Technology Networks

The Scientific Observer

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Longevity and the Intricacies of Aging

Diet and the Gut Microbiome: What Do We Know?

Making Cancer Medicines With Microbes

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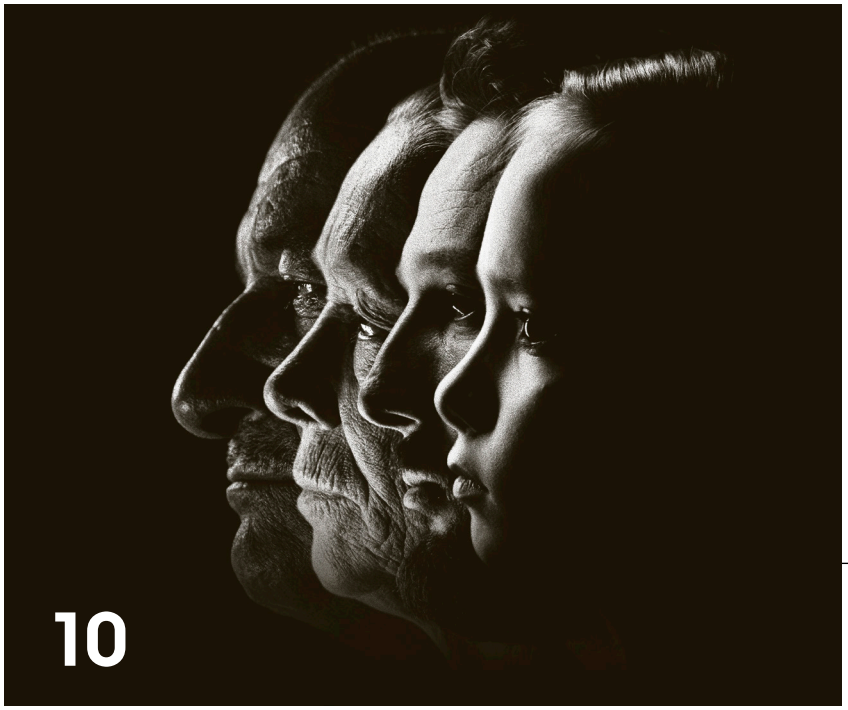
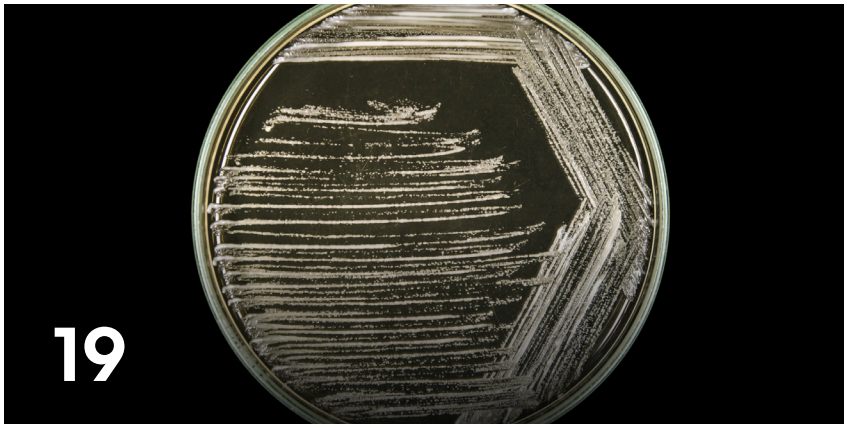


FEATURE

Longevity and the Intricacies of Aging

Tanaaz Khan



EDITORS' NOTE

Welcome to issue nineteen of *The Scientific Observer*, the monthly online magazine brought to you by *Technology Networks*.

This month's feature article confronts a growing area of research in biology and biotech: aging. What do we *really* know about the healthy aging process and what are the key gaps in our knowledge? How are academics and members of industry studying the aging process, perhaps with the aim of extending lifespan? What are the societal implications of this? Tanaaz Khan explores, featuring interviews with renowned scientists.

From the newsroom, we cover the recent discovery that mitochondrial DNA is sneakily making its way into the nuclear genome, and what repercussions this might have. Focus is also given to a recent study outlining an increased risk of developing motor neuron disease (MND) in rugby players, and a novel "robot" capsule that can deliver drugs directly to the gut.

The medicinal qualities of plants have been used to treat human diseases for thousands of years. For many plant-derived therapeutics – such as those used to treat cancer – there is a demand vs supply issue. Molly Campbell interviewed experts in the field to learn how microbes, including yeast, could be used as vehicles for producing plant-derived compounds.

We hope you enjoy this issue of *The Scientific Observer*. Subscribe to make sure you never miss an issue.

Have an idea for a story?

If you would like to contribute to *The Scientific Observer*, please feel free to email our friendly editorial team.

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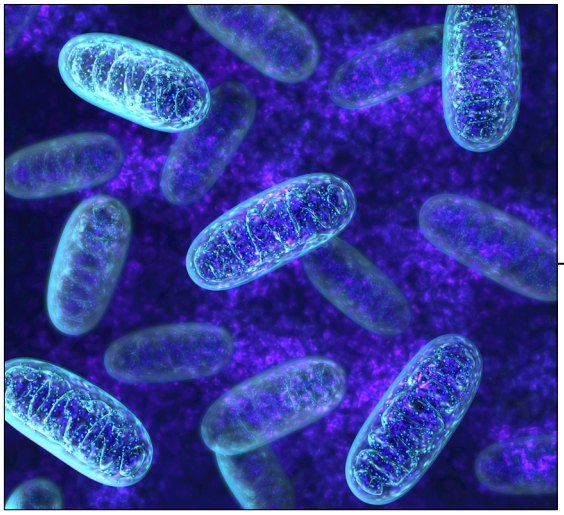
From the Newsroom

EX-RUGBY PLAYERS FACE 15 TIMES HIGHER RISK OF MOTOR NEURON DISEASE

RUAIRI J MACKENZIE

Researchers at the University of Glasgow have found that former international rugby union players have a higher risk of developing neurodegenerative diseases.

JOURNAL: *Journal of Neurology, Neurosurgery and Psychiatry.*

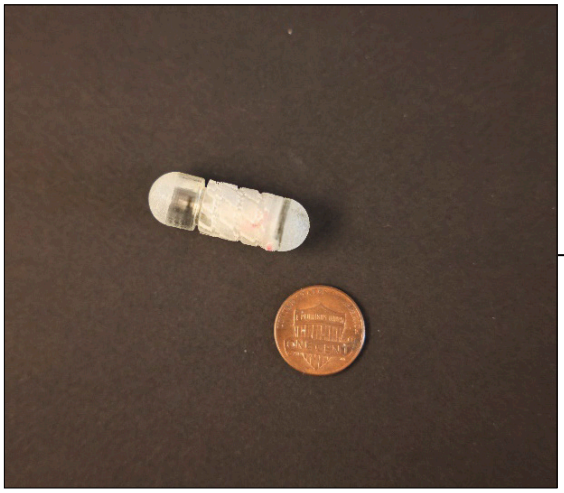


MITOCHONDRIAL DNA IS WORKING ITS WAY INTO THE HUMAN GENOME

MOLLY CAMPBELL

Scientists at the University of Cambridge and Queen Mary University of London have discovered that mitochondrial DNA can make its way into nuclear DNA.

