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Poster Sessions

Acetyl-CoA carboxylase 1 and 2 inhibition ameliorates hepatic fibrosis and steatosis in a murine model of nonalcoholic steatohepatitis

Mitsuharu Matsumoto¹, Hiroaki Yashiro², Hitomi Ogino¹, Kazunobu Aoyama¹, Tadahiro Nambu¹, Mayumi Nishida¹, Xiaolun Wang², Derek Erion², Manami Kaneko¹

¹*Axcelead Drug Discovery Partners, Inc.*, ²*Takeda Pharmaceuticals*

De novo lipogenesis is increased in livers of patients with nonalcoholic steatohepatitis (NASH). Acetyl-CoA carboxylase (ACC) catalyzes the rate-limiting step in this process. Although ND-630, an inhibitor of ACC1 and ACC2, reduced hepatic steatosis and fibrosis marker serum TIMP1 in patients with NASH in a randomized-controlled trial, the influences on degree of liver fibrosis are not fully elucidated. We evaluated effects of inhibition of ACC on fibrosis in addition to hepatic steatosis using melanocortin 4 receptor-deficient (MC4R-KO) mice fed Western Diet (WD) that progressively develop hepatic steatosis and fibrosis. After pre-feeding with WD for 13 weeks, 9-week treatment with ND-630 (2 and 8 mg/kg, p.o., BID) with lowering malonyl-CoA contents in the liver decreased hepatic triglyceride contents. Furthermore, ND-630 lowered Sirius red-positive area, hydroxyproline contents, and mRNA expression levels of type I collagen, showing an improvement of fibrosis. The treatment was also accompanied by reduction of plasma ALT and AST levels. These data suggest improvement of hepatic lipid metabolism by ACC1 and ACC2 inhibition could be a new option to suppress fibrosis progression as well as improve hepatic steatosis in NASH.