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Sirtris unveils promising, novel SIRT1 activators for treating diseases of aging

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Sirtris Pharmaceuticals, Inc., a biopharmaceutical company focused on discovering and developing small molecule drugs to treat diseases of aging, announced today that findings in the journal Nature demonstrate that Sirtris has developed novel drug candidates that offer a promising, new approach to treating diseases of aging, including Type 2 Diabetes, by targeting SIRT1, a gene that controls the aging process.

In November 2006, Sirtris scientists and Sirtris co-founder, Prof. David Sinclair from Harvard Medical School, published consecutive papers in the journals *Cell* and *Nature* showing that resveratrol, a SIRT1 activator found in red wine, could reduce the impact of a high fat diet, increase stamina two fold and significantly extend lifespan of mice. Unfortunately, it was estimated that a person would need to drink 1000 bottles of red wine to obtain an equivalent dose of resveratrol. Now, scientists at Sirtris have developed SIRT1 activating molecules that are chemically distinct from resveratrol and are 1000 times more potent.

"The new drug candidates represent a significant milestone because they are the first molecules that have been designed to act on genes that control the aging process. For this reason, we feel they have considerable potential to treat diseases of aging such as Type 2 Diabetes," said Christoph Westphal, M.D., Ph.D., Chief Executive Officer and Vice Chair of Sirtris Pharmaceuticals. "The breakthrough in potency we have achieved with the novel chemical entities (NCEs) means that we can obtain the health benefits of resveratrol with a considerably lower dose."

The Nature paper from Sirtris shows that in diet-induced obese and genetically obese mice, Sirtris' small molecule NCEs improve insulin sensitivity, lower plasma glucose levels and increase the function of mitochondria (the powerhouses of all cells). In another well-established preclinical model of Type 2 Diabetes and insulin resistance (Zucker fa/fa rats), these SIRT1 activators improved whole-body glucose homeostasis and insulin sensitivity in adipose tissue, skeletal muscle and liver. These rodent models of diabetes are considered highly predictive of efficacy in humans.

The World Health Organization (WHO) indicates that Type 2 Diabetes (formerly called adult-onset diabetes) results from the body's ineffective use of insulin. Type 2 Diabetes accounts for 90% of diabetes around the world, and is largely the result of excess body weight and physical inactivity. WHO estimates that more than 180 million people worldwide have diabetes and this number is likely to more than double by 2030. Furthermore, WHO projects that deaths due to diabetes will increase by more than 50% in the next 10 years. Activating SIRT 1 appears to mimic the beneficial effects of calorie restriction on mitochondrial and metabolic function in mammals in vivo and holds promise for treating diseases of aging, such as Type 2 Diabetes.

"We are very excited about these findings, which expand on the breakthrough data published in 2006 in the journals *Nature* and *Cell*, which demonstrated that SIRT1 activators mimic calorie restriction and extend lifespan. For the first time, the article published today shows that the novel drug candidates we have identified are the most potent SIRT1 activators ever to be published -- 1,000 times more potent than resveratrol -- and can potentially unlock a whole new approach to treating Type 2 Diabetes," stated Jill C. Milne, Ph.D., lead author of the Nature study and Senior Director of Biology at Sirtris.

Westphal added, "Now we have an even more potent way of eliciting the

beneficial effects observed in earlier research with resveratrol. The NCEs characterized in this study are significantly more potent than and structurally unrelated to resveratrol. These findings highlight the tremendous potential of our NCE program to treat diseases of aging, and we look forward to advancing one of these promising new compounds into human clinical studies in the first half of 2008."

Sirtuins are a recently-discovered family of enzymes that promote the body's natural defense against disease. There are seven human sirtuins (SIRT1-7). Sirtuins are attractive drug targets because some have a specialized function in mitochondrial activity which may be therapeutically beneficial for metabolic and other diseases of aging. Sirtuin therapeutics offer the potential for a novel class of drugs that can treat diseases of aging in a new way.

Source: Pure Communications Inc.