

Short life span for long-life-span resveratrol?

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Has resveratrol's reign as sovereign panacea abruptly ended? In early December GlaxoSmithKline PLC, the British pharmaceutical behemoth, announced it had given up on resveratrol research to extend life span, because of ineffectiveness and adverse effects on the kidneys of subjects in a recent trial. Resveratrol (called SRT501 by Glaxo), the most prominent of red wine's polyphenolic antioxidants, has been thought to hold major salutary cardiovascular and other benefits. But it was its mimicry of life-lengthening calorie restriction, now much in the news, that dramatically focused attention. Let's review the story.

The stress of severe calorie restriction (30 to 40% fewer than normal) had been known to slow the pace of aging and to increase the life span of various species, apparently by a mechanism that had evolved to promote survival. The restriction of calories activates the sirtuin enzyme group, which stabilizes DNA, prevents the lethal accumulation of toxic products in older cells, and has a number of other metabolic rewards. It all added up to the exciting prospects of increasing life span, reducing risks of disorders of aging, including cardiovascular disease, diabetes, cancer, dementia, inflammation, and cataracts, alleviating obesity and even jet lag, and improving physical fitness, if a drug could be found that would painlessly mimic starvation. The polyphenols of red wine, especially resveratrol, passed audition, and entered into research.

Based on work of groups such as those led by Leonard Guarente of Massachusetts Institute of Technology, Johan Auwerx of the Institute of Genetics and Molecular and Cellular Biology in Alsace, and, most prominently, by David Sinclair of Harvard University, encouraging results were reported in an ascending order of species: yeast, roundworm, fruitfly, fish, mouse. Life was extended 70% by resveratrol administered to yeasts, 14% in roundworms, 29% in fruitflies. Youthfulness, vigour, and fertility increased among the mice. There is strong reason to believe the same is true of rhesus monkeys, frequent avatars for humans in research.

So promising was the outlook, that Sinclair and others formed a corporation, Sirtris Pharmaceuticals Inc., in Cambridge, Massachusetts, to exploit resveratrol, garnering formidable investors: John Henry,

principal owner of the Boston Red Sox and now too the Liverpool Reds, Wyc Grousbeck, managing partner of the Boston Celtics, Peter Lynch, former money manager of Fidelity Investments, and Joseph Kennedy II, former congressman and son of the late Robert F. Kennedy. So promising was the outlook, that GlaxoSmithKline purchased Sirtris in the spring of 2008 for \$720 million. Reflecting the current state of things, most of subsequent news about research at Sirtris continued to appear in the business pages of newspapers.

Biological complexity and conflicting experimental results have hampered and political and commercial spats have punctuated, perhaps punctured, progress. Glaxo, miffed when Massachusetts proposed a ban on gifts to physicians by drug companies, denied it had threatened to withdraw its investments from the state. More recently, Glaxo ordered former Sirtris CEO Christoph Westphal to stop his separate online company from selling resveratrol to hopeful consumers. In December, Glaxo ceased development of resveratrol by Sirtris, but is continuing related research.

We cannot ignore the impressive evidence that has been elucidated supporting optimism about resveratrol, though not forgetting that its safety and effectiveness when isolated as a compound and administered in high doses (so different from its form in wine) in humans has not been established. Some of the difficulties may relate to experimental conditions, concentration and dose. Accordingly, we should not give up on its potential promise, for Glaxo's must be viewed as a business decision, not a scientific conclusion.

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