DIABETES

Concentrating the benefits of red wine?

The protein deacetylase SIRT1 is an important mediator of the beneficial effects of calorie restriction on lifespan, glucose homeostasis and insulin sensitivity. As these beneficial effects can be mimicked by resveratrol, a constituent of red wine that activates SIRT1, there has been much interest in developing more drug-like modulators of SIRT1. Reporting in *Nature*, Westphal and colleagues have now identified a series of small-molecule SIRT1 activators — structurally unrelated to resveratrol — that show promising beneficial effects in animal models of type 2 diabetes.

The authors first developed a high-throughput *in vitro* fluorescence polarization assay to screen a large library of compounds for their ability to activate SIRT1. Subsequent optimization of hits from this screen using a mass-spectrometry-based assay identified multiple selective SIRT1 activators with potencies 1,000-times greater than resveratrol.

Calorimetric titrations suggested that these compounds bind to the SIRT1–substrate complex at an allosteric site, which becomes exposed upon substrate binding, and induces a conformational change that favours enzyme activity. This site appears to be unique, as the effects of these SIRT1 activators and resveratrol were additive, and comprises a stretch of amino acids (188–225) that is situated amino-terminally to the core catalytic domain of SIRT1.

Type 2 diabetes, characterized by insulin resistance, often arises as a result of excess body mass and physical inactivity, and is one of the most common chronic diseases of ageing. To determine whether the newly identified SIRT1 activators could be used for the treatment of type 2 diabetes, the authors administered one of them, SRT1720, to genetically obese and diet-induced obese mice. In both cases, SRT1720 lowered blood glucose levels and reduced hyperinsulinaemia, without affecting glucose or insulin levels in wild-type or chow-fed controls. Furthermore, SRT1720 improved glucose homeostasis and insulin sensitivity in adipose tissue, skeletal muscle and liver in Zucker *fa/fa* rats, a well-established model of type 2 diabetes and insulin resistance. On the basis of these promising findings and others supporting the potential of this novel strategy, clinical trials of SIRT1 activators are anticipated to start in the first half of 2008.

Monica Hoyos Flight

ORIGINAL RESEARCH PAPER Milne, J. C. *et al.* Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. *Nature* **450**, 712–716 (2007)

FURTHER READING Baur, J. A. & Sinclair, D. A. Therapeutic potential of resveratrol: the *in vivo* evidence. *Nature Rev. Drug Discov.* **6**, 493–506 (2006)