PPAR γ : none is more

By Chris Cain, Staff Writer

A team from **Scripps Florida** and the **Dana-Farber Cancer Institute** has developed peroxisome proliferation-activated receptor- γ -binding compounds that have potent antidiabetic activity but do not actually agonize the receptor and thus lack the side effects commonly associated with the target.¹ The researchers have founded **Adipothermics Inc.**, with backing from **Third Rock Ventures**, to advance the new class of compounds into the clinic.

Peroxisome proliferation-activated receptor- γ (PPARG; PPAR γ) agonists marketed to treat type 2 diabetes include **GlaxoSmithKline plc's** Avandia rosiglitazone and **Takeda Pharmaceutical Co. Ltd.'s** Actos pioglitazone. The insulin sensitizers posted 2010 sales of \$677 million and \$4.7 billion, respectively.²

However, both drugs have faced regulatory scrutiny because of safety concerns. Last year, the EMA recommended suspending its approval of Avandia based on a retrospective analysis suggesting the drug increases the rate of heart attacks. This year, Takeda withdrew Actos from the French market after a retrospective analysis indicated the drug may be associated with an increased risk of bladder cancer.

PPAR γ agonists also cause weight gain, edema and a greater risk of bone fractures, all of which are noted on the drugs' labels.

Last year, the Scripps-Dana-Farber team published in *Nature* that the insulin-sensitizing effects of Avandia and Actos might not actually be caused by PPAR γ agonism, but instead may be caused by the compounds' ability to block the phosphorylation of PPAR γ by cyclin dependent kinase 5 (CDK5).^{3,4}

However, it remained unknown whether it would be possible to pharmacologically block phosphorylation without agonizing PPAR γ and, if it could be done, whether such a compound would sensitize cells to insulin with a better safety profile than a PPAR γ agonist.

"The correlation seen in our first paper was strongly suggestive that blocking CDK5 phosphorylation could improve insulin sensitivity, but there were no data to show causality," said Bruce Spiegelman, professor of cell biology at **Harvard Medical School** and Dana-Farber.

The team now has shown that blocking CDK5 phosphorylation can increase insulin sensitivity by using new compounds that separate the effects of phosphorylation from PPAR γ agonism. Results were published in *Nature*.

The compounds were synthesized in the lab of Patrick Griffin, professor and chair of molecular therapeutics and director of the Translational Research Institute at Scripps Florida. He was senior author of the study.

In vitro, lead synthetic compound SR1664 bound PPAR γ and decreased its phosphorylation by CDK5 at nanomolar concentrations.

The compound did not agonize the receptor at any concentration tested.

In a mouse model of diet-induced obesity, SR1664 improved insulin sensitivity compared with vehicle. In a second mouse model of obesity, the compound increased glucose tolerance and lowered insulin levels.

The compound also appears safer than Avandia. In diabetic mice, Avandia caused significant weight gain and fluid retention compared with vehicle. In cell culture, Avandia stimulated fat cell differentiation and reduced osteoblast mineralization. SR1664 showed no differences compared with vehicle in either case.

Griffin and Spiegelman emphasized that although SR1664 provided proof of mechanism, the compound itself is not a suitable clinical candidate. "The pharmacokinetics are terrible—you need twice-a-day injection, which would obviously never fly clinically," said Spiegelman.

Overcoming the stigma

Last November, Spiegelman and Griffin cofounded Adipothermics to develop next-generation molecules with better pharmacokinetics that could be brought to the clinic.

The company has received seed funding from Third Rock in the low single-digit million dollar range.

Third Rock is aiming to complete a series A round for Adipothermics in 4Q11. "Because of considerable pharma interest we are likely to co-invest in Adipothermics with a major pharmaceutical company, where they would be making a financial investment through their venture division," said Lou Tartaglia, interim president and CEO of Adipothermics and a partner at Third Rock.

He said the VC initially was concerned about the pharmaceutical industry's appetite for a new PPAR γ -targeted compound.