JOURNAL: *Nature.*



ROBOCAP – THE ROBOTIC CAPSULE DESIGNED TO IMPROVE DRUG DELIVERY IN THE GUT

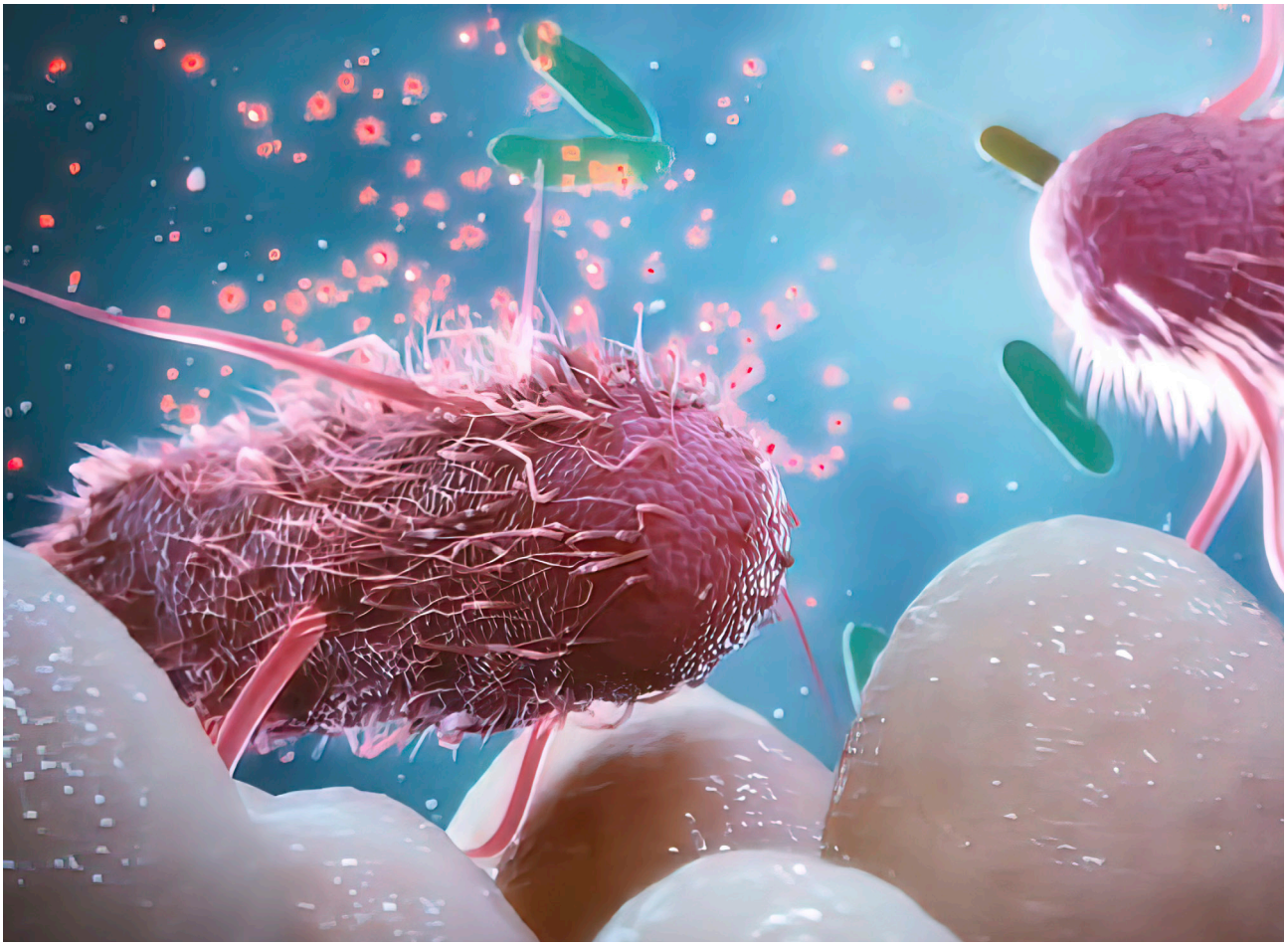
SARAH WHELAN

Scientists at MIT have developed a robotic capsule to increase drug absorption by clearing away layers of mucus in the gut and depositing drugs directly on the intestinal surface. This increased the absorption of drugs such as insulin.

JOURNAL: *Science Robotics.*

Traverso lab/MIT and BWH

Want to learn more?
Check out the Technology Networks newsroom.



Diet and the Gut Microbiome: What Do We Know?

SARAH WHELAN

Inside all of us lives a collection of bacteria, viruses, fungi and other microbes collectively known as the microbiome. These microbe populations vary between people and across organs and systems such as the skin, mouth, respiratory tract and – most importantly – the gut.

Microbiomes remain relatively stable throughout an organism's life, though diet is a key factor in their maintenance. Even back in 1919, John C. Torrey explained that "it is now well-known that diet exercises a profound influence on the determination of the types of bacteria developing in the intestinal tract." The microbes residing in the gut depend on their hosts for nutrients as they metabolize the end-products left over from digestion to produce a variety of secondary metabolites.

Changes in microbiome composition have been linked to fluctuations in our immune, metabolic and neuro-behavioral health. The field of gut microbiome research has therefore gathered a lot of interest, as these microbes and their metabolites can influence the rest of the body in health and disease. What have we learned from recent research?

HIGH-PROTEIN DIET CHANGES THE GUT MICROBIOME AND TRIGGERS IMMUNE RESPONSE

The surface of the gut is continuously exposed to the outside environment, and the gut has many features that protect the rest of the body. Immunoglobulin A (IgA) antibodies are the most abundantly produced antibody in both mice and humans, specialized in protecting mucosal surfaces like the gastrointestinal (GI) tract and airways. IgAs regulate the composition of the gut microbiome by maintaining populations of non-invasive bacteria and neutralizing pathogens.

A study from Dr. Laurence Macia and colleagues at the University of Sydney demonstrated that the type of food consumed can affect our microbiome, which in turn can influence IgA

production and the immune response. Using mice, the study investigated how 10 diets, each with a different ratio of macronutrients – i.e., fats, proteins and carbohydrates – could affect IgA levels in the gut.

"We found protein had a huge impact on the gut microbiota and it was not so much about the type of bacteria that were there, but the type of activity," said Macia.

The results indicated an association between protein consumption and IgA production. Additionally, mice fed on a high-protein diet secreted larger numbers of bacterial extracellular vesicles, which activate the immune system and stimulate the migration of immune cells into the gut. However, the authors state that this phenomenon still needs to be confirmed to occur in humans, and they don't yet know whether these findings are beneficial or detrimental to health.

GUT MICROBIOME LINKED TO INFLAMMATORY PROTEINS

Imbalances in the microbial populations that make up the gut microbiome can lead to abnormal production of inflammatory signaling molecules called cytokines. But how does the gut microbiome influence immune signaling in healthy individuals?

Researchers from Radboud University Medical Center in the Netherlands used blood and stool samples from 500 healthy trial participants to investigate how immune responses to pathogens vary between individuals. Participants' immune cells were exposed to bacterial and fungal pathogens, and they measured their responses using the production of cytokines. Clear patterns emerged in which the population and functions of the microbiome can interact with the immune response. These interactions depended on either the pathogen, the cytokines or both. For example, depending on the pathogen, breakdown of the amino acid tryptophan can inhibit the production of the cytokine tumor necrosis factor alpha (TNFα).

"We still don't have all the components, but the overall picture suggests that variations in the gut microbiome change production of the metabolites that go on to educate or influence immune cells, leading to differential outcomes when immune cells are exposed to various infections," said Dr. Ramnik Xavier, core institute member of the Broad Institute of MIT and Harvard.

GUT MICROBIOME CAN IMPACT OUR ABILITY TO LOSE WEIGHT

The gut microbiome has been shown to contribute towards weight gain in mice, and the composition and diversity of the gut microbiome have also been linked to body mass index (BMI). Human feeding studies have found that the composition of the gut microbiome can determine responses to diet changes, but the mechanisms underlying these effects remain unclear.

A study from Dr. Christian Diener and colleagues at the Institute for Systems Biology in Seattle, Washington investigated these phenomena. The researchers studied participants from a lifestyle intervention study that involved behavioral coaching and guidance from dieticians and nurses. Blood tests, dietary questionnaires and gut bacteria from stool samples were analyzed between two groups identified from the study results: one group lost over 1% of their body weight per month over 6–12 months, and the second group did not lose weight and had a stable BMI.

The major finding from the study was that the gut microbiome's ability to break down starches was increased in people who did *not* lose weight. Additionally, increased expression of genes that aid bacterial growth and replication was linked to individuals who lost more weight. The researchers suggest that people with bacterial genes in their gut that are associated with reduced weight loss may be able to change their diet, and consequently change their microbiome, to help them lose weight.

"Before this study, we knew the composition of bacteria in the gut was different in obese people than in people who were nonobese, but now we have seen that there are a different set of genes that are encoded in the bacteria in our gut that also responds to weight loss interventions," said Dr. Diener. "The gut microbiome is a major player in modulating whether a weight loss intervention will have success or not. The factors that dictate obesity versus non-obesity are not the same factors that dictate whether you will lose weight on a lifestyle intervention."

DOG'S GUT MICROBIOME MAY BE TRANSFORMED WITHIN A WEEK OF CHANGING FOOD

When starting a new diet, the composition of microbes in our microbiome can also change. However, we don't yet fully understand how long it takes for a dietary change to permanently alter the microbial communities in our microbiome.

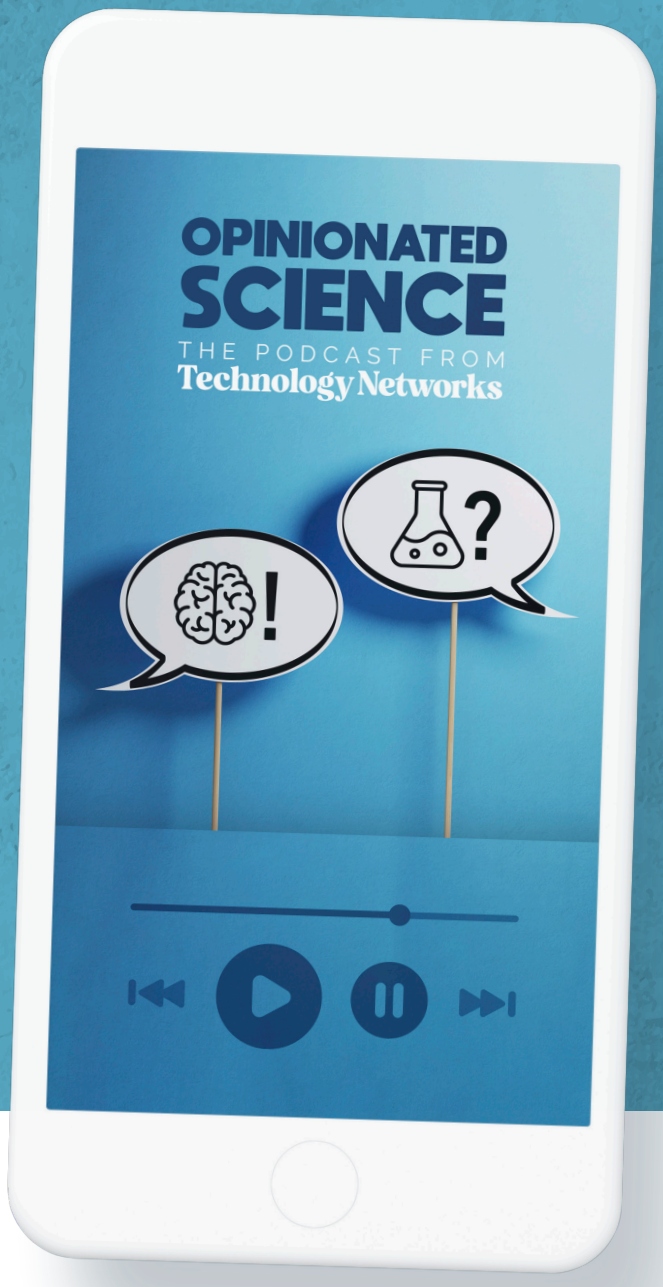
Scientists studying the interaction between changing diet and the composition of the microbiome in dogs found that both microbial species and their metabolic byproducts can completely change in less than a week. Within just two days of starting a new diet, dogs' microbiomes start to make new chemical products, and these microbial communities stabilize in just six days. Study co-author Dr. Kelly Swanson stated that this research aimed to determine how long to feed a new diet before collecting samples when conducting animal nutrition research, as "no one has ever tested it definitively". Another key takeaway from the research is that it supports the recommendation that changing your dog's brand of food should be done gradually over a seven-day period.

