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Never Say Die

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Drug companies are mired in a slump. Their drugs are failing in clinical trials, and safety scandals have rocked the industry. Yet Harvard Medical School longevity researcher David Sinclair thinks pharmaceutical science is on the brink of a new generation of supermedicines that will prolong the human life span. "If we are right, the impact on society could be as great as the development of antibiotics by Alexander Fleming," he decrees.

Sinclair, aged a mere 39, is famous for discovering that resveratrol, a chemical found in red wine, helps fat mice live longer. He hopes his research will lead to pills that will treat or prevent numerous diseases simultaneously. "We have split the atom in this field," he proclaims. "It could be one pill for 20 diseases at once." He figures the compounds will save trillions in medical costs as people live to a ripe old age with few health problems. He is writing a book on his vision: *Just in Time.*

U.S. life expectancy soared in the first half of the 20th century with help from clean water and better medical care. It has grown slowly since to 78. An upward creep in obesity and diabetes could send it back down.

Sinclair hopes to restore the longevity curve to a steep upward trajectory. The key, he and a few others believe, is a group of enzymes called sirtuins that exist inside every cell. The theory is that sirtuins are master regulators that divert energy into cellular preservation in times of famine, in order to preserve the organism for reproduction later when times are better. "They are the body's natural defense against disease," Sinclair says.

Resveratrol activates one of the sirtuin enzymes. In 2006 Sinclair reported that large doses of resveratrol appeared to cancel out the ill effects of a poor diet in overweight mice. Minus the protective resveratrol, the bad diet (with 60% of calories from coconut oil) chopped away at a fat mouse's life span and clogged the animal's liver with fat. No surprise that Sinclair picked up some headlines with this experiment. It hinted that a pill would someday let you eat greasy cheeseburgers all day long with no health downside.

Last year Sinclair's lab showed that feeding resveratrol to healthy mice did not extend their lives. (It did prevent cataracts and improve bone strength.) Unlike his previous results, this finding got relatively little publicity. Sinclair is confidently redoing the experiment. He figures that the mice didn't start taking resveratrol early enough in life. Sinclair is so sure that he is on to something that he takes resveratrol himself, as do his wife and parents. He won't say where he gets it or what dose he uses. Numerous supplement companies sell the stuff, despite the lack of evidence it will boost human longevity.

Sinclair has wide eyes and a slight Australian accent. He speaks softly and earnestly, as if he is letting you in on a secret discovery. Phrases like "This was a unique moment in history" and "I told my wife something big has happened" pepper the conversation. He calls himself "one of these Benjamin Franklin types who want to put discoveries to practice." But just when you think he is about to go too far, he backs off, admitting that it is possible that the sirtuin research won't pan out in humans. "I don't know if it is me who is going to be successful," he says. A moment later he is insisting that if not he, then someone will eventually develop drugs against aging.

Balderdash, says veteran UCSF gerontologist Leonard Hayflick. Hayflick, 81, was the first to show, in the 1960s, that normal cells have finite life spans. He thinks life expectancy can't go much higher than 92. "The Sinclairs of the world appear every five years or so, and they have never been right yet," he says.

And then there are Sinclair supporters. "He is a bold scientist. He is willing to take chances and try risky experiments," says Sinclair's mentor, MIT biologist Leonard Guarente. Guarente first discovered the link between sirtuins and aging, but says it wasn't at all clear that one would be able to find effective compounds that activate sirtuins until Sinclair and collaborators did it.

Proving that sirtuin-boosting compounds can treat human disease will be up to GlaxoSmithkline. Last June it bought Sirtris Pharmaceuticals, which Sinclair cofounded in 2004, for $720 million. Sinclair got $8 million from the deal, but he doesn't appear to be particularly focused on money. He drives a Toyota Camry.

Glaxo has concocted sirtuin boosters far more potent than resveratrol. Among other effects, the compounds lower blood sugar, and Glaxo is testing them to treat diabetes. But preliminary lab experiments suggest that sirtuins could have a role in everything from Alzheimer's disease to colon cancer. "We are talking about retarding the progression of certain age-related diseases," says Glaxo drug discovery head Patrick Vallance. "The application could be pretty broad."

Sinclair grew up in Australia and was fixated on death from an early age. "Most adults repress [thoughts about mortality], but I find it hard to put it in the back of my mind," he says. After getting a Ph.D. in yeast genetics from the University of New South Wales in 1995, he became a postdoctoral student with Guarente, who had just started searching for yeast-longevity genes. Guarente's project "was what I had been waiting to hear my entire life," Sinclair says.

Even to others at MIT, Guarente's yeast aging project seemed a long shot. What could yeast possibly teach us about human aging? "Everyone else in the lab was saying this was crazy--how could you bet your career on it?" Sinclair recalls.

But the work slowly yielded results. Sinclair found one obscure cause of aging in yeast in 1997. In 1999 others in Guarente's lab found a second: they showed that yeast cells with high levels of a sirtuin gene called sir2 lived 30% longer than usual. It seemed this finding could be relevant to humans. Guarente theorized that sir2 might be responsible for the effects of calorie restriction, the decades-old finding that a near-starvation diet can extend the lives of various lab animals. Indeed, when Guarente and colleagues deleted the sir2 gene from the yeast and then restricted calories, the diet no longer lengthened life span.

In 1999 Sinclair snagged a job at Harvard Medical School and started competing with his old boss. Guarente had one theory of the biochemical mechanism behind sir2's role; Sinclair came up with a rival theory that contradicted it. "There was definitely a race. We drove each other forward at every step. It was hugely competitive," Sinclair says.

The next big thing was to devise drugs that affected sir2. A break came when biochemist Konrad Howitz made a serendipitous discovery: He found that resveratrol could activate sir2. He told Sinclair about the unpublished result. When Sinclair fed resveratrol to yeast cells, they lived 70% longer, Howitz and Sinclair reported in 2003 in the journal *Nature*. It also kept worms and fruit flies alive longer. Howitz says his role was minimized by Sinclair in some interviews. "He makes it sound like this was a project of his and he was thinking about this all along," says Howitz, at Enzo Life Sciences Intl. (Sinclair says he "always" credits Howitz.)

Sinclair's hope is that sirtuin-boosting drugs will first get approval for treating diseases like diabetes and cancer. As millions take the drugs, it will become evident if those on the drugs die less often from heart disease, Alzheimer's or other diseases of aging. This would be a sign the drugs influence the aging process.

University of Washington molecular biologist Matt Kaeberlein is dubious. He says his experiments show that sirtuins aren't responsible for the antiaging effects of calorie restriction. Another molecule, MTOR (mammalian target of rapamycin), plays a bigger role in the aging process, he says.

Sinclair concedes that multiple molecules are involved in aging. A successful drug may have to hit many of them. There are seven forms of sirtuin in the human body, and most studies to date have focused on only one. His laboratory is now furiously exploring the roles of the other six. "There will be a whole wave of new drugs coming from the field of aging research," he promises. "It is only a matter of time."