BIOTECHNOLOGY

Metabolic Solutions Development Co. LLC

Treating metabolic disease by way of the mitochondria

Metabolic Solutions Development Co. LLC
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Contact: Stephen Benoit, CEO
Business: Therapeutics for metabolic diseases
Founded: January 2006
Founders: Jerry Colca, PhD, President & CSO; Rolf Kletzien, PhD, SVP Research
Employees: 14
Financing To Date: $55 million
Investors: Hopen Life Science Ventures; SWMF Life Science Fund
Board of Directors: Stephen Benoit; Jerry Callahan, PhD (Hopen Life Sciences and Van Andel Research Institute); Jerry Colca; Mike Jandernoa (director, Perrigo Co.); Rolf Kletzien; John Landis, PhD (formerly Schering-Plough); Mark Olesnavage (Hopen Life Sciences); William U. Parfet (MPI Research)
Scientific Advisory Board: John Amatruda, MD (formerly Merck & Co); William Baer, MD, PharmD (ClinXus),; Charles F. Burant, MD, PhD (University of Michigan Medical School); Douglas R. Morton Jr., PhD (formerly Pharmacia Corp.)

Recent news about "brown fat" has got metabolic researchers buzzing, and the implications are intriguing. Unlike white fat, which stores energy, brown fat burns energy. As it turns out, studies in just the past few years show that adults have some amount of brown fat in their bodies, and that activating and augmenting it can lower blood glucose and cause weight loss. It was previously thought that the brown fat infants have in quantity, presumably to keep them warm, all shifted to white fat in adults. Voila! A star is born in the ongoing search for effective anti-diabetic drugs and possibly weight-loss agents.

Excitement about brown fat is building at the very same time that an increasing number of scientists are questioning the validity of a once-popular molecular target for diabetes, known as PPAR-γ. This nuclear receptor was shown to mediate glucose and fat metabolism, and many companies followed the lead of Japan's **Takeda Pharmaceutical Co. Ltd.** and developed compounds to stimulate it. Three drugs directed against this putative target, all considered insulin sensitizers and all classified as thiazolidinediones or "glitazones," came to market in the late 1990s. Later one of the compounds was formally removed from the world market, while a second one was put under selling restrictions in the US and taken off the market altogether in the EU.

Stephen Benoit, the CEO of **Metabolic Solutions Development Co. LLC** (MSDC) says he knows why those glitazones ran into trouble. In fact, the start-up, based in Kalamazoo, MI, is leveraging insights about what *not* to do, as it works to create an insulin sensitizer that lowers blood glucose levels without increasing white fat and without causing dangerous side effects. "We are developing a novel insulin sensitizer that we believe will deliver a durable anti-diabetic treatment outcome without the side effects of the currently marketed agents. It's what everyone wants," he declares.

The problem with glitazones is simple, Benoit asserts, but only became apparent with hindsight: "Basically, people were trying to activate PPAR-γ when what you want to do is avoid activating it." After glitazones were first discovered 25 to 30 years ago, some scientists observed activation of PPAR-γ with several of those compounds and assumed that was the reason for the desirable effects, including lower glucose levels. Now it appears that the receptor's activation was not linked to efficacy, but rather to side effects such as cardiovascular complications. The literature now shows that the more potent agonists of PPAR-γ turned out to be, the worse side effects they caused. The lone insulin sensitizer still widely prescribed is Takeda's *Actos* (pioglitazone) and Benoit says that is not a surprise: it was chosen for its safety profile by MSDC's founders when they were at The Upjohn Co. and it is a relatively weak activator of PPAR-γ.

"The hypothesis about PPAR-γ was wrong. We need to turn 180 degrees on this," Benoit declares. His firm is not the only company seeking commercial traction from fresh insights into insulin sensitization and brown fat. **Ember Therapeutics Inc.**, founded in December 2011 with a first financing of $34 million, has also been pointing the finger at PPAR-γ, and touting its founders' publications about its link to drug side effects. (*See "Ember Therapeutics Inc." — START-UP, February 2012.*) Ember thinks it can achieve desired anti-diabetic effects without the side effects of current treatments, by avoiding the classical PPAR-γ agonism, and instead blocking the CDK5 phosphorylation of that receptor.

