This 1463-day-old mouse is part of a long-lived cohort at The Jackson Laboratory.

DEATH–DEFYING EXPERIMENTS

Pushing the limits of life span in animals could someday help lengthen our own

By **Jon Cohen**

On 8 January 2003, a mouse made news because it died.

Unlike other caged animals that gain notoriety, this dwarf mouse was not particularly cute or charismatic. He had not performed a silly pet trick or some astonishing intellectual feat. This laboratory mouse, a resident of Southern Illinois University in Carbondale, won notoriety because he lived 1819 days. "He missed his fifth birthday by a week, which is kind of unheard of in life span for a mouse," says Andrzej Bartke, the zoologist who ran the lab that bred and studied the murine wonder unimaginatively dubbed GHR-KO 11C.

Bartke is too modest: It *was* unheard of. Lab mice typically live half as long, and GHR-KO 11C had, by Bartke's calculations, lived beyond 180 human years. "As pleasant as it was for us to get this notice and publicity, it's an n of 1," he stresses. "I didn't get too excited." (Some colleagues suspect there was a lab mix-up and GHR-KO 11C did not live as long as reported, but—reluctant to be seen as competing for a ridiculous title—keep their doubts quiet.)

Deliberately mutated to knock out a gene for a growth hormone receptor, GHR-KO 11C was a beneficiary of Bartke's effort to tease out the forces that drive aging. Other researchers have bred or engineered animals from mice down to flies, worms, and even yeast to vastly exceed their normal spans. The effort is yielding insights into aging, but researchers concede that there is also a *Guinness World Records*–ish fascination about it. "'My animal lives longer than yours' is highly clickable," says Richard Miller, who studies the biology of aging at the University of Michigan, Ann Arbor.

Miller's own elderly mice have enjoyed a few brief moments in the limelight. The first came 2 years before GHR-KO 11C squeaked to fame when Miller claimed the title of having "the world's oldest normal lab mouse." Dubbed IdG1-030, the mouse lived 1449 days, and its death elicited an obituary in the ironically short-lived *Science of Aging Knowledge Environment*. "Born and raised in a small plastic cage in Ann Arbor, Michigan, IdG1-030 was one of a set of quintuplets born to a mated pair whose own parents had romped, poor but free, in the barnyards of Moscow, Idaho," read the heart-wrenching obit. The goal was to compare wild mice with their laboratory cousins, which have been bred for short life spans to make it easier to complete experiments.

As Miller stressed in IdG1-030's death notice, his lab had not restricted the caloric intake of the mouse, a tried-and-true way to extend the life span of many species, including mice. Miller wrote that his mouse "was clearly willing to accept an asterisk in the record books as the price for a life of ready access to all-you-can-eat meals." Today, several lab mice have passed their fourth birthdays, including one in Miller's lab named Yoda, a nod to the oldest Jedi master in *Star Wars*. "We now have at least five genes, two diets, and five drugs that extend mouse life spans," Miller says. "There's an enormous amount that's been learned."

Geneticist Gary Churchill at The Jackson Laboratory in Bar Harbor, Maine, currently has the oldest living mice, several of which are 4.5 years old. "They've been dropping off," Churchill laments. "I'm not holding my breath, but we could still make it to 5 years."

RESEARCHERS WHO STUDY *Drosophila melanogaster*, the fruit fly elevated to superstar status in genetic studies by Nobel laureate Thomas Hunt Morgan, have never reported a Yoda, GHR-KO 11C, or IdG1-030. "There is no oldest fly," says Marc Tatar, an

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evolutionary biologist at Brown University. "We don't really pay that much attention. People who work on *Drosophila* look at cohorts and populations."

Nobody even knows the average life span of *Drosophila*, Tatar says, because the flies are so sensitive to diet, temperature, access to mates, and other environmental forces. "In my lab, the average might be 40, 50 days, and long-lived ones might be 80 or 90." That said, his lab and others have shown that they can produce long-lived fly populations by mutating genes—including the comically named *Indy* (I'm not dead yet)—that affect metabolic pathways.

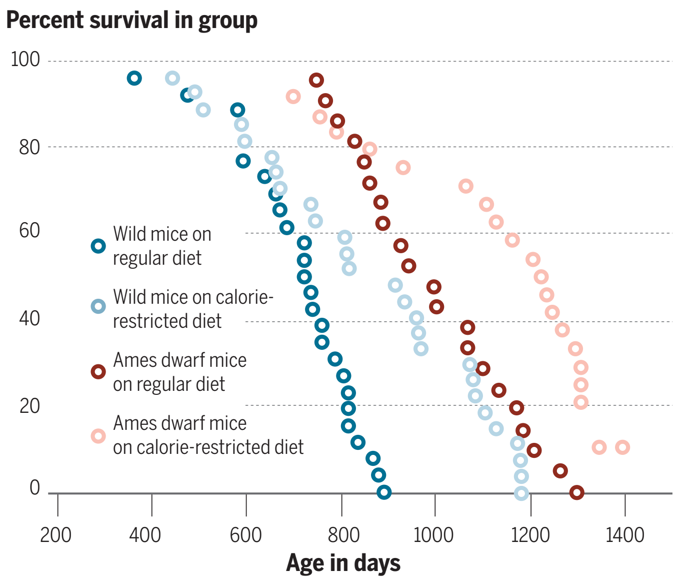
Evolutionary biologist Michael Rose, whom Malcolm Gladwell profiled in *The New Yorker* in 1996 for his creation of "Methuselah" flies, pushed their life spans to 4 months and more by selectively breeding them for longevity. Rose, who works at the University of California (UC), Irvine, insists that he no longer is interested in setting records. Just the same, he says, "Our Methuselah flies wipe the floor with everyone else's mutant *Drosophila*," adding, "what most people work with in most labs is inbred garbage." His lab now studies how aging can be stopped. "It renders the question of the longest-lived organism meaningless," he says.