"Metabolites change really quickly, within a couple of days. Bacteria responsively metabolize and deal with the substrates they're given in the new diet. Then it takes a few more days to sort out the microbial pecking order, if you will," Swanson says. "Our data show everything stabilizes by day 6, so animal nutrition researchers could confidently sample and find a stable microbiome within 10 days."

MUCH MORE YET TO DISCOVER ABOUT DIET-MICROBIOME INTERACTIONS

With the importance of the microbiome in our health well-known, and increased awareness of how diet can impact our microbiome, more research than ever is being conducted in this field.

The more knowledge we can gain regarding the relationship between diet and our microbiomes, the more likely we are to be able to improve our health by looking after our microscopic guardians.



From Culture Plate to Dinner Plate – The Lingering Promise of Lab-Based Meat

The latest episode of *Opinionated Science* is an audio version of a cover story from our online magazine, *The Scientific Observer*. In that article, writer Tanaaz Khan explores the "lingering" promise of lab-based meat, investigating whether this future food will deliver for the world's rapidly growing population.

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Longevity and the Intricacies of Aging

GettyImages, Jasmin Merdan

THE QUEST FOR LONGEVITY

In the 1980s, a young girl from the Old Order Amish community in Indiana was rushed to hospital as her head bled severely in response to a minor injury. She survived the ordeal, but the doctors were perplexed as to why it happened in the first place, resulting in an in-depth genetic investigation. Soon, they discovered she carried a mutated copy of the *SERPINE1* gene, which encodes a protein known as plasminogen activator inhibitor–1, or PAI-1.

PAI-1 is now known to be a "biological controller of aging". While having two mutated copies of *SERPINE1* can cause a rare blood-clotting disorder, having only one mutated copy can have implications for metabolism and a longer lifespan. Individuals carrying one mutated copy of this gene live ~10 years longer than those who don't. They also have better heart health and a lower risk of diabetes.

The discovery of *SERPINE1* led to an emerging field of research that aims to understand the underlying mechanisms of aging – the motivations of which are varied. In this article, we'll focus on understanding some of those motivations, asking: why are we so obsessed with longevity? What does the current state of aging research look like, and what might the future hold regarding anti-aging interventions?

WHAT IS BIOLOGICAL VS CHRONOLOGICAL AGE?

Chronological age refers to the number of years you've been alive and doesn't account for any additional factors like lifestyle, disease, etc. Everybody ages at the same rate as it only depends on the time passed.

Biological age or physiological age accounts for various lifestyle and disease conditions. It depends on the epigenetic alterations and DNA methylation patterns in your body which dictate how able and functioning you are right now.

As it depends on several external factors, nobody ages at the same rate.

HOW WE DEFINE AGING

To study, quantify and perhaps intercept aging, we first need to define it.

Dr. Luigi Ferrucci, scientific director of the National Institute on Aging defines aging as the "ratio between damage accumulation and compensatory mechanisms". The scales tip when the ratio changes and damage accumulates but doesn't get repaired. When this happens, it's likely that an organism starts to feel and observe the signs of aging.

Essentially, there are two kinds of aging: mechanical and genetic. Mechanical aging happens when the body is deteriorating at the *organ* level. It can usually be treated using surgical interventions like knee or hip replacement surgery. On the other hand, genetic aging is when the body is deteriorating at the *molecular level.*

The average human has ~35 trillion cells in their body – meaning your cells divide at least 10 quadrillion times throughout your entire life. With each cell division, the opportunity for cell damage to occur increases. Each cell reaches its peak ability to divide and then stops, entering a stage of senescence. This is known as the Hayflick limit, discovered by Leonard Hayflick – an anatomist – in 1961. On average, a human cell can divide between 40 to 70 times, after which it stops, becoming a "zombie cell" – it's alive, yet it acts dead, since it can't grow anymore.

A 2013 study identified nine different hallmarks of aging. Each of these hallmarks has a common denominator, i.e., they can be found in aging cells (Figure 1). They were chosen based on three criteria:

- They should be visible during the aging process
- Experimental aggravation should hasten the aging process
- Experimental rectification should decelerate the aging process

Identifying the hallmarks of aging truly changed our understanding of the aging process. Now that we know what the tell-tale signs are, we can explore it further. It's arguable that this research has never been so pertinent considering that we have an aging population. Between 2015 and 2050, the proportion of the world's population aged 60 years and over will nearly double from 12% to 22%. This number will only continue to increase with time.

But this isn't the *only* reason we're investing in longevity research.

A PARADIGM SHIFT IN HOW HUMANS THINK ABOUT AGING

We're also observing a paradigm shift in the way we think about aging. Previously, it was considered an inevitable outcome, but now it's considered a disease that can underpin many chronic conditions. Aging is the common denominator in chronic diseases like Alzheimer's disease, cardiovascular issues, arthritis, etc. In 2019, Professor David Sinclair from the Harvard School of Medical Genetics said, "We're generally in denial that, for most of the diseases that we get these days, the root cause is aging. Now, we have the knowledge. We're developing the technologies to not just delay these diseases of aging, but actually reverse aspects of them. Imagine you have a treatment for heart disease, but as a side effect you'd also be protected against Alzheimer's, cancer and frailty. You'd live a longer and healthier life."

Mortality rates have decreased over centuries thanks to modern medical

interventions like infection control, high-tech medical treatments and novel diagnostics. Many research studies have uncovered previously unknown aspects of the aging process, even helping to refute old theories in some instances. Once, the scientific community believed we *could* slow aging down, but a complete reversal was impossible. Earlier this year, researchers from the Babraham Institute reported that they managed to reverse the aging process in human skin cells by 30 years, as measured by a novel transcriptome clock.

It's now conceivable to many scientists that aging is a disease we can cure – or at the very least, slow down. Immortality might be a stretch, but longevity – not so much. So, what progress have we made in anti-aging, or "longevity" research?

THE CURRENT STATE OF ANTI-AGING RESEARCH

We've come a long way from fantasizing about aging reversal to achieving it. Several landmark studies, like the discovery of the Hayflick limit, have contributed to our existing knowledge and have paved the way for in-depth explorations and better interventions. Let's explore some examples:

FIGURE 1: *The nine hallmarks of aging (the green regions indicate the initial signs of aging, camel regions indicate the response mechanism to those signs and dark brown regions represent the integrative hallmarks that occur as a result of the initial signs and responses). (Image derived from Vujin & Dick, 2020).*

THE EPIGENETIC CLOCK

You've likely noticed how different people seem to age at different paces, at least from a physical perspective. It turns out there is scientific evidence exploring why this occurs – the existence of an internal epigenetic clock. Epigenetics refers to molecular processes that cause changes to how genes are expressed, or "used", rather than the DNA code itself. Scientists are using such clocks to calculate biological age, which are trained using supervised machine learning models or epigenome-wide association studies.

Epigenetic clocks are used to identify predictable changes in your epigenome – usually DNA methylation – to foresee phenotypical outcomes related to your age. Considering that epigenetic changes are associated with aging and cancer-related processes, they can help us predict age-related diseases and the risk of mortality. Steve Horvath, professor of human genetics and biostatistics at the University of California Los Angeles, used phenotypic markers like blood glucose, kidney and liver function to create epigenetic clocks called "DNAm PhenoAge" and GrimAge, both of which can capture the risk of disease and mortality across tissues and cells.

However, it turns out that biological age can be influenced by other mechanisms too – some of which we're likely yet to discover.

CELLULAR SENESCENCE AND REPROGRAMMING

Cellular senescence occurs when a cell loses its ability to divide, turning into a zombie cell. The more zombie cells you accumulate, the older your biological age. Several stimuli contribute to this process and are intertwined with other genetic mechanisms that contribute to aging (Figure 2).

Dr. Nathan Basisty, tenure-track investigator at the National Institute of Aging, says "Our recent work showed that a subset of proteins that increase in the blood as we age are due to the accumulation of a specific type of 'damaged' cell called senescent cells. Our studies found that a subset of these factors in the blood are associated with aging, mortality, multimorbidity, or the presence of several diseases." Now, these cells are being used as biological markers to identify the signs of aging and predict health outcomes.

