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The Enthusiast

A controversial biologist at Harvard claims he can extend life span and treat diseases of aging. He may be right.

By David Ewing Duncan

David Sinclair is very good at persuading people. The catch, says a longtime colleague and scientific rival, is that he is sometimes overly optimistic about his results. "David is brilliant, but sometimes he is too passionate and impatient for a scientist," says another colleague. "So far, he is fortunate that his claims have turned out to be mostly true."

Sinclair's basic claim is simple, if seemingly improbable: he has found an elixir of youth. In his Australian drawl, the 38-year-old Harvard University professor of pathology explains how he discovered that resveratrol, a chemical found in red wine, extends life span in mice by up to 24 percent and in other animals, including flies and worms, by as much as 59 percent. Sinclair hopes that resveratrol will bump up the life span of people, too. "The system at work in the mice and other organisms is evolutionarily very old, so I suspect that what works in mice will work in humans," he says.

Sinclair thinks resveratrol works by activating *SIRT1*, a gene that many scientists believe plays a fundamental role in regulating life span in animals. Biologists have found that increasing the expression of *SIRT1* slows aging and fends off maladies associated with growing old, including cancer and heart disease. If Sinclair is right, and resveratrol can activate *SIRT1*--and if the gene does in fact help control aging--he has found something truly remarkable.

The scientific uncertainty surrounding Sinclair's claims hasn't stopped him from raising millions of dollars. In 2004 it took him a single lunch meeting to persuade California philanthropist Paul Glenn to put up \$5 million for a new Harvard institute on aging, of which Sinclair is now a director. Sinclair also cofounded Sirtris Pharmaceuticals to develop drugs based on resveratrol and helped persuade an A-list of venture investors to pony up \$103 million in private funding. In late May, the company made an initial public offering that netted \$62 million more. The stock price quickly rose 20 percent, providing Sinclair, who holds less than 1 percent of the shares, with a pleasant (if, for now, notional) addition to his academic salary--and possibly a big payday should the company ever produce a fountain-of-youth pill. "I grew up middle class in Sydney," he says, flashing a characteristically shy though confident smile. "As an academic, I never expected to be wealthy, so any extra is unexpected, although [it] feels pretty good."

Later, Sinclair winces when I mention that some colleagues describe him as a good salesman. "Scientists don't like to be called salesmen," he says. "It's an insult." Still, he says, "I believe in my work and advocate for my conclusions." One thing is certain: Sinclair's persuasiveness gives him an edge over his rivals in a field where a good deal of money and glory is at stake--not to mention potential impact on the future of medicine.

Obsessed

Sinclair says his bravado and drive come from his grandmother Vera, who fled to Australia in the wake of the failed 1956 revolution in her native Hungary. Her son, David's father, changed the family name from Szigeti. "My grandmother is the black-sheep rebel of the family," he says. "She gave birth to my dad at age 15 in 1939--imagine the scandal then--and has lived with natives in New Guinea and eaten human flesh, among other things. She once got in trouble with the police for being the first person to wear a bikini on a Sydney beach. She's a '60s bohemian who helped raise me and taught me how to think differently and to question dogma."

A slight man with a mischievous smile, Sinclair grew up in St. Ives, near Sydney, where as a boy he liked to make bombs from chlorine or gunpowder to blow things up. "It was rebellious and dangerous," he says. "That was the thrill. I think I was bored." When he was seven years old, he came up with a list of 10 ways to change the world, and one was to create inventions to make money. Later, he took up windsurfing and racing around in cars. He got so many speeding tickets that he once had his license confiscated. "He was always quite cheeky and could get under your skin if he knew you well enough," says Mark Sumich, his best friend growing up.

"I think the day I got most scared in my life was when he showed me his brother's new compound bow," recalls Sumich, who now owns a market-research company in Australia. "We went up to the park, and he would shoot it straight up in the air, and having lost sight of it, we would scatter for cover. That, to this day, is still the most stupid thing I have ever done."

Sinclair attended the University of New South Wales and was studying gene regulation in yeast when he learned about longevity research during a conversation with Leonard - Guarente, an MIT molecular biologist who was in Australia giving lectures. Back then--1993--most people assumed that aging was a complex and inevitable process that could not be regulated by just a few genes. But that year, Cynthia Kenyon, a biologist at the University of California, San Francisco, published a study showing how manipulating a single gene, *daf2*, could double the life span of a tiny roundworm. Guarente himself was beginning experiments on yeast that would lead to the discovery of the antiaging gene *sir2* in 1995.

