Researchers have uncovered an ancient mechanism that retards aging. Drugs that tweaked it could well postpone cancer, diabetes and other diseases of old age

By David Stipp
ON A CLEAR NOVEMBER MORNING IN 1964

the Royal Canadian Navy's Cape Scott embarked from Halifax, Nova Scotia, on a four-month expedition. Led by the late Stanley Skoryna, an enterprising McGill University professor, a team of 38 scientists onboard headed for Easter Island, a volcanic speck that juts out from the Pacific 2,200 miles west of Chile. Plans were afoot to build an airport on the remote island, famous for its mysterious sculptures of enormous heads, and the group wanted to study the people, flora and fauna while they remained largely untouched by modernity.

The islanders warmly welcomed Skoryna's team, which brought back hundreds of specimens of plants and animals, as well as blood and saliva from all 949 of the residents. But a test tube of dirt turned out to be the biggest prize: it contained a bacterium that made a defensive chemical with an amazing property—the ability to prolong life in diverse species.

Several research teams have now demonstrated that the chemical, named rapamycin, boosts the maximum life span of laboratory mice beyond that of untreated animals. Dubious anti-aging claims are sometimes made based on data showing increased average life span, which can be achieved by antibiotics or other drugs that reduce premature death yet have nothing to do with aging. In contrast, increased maximum life span (often measured as the mean life span of the longest-lived 10 percent of a population) is a hallmark of slowed aging. No other drug has convincingly extended maximum life span in any of our mammalian kin—gerontology's long-awaited version of breaking the sound barrier. The success in mice has therefore been a game changer for scientists who study aging and how to mitigate its effects. Gerontologists dearly want to find a simple intervention for slowing aging, not merely to increase longevity, but because putting a brake on aging would be a broad-brush way to delay or slow progression of so much of what goes wrong with us as we get old, from cataracts to cancer.

For years gerontologists' hopes of discovering antiaging compounds had been on a roller coaster. Optimism rose with the discovery of gene mutations that extend maximum life span in animals and with new insights into how calorie restriction produces the same effect in many species. Yet the advances, for all their promise, did not reveal any drugs that could stretch the outer limits of longevity in a mammal. Although calorie restriction, which involves nutritionally adequate near-starvation diets, can both do that and delay cancer, neurodegeneration, diabetes and other age-related disorders in mice, very stringent dieting is not a feasible option for slowing aging in most mortals.

In 2006 resveratrol, the famous ingredient in red wine that replicates some of calorie restriction's effects in mice, seemed likely to break through the barrier when it was shown to block the life-shortening consequences of high-fat diets in the rodents. But this substance, which is thought to act on enzymes known as sirtuins, later failed to extend maximum life span in mice fed normal diets. The disappointing picture suddenly brightened again when the rapamycin results were announced in mid-2009. A trio of labs jointly reported that rapamycin, by then known to inhibit cell growth, extended maximum life span by some 12 percent in mice in three parallel experiments sponsored by the National Institute on Aging. What is more, to gerontologists' amazement, the drug extended average survival by a third in old mice that were presumed to be too damaged by aging to respond.

Rapamycin's shattering of the life span barrier in mammals has riveted attention on a billion-year-old mechanism that appears to regulate aging in mice and other animals and may well

In 2009 scientists discovered that a drug called rapamycin could significantly extend life span in mice, doing so by interfering with the activity of a protein called mammalian TOR, or mTOR.
The finding is the most compelling evidence to date that mammalian aging can be slowed pharmacologically, and it galvanized interest in mTOR's role in the aging process.
The result also highlighted a mystery: Why would suppressing cellular growth and replication—one effect of interfering with mTOR—extend life span?

