

INCYTE CORPORATION



**Selective Orally-Available Small
Molecule Inhibitors of 11-beta
hydroxysteroid dehydrogenase type 1
(11 β HSD1)**

As of June 2006

A New Approach for Treating Type 2 Diabetes

We have developed a novel proprietary compound with the potential to treat Type 2 diabetes by controlling both insulin production and insulin resistance. The compound, INCB13739, is a selective orally-available small molecule inhibitor of 11-beta hydroxysteroid dehydrogenase type 1 (11 β HSD1), an enzyme that converts the biologically-inactive steroid cortisone into the potent biologically-active hormone cortisol.

Unlike insulin, which is produced by beta-cells in the pancreas and *maintains* normal blood glucose levels, cortisol *elevates* blood glucose levels by promoting glucose production in the liver and inhibiting the uptake and disposal of glucose in muscle and adipose tissue. In this way, cortisol acts an *antagonist of insulin*. Recent preclinical findings suggest that 11 β HSD1-mediated production of cortisol may increase the body's resistance to insulin and lead to elevated blood glucose and Type 2 diabetes. Inhibition of cortisol production may prevent the progression of insulin resistance to Type 2 diabetes.

Current treatments for Type 2 diabetes increase the production of insulin or the body's sensitivity to insulin but few address both components of insulin control and most produce unwanted side effects. As a result, many patients do not achieve optimal reductions in blood glucose levels and experience life-threatening disease complications. By selectively inhibiting 11 β HSD1 and reducing the level of cortisol available in multiple key tissues, we believe INCB13739 may address both components of the disease – insulin production and insulin resistance – and offer a new approach to treating Type 2 diabetes and other conditions often associated with this disease, such as dyslipidemia, atherosclerosis, and coronary heart disease.

Preclinical Studies Confirm Potential Value of Inhibiting 11 β HSD1

The role of 11 β HSD1 in insulin resistance and diabetes has been well established in animal studies. Adipose-specific over-expression of 11 β HSD1 in the mouse produces a phenotype closely resembling human Type 2 diabetes, including obesity, insulin-resistant diabetes, hyperlipidemia, and high blood pressure. The fact that these pathologies are observed simply by increasing the cortisol levels within adipose tissue supports the critical role this hormone may play in Type 2 diabetes. Conversely, loss of 11 β HSD1 in adipose tissue is sufficient to avoid weight gain on high-fat diets, improve insulin sensitivity, and correct dyslipidemia. Thus, effective inhibition of the adipose 11 β HSD1 enzyme is critical to achieving maximal blood glucose and insulin balance.

We and other investigators have shown that small molecule inhibitors of 11 β HSD1 that target the enzyme in *both* adipose tissue and liver can significantly improve insulin sensitivity and normalize fasting blood glucose levels in obese, diabetic mice. A recent study has also revealed that inhibition of 11 β HSD1 can

improve levels of serum lipids and reduce atherosclerosis in mice. These data also substantiate the potential clinical relevance of 11 β HSD1 and cortisol production to diseases often associated with Type 2 diabetes.

Based on this evidence, we believe that inhibiting 11 β HSD1 in key metabolic tissues such as liver and adipose may suppress cortisol production, increase peripheral insulin sensitivity and lead to clinically meaningful reductions in blood glucose levels. Inhibition of 11 β HSD1 may also affect other serious diseases often associated with Type 2 diabetes, including dyslipidemia and atherosclerosis. As a result, we believe that a selective orally-available inhibitor of 11 β HSD1, like INCB13739, has the potential to become an important new approach for treating Type 2 diabetes.

We began Phase I testing of INCB13739 in June 2006.