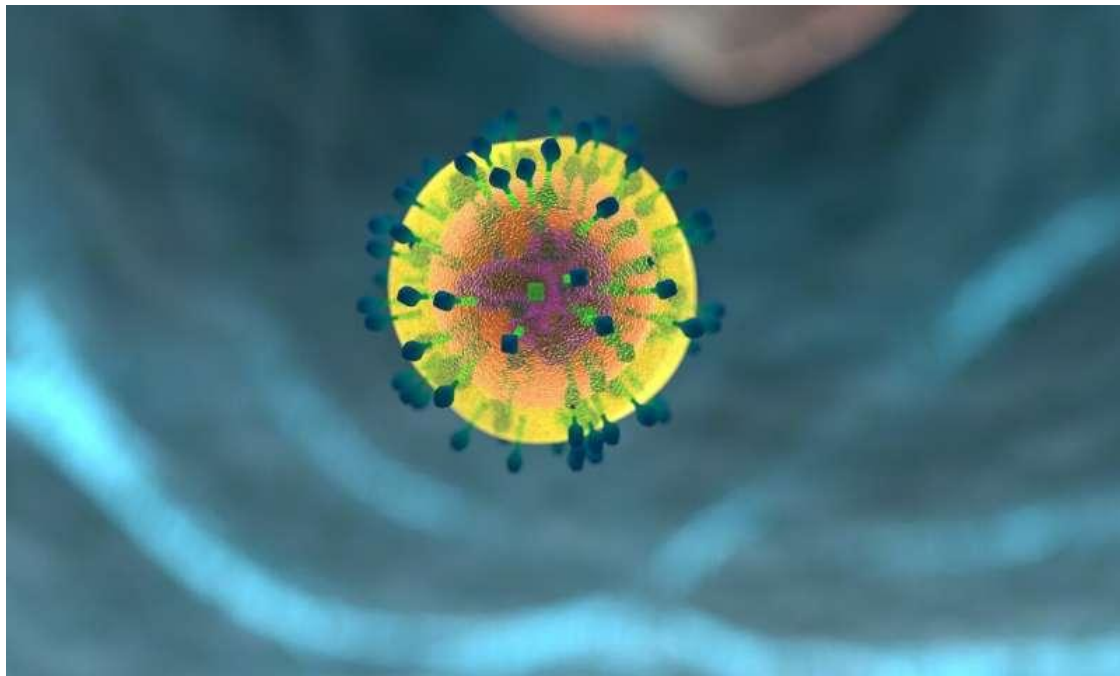
Journal information: [Nature Metabolism](#)

Provided by [Stanford University Medical Center](#)

JANUARY 10, 2025

A battle of rafts: How molecular dynamics in CAR T cells explain their cancer-killing behavior

by [Baylor College of Medicine](#)



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A study [published](#) in *Science Advances* shares new insights into how two of the most common types of chimeric antigen receptor (CAR) T cells kill cancer.

Investigators from Baylor College of Medicine, Texas Children's Cancer Center and the Center for Cell and Gene Therapy at Baylor, Houston Methodist Hospital and Texas Children's Hospital examined how molecular dynamics at the immune synapse—where CAR T cells bind to cancer cells—affect anticancer activity.

In this study, researchers aimed to understand how CAR T cells with different signaling domains work at the molecular and cellular levels to lay the foundation for designing CAR molecules that maximize antitumor activity beyond B cell malignancies.

"We looked at two different types of CAR T cells. The first, CD28.ζ-CART cells, are like sprinters. They kill cancer cells quickly and efficiently, but their activity is short-lived. The second, 4-1BB.ζ-CART cells, are like marathon runners. They kill cancer cells consistently over a long period," said senior author Dr. Nabil Ahmed, professor of pediatrics—hematology and oncology at Baylor and Texas Children's.

"We need to understand what's happening at the molecular level so we can engineer CAR T cells to adapt their killing behavior to target hard-to-treat malignancies, such as [solid tumors](#)," Ahmed is also a member of the Center for Cell and Gene Therapy and the Dan L Duncan Comprehensive Cancer Center.

Led by first author Dr. Ahmed Gad, postdoctoral associate in Ahmed's lab, the research team examined [molecular dynamics](#) at the immune synapse. The team biopsied the CAR T cell immunological synapse by isolating the membrane lipid rafts—cholesterol-rich molecules on the cell surface where most molecular interactions between cells take place.

They found that CD28.ζ-CAR molecules shuttle through the immune synapse quickly, working within minutes to kill cancer cells. This enabled fast CAR T cell recovery and a mastery of "serial killing" of cancer cells. In contrast, researchers found that 4-1BB.ζ-CAR molecules linger in the [lipid rafts](#) and immune synapse. The 4-1BB.ζ-CAR T cells multiply and work together, resulting in sustained "collaborative" killing of tumor cells.

"Observing the distinct pattern of dynamics between single molecules helps us understand the big picture of how these products work," Gad said. "Next, we are studying how to dynamically adapt these CAR T cells at the synapse level to make them more effective."

"Tumors are very sophisticated. We need to adapt our tools to the biology of the disease. This may involve using multiple tools that work in different ways at different stages," Ahmed added.

More information: Ahmed Gad et al, Molecular dynamics at immune synapse lipid rafts influence the cytolytic behavior of CAR T cells, *Science Advances* (2025). DOI: [10.1126/sciadv.adq8114](https://doi.org/10.1126/sciadv.adq8114). www.science.org/doi/10.1126/sciadv.adq8114

Journal information: [Science Advances](#)
Provided by [Baylor College of Medicine](#)

Plant hormones that help roots reach deeper water provide potential strategy for drought-resistant crops

by [University of Nottingham](#)



Watered

(left) vs. water stressed (right) image – showing change in root angle to make the architecture steeper. Credit: University of Nottingham

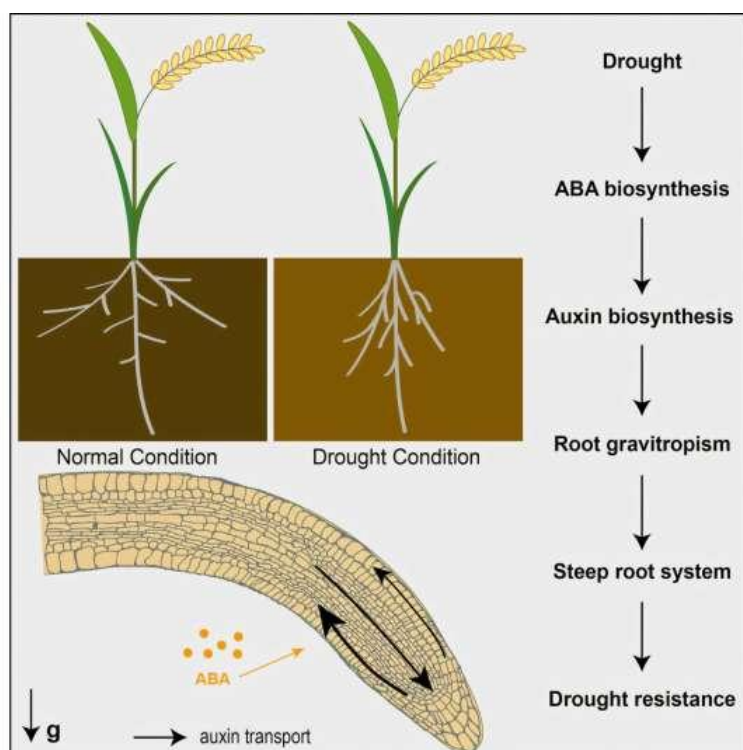
Scientists have discovered how plants adapt their root systems in drought conditions to grow steeper into the soil to access deeper water reserves.

Plant scientists from the University of Nottingham, in collaboration with Shanghai Jiao Tong University, have identified how [abscisic acid](#) (ABA), a plant hormone known for its role in [drought response](#), influences root growth angles in [cereal crops](#) such as rice and maize. The results have been [published](#) in *Current Biology*.

The study highlights how ABA and auxin, another key hormone, work together to shape root growth angle, providing a potential strategy to develop drought-resistant crops with improved root system architecture.

Drought poses a major threat to global food security, and enhancing the ability of crops to withstand water shortages is crucial. Drought, a major abiotic stressor, has caused substantial crop production losses of approximately \$30 billion over the past decade. With a projected population of 10 billion by 2050 and serious freshwater depletion, developing drought-resistant crops is of paramount importance.

Plants rely on their [root systems](#), the primary organs for interacting with soil, to actively seek water. In [drought conditions](#), water often depletes in the topsoil and remains accessible only in the deeper subsoil layers. Abscissic acid (ABA) plays an important role in helping plants adapt to these challenging conditions. This new study gives new insights into how ABA changes root growth angles to enable plants to reach out deeper subsoils in search of water.



Graphical abstract. Credit: *Current Biology* (2025). DOI: 10.1016/j.cub.2024.12.003

The researchers discovered a new mechanism where ABA promotes the production of auxin, which enhances root gravitropism to grow them at steeper angles in response to drought. Experiments showed that plants with [genetic mutations](#) that block ABA production had shallower root angles and weaker root bending response to gravity compared to normal plants. These defects were linked to lower auxin levels in their roots. By adding auxin externally, the researchers restored normal root growth in these mutants, showing that [auxin](#) is key to this process.

The findings were consistent across both rice and maize, suggesting that this mechanism could apply to other cereal crops as well.

Dr. Rahul Bhosal, Assistant Professor from the School of Bioscience is one of the lead authors on the study, said, "Finding ways to tackle food insecurity is vital and the more we

understand the mechanisms that control plant growth, the closer we are to designing systems to help plants to do this and improve crop yields during droughts."

More information: Yali Xiong et al, ABA-auxin cascade regulates crop root angle in response to drought, *Current Biology* (2025). DOI: [10.1016/j.cub.2024.12.003](https://doi.org/10.1016/j.cub.2024.12.003)

Journal information: [Current Biology](#)

Provided by [University of Nottingham](#)

NOVEMBER 14, 2024

Discovery enables effective use of gene therapy for muscular dystrophies and other large-gene diseases

by [University of Rochester Medical Center](#)



Credit:

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Gene therapy can effectively treat various diseases, but for some debilitating conditions like muscular dystrophies there is a big problem: size. The genes that are dysfunctional in muscular dystrophies are often extremely large, and current delivery methods can't courier such substantial genetic loads into the body.

A new technology, dubbed "StitchR," surmounts this obstacle by delivering two halves of a gene separately; once in a cell, both DNA segments generate messenger RNAs (mRNAs)

that join seamlessly together to restore expression of a protein that is missing or inactive in disease.

Published in the journal *Science*, StitchR—short for "stitch RNA"—[restored expression](#) of large therapeutic muscle proteins to normal levels in two different animal models of muscular dystrophy. StitchR enabled expression of the protein Dysferlin, which is lacking in individuals with limb girdle muscular dystrophy type 2B/R2, as well as the protein Dystrophin, which is absent in patients with Duchenne muscular dystrophy.

Duchenne muscular dystrophy is the most common early onset form of muscular dystrophy; many boys become wheelchair bound in their teens and die in their twenties. People with limb girdle muscular dystrophy experience weakness and wasting in the shoulder, hip, and thigh muscles, and often have difficulty standing, moving, and doing everyday tasks.

"Gene therapy is a powerful tool for delivering a healthy gene copy back to a patient's cells to correct [genetic diseases](#), but the vectors used to deliver this information are small, which has so far precluded their use for treating a whole host of diseases caused by mutations in large genes," said Douglas M. Anderson, Ph.D., lead study author and assistant professor of Medicine in the Aab Cardiovascular Research Institute at the University of Rochester School of Medicine and Dentistry (SMD).

"Instead of delivering the full gene in a single vector, which isn't possible, we've developed an efficient dual vector system where two halves of a gene are delivered separately but come together to reconstitute the large mRNA in the affected tissues."

The technology first arose from a serendipitous observation made in the lab several years ago, that when two separate mRNAs were cut by small RNA sequences called ribozymes, they became seamlessly ligated (joined) and translated into full-length protein. The team found that when ribozymes cleave or cut RNA, they leave ends that are recognized by a natural repair pathway.

"Similar to when CRISPR enzymes are used to cut DNA, the CRISPR enzymes are just the scissors, and it's a cell's natural repair enzymes that glue the DNA back together," noted Anderson, who is also a member of the University of Rochester Center for RNA Biology.

"We think something similar is happening here, but for RNA. The ribozymes are acting as the scissors and the cell's natural repair pathways are able to join the two RNAs back together. It's remarkable that two separate mRNAs are able to find themselves and that the process can be so efficient."

The lab optimized efficiency of the process (over 900-fold from their initial experiments) and adapted the technology into a powerful gene delivery mechanism.

When two halves of a large therapeutic gene are encoded into adeno-associated virus (AAV) vectors, which are the most commonly used vectors for [gene therapy](#) because they

are safe and don't cause disease in humans, the ribozymes cut the ends of the mRNAs and they subsequently join, forming a single, seamless mRNA capable of producing protein in a desired tissue.

The research team, including co-first author Sean Lindley, who recently received his Ph.D. from the Anderson lab, found that the stitched mRNAs appear to behave essentially the same way as their natural full-length counterparts, effectively translating genetic information into functional proteins.

Self-cleaving ribozymes, which are essential for StitchR activity, are found naturally throughout the animal kingdom and are comprised of different families, which exhibit different cleavage activities. After testing numerous ribozyme families and sequences, they ultimately identified a formula that led to a high level of protein production and approached the levels achieved by genes expressed from just a single vector.

"Doug is extremely creative and detail oriented, and the fact that he's worked out how two different pieces of mRNA can find one another in a cell and be joined seamlessly to create a functional mRNA is really exciting," said Lynne E. Maquat, Ph.D., director of the UR Center for RNA Biology.

"The concept sounds simple, but this required considerable bench work to optimize the molecules involved, ensure they are stable in cells, and make the process as efficient as possible."

According to Anderson, StitchR can be coupled with many different types of vectors that are used to deliver or express a gene in cells and it appears to work efficiently with any mRNA sequence, opening the door for its use in a wide range of diseases and applications.

"StitchR is really plug and play at this point. The sequence requirements for StitchR are minimal, and we've now tested this with many different genes and sequences," he said.

Another feature of this technology is that only the full-length protein is produced.

"Other dual vector approaches have been in development for decades but have been plagued by lack of efficiency and the production of less than full-length products. Because StitchR occurs at the level of RNA, we can control and ensure that only the full-length protein product gets made. This differentiates StitchR from other dual vector technologies, for example inteins, a protein-ligation technology, which can be efficient but requires the expression of smaller [protein](#) fragments that may have unknown effects in a cell," added Anderson.

"It's been a long but fulfilling process to go from an initial research observation to a therapeutic application, but that's always been a major goal of our lab, and I think the promise of basic research. With StitchR and other tools we are working towards treatments for some of the most debilitating genetic diseases on the planet, many of which have no current treatments or cures," said Anderson.

The lab is now in the process of forming collaborations with other research labs and generating StitchR vectors to treat numerous diseases caused by large genes, of which there are thousands.

More information: Sean R. Lindley et al, Ribozyme-activated mRNA trans-ligation enables large gene delivery to treat muscular dystrophies, *Science* (2024). DOI: [10.1126/science.adp8179](https://doi.org/10.1126/science.adp8179). www.science.org/doi/10.1126/science.adp8179

Journal information: *Science*

Provided by [University of Rochester Medical Center](#)

DECEMBER 5, 2024

Engineered immune cells may be able to tame inflammation

by [University of California, San Francisco](#)

Credit: CC0 Public Domain

When the immune system overreacts and starts attacking the body, the only option may be to shut the entire system down and risk developing infections or cancer. But now, scientists at UC San Francisco may have found a more precise way to dial the immune system down.

The technology uses engineered T cells that act as immune "referees" to soothe overreacting immune responses. They also can mop up inflammatory molecules.

The new approach could be used to stop the body from rejecting transplanted organs and tissues, such as [pancreatic islet cells](#), which are sometimes used to treat type 1 [diabetes](#). That way, recipients would not need to take harsh immunosuppressant drugs.

"This technology can put the immune system back into balance," said Wendell Lim, Ph.D., UCSF professor of cellular and molecular pharmacology and co-senior author of the paper, which appears Dec. 5 in [Science](#). "We see it as a potential platform for tackling all kinds of immune dysfunction."

Lim and his colleagues were inspired by "suppressor" cells, which are the immune system's natural brakes. They wanted to take advantage of these suppressor cells' power to temper immune responses, such as inflammation.

Unfortunately, suppressor cells can't always stop a dangerous immune response. In type 1 diabetes, for example, the immune system destroys pancreatic islet cells, while these suppressor cells just stand by.

The team adapted the [suppressor cells](#)' anti-inflammatory abilities to work in CD4 immune cells. These are the same cells that are used to make cancer-killing CAR T cells. They also gave these cells a molecular sensor to guide them to their target tissue in the body.

Proof of principle in type 1 diabetes

The scientists tailored a batch of immune referees to search for human pancreatic islet cells and then produce TGF-Beta and CD25, molecules that can muzzle killer T cells.

They introduced the engineered referee cells into mice that had received a transplant of human islet cells, modeling the treatment for type 1 diabetes.

The referee cells found the vulnerable islet cells and stopped the killer T cells from attacking, and the islet cells survived.

"It would be life changing for people with type 1 diabetes if they could get new islet cells without needing to take immunosuppressants, and stop having to take insulin every day," said Audrey Parent, Ph.D., associate professor in the UCSF Diabetes Center and a co-senior author of the paper.

Lim envisions a future in which organ transplant patients, or those with [autoimmune diseases](#), receive therapies that only treat the specific regions of the body where the immune system is misbehaving.

This could prevent the significant side effects from general immunosuppressants as well as the infections and cancers that arise when the immune system is disabled completely.

The new technology also could be used to fine-tune CAR T cell therapies for cancer, so these CAR T cells only attack tumors, and not healthy tissue.

"This puts so many more options on the table for dealing with some of the biggest challenges in medicine," said Lim, who directs the UCSF Cell Design Institute. "We hope this can benefit patients in the not-so-distant future."

