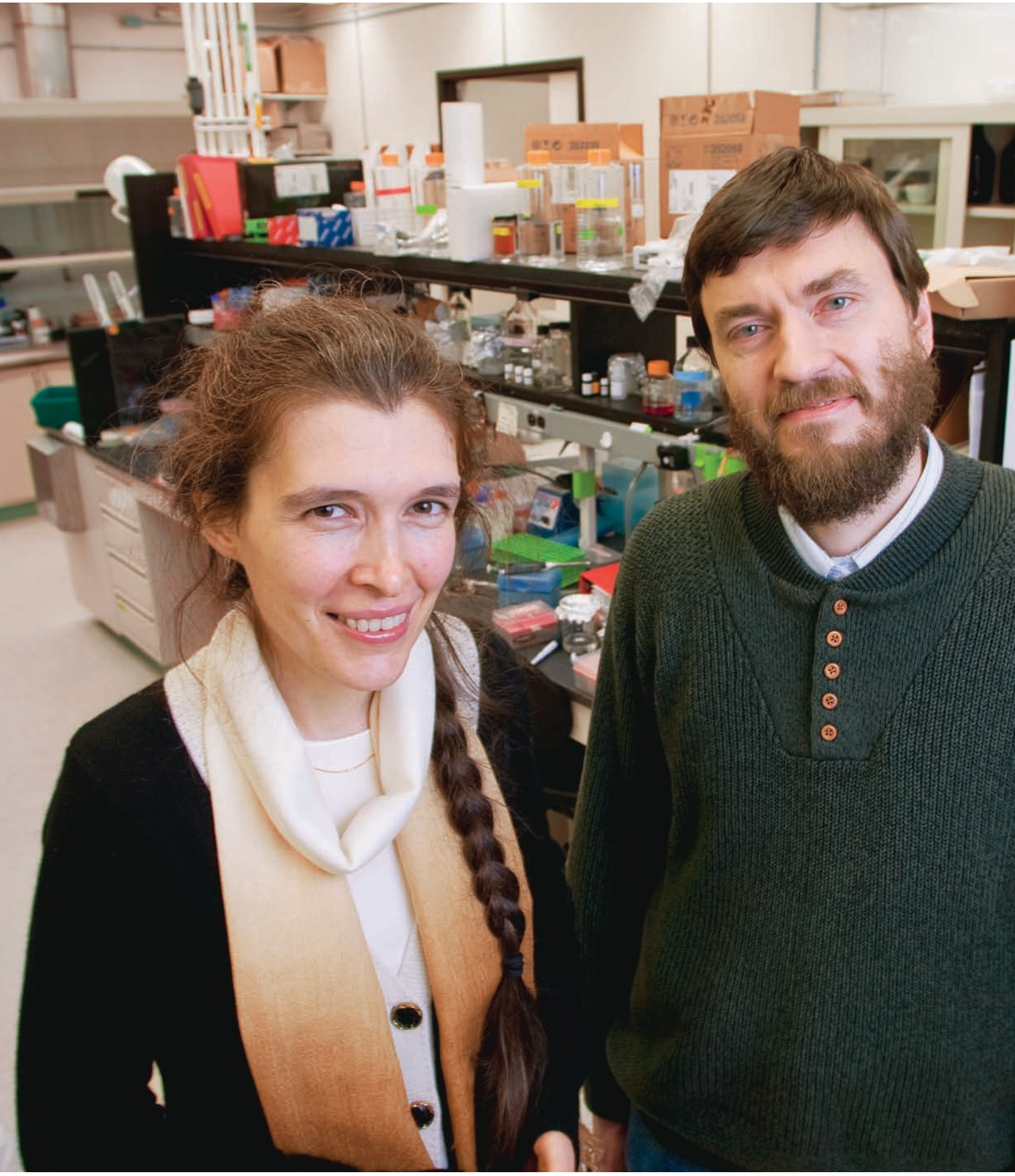

CANCER CURIOSITY: Gorbunova and Seluanov focused on the biology of cancer after noticing that rates of the disease vary widely across a set of 15 species of rodents that included beavers (inset).

