



Creating Revolutionary Medicines for Diseases of Aging

Sirtris, a GSK company, is focused on discovering and developing proprietary, orally available, small molecule drugs with the potential to treat diseases associated with aging, including metabolic, inflammatory and neurodegenerative diseases.

The Benefits of Calorie Restriction

For decades, we have understood that reducing normal calorie intake by about a third (called calorie restriction) can extend the lifespan of multiple species, including mammals. Calorie-restricted mammals are healthy, energetic and youthful looking. They also show improvement in a number of factors associated with Type 2 Diabetes, such as reduced glucose levels and improved insulin sensitivity. Conversely, their peers fed Western diets age more rapidly and die younger. Research by Sirtris' Scientific Advisory Board co-chairs David Sinclair, Ph.D., Harvard Medical School, and Leonard Guarente, Ph.D., Massachusetts Institute of Technology, found that calorie restriction activates SIRT1, the founding member of the mammalian sirtuin family of enzymes.



Sirtuin Therapies for Diseases of Aging

The sirtuins are a family of seven enzymes (SIRT1-7) with the potential to protect against disease. Drug development targeting the sirtuin platform has the potential to address a broad range of diseases of aging.

MAMMALIAN SIRTUIN ■ Catalytic Domain	Cellular Localization	Deacetylase	NAD ⁺ -ribosyl transferase	Potential Indications
SIRT1 	Nucleus, Cytoplasm	✓		Metabolic, Inflammatory and Cardiovascular Disease, Neurodegeneration
SIRT2 	Nucleus, Cytoplasm	✓		Cancer, Neurological
SIRT3 	Mitochondria	✓		Metabolic Disease, Cancer, Mitochondrial Rare Diseases
SIRT4 	Mitochondria		✓	Metabolic Disease, Mitochondrial Rare Diseases
SIRT5 	Mitochondria	✓		Metabolic Disease
SIRT6 	Nucleus	✓	✓	Metabolic and Inflammatory Disease
SIRT7 	Nucleus	✓	✓	Unknown

Product Candidate Programs

Sirtris researchers are working to translate this research into a potential new class of pharmaceuticals to treat diseases of aging, offering the ability for people to live longer, healthier lives. Working from the solid foundation established over the last few years, Sirtris has focused on developing many novel small molecule activators of SIRT1, the most studied member of the sirtuin family. These new chemical entities or NCEs are novel compounds that are structurally and chemically unrelated to resveratrol, a naturally occurring compound that was used as an early proof-of-concept for SIRT1 activation. Besides being structurally differentiated from resveratrol, the NCEs are more specific for the target SIRT1 and have improved drug-like properties. The company has recently completed several early-stage translational clinical studies with the first generation NCEs and has several active clinical trials under way (see Pipeline).

In June 2008, GSK acquired Sirtris, allowing for the acceleration of the science and the rapid development of new therapeutic candidates. Sirtris operates as an independent discovery performance unit within GSK.

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Sirtris Publications

04/11
Guarani V, DeFlorian G, Franco CA, Krüger M, Phng LK, Bentley K, Toussaint L, Dequiedt F, Mostoslavsky R, Schmidt MH, Zimmermann B, Brandes RP, Mione M, Westphal CH, Braun T, Zeiher AM, Gerhardt H, Dimmeler S, Potente M. Acetylation-dependent regulation of endothelial Notch signalling by the SIRT1 deacetylase. *Nature*. 2011 Apr 17. [Epub ahead of print]

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Breitenstein A, Stein S, Holy EW, Camici GG, Lohmann C, Akhmedov A, Spescha R, Elliott PJ, Westphal CH, Matter CM, Lüscher TF, Tanner FC. Sirt1 inhibition promotes in vivo arterial thrombosis and tissue factor expression in stimulated cells. *Cardiovasc Res*. 2011 Feb 1;89(2):464-72

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Blum CA, Ellis JL, Loh C, Ng PY, Perni RB, Stein RL. SIRT1 modulation as a novel approach to the treatment of diseases of aging. *J Med Chem*. 2011 Jan 27;54(2):417-32.

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Robers MB, Loh C, Carlson CB, Yang H, Frey EA, Hermanson SB, Bi K. Measurement of the cellular deacetylase activity of SIRT1 on p53 via LanthaScreen® technology. *Mol Biosyst*. 2011;7(1):59-66.

Links to the full articles can be accessed at www.sirtrispharma.com.



Upcoming Scientific Meetings

Abstracts to be presented at the 71st Scientific Sessions of the American Diabetes Association Meeting in San Diego, CA, in June 2011:

SRT2104, A Novel Small Molecule SIRT1 Activator Ameliorates High Fat Diet Induced Insulin Resistance, Promotes Glucose Utilization by Enhancing Glycolysis and Increases both Carbohydrate and Lipid Oxidation in Mice.

The Metabolomic Profile of SRT2104, a Selective SIRT1 Activator in High Fat Diet Fed Mice Reveals Significant Improvements in Metabolic Function in Liver, Heart and Skeletal Muscle

SIRT1-Mediated Regulation of FGF21 Expression in Lean Mice Probed with Small Molecule Activators and Genetic SIRT1 Deletion

Abstracts to be presented at the 10th World Congress on Inflammation in Paris, France, in June 2011:

The First Demonstration of Clinical Activity by a Small Molecule SIRT1 Activator: SRT2104 Reduces Cytokine Release and Coagulation Activation in a Human Endotoxemia Model

SRT2104, A Novel and Selective Small Molecule SIRT1 Activator, Inhibits DSS-induced Colitis in a SIRT1-Dependent Manner.



Activating SIRT1: Broad potential for diseases of aging



Pipeline

Product	Indication	Phase I	Phase II
SRT2104	Healthy Volunteers	Complete	
SRT2104	Metabolic		Complete
SRT2104	Inflammation	Complete	Ongoing
SRT2104	Cardiovascular		Ongoing
SRT2379	Healthy Volunteers	Complete	
SRT2379	Inflammation	Complete	

Leading the Fight Against the Diseases of Aging

Sirtris is proud to be the leading company focused on discovering and developing drug candidates that target sirtuins and, in particular, drug candidates that mimic the beneficial effects of calorie restriction by activating SIRT1. Our scientific founder and members of our scientific advisory board include many of the leading researchers in the sirtuin field, and we have exclusively licensed or own over 200 patents and patent applications pertaining to sirtuins and their role in diseases of aging. Members of our management team have previously advanced more than 20 small molecule drugs into clinical trials and played key roles in developing several FDA-approved drugs.

Life at Sirtris

The Sirtris team is joined together by a shared passion for creating therapies that allow people to live healthier lives. We believe that this passion is something that thrives in the right environment -- a place where people are challenged, encouraged and rewarded. To learn more about our vibrant corporate culture and opportunities to join our team, visit www.sirtrispharma.com/careers.

SIRTRIS SCIENTIFIC ADVISORY BOARD

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