The field was so new and unproven, though, that Guarente talked about it only informally--as, for instance, when a young Australian scientist sat down next to him during a group lunch. "This was incredibly serendipitous," says Sinclair. Inspired, he sold his Mazda Miata to buy a ticket to Boston to interview for a postdoc position in - Guarente's lab. During his interview, he gave a spirited whiteboard presentation arguing that scientists studying aging should look for genes that prolong life rather than genes and mechanisms that end it. He got the job.

While Sinclair was in Guarente's lab in the late 1990s, he discovered that *sir2* prevents aging in yeast by slowing down the accumulation of ERCs, circular strands of DNA that build up in organisms as they age, eventually killing them. Around the same time, others

in Guarente's lab made another crucial discovery: that a link may exist between *sir2* and a molecule critical for metabolizing food, called NAD. The connection suggested that the longevity gene might be related to diet--specifically, Guarente postulated, to caloric restriction. A nutritionally complete diet containing 30 to 40 percent fewer calories than normal had long been known to extend life span in some animals, ramping up cell defenses and slowing down aging. Guarente and others theorize that in times of scarcity, such as famine or drought, this mechanism allows an organism to survive--and postpone reproduction--until the crisis is over. The link between *sir2* and NAD, therefore, suggested to Guarente that caloric restriction might be affecting longevity by activating the antiaging gene.

Colleagues who were students in Guarente's lab during this period remember Sinclair as highly ambitious. Shin-ichiro Imai, then a postdoc, now a molecular biologist at Washington University in St. Louis, and still a friend, describes him as "obsessed," with a penchant for aggressively pursuing his ideas. "He is an introvert who becomes an extrovert for what he's working on," Imai says.

Sinclair's ambition has also complicated his relationship with his mentor, who helped him secure an appointment in Harvard Medical School's department of pathology in 1999. Guarente, a lanky man with a shaved head and intense eyes, says he is proud of his protégé. In 2004, however, an article in *Science* described a rivalry between the two men that began during a meeting at Cold Spring Harbor in New York, where Sinclair stunned Guarente by disagreeing with him about how a key gene associated with caloric restriction increases life span in yeast. The two began publishing competing papers, vying head to head to figure out how *sir2* and, later, other antiaging genes are regulated. "Most young scientists would not compete directly with their mentors, but David did," says Imai.

Sinclair also said no to signing on with Elixir Pharmaceuticals, the company cofounded by Guarente and Cynthia Kenyon in 1999, which for a time he had hoped to join. By the time Elixir called, he had discovered the effects of resveratrol; in 2004 he surprised his former teacher by cofounding Sirtris, a company whose name incorporated that of the *SIR* genes that Guarente had helped to discover.

Both men say that *Science* overstated the extent of the rift between them. There was some tension for a couple of years, they say, but that has died down. They now collaborate on some experiments and articles, and they talk frequently. In a curious turnaround, Guarente left Elixir last year and has considered working with Sirtris, although he can't join the company until the fall of 2007 because of a one-year noncompete clause in his contract with Elixir.

Breakthrough

In 2003, one unsolved mystery among the still-small cadre of longevity researchers was how to modulate genes, such as *SIRT1*, that regulate life span. Was there a compound that could be taken as a pill? Elixir and other companies and labs were beginning to screen thousands of chemicals to see if one would work as a gene activator, but none fit the bill.

In February 2003, in what was then his small, shoestring lab at Harvard, Sinclair was doing his own screening when he learned that scientists at Biomol Research Laboratories, a biotech company in Plymouth Meeting, PA, had observed that *SIRT1* was activated by certain polyphenols, including resveratrol. Sinclair and Konrad Howitz, Biomol's director of molecular biology, collaborated to isolate resveratrol and test it in yeast and fruit flies. "Never in my wildest dreams did I think we would find an activator of *sir2*," says Sinclair.

In a 2004 *Science* interview, Sinclair added to his reputation as a zealot, calling resveratrol "as close to a miraculous molecule as you can find." "One hundred years from now," he said, "people will maybe be taking these molecules on a daily basis to prevent heart disease, stroke, and cancer."