Research into that question could lead to medicines that postpone or mitigate aging-related disorders—from Alzheimer's disease to cancer to heart failure—and perhaps even extend how long humans can live.
do the same in humans. Its mainspring is a protein called TOR (target of rapamycin) and the gene that serves as the protein’s blueprint. TOR is now a subject of intense scrutiny in both gerontology and applied medicine because a growing number of animal and human studies suggest that suppressing the activity of the mammalian version (mTOR) in cells can lower the risk of major age-related diseases, including cancer, Parkinson’s, heart muscle degeneration, type 2 diabetes, osteoporosis and macular degeneration. The remarkable diversity of potential benefits implies that if medicines able to target mTOR safely and reliably could be found, they might be used to slow the aging process in people, as rapamycin has in mice and other species—a possibility with profound implications for preventive medicine. (Rapamycin itself, unfortunately, has side effects that probably preclude testing whether it slows human aging.)

Similar predictions have been made for drugs that act on other molecules, notably the sirtuins. So what is different with mTOR? The finding that a drug has convincingly extended maximum life span in a mammal by acting on the molecule means that mTOR is central to mammalian aging and that researchers are now a lot closer than ever before to finding ways to brake the aging process. “It sure looks like [TOR] is the biggest game in town today and probably for the next decade,” says Kevin Flurry, a gerontologist at the Jackson Laboratory in Bar Harbor, Me., and a co-author of the rapamycin study in mice.

**TOR’S STORY**

The research leading to the discovery of TOR’s influence on aging took shape when the Skorony expedition turned over its soil samples to what was then Ayerst Laboratories in Montreal. Pharmaceutical researchers had been finding antibiotics in pinches of dirt since the 1940s, and so Ayerst’s researchers screened the samples for antimicrobials. In 1972 they sifted out a fungal inhibitor and named it rapamycin because Easter Island is also known locally as Rapa Nui. Ayerst initially hoped to use it to treat yeast infections. But then, scientists exploring its properties in cell-culture studies and on animals’ immune systems found that it can hinder proliferation of immune cells, prompting its development instead to prevent immune rejection of transplanted organs. In 1999 rapamycin received U.S. Food and Drug Administration approval for patients who had received a kidney transplant. In the 1980s researchers also learned that the drug inhibits tumor growth, and since 2007 two derivatives of it—Pfizer’s temsirolimus and Novartis’s everolimus—have been approved to treat various kinds of cancer.

Biologists found rapamycin’s ability to depress proliferation of both yeast and human cells highly intriguing—it suggested that the compound suppresses the actions of a growth-regulating gene conserved across the billion years of evolution between yeast and people. (Cells grow, expanding in size, when they are preparing to divide and proliferate.) In 1991 Michael N. Hall and his colleagues at the University of Basel in Switzerland identified the ancient target by discovering that rapamycin inhibits the effects of two growth-governing yeast genes, which they named **TOR1** and **TOR2**. Three years later a number of investigators, including Stuart Schreiber of Harvard University and David Sabatini, now at the Whitehead Institute for Biomedical Research in Cambridge, Mass., independently isolated the mammalian **TOR** gene. Many other species, including worms, insects and plants, are now known to possess **TOR** genes that govern cell growth.

Through the 1990s researchers learned much more about the gene’s roles in cells and the body as a whole—many of which ultimately turned out to have a bearing on aging. They found, notably, that the gene encodes an enzyme, or catalytic protein, that combines in the cytoplasm with several other proteins to form a complex, called TORC1, which supervises a whole slew of growth-related activities in cells. Rapamycin mainly affects TORC1. A less well-understood, second complex, called TORC2, also incorporates the TOR enzyme.

The teams further demonstrated that TOR is a nutrient sensor. When food is abundant, its activity rises, prompting cells to increase their overall production of proteins and to divide. When food is scarce, TOR settles down, and the resulting reduction in overall protein manufacture and cell division conserves resources. At the same time, a process called autophagy amps up: cells break down defective components such as misshapen proteins and dysfunctional mitochondria (the cell’s energy powerhouses), generating by-products that can be exploited as fuel or building materials; newborn mice rely on autophagy to supply energy be-

---

**The Making of Supermice**

In 2009 three parallel experiments in mice showed that a drug called rapamycin extended the animals’ maximum life span by 7 to 14 percent. (‘‘Maximum life span’’ was defined as the average longevity of the oldest 10 percent of a population.) It was the first time a drug had convincingly boosted maximum longevity in a mammal. The feat has raised new hope that, one day, a simple medicine might retard aging and protect late-life health in humans, although rapamycin’s side effects probably bar it from serving as that drug.

