Liver-Directed Allosteric Inhibitors of Acetyl-CoA Carboxylase Favorably Impact Pathophysiology in the Progression from NAFLD to NASH and Hepatocellular Carcinoma, Including Hepatic Steatosis, Inflammation, and Fibrosis

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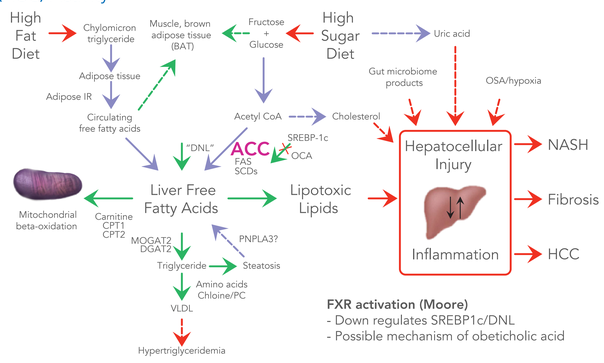
NIMBUS THERAPEUTICS

OVERVIEW

- Liver disease progression from Nonalcoholic Fatty Liver Disease (NAFLD) to Nonalcoholic Steatohepatitis (NASH) and Hepatocellular Carcinoma (HCC) has been well documented
- Hepatoselective (ND-630) and Hepatospecific (ND-654) inhibitors of Acetyl-CoA Carboxylase (ACC) have been developed to address the continuum of these liver diseases
- These potent and selective allosteric inhibitors demonstrate excellent PK-PD relationships in target tissues (exposure vs target engagement and efficacy) and are effective at modulating NASH/HCC relevant endpoints across several *in vivo* models
- ND-630 and ND-654 demonstrate the ability for tissue targeted ACC inhibition to improve metabolic syndrome endpoints, decrease liver steatosis, decrease expression of inflammatory markers and improve fibrosis

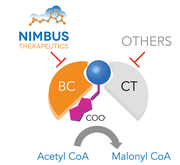
1. Lipotoxic Liver Injury in NASH, Key Role of Acetyl CoA Carboxylase (ACC) Activity[1]



FXR activation (Moore)
- Down regulates SREBP1c/DNL
- Possible mechanism of obeticholic acid

2. Nimbus Solves ACC Druggability Challenge by Targeting Allosteric Site in Biotin Carboxylase Domain

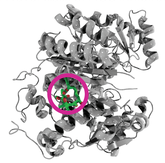
Challenges in Drugging ACC



- Natural product Soraphen A binds BC domain of ACC but is not druggable
- Industry efforts on analoging soraphen proved unsuccessful
- Allosteric binding site implicated in dimerization of ACC
- Highly lipophilic binding site
- Past programs exhibited poor drug-like properties

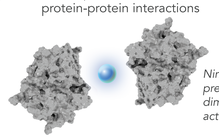
Nimbus Breakthrough

1. Novel class of ACC inhibitors



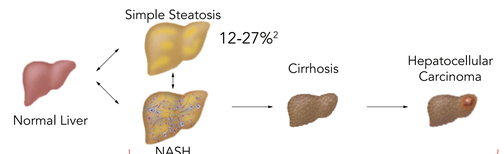
ND-630 *binds to the same site as Soraphen A*

2. Prototype for modulating protein-protein interactions



Nimbus inhibitors prevent ACC dimerization and activation

3. Liver Health: Unmet Need in Nonalcoholic Steatohepatitis & Hepatocellular Carcinoma



ND-630 Liver: Muscle 100:1

ND-654 Liver : Muscle 2700:1

% of Population	70-83%[2]	3-5%[3]	5-20% of NASH Patients[4]	1 in 200 NASH Patients[4]
Prevalence (US)[5]		9-16M	0.5-3.2M	45-80K[7]
Annual HCC Incidence (US)[6]				15K

4. ND-630: Hepatotropic ACC Inhibitor

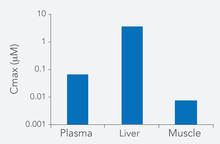
ND-630

Target potency
- ACC1 IC_{50} = 2 nM
- ACC2 IC_{50} = 7 nM
- HepG2 EC_{50} = 9 nM (serum free)
  = 66 nM (10% serum)
- C2C12 FAOxn stim. = 2x @ 200 nM