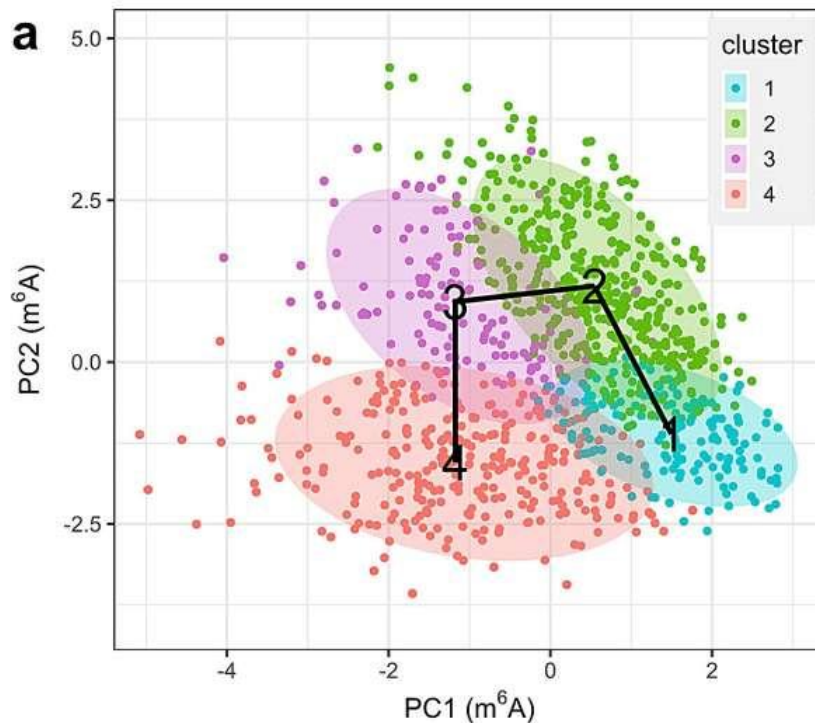
More information: Nishith R. Reddy et al, Engineering synthetic suppressor T cells that execute locally targeted immunoprotective programs, *Science* (2024). DOI: [10.1126/science.adl4793](https://doi.org/10.1126/science.adl4793). www.science.org/doi/10.1126/science.adl4793

Journal information: [Science](#)

Provided by [University of California, San Francisco](#)

Modeling tool enhances understanding of RNA modifications in individual cells

by Xi'an jiaotong-Liverpool University



RNA modifications are used to classify individual cells into four distinct groups, revealing how their characteristics change during different stages of the cell cycle. Credit: Wang et al., *Cell Genomics*, DOI: 10.1016/j.xgen.2024.100702

Researchers have developed a new tool that will help scientists study how genes are expressed in our cells. The tool, called SigRM, is used to analyze data from single-cell epitranscriptomics, a method for studying RNA modifications in individual cells. This research could lead to important insights into health and disease.

Recent advances in single-cell technology have enabled researchers to analyze thousands of [individual cells](#) at once, providing rich information about the expression and activity of genes and proteins, as well as chemical changes that affect [gene expression](#).

A major tool in these studies is single-cell epitranscriptomics, which studies RNA modifications like m6A methylation, which can significantly influence [gene regulation](#) and are important in various diseases.

RNA methylation is a chemical change that attaches a small marker molecule to RNA molecules. This change is crucial in many cell processes, including gene regulation and overall cell behavior. SigRM, which was [published](#) in the journal *Cell Genomics*, can be used to build condition-specific [regulatory networks](#) from the data, helping researchers map how RNA methylation is controlled in different situations.

With single-cell epitranscriptomics tools, researchers can focus specifically on RNA modifications in individual cells, enabling them to study the variation between different cells. However, existing techniques for analyzing this data are still quite basic, and many important questions about RNA methylation and its variability across different cells remain open.

"The SigRM framework addresses these challenges effectively, providing improved detection and quantification of RNA methylation sites," says Professor Jia Meng, Head of the Department of Biological Sciences at Xi'an Jiaotong–Liverpool University (XJTLU) and lead researcher of the study.

By analyzing single-cell epitranscriptomic data, researchers can track how RNA modifications happen across different cell groups. SigRM not only helps construct regulatory networks based on this data but also tracks how cells change states over time, a process known as trajectory inference.

The results from SigRM have been validated against existing biological knowledge, demonstrating its reliability. The new tool will be invaluable in understanding complex regulatory mechanisms, especially in diseases like cancer.

"The implications of SigRM reach far beyond the lab. Its development represents a significant advance in our understanding of how RNA modifications influence gene regulation," says Professor Meng.

"Our work not only addresses critical gaps in analysis techniques but also provides valuable insights that could pave the way for breakthroughs in [medical research](#) and biotechnology, enhancing our understanding of how RNA modifications impact health and disease."

More information: Haozhe Wang, et al. Statistical modeling of single-cell epitranscriptomics enabled trajectory and regulatory inference of RNA methylation, *Cell Genomics* (2024). DOI: [10.1016/j.xgen.2024.100702](https://doi.org/10.1016/j.xgen.2024.100702). [www.cell.com/cell-genomics/ful ... 2666-979X\(24\)00331-8](https://www.cell.com/cell-genomics/fulltext/S2666-979X(24)00331-8)

Journal information: [Cell Genomics](#)

Provided by [Xi'an jiaotong-Liverpool University](#)

Thylacine De-Extinction Achieves Mid-Gestation Marsupial Embryo Development In Artificial Uterus



The Colossal news comes with the de-extinction company's announcement of a further \$200 million in funding. - Image credit: Baker; E.J. Keller. 1904 from the Smithsonian Institution archives. Australian Zoologist 41 (2): 143–178. DOI:10.7882/AZ.2020.032. via Wikimedia Commons (public domain)© IFL Science

The de-extinction company Colossal Biosciences has reached another big milestone in its mission to make extinction a thing of the past, securing a further \$200 million in Series C funding from TWG Global. It brings their total funding to \$435 million to date, capital they have used to pioneer a de-extinction toolkit that has already contributed to advancements in [species preservation](#) and [human healthcare](#).

"Colossal is a revolutionary genetics company making science fiction into science fact," said Colossal co-founder Professor George Church, of Harvard Medical School and the Massachusetts Institute of Technology (MIT) in a statement emailed to IFLScience. "We are creating the technology to build de-extinction science and scale conservation biology particularly for endangered and at-risk species. I could not be more appreciative of the investor support for this important mission."

You may recognize Colossal as the company behind ambitious goals to de-extinct the [mammoth](#), [dodo](#), and [thylacine](#), goals that have seen them innovate revolutionary technologies with far-reaching applications. Newly-announced achievements include generating chromosome-scale reference genomes for the African elephant, Asian elephant, and rock hyrax, as well as acquiring ancient genomes for the woolly mammoth. A key part of their goal to reintroduce the mammoth's cold-tolerant phenotype into modern day equivalents involves tracking those genes down, and they've already successfully edited over 20 key genes linked to the core traits that enabled these animals to thrive in cold environments.

On the dodo front, they've generated a chromosome-scale assembly of the Nicobar pigeon, its closest relative, and established a flock that will act as primordial germ cell donors for Colossal's future dodos. Plus, they've developed a machine learning approach to identify genes associated with craniofacial shape so that they can work towards the unique bill morphology of the dodo.

This has major implications not only for de-extinction science but also in conservation.

Ben Lamm

Another key project centers around the [thylacine](#), an extinct marsupial that was native to Australia, Tasmania, and New Guinea. The last known individual died in 1936.

An ex-utero way of generating thylacines would be preferable as it could bypass the need for a surrogate, but mimicking the uterine environment is no mean feat. Now, Colossal has announced that it's not only made a prototype for an artificial uterus, but also used it to culture fertilized single-cell marsupial embryos to over halfway through pregnancy.

"The system is much more sophisticated than any existing device, with modulated precision microfluidics and gas control that enables us to control the environment the embryo is growing in, in a very precise way," [Colossal co-founder Ben Lamm](#) told IFLScience. "It also enables us to image the embryo as it develops to make sure all developmental milestones are on track."

"The device will be important for studying embryonic development and making sure the DNA edits we are making are driving the correct developmental changes. This will also enable us to generate thylacine young at scale for rewilding, without the need for surrogate mothers."

At this stage we are using the device for marsupial embryo culture, but we will expand this next to mice.

Ben Lamm

To borrow Church's words, it really is an achievement that's "making science fiction into science fact," but beyond resurrecting species from the past, the technology can also contribute to the [conservation of animals alive today](#).

"This has major implications not only for de-extinction science but also in conservation. An artificial womb would enable us to generate living animals from endangered animal cells that are preserved in biobanks – again without the complications of surrogacy."

Marsupials are a great starting point for testing this technology as they have a very short gestation (typically less than two weeks), and only form a very superficial placenta during pregnancy. There remain obstacles to overcome in meeting the changing nutritional demands of embryos at different stages of their development, but if successful, it could be adapted to different animal groups.

"At this stage we are using the device for marsupial embryo culture, but we will expand this next to mouse which has a longer gestation period and greater attachment to the mother through a larger placenta."

From mice to mammoths, these guys are providing plenty of inspiration for any aspiring sci-fi writers.

From first breath: How male and female brains really do differ at birth

CAMBRIDGE, England — The age-old debate about differences between male and female brains has taken a dramatic turn with new evidence suggesting these variations begin before a baby's first cry. In the largest study of its kind, researchers at Cambridge University's Autism Research Centre have discovered that structural brain differences between the sexes don't gradually emerge through childhood — they're already established at birth.

Brain development during the first few weeks of life occurs at a remarkably rapid pace, making this period particularly crucial for understanding how sex differences in the brain emerge and evolve. Previous research has primarily focused on older infants, children, and adults, leaving a significant gap in our understanding of the earliest stages of [brain development](#).

The research team analyzed brain scans of 514 newborns (236 females and 278 males) aged 0-28 days using data from the developing Human Connectome Project. The study represents one of the largest and most comprehensive investigations of sex differences in neonatal brain structure to date, addressing a common limitation of past research: small sample sizes.

Male newborns showed larger overall [brain volumes](#) compared to females, even after accounting for differences in birth weight. This finding was particularly significant because the research team carefully controlled for body size differences between sexes, a factor that has complicated previous studies in this field.



New research reveals how babies' brains show some developmental differences before at birth. (© unlimit3d – stock.adobe.com)

When controlling for total brain volume, female babies exhibited greater amounts of **gray matter** — the outer brain tissue containing nerve cell bodies and dendrites responsible for processing and interpreting information, such as sensation, perception, learning, speech, and **cognition**. Meanwhile, male infants had higher volumes of white matter, which consists of long nerve fibers (axons) that connect different brain regions together.

“Our study settles an age-old question of whether male and female brains **differ** at birth,” says lead author Yumnah Khan, a PhD student at the Autism Research Centre, in a statement. “We know there are differences in the brains of older children and adults, but our findings show that they are already present in the earliest days of life.”

Several specific brain regions showed notable differences between males and females. Female newborns had larger volumes in areas related to **memory** and emotional regulation, while male infants showed greater volume in regions involved in sensory processing and motor control.

Dr. Alex Tsompanidis, who supervised the study, emphasizes its methodological rigor: “This is the largest such study to date, and we took additional factors into

account, such as birth weight, to ensure that these differences are specific to the brain and not due to general size differences between the sexes.”

The research team is now investigating potential prenatal factors that might contribute to these differences. “To understand why males and females show differences in their relative grey and [white matter](#) volume, we are now studying the conditions of the prenatal environment, using population birth records, as well as in vitro cellular models of the developing brain,” explains Dr. Tsompanidis.

Importantly, the researchers stress that these findings represent group averages rather than individual characteristics.

“The differences we see do not apply to all males or all females, but are only seen when you compare groups of males and females together,” says Dr. Carrie Allison, Deputy Director of the Autism Research Centre. “There is a lot of variation within, and a lot of overlap between, each group.”

These findings mark a significant step forward in understanding early brain development, while raising new questions about the role of prenatal factors in shaping neurological differences. The research team’s ongoing investigations into prenatal conditions and cellular models may soon provide even more insights into how these sex-based variations emerge.

“These differences do not imply the brains of males and females are better or worse. It’s just one example of neurodiversity,” says Professor Simon Baron-Cohen, Director of the Autism Research Centre. “This research may be helpful in understanding other kinds of neurodiversity, such as the brain in children who are later diagnosed [as autistic](#), since this is diagnosed more often in males.”

Paper Summary

Methodology Explained

The researchers used magnetic resonance imaging (MRI) to scan the brains of healthy, full-term newborns without sedation. They carefully controlled for factors like birth weight and age at scanning. The images were processed using specialized software designed for analyzing newborn brains, which separated

different tissue types and measured volumes of specific brain regions. Statistical analyses compared these measurements between males and females while accounting for various factors that could influence the results.

Key Results

Males showed 6.16% larger total brain volume and 5.64% larger intracranial volume (total space inside the skull) compared to females, even after accounting for birth weight. Females showed relatively larger gray matter volumes, while males had relatively larger white matter volumes when controlling for overall brain size. Specific regions showed sex differences with small to medium effect sizes, meaning the differences were consistent but not dramatic.

Study Limitations

The study wasn't longitudinal, meaning it couldn't track how individual brains changed over time. The researchers couldn't establish direct causal relationships between prenatal factors (like hormones) and brain differences. Additionally, brain structure differences don't necessarily translate to functional differences, and the study couldn't account for all possible social and environmental influences.

Discussion and Takeaways

The research suggests three patterns: some sex differences present at birth persist throughout life, some appear later in development, and some are unique to the newborn period. This indicates that both prenatal and postnatal factors shape sex differences in the brain, with prenatal factors playing a particularly important role in establishing initial differences.

Funding and Disclosures

The study was funded by several organizations including the European Research Council, Wellcome Trust, Innovative Medicines Initiative, Cambridge University

Development and Research, Trinity College, the Cambridge Trust, and the Simons Foundation Autism Research Initiative. One author disclosed being a director of and holding equity in Centile Bioscience Ltd.

Publication Information

Published in *Biology of Sex Differences* (2024) 15:81, the study titled “Sex Differences in Human Brain Structure at Birth” was conducted by researchers primarily from the University of Cambridge, with lead author Yumnah T. Khan and corresponding author Simon Baron-Cohen.

Caterpillar fungus could be the surprising ingredient that stops cancer

NOTTINGHAM, United Kingdom — In a remarkable discovery, researchers have uncovered the key behind a traditional Asian medicine’s potential to combat cancer. The compound in question, **cordycepin**, is produced by a caterpillar fungus and has long been touted for its health benefits, but its precise effects on the body have remained elusive – until now.

The study, published in the journal [FEBS Letters](#), was led by Dr. Cornelia de Moor from the University of Nottingham’s School of Pharmacy. Her team used advanced techniques to analyze the impact of cordycepin on thousands of genes across multiple cell lines. Their findings reveal that this fungal compound works by interrupting the very signals that [drive uncontrolled cell growth](#) – a hallmark of cancer.

“We have been researching the effects of Cordycepin on a range of diseases for a number of years and with each step we get closer to understanding how it could be used as an [effective treatment](#),” explains Dr. de Moor in a university release. “One of the exciting things to have been happening is that it has become easier and less expensive to do these very large experiments, so we were able to examine thousands of genes at the same time.”



A caterpillar infected with *Cordyceps militaris*, the pretty orange fungus that produces Cordycepin. (Credit: Daniel Winkler – Mushroaming)

The researchers discovered that once inside the cell, cordycepin is converted into a molecule that closely resembles the cell's primary energy carrier, ATP. This cordycepin-based compound then [directly interferes](#) with the cell's growth-promoting pathways, potentially slowing the rapid division seen in cancer cells.

Importantly, this mechanism of action suggests cordycepin derivatives could offer a less damaging alternative to many current cancer treatments, which often take a [heavy toll on healthy cells](#) and tissues.

"Our data confirms that cordycepin is a good starting point for novel cancer medicines and explains its beneficial effects," says Dr. de Moor.

The caterpillar fungus, known as *Cordyceps militaris*, has long been prized in [traditional Chinese and Tibetan medicine](#) for its supposed restorative and

invigorating properties. Now, modern science is beginning to unravel the secrets behind this fungus's medicinal potential.

While much work remains to be done, these findings represent an important step forward in the development of new, more targeted cancer therapies. By harnessing the power of nature's own compounds, researchers hope to one day provide patients with effective treatments that minimize harmful side-effects. The road ahead may be long, but the promise of this mushroom-derived molecule has renewed hope in the fight against cancer.

Paper Summary

Methodology

The study aimed to see how cordycepin, a compound derived from fungi, affects cell signaling related to growth. Researchers used various cell types, including cancer cell lines, to see how cordycepin influenced pathways known to drive cell growth and survival. They treated cells with cordycepin, sometimes alongside other compounds like pentostatin (to prevent cordycepin's breakdown), then observed changes in gene expression and protein activity. Techniques like western blotting, RNA sequencing, and cell growth assays helped confirm the effects.

Key Results

Cordycepin slowed down cell growth by disrupting two major signaling pathways, PI3K/mTOR and MEK/ERK. These pathways are crucial for cell division and survival, especially in cancer cells. The compound also reduced the cells' ability to repair wounds (important in cancer spread) and even shrank tumors in animal models. The effects were more pronounced when paired with pentostatin, indicating that preventing cordycepin breakdown increased its potency.

Study Limitations

The study doesn't fully explain how cordycepin disrupts the specific pathways, and results may vary depending on cell types. Also, the study primarily used lab-

grown cells and a single animal model, which might not fully replicate how cordycepin would work in human patients. There are also questions about potential side effects that weren't covered.

Discussion & Takeaways

The findings suggest cordycepin could be a valuable tool in cancer treatment, as it targets key pathways that many cancer cells rely on. By blocking multiple growth signals, cordycepin may reduce the chances of drug resistance, which is a major issue with some cancer therapies. Its effectiveness could improve when used alongside other treatments that prevent its breakdown. However, more studies, particularly on humans, are needed to validate these results.

Funding & Disclosures

The study received funding from sources including the University of Nottingham, Versus Arthritis, and other research scholarships. Collaborations involved various institutions, including the University of Dundee and the MRC Toxicology Unit. The study authors disclosed financial support and the contributions of researchers and students who assisted in pilot and supporting experiments.

Antibiotic resistance makes once-lifesaving drugs useless. Could we reverse it?

The world is facing an ever-increasing threat from bacteria evolving resistance to known antibiotics, rendering the essential drugs ineffective. But now, researchers are exploring promising new treatment strategies, with the aim of making those resistant bacteria susceptible to drugs once more.

The rise of antibiotic-resistant bacteria has been dubbed the "[silent pandemic](#)" due to its stealthy global spread and lack of urgent public attention, in comparison to other pandemics such as [COVID-19](#), especially in regions where antibiotic use remains largely unchecked. Estimates from a 2019 report [published by the Centers for Disease Control and Prevention \(CDC\)](#) suggest that resistant bacteria killed at least 1.27 million people worldwide that year, with 35,000 of

those deaths occurring in the U.S. alone. That marked a 52% increase in U.S. deaths from resistant microbes since the [CDC's previous report in 2013](#).

"Antibiotic resistance is a major public health threat because so much of modern medical care depends on antibiotics — childbirth, cancer treatment, transplants, operations, and infections," [Zamin Iqbal](#), a professor of algorithmic and microbial genomics at the University of Bath in the U.K., told Live Science in an email.

What's causing this mounting disaster? The [overuse and misuse of antibiotics](#) in both medicine and agriculture are the major culprits.

That's because antibiotic resistance arises from a [natural evolutionary process](#) — one in which the fittest bacteria with the right tools to outcompete an antibiotic survive to pass on those tools.

When a population of bacteria is exposed to an antibiotic, any genetic mutations that allow the bacteria to survive the drug will quickly spread between bacterial cells. Repeatedly using different antibiotics can lead bacteria to develop resistance to multiple drugs, resulting in strains that are no longer treatable with any known antibiotics — [with potentially fatal consequences](#).

In light of this chilling reality, we must prolong the effectiveness of the antibiotics we already have as long as possible as [new, alternative solutions are devised in the background](#). One way to achieve this is by finding strategies that can reverse the process by which bacteria become resistant, pushing them back into a drug-sensitive state.

To achieve this, [Joana Azeredo](#), an associate professor at the University of Minho in Portugal, exploits a natural enemy of bacteria: bacteriophages, or viruses that infect bacteria. Known as phages for short, these viruses are often discussed as a [promising treatment strategy](#) against antibiotic-resistant bacteria because of their potential to kill the cells they infect. However, rather than killing the bacteria, the phages Azeredo is interested in insert themselves into the bacteria's genomes.