Another remarkable discovery has been the ability to reprogram cells. In 2012, two scientists – Dr. Shinya Yamanaka and Dr. John B. Gurdon, were awarded the Nobel Prize in Physiology and Medicine for the discovery that mature cells can be reprogrammed to become pluripotent.

With the help of these developments, earlier this year scientists from the Salk Institute tested long-term partial reprogramming regimens to "dial back" epigenetic clocks in mice. The anti-aging regimen had no adverse effects, with evidence suggesting that it not only pauses aging, but also reverses it.

TELOMERES AND TELOMERASE

Telomeres are caps that protect the end of our chromosomes. With every cell division that occurs, the caps shorten over time. When the telomere's length reaches a critical limit i.e., the Hayflick limit, the cells die. In healthy cells, the telomeres shrink but they are brought back to their original length by telomerase. Telomerase is an enzyme that synthesizes telomeric DNA repeats ensuring that they maintain their length. However, in aging cells, telomerase activity is almost minimal – resulting in senescent cells.

This discovery was first made in 1984 by Dr. Elizabeth Blackburn, now the Morris Herztein professor of biology and physiology at the University of California San Francisco, and Carol Greider, professor of molecular biology and genetics at Johns Hopkins University. It earned them the Nobel Prize for Physiology and Medicine in 2009.

In addition to these landmark scientific discoveries, other molecular mechanisms, like mitophagy and autophagy – the process of removing dead mitochondria or cells – are also being studied in the field of anti-aging and longevity research. As these processes contribute to the cell renewal and cleaning cycle of the body, they may hold the answers to many unanswered questions within the field.

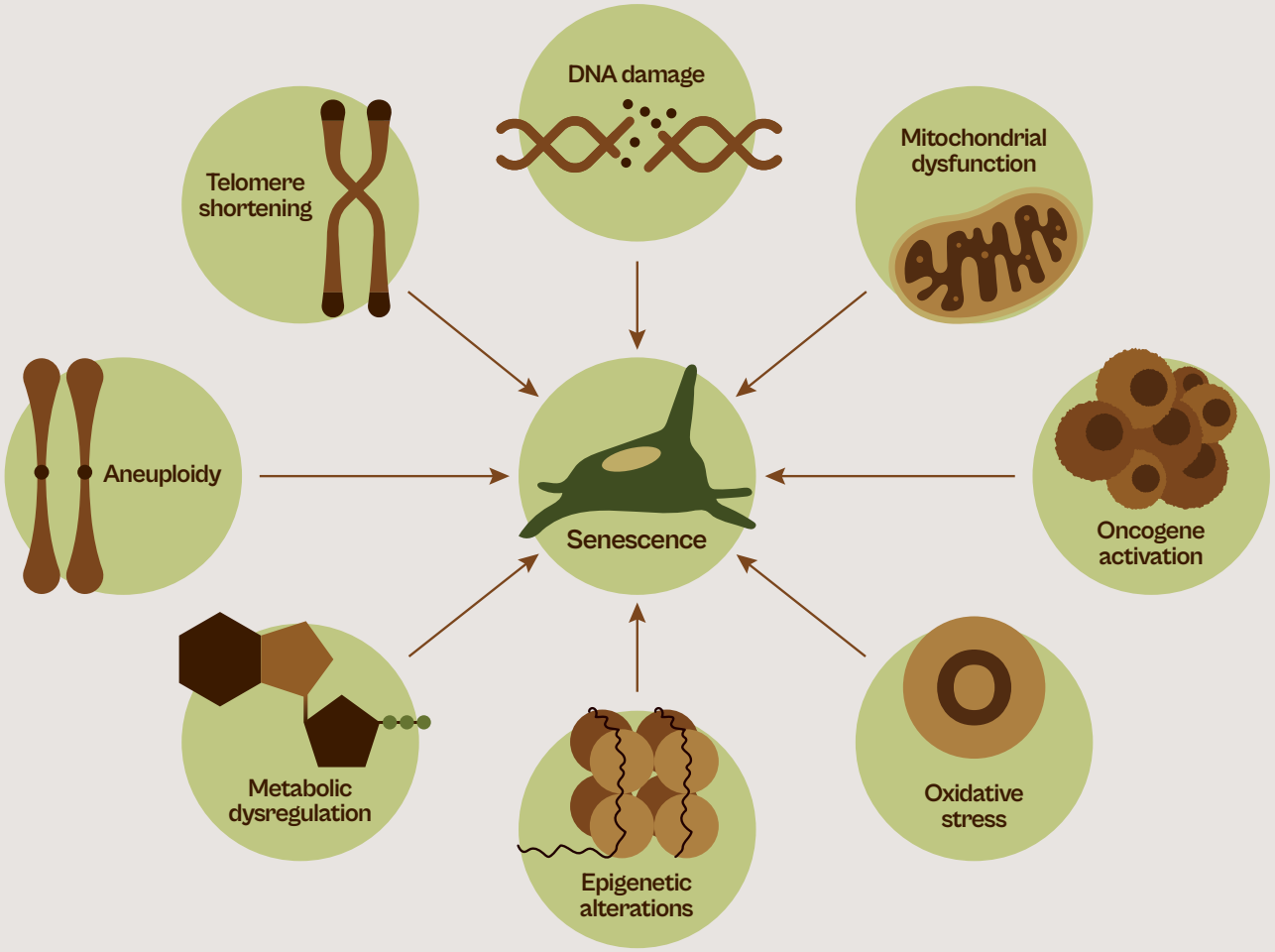

FIGURE 2: *The various stimuli that induce cellular senescence (Imaged derived from Kudlova et al., 2022).*

ANTI-AGING INTERVENTIONS UNDER INVESTIGATION: PHARMACOLOGICAL AND OTHER

The molecular mechanisms of aging are one of the most sought-after targets for identifying potential anti-aging pharmacological interventions. While studying DNA damage and senescence mechanisms can help us understand the process of aging, identifying biological markers can help researchers identify those that might benefit from anti-aging treatments, and are central to testing the efficacy of such treatments. Anti-aging and longevity research is flourishing not only within the academic field, but also in big pharma.

Many for-profit companies are jumping in the game – enabling the acceleration of this field of research. In 2013, the founders of Google invested in a US-based startup aiming to develop therapies for neurodegeneration and cancer – the progress of this venture is, at this stage, unclear. Later, in 2021, Jeff Bezos reportedly invested in a startup that's main goal is to use cellular reprogramming to restore cell health and resilience, reversing the aging process.

Many other organizations are also working on launching anti-aging therapies that can walk the talk. Hormonal replacement therapy (HRT) is one such example, where pellets, creams, pills, patches or shots are used to deliver hormones that allegedly slow the aging process.

Another line of research in anti-aging interventions focuses on the mitochondria, as damage to mitochondrial DNA (mtDNA) is also known to contribute to aging. The accumulation of reactive oxygen species (ROS), a byproduct of the NAD-dependent oxidoreductase reaction in the mitochondria, can lead to mtDNA damage. The simultaneous depletion of NAD+ molecules and increase in ROS has been linked with senescence (Figure 3).

To counter this process, newly devised interventions called "senolytics" are being developed to clear senescent cells using genetic or pharmacological pathways. Drugs like metformin and rapamycin have been studied extensively for this purpose. A 2020 study found that metformin can improve autophagy and even increase mitochondrial bioenergetics when tested *in vitro*. Simply put, the drug appears to clear out "zombie" cells and increases cellular activity