James Carey's landmark fly studies also challenge the notion of an upper age limit. Carey, an entomologist at UC Davis, and colleagues studied 1.2 million medflies at a factory in Mexico that bred sterile versions of these fruit-destroying pests as part of a biological control strategy. The work, reported in *Science* in 1992, helped overturn the theory that mortality risks increase with age. The percentage of medflies that die at a certain day, it turns out, decreases as they age. So if you have a population of medflies that reaches 100 days, you might see 10% of them die by 110 days, but between 110 and 120 days the mortality rate could drop to 9%. "It was a big surprise that there's a slowing of mortality," Carey says. "You still have a high probability of dying, but it's just not as high."

The findings suggest that "there's not a wall of death," he says. He points to Jeanne Calment, the longest-lived human on record, who died in France at age 122. "It's inconceivable to me that 122 will never ever be broken in the history of humankind," he says.

Getting more mileage from mice

Dwarf genes and very low-calorie diets independently contribute to mouse survival.



LONGEVITY RESEARCHERS have had the most success increasing the life span of *Caenorhabditis elegans*, the soil roundworm that Nobel laureate Sydney Brenner brought into the lab in 1963 to study neural development. "We have single gene mutations with the greatest percentage increase in any animal life span by far," says molecular geneticist Robert Shmookler Reis of the University of Arkansas for Medical Sciences in Little Rock.

In 2008, Reis and colleagues reported in *Aging Cell* that two strains of *C. elegans* with mutations in the same gene, *age-1*, had an average life span of 145 to 190 days—nearly 10 times longer than the wild-type worms living in the same environment. The oldest worm in their study lived 270 days. "We were astonished," Reis says. "The first time we did it I said 'No, no, they can't still be alive, you must be looking at descendants of the starting worms.' Except these worms were absolutely sterile!" The researchers are still working to explain the extraordinarily long life spans, but have evidence that their longevity is tied to silencing of insulinlike signaling pathways and stress responses.

The worms, bizarrely, had "near normal" motility and feeding rates—similar to wild-type worms at one-tenth their age—until they neared death. "The last few worms to die are always on their last legs," says Reis, who quickly adds, "I know they don't have legs, but they don't look that great."

THE SPECIES that still holds the lab longevity sweepstakes is *Hydra vulgaris*, a tiny relative of the jellyfish made up of three lineages of self-renewing stem cells that—unlike in other species—do not lose their capacity to replace themselves as they age. Evolutionary biologist Daniel Martínez of Pomona College in Claremont, California, in 1998 published a study in *Experimental Gerontology* describing how 145 *Hydra* had lived in his lab for 4 years without any signs of aging, leading to his claim that they "may be potentially immortal." His work purported to end a century-old scientific debate about whether these creatures age.

"After I published this initial paper I stopped," Martínez says. "I couldn't figure out what to do. You can't study aging in something that doesn't age." The *Hydra* had to be fed three times a week with live brine shrimp and were fussy about salinity (hate it), their own waste, temperature, and overfeeding. "I was just sick of them," he said. "I put them in alcohol and killed them."

When researchers from a Max Planck institute in Germany convinced Martínez that there was more to learn from these apparently immortal animals, he restarted his experiments. Working together, the two groups now have *Hydra* that are 10 years old. "There's no evidence of aging, no decay in reproduction, and no sign of mortality," he says. The team also has shown that *FoxO*, a gene that increases tolerance to oxidative stress—and is linked to longevity in *Drosophila* and *C. elegans*—may play a central role in *Hydra*'s ability to maintain its stem cells.

In contrast to *H. vulgaris*, its cousin, *H. oligactis*, will senesce if confronted by lowering water temperatures. Basically, the cooler water prompts the *Hydra* to switch from its usual, asexual mode of reproduction to sexual reproduction. "They switch from being stem cells into differentiated cells," Martínez notes. Now, he's comparing the two *Hydra* species to learn what controls the change.

Last year Martínez's collaborators claimed in *Nature* that 5% of adults cared for in a lab would still be alive after 1400 years; the others would have died of accidents and disease, but not old age. "I'm reluctant to say that what we're going to learn in *Hydra* will make us immortal," Martínez says. "But you never know when you're going to learn something that will apply to humans." ■