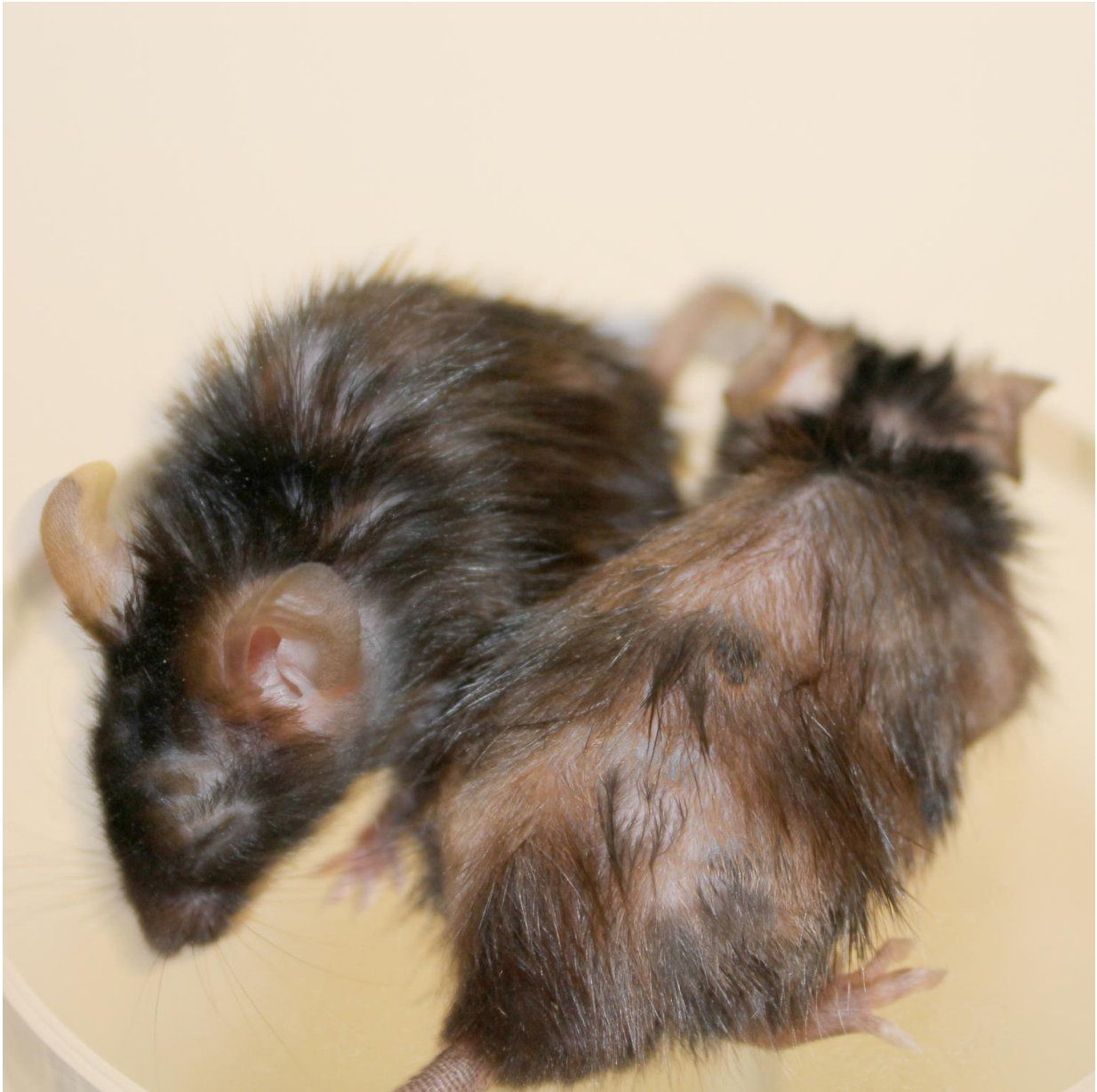


Peptide targeting senescent cells restores stamina, fur, and kidney function in old mice