---

**Table: Longer Life for Mice**

<table>
<thead>
<tr>
<th>Females</th>
<th>Control group</th>
<th>With rapamycin</th>
<th>14% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table: Longer Life for Mice**

<table>
<thead>
<tr>
<th>Males</th>
<th>Control group</th>
<th>With rapamycin</th>
<th>9% increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Graphic by Jen Christiansen**

January 2012, ScientificAmerican.com 35
**MECHANISM**

**TOR Story: A Jekyll and Hyde Molecule**

Rapamycin extends life in yeast and animals by inhibiting a protein called TOR; calorie restriction, too, slows aging in part by acting on TOR. Research into how the protein functions in cells and into why its inhibition slows aging indicates that TOR is both angelic and diabolical. It is a nutrient sensor critical to organismal growth and development early in life (near right). Yet its continued activity after maturity can impair cell function (far right) and thus damage tissues. Investigators suspect that these late-life effects on TOR contribute to aging and its associated diseases in humans. The figures here, which focus on mammalian TOR (mTOR) are highly simplified; mTOR is affected by and affects a complex network of molecules in cells. (The pointed arrows represent stimulation; the others represent inhibition.)

The Good Guy: A Key Nutrient Sensor Early in Life

Mammalian TOR exerts many of its effects as part of a complex called mTORC1. When food is plentiful (top), which evokes increased production of insulin and related proteins (known as growth factors), mTORC1 reacts to the nutrients and the growth factors by stimulating the synthesis of cellular components (especially proteins and fat) and prompting cell growth and division. At the same time, the complex structures cells to pull back on autophagy—a process that degrades damaged mitochondria (the cell’s energy factories) and molecules.

When food or other resources are scarce (bottom), mTORC1 quiets down, causing cells to focus on self-preservation over replication. Meanwhile, autophagy increases to provide an emergency supply of raw materials for cellular repair and energy generation.

**CONDITION:** Abundant resources

- Proteins and fats are synthesized; cells grow and proliferate
- Nutrient

**CONDITION:** Scarce resources

- Proteins and fats
- Damaged mitochondrion
- Damaged molecule
- Autophagosome
- Autophagy ramps up, providing materials for cell maintenance and repair
- Recyclable components

Before they start nursing. When food returns, the seesaw relation between TOR and autophagy swings back again: TOR activity rises, and autophagy slows.

Researchers also discovered that signaling pathways headed by TOR and insulin in animals are intertwined; signaling pathways are sequences of molecular interactions that control a cell’s activities. Insulin is the hormone released by the pancreas after meals to signal muscle and other cells to absorb glucose from the blood for energy. But that is not all insulin does. It is a growth factor; both it and related proteins help to rev up the TOR pathway, a behavior that helps induce cells throughout the body to grow and proliferate in response to nutrient intake. In another feature important for health, the wiring between the TOR and insulin pathways includes a negative feedback loop: stimulating TOR makes cells less sensitive to insulin’s signals. Chronic overeating, then, will activate TOR excessively and make cells increasingly deaf to insulin; this insulin “resistance,” in turn, can lead to high blood sugar levels and diabetes and can also contribute to other age-related disorders, such as heart problems.

TOR also reacts to cellular stresses beyond nutrient shortages, including low oxygen levels and DNA damage. In general, when cells sense threats to survival, TOR activity dials back. The consequent slowing of protein production and cell proliferation frees up resources so that cells can channel them into DNA repair and other defensive measures. Studies in fruit flies indicate that as protein synthesis gets broadly curtailed in this red-alert mode, protein manufacturing also shifts in a way that leads to selective production of key mitochondrial components, perhaps helping cells rejuvenate their energy systems. No doubt this multifaceted “stress response” evolved to help cells cope with harsh conditions, but it may also inadvertently harden them against the ravages of time.