Her research uses [genetically engineered phages](#) as "Trojan horses" to deliver genes that ultimately make bacteria vulnerable to antibiotics [by eliminating the resistance genes](#) they carry.



Bacteriophages, or phages, are viruses that infect bacteria. Some split bacteria open from the inside, while others incorporate their genetic material into the bacterial genome. (Image credit: NANOCLUSTERING/SCIENCE PHOTO LIBRARY via Getty Images)

A common resistance mechanism bacteria use against both phages and antibiotics are biofilms, which shield the bacterial cells from harm. [Fredrik Almqvist](#), a professor of organic chemistry at Umeå University in Sweden, together with molecular biologist [Christina Stallings](#), a professor of molecular microbiology at Washington University, are developing chemical compounds that [break down the biofilms of drug-resistant bacteria](#), effectively resensitizing them to antibiotics.

Almqvist and Stallings' research has uncovered a small molecule that [disrupts the genetic pathways that allow microbes to form biofilms](#). The molecule not only blocks this resistance mechanism from evolving in the first place but also restores antibiotic sensitivity to bacteria that have already evolved to use it.

Other researchers are taking a different approach: They're targeting the downstream mechanism of resistance, rather than eliminating its root genetic cause. For example, research from [Despoina Mavridou](#), an assistant professor at

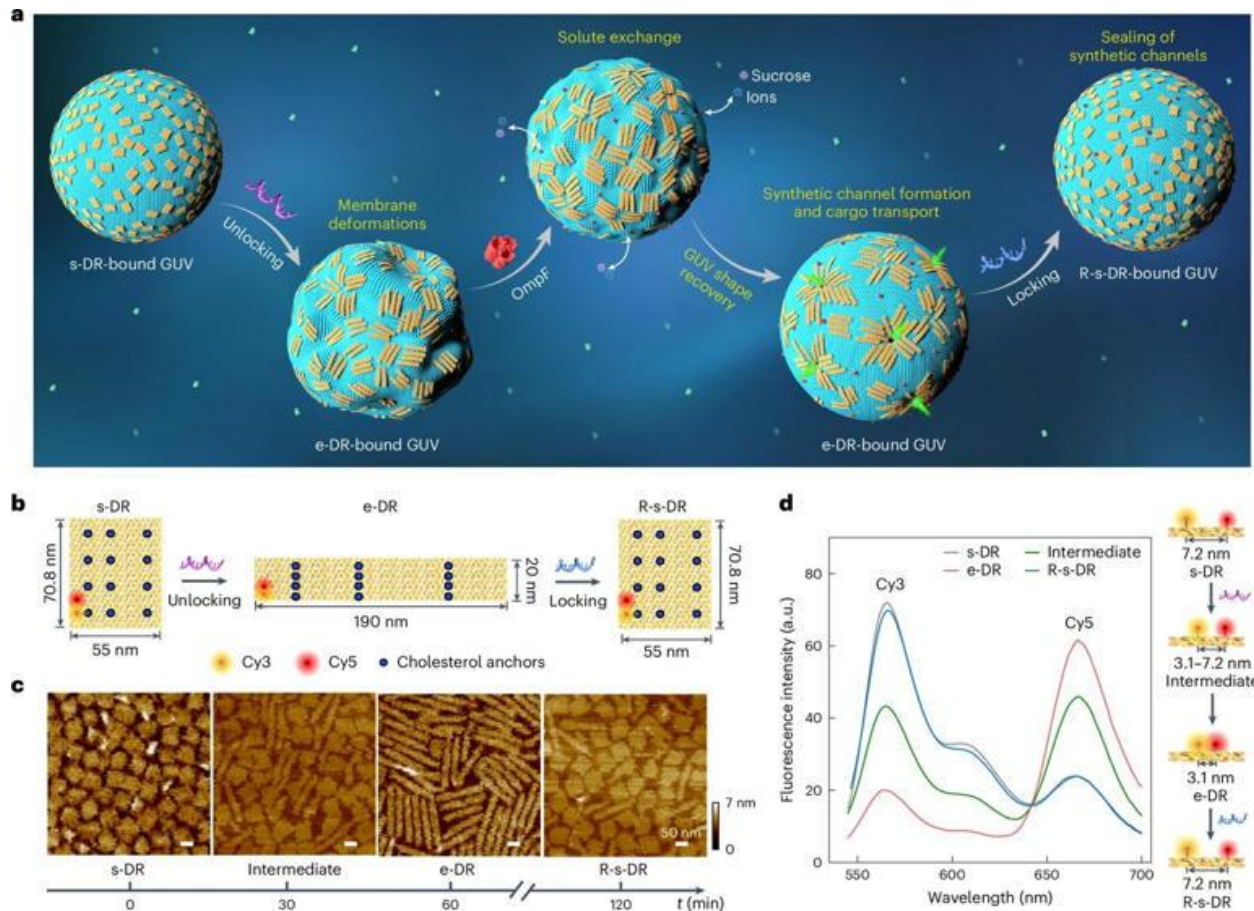
the University of Texas at Austin, aims to resensitize resistant bacteria by stopping cells from making a protein that helps fold other proteins.

Folding is a key step that enables a newly made protein to execute a particular function. Mavridou's approach prevents the folding of proteins that enable the bacteria to resist antibiotics. In studies, [inhibiting this folding-assistant protein](#) restored the sensitivity of multidrug-resistant bacteria. The inhibitors used in the study have not yet been approved for human use, though, so further research is needed to bring these discoveries to the clinic.

Designing new antibiotics is [expensive and difficult](#), which is one of the many reasons [so few are in development](#). Thus, it's crucial to protect and extend the effectiveness of the antibiotics we already have. The future of the antibiotic resistance crisis is uncertain, but ongoing research offers hope for innovative strategies that could change the course of this global challenge. It is imperative, however, that we learn from previous mistakes. Any new strategies we adopt should anticipate the ways in which bacteria could evolve to resist the treatments.

"It's important to understand how bacteria respond to the selection pressure imposed by antibiotics," [Andrew Preston](#), a professor in microbial pathogenicity at the University of Bath and the [editor-in-chief of the journal Microbiology](#), told Live Science in an email. "We will have some novel treatment strategies come through the pipeline, so it's imperative we consider how we might mitigate/reduce the selection for resistance to prolong their use."

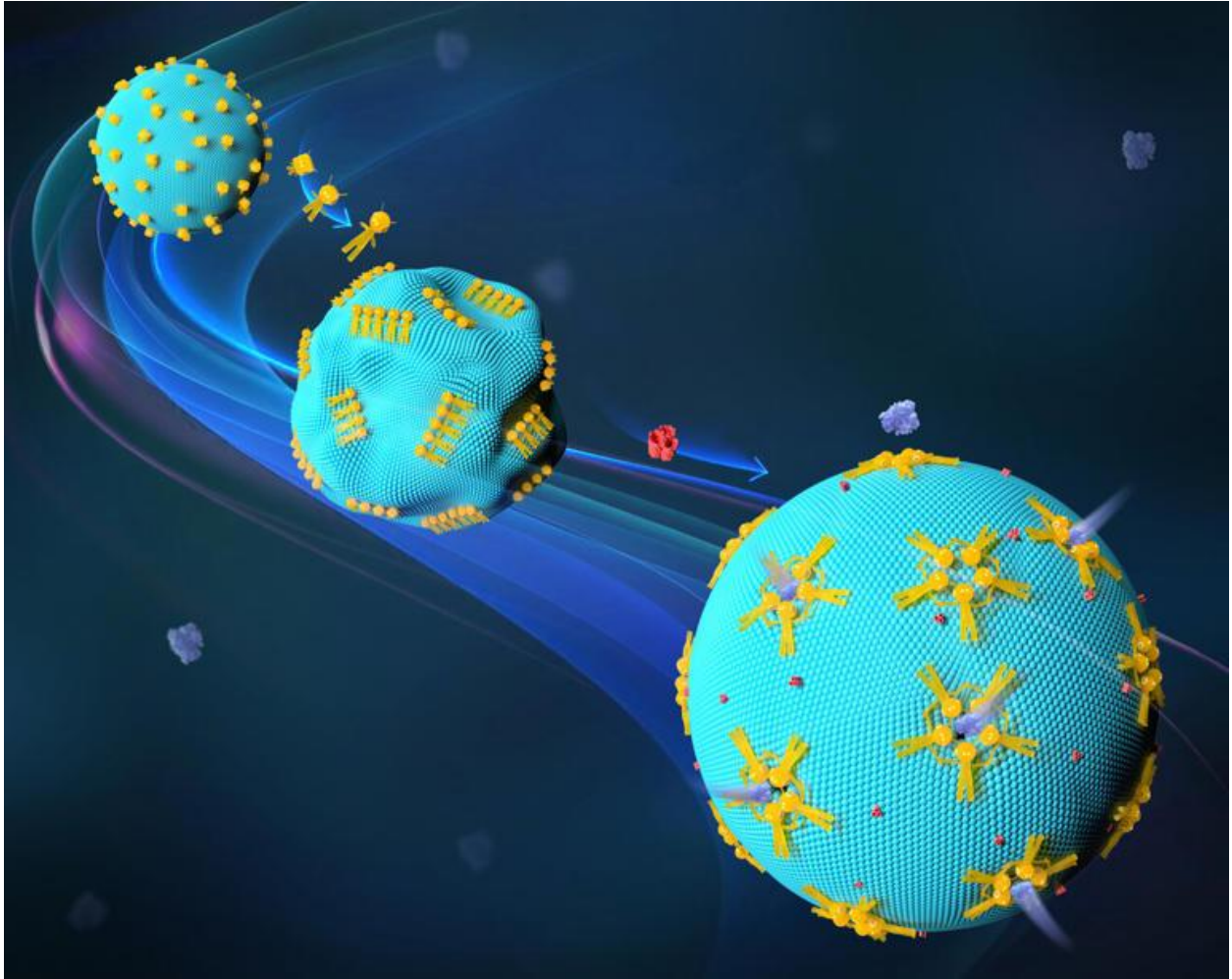
DNA nanorobots that can alter artificial cells offer a new tool for synthetic biology



Reconfigurable DNA rafts working on lipid membranes. Credit: Nature Materials, DOI: 10.1038/s41563-024-02075-9

The shape and morphology of a cell play a key role in the biological function. This corresponds to the principle of "form follows function," which is common in modern fields of design and architecture. The transfer of this principle to artificial cells is a challenge in synthetic biology. Advances in DNA nanotechnology now offer promising solutions. They allow the creation of novel transport channels that are large enough to facilitate the passage of therapeutic proteins across cell membranes.

In this emerging field, Prof. Laura Na Liu, Director of the 2nd Physics Institute at the University of Stuttgart and Fellow at the Max Planck Institute for Solid State Research (MPI-FKF), has developed an innovative tool for controlling the shape and permeability of lipid membranes in synthetic cells. These membranes are made up of lipid bilayers that enclose an aqueous compartment and serve as simplified models of biological membranes. They are useful for studying membrane dynamics, protein interactions, and lipid behavior.



Reconfigurable DNA nanorobots that are working on the surface of synthetic cells. Credit: 2nd Physics Institute, University of Stuttgart

The work is [published](#) in *Nature Materials*.

A milestone in the application of DNA nanotechnology

This new tool may pave the way for the creation of functional synthetic cells. The work of Laura Na Liu aims to significantly influence the research and development of new therapies. Liu and her team have succeeded in using signal-dependent DNA nanorobots to enable programmable interactions with synthetic cells.

"This work is a milestone in the application of DNA nanotechnology to regulate cell behavior," Liu says.

The team works with giant unilamellar vesicles (GUVs), which are simple, cell-sized structures that mimic living cells. Using DNA nanorobots, the researchers were able to influence the shape and functionality of these synthetic cells.

New transport channels for proteins and enzymes

DNA nanotechnology is one of Laura Na Liu's main research areas. She is an expert in DNA origami structures—DNA strands that are folded by means of specifically designed shorter DNA sequences, so-called staples. The team of Liu used DNA origami structures as reconfigurable nanorobots that can reversibly change their shape and thereby influence their immediate environment in the micrometer range.

The researchers found that the transformation of these DNA nanorobots can be coupled with the deformation of the GUVs and the formation of synthetic channels in the model GUV membranes. These channels allowed large molecules to pass through the membrane and can be resealed if necessary.

Fully artificial DNA structures for biological environments

"This means that we can use DNA nanorobots to design the shape and configuration of GUVs to enable the formation of transport channels in the membrane," says Prof. Stephan Nussberger, who is a co-author of this work.

"It is extremely exciting that the functional mechanism of the DNA nanorobots on GUVs has no direct biological equivalent in living cells."

The new work raises new questions: Could synthetic platforms—such as DNA nanorobots—be designed with less complexity than their biological counterparts, which would nevertheless function in a biological environment?

Understanding disease mechanisms and improving therapies

The new study is an important step in this direction. The system of cross-membrane channels, created by DNA nanorobots, allows efficient passage of certain molecules and substances into the cells. Most importantly, these channels are large and can be programmed to close when needed.

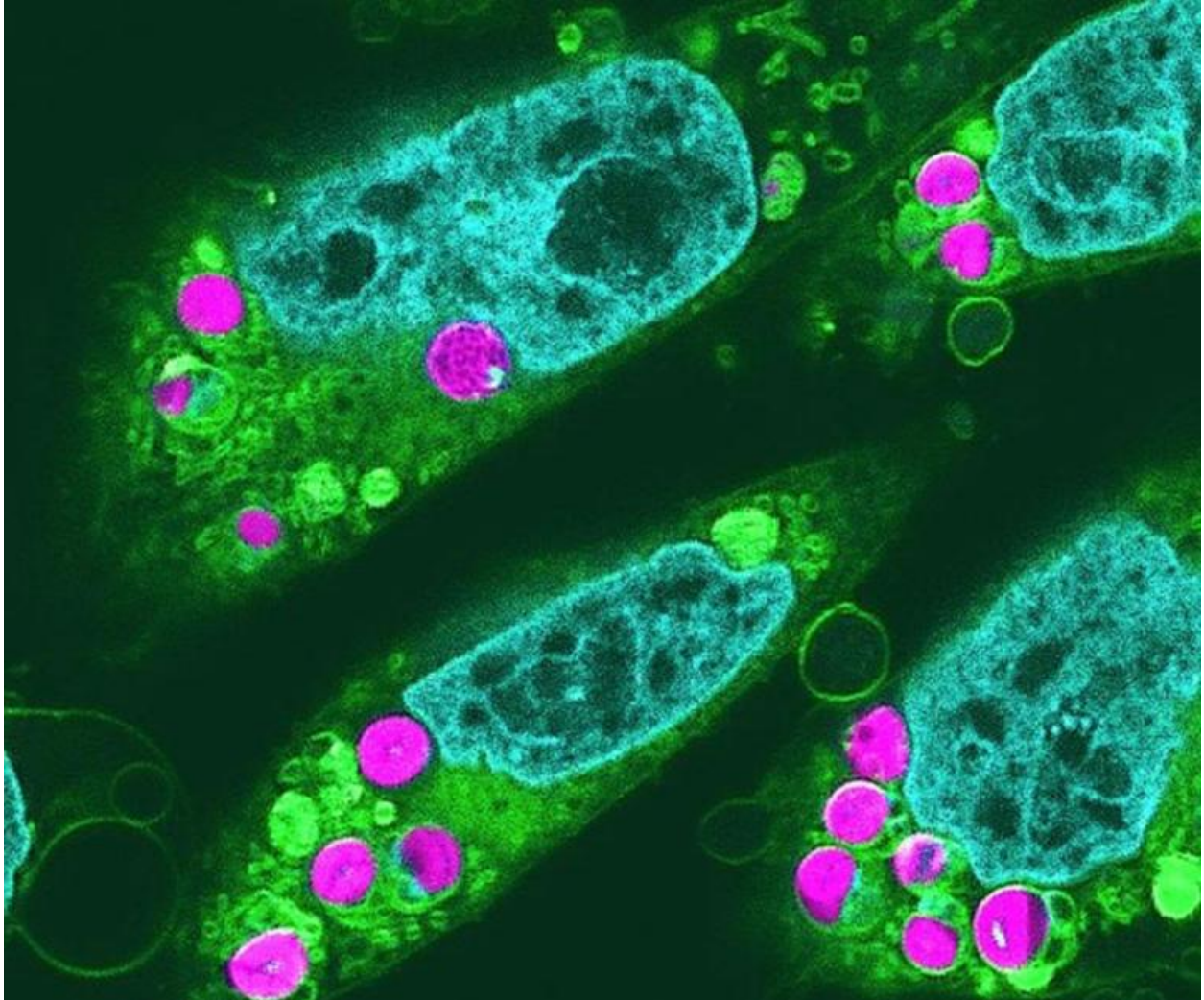
When applied to living cells, this system can facilitate the transportation of therapeutic proteins or enzymes to their targets in the cell. It thus offers new possibilities for the administration of drugs and other therapeutic interventions.

"Our approach opens up new possibilities to mimic the behavior of living cells. This progress could be crucial for future therapeutic strategies," says Prof. Hao Yan, one of the co-authors of this work.

More information: Sisi Fan et al, Morphological transformation and formation of membrane channels in synthetic cells through reconfigurable DNA nanotubes, *Nature Materials* (2025). DOI: [10.1038/s41563-024-02075-9](https://doi.org/10.1038/s41563-024-02075-9) www.nature.com/articles/s41563-024-02075-9

Provided by University of Stuttgart

Photosynthesis In Animal Cells Achieved For The First Time Using Implanted Chloroplasts



The hamster cells successfully incorporated the chloroplasts, in magenta. - Image credit: R. Aoki, Y. Inui, Y. Okabe et al. 2024/ Proceedings of the Japan Academy, Series B© IFL Science

After decades of failed attempts, scientists have finally succeeded in coaxing animal cells into [photosynthesizing](#). So far, the researchers have only managed to achieve the feat in cultured cells – which means that while sunlight-eating mammals are still some way off, we may eventually be able to use this technology for medical purposes or the creation of lab-grown meat.

Most [plants](#) (as well as algae) use chloroplasts to harness the energy of sunlight, which they mix with water and carbon dioxide to produce the carbohydrates they

need to grow, releasing oxygen as a byproduct. For years, scientists have dreamed of creating photosynthetic livestock, which would be essentially free to feed and leave a negative carbon footprint.

The problem, however, is that animals' immune systems tend to destroy chloroplasts the moment they are introduced into their cells, which is why no one has ever managed to get them to stick before. Even if these organelles could find a way to survive such an attack, they are unlikely to be able to function in the relatively hot environment of an animal cell, where temperatures are typically around 37°C (98.6°F).

To get around these issues, researchers used isolated chloroplasts from a type of primitive red algae called *Cyanidioschyzon merolae* - or schyzon, for short - which grows in volcanic hot springs in Italy and is capable of photosynthesizing at temperatures above 37°C. Rather than forcing these schyzon chloroplasts into animal cells, the team added them to a culture that was then fed to Chinese hamster ovary cells.

Reporting their findings in a new study, the authors reveal that shortly after this two-day co-cultivation, one percent of the cells had become "chloroplast-rich", meaning they had taken up seven or more chloroplasts. A further 20 percent of cells were found to contain between one and three chloroplasts.

Importantly, these imported chloroplasts displayed activity for two further days, during which time their host cells grew at an accelerated rate. This indicates that [photosynthesis](#) was indeed occurring, with the chloroplasts potentially acting as a carbon source.