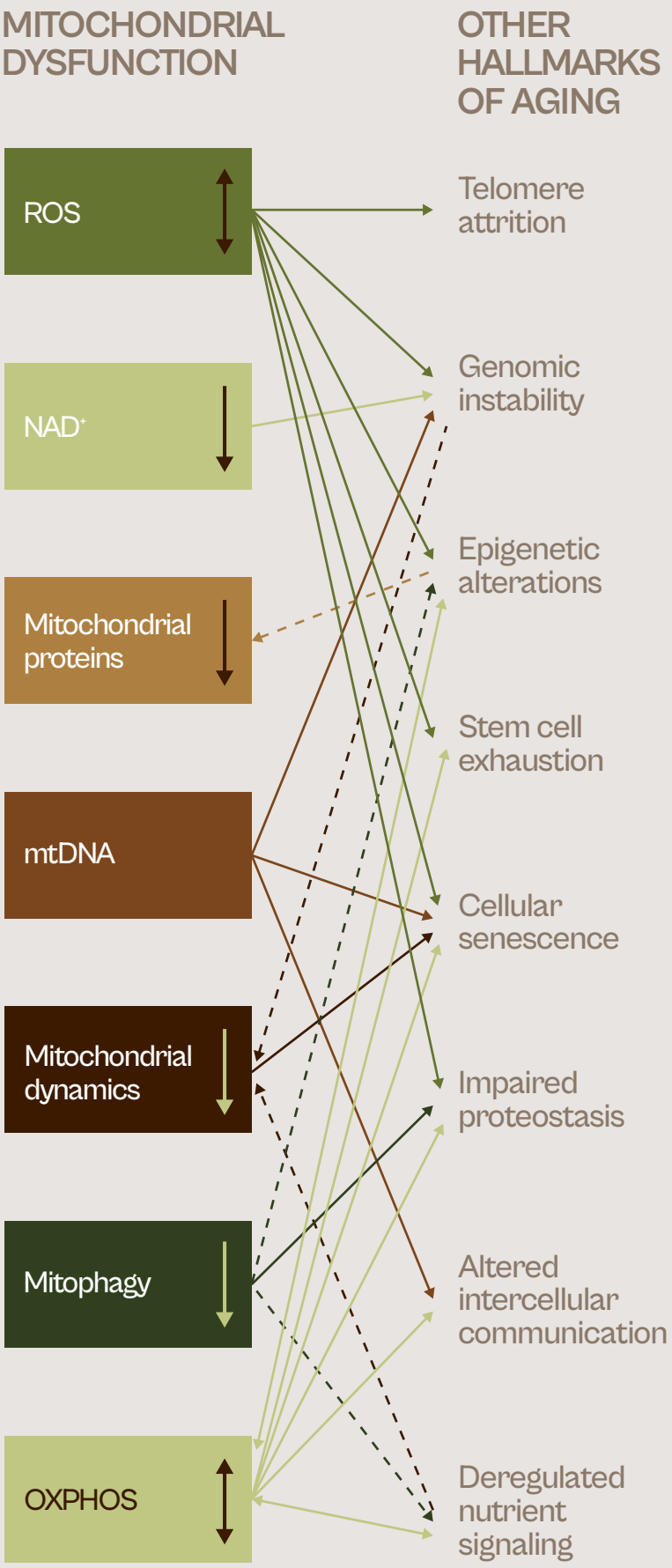

FIGURE 3: *Mitochondrial dysfunction and its correlation with the hallmarks of aging (van der Rijt et al., 2020).*

leading to healthier cells. Rapamycin, on the other hand, has been reported to reduce senescence in human skin. A 2019 prospective randomized trial found that topical application of rapamycin reduced $p16^{INK4A}$ protein levels (a biomarker of cell senescence) and increased the formation of Collagen VII, although the dropout rate of this study was 47.2% due to reasons such as non-compliance and unrelated injuries. However, many studies have indicated that rapamycin can extend lifespan in murine models but in humans, it still needs further exploration.

Outside of pharmacological interventions, changes to lifestyle and habits such as exercising, hydrating and eating a nutrient-dense diet are also being explored as anti-aging remedies. One interesting avenue of research is the impact of calorie restriction. For over 75 years, scientists have endeavored to understand the mechanisms by which food restriction induces beneficial effects on health. While a conclusive answer has not yet been reached, calorie restriction appears to positively impact the molecular pathways associated with an extended lifespan via the mechanistic target of rapamycin (mTOR) pathway. A 2018 meta-analysis assessed studies performed on model organisms (such as *C. elegans* and *D. melanogaster)* to explore the potential of calorie restriction as an anti-aging treatment. The key findings suggest that genetic manipulation and calorie restriction appear to perform better than medications for extending the lifespan of both models. Since metformin and rapamycin can mimic the effects of eating less, this therapy shows potential, but it still needs to be investigated further.

THE POTENTIAL RAMIFICATIONS OF SUCH INTERVENTIONS

While the premise of longevity seems exciting, there are ramifications of such interventions that need to be considered. There are many concerns that we may not have the resources to sustain longer-living populations,

with the current global population standing at ~8 billion.

In addition, many therapies in the market tout the promise of slowing down aging but could also elicit harmful effects. Dr. Bruce Bassi, a certified clinician, emphasizes, "It's important to keep in mind the difference between well-marketed products for aging versus well-studied and well-researched processes that reduce the aging process." Even the US Food and Drug Administration warned the general public against using medicines for purposes other than what they've approved them for – especially in the context of HRT.

Outside of pharmacological interventions, changes to lifestyle and habits such as exercising, hydrating and eating a nutrient-dense diet are also being explored as anti-aging remedies.

There are several gaps in our knowledge surrounding the fundamentals of aging too. One such aspect is the glaring difference between the number of studies focusing on men versus women. Dr. Cory Rice, chief clinical advisor of a precision medicine company says, "If you can avoid disease and disability, you can prevent death. There are vastly different ways disease and treatment affect men and women due to fundamental genomic, metabolic and hormonal differences. And yet, just four percent of all healthcare research and development focuses on women's health." As there has been a shift in the way we think about aging, i.e., more of a disease instead of an inevitable consequence – there is an urgent need to study the differences between these groups.

When discussing the pace of development in this field, Dr. George Church, renowned professor of genetics at Harvard University, comments, "We know enough about the major pathways of aging and related diseases, such that therapies and /or interventions aimed at all of them at once are being developed. The gaps will continue to be filled, but may be approached in part while debugging therapies (just as smallpox elimination started long before a full understanding of virology and immunology)."

THE FUTURE OF ANTI-AGING RESEARCH

The field of anti-aging research is propelling forward, but there are many things we need to account for before coming to conclusions. Some of the most promising studies in this field are primarily focused on animal models, and while a few interventions for humans are available, there's no magic bullet for aging, yet. Dr. Basisty emphasizes, "Targeting the aging process will potentially have enormous public health and economic effects. If findings in animal models translate to humans, it has the potential to slow the onset of multiple diseases, such as heart disease, cancer, and Alzheimer's disease, simultaneously. From a public health perspective, keeping us healthy and free of disease late into life is a huge boon. From an economic perspective, targeting basic aging processes is more efficient than focusing one at a time on the multitude of complex diseases that arise later in life."

Also, the availability of such interventions could come at an immense cost to society. Many people are questioning how such treatments would be made accessible, a pertinent query in the midst of a global health crisis that has seen disparities in healthcare access widen. Products like targeted gene therapies, HRT and supplements that are in the market or under investigation range in price from $2 per dose, $150 for a month's supply or even higher in the case of personalized treatment.

The implications of anti-aging and longevity research could go beyond biology too. With population explosion and global hunger being the burning issues of the century, the question remains: are we prepared to sustain humans that age slowly? According to Dr. Church, aging reversal could delay population implosion if the trend toward lower birth rates (~1.2 children per family in cities) continues.

At present, most anti-aging therapies available are additive at best. The real work comes down to taking care of your own body. There are various factors that we need to focus on to live healthy, long lives, including: eating a nutrient-dense diet, exercising regularly, limiting our exposure to toxins and getting enough sleep; the age-old advice (pun intended) of eating, drinking and sleeping well still holds true – and will continue to do so.

A lot is happening in the anti-aging industry – on the academic and industrial front. Science has progressed massively in just six decades of research and, at the pace at which we're uncovering the intricacies of the aging process, we might have promising interventions on the market sooner than we think.

LEVERAGE OUR

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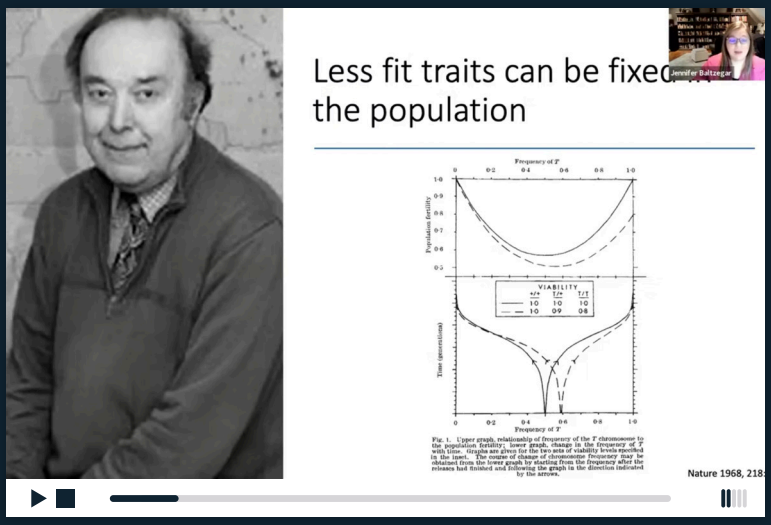

Gene Drive Research

WITH DR. JENNIFER BALTZEGAR

For this issue of *The Scientific Observer,* we're highlighting a Teach Me in 10 brough to you by Dr. Jennifer Baltzegar, a population geneticist working as a postdoctoral research fellow at North Carolina State University.

Dr. Baltzegar talks us through a topical area of research – gene drives. A gene drive is a selfish genetic construct that spreads rapidly through a population and can be used to reduce the environmental impact of pests. You might have heard about gene drives in the media lately as there are many discussions taking place as to how this research can be taken from the laboratory and implemented into society ethically. Dr. Baltzegar teaches us about how the maturation of genetic engineering approaches has advanced gene drives, the two different strategies for gene drives and some of the key questions surrounding the application of gene drives in society.

