STOP GETTING OLD

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AGE REVERSAL IS HERE. ARE YOU BRAVE ENOUGH TO BE ONE OF THE FIRST HUMAN TEST SUBJECTS?

- Thousands of doctors will give you steroid enhancers and age reversal drugs even though they are not yet legal. Is it worth the risk?

By Lindsay Brownell

(BOSTON) — As we age, our bodies tend to develop diseases like heart failure, kidney failure, diabetes, and obesity, and the presence of any one disease increases the risk of developing others. In traditional drug development, a drug usually only targets one condition, largely ignoring the interconnectedness of age-related diseases, such as obesity, diabetes, and heart failure, and requiring patients to take multiple drugs, which increases the risk of negative side effects.

> The AAV-based gene therapy improved the function of the heart and other organs in mice with various age-related diseases, suggesting that such an approach could help maintain health during aging. Credit: Adobe Stock

A new study from the Wyss Institute for Biologically Inspired Engineering at Harvard University and Harvard Medical School (HMS) reports that a single administration of an adeno-associated virus (AAV)-based gene therapy delivering combinations of three longevity-associated genes to mice dramatically improved or completely reversed multiple age-related diseases, suggesting that a systems-level approach to treating such diseases could improve overall health and lifespan. The research is reported in *PNAS*.

“The results we saw were stunning, and suggest that holistically addressing aging *via* gene therapy could be more effective than the piecemeal approach that currently exists,” said first author Noah Davidsohn, Ph.D., a former Research Scientist at the Wyss Institute and HMS who is now the Chief Technology Officer of Rejuvenate Bio. “Everyone wants to stay as healthy as possible for as long as possible, and this study is a first step toward reducing the suffering caused by debilitating diseases.”

The study was conducted in the lab of Wyss Core Faculty member George Church, Ph.D. as part of Davidsohn’s postdoctoral research into the genetics of aging. Davidsohn, Church, and their co-authors honed in on three genes that had previously been shown to confer increased health and lifespan benefits when their expression was modified in genetically engineered mice: FGF21, sTGFβR2, and αKlotho. They hypothesized that providing extra copies of those genes to non-engineered mice *via* gene therapy would similarly combat age-related diseases and confer health benefits.

The team created separate gene therapy constructs for each gene using the AAV8 serotype as a delivery vehicle, and injected them into mouse models of obesity, type II diabetes, heart failure, and renal failure both individually and in combination with the other genes to see if there was a synergistic beneficial effect.

FGF21 alone caused complete reversal of weight gain and type II diabetes in obese, diabetic mice following a single gene therapy administration, and its combination with sTGFβR2 reduced kidney atrophy by 75% in mice with renal fibrosis. Heart function in mice with heart failure improved by 58% when they were given sTGFβR2 alone or in combination with either of the other two genes, showing that a combined therapeutic treatment of FGF21 and sTGFβR2 could successfully treat all four age-related conditions, therefore improving health and survival. Administering all three genes together resulted in slightly worse outcomes, likely from an adverse interaction between FGF21 and αKlotho, which remains to be studied.

Importantly, the injected genes remained separate from the animals’ native genomes, did not modify their natural DNA, and could not be passed to future generations or between living animals.

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>
> George Church

“Achieving these results in non-transgenic mice is a major step toward being able to develop this treatment into a therapy, and co-administering multiple disease-addressing genes could help alleviate the immune issues that could arise from the alternative of delivering multiple, separate gene therapies for each disease,” said Church, who is also a Professor of Genetics at HMS and Professor of Health Sciences and Technology at Harvard and MIT. “This research marks a milestone in being able to effectively treat the many diseases associated with aging, and perhaps could lead to a means of addressing aging itself.”

Church, Davidsohn, and co-author Daniel Oliver, M.B.A. are co-founders of Rejuvenate Bio, a biotechnology company that is pursuing gene therapy treatments for dogs. Each holds equity in Rejuvenate Bio.

“The finding that targeting one or two key genes has therapeutic effects in multiple diseases makes enormous sense from the perspective of pathophysiology, but this is not how drugs are normall developed. This ability to tackle several age-related diseases at once using gene therapy offers a potential path to make aging a more manageable and less debilitating process,” said Wyss Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at HMS and the Vascular Biology Program at Boston Children’s Hospital, as well as Professor of Bioengineering at Harvard’s John A. Paulson School of Engineering and Applied Sciences. “We are excited to see how this research progresses in the future.”

“Gene therapy holds enormous promise for treating a variety of diseases, and the ability to tackle several age-related diseases at once could help make aging a more manageable and less debilitating process,” said Wyss Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at HMS and the Vascular Biology Program at Boston Children’s Hospital, as well as Professor of Bioengineering at Harvard’s John A. Paulson School of Engineering and Applied Sciences. “We are excited to see how this research progresses in the near future.”

Additional authors of the paper include Wyss Institute members Andyna Vernet, and Amanda Graveline; former Wyss Institute members Daniel Oliver, Matthew Pezone, Shimyn Slomovic; Sukanya Punthambaker from the Wyss Institue and HMS; and Xiaoming Sun, Joseph Bonventre, and Ronglih Liao from Brigham and Women’s Hospital. The research was supported by the National Institutes of Health, the Merkin Family Foundation and the Wyss Institute.

Across the way in Los Angeles, another treatment test has shown promise.