"We did a lot of diligence and called about 12 top pharma companies before even seeding this company, asking about their openness to a nonagonist PPAR γ program. Half were spooked just by hearing 'PPAR' because they had put so much money into programs focused on the target," he said.

He added: "The other half recognized that this is a validated diabetes target, that there is nothing good in the pipeline that improves insulin sensitivity and that there is a rational reason that this would avoid the toxicology that results from agonism."

"If you don't impact insulin resistance, then increasing insulin secretion using drugs such as dipeptidyl peptidase-4 inhibitors will only help so much—eventually you can't overcome resistance," said Griffin.

Griffin was previously senior director of basic chemistry at **Merck & Co. Inc.**, where he was involved in the drug discovery efforts that led to the development of Januvia sitagliptin. The dipeptidyl peptidase-4 (DPP-4) inhibitor is approved to treat type 2 diabetes.

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Steven Kliewer, professor of molecular biology at **The University of Texas Southwestern Medical Center at Dallas**, said the mechanistic rationale for the approach makes it convincing. “A number of groups developed compounds with less agonism and better safety” than Avandia and Actos, he said. “But in the absence of a specific mechanism that explained what really made those compounds different, it was psychologically difficult to build momentum for the programs.”

Recent attempts to develop safer PPAR γ -targeted compounds have not made it past Phase II testing. **Metabolex Inc.**’s arhalofenate (MBX-102) and **InteKrin Therapeutics Inc.**’s INT131 are selective PPAR γ modulators that are partial agonists of the receptor.

Development of arhalofenate was discontinued in type 2 diabetes in 2010 due to lack of efficacy. The company is running a Phase II trial of the compound in gout.

INT131 completed a Phase IIb trial in 2009 in which it met the primary endpoint of significantly decreasing hemoglobin A1c (HbA1c) from baseline compared with placebo at 24 weeks. The company said the compound had comparable efficacy and a superior side-effect profile to Actos.

Dennis Lanfear, founder and president of InteKrin, told *SciBX* the company is continuing to seek a partner. He said the compound has “demonstrated a new safety profile” but has been “tainted with the PPAR brush.”

Tartaglia said a complete lack of agonism is critical for modulating PPAR γ . “Even partial agonism is enough to get you into trouble. We have *in vitro* primary screens where we first optimize to block the phosphorylation event, because it is predictive of action in animals. But when we do chemistry to optimize that property, it must remain a nonagonist,” he said.

Scaffolding the company

Adipothermics has been developing derivatives of SR1664 and new nonagonist scaffolds. “Griffin described the compound reported in this paper even before we began funding him last November. Using his HDX technology, he has now identified several different nonagonist scaffolds,” said Tartaglia.

The HDX technology, hydrogen deuterium exchange mass spectroscopy (HDX-MS), is used to identify distinct conformational changes in PPAR γ upon compound binding. It allows Griffin’s team to optimize compounds that eliminate agonism and block CDK5 phosphorylation based on dynamic structural information.

The goal for new derivatives and scaffolds is to improve both pharmacokinetics and IP standing. SR1664 was inspired by and is closely

related to a high-affinity, partial PPAR γ agonist described last year by GlaxoSmithKline.⁵

Tartaglia said SR1664 is “too close in space to preexisting intellectual property.” He noted that distinct compounds have since been developed by Griffin and nine patent applications covering these compounds have been filed since Third Rock’s funding of Adipothermics.

Adipothermics has exclusively licensed IP from Dana-Farber and Scripps. The company is running long-term preclinical studies of its compounds.

In addition to the PPAR γ compounds, Adipothermics is exploring other undisclosed projects in metabolic disease. Along with Spiegelman and Griffin, the third cofounder of the company is C. Ronald Kahn, professor of medicine at Harvard Medical School and vice chairman of the **Joslin Diabetes Center**, who is exploring the role of brown adipose tissue in disease.

Spiegelman and Griffin are continuing to explore the biology underlying how CDK5 phosphorylation of PPAR γ is regulated and how this modification signals through the receptor to regulate downstream genes involved in insulin sensitivity.

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COMPANIES AND INSTITUTIONS MENTIONED

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