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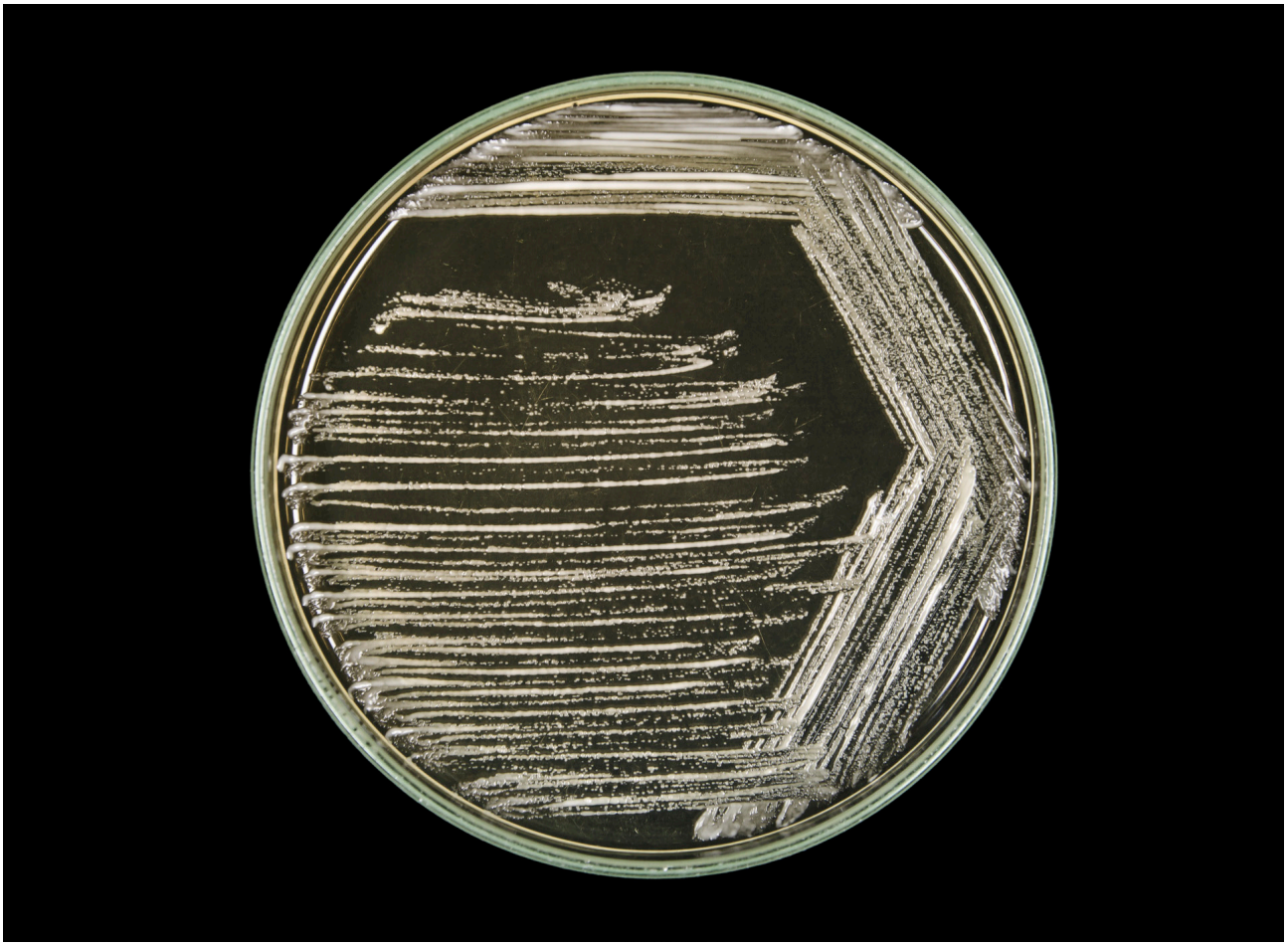

Making Cancer Medicines With Microbes

MOLLY CAMPBELL

USING PLANTS TO TREAT HUMAN DISEASES

The medicinal qualities of plants have been used to treat human diseases for thousands of years. While the exact timeframe isn't clear, archaeological studies suggest herbal medicine was practiced 60,000 years ago. During the 21st century, "conventional" or "Western" practices dominated the medical landscape, largely owing to new capabilities in chemically synthesizing drugs. "Despite the current preoccupation with synthetic chemistry as a vehicle to discover and manufacture drugs, the contribution of plants to disease treatment and prevention is still enormous," writes Professor Ciddi Veeresham from the Department of Pharmacy at Kakatiya University. "Even at the dawn of 21st century, 11% of the 252 drugs considered as basic and essential by the World Health Organization were exclusively of flowering plant origin."

For oncology, plant-based anti-cancer drugs have proven instrumental in the fight against a disease that claims approximately 609,360 lives in the United States alone. Examples of essential plant-based anti-cancer compounds include podophyllotoxin analogs, taxanes, vinblastine and vincristine. The latter two are examples of monoterpene indole alkaloids (MIAs), derived from the Madagascar periwinkle (*Catharanthus roseus*). During cell proliferation, vinblastine inhibits the cell cycle by binding to microtubules, preventing the formation of the mitotic spindle. It can be used as a chemotherapy agent to treat cancers such as lymphomas, ovarian, breast, testicular and lung cancer.

While plants represent a bountiful source of novel and potentially therapeutic compounds, their abundance is finite, and environmental concerns surround their utility at large-scales.

The demand also far outweighs availability. Let's look at MIAs, for example. Vinblastine and vincristine require 500 and 2000 kg respectively

of dried *C. roseus* leaves to synthesize 1 g of active product, which could treat approximately 10 patients. "It goes without saying that a lot of crops must be farmed when relying on low-yielding plant-based extraction of these APIs. This is problematic in its own sense," says Dr. Michael Krogh Jensen, senior researcher at the Novo Nordisk Foundation Center for Biosustainability (DTU Biosustain).

Ultimately, the current pipeline for these anti-cancer drugs is costly, both from an environmental and financial perspective. Jensen explains further: "The extraction of minute amounts of vinca alkaloids from plants uses harsh chemistries. When it comes to the socioeconomic aspects, it must be noted that even though governments and the World Health Organization take measures to regulate the price of these essential medicines, the fact is that many of them are not evenly distributed globally. Many countries cannot subsidize their usage in the clinic."

"An effective anti-cancer drug called paclitaxel [Taxol] was developed from the Pacific yew tree. However, it was based on a chemical that exists in very low yields," says Dr. Melanie-Jayne Howes, research lead at the Royal Botanical Gardens, Kew. "Hundreds of trees had to be cut down to develop the drug. As a result, the tree is now classified as near threatened."

ALTERNATIVE BIOSYNTHESIS PATHWAYS

After vinblastine and vincristine received Food and Drug Administration (FDA) approval in the early 1960s, approaches to synthesize them using partially chemical methods were explored. In 1974, scientists successfully coupled the precursor monomers vindoline and catharanthine required to produce the biologically active vinblastine. The process, however, is not straightforward. "The complex chemistry of alkoloids primarily arises from their numerous stereocenters and reactive side groups. This makes total synthesis, or even semi-synthesis, particularly challenging when needing to obtain regio- and enantio-selective molecules," says Jensen.

The FDA included vinblastine and vincristine on its "drugs with shortages" list for 2019–2020.

These issues extend beyond the vinca alkaloids. "Like MIAs, taxanes display complex structures that make bulk chemical synthesis impossible in a cost-effective manner," writes Dr. Vincent Courdavault, group leader in alkaloid biosynthesis at the University of Tours, in a 2020 review of the field. For many decades now, scientists in the field have considered whether alternate production systems could be utilized for the biosynthesis of vinca alkaloids and other anti-cancer drugs, such as microbial synthesis.

In 2015, this became Jensen and colleagues' focus, looking specifically at MIAs. Their refactoring into another production system would require a comprehensive understanding of how *C. roseus* produces the natural compounds in the first place. What enzymes are necessary? What genes encode these enzymes?

In 2018, this information became available. A paper published in *Science* outlined the entire biosynthetic pathway for vinblastine, including the discovery of two "missing" enzymes. Equipped with the knowledge of how *C. roseus* produces the drug, researchers next considered which "host" could be genetically engineered to express this pathway.

USING BREWER'S YEAST TO MAKE ANTI-CANCER DRUGS

Jensen and colleagues – including Courdavault – turned to *Saccharomyces cerevisiae*, also known as brewer's yeast. "When it comes to small molecule manufacturing, yeast excels for numerous reasons. Firstly, it is a biotechnology work-horse able to sustain high pressures, long fermentation processes and low pH. All sought-for traits for scalable fermentation-based manufacturing," Jensen says. "As for complex small molecules like alkaloids, flavonoids and larger classes of terpenoids, yeast is sought for due to its high membrane capacity for an important class of membrane-anchored enzymes called P450."

YEAST AS A "CELL FACTORY"

Yeast has many cellular components, such as the nucleus, mitochondria and peroxisomes, which can be useful for compartmentalizing enzyme reactions needed for coupling molecules or mitigating toxic intermediate build-ups.

Professor Jay Keasling, a senior faculty scientist at Lawrence Berkeley

National Laboratory and scientific director at DTU Biosustain, had previously succeeded in engineering yeast to produce other plant-derived compounds, including cannabinoids. Jensen, Keasling and Courdavault, among other colleagues, set out to refactor the vinblastine pathway into the microbial "cell factory". It wouldn't be an easy feat – the pathway is 31 steps in length, and Jensen emphasizes that multi-disciplinary scientists were needed, including expertise in chemistry, data science, bioengineering and fermentation.

Their approach utilized genome engineering technologies such as CRISPR-Cas9, which enables precise cuts to be made in the genome for the insertion or removal of genes. The researchers set their sights on achieving the synthesis of intermediate molecules, including strictosidine – a foundational molecule for the production of all MIAs. "In our study we built different modules of the pathway and optimized each of these individually before combining to get to the final best-performing vindoline and catharanthine production strain," says Jensen.