"Our study is the first to measure the photosynthetic activity of chloroplasts in mammalian cells," write the authors in the study.

"We expect plant cells to be game-changing cells, which in the future can help us achieve a 'green transformation' to a more carbon-neutral society," added lead researcher Sachihito Matsunaga in a [statement](#).

As awesome as this breakthrough may be, further observations revealed that the imported chloroplasts began to degrade after two days and were completely destroyed by day four. Further work is therefore needed to perfect the technique, although the researchers have already seen enough to suggest that their

"synthetic biology-based approach may serve as a foundation for creating artificially photosynthetic animal cells."

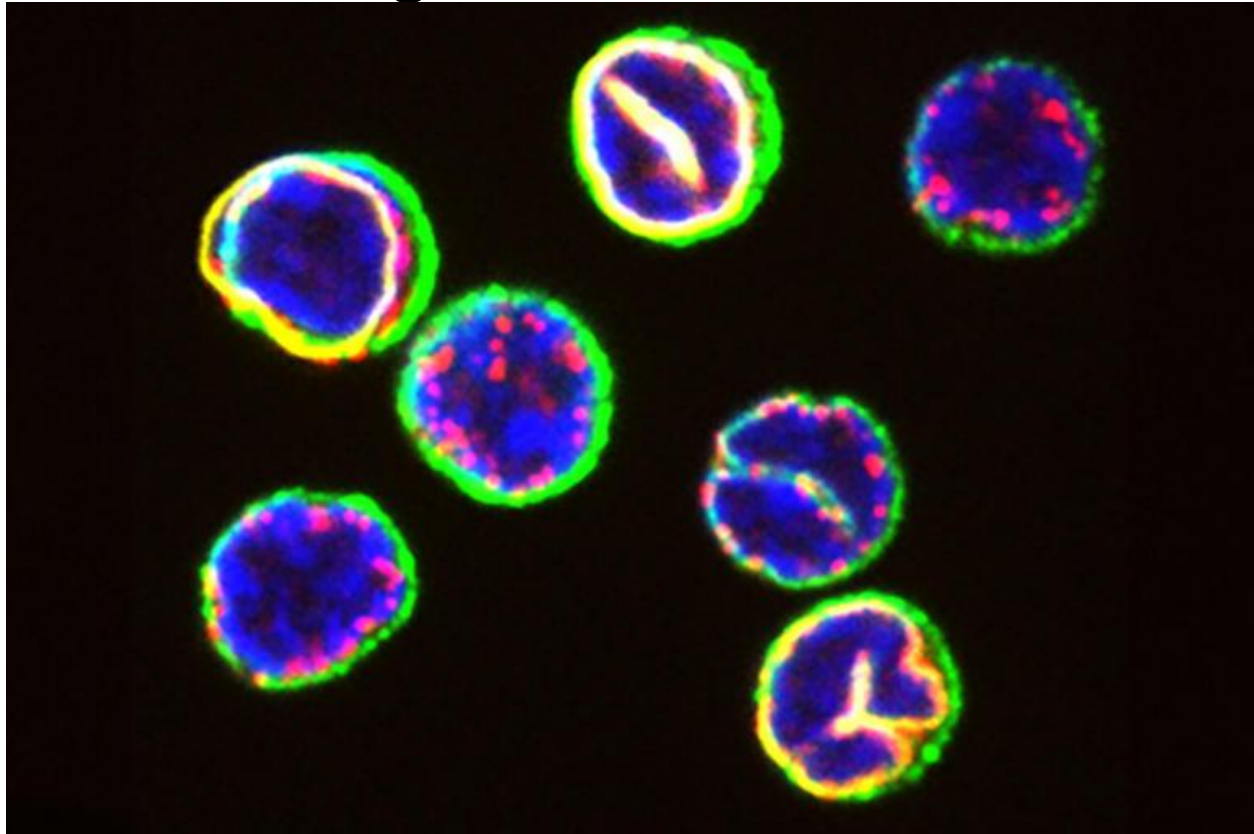
"We believe this work will be useful for cellular-tissue engineering," said Matsunaga. In particular, he sees the technology as as a potential game-changer for the production of "lab-grown tissues, such as artificial organs, [artificial meat](#) and skin sheets,"

At present, the creation of such multi-layered cellular products is complicated because a lack of oxygen between the layers inhibits cell division and therefore limits growth. However, Matsunaga says that "by mixing in chloroplast-implanted cells, oxygen could be supplied to the cells through photosynthesis, by light irradiation, thereby improving the conditions inside the tissue to enable growth."

So while photosynthetic cattle are unlikely to be appearing on any farms in the near future, planimal cells could still have a major role to play in both food production and medicine.

The study is published in the journal [Proceedings of the Japan Academy, Series B](#).

Researchers identify key differences in inner workings of immune cells



Freshly isolated T cells from the blood of a healthy human donor. Nuclear components (red, yellow and blue) and T cell receptors (green) highlight the remarkable variability in the subcellular spatial organization of our T cells. Credit: Ben Hale / ETH Zurich© Provided by Medical Xpress

Cytotoxic T cells are an important component of the immune system. Once activated, they differentiate into either short-lived effector cells or long-lived memory cells. Studies by researchers at ETH Zurich have found that the cellular architecture of T cells influences which of these two functions the cells adopt when they undergo pathogen-induced activation.

As well as improving our understanding of the immune system, these [findings](#), appearing in *Science*, could also potentially lead to better cancer therapies.

From the outside, most T cells look the same: small and spherical. Now, a team of researchers led by Berend Snijder from the Institute of Molecular Systems Biology at ETH Zurich has taken a closer look inside these cells using advanced techniques. Their findings show that the subcellular spatial organization of

cytotoxic T cells—which Snijder refers to as their cellular architecture—has a major influence on their fate.

Characteristics that determine a cell's fate

When cells with nuclear invaginations encounter a pathogen, they turn into powerful effector cells that rapidly proliferate and kill the pathogen. Their fellow cells with a spherical nucleus—that is, with no nuclear invaginations—evolve at a more leisurely pace: they take longer to activate and eventually differentiate into long-lived memory cells that defend the organism against future attacks by the same pathogen.

Scientists identified these two functionally distinct populations of T cells some 50 years ago. "But until now we weren't sure which characteristics determined whether a T cell would become an effector cell or a memory cell," says Ben Hale, a postdoc in Snijder's research group and lead author of the article.

To help identify these characteristics, the researchers developed a platform that automatically analyzes microscopy images of immune cells. They then presented this platform with thousands of T cells from 24 healthy volunteers who donated their blood to the Zurich Blood Donation Service of the Swiss Red Cross.

Unexpected differences

Using a machine-learning approach, the platform classified the cells into three different groups. "We'd already seen how some T cells appear bottle-shaped when activated," Snijder says. "But we didn't expect the platform to split the round cells into two different groups."

On further investigation, the researchers also discovered that the differences in cellular architecture between the two classes of round cells also has a functional significance. "The cells with nuclear invaginations are designed to activate rapidly: many of them convert into bottle-shaped effector cells within 24 hours," Hale says.

"They also mount a stronger response when activated—and they proliferate much faster than cells without nuclear invaginations," Snijder adds. He and his

team also identified the molecular mechanism that leads to the faster and stronger activation of cells with nuclear invaginations: "Their special cellular architecture enables a heightened influx of calcium ions," Snijder says.

Both researchers emphasize that there are still many questions to be answered. For example, Snijder and his team now hope to discover how the organism consistently ensures that around 60 percent of cytotoxic T cells in the blood have nuclear invaginations, while 35% have no invaginations and the remaining 5% are bottle-shaped.

Making therapies more clinically effective

Snijder and Hale note that their results are not only "important for gaining a better understanding of how our immune cells work," but also play a crucial role in the fight against cancer, for example, "Many novel therapies use T cells to kill cancer cells," Snijder says.

"If we can find a way to specifically select and deploy these cellular architectures, we may be able to improve the clinical efficacy of such therapies."

More information: Benjamin D. Hale et al, Cellular architecture shapes the naïve T cell response, *Science* (2024). DOI:

[10.1126/science.adh8967](https://doi.org/10.1126/science.adh8967). www.science.org/doi/10.1126/science.adh8967

Provided by ETH Zurich

Tagging gene-regulating DNA sequences with barcodes provides insights into human genome



An international team of researchers has taken an important step toward understanding how gene expression is controlled across the human genome. Credit: ASHBi/Kyoto University

An international team of researchers has taken an important step toward understanding how gene expression is controlled across the human genome. The research is [published](#) in the journal *Nature*.

The study comprehensively analyzed "cis-regulatory elements" (CREs), which are the DNA sequences that regulate gene transcription. This work sheds light on how these elements contribute to cell-specific gene expression and how mutations within them may influence health and disease.

CREs, including enhancers and promoters, are essential for controlling when and where genes are turned on or off. While their importance is well established, studying their activity at a large scale has been a challenge.

"The human genome contains a myriad of CREs, and mutations in these regions are thought to play a major role in human diseases and evolution," explained Dr. Fumitaka Inoue, one of the co-first authors of the study. "However, it has been very difficult to comprehensively quantify their activity across the genome."

To address this, the team used a cutting-edge technology called the lentivirus-based massively parallel reporter assay (lentiMPRA), which the authors had previously developed. This approach enables simultaneous analysis of thousands of CREs by tagging them with unique DNA barcodes that track their activity.

Applying lentiMPRA, the researchers examined as many as 680,000 candidate CREs in three widely used cell types: hepatocytes (cells from the liver), lymphocytes (a type of white blood cell), and induced pluripotent stem cells (a type of artificial stem cell made from a normal body cell).

The study revealed several key insights. Across the three cell types, approximately 41.7% of the analyzed CREs exhibited activity. Promoters, which start gene transcription, showed a dependence on sequence orientation but were less specific to cell types.

Enhancers, which boost gene transcription, were active regardless of their orientation and exhibited cell-type specificity. These findings highlight fundamental differences in how these two types of CREs function.

In the study, several machine learning models were developed to predict the regulatory activity of CREs based on large-scale experimental data. MPRALegNet, a model trained on the vast lentiMPRA dataset, was found to be the most accurate and efficient in predicting the regulatory activity of any DNA sequence. Its predictions align closely with experimental results, performing as well as experimental replicates in some cases.

The model also demonstrated its ability to identify important transcription factor binding motifs—that is, short DNA sequences that determine CRE activity—thus providing insights into how specific factors drive cell-type-specific gene expression. For example, the study identified HNF4 and GATA motifs as crucial for activity in hepatocytes and lymphocytes, respectively.

By enabling the precise identification and quantification of enhancer activity, the study opens avenues for exploring the molecular mechanisms of human diseases.

Future research will focus on applying this approach to study genetic polymorphisms, the variations in DNA sequence that contribute to individual differences and disease susceptibility.

"Recently, the nearly complete human genome has been sequenced, but many of its functional regions remain unknown. Our findings link DNA sequence information with its functional roles. We hope that these results will contribute to a deeper understanding of biological phenomena, including human diseases and evolution," said Dr. Inoue.

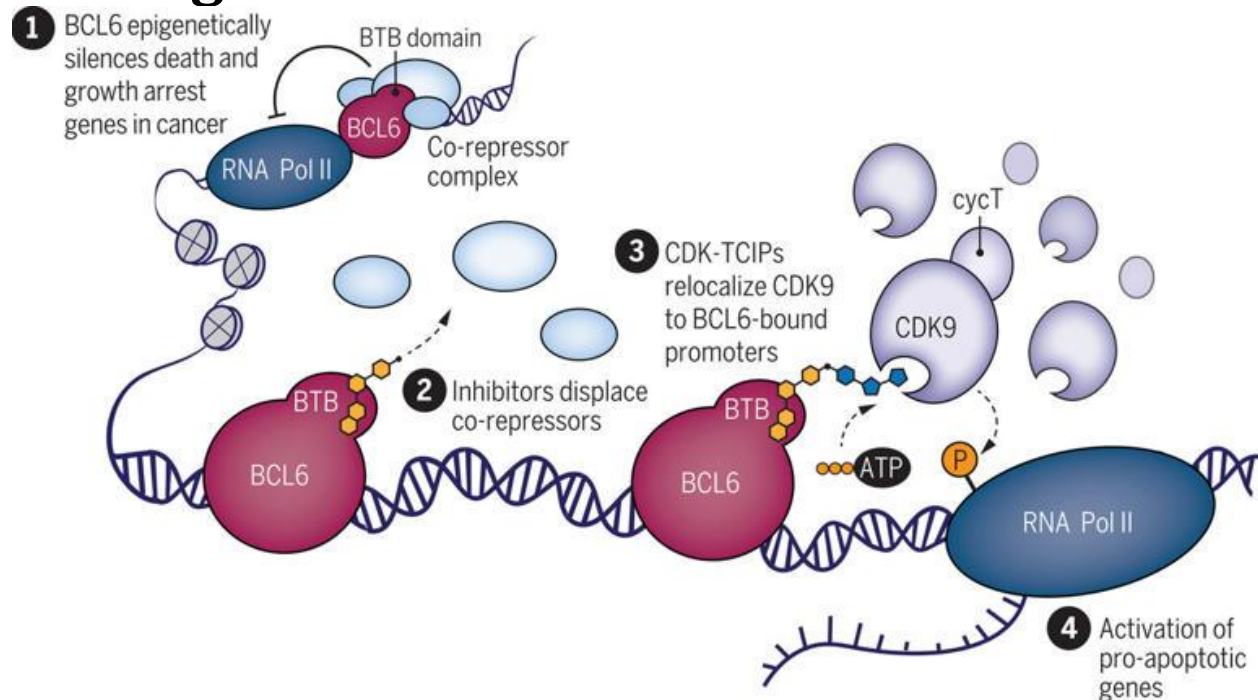
This study also contributes a publicly accessible database of CRE activity to the [ENCODE portal](#), providing a valuable resource for researchers worldwide. By integrating large-scale experimental data with machine learning, the work sets a foundation for future discoveries in genomics and personalized medicine.

In addition, the use of tools like lentiMPRA and MPRALegNet will help to better equip researchers to unravel the complexities of gene regulation and to explore the vast, uncharted territories of the human genome.

More information: Vikram Agarwal et al, Massively parallel characterization of transcriptional regulatory elements, *Nature* (2025). DOI: [10.1038/s41586-024-08430-9](https://doi.org/10.1038/s41586-024-08430-9)

Provided by Kyoto University

Scientists glue two proteins together, driving cancer cells to self-destruct



Turning kinase inhibitors into activators of therapeutic genes. Credit: Science (2024). DOI: 10.1126/science.adl5361

Our bodies divest themselves of 60 billion cells every day through a natural process of cell culling and turnover called apoptosis. These cells—mainly blood and gut cells—are all replaced with new ones, but the way our bodies rid themselves of material could have profound implications for cancer therapies in a new approach developed by Stanford Medicine researchers.

They aim to use this natural method of cell death to trick cancer cells into disposing of themselves. Their method accomplishes this by artificially bringing together two proteins in such a way that the new compound switches on a set of cell death genes, ultimately driving tumor cells to turn on themselves.

The researchers describe their [latest such compound](#) in a paper published Oct. 4 in *Science*.

The idea came to Gerald Crabtree, MD, a professor of development biology, during a pandemic stroll through the forests of Kings Mountain, west of Palo Alto, California. As he walked, Crabtree, a longtime cancer biologist, was thinking about major milestones in biology.

One of the milestones he pondered was the 1970s-era discovery that cells trigger their own deaths for the greater good of the organism. Apoptosis turns out to be critical for many biological processes, including proper development of all organs and the fine-tuning of our immune systems. That system retains pathogen-recognizing cells but kills off self-recognizing ones, thus preventing autoimmune disease.

"It occurred to me, well gee, this is the way we want to treat cancer," said Crabtree, a co-senior author on the study who is the David Korn, MD, Professor of Pathology. "We essentially want to have the same kind of specificity that can eliminate 60 billion cells with no bystanders, so no cell is killed that is not the proper object of the killing mechanism."

Traditional treatments for cancer—namely chemotherapy and radiation—often kill large numbers of healthy cells alongside the cancerous ones. To harness cells' natural and highly specific self-destruction abilities, the team developed a kind of molecular glue that sticks together two proteins that normally would have nothing to do with one another.

Flipping the cancer script

One of these proteins, BCL6, when mutated, drives the blood cancer known as diffuse large cell B-cell lymphoma. This kind of cancer-driving protein is also referred to as an oncogene. In lymphoma, the mutated BCL6 sits on DNA near apoptosis-promoting genes and keeps them switched off, helping the cancer cells retain their signature immortality.

The researchers developed a molecule that tethers BCL6 to a protein known as CDK9, which acts as an enzyme that catalyzes gene activation, in this case, switching on the set of apoptosis genes that BCL6 normally keeps off.

"The idea is, can you turn a cancer dependency into a cancer-killing signal?" asked Nathanael Gray, Ph.D., co-senior author with Crabtree, the Krishnan-Shah Family Professor and a chemical and systems biology professor. "You take something that the cancer is addicted to for its survival and you flip the script and make that be the very thing that kills it."

This approach—switching something on that is off in cancer cells—stands in contrast to many other kinds of targeted cancer therapies that inhibit specific drivers of cancer, switching off something that is normally on.

"Since oncogenes were discovered, people have been trying to shut them down in cancer," said Roman Sarott, Ph.D., a postdoctoral scholar at Stanford Medicine and co-first author on the study. "Instead, we're trying to use them to turn signaling on that, we hope, will prove beneficial for treatment."

When the team tested the molecule in diffuse large cell B-cell lymphoma cells in the lab, they found that it indeed killed the cancer cells with high potency. They also tested the molecule in healthy mice and found no obvious toxic side effects, even though the molecule killed off a specific category of the animals' healthy B cells, a kind of immune cell, which also depends on BCL6.

They're now testing the compound in mice with diffuse large B-cell lymphoma to gauge its ability to kill cancer in a living animal.

Because the technique relies on the cells' natural supply of BCL6 and CDK9 proteins, it seems to be very specific for the lymphoma cells—the BCL6 protein is found only in this kind of lymphoma cell and in one specific kind of B cell. The researchers tested the molecule in 859 different kinds of cancer cells in the lab; the chimeric compound killed only diffuse large cell B-cell lymphoma cells.

And because BCL6 normally acts on 13 different apoptosis-promoting genes, the researchers hope their strategy will avoid the treatment resistance that seems so common in cancer. Cancer is often able to rapidly adapt to therapies that target only one of the disease's weak spots, and some of these therapies may stop cancer from growing without killing the cells entirely.

The research team hopes that by blasting the cells with multiple different cell death signals at once, the cancer will not be able to survive long enough to evolve resistance, although this idea remains to be tested.

"It's sort of cell death by committee," said Sai Gourisankar, Ph.D., a postdoctoral scholar and co-first author on the study. "And once a cancer cell is dead, that's a terminal state."