The MYSTERY of an Anticancer Mechanism

A genetic twist in a rarely studied animal may have big implications for the fight against cancer in humans.

By Jonathan Sherwood '04 (MA), '09S (MBA)

PHONE CALLS AT 3 a.m. rarely involve good news. Especially if the caller is a man toting a firearm.

But to Vera Gorbunova, an associate professor of biology, the call that woke her was a welcome one. On the phone was a hunter fresh from the swamps of the Montezuma National Wildlife Refuge near Cayuga Lake, east of Rochester.

The hunter knew that the Rochester professor was on the lookout for hard-to-come-by rodents. And beavers fit the bill. Normally protected from hunting and trapping in New York, the mostly nocturnal animals are considered pests in the wildlife refuge because of the damage they can do to the swamp's white oak and birch trees.

Beavers were among the 15 rodents Gorbunova was studying to investigate a hunch she had about cancer.

Why, she had asked, can a squirrel live nearly two decades—well into the golden years for a relatively small mammal—and not show signs of cancer? Yet mice, if they manage to live past two years old, often succumb to the disease?

Is it possible, Gorbunova wondered, that some rodents have ways to protect against cancer that are completely unknown to humans?

"We know that some species of rodents live to an extreme old age and don't seem to get cancer," say Gorbunova. "Do some rodents

ADAM FENSTER (GORBUNOVA AND SELUANOV); ISTOCKPHOTO (BEAVER)

"Selecting the rodents was easy, but getting the tissue samples from each of them was much, much harder. Some of the rodents, like the beaver, are protected species. Some don't exist in North America. Some weigh more than a hundred pounds. It's not like you can order them out of a catalog. It took us more than a year of calling and e-mailing all sorts of people to find all the rodents we needed."

have an undiscovered anticancer mechanism? If so, what are the implications for fighting cancer in humans?"

This fall, Gorbunova may have found an intriguing answer in one of the stranger rodents on her list—the east African naked mole rat, mice-like creatures that spend their lives underground in highly social colonies. Naked mole rats can live up to 28 years, the longest lifespan of any rodent, yet they have never been observed to develop cancer.

In a paper published in the *Proceedings of the National Academy of Sciences,* Gorbunova reported that naked mole rats seem to have a genetic ability to stop cells from replicating if too many crowd together. And runaway cellular replication, she notes, is the very definition of cancer.

"Gorbunova has put her finger on the mechanism that gives a dramatic cancer resistance to this rodent," says John Sedivy, a professor of biology and medical science at Brown University. "Her work elegantly demonstrates the value of studying 'unusual' animals because this mechanism simply does not appear to exist in mice."

Searching for such anticancer mechanisms in animals that are naturally long-lived has been the goal of Gorbunova and her husband and long-time collaborator, Andrei Seluanov, an assistant professor of biology, since they arrived at the University in 2004. Attracted by Rochester's unusually strong combination of both molecular and evolutionary biology, the pair set up a lab in Hutchison Hall, where they now oversee a research team that includes a half-dozen graduate students and a half-dozen undergraduates.

One of only a few research groups across the country to study the seemingly "cancer-proof" naked mole rats, the team focuses on the role of telomerase, an enzyme that plays a key role in cellular replication that has been an important vein of cancer research over the past 25 years. (The team that discovered the enzyme's role in 1985 received the Nobel Prize in Medicine and Physiology in December.) Something like a molecular housekeeper, telomerase makes sure that the ends of chromosomes—brief sections of DNA called telomeres—stay intact. As each cell divides, its telomeres slowly shorten, eventually resulting in the death of the cell. Without telomerase, the telomeres would shorten much sooner. If telomerase were to act just right, cells conceivably could reproduce forever.

For Gorbunova, as with most cancer researchers, studying the disease traditionally has meant focusing on one of two models: mice or humans. A key difference between the two organisms is that in mice, telomerase is very active, allowing cells to reproduce quickly. In humans, telomerase is much less active. On the plus side, that means mice heal from injuries far faster than humans do. But there's a downside—increased cancer risk as unwanted cells reproduce quickly and indefinitely.