**FINDING THE AGING LINK**

The idea that TOR influences aging dates from findings in the mid-1990s indicating that nutrient-starved cells curtail growth by reducing TOR activity. Geologists had seen something like this before: in 1935 Cornell University nutritionist Clive McCay showed that putting young rats on near-starvation diets made them slow-growing and extraordinarily long-lived. Calorie restriction has since been shown to extend maximum life span in species ranging...
from yeast to spiders to dogs; preliminary evidence suggests that it also does so in monkeys. Cutting normal calorie intake by about a third early in life generally boosts maximum life span by 30 to 40 percent, apparently by postponing the deterioration of aging; elderly rhesus monkeys in long-term studies of calorie restriction are extraordinarily healthy and youthful-looking for their ages.

The approach does not always work—in some strains of lab mice, it actually shortens life—but mounting evidence implies that calorie restriction can promote healthy aging in people just as it does in monkeys. Thus, identifying compounds that evoke calorie restriction’s effects without inducing hunger is a grail for scientists who study aging.

By the early 2000s researchers knew enough about TOR’s functions to suspect that blocking its influence in cells might mimic calorie restriction. In 2003 Tibor Vellai, a Hungarian researcher visiting at the University of Fribourg in Switzerland, led a roundworm study offering the first evidence that inhibiting TOR may oppose aging: by genetically suppressing TOR synthesis in worms, he and his colleagues more than doubled the worms’ average life span. A year later a study at the California Institute of Technology led by Pankaj Kapahi, now at the Buck Institute for Research on Aging in Novato, Calif., demonstrated that quelling TOR activity in fruit flies extended their average life span, too, and protected them from the consequences of rich diets, just as calorie restriction does. And in 2005 Brian Kennedy, then at the University of Washington, and his colleagues hammered home the link between TOR and aging by showing that disabling various TOR pathway genes in yeast cells increased longevity.

These studies, along with others on TOR, were especially intriguing because they suggested that inhibition of TOR mimics not only calorie restriction but also mutant genes known to extend life span. The first such “gerontogenes” had been discovered about a decade earlier in roundworms whose mean and maximum life spans were doubled by mutations later shown to interrupt their species’ version of insulin signaling. The discovery that aging, previously thought to be intractably complex, could be dramatically slowed by altering a single gene had helped make gerontology a hot topic; among other things, it suggested that human aging might be retarded with drugs. That idea was reinforced by the discovery of various mouse gerontogenes in the late
1990s and early 2000s that block growth signals, including ones conveyed into cells by insulin and a closely related hormone called insulinlike growth factor 1. In 2003 a mouse with one such mutation set the record for its species’ longevity: nearly five years. Lab mice generally live less than 30 months.

You might think the connections between TOR, calorie restriction and gerontogenes would have inspired a heated race to test rapamycin’s life-extending effect in mammals. Yet experts on mammalian aging “didn’t really take TOR seriously” before the late 2000s, says Steven Austad, a gerontologist at the Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center at San Antonio. The reason is that rapamycin was known as an immunosuppressant; hence, long-term administration, it was widely assumed, would be toxic to mammals. Still, Zelton Dave Sharp, one of Austad’s independent-minded colleagues at the Barshop Institute, concluded otherwise after studying the TOR literature. In 2004 he instigated a major study on life span in mice that were chronically dosed with rapamycin.

Funded by the National Institute on Aging, the study seemed to go badly at first—trouble formulating the drug in mouse chow delayed the initiation of doses until the study’s rodents were 20 months old, the human equivalent of 60 years. At that point, Austad says, “no one—and I mean no one—really expected it to work.” Indeed, not even calorie restriction reliably extends life span in such old animals. But in 2009 three gerontology labs that jointly conducted the study—Randy Strong’s at the Barshop Institute, David E. Harrison’s at the Jackson Laboratory and Richard A. Miller’s at the University of Michigan and Ann Arbor—made history by reporting that the drug had upped life expectancy by an astounding 28 percent in the aged male rodents and 38 percent in the females versus control animals. Maximum life span was increased by 14 percent in females and 9 percent in males.