March 23 2017



Two fast-aging mice. The mouse on the left was treated with a FOXO4 peptide, which targets senescent cells and leads to hair regrowth in ten days. The mouse on the right was not treated with the peptide. Credit: Peter L.J. de Keizer

Regular infusions of a peptide that can selectively seek out and destroy broken-down cells that hamper proper tissue renewal, called senescent cells, showed evidence of improving healthspan in naturally-aged mice and mice genetically engineered to rapidly age. The proof-of-concept study, published March 23 in *Cell*, found that an anti-senescent cell therapy could reverse age-related loss of fur, poor kidney function, and frailty. It is currently being tested whether the approach also extends lifespan, and human safety studies are being planned.

The peptide took over four years of trial and error to develop and builds on nearly a decade of research investigating vulnerabilities in [senescent cells](#) as a therapeutic option to combat some aspects of aging (*Trends in Molecular Medicine*, 10.1016/j.molmed.2016.11.006). It works by blocking the ability of a protein implicated in senescence, FOXO4, to tell another protein, p53, not to cause the cell to self-destruct. By interfering with the FOXO4-p53 crosstalk, the peptide causes senescent cells to go through apoptosis, or cell suicide.

"Only in senescent cells does this peptide cause cell death," says senior author Peter de Keizer, a researcher of aging at Erasmus University Medical Center in the Netherlands. "We treated [mice](#) for over 10 months, giving them infusions of the peptide three times a week, and we didn't see any obvious side effects. FOXO4 is barely expressed in non-senescent cells, so that makes the peptide interesting as the FOXO4-p53 interaction is especially relevant to senescent cells, but not normal cells."

Results appeared at different times over the course of treatment. Fast-

aging mice with patches of missing fur began to recover their coats after 10 days. After about three weeks, fitness benefits began to show, with older mice running double the distance of their counterparts who did not receive the peptide. A month after treatment, aged mice showed an increase in markers indicating healthy [kidney function](#).

Senescent cell therapy is one of several strategies being tested in mice aimed at reversing aging or lengthening healthspan. In 2015, the Valter Longo laboratory at the University of Southern California reported that mice on a calorie-restricted diet that mimics fasting benefited from a longer life, a reduction in inflammatory disease, and improved memory (*Cell Metabolism*, 10.1016/j.cmet.2015.05.012). And last December, Juan Carlos Izpisua Belmonte at the Salk Institute of Biological Science and colleagues made headlines with their discovery that cellular reprogramming of epigenetic marks could extend lifespan and improve health in fast-aging mice (*Cell*, 10.1016/j.cell.2016.11.052).

"This wave of research on how we can fight aging is complementary, and not in competition," says de Keizer. "The common thread I see for the future of anti-aging research is that there are three fronts in which we can improve: The prevention of cellular damage and senescence, safe therapeutic removal of [senescent cells](#), to stimulate stem cells—no matter the strategy—to improve tissue regeneration once senescence is removed."

de Keizer aims to start a company based on these findings, but in the short term, he and his group want to show that their peptide is non-toxic in humans with no unforeseen side effects. They plan to offer a safety clinical trial in people with Glioblastoma multiforme, an aggressive brain tumor, which also shows high levels of the biomarkers needed for this FOXO4 peptide to be effective.

More information: *Cell*, Baar et al.: "Targeted Apoptosis of Senescent

Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging" [www.cell.com/cell/fulltext/S0092-8674\(17\)30246-5](http://www.cell.com/cell/fulltext/S0092-8674(17)30246-5) DOI: [10.1016/j.cell.2017.02.031](https://doi.org/10.1016/j.cell.2017.02.031)

Sebastian Brandhorst et al. A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan, *Cell Metabolism* (2015). DOI: [10.1016/j.cmet.2015.05.012](https://doi.org/10.1016/j.cmet.2015.05.012)

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