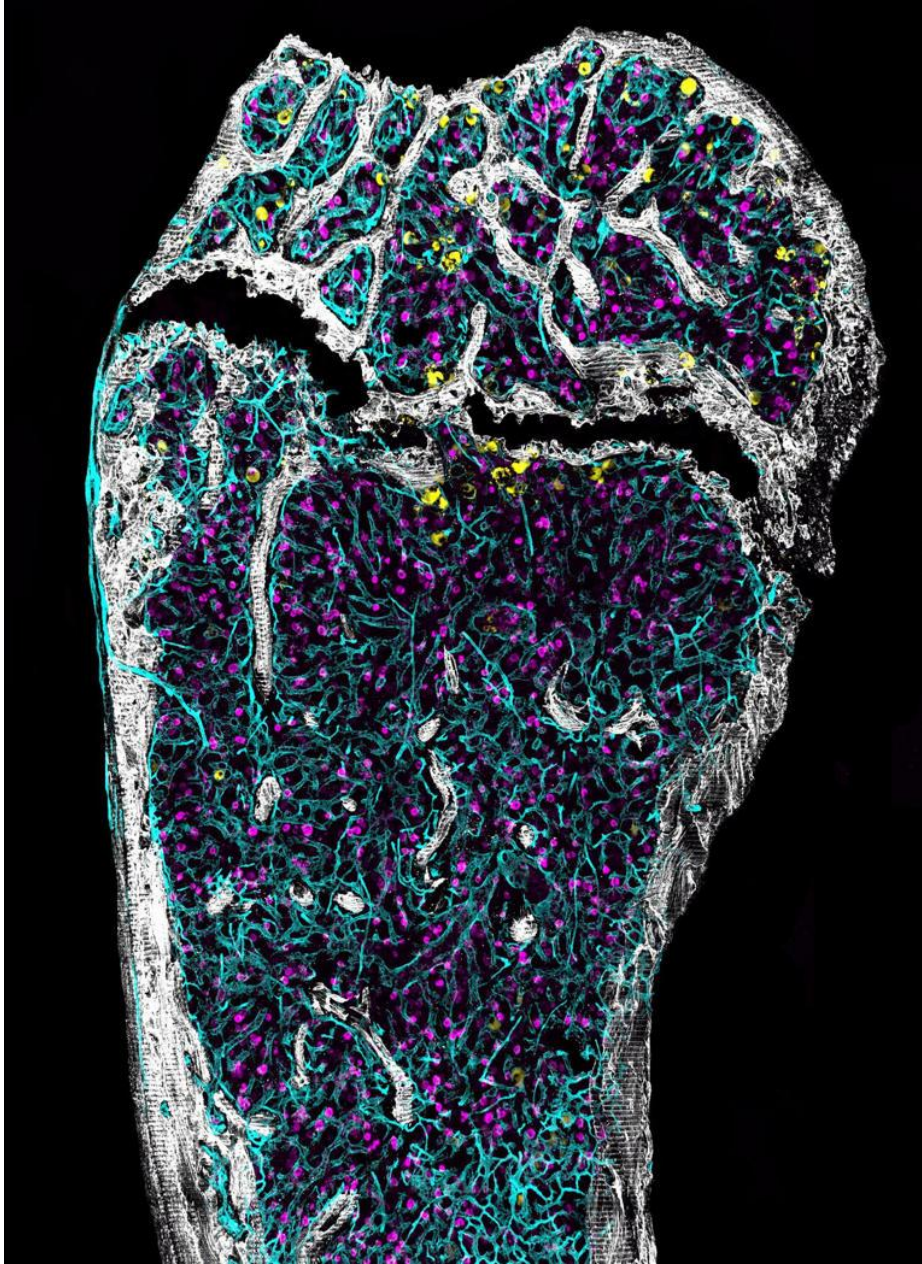
Crabtree and Gray, both members of the Stanford Cancer Institute, are co-founders of a biotech startup, Shenandoah Therapeutics, that aims to further test this molecule and a similar, previously developed molecule in hopes of gathering enough pre-clinical data to support launching clinical trials of the compounds.

They also plan to build similar molecules that could target other cancer-driving proteins, including the oncogene Ras, which is a driver of several different kinds of cancer.

More information: Roman C. Sarott et al, Relocalizing transcriptional kinases to activate apoptosis, *Science* (2024). DOI: [10.1126/science.adl5361](https://doi.org/10.1126/science.adl5361)

Provided by Stanford University Medical Center

Growth factors linked to stem cell aging in bone marrow study



The immunofluorescence image details the morphology and cell composition of a femur from a middle-aged mouse. Credit: The Jackson Laboratory© Provided by Medical Xpress

Our bone marrow—the fatty, jelly-like substance inside our bones—is an unseen powerhouse quietly producing 500 billion new blood cells every day. That process is driven by hematopoietic stem cells that generate all of the various

types of blood cells in our bodies and regenerating themselves to keep the entire assembly line of blood production operating smoothly.

As with any complex system, hematopoietic stem cells lose functionality as they age—and, in the process, contribute to the risk of serious diseases, including blood cancers. We know that the risk of developing aging-associated diseases is different among different individuals. Surprisingly, however, little is known about whether hematopoietic stem cells age differently between individuals.

"If you take a room full of 50-year-olds, some will be completely gray-haired, others will be salt-and-pepper, and a few will not have any gray hairs at all," said Jennifer Trowbridge, Dattels Family Endowed Chair and professor at the Jackson Laboratory. "Logically, you'd expect to see the same kind of variation in the function of hematopoietic stem cells—but until now, nobody has studied that directly."

For good reason: because these hematopoietic stem cells are so rare, researchers typically pool all of these stem cells together, studying them in aggregate. In a paper [published](#) in *Blood*, Trowbridge and colleagues studied hematopoietic stem cells at the single cell level in nine individual, genetically identical middle-aged mice—offering the first close look at how subtle changes in the bone marrow microenvironment ages hematopoietic stem cells across individual mice.

Trowbridge and team found that despite the mice being all the same age, the hematopoietic stem cells in the bone marrow of these individual mice aged differently. But that's not all. The team could predict the function of the hematopoietic stem cells based on the activity of two growth factors that are also present in humans.

The two growth factors—Kitl and Igf1—are produced by mesenchymal stromal cells (MSC) that surround the stem cells in the bone marrow microenvironment. By profiling the RNA transcriptome in these MSCs across individual mice, Trowbridge found that the decline of these growth factors correlated with age-associated molecular programs in hematopoietic stem cells.

"The amount of the growth factors that are being produced directly correlates to the declining function of the stem cells—and we found markedly more variation in hematopoietic stem cells than in other cells in the bone marrow," Trowbridge said. "This is really a snapshot of the aging process at work, at the cellular level."

In humans, who are genetically diverse and have varying lifestyles, variations in hematopoietic stem cell aging are likely to be even greater than in carefully controlled animal models, explained Trowbridge. While the current study didn't explore whether cellular aging of stem cells directly triggers adverse health outcomes, it's likely that such variations play a role in a wide range of health outcomes for both mice and humans.

More information: Kira A. Young et al, Variation in Mesenchymal KITL/SCF and IGF1 Expression at Middle Age Underlies Steady-State Hematopoietic Stem Cell Aging, *Blood Journal* (2024). DOI: [10.1182/blood.2024024275](https://doi.org/10.1182/blood.2024024275)

Provided by Jackson Laboratory



DentiCore

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We are proud to offer DentiCore, made with all-natural, non-GMO and gluten-free ingredients.



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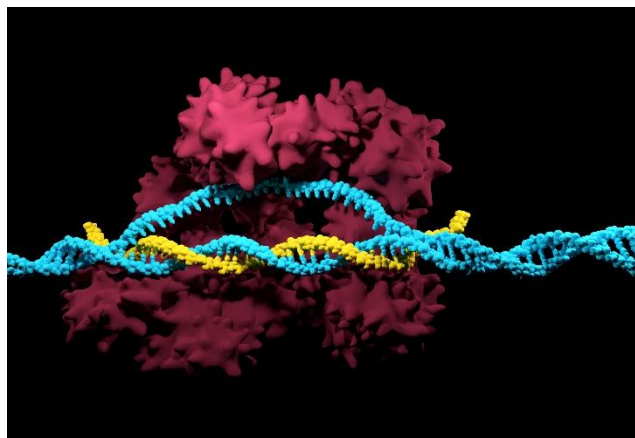
Target Genome Editing Service

Definition of Target Genome Editing

Gene Knockout

Gene Overexpression

Relevant ServicesFAQResources



With decades of experience, **Creative Biolabs** has established itself as a leader in the field of target genome editing, a transformative approach in genetic research that allows precise modifications to DNA sequences. Scientists in Creative Biolabs utilize the advanced CRISPR-based system as a genome-editing tool to knock out or silence specific genes, modulate gene expression, or upregulate genes to enhance protein

production. This cutting-edge system contributes to the targeted modification of gene expression, facilitating the screening of potential therapeutic targets, and enabling the study of how genomic alterations may impact organisms. The versatility of CRISPR-based system makes it ideal for various applications, from basic research to drug discovery and therapeutic development.

What is Target Genome Editing?

Target genome editing refers to the process of precisely altering specific sequences in an organism's DNA to understand gene function, model diseases, or develop new therapeutic strategies. Researchers can induce targeted mutations or edits in specific genes by employing a range of engineered nucleases such as the CRISPR-based system and transcription activator-like effector nuclease.

Gene Knockout

Gene knockout involves deleting or inactivating a specific gene to assess its function. This is typically achieved by inducing double-strand breaks (DSBs) in the DNA at the target site, followed by repair *via* non-homologous end joining (NHEJ), which often introduces insertions or deletions (indels) that disrupt the gene's coding sequence. This results in a complete loss of function in the targeted gene.

At Creative Biolabs, CRISPR technology has been fully integrated into our gene editing platform, offering a powerful tool for gene knockout studies. The CRISPR-based system is engineered to disrupt genes efficiently, facilitating the creation of isogenic cell lines and animal models. Our optimized protocols minimize off-target effects while maximizing editing efficiency.

Platforms Used for Gene Knockout

- **CRISPR-based System**

: The most widely used system for gene knockout, CRISPR-based system, utilizes a single-guide RNA (sgRNA) to direct the Cas9 enzyme to the specific DNA sequence. Once bound, Cas9 introduces DSBs at the target site, leading to gene disruption through NHEJ.

- **Transcription Activator-Like Effector Nucleases**

: Transcription activator-like effector nuclease employs customizable DNA-binding proteins fused with a nuclease (FokI) to introduce breaks at target sequences. Although highly specific, they are less user-friendly compared to CRISPR-based system.

The types of our genetic manipulation techniques including but not limited to:

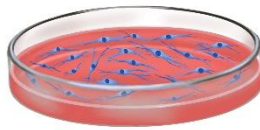
Platforms	Advantages
CRISPR-basedSystem	• Small guide RNA serves as the recruiter • Highly versatile and easy to design • High-efficiency andcost-effective • High Throughput Screening • Potentially adaptable for almost any gene disruption
Transcription Activator-like Effector Nuclease	• Highly specific and low off-target effects • Programmable with modular arrays • Each module recognizes a single base pair • Effective for targeted modifications with greater accuracy than CRISPR-based system

CRISPR Gene Knockout Workflow

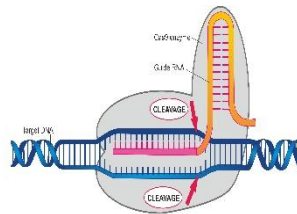
Our CRISPR-based gene knockout process follows a streamlined workflow, ensuring high precision and reproducibility in genomic alterations:



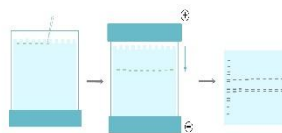
Design and Synthesis of gRNA



CRISPR-based System Delivery



Targeted Gene Editing



Screening and Validation



Functional Analysis

Gene Overexpression

Gene overexpression aims to increase the expression of a specific gene to study its effects on cellular processes. This approach is crucial for understanding the impact of gene dosage on phenotypes and can be used in disease models or biotechnological applications such as enhanced protein production.

Technologies Used for Gene Overexpression

- **CRISPRa (CRISPR Activation)**

: A modified version of the CRISPR system, CRISPRa uses a catalytically dead Cas9 (dCas9) fused with transcriptional activators to upregulate gene expression. This tool is highly versatile, as it can be targeted to any gene promoter.

- **Viral Vectors**

: Lentiviral or adeno-associated viral (AAV) vectors are often employed to introduce an exogenous gene or activate an endogenous gene. They integrate into the genome or exist as episomes in the host cell, leading to stable or transient gene overexpression.

- **Transcription Activator-Like Effectors (TALEs)**

Technology	Advantages	Conditions
CRISPRa (CRISPR Activation)	- Highly flexible, reversible control over gene expression.	- Suitable for precise, reversible gene activation function in model organisms.

Viral Vectors	- Efficient and stable long-term overexpression.	- Ideal for stable overexpression <i>in vivo</i> and therapeutic studies.
TALE Transcription Activators	- Highly specific with minimal off-target effects.	- Ideal for precise overexpression in complex in tightly regulated gene systems.

: Similar to transcription activator-like effector nuclease, TALEs can be modified to serve as transcriptional activators that enhance the expression of a target gene without introducing DSBs.

Applications for Gene Overexpression

Creative Biolabs offers gene overexpression services to support a wide range of scientific research, including the following applications:

Heterologous Expression	Overexpressing genes in different organisms allows for functional studies in alternative model organisms.
Drug Target Identification	Overexpressing genes help uncover target protein functions in drug interactions.
Pathway Analysis	Wild-type protein overexpression in mutants reveals drug-related pathways and compensatory mechanisms.
Epistasis Testing	Overexpression aids in epistasis tests, revealing genetic interactions and pathway hierarchies.
Mutation Reversion	Mutant protein overexpression restores functionality in deficient cells for functional studies.
Loss-of-Function Substitute	Overexpression generates mutations when loss-of-function studies are impractical.
Interaction Mapping	Overexpression outputs assist in mapping protein-protein interaction networks.
Modifier Screens	Overexpression identifies genetic modifiers that alter specific phenotypes.

As a leader in target genome editing, **Creative Biolabs** continues to push the boundaries of gene manipulation for research and therapeutic purposes. From gene knockout to overexpression, our platform leverages the latest technologies, including CRISPR-based system, to offer precision and reliability. Whether in disease modeling, drug discovery, or agricultural applications, Creative Biolabs ensures that every project benefits from our expertise and state-of-the-art methodologies. Please do not hesitate to contact us for more details.

Relevant Services

Gene Conditional Overexpression

Gene Conditional Overexpression enables controlled gene activation in response to specific stimuli, providing precise control over expression timing, location, and intensity. **Creative Biolabs** offers customized gene conditional overexpression services, employing tailored regulatory systems to provide dynamic, reproducible control over gene activity. This approach is especially beneficial for studying gene essentiality, function, and large-scale gene validation in pathogenic microorganisms.

Gene Silencing Creative Biolabs offers a comprehensive RNA interference (RNAi) service platform, enabling effective gene silencing for various research applications. Our services include:

- Custom design and synthesis of siRNA or shRNA.
- Construction of siRNA or shRNA expression vectors.
- siRNA or shRNA transfection services.
- Validation of gene silencing through mRNA quantification *via* RT-PCR and protein expression analysis *via* Western Blot.

FAQs

What is the difference between gene knockout and gene silencing?

Gene knockout completely disrupts a gene's function by introducing a mutation or deletion, while gene silencing reduces or inhibits gene expression without altering the underlying DNA sequence. Both methods are used to study gene function but operate through different mechanisms.

How does Creative Biolabs ensure high specificity in CRISPR-based system genome editing?

What are the advantages of CRISPR-based system over transcription activator-like effector nuclease for gene knockout?

What applications can genome editing be used for in drug discovery?

How does Creative Biolabs validate successful gene knockouts or overexpression experiments?

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‘Healer army’ cells tackle inflammation, promote healing in body

Scientists at the University of Cambridge have shattered conventional wisdom about regulatory T cells, uncovering a previously unknown capability that could revolutionize disease treatment.

The researchers conducted a study on mice where they directed regulatory T cells to a specific part of the body, increased their number, and activated them to turn off the immune response, a game-changer in disease treatment.

Current treatments for inflammatory disease in particular impact the entire body not just the affected areas. Thus they hit the body “like a sledgehammer,” according to senior author Professor Adrian Liston.

However, the discovery that regulatory T cells, a group of white blood cells operate as an army or group and constantly move throughout the body contradicts previous thought that T cells only existed locally.

Researchers from Cambridge successfully tapped into this mechanism with a drug that sends this healing army only to the affected areas of the body which will lead to focused treatment strategies.

“We’ve uncovered new rules of the immune system,” Liston said. “This ‘unified healer army’ can do everything – repair injured muscle, make your fat cells respond better to insulin, regrow hair follicles.”

The implications of this discovery go beyond treating diseases, hinting at potential breakthroughs in hair loss treatments.

“It’s got the potential to be used for almost everything,” he added.

What are T cells?

Professor Liston told *Interesting Engineering* that there are approximately a 100 types of immune cells. He and his team decided to target a subset of T cells called regulatory T cells because they are an “oddity in the immune system.”

T cells or Tregs regulate the immune system's response; how it reacts to foreign agents or what it deems to be a threat. They play a significant role in autoimmune diseases which are defined as an immune system malfunction. It begins attacking healthy cells.

"Different immune cell types specialize in promoting different types of inflammation that are good at getting rid of different types of infections," Liston explained. "But regulatory T cells are different, because they are actually wired for the opposite effect — they shut down the immune response."

So in diseases for which inflammation is a feature, and furthermore, inflammation has been called the [precursor](#) for all diseases even, this novel drug could make unprecedented headway in the treatment of disease and [inflammation](#).

Drugs help the body in combating diseases and easing symptoms, yet researchers have unearthed a natural healing mechanism that has largely been overlooked until now, even harnessing it to address symptoms effectively.

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Let's optimize healing by turning off the immune system

In the case of COVID, for example, the symptoms that present themselves arise from the immune system's response to the virus rather than the virus itself. This new study suggests that the immune system response can be shut down in the lungs while the rest of the body maintains a normal state.

Achieving a robust immune response is crucial for overall health. However, during illness, it can inadvertently increase susceptibility to further infections. Now, the

body can fight disease more efficiently by capitalizing on how these [cells function](#). Even increase their numbers.

Dosages could be increased on the one hand because the drug isn't impacting the whole organism leading to faster results as these T cells turn out to be everywhere and ready for action.

