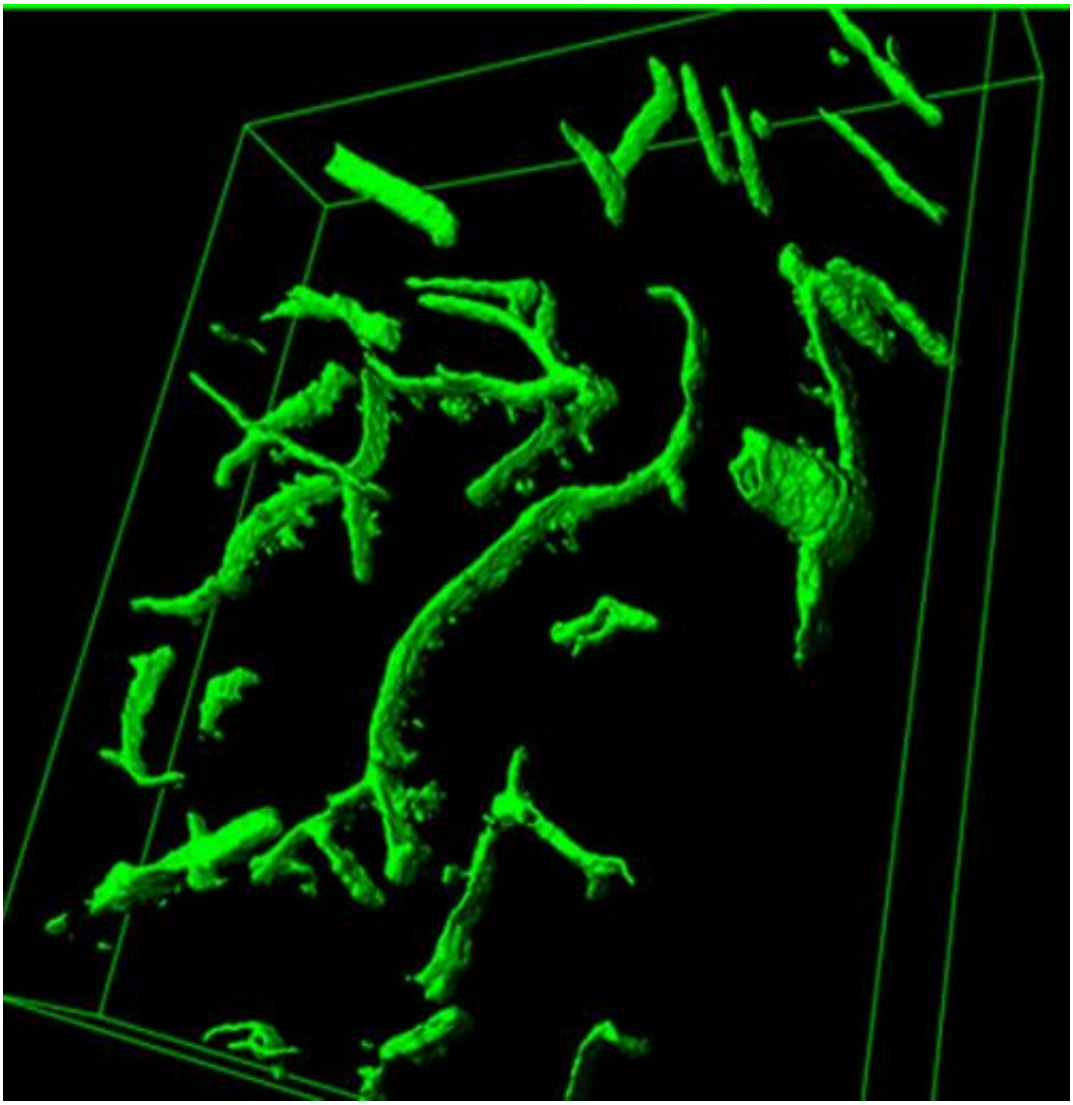
MedicalXpress

Functioning of aged brains and muscles in mice made younger

May 4 2014



3-D reconstruction of blood vessels in a rejuvenated (heterochronic) old mouse. Credit: Lida Katsimpardi

Harvard Stem Cell Institute (HSCI) researchers have shown that a protein they previously demonstrated can make the failing hearts in aging mice appear more like those of young health mice, similarly improves brain and skeletal muscle function in aging mice.