The founders of MSDC have indisputably deep knowledge of insulin sensitization that they believe they can leverage. Jerry Colca, now the start-up's president and CSO and Rolf Kletzien, its SVP of research, both participated in the selection and early development of pioglitazone at The Upjohn Co. before its merger with Pharmacia and eventual acquisition by **Pfizer Inc.** The drug became a blockbuster, but through the years, both men maintained a longstanding belief that there was no empirical evidence for assuming PPAR-γ was benefiting glucose metabolism. Benoit explains that ultimately, the two scientists felt compelled to figure it out and founded MSDC to do so.

Benoit, a seasoned life sciences executive who last served as president and CEO of NanoMed Pharmaceuticals Inc., says he is confident that MSDC has found a way to safely initiate metabolic processes that will favor "lipid oxidation," turning white fat into brown, limiting glucose production, increasing cells' sensitivity to insulin,

and thereby giving rise to a valuable drug to treat insulin resistance. The start-up's lead compounds have been designed through medicinal chemistry to selectively interact with the newly defined mitochondrial target of the thiazolidinediones (mTOT), without activating PPAR-γ.

MSDC has not yet shared many details of the target it calls mTOT, but Benoit says the firm expects to share its findings with the scientific community over the next six months. "We're now seeing what the mechanism of action leading to insulin sensitization has always been, and how that realization can shape future drug discovery," he declares, adding, "We think our work is going to explain what people couldn't see before."

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The first compound the company took through Phase IIb trials, MSDC-0160, established clinical proof that PPAR-γ is not what drives insulin sensitization, Benoit asserts. In addition to its potential for treating diabetes, he says this molecule also appears to be amenable to uptake into the brain and therefore could possibly treat neurodegenerative diseases associated with mitochondrial dysfunction.

In August 2011, the company announced it had begun testing MSDC-0160 in people with Alzheimer's disease, who have not had diabetes. The indication could be promising, Benoit claims, because mitochondrial function is increasingly thought to play an important role in brain cell survival. Also, it now appears that in early Alzheimer's disease, mitochondria in brain cells lose ability to convert glucose into energy. So a drug that stimulates that ancient organelle might help people suspected of having the disease function better.

Meanwhile, MSDC is producing clinical supplies of the next compound in its pipeline, MSDC-0602, so it can take the molecule into Phase IIb clinical development later this year. This second-generation compound has been built on understanding of the target gained through the development of MSDC-0160, Benoit says – enough so that the company refers to its novel insulin sensitizers as "mTOT modulators." Plans for a third-generation molecule based on the fresh insights are arousing a lot of interest among potential pharma partners, he claims.

"We understand the mechanism of action more fully than we did even 12 months ago," Benoit declares, enthusiastic about the prospect of treating the root cause of diabetes, not just the symptoms. Benoit says the data generated so far show it is possible to restore the body's ability to make efficient use of insulin, so that glucose does not accumulate in the blood and healthy metabolism function is restored. He explains: "Once our drug candidates bind and modulate mTOT, metabolism is affected so that specialized stem cells in the body can become brown fat cells and participate in improvement of the person's lipid and metabolic profile."

Beyond diabetes and Alzheimer's disease, Benoit envisions the company's compounds as potential treatments for fatty liver disease and polycystic kidney disease. Public and private grant funding has allowed the firm to begin studying several of these indications, stretching the $55 million invested by Hopen Life Sciences and Southwest Michigan First Life Science Fund.

Benoit says he is now weighing several options for fundraising, and it's clear he is thinking big. While developing a novel insulin sensitizer remains the priority for Metabolic Solutions, Benoit says the firm's mission is to provide "New hope for the treatment and prevention of metabolic and age-related diseases."

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– Deborah Erickson