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# Sirtris and Genstruct Pursue the Fountain of Youth

**By John Russell**

**July 14, 2008** | If it turns out that Sirtris Pharmaceuticals has discovered a family of SIRT1 activators able to combat aging-related diseases—and GlaxoSmithKline must think so, having just paid $700 million for the company—then systems biology technology from Genstruct will have helped speed Sirtris's pursuit of drugs with fountain-of-youth-like properties.

Using Genstruct's *in silico* causal network modeling (CNM) platform, which derives MOA hypotheses from molecular profiling datasets, the two companies collaborated to characterize several of Sirtris' compounds more quickly and cost effectively than would otherwise have been possible.

In one example, the strongest hypothesis for the results seen in the Sirtris Type 2 diabetes study was caloric restriction (CR)—showing that Sirtris' SIRT1 activators are mimicking the effects of CR. The two companies report these results were later confirmed by *in vitro* and *in vivo* experimentations.

For this impressive combination of experimental and computational biology, Sirtris and Genstruct were awarded Bio-IT World's 2008 Best Practices Award in the Drug Discovery category.

"Through Genstruct's [causal modeling platform], we were able to characterize key beneficial effects of a proprietary formulation of resveratrol which are mediated through SIRT1. Importantly, we showed that a proprietary, more potent Sirt1-specific agonist could reproduce those benefits *in vivo*. Our collaboration enabled a comprehensive investigation of a biological experiment that could not have been performed any other way," says Michael Jirousek, senior vice president, Research

Genstruct's modeling approach differs from most others, which typically rely on traditional mathematics such as systems of ordinary differential equations. Instead, Genstruct assembles "knowledge bases" in which various entities (genes, proteins, etc) have assigned states (e.g. up or down regulated, phosphorylated, etc.), which change based on defined interactions with other entities. "Painting on data" generates a set of hypotheses which can be ranked by likelihood.

Here's an extract from the entry: "One key application of the platform is the elucidation of signaling networks using empirical evidence derived from large-scale molecular profiling. The resulting network models causally explain the data (transcriptomic, proteomic and/or metabolomic) and are derived using a Reverse Causal Analysis (RCA) methodology on a computable knowledge base of causal biological reactions. Sirtris Pharmaceuticals and Genstruct have collaborated to characterize the molecular MOA of a revolutionary set of bioactive, Sirt1 activating small molecules. Examples of these compounds include SRT1720 and SRT501, which have been shown to mimic calorie restriction (CR) in liver of a Type 2 diabetes mouse model using CNM."

"We were able to help develop a deep understanding of the SIRT1 pathway and allowed Sirtris to efficiently analyze a vast quantity of data," says Keith Elliston, president and CEO, Genstruct. (See, "Patience, Persistence, and Payoff," *Bio-IT World*, May 2008)

Sirtris' collaboration with Genstruct officially began in December of 2006, but Jirousek was already familiar with Genstruct, having worked with it earlier on a number of diabetes studies at Pfizer, where he was previously the Diabetes Therapeutics Head. Both companies say more work is planned, but decline to discuss the specific program.