In two separate papers given early online release today by the journal *Science* – which is publishing the papers this coming Friday, Professors Amy Wagers and Lee Rubin, of Harvard's Department of Stem Cell and Regenerative Biology (HSCRB), report that injections of a protein known as GDF11, which is found in humans as well as mice, improved the exercise capability of mice equivalent in age to that of about a 70-year-old human, and also improved the function of the olfactory region of the brains of the older mice – they could detect smell as younger mice do.

Rubin and Wagers each said that, baring unexpected developments, they expect to have GDF11 in initial human clinical trials within three to five years. Postdoctoral fellow Lida Katsimpardi is the lead author on the Rubin group's paper, and postdocs Manisha Sinha and Young Jang are the lead authors on the paper from the Wagers group.

Both studies examined the effect of GDF11 in two ways. First, by using what is called a parabiotic system, in which two mice are surgically joined and the blood of the younger mouse circulates through the older mouse. And second, by injecting the older mice with GDF11, which in an earlier study by Wagers and Richard Lee, of Brigham and Women's Hospital who is also an author on the two papers released today, was shown to be sufficient to reverse characteristics of aging in the heart.

Doug Melton, co-chair of HSCRB and co-director of HSCI, reacted to the two papers by saying that he couldn't "recall a more exciting finding to come from stem cell science and clever experiments. This should give us all hope for a healthier future. We all wonder why we were stronger

and mentally more agile when young, and these two unusually exciting papers actually point to a possible answer: the higher levels of the protein GDF11 we have when young. There seems to be little question that, at least in animals, GDF11 has an amazing capacity to restore aging muscle and brain function," he said.

Melton, Harvard's Xander University Professor continued, saying that the ongoing collaboration between Wagers, a stem cell biologist whose focus has been on muscle, Rubin, whose focus is on neurodegenerative diseases and using patient generated stem cells as targets for drug discover, and Lee, a practicing cardiologist and researcher, "is a perfect example of the power of the Harvard Stem Cell Institute as an engine of truly collaborative efforts and discovery, bringing together people with big, unique ideas and expertise in different biological areas."

As Melton noted, GDF11 is naturally found in much higher concentration in young mice than in older mice, and raising its levels in the older mice has improved the function of every organ system thus far studied.

Wagers first began using the parabiotic system in mice 14 years ago as a post doctoral fellow at Stanford University, when she and colleagues Thomas Rando, of Stanford, Irina Conboy, of UC Berkley, and Irving Weissman, of Stanford, observed that the blood of young mice circulating in old mice seemed to have some rejuvenating effects on muscle repair after injury.

Last year she and Richard Lee published a paper in which they reported that when exposed to the blood of young mice, the enlarged, weakened hearts of older mice returned to a more youthful size, and their function improved. And then working with a Colorado firm, the pair reported that GDF11 was the factor in the blood apparently responsible for the rejuvenating effect. That finding has raised hopes that GDF11 may

prove, in some form, to be a possible treatment for diastolic heart failure, a fatal condition in the elderly that now is irreversible, and fatal.

"From the previous work it could have seemed that GD11 was heart specific," said Wagers, "but this shows that it is active in multiple organs and cell types… Prior studies of skeletal muscle and the parabiotic effect really focused on regenerative biology. Muscle was damaged and assayed on how well it could recover," Wagers explained.

