

Renal safety signal slows GSK trial of sirtuins



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Because of renal safety signals, GlaxoSmithKline has suspended enrolment in a phase II trial of SRT501, part of the early-stage sirtuin franchise it acquired with its purchase of Sirtris Pharmaceuticals two years ago ([Results - Glaxo spices up Q1 with \\$720m acquisition, April 23, 2008](#)). The question of whether there will be a read-through to the other 10 sirtuin candidates in Glaxo's pipeline will depend on whether trial investigators can detect if it is the candidate or the condition being treated, multiple myeloma, that is to blame for the safety signal.

Sirtuins are a promising area of research for a number of conditions ranging from cancer to diabetes to aging because of their influence on metabolism and programmed cell death. In purchasing Sirtis Pharmaceuticals, Glaxo largely ring-fenced the field of research and now owns all of the candidates in clinical trials and a bulk of the assets undergoing pre-clinical work (see table).

Sirtuin Pipeline

	Pharmacological Class	Product	Therapeutic Subcategory	Company
Phase II	Sirtuin (SIRT1) activator	SRT501	Anti-diabetics	GlaxoSmithKline
	Sirtuin (SIRT1) activator	2245840	Anti-diabetics	GlaxoSmithKline
	Sirtuin (SIRT1) activator	184072	Anti-diabetics	GlaxoSmithKline
	Sirtuin (SIRT1) activator	SRT2104	Immunosuppressants	GlaxoSmithKline
Pre-clinical	Sirtuin (SIRT1) modulator	SIRT1 Modulator Program	Other therapeutic products	GlaxoSmithKline
	Sirtuin (SIRT1) inhibitor	SIRT1 Inhibitor	Other therapeutic products	Elixir Pharmaceuticals
	Sirtuin (SIRT2) inhibitor	SIRT2 Inhibitor	Anti-diabetics	Elixir Pharmaceuticals
	Sirtuin (SIRT1) activator	SIRT1 Activator	Anti-diabetics	Elixir Pharmaceuticals
Research project	Sirtuin (SIRT2) modulator	SIRT2 Modulator Program	Other anti-cancers	GlaxoSmithKline
	Sirtuin (SIRT3) modulator	SIRT3 Modulator Program	Other therapeutic products	GlaxoSmithKline
	Sirtuin (SIRT4) modulator	SIRT4 Modulator Program	Other therapeutic products	GlaxoSmithKline
	Sirtuin (SIRT5) modulator	SIRT5 Modulator Program	Other therapeutic products	GlaxoSmithKline
	Sirtuin (SIRT6) modulator	SIRT6 Modulator Program	Other anti-cancers	GlaxoSmithKline
	Sirtuin (SIRT7) modulator	SIRT7 Modulator Program	Other therapeutic products	GlaxoSmithKline
	Sirtuin inhibitor	Sirtuin inhibitor program	Other cytostatics	Otsuka Pharmaceutical
	Sirtuin inhibitor	Sirtuin inhibitor program	Other cytostatics	MethylGene
	Sirtuin modulator	SIRT deacetylase-modulators	Other musculoskeletal agents	Santhera Pharmaceuticals

Disease or drug responsible?

A Glaxo spokeswoman was quick to point out that the safety signal, cast nephropathy, is a complication of multiple myeloma so it is not certain that SRT501, known generically as resveratrol, had anything to do with it. Recruitment to the open-label study was stopped after five of 24 patients showed the renal signal, out of a total of 61 patients planned to take part.

At the time Glaxo suspended enrolment five other patients were on active treatment and carried on.

No sign of cast nephropathy emerged in two phase IIa trials in diabetes, one of 28 days and one of three months, according to Glaxo.

Exploiting the 'French Paradox'

Known colloquially as the “red wine drug,” resveratrol is a substance found in the skin of grapes and has been suggested as the explanation for the “French paradox,” or the extended lifespan of French people in spite of their greater consumption of artery-blocking fatty foods. Sirtuins are activated when calorie intake is reduced, so it is believed that modulating their activity will cause cellular changes that will emulate the beneficial effects of a calorie-restricted diet.

Sirtuin activators, inhibitors and modulators are being tested for efficacy in cancer, musculoskeletal disorders, immunosuppression and diabetes, according to *EvaluatePharma* data.

Despite their promise, sirtuins are not an area of research that Novartis seemed particularly keen on when it signed an option deal to purchase Elixir Pharmaceuticals or license its ghrelin antagonist programme, ceding the sirtuin field to Glaxo for now among big pharma players. Privately held Elixir, which has two of the five non-Glaxo sirtuin candidates in pre-clinical research, held on to the rights to license its sirtuin pipeline to other partners ([*Sirtuins and ghrelins in the spotlight with Novartis-Elixir deal, June 8, 2009*](#)).

While a safety signal in an early-stage drug is worrying news for patients, companies and investors, it is not at all clear that the SRT501 is responsible. With \$720m already invested in this target, Glaxo had better hope it is not.