That same year, two scientists who were students in Guarente's lab when Sinclair was there published a paper casting doubt on the underpinning of Guarente's hypothesis that caloric restriction activates *sir2*--a hypothesis that is critical to Sinclair's own theories. ("I have independent-minded students, I guess," Guarente told me with a wry smile.) The former students, Brian Kennedy and Matt Kaeberlein, both biologists at the University of Washington, claimed that, at least in yeast, caloric restriction could exert antiaging effects in the absence of sirtuins--the enzymes produced by *sir2* and its mammalian homologues (such as *SIRT1*). Studies published soon after posed a more direct challenge to Sinclair's contention that resveratrol mimics caloric restriction by activating sirtuins. Peter DiStefano, a coauthor of one of these studies and the chief scientific officer of Elixir, told me in 2005 that resveratrol does wondrous things, but it is unlikely to be an activator of the SIRT1 enzyme.

That skepticism, however, didn't deter Sinclair. In 2004 he set out to prove that resveratrol indeed mimicked some effects of caloric restriction, joining with Rafael de Cabo of the National Institute on Aging to test the chemical on mice.

Mice live about two to three years; when I first visited Sinclair's lab, in 2005, his test mice were about a year old. Sinclair was already ecstatic, because the resveratrol-fed mice seemed healthier than the controls; their cells were also aging remarkably slowly, even though the mice were being fed a fatty, unhealthy diet. When the paper on these experiments came out the following year in *Nature*, the results supported the claims Sinclair had been making about resveratrol in mammals. They showed that mice on a high-fat diet fed large doses of resveratrol were as healthy as mice on a regular diet. Resveratrol also improved the mice's insulin sensitivity and increased their energy production.

The mice were given very high doses of resveratrol--22 milligrams per kilogram of weight. In comparison, a liter of red wine delivers 1.5 to 3 milligrams. To consume - resveratrol at the same rate as the mice, a 150-pound human would need to drink roughly 1,500 bottles of wine (or take scores of pills) each day.

Sinclair's paper came out within days of a study in *Cell* from the lab of Johan Auwerx of the Institute of Genetics and Molecular and Cellular Biology in Illkirch, France. - Auwerx's team, which was partially funded by Sirtris (Auwerx is on the company's scientific advisory board), had given mice even higher doses of resveratrol--400 milligrams per kilogram. These mice stayed slender and strong on a high-fat diet, with the energy-charged muscles and reduced heart rate of athletes. The number of mitochondria in their cells increased, which improved the cells' energy output.

Sinclair's and Auwerx's success in extending the life span and improving the health of mice has partly assuaged critics' doubts that resveratrol can work in mammals. "Both studies are extremely exciting," says Kaerberlein; it's "pretty clear" that resveratrol modifies certain proteins, such as mitochondrial proteins associated with energy production. Kaerberlein points out, however, that the tests involved mice on a high-fat diet and should be duplicated with mice on a normal diet.

And Kaerberlein is not yet convinced that resveratrol is an activator of the SIRT1 enzyme. "We were unable to reproduce the work from the Sinclair lab in yeast," he says, adding that results have been mixed in flies, worms, and other animals. He also still disagrees that *sir2* is the pathway by which caloric restriction increases longevity in yeast. "*Sir2* regulates longevity, and caloric restriction regulates longevity," he says. But it doesn't follow that caloric restriction necessarily increases life span by activating *sir2*.

Critics point out, too, that no one yet knows whether resveratrol will work in humans. According to Harvard population biologist Lloyd Demetrius, the evolutionary forces determining life span are so radically different in mice and humans that mechanisms responsible for slower aging in mice are unlikely to have much effect in people. Demetrius has studied caloric restriction, not resveratrol, but he's still skeptical of the chemical's viability as a drug. "I think its effects on the maximal life span in humans will be almost zero," he says.

A Believer

One convert to Sinclair's views on the effects of resveratrol was Christoph Westphal, then a partner at Polaris Venture Partners, based in Waltham, MA. Though only 35 years old, Westphal had already cofounded two publicly traded companies, Momenta Pharmaceuticals and Alnylam Pharmaceuticals--both Cambridge, MA, biotech startups developing novel drugs. Westphal read the paper and e-mailed Sinclair, who was already working on starting a company. Sinclair had had someone else in mind as CEO, but he and Westphal hit it off.