She continued: "The additional piece is that while prior studies of young blood factors have shown that we achieve restoration of muscle stem cell function and they repair the muscle better, in this study, we also saw repair of DNA damage associated with aging, and we got it in association with recovery of function, and we saw improvements in unmanipulated muscle. Based on other studies, we think that the accumulation DNA damage in muscle stem cells might be reflect an inability of the cells to properly differentiate to make mature muscle cells, which is needed for adequate muscle repair.

Wagers noted that there is still a great deal to be learned about the mechanics of aging in muscle, and its repair. "I don't think we fully understand how this happening or why. We might say that the damage is modification to the genetic material; the genome does have breaks in it. But whether it's damaging, or a necessary part of repair, we don't know yet."

Rubin, whose primary research focus is on developing treatment for neurodegenerative diseases, particularly in children, said that that when his group began its GDF11 experiments, "we knew that in the old mouse things were bad in the brain, there is a reduced amount of neurogenesis (the development of neurons), and it's well known that cognition goes down. It wasn't obvious to me that those things that can be repaired in peripheral tissue could be fixed in the brain."

Rubin said that post doctoral fellow Lida Katsimpardi, the lead author on his group's paper, was taught the parabiotic experimental technique by Wagers, but conducted the Rubin group's experiments independently of the Wagers group, and "she saw an increase in neural stem cells, and saw increased development of blood vessels in the brain." Rubin said that 3D reconstruction of the brain, and magnetic resonance imaging (MRI) of the mouse brain showed "more new blood vessels and more blood flow," both of which are normally associated with younger, healthier brain tissue." Younger mice, Rubin said, "have a keen sense of olfactory discrimination," they can sense fine differences in odor. "When we tested the young mice, they avoided the smell of mint; the old mice didn't. But the old mice exposed to the blood of the young mice, and those treated with GDF11 did.

"We think an effect of GDF 11 is the improved vascularity and blood flow, associated with increased neurogenesis," Rubin said. "This should have other more widespread effect on other areas of the brain. We do think that, at least in principal, there will be a way to reverse some of the decline of aging with a single protein. It could be that a molecule like GDF 11, or GDF 11 itself, could" reverse the damage of aging.

"It isn't out of question that GDF11," or a drug developed from it, "might be worthwhile in Alzheimer's Disease," Rubin said. "You might be able to separate out the issues of treating the plaque and tangles associated with the disease, and the decline in cognition, and perhaps improve cognition." Wagers said that the two research groups are in discussions with a venture capital group to obtain funding to "be able to do the additional pre-clinical work" necessary before moving GDF 11 into human trials.

"I would wager that the results of this work, together with the other work, will translate into a clinical trial and a treatment," said the stem cell biologist. "but of course that's just a wager."

"We think an effect of GDF 11 is the improved vascularity and blood flow, which is associated with increased neurogenesis," Rubin said. "However, the increased blood flow should have more widespread effects on brain function. We do think that, at least in principle, there will be a way to reverse some of the cognitive decline that takes place during aging, perhaps even with a single protein. It could be that a molecule like GDF 11, or GDF 11 itself, could" reverse the damage of aging.

"It isn't out of question that GDF11," or a drug developed from it, "might be capable of slowing some of the cognitive defects associated with Alzheimer's Disease, a disorder whose main risk factor is aging itself," Rubin said. It is even possible that this could occur without directly changing the "plaque and tangle burden" that are the pathological hallmarks of Alzheimer's. Thus, a future treatment for this disease might be a combination of a therapeutic that reduces plaques and tangles, such as an antibody directed against the β-amyloid peptide, with a potential cognition enhancer like GDF-11.

Wagers said that the two research groups are in discussions with a venture capital group to obtain funding to "be able to do the additional preclinical work" necessary before moving GDF 11 into human trials.

"I would wager that the results of this work, together with the other work, will translate into a clinical trial and a treatment," said the stem cell biologist. "but of course that's just a wager."

More information: "Vascular and Neurogenic Rejuvenation of the Aging Mouse Brain by Young Systemic Factors," by L. Katsimpardi et al. *Science*, 2014.