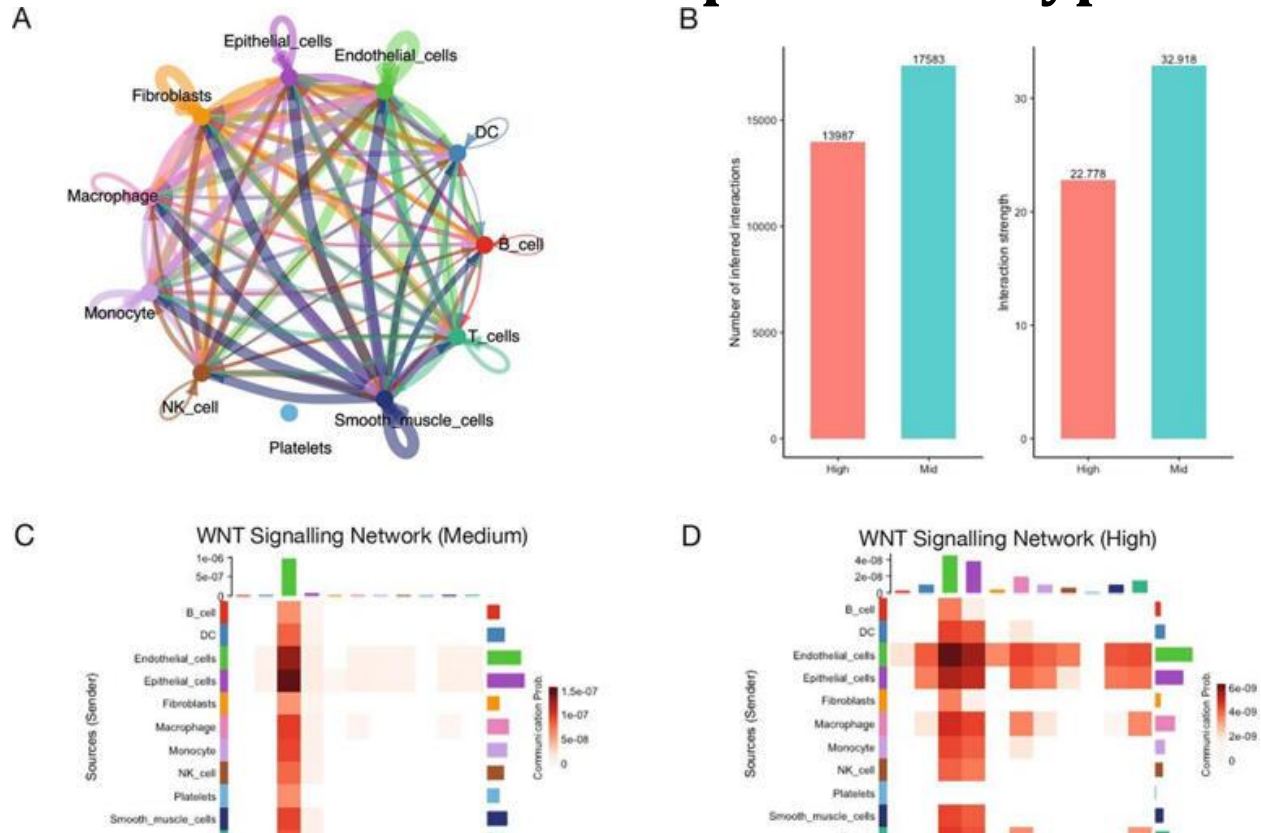
Professor Liston said our fight against so many diseases stands to benefit from shutting down the immune system and triggering a repair response as the body cannot heal optimally in a stressful state. "Rest and repair" is the healing state.

We want the antibodies to fight off the infections, but if the body can maintain lower levels of stress the results would be optimized. And these T cells specifically instruct the body to repair itself after the immune system is done.

"It's difficult to think of a disease, injury or infection that doesn't involve some kind of immune response, and our finding really changes the way we could control this response," Liston [said](#) in the press release.

The study, 'The tissue-resident regulatory T cell pool is shaped by transient multi-tissue migration and a conserved residency program,' was published in the journal [Immunity](#).

Scientists reveal genetic drivers of metastasis across multiple cancer types



Identification of WNT signaling as a key driver of communication networks in metastatic cells. Credit: Molecular Cancer (2025). DOI: 10.1186/s12943-024-02182-w

Cancer metastasis—the spread of cancer to other organs—is the leading cause of death among cancer patients. Researchers have now uncovered a "genetic signature" of 177 genes shared across multiple cancer types that drives this deadly process.

"Through our research, we have uncovered critical pan-cancer drivers of metastasis that not only enhance our understanding of cancer progression but also pave the way for innovative therapeutic strategies," says Professor Vijay Tiwari from the Department of Molecular Medicine, University of Southern Denmark, who led the study.

Among the findings are two key genes:

- SP1, which accelerates metastasis.

- KLF5, which helps suppress it.

The discovery of these shared genetic drivers—applicable to cancers from the lungs to the liver—challenges the long-held belief that metastasis mechanisms vary greatly between cancer types.

This so-called "pan-cancer" perspective offers a powerful opportunity to develop treatments effective for many cancer patients, regardless of their specific diagnosis.

New hope for earlier diagnosis and treatment

One of the most promising aspects of the study is its ability to predict a patient's risk of metastasis. By analyzing the 177-gene signature in a tumor, the researchers could identify whether the cancer is likely to spread and intervene earlier.

"This could save lives, particularly for patients whose cancers are detected before they metastasize to critical organs. In these cases, new treatments—such as repurposed drugs identified in the study—could disrupt the metastasis process before it becomes life-threatening," Tiwari explains.

For example, the research highlights Vorinostat, an existing FDA-approved drug, as a potential therapy to block metastasis.

"Repurposing approved drugs could make these treatments available to patients much sooner than if entirely new medications were developed."

Ryan Lusby from Queens University Belfast is the study's first author and he emphasizes the potential impact. "It is remarkable to uncover common principles of metastasis across different cancers and then use this information to identify biomarkers of metastasis and develop new drugs that can be applied to a wide range of cancers."

Why this matters to cancer patients

This discovery has far-reaching implications for cancer care

- Broader treatment options: Targeting shared genetic drivers could lead to therapies effective across multiple cancer types. Faster drug access: Repurposing existing medications could shorten the time it takes for new treatments to reach patients.
- Personalized risk assessment: Using the gene signature, doctors could tailor treatments to a patient's specific risk of metastasis.

The findings also set the stage for a shift in how cancer is understood. Rather than focusing solely on the type of cancer, treatments may increasingly target shared genetic vulnerabilities, benefiting more patients than ever before.

Dr. Engin Demirdizen, a co-author of the study, highlights an intriguing finding, "As metastasis progresses, tumor cells and the microenvironment engage in increasingly dynamic communication through WNT signaling, a process driven by the transcription factor SP1."

As Dr. Mohammed Inayatullah, a co-author of the study, notes, "We are thrilled to showcase how genomics has empowered us to repurpose existing drugs for cancer therapy."

A breakthrough for families and society

For patients and their families, cancer metastasis often represents a turning point—a moment when the disease becomes far harder to treat and more devastating in its impact.

By understanding and targeting the genetic triggers behind metastasis, this research offers a lifeline: longer, healthier lives and a reduction in the emotional and financial burdens of advanced cancer.

More information: Ryan Lusby et al, Pan-cancer drivers of metastasis, *Molecular Cancer* (2025). DOI: [10.1186/s12943-024-02182-w](https://doi.org/10.1186/s12943-024-02182-w)

Provided by University of Southern Denmark

Autoimmune conditions linked to reactivated X chromosome genes



In female mammals, genes on one copy of the X chromosome are usually inactivated vchal/Shutterstock© Provided by New Scientist

Female mammals have a higher risk of developing autoimmune conditions such as lupus because extra copies of genes that are supposed to be permanently turned off get reactivated as they grow older, a study of mice suggests.

The findings are likely to apply to all mammals, including humans, says [Céline Morey](#) at the Paris Cité University in France, and could explain why older women aHow to tell if your immune system is weak or strong

Whereas male mammals usually have one X and one Y chromosome, most female mammals [have two copies of the X chromosome](#). If all the genes on both X chromosomes were active, females would get a double dose of the gene products compared with males.

Instead, soon after embryos start developing, most of the genes on one of the two copies of the X chromosome get turned off, a phenomenon known as X inactivation.

Morey and her colleagues set out to study this process by creating mice that lack one of the genes involved in X inactivation. This deletion doesn't prevent X inactivation entirely – that would be fatal – but it does diminish its strength.

At first, the mice appeared normal. “We had to wait for the mice to grow old to finally see something wrong, because otherwise they were happy,” says Morey.

In older age, the mice developed symptoms resembling those of lupus, such as an enlarged spleen.

The team found that several key genes on the inactivated X chromosome in their immune cells were becoming reactivated as the mice got older. These genes regulate the immune system and one of them, called *TLR7*, is already [known to affect the risk of people developing lupus](#).

It has been suspected that higher doses of genes such as *TLR7* make people with two X chromosomes [more resistant to many infectious diseases](#) but also [more prone to autoimmune conditions](#). The new study provides the strongest evidence so far that higher doses could come about because of the failure to maintain X inactivation.

Morey hopes the findings could lead to better treatments for autoimmune conditions such as rheumatoid arthritis, which are more common in older age and in women compared with men.

“If we identify the genes that are involved, we could maybe design some treatments that are targeting specific key factors,” says Morey.

Journal reference:

Science Advances DOI: [10.1126/sciadv.adn6537](https://doi.org/10.1126/sciadv.adn6537)

Scientists May Have Found Traces of an Extinct Genetic Code That Came Before DNA

UNIVERSITY OF ARIZONA FEBRUARY 2, 2025



Conventional wisdom about the evolution of the universal genetic code, used by nearly all living organisms to translate genetic information into proteins, is likely in need of revision. Credit: SciTechDaily.com

Scientists have long believed they understood how life's genetic code evolved, but new research upends that assumption.

By analyzing ancient protein sequences, researchers discovered that early life preferred smaller amino acids and incorporated sulfur-based compounds much earlier than previously thought. This challenges long-standing experiments and opens the door to the possibility that extinct genetic codes existed before ours.

Cracking the Code of Life's Origins

Despite awe-inspiring diversity, nearly all life on Earth — from tiny bacteria to massive blue whales — shares the same genetic code. But exactly how and when this code emerged remains a topic of scientific debate.

Sawsan Wehbi, a doctoral student in the Genetics Graduate Interdisciplinary Program at the University of Arizona, has uncovered strong evidence that challenges the widely accepted view of genetic code evolution. In a study published in *PNAS*, Wehbi, and her team suggest that the order in which amino acids — the fundamental building blocks of the code — were incorporated into the genetic code does not align with the long-standing “consensus” theory. Their findings call for a reevaluation of how life’s universal blueprint came to be.

The Surprisingly Strategic Evolution of the Code

“The genetic code is this amazing thing in which a string of DNA or RNA containing sequences of four nucleotides is translated into protein sequences using 20 different amino acids,” said Joanna Masel, the paper’s senior author and a professor of ecology and evolutionary biology at the U of A. “It’s a mind-bogglingly complicated process, and our code is surprisingly good. It’s nearly optimal for a whole bunch of things, and it must have evolved in stages.”

The study revealed that early life preferred smaller amino acid molecules over larger and more complex ones, which were added later, while amino acids that bind to metals joined in much earlier than previously thought. Finally, the team discovered that today’s genetic code likely came after other codes that have since gone extinct.

Reevaluating Classic Experiments

The authors argue that the current understanding of how the code evolved is flawed because it relies on misleading laboratory experiments rather than evolutionary evidence. For example, one of the cornerstones of conventional views of genetic code evolution rests on the famous Urey-Miller experiment of 1952, which attempted to simulate the conditions on early Earth that likely witnessed the origin of life.

While valuable in demonstrating that nonliving matter could give rise to life’s building blocks, including amino acids, through simple chemical reactions, the experiment’s implications have been called into question. For example, it did not yield any amino acids containing sulfur, despite the element being abundant on early Earth. As a result, sulfuric amino acids are believed to have joined the code much later. However, the result is hardly surprising, considering that sulfur was omitted from the experiment’s ingredients.

Sulfur and the Search for Alien Life

According to co-author Dante Lauretta, Regents Professor of Planetary Science and Cosmochemistry at the U of A Lunar and Planetary Laboratory, early life's sulfur-rich nature offers insights for astrobiology, particularly in understanding the potential habitability and biosignatures of extraterrestrial environments.

"On worlds like Mars, Enceladus, and Europa, where sulfur compounds are prevalent, this could inform our search for life by highlighting analogous biogeochemical cycles or microbial metabolisms," he said. "Such insights might refine what we look for in biosignatures, aiding the detection of lifeforms that thrive in sulfur-rich or analogous chemistries beyond Earth."

A New Approach to Tracing Evolution

The team used a new method to analyze sequences of amino across the tree of life, all the way back to the last universal common ancestor, or LUCA, a hypothesized population of organisms that lived around 4 billion years ago and represents the shared ancestor of all life on Earth today. Unlike previous studies, which used full-length protein sequences, Wehbi and her group focused on protein domains, shorter stretches of amino acids.

"If you think about the protein being a car, a domain is like a wheel," Wehbi said. "It's a part that can be used in many different cars, and wheels have been around much longer than cars." To get a handle on when a specific amino acid likely was recruited into the genetic code, the researchers used statistical data analysis tools to compare the enrichment of each individual amino acid in protein sequences dating back to LUCA, and even farther back in time. An amino acid that shows up preferentially in ancient sequences was likely incorporated early on. Conversely, LUCA's sequences are depleted for amino acids that were recruited later but became available by the time less ancient protein sequences emerged.

Discovering the Genetic Echoes of Extinct Codes

The team identified more than 400 families of sequences dating back to LUCA. More than 100 of them originated even earlier and had already diversified prior to LUCA. These turned out to contain more amino acids with aromatic ring structures, like tryptophan and tyrosine, despite these amino acids being late additions to our code. "This gives hints about other genetic codes that came before ours, and which have since disappeared in the abyss of geologic time," Masel said. "Early life seems to have liked rings."

Reference: "Order of amino acid recruitment into the genetic code resolved by last universal common ancestor's protein domains" by Sawsan Wehbi, Andrew Wheeler, Benoit Morel, Nandini Manepalli, Bui Quang Minh, Dante S. Lauretta and Joanna Masel, 12 December 2024, *Proceedings of the National Academy of Sciences*.

DOI: [10.1073/pnas.2410311121](https://doi.org/10.1073/pnas.2410311121)

With generative AI, chemists quickly calculate 3D genomic structures

by [Massachusetts Institute of Technology](#)

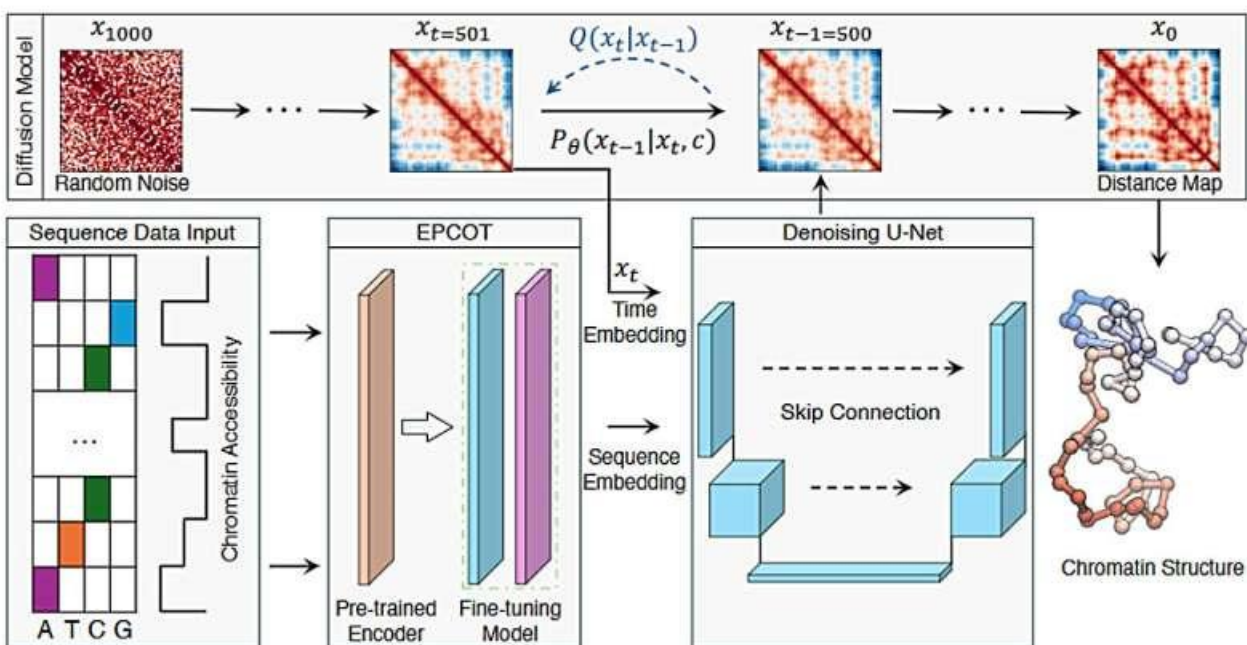


Illustration of the procedure followed by ChromoGen when making predictions of chromatin organization using sequence data. Credit: Greg Schuette et al

Every cell in your body contains the same genetic sequence, yet each cell expresses only a subset of those genes. These cell-specific gene expression patterns, which ensure that a brain cell is different from a skin cell, are partly determined by the three-dimensional structure of the genetic material, which controls the accessibility of each gene.

MIT chemists have now come up with a new way to determine those 3D genome structures, using generative artificial intelligence. Their technique can predict thousands of structures in just minutes, making it much speedier than existing experimental methods for analyzing the structures.

Using this technique, researchers could more easily study how the 3D organization of the genome affects individual cells' gene expression patterns and functions.

The findings are [published](#) in the journal *Science Advances*.

"Our goal was to try to predict the three-dimensional genome structure from the underlying DNA sequence," says Bin Zhang, an associate professor of chemistry and the senior author of the study. "Now that we can do that, which puts this technique on par with the cutting-edge experimental techniques, it can really open up a lot of interesting opportunities."

MIT graduate students Greg Schuette and Zhuohan Lao are the lead authors of the paper.

From sequence to structure

Inside the [cell nucleus](#), DNA and proteins form a complex called chromatin, which has several levels of organization, allowing cells to cram 2 meters of DNA into a nucleus that is only one-hundredth of a millimeter in diameter. Long strands of DNA wind around proteins called histones, giving rise to a structure somewhat like beads on a string.

Chemical tags known as epigenetic modifications can be attached to DNA at specific locations, and these tags, which vary by cell type, affect the folding of the chromatin and the accessibility of nearby genes. These differences in chromatin conformation help determine which genes are expressed in different cell types, or at different times within a given cell.

Over the past 20 years, scientists have developed experimental techniques for determining chromatin structures. One widely used technique, known as Hi-C, works by linking together neighboring DNA strands in the cell's nucleus. Researchers can then determine which segments are located near each other by shredding the DNA into many tiny pieces and sequencing it.

This method can be used on large populations of cells to calculate an average structure for a section of chromatin, or on [single cells](#) to determine structures within that specific cell. However, Hi-C and similar techniques are labor-intensive, and it can take about a week to generate data from one cell.

To overcome those limitations, Zhang and his students developed a model that takes advantage of recent advances in generative AI to create a fast, accurate way to predict chromatin structures in single cells. The AI model that they designed can quickly analyze DNA sequences and predict the chromatin structures that those sequences might produce in a cell.

"Deep learning is really good at pattern recognition," Zhang says. "It allows us to analyze very long DNA segments, thousands of base pairs, and figure out what is the important information encoded in those DNA base pairs."

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ChromoGen, the model that the researchers created, has two components. The first component, a [deep learning](#) model taught to "read" the genome, analyzes the information encoded in the underlying DNA sequence and chromatin accessibility data, the latter of which is widely available and cell type-specific.

The second component is a generative AI model that predicts physically accurate chromatin conformations, having been trained on more than 11 million chromatin conformations.

These data were generated from experiments using Dip-C (a variant of Hi-C) on 16 cells from a line of human B lymphocytes.

When integrated, the first component informs the generative model about how the cell type-specific environment influences the formation of different chromatin structures, and this scheme effectively captures sequence-structure relationships. For each sequence, the researchers use their model to generate many possible structures. That's because DNA is a very disordered molecule, so a single DNA sequence can give rise to many different possible conformations.