The galvanizing mouse results were quickly followed by others highlighting TOR’s importance in aging. Researchers at University College London reported that disabling a gene called S6K1, which gives rise to an enzyme that mediates mTOR’s control of protein manufacturing, makes female mice resistant to age-related diseases and extends their maximum life span. (Mysteriously, males showed scant benefit.) And the three U.S. labs that first tested rapamycin in mice reported that initiating doses in the rodents at nine months of age extended their life spans by about the same amount that starting them at 20 months did—suggeting that rapamycin mainly confers benefits after midlife, possibly because that is when the deterioration it opposes mostly occurs.

The fact that inhibiting TOR prolongs life across species now stands out like a beacon in the molecular murky surrounding aging. That prominence does not mean, however, that other aging-related pathways are unimportant for longevity. Indeed, gerontologists increasingly picture the pathways that calorie restriction affect as belonging to a complex, many-pronged network that can be tweaked in various ways to promote healthy aging. The network’s components include insulin-related enzymes and proteins called FoxOs that activate stress responses in cells. Considerable evidence also indicates that sirtuins help to induce calorie restriction’s benefits in mammals and may, in some circumstances, participate in TOR inhibition. At this point, though, TOR appears to be the closest thing to the network’s central processing unit, integrating various inputs to control the rate of aging, at least in various animal species and perhaps humans, too.

**AN ENIGMA UNRAVELS**

**IN TRYING TO BETTER UNDERSTAND how TOR inhibition and calorie restriction extend life span in so many species, researchers have come up against a long-standing mystery: Why would any mechanism evolve to retard aging?**

The issue has evolutionary biologists scratching their heads because natural selection works to foster successful reproduction, not to enable organisms to go into overtime in the game of life by remaining vibrant at ages when members of their species have typically been wiped out by predators, infections, accidents, and the like. Because of such “extrinsic” risks to survival, evolution effectively equips creatures to live long enough to reproduce before the environment does them in; then, as their odds of continued survival decline they deteriorate like abandoned houses. Yet calorie restriction retards late-life decline in widely differing species, which implies that it evokes an ancient, conserved mechanism that has been shaped by natural selection to slow aging under some circumstances.

A frequently cited solution to the puzzle holds that calorie restriction taps an evolved starvation response that brakes organisms’ aging during lean times so they can last long enough to reproduce when conditions improve. Skeptics, such as the Barshop Institute’s Austad, counter that there is no evidence that low-calorie diets make animals in the wild live longer; calorie restriction has been observed to extend life span only in pampered lab animals. Already lean wild animals weakened by hunger may have little chance of surviving long enough to benefit from, and pass on, genes that slow aging and thus give rise to an evolved starvation response.

Some gerontologists think another solution to the conundrum makes more sense: calorie restriction extends life span as a side effect of responses evolved for purposes unrelated to aging. Austad, for example, theorizes that during lean times, animals branch out and eat unfamiliar things in the wild, exposing themselves to toxic substances not present in their regular food. Such “hard foraging” might have selected for a tendency to rev up inner defens-
es against poisons as hunger sets in, activating the cellular stress-response and repair processes that accompany it and thereby inadvertently slowing aging.

A few years ago Mikhail V. Blagosklonny, a cancer researcher at the Roswell Park Cancer Institute in Buffalo, N.Y., seized on discoveries about TOR to propose another theory that explains calorie restriction's magic as a kind of accident. A native of Russia whose work has ranged widely across cancer research and cell biology, he was inspired by an unorthodox idea: the capacity for growth, which seems the very essence of youthfulness, drives us into the grave later in life. Calorie restriction prolongs life, he posits, by interfering with the untoward, late-life effects of growth pathways, TOR's most important among them.