In total, it took 56 gene edits, including the insertion of 34 plant genes, deletions, knock-down and overexpression of wild type yeast genes – to achieve successful production of vindoline and catharanthine in yeast. If you're thinking – well, those are the precursor molecules, right? You're correct. The researchers note that biosynthesis in yeast "mirrors" that of plant-based production processes, whereby vindoline and catharanthine are coupled after they have been purified from the *C. roseus* leaves.

AN INFINITE CHEMICAL SPACE

Will microbes offer a novel supply chain for future anti-cancer drugs? It's early days, the researchers emphasize. The quantities achieved by this pathway (10 ug/L of vindoline and 100 ug/L of catharanthine per L of cultivation) are not yet competitive with industry standards, but it's a huge feat – the paper marks the largest biosynthetic pathway to be refactored into a microbial cell factory.

"The pathway could also be augmented to produce new-to-nature MIAs, which may have improved pharmacological properties such as higher efficacy or fewer side effects," says Dr. Jie Zhang, senior researcher at DTU Biosustain, and lead author of the work. "This will potentially enable us to explore the almost infinite chemical space with many new bioactivities," he concludes.

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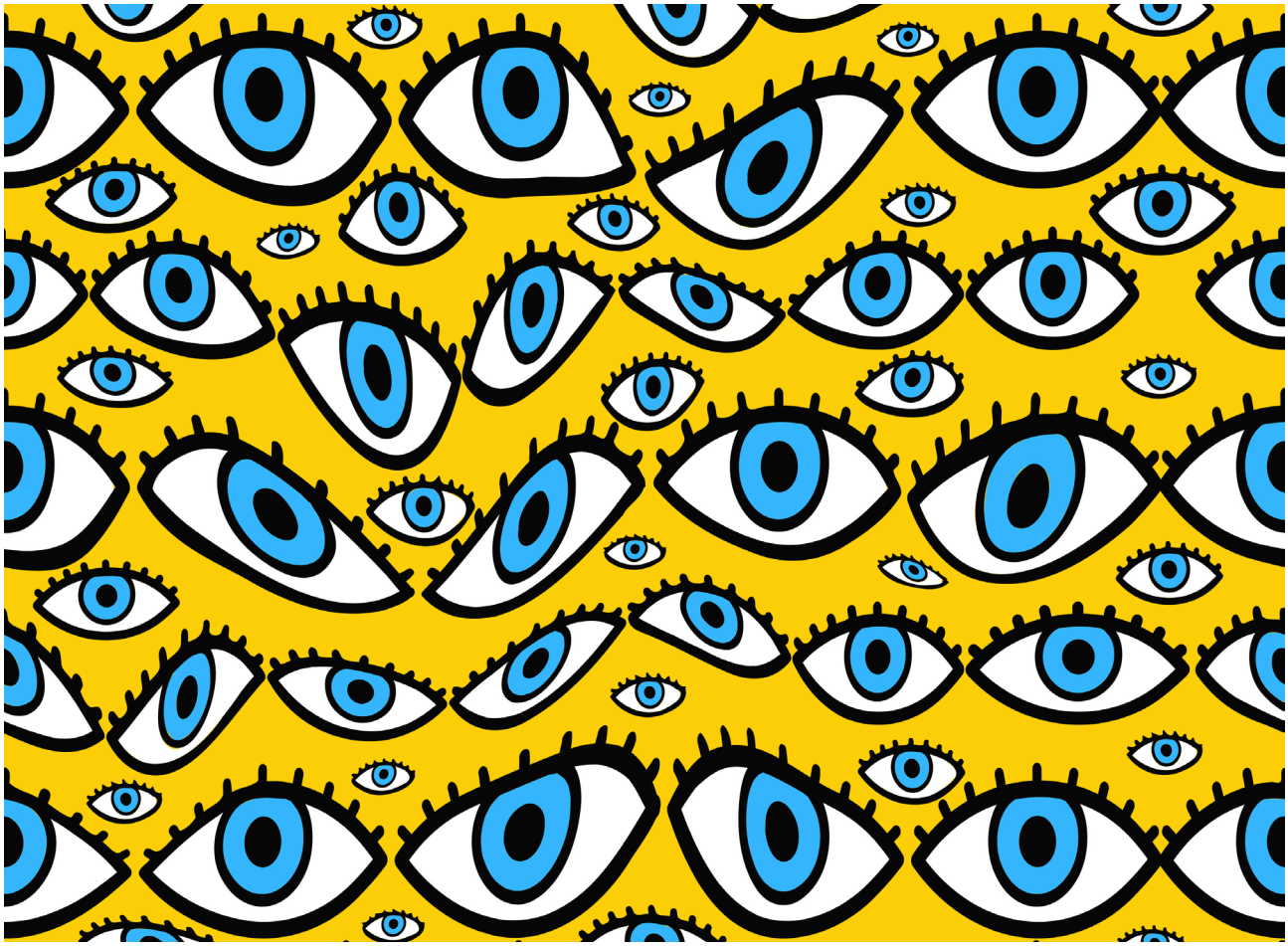


LSD for Anxiety: A Deep Dive Into a New Clinical Trial

RUAIRI J MACKENZIE

A Phase II clinical trial investigating the efficacy of the psychedelic compound lysergic acid diethylamide (LSD)-assisted psychotherapy for the treatment of anxiety has reported positive results in the journal *Biological Psychiatry*. Participants given LSD showed greater reductions in their self-reported anxiety than those given a placebo. However, mixed data from a second group in the trial somewhat complicates the picture, highlighting the complex challenges of psychedelic clinical trial design.

The study took place across two centers: the University Hospital Basel and the clinic of Dr. Peter Gasser, who was also one of the study's co-authors. Gasser, alongside first author Dr. Friederike Holze, a postdoctoral researcher in the Liechti lab at the University of Basel, presented the trial's results at the recent Interdisciplinary Conference on Psychedelic Research (ICPR) in Haarlem, The Netherlands.

CROSSOVER CONUNDRUMS

Holze and Gasser's study aimed to recruit people with anxiety disorders. Of the 42 participants enrolled, half of the group also had a life-threatening illness, such as cancer. The original goal of the trial was to examine how LSD-assisted psychotherapy affected anxiety symptoms with and without the context of a potentially fatal illness. The study used a "crossover" design, where participants were split into two groups, one of which received LSD and the other a non-psychedelic placebo. After a 24-week study period, the two groups were then brought back in, but this time their treatments were reversed. This approach, Gasser explained in his presentation, was an "ethical choice" – to make sure that everyone in the trial had a chance to access the LSD-assisted psychotherapy.

However, it was this well-intentioned design that ultimately necessitated a major rethink for the authors.

The trial involved two dosing sessions where patients were given an oral solution of 200 µg of LSD mixed in ethanol, or an ethanol-only placebo. These two sessions, six weeks apart, were supplemented by multiple non-psychedelic therapy sessions to help patients comprehend and integrate their experiences. The patients' anxiety levels were measured using a patient-reported scoring system called the Spielberger's State-Trait Anxiety Inventory–Global (STAI-G). Their anxiety was measured at baseline, 2, 8 and 16 weeks after their second dose of LSD.

After this period, Holze and Gasser intended to swap their study arms over to complete their crossover design.

The snag: their LSD patients were having too good a time.

CARRYOVER EFFECTS AND POWERFUL PLACEBOES

"We underestimated the duration of the LSD effect. Patients essentially stayed well after the first dose until they switched over into the placebo group," Holze explains to *Technology Networks*. This meant that this group, termed the "LSD-first" group, had much lower anxiety scores when they began receiving placebo alongside psychotherapy in the study's second half. This type of clinical trial issue is termed a *carryover* effect. On top of this, the LSD-first group continued to improve their scores in the study's second half, even without any additional LSD being given.

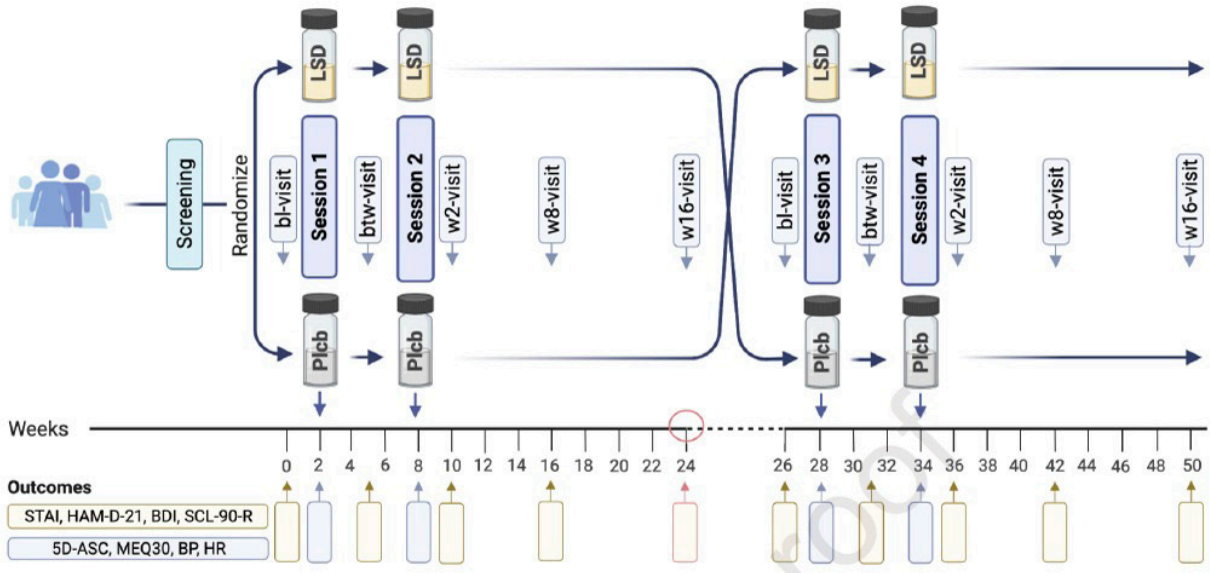
While great for the patients, these issues were problematic for Holze and Gasser's data, as the effects of the LSD in the first half of the trial could influence the results of the second half of the trial. The authors took the decision to analyze only the first half results.

