Acetyl-CoA Carboxylase Inhibition by ND-630 Inhibits Fatty Acid Synthesis, Stimulates Fatty Acid Oxidation, Reduces Body Weight, Improves Insulin Sensitivity, and Modulates Dyslipidemia in Rats

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FIGURE 2: LQKLELWRUV ELQGV

FIGURE 3: Acetyl-CoA Carboxylase (ACC): Master Regulator of Fatty Acid Synthesis & Oxidation

FIGURE 4: 6-D30 Displays Excellent Drug-like Properties

FIGURE 5: Proof of Mechanism: ND-630 Acutely Inhibits ACC Protects Mitochondrial Acetyl-CoA Production in the Liver (mg/kg, 1.5 mg/kg)

FIGURE 6: ND-630 in vivo Proof of Concept: ND-630 In Vivo Treatment Reduces Plasma Free Fatty Acids & Total Triglycerides

FIGURE 7: Data Summary of ND-630 in High Fat and High Sucrose DIO Rat Studies

FIGURE 8: Weight Neutral Profile: Well Tolertated. Reduction in Weight Gain at High Dose

FIGURE 9: Reduction in Whole Body Fat at All Doses

FIGURE 10: Improvement in Insulin Sensitivity

FIGURE 11: Normalization of Hepatic Triglycerides and Reduced Hepatic Cholesterol

FIGURE 12: Dose Dependent Decrease of Plasma Triglycerides and Free Fatty Acids

FIGURE 13: Dose Dependent Decrease of Plasma Cholesterol

FIGURE 14: Increase Noted in Total Ketonons

SUMMARY

A structure-based virtual screen and drug design approach utilizing WaterMap Modeling allowed to identify allosteric inhibitors of ACC that uniquely bind to the BC domain

Inhibitors were successfully optimized for excellent potency, drug-like properties and in vivo efficacy in 16 months

ND-630 demonstrated in vivo proof of concept in pharmacologically relevant models of target engagement and efficacy (rat FAS/EGP = 0.14 mg/kg, PO & rat PQ MED = 3 mg/kg, PO, MED 3 mg/kg DIO model)

Ongoing Studies

- Evaluation of ND-630 in ZDF diabetic rat model
- Evaluation of ND-630 In Hamster Lipid-lowering model

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ABSTRACT

Simultaneous inhibition of the acetyl-CoA carboxylase isozymes, ACC1 & ACC2, results in concomitant inhibition of fatty acid synthesis (FAS/yny) and stimulation of fatty acid oxidation (FAO/HN) and may favorably affect obesity, diabetes, and fatty liver disease. Our efforts to discover ACC inhibitors have focused on interaction with the substrate-dimerization site on the biaryl carboxylase (BC) domain of the enzyme to which the phosphoprotein of phosphoACC binds to prevent dimerization and to which the fungal metabolite Soraphen A binds. Using state-of-the-art structure-based drug design and crystal structures of human ACC2 BC domain, we identified a unique series of allosteric inhibitors that bind to the Soraphen binding site. While enzymatically active, exhibit functional activity in cultured cells, and exhibit favorable drug-like properties and in vivo efficacy. For example, ND-630 inhibits human ACC1A2 (IC50 ≈ 2.0 µM), inhibits HepG2 and 3T3-L1 cells (IC50 ≈ 69 µM, stimulates C2C12 cell FAO (2-fold 200 µM), inhibits rat liver FASyn (ED50 ≈ 0.14 µM), and stimulates rat whole body FAOx (MED 3 mg/kg). When administered orally daily for 14 days to high-fat-fed-diabetic obese (DIO) rats at doses 3.35 mg/kg, ND-630 reduced weight gain while increasing food intake, reduced the hyperlipidemia and hyperinsulinemia produced by the high-fat diet without altering plasma glucose, improved insulin sensitivity (oral glucose tolerance testing), and reduced hepatic triglycerides to chow-fed control levels. When administered as above for 28 days to high sucrose-fed DIO rats, in addition to the above effects, ND-630 also reduced plasma triglycerides and free fatty acids to chow-fed control levels and markedly reduced plasma cholesterol. These observations suggest that our allosteric ACC inhibitors may favorably affect obesity, diabetes, and fatty liver disease.