



**Press Release**

**26 November 2007**

**Mercury Therapeutics, Inc.**

- *Significant progress made in small molecule AMPK activator development program*
  - *Promising preclinical results anticipated before the end of Q4*

WOBURN, Massachusetts, November 26 - Mercury Therapeutics, Inc. (MTI) has developed a novel lead generation platform to identify small molecule activators of protein kinases involved in the regulation of energy metabolism. The technology employed is in an interrelated series of in-vitro and cell-based protein kinase and cell metabolism assays that allow for the rapid filtering of the numerous hits that are routinely identified in most types of high throughput screening campaigns, particularly those seeking to develop activators of protein kinases. MTI's specific implementation of this technology is to identify and develop small molecule activators of AMP activated protein kinase (AMPK) to treat type-2 diabetes ("T2DM") and metabolic syndrome utilizes both proprietary technology and in-house improvements in assay development for activators of protein kinases with structures that include multiple subunits like AMPK.

T2DM is of epidemic proportions in the western hemisphere, having doubled in incidence in the past two decades. According to an article in the New York Times on May 16, 2006, diabetes is the only disease in the U.S. with a death rate that is still rising, accounting for over 225,000 deaths per year. It is estimated that there are at least 20 million diabetics in the USA, with a third still undiagnosed. In addition to the direct morbidity and mortality due to diabetes, elevated fasting blood glucose levels, even levels below the threshold for a diabetes diagnosis, have been associated with a significantly increased risk of heart attack and stroke. The American Diabetes Association has estimated that \$92 billion was spent in 2002 on diabetes care. Of that, \$20 billion was for the diabetes drug market, accounting for over 12% of total pharmaceutical sales.

Through its proprietary screening platform, MTI has identified multiple small molecule chemotypes that potently activate AMPK directly in-vitro as well as in cultured cells. MTI is in the process of applying for patent protection on these novel core structures and simultaneously initiating preclinical studies on these lead series. MTI has also identified a number of small molecules that stimulate AMPK activity indirectly in a variety of mouse, rat and human cell lines. Of these cellular actives, MTI has been able to demonstrate that this activity in cell culture corresponds to an effect in-vivo, inducing the accelerated clearance of elevated blood glucose levels in mouse models. These assays were performed in two ways. In the first model, normal lean mice were challenged with a large dose of glucose and were treated 20 minutes later with an AMPK activator. Mice that were treated with a known AMPK activator or with the MTI compounds showed an accelerated rate of clearance of blood glucose levels within 30 to 90 minutes of treatment, compared to mice who only received glucose.

AMPK plays a key role in maintaining cellular and whole body energy balance. It is found in all cells and tissues, but most importantly in skeletal muscle, liver, and adipose tissue. AMPK activation shifts both intracellular and whole body metabolism away from cholesterol, fatty acid and triglyceride synthesis (fat storage) and toward  $\beta$ -oxidation (fat breakdown, energy production). Because exercise has similar metabolic effects in skeletal muscle to AMPK activation, AMPK has lightly been referred to as “exercise in a bottle” or the “jogging pill.” There are several isoforms of each of the 3 subunits that comprise the AMPK protein, with AMPK $\alpha$ 2 being thought of as the most appropriate target in skeletal muscle, while AMPK $\alpha$ 1 is the predominant isoform in liver, which is thought to be activated indirectly by a number of anti-diabetic drugs. AMPK activity is also upregulated by hormones secreted from the GI tract and from adipose tissue, including ghrelin, leptin, and adiponectin, and is inhibited by increases in amino acids, glucose, or insulin.

In T2DM, a build-up of lipid within skeletal muscle suppresses the muscle cell's ability to take in glucose from the blood when stimulated to do so by insulin (termed insulin resistance), resulting in elevated blood glucose levels. The spillover of glucose is taken up by the liver for triglyceride synthesis, thereby contributing to the higher plasma triglycerides and lower HDL levels associated with insulin resistance. In addition the higher blood glucose levels evoke pancreatic beta cell insulin secretion that sustained over time contributes to the development of beta cell failure. A direct small molecule activator of AMPK that works independently of insulin levels has been shown in published reports to reduce insulin resistance in skeletal muscles of rat and mice models of T2DM, along with reductions in blood glucose, serum triglycerides (TGs), and intramuscular fat stores, suggesting that activators of AMPK may be useful in the treatment of T2DM.

In a second animal assay, mice were maintained on a high fat diet for 20 weeks, causing accelerated weight gain, insulin resistance and elevated blood glucose levels. When these DIO (diet induced obesity) mice were treated with AMPK activators, the blood glucose levels dropped to normal levels and were maintained at that level for at least several hours. Two cell-based actives have tested positive thus far in whole animal studies and have been entered in PK and toxicology studies for further consideration for nomination as clinical candidates. One of these cell based actives is the subject of ongoing negotiations for a license and collaboration agreement with a local biotech company.

Dr. Joseph Avruch, Chairman of the MTI Scientific Advisory Board and a co-founder of MTI, says: "MTI's focus on developing a direct orally available AMPK activator to treat T2DM and insulin resistance represents a novel and important new approach that could substantially improve the effective management of blood glucose levels without the need for insulin injections, with an added crucial benefit of improving blood lipid profiles. In T2DM, hyperglycemia combines with an array of lipid abnormalities to create a markedly increased risk for atherosclerotic cardiovascular disease. Activation of AMPK in muscle and liver is likely to address these multiple abnormalities in a strongly favorable way. We desperately need drugs that will reduce the risk for vascular disease in patients with T2DM, and I am therefore very encouraged by MTI's progress to date in identifying potent, specific AMPK activators."

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