"David was young and controversial," says Westphal. "Half the people thought he was crazy, and they were pounding on him. But I saw something in him and believed in his science." Westphal and Sinclair are now close friends, with adjacent desks in a small office at Sirtris. Sinclair spends his Saturdays at work, often bringing his two older children to play with Westphal's two kids. Sinclair says that he and Westphal exchange 50 e-mails a day.

I accompanied Westphal one day last winter on his morning walk from his home in Brookline, MA, across the Charles River to Sirtris's offices in Cambridge. He explained that Sirtris's intention is not to produce drugs that extend life span. "That is not an end point recognized by the FDA," he said. "Our end points will be specific diseases." The company has developed a supercharged version of resveratrol, called SRT501. It has also discovered novel small molecules that are not related to resveratrol but, it claims, are a thousand times as potent in activating the sirtuins. So far, animal tests have shown that the drugs may help treat neurological disorders and diabetes.

This past spring, the company launched phase I human trials of SRT501 in patients with diabetes; it also plans human trials later this year to test the drug as a treatment for Melas syndrome, a rare disorder that hastens aging and causes fatal deterioration of the brain and muscles. Sirtris expects to begin human trials of its non-resveratrol compounds in the first half of 2008.

Keeping Score

From his modern ninth-floor office on the Harvard Medical School Campus in Boston, Sinclair has a view that includes Fenway Park. "I can see the scores light up at night," he says. I'm there on an oddly warm day in January, when a few trees are budding and the sky is crystal blue. On a shelf are a book by the Australian golfer Greg Norman called *The Way of the Shark* and a number of textbooks. Behind Sinclair's desk are pictures of his wife and children.

Sinclair's Harvard lab, now well funded, is working feverishly to clarify the health benefits of resveratrol and other compounds, and to discover exactly how sirtuins work on aging and the diseases of aging. In experiments involving thousands of mice, researchers are homing in on different sirtuin pathways and determining how they affect different diseases. Sinclair smiles and tells me they are getting great results, but he can't say any more on the record. He does say he is working with Guarente on some experiments. "Lenny and I typically don't work on things that aren't important," he says.

It has been two years since I last saw him, and in that time Sinclair has become more seasoned, more confident about fending off critics, and more comfortable with his stance as a scientist-zealot. "I am a science rebel," he says. "That's who I am. Everything we publish is criticized."

In the conference room where I join his team to watch a presentation, the table is made of blond wood, and the black mesh chairs look expensive. Sinclair is dressed conservatively in a dark-red button-down shirt and gray slacks--not exactly the clothes of a rebel. A postdoc, Juan J. Carmona, gives a talk about what happens to the *SIR* system when a worm is exposed to the stressor of heat; Sinclair asks questions, pushing hard. Like most leading academic scientists with labs, he does little bench research himself, leaving the experiments to his students. His own success is highly dependent on their work. In the end, Sinclair looks pleased when Carmona describes how heat activated the *sir2* pathway and increased life span in the worms.

Students in Sinclair's lab say he sometimes seems driven, and he admits that he is: "I'm driven to get to goals as fast as possible. It frustrates people in my lab who have something they think is cool, but if it doesn't move us forward, I don't want to do it." He says he views all the experiments being done at Sirtris, all his work, as part of a master plan. "I see this laid out in my mind, every step. But it's happening faster than I imagined--it's taking 10 years instead of 20 years."

"When will it be ready for humans?" I ask.

"This will impact humans within a decade," he says. "That's why I don't think there is anything more important than this quest. That's why I take chances, and why the controversy is worth it: because I think we are right."

He is also not averse to discussing the possibility that a Nobel Prize will someday be awarded to longevity researchers--something Lenny Guarente has also mentioned, though with the "I don't really think much about it" attitude that is typical of senior scientists talking about the ultimate award. If such a prize is given, Sinclair says, Guarente and Cynthia Kenyon are likely to be two of the winners--out of a possible maximum of three.

"And the third person on the prize, who will that be?" I ask.

Sinclair smiles coyly and says nothing.

David Ewing Duncan is a freelance journalist. His last article for Technology Review was "Brain Boosters," in the July/August issue.

To read a detailed explanation of the science behind resveratrol and sirtuins, go to technologyreview.com/sirtuins.

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