Extending lives of old mice by connecting vessels to young ones

August 13 2023, by Clea Simon

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It's more complicated than a fountain of youth, but a team of scientists co-led by Harvard Medical School Professor of Medicine Vadim

Gladyshev extended the lives of old mice by connecting their circulatory systems to those of young mice. Using a process called heterochronic parabiosis, the researchers connected their vessels for three months.

The results were striking: The old mice lived for an average of 6 percent to 9 percent longer than their control peers, and biological age determined with biomarkers of aging in both the old and young mice was affected by the three-month blood-sharing procedure. The Gazette spoke with Gladyshev about this research, which was published in *Nature Aging*. The interview was edited for length and clarity.

Q&A: Vadim Gladyshev

GAZETTE: Who came up with the idea of this unusual study?

GLADYSHEV: The idea was conceived by Bohan Zhang, at the time a graduate student in Harvard's Biological and Biomedical Sciences program. He is the first author of the Nature Aging paper.

GAZETTE: Is this like a blood transfusion?

GLADYSHEV: No, it's quite different. It's not just an infusion of young blood: The young and old mice share much more in this procedure. For example, old mice have access to the younger organs and the mice exchange blood factors in both ways so that the damage accumulated with age is distributed, together with other factors that might influence biological age.

GAZETTE: What did you observe?

GLADYSHEV: Basically what we observed is that following this

procedure, the older mice became younger, and they lived longer than the controls. The difference in lifespan is significant, but it's not huge. A much larger difference is in the biological age at the time of parabiosis. So in that sense, the course of their aging changed because the older mice initially got partially rejuvenated, but then they aged differently than the control mice.

GAZETTE: How do you measure aging?

GLADYSHEV: Biological age can now be better quantified than before. By looking at a person, we may estimate that person's chronological age, which is, say, 60 years old. But some 60-year-olds may look and actually be more like they're 50 years old—and some 70-year-olds. People age at somewhat different rates, right? The biomarkers of aging allow us to quantify that and also quantify responses to interventions that affect biological age. For example, if we subject mice to caloric restriction and have controls of the same chronological age, we find that calorically restricted animals are biologically younger. Likewise, we applied aging biomarkers to ask a question: What is the biological age of the mice following parabiosis and later in life?

GAZETTE: What are these biological markers?

GLADYSHEV: The most common one is known as the epigenetic clock. It is based on the assessment of the methylation status of cytosines in the DNA. Some cytosines become more methylated, and some lose methylation with age. Out of the millions of cytosines, we select a few hundred that best represent the aging process and allow us to quantify biological age. In addition to the epigenetic clock, we also use transcriptomic biomarkers. These allowed us to determine that the biological age of the old mice is reduced compared to control.

GAZETTE: And these effects persisted in the two months following the experiment?

GLADYSHEV: In the old mice, yes. They remained younger than controls and they lived longer. In a separate study (published several months ago in *Cell Metabolism*), we looked at the younger animals and found that their biological age increased following parabiosis, but after detachment from old mice, it decreased again back to normal.

In the Nature Aging paper we only quantified biological age at the time of the three months of the parabiosis procedure and then two months later, and the overall impression is that initially the rejuvenating effect was strong. It seemed to diminish later on, but we still observed a difference in lifespan. Also, it seemed it's more difficult to rejuvenate animals than to increase their biological age.

GAZETTE: What do you think causes this?

GLADYSHEV: I can only speculate, but we may view this in terms of the accumulated molecular damage. When the mice develop a joint circulatory system, the damage from the old mice goes to the young mice and increases their biological age. But in the case of the old mouse, this process dilutes their damage. After detachment, the damage transferred to the young mice from the old can be cleared over time, whereas in the old mice, this damage is diluted permanently.

We don't know exactly how this happens. Maybe there are so-called youthful factors in the blood of the young mice that promote the youthfulness in the old. Another possibility is that parabiosis supports damage dilution, and yet another idea is that the old animals have access to the younger organs of the young mice that detoxify the damage via their livers and kidneys. It's probably a combination of different factors

that leads to the rejuvenating effect. But it's clearly not just that an infusion of young blood rejuvenates. It's more complex than that.

More information: Bohan Zhang et al, Multi-omic rejuvenation and life span extension on exposure to youthful circulation, *Nature Aging* (2023). DOI: 10.1038/s43587-023-00451-9