Nature Publication Reports on Key Role of Bile Acids in Glucose Metabolism and Insulin Signaling

Intercept Pharmaceuticals is Advancing Bile Acid-Derived Small Molecules with Potential Applications in Treating Metabolic Diseases

NEW YORK, Aug. 7 /PRNewswire/ -- Historically, bile acids have been recognized primarily as natural detergents that regulate the absorption of dietary lipids and cholesterol homeostasis. However, recent research advances provide evidence that bile acids have broader systemic endocrine functions, acting as important mediators of glucose metabolism and insulin signaling. The featured article in the current issue of Nature Reviews Drug Discovery (Vol. 7, Number 8, August 2008) describes why bile acid receptors are promising targets for drug development in obesity, type 2 diabetes, atherosclerosis and other chronic metabolic disorders such as nonalcoholic steatohepatitis.

Highlights of the article, "Targeting bile acid signaling for metabolic diseases," authored by Drs. Charles Thomas, Roberto Pellicciari, Mark Pruzanski, Johan Auwerx and Kristina Schoonjans, include:

-- Bile acids serve as metabolic integrators, activating major signaling pathways regulated by nuclear hormone receptors including the farnesoid X receptor (FXR) and G protein-coupled receptors (GPCRs) such as TGR5.
-- Bile acids play a major role in lipid metabolism and homeostasis. For example, bile acid activation of FXR results in a decrease in serum triglyceride levels.
-- The activation of TGR5 by bile acids increases energy expenditure and reduces diet-induced obesity. Conversely, "knockout" animal models engineered to lack TGR5 show a tendency towards weight gain.
-- Bile acids have broad effects on glucose homeostasis, including a decrease in gluconeogenesis (glucose synthesis by the liver). These effects have been attributed primarily to activation of FXR. Additionally, mice that lack FXR have impaired glucose tolerance and are insulin-resistant.

Dr. Schoonjans, Ph.D., a group leader at the Ecole Polytechnique Federale de Lausanne commented, "Our research efforts have uncovered a number of endocrine effects mediated by bile acids acting on receptors such as FXR and TGR5. This review is one of the first to provide a comprehensive summary of what is now known about bile acid signaling and its relevance for metabolic function. From this broad viewpoint, we can see the potential for identifying important new therapeutics that can address a number of important disorders."

Dr. Pruzanski, founder, President and CEO of Intercept Pharmaceuticals, commented, "At Intercept, we have proprietary insight into the rational design of potent FXR and TGR5 agonists derived from bile acid scaffolds. To date, we have advanced our lead compound, INT-747, a first-in-class FXR agonist, into three ongoing Phase II trials. The innovative research being reported in the current issue of Nature Reviews provides additional support for our programs, and we look forward to reporting the progress of our discovery and development efforts in the appropriate forums."

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 scientists and affiliated researchers have published extensively on the role of bile acid signaling via the nuclear hormone receptor FXR and the G protein-coupled receptor TGR5. These receptors are key mediators of energy homeostasis and are involved in maintaining integral functions of the liver, intestine and kidney, organs exposed to bile acid flux. The company's chemocentric discovery programs are based on proprietary expertise in the rational design and synthesis of natural and synthetic small molecule derivatives targeting FXR, TGR5 and other related targets. For more information on Intercept, please visit the company's website at www.interceptpharma.com.

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