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New Longevity Drugs Poised to Tackle Diseases of Aging

By Brandon Keim  November 21, 2008 | 6:55:37 PM Categories: [Medicine & Medical Procedures](#)

Cancer, diabetes, Alzheimer's, Parkinson's, heart disease: All have stubbornly resisted billions of dollars of research conducted by the world's finest minds. But they all may finally be defied by a single new class of drugs, a virtual cure for the diseases of aging.

In labs across the country, researchers are developing several new drugs that target the cellular engines called mitochondria. The first, resveratrol, is already in clinical trials for diabetes. It could be on the market in four years and used off-label as an all-purpose longevity enhancer. Other drugs promise to be more potent and refined. They might even be cheap.

"It's going to revolutionize western medicine," said Doug Wallace, a pioneer of mitochondrial medicine at the University of California at Irvine. "All the things that are common for an aging society, and nobody worried about when they died of infectious disease," he said, could be treated.

If the idea of a cure-all sounds fantastic, that's because it is. History is littered with failed wonder drugs, elixirs of youth and miracle cures. But these new drugs have shown tremendous promise in mice. And though success in animals is far from a guarantee for humans, the research has gone from tantalizing curiosity to a possible foreshadowing of human health care in the 21st century.

As fewer people in the West die of infectious diseases, these new mitochondrial drugs could prevent a wide range of age-related illnesses, though they likely won't extend the lifespans of healthy individuals.

Not long ago, the silver-bullet approach was disregarded, and it's still far from achieving a consensus in the scientific community. But standard research approaches to cancer, dementia and heart disease have provided relatively small benefits, and evidence has continued to accumulate in favor of Wallace and like-minded researchers who advocate a mitochondrial theory of disease.

The new drugs work by stimulating enzymes that regulate the function of mitochondria. Hundreds of these structures are found in every cell in the body, ceaselessly converting glucose into usable energy. But over time, mitochondria degenerate. They lose strength and efficiency, releasing highly reactive oxygen molecules that bind easily with other molecules and wreak cellular havoc.

A growing number of scientists suspect that the breakdown of mitochondria is among the most important causes of cell-level changes that eventually cause the body's tissues to degenerate with age. The damage accumulates gradually until hitting some critical mass of malfunction, at which point diseases arrive rapidly. That may be why so many diseases first occur during middle age, and become steadily more common afterwards.

Repair and prevent this damage, say proponents of the mitochondrial theory of disease, and those afflictions can be averted.

In the last year, mitochondrial malfunction was [associated with heart disease](#), just as it's also been associated with Alzheimer's disease and diabetes. Researchers verified that the cellular changes produced by caloric restriction — a

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longevity-enhancing dietary intervention — are [enjoyed by mice](#) taking resveratrol, the first and best-known mitochondrial drug. Resveratrol, which also occurs naturally in red wine, didn't extend the maximum lifespan of the mice, but it did protect them from the ravages of aging. Most recently, a next-generation longevity drug with the same molecular target as resveratrol allowed mice to gorge on high-fat food for four months [without gaining weight or developing diabetes](#).

[Early-stage human trials](#) of resveratrol for diabetes appear promising and have been expanded. Those trials are led by Sirtris Pharmaceuticals in Cambridge, Massachusetts, which claims to have several compounds in its pipeline that are stronger than resveratrol. The company was purchased last year by GlaxoSmithKline, signaling how seriously mitochondrial medicine is now taken by the pharmaceutical industry. According to Sirtris CEO Christoph Westphal, every major drug company is now researching mitochondrial targets.

For many sober-minded scientists, the question is no longer whether an intervention in age-related diseases will happen, but when. And they say it could be soon.

"Enough evidence has come out to suggest that, since we've now accomplished this successfully in other species, there's reason to think we could do it in people," said Stephen Jay Olshansky, a University of Illinois public health and aging expert, who recently co-authored a [British Medical Journal article](#) on the near future of anti-aging research.

Olshansky also co-authored an upcoming analysis of American demography in 2050 as part of a \$3.9-million MacArthur Foundation [research project on aging in America](#). The analysis assumes a multi-target breakthrough against the diseases of aging.

"We genuinely think it's going to happen," he said. "We said that we not only believe it's possible, but should be aggressively pursued as the new approach to health and disease prevention for this century."

But not everyone is so enthusiastic. Steve Austad, a University of Texas gerontologist who [warned two years ago](#) against thinking of mice "as small little furry humans with long tails," is still unconvinced and doesn't think that mitochondria will be an easy drug target. University of Southern California gerontologist Valter Longo noted associations between mitochondria and health aren't yet as firm as their proponents suggest.

"As far as aging itself and the major diseases of aging are concerned, such as cancer and Alzheimer's, we really have no idea how important mitochondrial damage is to it. It's not clear that major diseases are caused by mitochondrial damage, though that's still a good bet for where to go," Longo said. He added that resveratrol does appear promising for obesity and diabetes.

There's also the issue of side effects. Resveratrol has proven safe in animals and early clinical trials, but much more testing is required. As a cautionary, Longo offered the example of his own research on caloric restriction and genetic manipulation of IGF-1, a cell-growth-regulating gene. In simple organisms, it's produced the [most-dramatic life extension ever](#) seen — yeast lived 10 times its normal lifespan — but a group of Ecuadorians who naturally have that mutation have severe growth deficits and other health problems.

Even Longo, however, thinks resveratrol will enjoy some success in the near future, and mitochondrial approaches are being steadily embraced within the medical research community, which has been largely frustrated in its disease-by-disease, gene-centered approach.

"The approach we've taken is to go one disease at a time," said Olshansky. "We've created national institutes to go after all these major diseases, and every time we identify a new gene, or do something that lets us attack disease a little more efficiently than before, everyone jumps up and says we've succeeded and that's wonderful."

Such research is important, said Olshansky, but not as promising as hitting diseases at a common root. And though he won't yet commit to resveratrol as a wonder drug, he suspects that mitochondria-targeting drugs will provide a breakthrough. The most important question now, he said, is how much the drugs will cost.

Harvard gerontologist David Sinclair, who co-founded Sirtris Pharmaceuticals and first showed resveratrol's effect on mice, says the drug [will be inexpensive](#). Since the company is testing its own formulation as a diabetes drug, it will need to be priced at just a few dollars per dose, competitive with other diabetes treatments. People who use it off-label for other diseases would pay the same price.

But that's still speculative, said Olshansky, and there's no guarantee of resveratrol's efficacy. To make sure of success, he said, there needs to be a massive public investment in research.

"We believe we know how much it will cost to generate an intervention that slows aging in people," he said. "It will cost about \$3 billion. It could be developed in enough time to influence the health and longevity of baby boomers. And any intervention that helps them will help all subsequent generations."

This may seem far-fetched. The makers of resveratrol and other mitochondrial medicines are merely the latest scientists to promise easy and universal health in a bottle. But everything is unproven until it's proved.

"Powered flight research was fruitless until it wasn't," said Aubrey de Grey, founder of the longevity-research-sponsoring [Methuselah Foundation](#). "The harder we try, the sooner we'll succeed."

Video: A mouse taking resveratrol (right) runs twice as far as a control mouse in the laboratory of David Sinclair / [a4m1510](#)

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