ISTOCKPHOTO

Because telomerase allows cells to reproduce very quickly, biologists had long assumed that the reason humans suppress the action of telomerase and mice don't is that mice live on average only about two years. Their risk of getting cancer is low because they're not likely to live long enough to get the disease. But humans live for 80 years, plenty of time to develop a few cells that will become cancerous.

Gorbunova, however, didn't accept that explanation.

In tests of several closely related rodents that varied greatly in lifespan, she explored whether longer-lived animals suppressed

their telomerase more than shorter-lived ones.

"Selecting the rodents was easy, but getting the tissue samples from each of them was much, much harder," says Gorbunova. "Some of the rodents, like the beaver, are protected species. Some don't exist in North America. Some weigh more than a hundred pounds. It's not like you can order them out of a catalog. It took us more than a year of calling and e-mailing all sorts of people to find all the rodents we needed."

The list included regular mice, squirrels, otters, and gerbils, as well as more exotic animals such as giant capybara from South America, chinchillas, and the naked mole rat.

As Gorbunova studied the tissue samples over the years, she was surprised to find no correlation between how long a rodent lived and the action of its telomerase. Some animals, such as the naked mole rat, lived nearly three decades yet expressed as much telomerase as a regular mouse.

Instead, another correlation came to light—body mass. Larger animals, like humans and capybara, simply have more cells that can become cancerous, and so telomerase is suppressed to reduce the chance that any particular cell will set off a tumorous cascade.

But what about the naked mole rat? Despite their long lives and the large numbers of naked mole rats under observation, there has never been a single recorded case of a mole rat contracting cancer, says Gorbunova.

Adding to the mystery is the fact that mole rats appear to age very little until the very end of their lives.

When Gorbunova and her team began investigating mole rat cells, they were surprised at how difficult it was to grow the cells in the lab. The cells simply refused to replicate once a certain number occupied a space. The mole rats seemed to be able to turn the process of replication off regardless of the action of telomerase.

Other cells, including human cells, also cease replication when their populations become too dense, but the mole rat cells were reaching their limit much earlier than those of other animals. Gorbunova and Seluanov have named the phenomenon "early contact inhibition."

"Since cancer is basically runaway cell replication, we realized that whatever was doing this was probably the same thing that prevented cancer from ever getting started in the mole rats," says Gorbunova.

That early contact inhibition was so pronounced that when Gorbunova's team mutated cells to induce a tumor, the growth of cells in the naked mole rats barely changed, whereas mouse cells became fully cancerous.

"We think we've found the reason these mole rats don't get cancer, and it's a bit of a surprise," says Gorbunova. "It's very early to speculate about the implications, but if the effect of early contact inhibition can be simulated in humans we might have a way to halt cancer before it starts."

The key, according to Gorbunova, can be found in the action of a gene known as *p16*, which, in naked mole rats, triggers an early anticancer mechanism that appears to tell the cells to stop replicating. As in many animals, including humans, the mole rats also have a gene called *p27* that limits how many cells can crowd together.

"In humans and mice, *p16* doesn't play a major role in contact inhibition, but in the naked mole rat *p16* gets activated when the cells just begin crowding and arrests cell proliferation," Gorbunova says. "Cancer cells tend to find ways around *p27*, but mole rats have a double barrier that a cell must overcome before it can grow uncontrollably.

"We believe the additional layer of protection conferred by this two-tiered contact inhibition contributes to the remarkable tumor resistance of the naked mole rat," says Gorbunova.

Gorbunova and Seluanov plan to delve deeper into the mole rat's genetics to see if the animals' cancer resistance might be applicable to humans.

"The approach is promising as humans also have the *p16* gene, but it plays a different role in anticancer protection," says Gorbunova. "When we learn more about the differences between the gene in humans and naked mole rats we may learn how to activate the earlier protection in human cells.

"It's also important to study other genes involved in cell-to-cell contact in order to understand how early contact inhibition can serve to cure or even to prevent human cancer."

ANTICANCER KEY? Despite a long lifespan, naked mole rats (this page) have never been observed to have cancer, a disease that occurs in varying rates in squirrels, capybaras, otters (opposite), and other rodents, according to Gorbunova.

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