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The Longevity Pill?

Drugs much more powerful than the resveratrol found in red wine will be tested to treat diabetes.

By Emily Singer

A novel group of drugs that target a gene linked to longevity could provide a way to turn back the clock on the diseases of aging. The compounds are 1,000 times more potent than resveratrol, the molecule thought to underlie the health benefits of red wine, and have shown promise in treating rodent models of obesity and diabetes.

Human clinical trials to test the compounds in diabetes are slated to begin early next year, according to Sirtris Pharmaceuticals (http://www.sirtrispharma.com/), based in Cambridge, MA, which developed the drugs. "As far as I'm aware, this is the first anti-aging molecule going into [testing in] man," says David Sinclair (http://www.hms.harvard.edu/dms/bbs/fac/sinclair.html), a biologist at Harvard Medical School, in Boston, and cofounder of Sirtris. (See "The Enthusiast (http://www.technologyreview.com/Biotech/19172/)") "From that standpoint, this is a major milestone in medicine."

The new drugs target an enzyme called SIRT1, which belongs to a class of proteins known as sirtuins that have been shown to lengthen life span in lower organisms. Sinclair and others theorize that activating these enzymes, which play a role in cell metabolism, mimics the effects of caloric restriction--a low-calorie but nutritionally complete diet that dampens disease and boosts longevity in both invertebrates and mammals.

For several years, scientists have been on the hunt for a drug that could bring the benefits of caloric restriction without the strict diet. (See "The Fountain of Health (http://www.technologyreview.com/Biotech/16482/)") Last fall, Sinclair and his colleagues took a first step when they showed that mice given resveratrol, a molecule that activates SIRT1, stayed healthy when fed high-fat foods. (See "A Life-Extending Pill for Fat Mice (http://www.technologyreview.com/Biotech/17704/)") But there was a catch: mice were dosed with the human equivalent of more than 1,000 wine bottles' worth of the compound, an amount not possible for humans to imbibe or take in pill form.

Now a team at Sirtris, led by CEO Christoph Westphal (http://www.sirtrispharma.com/People/Management/tabid/3689/Default.aspx#WESTPHAL), has identified a group of compounds that activate SIRT1 1,000 times more potently than resveratrol does. According to findings published today in the journal *Nature (http://www.nature.com/nature)*, the compounds bind to the enzyme and dramatically increase its activity. Because the new compounds are more powerful, much lower doses are likely needed to achieve the same beneficial effects. "We believe doses needed in humans for the novel compounds are probably on the order of hundreds of milligrams, similar to many marketed drugs," says Westphal.

The Sirtris team focused initial animal tests on type 2 diabetes, a disease that results from the impaired ability to use insulin, and whose risk increases with aging. They found that the drugs improved insulin sensitivity and blood glucose levels in three rodent models: diet-induced obese mice, genetically obese mice, and a rat model of type 2 diabetes. "Theoretically, this is a perfect drug," says Charles Burant (http://www2.med.umich.edu/departments/endocrinology/index.cfm?fuseaction=endocrinology.facultyBio&individual_id=67438&um_department=Internal%20Medicine), head of the Michigan Metabolomics and Obesity Center at the University of Michigan, in Ann Arbor. "Animals seem to have no change in weight, yet they have improved metabolic status."

Still, Burant and others caution that it's too soon to tell how well the drug will work in humans, whose metabolism drastically differs from that of rodents. Sirtris is also testing a resveratrol-like compound in clinical trials for

treating diabetes, with initial results expected later this year or early next year.

Both Sinclair and Westphal have high hopes for the drugs, in part because they appear to mimic the effects of caloric restriction, which has been shown to delay or slow the progression of a variety of age-related diseases. So the novel SIRT1 activators might have the potential to treat illnesses ranging from Alzheimer's disease to heart disease to cancer. "The big news here is that maybe all big diseases of aging fall into the same category and can be treated with sirtuin activators," says Leonard Guarente (http://web.mit.edu/biology/www/facultyareas/facresearch/guarente.html) , an MIT biologist whose lab discovered the first sirtuin gene. Guarente recently joined Sirtris's advisory board.

Initial studies suggest that activating SIRT1 can slow neurodegeneration, and tests of the compounds' impact on animal models of different diseases are ongoing.

However, many questions remain to be answered. While Sinclair and Guarente argue that the new findings support the idea that sirtuins lie at the heart of caloric restriction's health and longevity benefits, not everyone agrees. And the issue that has garnered the most media attention--whether or not such compounds will provide a molecular fountain of youth--is still unclear. While the diabetes research is promising, says Burant, "the life-extension part of this story is still incomplete."

In fact, that question may remain open for a few more years. Sinclair's team is testing the compounds' effect on life span, "but we may know if they can treat a disease in humans before we know if mice live longer," he says.