"A major complicating factor of predicting the structure of the genome is that there isn't a single solution that we're aiming for. There's a distribution of structures, no matter what portion of the genome you're looking at. Predicting that very complicated, high-dimensional statistical distribution is something that is incredibly challenging to do," Schuette says.

Rapid analysis

Once trained, the model can generate predictions on a much faster timescale than Hi-C or other experimental techniques.

"Whereas you might spend six months running experiments to get a few dozen structures in a given cell type, you can generate a thousand structures in a particular region with our model in 20 minutes on just one GPU," Schuette says.

After training their model, the researchers used it to generate structure predictions for more than 2,000 DNA sequences, then compared them to the experimentally determined structures for those sequences. They found that the structures generated by the model were the same or very similar to those seen in the experimental data.

"We typically look at hundreds or thousands of conformations for each sequence, and that gives you a reasonable representation of the diversity of the structures that a particular region can have," Zhang says. "If you repeat your experiment multiple times, in different cells, you will very likely end up with a very different conformation. That's what our model is trying to predict."

The researchers also found that the model could make accurate predictions for data from cell types other than the one it was trained on. This suggests that the model could be useful for analyzing how chromatin structures differ between cell types, and how those differences affect their function. The model could also be used to explore different chromatin states that can exist within a single cell, and how those changes affect gene expression.

Another possible application would be to explore how mutations in a particular DNA sequence change the [chromatin](#) conformation, which could shed light on how such mutations may cause disease.

"There are a lot of interesting questions that I think we can address with this type of model," Zhang says.

The researchers have made all of their data and the model [available](#) to others who wish to use it.

More information: Greg Schuette et al, ChromoGen: Diffusion model predicts single-cell chromatin conformations, *Science Advances* (2025). DOI: [10.1126/sciadv.adr8265](https://doi.org/10.1126/sciadv.adr8265)

Journal information: [Science Advances](#)

Provided by [Massachusetts Institute of Technology](#)

JANUARY 30, 2025

Next-generation gene-editing tool offers enhanced capabilities for cancer and medical research

by [La Trobe University](#)



Credit: Unsplash/CC0 Public Domain

Australian cancer researchers are the first to establish a next-generation gene-editing tool for modeling and interrogating human disease.

A novel pre-clinical model expressing an enhanced version of a new genome-engineering enzyme called Cas12a was generated by researchers at the Olivia Newton-John Cancer Research Institute (ONJCRI), WEHI and Genentech, a member of the Roche Group.

Cas enzymes are required to cut specific sections of DNA or RNA during CRISPR experiments. CRISPR is a revolutionary gene-editing tool widely used for [cancer research](#), which is currently in the early stages of clinical application in patients.

The researchers were also able to identify genes that led to accelerated lymphoma growth in the pre-clinical model by using unique Cas12a-compatible mouse whole-genome CRISPR "libraries."

This new research contributes to a better understanding of the limitations of CRISPR technology, with the ultimate goal of making it a viable option for cancer treatment in patients.

Over the past decade, the most widely used Cas enzyme, Cas9, has led to many important discoveries in [medical research](#).

Postdoctoral Researcher at the ONJCRI and WEHI Dr. Eddie La Marca, who is a co-lead author on the paper published in *Nature Communications*, said, "This is the first time Cas12a has been used in pre-clinical models, which will greatly advance our genome engineering capabilities. In contrast to Cas9, Cas12a can delete multiple genes at the same time with extremely high efficiency."

The researchers also used Cas12a in combination with other genome engineering tools, allowing for "multiplexed" gene manipulation. Co-lead authors Ms. Wei Jin and Dr. Yexuan Deng (ONJCRI and WEHI) elaborated, "We have also crossed our Cas12a [animal model](#) with a model that expresses an altered version of Cas9, allowing us to both delete and activate different genes simultaneously. This will allow researchers to use this tool to model and interrogate complex genetic disorders."

Professor Marco Herold, Chief Executive Officer of the ONJCRI and Head of the La Trobe University School of Cancer Medicine, said, "We are certain that this work will encourage other research teams to use this Cas12a pre-clinical model which, in combination with the screening libraries, are a powerful new suite of gene-editing tools to improve our understanding of the mechanisms behind many different cancers."

Professor Herold's team at the ONJCRI are also focusing their efforts on developing methods to administer CRISPR-based therapies to patients, highlighting the growing importance of gene-editing tools such as Cas12a.

Professor Herold said, "This Cas12a pre-clinical model will also be instrumental to advancing our understanding of how CRISPR tools could be translated to clinical usage."

More information: Australian researchers enhance next-generation gene-editing technologies for cancer and medical research, *Nature Communications* (2025). DOI: [10.1038/s41467-025-56282-2](https://doi.org/10.1038/s41467-025-56282-2)

Journal information: [Nature Communications](#)
Provided by [La Trobe University](#)

JANUARY 30, 2025

Complex engineering of human cell lines reveals genome's unexpected resilience to structural changes

by [Wellcome Trust Sanger Institute](#)

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The most complex engineering of human cell lines ever has been achieved by scientists, revealing that our genomes are more resilient to significant structural changes than was previously thought.

Researchers from the Wellcome Sanger Institute, Imperial College London, Harvard University in the US and their collaborators used CRISPR prime editing to create multiple versions of human genomes in cell lines, each with different structural changes. Using genome sequencing, they were able to analyze the genetic effects of these structural variations on [cell survival](#).

The research, [published in Science](#), shows that as long as essential genes remain intact, our genomes can tolerate significant structural changes, including large deletions of the genetic code. The work opens the door to studying and predicting the role of structural variation in disease.

Structural variation is a change in the structure of an organism's genome, such as deletions, duplications and inversions of the genetic sequence. These structural changes to the genome can be significant, sometimes affecting hundreds to many thousands of nucleotides—the basic building blocks of DNA and RNA.

Structural variants are associated with developmental diseases and cancer. However, our ability to study the effects of structural variation in the genomes of mammals, and the role they play in disease, has been difficult due to the inability to engineer these genetic changes.

To overcome this challenge, Sanger Institute researchers and their collaborators set out to develop new approaches for creating and studying structural variation.

In a new study, the team used a combination of CRISPR prime editing and [human cell](#) lines—groups of human cells in a dish—to generate thousands of [structural variants](#) in human genomes within a single experiment.

To do this, researchers used prime editing to insert a recognition sequence into the genomes of the human cell lines to target with recombinase—an enzyme that enabled the team to 'shuffle' the genome.

By inserting these recombinase handles into repetitive sequences, which are hundreds and thousands of identical sequences in the genome, with a single prime editor they were able to integrate up to almost 1,700 recombinase recognition sites into each cell line.

This resulted in more than 100 random large-scale genetic structural changes per cell. This is the first time that it's been possible to 'shuffle' a mammalian genome, especially at this scale.

The team then studied the impacts of the structural variation on the human cell lines. Using genomic sequencing, the team was able to take 'snapshots' of the human cells and their 'shuffled' genomes over the course of a few weeks, watching which cells survived and which died.

As expected, they found that when structural variation deleted essential genes, this was heavily selected against and the cells died. However, they found that groups of cells with large-scale deletions in the genomes that avoided essential genes survived.

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The team also conducted RNA sequencing of the human cell lines, which measures gene activity, known as gene expression. This revealed that large-scale deletions of the genetic code, especially in non-coding regions, did not seem to impact the gene expression of the rest of the cell.

The researchers suggest that human genomes are extremely tolerant of structural variation, including variants that change the position of hundreds of genes, as long as essential genes are not deleted⁴. Plus, they query whether much of the non-coding DNA in human genomes is dispensable, but further research that engineers additional deletions in more cell lines is needed.

In a related paper, also published in [published in Science](#), researchers from the University of Washington had a similar goal of creating structural variants at large scale and studying their effects on the human genome.

This team used a different approach, adding recombinase sites to transposons—mobile genetic elements—that randomly integrated in the genomes of human cell lines and mouse embryonic stem cells.

Using their method, they demonstrated that the effects of the induced structural variants can be read out using single-cell RNA sequencing. This advance paves the way for large screens of structural variant impact, potentially improving the classification of structural variants found in human genomes as benign or clinically significant.

Both studies came to similar conclusions that human genomes are surprisingly tolerant to some substantial structural changes, although the full extent of this tolerance remains to be explored in future studies enabled by these technologies.

Overall, this research presents the most engineered human cell lines to date. For the first time, researchers are able to create structural variants in human genomes, at large scales in a single experiment, and analyze the many random versions of our genomes.

This work will increase our understanding of the role of structure variants in disease, which may eventually lead to predictions being made around how damaging structural variants could be in an individual. This research also helps narrow the range of the genome for exploring structural variation that leads to disease, especially if non-coding DNA can be discounted.

Plus, with this new tool, scientists can generate new, streamlined cell lines with evolved properties, such as being optimized for growth, studying drug resistance, or bioengineered to create medicines.

"If the genome was a book, you could think of a single nucleotide variant as a typo, whereas a structural variant is like ripping out a whole page. These structural variants are known to play roles in developmental diseases and cancer, but it has been difficult to study them experimentally," says Dr. Jonas Koeppel, co-first author previously at the Wellcome Sanger Institute, and now at the University of Washington.

"Through creative and collaborative thinking, we've been able to do complex engineering in human cells that no-one has done before. By shuffling the genomes of human [cell lines](#) at large scale, we've shown that our genomes are flexible enough to tolerate significant structural changes. These tools will help focus future studies into structural variations and their roles in disease."

"Our studies were only made possible because the right mix of ingredients came together at the right time: the scale of [genome sequencing](#), cutting-edge genome engineering, and the use of recombinases. And importantly, the open and collaborative nature of our science across global borders. Our teams independently had similar ideas and came together to make these pioneering studies happen," says Dr. Raphael Ferreira, co-first author and a postdoctoral researcher in the Church Lab at Harvard Medical School.

"Ten years ago, people thought it would take decades of work and hundreds of millions of dollars to engineer a rearrangeable human genome that scientists could use to study

genome structure, but this work shows a way to make this possible right now. It's exciting to think about what new biology we can learn from rearrangeable genomes and where this might go next," says Professor Tom Ellis, an author of the study and Associate Faculty at the Wellcome Sanger Institute, based at the Department of Bioengineering at Imperial College London.

"These studies represent a step change in the parallel creation and evaluation of structural variation in human genomes. The tools to create a single variant at a time had been available for decades, but we have demonstrated that interrogating variants and making randomized human genomes at scale is now doable. This gives new entry points both into the study of disease-associated variation, as well as opportunities for bioengineering," says Dr. Leopold Parts, co-lead author at the Wellcome Sanger Institute.

More information: Jonas Koeppel et al, Randomizing the human genome by engineering recombination between repeat elements, *Science* (2025). DOI: [10.1126/science.ad03979](https://doi.org/10.1126/science.ad03979). www.science.org/doi/10.1126/science.ad03979

Science (2025). DOI: 10.1126.science.ad05978

Journal information: [Science](#)

Provided by [Wellcome Trust Sanger Institute](#)

JANUARY 28, 2025

Mouse with two fathers survives to adulthood, marking scientific milestone

by [Cell Press](#)

Credit: Pixabay/CC0 Public Domain

A team of stem cell scientists have successfully used embryonic stem cell engineering to create a bi-paternal mouse—a mouse with two male parents—that lived until adulthood.

Their results, [published](#) on January 28, 2025, in *Cell Stem Cell*, describe how targeting a particular set of genes involved in reproduction allowed the researchers to overcome previously insurmountable challenges in unisexual reproduction in mammals.

Scientists have attempted to create bi-paternal mice before, but the embryos developed only to a certain point and then stopped growing. Here, the investigators, led by corresponding author Wei Li of the Chinese Academy of Sciences (CAS) in Beijing, focused on targeting imprinting genes, which regulate [gene expression](#) in a number of ways.

"This work will help to address a number of limitations in stem cell and regenerative medicine research," says Li.

"The unique characteristics of imprinting genes have led scientists to believe that they are a fundamental barrier to unisexual reproduction in mammals," says co-corresponding author Qi Zhou, also of CAS.

"Even when constructing bi-maternal or bi-paternal embryos artificially, they fail to develop properly, and they stall at some point during development due to these genes."

Earlier attempts to make a bi-paternal mouse used ovarian organoids to derive oocytes from male pluripotent stem cells; those oocytes were then fertilized with sperm from another male. However, when the [homologous chromosomes](#)—the chromosomes that divide during meiosis to create oocytes and sperm—originated from the same sex, imprinting abnormalities arose, leading to severe developmental defects.

In this study, the researchers modified 20 key imprinting genes individually using a number of different techniques, including frameshift mutations, gene deletions, and regulatory region edits. They found that not only did these edits allow the creation of bi-paternal animals that sometimes lived to adulthood, but they also led to stem cells with more stable pluripotency.

"These findings provide strong evidence that imprinting abnormalities are the main barrier to mammalian unisexual reproduction," says co-corresponding author Guan-Zheng Luo of Sun Yat-sen University in Guangzhou.

"This approach can significantly improve the developmental outcomes of embryonic stem cells and cloned animals, paving a promising path for the advancement of regenerative medicine."

The researchers note several limitations that their work still needs to address. For one thing, only 11.8% of the viable embryos were capable of developing until birth, and not all the pups that were born lived to adulthood due to developmental defects. Most of those that did live to adulthood had altered growth and a shortened lifespan. Also, the mice that lived to adulthood were sterile, although they did exhibit increased cloning efficiency.

"Further modifications to the imprinting genes could potentially facilitate the generation of healthy bi-paternal mice capable of producing viable gametes and lead to new therapeutic strategies for imprinting-related diseases," says co-corresponding author Zhi-Kun Li of CAS.

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The team will continue to study how modifying imprinting genes may lead to embryos with higher developmental potential. They also aim to extend the experimental approaches developed in mice to larger animals, including monkeys. However, they note that this will require considerable time and effort because the imprinting gene combinations in monkeys differ significantly from those in mice.

Whether this technology will ultimately be applied towards solving [human disease](#) remains unclear. The International Society for Stem Cell Research's ethical guidelines for [stem cell research](#) does not allow heritable genome editing for reproductive purposes nor the use of human stem cell-derived gametes for reproduction because they are deemed as currently unsafe.

More information: Adult bi-paternal offspring generated through direct modification of imprinted genes in mammals, *Cell Stem Cell* (2025). DOI:

[10.1016/j.stem.2025.01.005](https://doi.org/10.1016/j.stem.2025.01.005). [www.cell.com/cell-stem-cell/fulltext/S1934-5909\(25\)00005-0](https://www.cell.com/cell-stem-cell/fulltext/S1934-5909(25)00005-0)

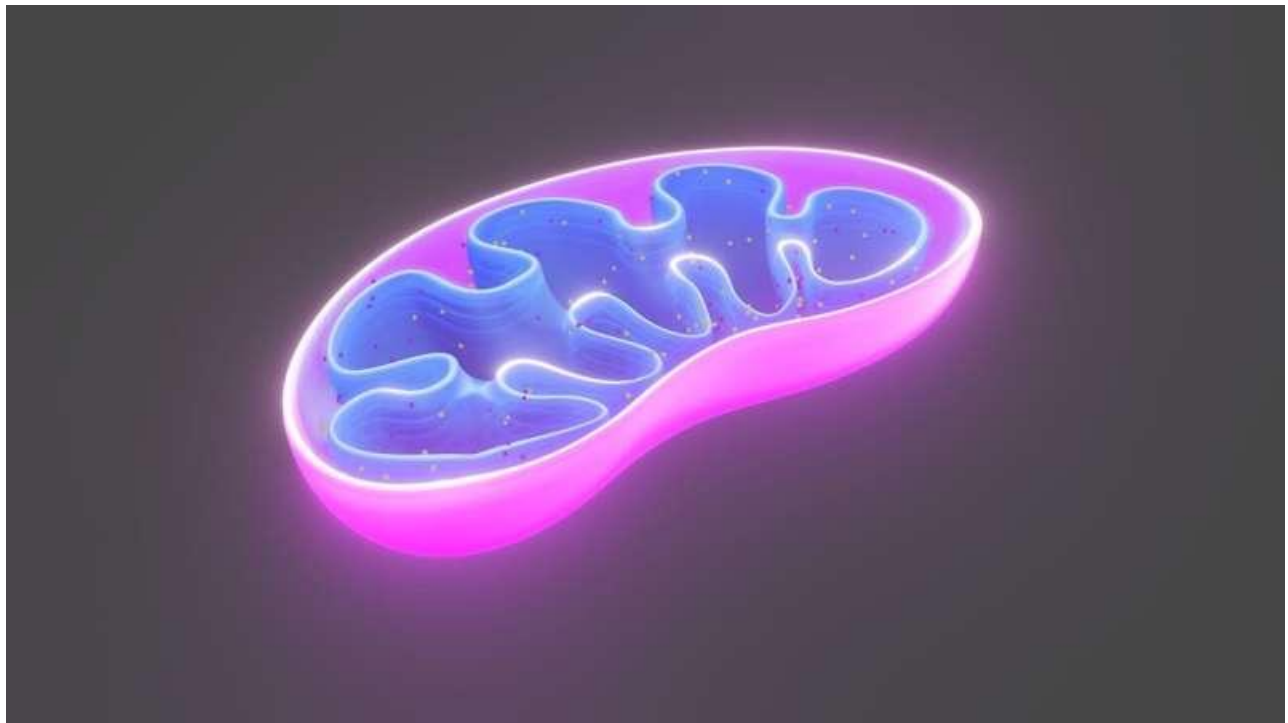
Journal information: [Cell Stem Cell](#)

Provided by [Cell Press](#)

JANUARY 23, 2025

Mitochondria may be a promising therapeutic target for inflammatory diseases

Northwestern University



Credit: Pixabay/CC0 Public Domain

Scientists in the laboratory of Navdeep Chandel, Ph.D., the David W. Cugell, MD, Professor of Medicine in the Division of Pulmonary and Critical Care, have discovered how mitochondria influence the body's immune response through modulating specific cell signaling pathways, according to a [study](#) published in *Science Advances*.

The findings highlight the potential of targeting [mitochondrial function](#) specifically in immune cells to treat a range of inflammation-related diseases.

"Therapies aimed at improving mitochondrial activity could benefit inflammatory diseases such as [inflammatory bowel disease](#), sepsis, and chronic infections by enhancing the immune system's ability to regulate inflammation," said Chandel, also a professor of Biochemistry and Molecular Genetics and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Mitochondria contain the mitochondrial electron transport chain (ETC), or a series of protein complexes in which electrons pass through and produce ATP, or energy, for the cell. Mitochondrial ETC function also controls macrophages, or specialized [immune cells](#) that are essential for fighting infections and regulating inflammation in the body.

Macrophages also release an anti-inflammatory protein called IL-10, which reduces inflammation and prevents excess immune responses that can harm the body. The underlying mechanisms that allow mitochondrial ETC to control macrophage immune responses, however, have remained poorly understood.

Using bulk-RNA sequencing to study mice with macrophages deficient in mitochondria ETC complex III, the scientists discovered that a type of reactive oxygen species (ROS), or unstable molecules that contain oxygen and easily react with other molecules in a cell, that is produced by mitochondrial complex III, called superoxide, is critical for macrophages to release IL-10.

The scientists also discovered those mice with the defective mitochondrial complex also struggled to recover from infection and inflammation because their cells released less IL-10. However, activating a specific ROS dependent signaling pathway in the cells restored IL-10 release, according to the study.