A cocktail of three common drugs appeared to not only slow aging but to reverse it in a small new study published in Nature on Thursday.

Nine people were given a growth hormone and two diabetes drugs for a year as part of the University of California, Los Angeles (UCLA), trial.

By the end of their cycles on the medications, the study participants had, biologically aged 2.5 years - in reverse.

At first blush it looks like a revelation for human health and life expectancy - but the small group of participants were all white men and there was no control group to compare the findings to, drawing some skepticism from experts.

To many, immortality is the holy grail of futurism and medicine.

And even if you don't idealize the notion of living forever, with aging comes disease and the body's degradation, so evading the damage that time does to us could mean living a healthier life as well as a longer one.

Much more critical to the length and quality of our lives than our numerical age or the lines on our faces is how our body's are changing at the cellular and molecular levels.

Scientists gauge biological aging by something called the 'epigenetic clock.' One method of doing so was developed by co-author of the new study, UCLA's Dr Steve Horvath.

This age assessment looks at changes to how DNA is expressed. As we age, chemical tags called methyls start to hang on to molecules of DNA.

Theses pesky changes don't alter the sequence of the DNA, but they can disrupt the way a section of the genetic code gets turned on and off or issues instructions to biological structures.

More methyls are added to DNA over time, so it becomes more predisposed to disruption, and we become more predisposed to aging itself as well as cancer.

Many factors influence this process, called methylation, and can make our biological clocks race ahead of or trail behind our age in years.

The process effects every organ and tissue in the body - including a vital gland called the thymus.

The thymus functions like finishing school for the white blood cells that drive much of the immune system.

White blood cells are made within the bone marrow, but it's in the thymus where they enter their final forms, becoming T cells that keep infections and cancer at bay.

The thymus starts to degrade with age and as levels of human growth hormone fall.

Previous research in animals suggested that giving people supplemental growth hormone might protect and restore the thymus.

So Dr Horvath's collaborator, immunologist and co-founder of Intervene Immune, Dr Gregory Fahy, recruited nine men between the ages of 51 and 65 to take the growth hormone DHEA.

Dr Fahy had actually experimented with the possibility of using DHEA to rejuvenate the thymus - on himself, in the 1990s.

Since unusually high levels of DHEA may trigger diabetes, the men in the trial were also given the two diabetes drugs.

Over the course of the year they were involved in the study, their thymus tissue was regularly tested.

By the end of the trial, seven of the participants thymuses had shed disruptive fat from the gland, and healthy thymus tissue had regrown in its place.

Dr Horvath happened to ask if he could analyze the mens' epigenetic markers of age.

Remarkably, all 10 participants had fewer methyl tags at the end of the study than they had in the beginning.

Biologically speaking, they appeared to have gotten 2.5 years younger.

'I'd expected to see slowing down of the clock, but not a reversal' Dr Horvath told Nature.

'That felt kind of futuristic.'

The thymus is located in the chest between the lungs and the breastbone and is crucial for efficient immune function. “White blood cells are produced in bone marrow and then mature inside the thymus, where they become specialized T-cells that help the body to fight infections and cancers,” *Nature* reported. “But the gland starts to shrink after puberty and increasingly becomes clogged with fat. Evidence from animal and some human studies shows that growth hormone stimulates regeneration of the thymus. But this hormone can also promote diabetes, so the trial included two widely used anti-diabetic drugs, dehydroepiandrosterone (DHEA) and metformin, in the treatment cocktail.”

Famous politicans and Silicon Valley oligarchs are looking for childrens blood. Could the secret to eternal youth be found in blood transfusions from young people? Some claim that transfusions with “young blood” from teenagers can reverse the aging process.

It’s being tested in patients over the age of 35 as part of a clinical trial called ambrosia, where people paid $8,000 to get the rich growth factors found in bloods plasma platelets.

“There are pretty much people from most states, people from overseas, people from Europe and Australia,” Dr. Jesse Karmazin said.

Results of the trial have not been published.

Dr. Karmazin, who plans to open a business selling young blood, says patients who've had it say they feel amazing, and he says he's seen evidence of reversing the aging process in rats.

"Their brains are younger, their hearts. Their hair, if it was gray, it turns dark again," he said.

There has also been encouraging Alzheimer's research using young blood at Stanford University.

"We found that it was safe and feasible to administer infusions of young plasma weekly," Dr. Sharon Shaw, an Alzheimer's researcher at Stanford, said.

Dr. Shaw is a researcher who says they have seen evidence of improvement in functional ability.

"It's all very exciting that there can be components in blood that can be healing," Dr. Shaw said.

Platelet-rich plasma, or PRP, treatments using a patient's own blood have been in demand as trendy "vampire facials" to fight wrinkles, and as joint and tissue treatments to accelerate healing.

It's also being tested to regrow hair.

"We can actually use your own blood to stimulate the body," said Dr. Hooman Khorasani, chief of the Division of Dermatologic and Cosmetic Surgery at Mount Sinai Health System.

The study hasn't concluded, but seeing even short-term results, the researcher is optimistic.

"It looks very positive," Dr. Khorasani said.

But experts agree, there is still more research that needs to be done.

"There's still a lot of unknowns and factors we don't know when we're we're actually getting another person's growth factors and nutrients injected in us," Dr. Khorasani said.

While blood transfusions are considered safe for people who need them, side effects can include hives, lung injury. or potentially deadly