Blagosklonny's theory holds that TOR, which is essential for development and reproduction, becomes the engine of aging after maturity is reached. Because of its progrowth signaling, it abets proliferation of smooth muscle cells in arteries (a key step in atherosclerosis), accumulation of fat (which helps to spur bodywide inflammation), development of insulin resistance, multiplication of cells called osteoclasts that break down bones, and growth of tumors. Further, by diminishing autophagy, TOR favors the buildup of aggregation-prone proteins and of dysfunctional mitochondria, which spew DNA-damaging free radicals and hurt cells' energy metabolism. It also contributes to the accumulation of degradation-resistant proteins in neurons, a process that plays a part in Alzheimer's and other forms of neurodegeneration. Blagosklonny has shown that, late in life, TOR's signals can also help trigger cell senescence, a kind of night-of-the-living-dead state that damages nearby cells and saps tissues' regenerative capacity.

All this shows, Blagosklonny argues, that evolution has not built a mechanism designed to slow aging. Rather the life-extending effects of rapamycin, calorie restriction and gene mutations that block progrowth hormones are merely accidents of nature—ones that happen to interfere with what he calls the "twisted growth" of aging, causing it to play out more slowly than usual. In effect, the TOR pathway behaves very much like an aging program even though it was built to aid early development.

Although Blagosklonny's theory is novel, one of its key inspirations was a well-regarded hypothesis proposed in 1957 by the late evolutionary biologist George Williams. He theorized that aging is caused by two-faced genes that are beneficial early in life but harmful later on. Such "antagonistic pleiotropic genes" are favored by evolution because, as Williams put it, natural selection is "biased in favor of youth over old age whenever a conflict of interest arises." Blagosklonny sees TOR as the quintessential example of such genes.

Like many novel theories, Blagosklonny's is controversial. It strikes certain scientists as putting too much weight on TOR, whereas others see aspects of TOR distinct from growth promotion as the key thing—for instance, some regard TOR's inhibition of autophagy, which renews cellular components, as its dominant influence on aging. Still, some TOR experts find the theory plausible, and Basel's Hall gives Blagosklonny credit for "connecting dots that others don't even see"—adding, "and I am inclined to think he is right."

TOR AND MEDICINE'S FUTURE

If TOR is a key driver of aging, what are the options for defanging it? Rapamycin's side effects may rule it out as a candidate antiaging drug in people because, among other things, it can increase blood cholesterol, cause anemia and interfere with wound healing.

Another drug, metformin, might be an alternative, although much testing would be needed to evaluate the idea. Metformin is the most widely prescribed diabetes treatment—millions have safely taken it for long periods to lower blood glucose. Its mechanism of action is not well understood, but it is known to inhibit the TOR pathway and to activate another aging-related enzyme called AMPK, which is likewise stimulated by calorie restriction and promotes the stress response in cells. Metformin also has been shown to emulate calorie restriction's effect on gene activity levels in mice, and some evidence indicates that it may increase maximum life span in the rodents. We are still years away from knowing whether metformin can mimic calorie restriction in people, although rigorous tests of its ability to extend life span in mice are now under way.

Boosting human longevity proportional to rapamycin's enhancement of mouse life span could potentially add, on average, five to 10 years to a human life. That would be huge. Indeed, life expectancy in the developed world has risen so much over the past century that when it comes to aging, we are like Olympic athletes trying to eke out ever smaller incremental gains—average life span in the U.S. rose by more than 50 percent during the 20th century; over the past decade it rose by less than 2 percent.

Because we have cut early-life mortality about as low as it can go, boosting life expectancy much at this point will require pushing back diseases of aging. The exploding costs of geriatric medicine suggest this is a very tall order. But drugs that slowed aging could affordably manage it. In effect, they would serve as preventive medicines that could postpone or retard our late-life ills—dementia, osteoporosis, cataracts, cancer, loss of muscle mass and strength, deafness, even wrinkles—just as medicines that cut blood pressure and cholesterol now help to push off middle-age heart attacks. And they would buy us quality time, extending our period of vibrancy before we become frail and die.

Developing such drugs would not be easy. One obstacle is the lack of a reliable way to measure the rate of human aging; a good yardstick would enable researchers to test efficacy without having to run untenably long trials. Yet finding safe antiaging medicines would be worth the effort, if only to promote healthy aging irrespective of increasing longevity. Who would have thought that a vial of dirt scooped up almost five decades ago would become such fertile soil for research that could lead to more years of quality life?