"This finding highlights a previously unknown connection between mitochondrial activity, inflammation control and the signaling pathways that regulate it," Chandel said.

Overall, the findings underscore mitochondria's essential role beyond [energy production](#) and suggest that mitochondria may be a promising therapeutic target for treating a range of [inflammatory diseases](#) and enhancing current therapies, according to Chandel.

"Boosting IL-10 levels through mitochondrial pathways offers promise for managing [autoimmune disorders](#) like rheumatoid arthritis and lupus, where the immune system mistakenly attacks the body. Enhancing the function of mitochondrial complex III, or mimicking its effects, may also improve recovery from severe infections. Additionally, inhibiting mitochondrial complex III would decrease IL-10 suppression of inflammation, and could cooperate with existing immunotherapies," Chandel said.

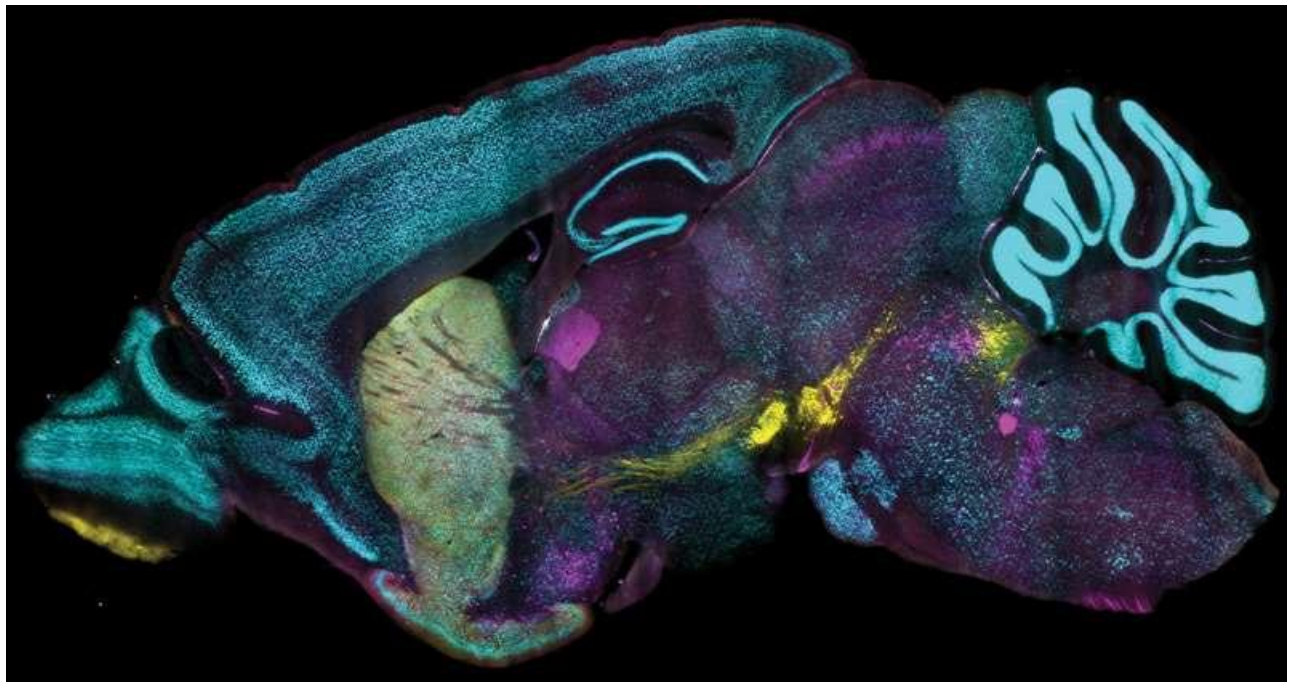
More information: Joshua S. Stoolman et al, Mitochondria complex III-generated superoxide is essential for IL-10 secretion in macrophages, *Science Advances* (2025). DOI: [10.1126/sciadv.adu4369](https://doi.org/10.1126/sciadv.adu4369)

Journal information: [Science Advances](#)
Provided by [Northwestern University](#)

JANUARY 24, 2025

New method enables protein labeling of tens of millions of densely packed cells in organ-scale tissues

by [Massachusetts Institute of Technology](#)



In this figure extracted from the research study, staining of proteins highlights various cell type markers: neurons overall (cyan), and cells specifically involved with neurotransmitters dopamine (yellow) and acetylcholine (magenta). Credit: Chung Lab/MIT Picower Institute
A new technology developed at MIT enables scientists to label proteins across millions of individual cells in fully intact 3D tissues with unprecedented speed, uniformity, and versatility. Using the technology, the team was able to richly label whole rodent brains and other large tissue samples in a single day.

In their new study in *Nature Biotechnology*, they also demonstrate that the ability to label proteins with antibodies at the single-cell level across whole brains can reveal insights left hidden by other widely used labeling methods.

Profiling the proteins that cells are making is a staple of studies in biology, neuroscience and related fields because the proteins a cell is expressing at a given moment can reflect the functions the cell is trying to perform or its response to its circumstances, such as disease or treatment.

As much as microscopy and labeling technologies have advanced, enabling innumerable discoveries, scientists have still lacked a reliable and practical way of tracking protein expression at the level of millions of densely packed **individual cells** in whole, 3D intact tissues such as an entire mouse brain or a full region of a human brain.

Often confined to thin **tissue** sections under slides, scientists therefore haven't had tools to thoroughly appreciate cellular protein expression in the whole, connected systems in which it occurs.

"Conventionally, investigating the molecules within cells requires dissociating tissue into single cells or slicing it into thin sections, as light and chemicals required for analysis cannot penetrate deep into tissues," said study senior author Kwanghun Chung, associate professor in The Picower Institute for Learning and Memory, the Departments of Chemical Engineering and Brain and Cognitive Sciences, and the Institute for Medical Engineering and Science at MIT.

"Our lab developed technologies such as **CLARITY** and **SHIELD**, which enable investigation of whole organs by rendering them transparent, but we now needed a way to chemically label whole organs to gain useful scientific insights."

"Imagine marinating a thick steak by simply dipping it in sauce. The outer layers absorb the marinade quickly and intensely, while the inner layers remain largely untouched unless the meat is soaked for an extended period. The same principle applies to chemical processing of tissues: if cells within a tissue are not uniformly processed, they cannot be quantitatively compared.

"The challenge is even greater for protein labeling, as the chemicals we use for labeling are hundreds of times larger than those in marinades. As a result, it can take weeks for these molecules to diffuse into intact organs, making uniform chemical processing of organ-scale tissues virtually impossible and extremely slow."

A mouse brain hemisphere stained with various cell type markers: neurons overall (cyan), and cells specifically involved with neurotransmitters dopamine (yellow) and acetylcholine (magenta). Credit: Chung Lab/MIT Picower Institute

The new approach, called "CuRVE," represents a major advance—years in the making—toward that goal by demonstrating a fundamentally new approach to uniformly processing large and dense tissues whole.

In the study, the researchers explain how they overcame the technical barriers via an implementation of CuRVE called "eFLASH," and provide copious vivid demonstrations of the technology, including how it yielded new neuroscience insights.

"This is a significant leap, especially in terms of the actual performance of the technology," said co-lead author Dae Hee Yun, a former MIT graduate student and now a senior application engineer at LifeCanvas Technologies, a startup company Chung founded to disseminate the tools his lab invents.

The paper's other lead author is Young-Gyun Park, a former MIT postdoctoral researcher now an assistant professor at KAIST in South Korea.

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Clever chemistry

The fundamental reason why large, 3D tissue samples are hard to label uniformly is that antibodies seep into tissue very slowly, but are quick to bind to their target proteins. The practical effect of this speed mismatch is that simply soaking a brain in a bath of antibodies will mean that proteins are intensely well labeled on the outer edge of the tissue, but virtually none of the antibodies will find cells and proteins deeper inside.

To improve labeling, the team conceived of a way—the conceptual essence of CuRVE—to resolve the speed mismatch. The strategy was to continuously control the pace of antibody binding while at the same time speeding up antibody permeation throughout the tissue.

To figure out how this could work and to optimize the approach, they built and ran a sophisticated computational simulation that enabled them to test different settings and parameters, including different binding rates and tissue densities and compositions.

Then they set out to implement their approach in real tissues. Their starting point was a previous technology, called "[SWITCH](#)," in which Chung's lab devised a way of temporarily turning off antibody binding, letting the antibodies permeate the tissue, and then turning binding back on. Staining of neurons (cyan) across an entire intact rat brain. Credit: Chung Lab/MIT Picower Institute

As well as it worked, Yun said, the team realized there could be substantial improvements if antibody binding speed could be controlled constantly, but the chemicals used in SWITCH were too harsh for such ongoing treatment.

So the team screened a library of similar chemicals to find one that could more subtly and continuously throttle antibody binding speed. They found that deoxycholic acid was an ideal candidate.

Using that chemical, the team could not only modulate antibody binding by varying the chemical's concentration, but also by varying the labeling bath's PH (or acidity).

Meanwhile, to speed up antibody movement through tissues, the team used another prior technology invented in the Chung Lab: stochastic electrotransport. That technology accelerates the dispersion of antibodies through tissue by applying electric fields.

Implementing this eFLASH system of accelerated dispersion with continuously modifiable binding speed produced the wide variety of labeling successes demonstrated in the paper.

In all, the team reported using more than 60 different antibodies to label proteins in cells across whole brains of mice and rats; whole mouse embryos; other whole mouse organs, including lung and heart; and blocks of brain tissue from larger animals, including humans.

Notably, each of these specimens were labeled within a day, an "ultra-fast" speed for whole, intact organs, the authors said. Moreover, different preparations did not require new optimization steps.

Valuable visualizations

Among the ways the team put eFLASH to the test was by comparing their labeling to another often-used method: genetically engineering cells to fluoresce when the gene for a protein of interest is being transcribed.

The genetic method doesn't require dispersing antibodies throughout tissue, but it can be prone to discrepancies because reporting gene transcription and actual protein production are not exactly the same thing.

Yun added that while antibody labeling reliably and immediately reports on the presence of a target protein, the genetic method can be much less immediate and persistent, still fluorescing even when the actual protein is no longer present.

In the study, the team employed both kinds of labeling simultaneously in samples. Visualizing the labels that way, they saw many examples in which antibody labeling and genetic labeling differed widely.

In some areas of mouse brains, they found that two-thirds of the neurons expressing PV (a protein prominent in certain inhibitory neurons) according to antibody labeling, did not show any genetically-based fluorescence.

In another example, only a tiny fraction of cells that reported expression via the genetic method of a protein called ChAT also reported it via antibody labeling. In other words, there were cases where genetic labeling both severely underreported or overreported [protein expression](#) compared to antibody labeling.

The researchers don't mean to impugn the clear value of using the genetic reporting methods, but instead suggest that also using organ-wide antibody labeling, as eFLASH allows, can help put that data in a richer, more complete context.

For instance, given that they saw cases of significant over-reporting of PV expression in mice (and significant variation among individual mice), researchers who use whole-brain antibody labeling of PV could gain a deeper basis for analyzing genetically indicated changes in the protein.

"Our discovery of large regionalized loss of PV-immunoreactive neurons in healthy adult mice and with high individual variability emphasizes the importance of holistic and unbiased phenotyping," the authors wrote.

Or as Yun put it, the two different kinds of labeling are, "two different tools for the job."

More information: Uniform volumetric single-cell processing for organ-scale molecular phenotyping, *Nature Biotechnology* (2025). DOI: [10.1038/s41587-024-02533-4](https://doi.org/10.1038/s41587-024-02533-4)

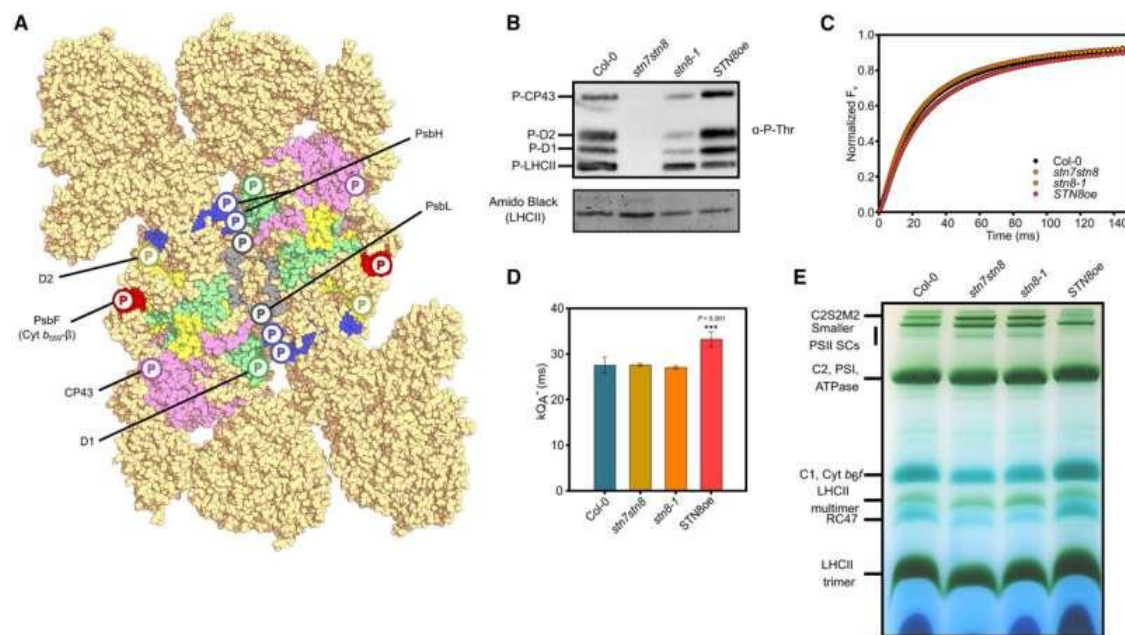
Journal information: *Nature Biotechnology*

Provided by [Massachusetts Institute of Technology](#)

FEBRUARY 10, 2025

Biochemists discover self-repair function in key photosynthetic protein complex

[Purdue University](#)



Protein phosphorylation as a driver of PSII disassembly. Credit: *Plant Communications* (2024). DOI: [10.1016/j.xplc.2024.101202](https://doi.org/10.1016/j.xplc.2024.101202)

Cyanobacteria began contributing oxygen to Earth's mostly noxious atmosphere more than 2 billion years ago. The photosystem II protein complex now shared by various lineages of cyanobacteria, algae and land plants has served as a major site of oxygen production throughout the history of life on Earth ever since.

Ironically, receiving too much light can damage photosystem II and erode the photosynthetic efficiency of plants. Purdue University biochemists Steven McKenzie and Sujith Puthiyaveetil have gleaned new, long-hidden details about how photosystem II

repairs itself. McKenzie and Puthiyaveetil's findings have been [published](#) in the journal *Plant Communications*.

"The photosystem II splits water and extracts electrons and protons, leaving oxygen as a by-product. Photosystem II thereby powers life on Earth," said Puthiyaveetil, associate professor of biochemistry. Even so, "it's still fairly poorly understood how these huge protein complexes that use [light energy](#) to produce oxygen are able to be repaired and maintained so efficiently across different lineages of plants, algae and cyanobacteria."

The long-term goal of the project is to learn how to engineer plants to have better photosynthetic efficiency, said McKenzie, a postdoctoral scholar in biochemistry.

"The repair of photosystem II is an energetically expensive process," said McKenzie, who completed his Ph.D. at Purdue in 2024. "You have to disassemble photosystem II, degrade the damaged proteins, resynthesize new proteins and reassemble new photosystems. That's energetically costly to the chloroplast."

The repair of photosystem II in chloroplasts—the sites of photosynthesis in plants and algae—is already fairly efficient, McKenzie said. "But you could make it more efficient by speeding up the repair process or making it less energy intensive."

Recent efforts to manipulate the photoprotective pathways of plant photosynthesis have led to increased photosynthetic efficiency in crop plants. Genetic engineering of different aspects of the photosystem II repair cycle similarly holds potential for improvement of photosynthetic efficiency.

Inhibiting the repair cycle can lower the efficiency of photosynthesis drastically, Puthiyaveetil said.

"This is a key process that's happening all the time. Even in low light, photosystem II is turning over. In high light, the rate of damage and repair really goes up. But sometimes the rate of repair cannot keep up with the rate of damage, especially under a combination of high light and other stressors such as drought, salinity and high temperature. This leads to a light-induced loss of photosynthesis," said Puthiyaveetil, who is also a member of Purdue's Center for Plant Biology.

As photosystem II undertakes the formidable job of splitting water using energy from sunlight, it suffers photodamage. For every 10 million photons—light particles—absorbed by leaves, one photosystem II gets damaged. On a sunny day, a plant leaf intercepts as many as 10 quadrillion photons per second.

How this [protein complex](#) gets taken apart to remove and replace the damaged protein for maintaining efficient photosynthesis has long persisted as an unresolved question. Photosystem II is huge by molecular standards, consisting of around 25 protein subunits, a few metallic centers, and scores of chlorophylls and other pigment molecules.

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The new paper shows how the chemical process of adding [phosphate groups](#) to proteins—"protein phosphorylation"—drives some of the photosystem II disassembly steps in Arabidopsis plants. Scientists have known since 1977 about the phosphorylation of photosystem II. What role it played in the photosystem II repair cycle, however, had remained unclear.

The Purdue scientists originally suspected that phosphorylation was solely responsible for photosystem II disassembly. Then McKenzie suggested that oxidative protein modification may also play a part.

"Steve thought that maybe the protein [oxidative damage](#) could also be a disassembly mechanism," Puthiyaveetil said. Further experimentation revealed that oxidative protein damage serves as a key mechanism that helps drive photosystem II disassembly, especially at the later stages. "We were quite surprised by the extent of it. Full credit to Steve."

Cyanobacteria, red and brown algae, and land plants all share the photosystem II repair mechanism, McKenzie said. What gave him the idea is that cyanobacteria and non-green algae lack photosystem II phosphorylation and yet are able to disassemble and repair their photosystems.

"We were interested to know whether there was an alternative mechanism that could be responsible for driving photosystem II disassembly," McKenzie said. "That's why we thought perhaps the damage to photosystem II itself could be driving the disassembly of the complex."

Phosphorylation seems to serve two functions. "It can drive disassembly, but also it could ensure a quality control mechanism for the repair," Puthiyaveetil said. "We say that because once you disassemble the complex you have to repair the complex." And plants don't repair their photosystems under persistent high light. "They wait for the high light to go away. There's some kind of molecular mechanism behind the delay between damage and repair."

Then, once light levels return to normal, repair and reassembly of the damaged protein begin. "That's the quality control," Puthiyaveetil noted. "Maybe phosphorylation will prevent the degradation of [damaged proteins](#) until they have been dephosphorylated as dephosphorylation has been shown to be a prerequisite for degradation."

In his experiments, McKenzie used genetically altered plants with varying levels of photosystem II phosphorylation. He also manipulated phosphorylation levels by altering light and the source of phosphate groups. By doing so, "we can see what changing the levels of phosphorylation on photosystem II do to the disassembly and repair cycle," he said. Steven D. McKenzie et al, Protein phosphorylation and oxidative protein modification promote plant photosystem II disassembly for repair, *Plant Communications* (2024). DOI: [10.1016/j.xplc.2024.101202](https://doi.org/10.1016/j.xplc.2024.101202) Provided by [Purdue University](#)