Cell Metabolism Publishes Novel TGR5-Mediated Mechanism for the Treatment of Diabetes and Obesity

Intercept Pharmaceuticals is Advancing the Selective TGR5 Agonist INT-777 to an IND

NEW YORK, Sept. 1 /PRNewswire/ -- Bile acids are known to be key regulators of lipid, glucose and overall energy metabolism. Bile acid activation of the G protein-coupled receptor TGR5 has been shown to induce energy expenditure in muscle and brown fat, thereby conferring resistance to weight gain. Now, a paper published in the current issue of *Cell Metabolism* (Vol. 10, Issue 3, Sept. 2, 2009) elaborates on a separate TGR5-regulated mechanism in the gut that drives secretion of the hormone glucagon-like peptide (GLP-1) and resulting insulin sensitization.

The paper reports on the mechanism of action of the selective TGR5 agonist INT-777, providing a clear rationale for its potential as a novel treatment in diabetes, obesity and associated metabolic disorders. INT-777 is a patent-pending modified human bile acid that is currently being advanced to an IND by Intercept Pharmaceuticals, Inc. This proprietary compound was discovered by the company's scientific founder and head of medicinal chemistry, Professor Roberto Pellicciari. The newly published results were generated through a longstanding exclusive Intercept research collaboration with Professor Pellicciari and his medicinal chemistry team at the University of Perugia (Italy), together with Professor Johan Auwerx and Dr. Kristina Schoonjans who lead a molecular biology and metabolic phenotyping group at the Ecole Polytechnique Federale de Lausanne (EPFL).

Highlights of the Cell Metabolism paper, titled "TGR5-Mediated Bile Acid Sensing Controls Glucose Homeostasis", authored by Dr. Charles Thomas, et al., include:

- INT-777, a derivative of the primary human bile acid cholic acid, is a potent and selective TGR5 agonist.
- INT-777 induces the release of GLP-1 in the gut in a TGR5-dependent manner, an effect that is markedly enhanced when the compound is given in combination with a DPP4 inhibitor such as sitagliptin.
- INT-777 normalizes glucose tolerance in obese, insulin resistant (DIO) and diabetic (db/db) mice; the treated mice maintain normal insulin levels and glucose uptake in liver and muscle.
- INT-777 prevents weight gain and fat accumulation in mice on a high fat diet by increasing energy expenditure and fat burning; liver function is also protected with reduced steatosis, fibrosis and serum markers of liver damage in the treated mice.

Professor Pellicciari, a co-author on the paper, commented, "Years of concerted discovery efforts and proprietary know-how in bile acid chemistry have resulted in our ability to rationally design molecules that are highly selective for bile acid receptors. The realization of this in the novel TGR5 agonist INT-777 and the characterization of its mechanism of action represent an important milestone in the establishment of a novel class of therapeutic agents targeting this receptor."

Professor Johan Auwerx, who has led the field in uncovering the role of the TGR5 receptor and representing the lead authors at EPFL, added, "Our collaboration with the joint Intercept-Pellicciari team has been extremely fruitful. We are very pleased with the performance of INT-777, a compound that has allowed us to further elucidate this critical mechanism of TGR5 regulated GLP-1 release in the gut."

Dr. Mark Pruzanski, founder, President and CEO of Intercept and a co-author on the paper, commented further, "Diabetes, obesity and other associated metabolic disorders are reaching epidemic proportions. At Intercept we are uniquely positioned to exploit the therapeutic potential of modified bile acids, molecules that nature has designed to play a central role in the maintenance of metabolic homeostasis. In this context, TGR5 has emerged as an important target and INT-777 as an excellent candidate that we plan to advance into the clinic in 2010."

About Intercept Pharmaceuticals

Intercept is a clinical stage biopharmaceutical company focused on discovering and developing small molecule drugs for the treatment of chronic fibrotic and metabolic diseases. The company's most advanced programs are focused on the development of modified bile acids that are selective for FXR, a nuclear receptor, and TGR5, a G protein-coupled receptor. Bile acid signaling through these receptors regulates key aspects of lipid, glucose and overall energy metabolism, while also serving to maintain the functional integrity of the liver, intestine and kidney, organs that are exposed to bile acid flux.

Intercept's lead compound, INT-747, is a modified human bile acid and first-in-class FXR agonist that is currently in Phase II testing. Clinical proof of concept was recently demonstrated in a Phase II, placebo-controlled trial of INT-747 in type 2 diabetics with fatty liver disease. Based on these results, the company plans to advance INT-747 in a Phase IIb trial in patients with nonalcoholic steatohepatitis (NASH) in 2010. INT-747 is completing two additional Phase II trials in patients with primary biliary cirrhosis, an autoimmune cholestatic liver disease and orphan indication. Results from the first of the two studies are expected in the fourth quarter of 2009.

INT-777 is a modified human bile acid and selective TGR5 agonist that is currently being assessed in IND-enabling studies.

For more information about Intercept, please go to www.interceptpharma.com; and for information about Intercept's lead investor, Genextra S.p.A., please go to www.genextra.it.

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