This data showed that patients given LSD had significantly greater reductions in their anxiety than those given placebo. The LSD group reported lower anxiety scores, on average 14.9 points lower on the STAI-G than at baseline, whereas the mean change for placebo was a 1.3-point increase. The difference between the two groups was statistically significant.

Additionally, the patients given LSD showed improvements in their scores on secondary outcomes, including measures of depression, as compared to placebo. The improvements patients experienced to their anxiety corresponded with the intensity of some of the psychedelic experiences they felt during LSD dosing, including the sensation of oceanic boundlessness (a commonly used metric in subjective measurement of psychedelic trips).

The patients' anxiety reduction was first detectable at the two-week mark post treatment, write the authors. Patients with a life-threatening illness showed similar improvements to those with only anxiety, Holze says: "The study was also not statistically powered to assess such a difference validly. You would need more patients for a valid sub-group analysis. But we can say that LSD worked in both groups."

Reassuringly, there was just one treatment-related adverse event encountered during the trial – a short-lived delusional state that was successfully treated with a combination of benzodiazepine and antipsychotic drugs.



The clinical trial design. One group is given two doses of LSD, while the other is given a placebo. The two groups are then swapped over after week 16. Participants are rated using various psychometric tests. Credit: Holze et al.

A NOTE OF CAUTION

This data all sits nicely together: LSD was extremely effective in reducing anxiety and depression, this benefit was linked to the psychedelic experience and there were limited side effects. But one observation in the paper's discussion adds a note of caution to the findings.

The participants who were given placebo first, before waiting 16 weeks and then being given LSD, benefited less from the drug than those given LSD in the first half of the trial. This isn't a psychedelic carryover effect, as these volunteers didn't initially receive any active compound for there to be an effect from. Holze admits that this data confused the team: "We do not have an answer. Just speculations," she says. "We were quite surprised to see a smaller response in those subjects who first had placebo and then LSD. These subjects mostly knew they would get LSD and still the response was somewhat smaller (still robust). Not clear why. They had more preparation and knew the therapist better, but this did not seem to enhance the response."

Holze suggests that the effect could be due to chance – crossover study designs are rare in psychedelic research, so there isn't data to suggest otherwise – but the finding does raise questions about how much of the powerful anti-anxiety effect experienced by the first group of participants receiving LSD was due to the drug and how much was due to the context of the trial, says Dr. Michiel van Elk, an assistant professor in the Institute of Psychology at the University of Leiden, who was not involved with the study.

van Elk, who presented at ICPR on the topic of improving clinical trials in psychedelics, points out that if the authors had pooled data from both groups receiving LSD, rather than only using data from the first group, the effects of the drug would have been markedly reduced.

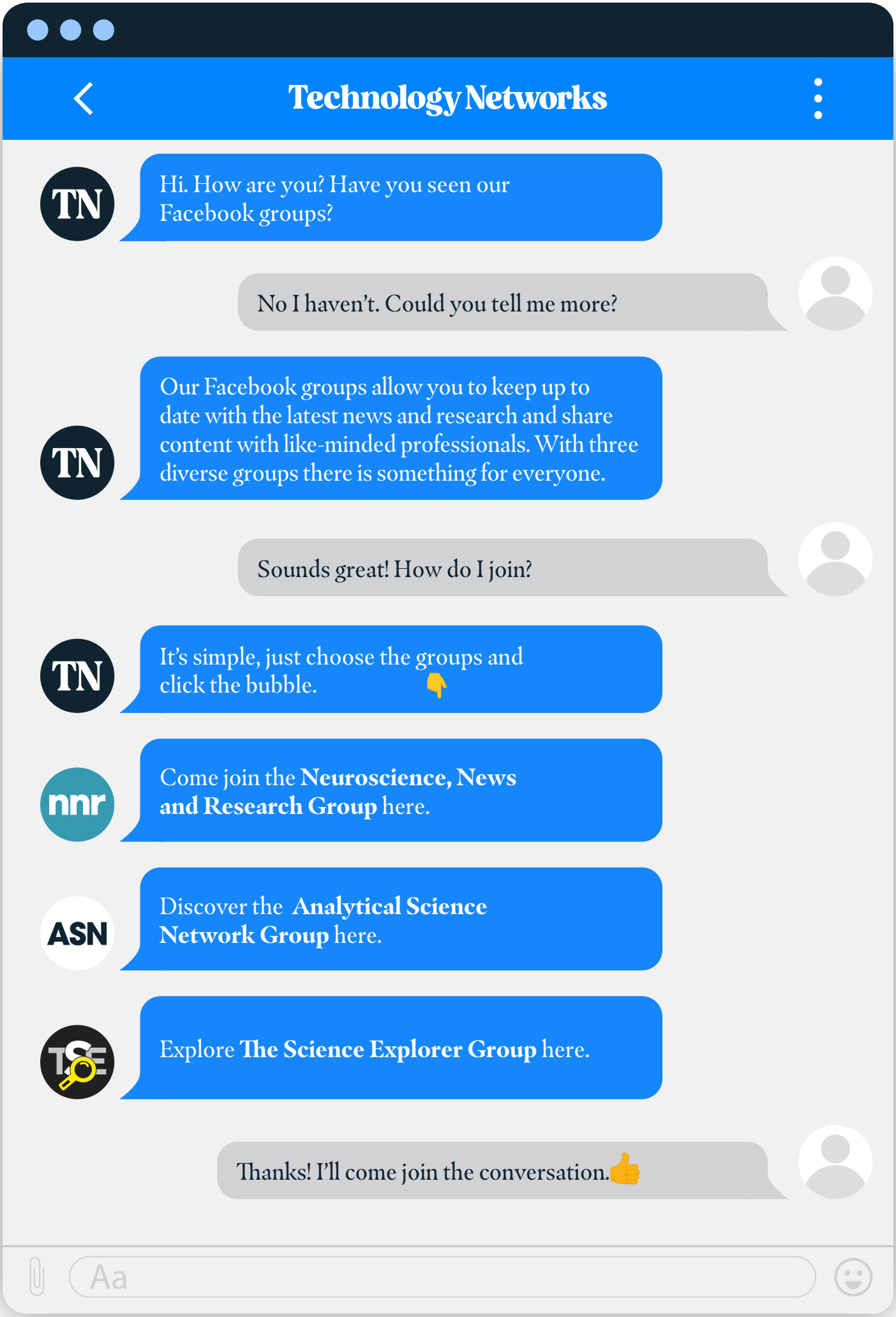
van Elk notes that the first group receiving a placebo showed very little improvement to their symptoms: "This looks very uncommon. Typically, you see an improvement, both for the placebo and for the psychedelic condition. People always improve because receiving something rather than nothing helps."

The improvements patients experienced to their anxiety corresponded with the intensity of some of the psychedelic experiences they felt during LSD dosing.

van Elk suggests that this absence of an effect could be due to the trial's crossover design. Placebo-receiving participants would likely have become unblinded, realizing what they had received during the first half of the study, although Holze and colleagues did not report blinding efficacy in the placebo group. Unblinding is an ongoing problem in a field where the active treatment usually induces intense hallucinations that are somewhat hard to miss. Given that participants were aware of the structure of the trial, placebo participants "would know the best is yet to come," says van Elk. This knowledge may have contributed to a reduction in the placebo effect in the *first* half of the trial, which in turn makes the performance of the LSD arm look even more impressive.

The final consideration in the trial structure was the "ethical" decision to give LSD to all participants. This discussion was a focus at ICPR, where proponents of this approach insisted that withholding such a treatment from patients would be morally suspect. van Elk sympathizes with this view but points out that LSD's efficacy for anxiety is not yet a sure thing: "We need to [withhold treatment from the placebo group] in the first place to establish whether a treatment is effective." The assumption that LSD should be given to everyone because it is going to work adds a bias of expectancy to both patients and the trial team that could further enhance the drug's effect, an issue discussed at length in a recent review of psychedelic clinical trials. van Elk notes a compromise approach that withholds the active drug from the placebo group but makes it freely available to that same cohort after the trial has concluded, which may strike a balance in this complex ethical dilemma.

As with many psychedelic trials, Holze and colleagues' work remains at an early stage. The going is long and painstaking: Gasser mentioned in his presentation that the project had taken nearly 15 years to complete. Promising initial results, however, don't disguise the need to improve and establish robust protocols for how psychedelic clinical trials should be designed.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