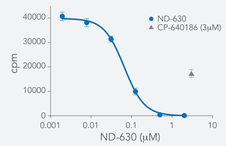
Pharmacology
- Rat FASyn ED_{50} = 0.14 mpk PO
- Rat RQ MED = 3 mpk PO
- Rat Malonyl-CoA ED_{50} = 0.8 mg/kg (liver)
- Rat Malonyl-CoA ED_{50} = 3 mg/kg (muscle)

ADME
- Low multispecies intrinsic clearance (human, mouse, rat, dog, monkey)
- Eliminated predominantly as parent
- P450 inhib >50 μM
- Protein binding (98%)

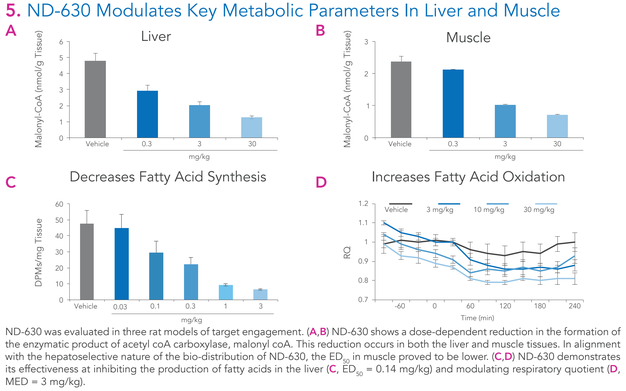
Exposure at 3 mg/kg



Hep-G2 Cell FA Synthesis
[^{14}C]acetate incorporation into FA

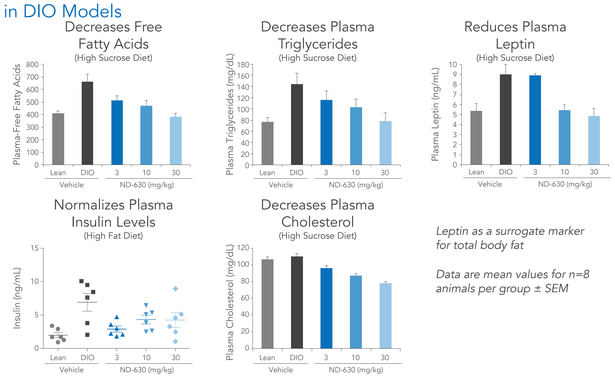


5. ND-630 Modulates Key Metabolic Parameters In Liver and Muscle



ND-630 was evaluated in three rat models of target engagement. (**A**,**B**) ND-630 shows a dose-dependent reduction in the formation of the enzymatic product of acetyl coA carboxylase, malonyl coA. This reduction occurs in both the liver and muscle tissues. In alignment with the hepatoselective nature of the bio-distribution of ND-630, the ED_{50} in muscle proved to be lower. (**C**,**D**) ND-630 demonstrates its effectiveness at inhibiting the production of fatty acids in the liver (**C**, ED_{50} = 0.14 mg/kg) and modulating respiratory quotient (**D**, MED = 3 mg/kg).

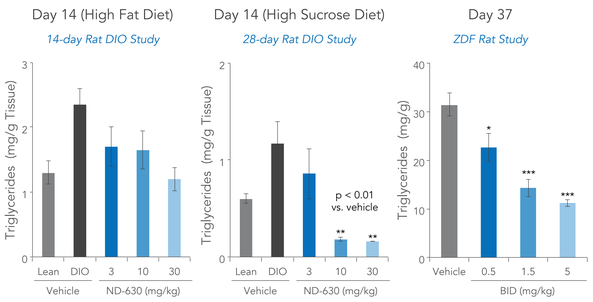
6. ND-630 Favorably Modulates Key Metabolic Parameters *in vivo* in DIO Models



Leptin as a surrogate marker for total body fat

Data are mean values for n=8 animals per group ± SEM

7. Liver Triglycerides Lowered Across DIO and ZDF Studies



- Profound hepatic triglyceride lowering in ZDF study at day 37
- Similar changes in liver cholesterol & free fatty acid

8. ND-654: Hepatoselective ACC Inhibitor

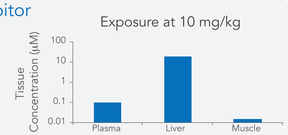
ND-654

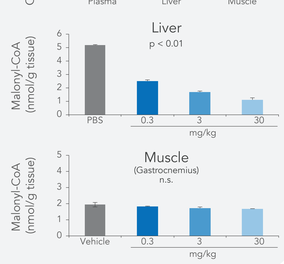
Target potency
- ACC1 IC_{50} = 3 nM
- ACC2 IC_{50} = 8 nM
- HepG2 EC_{50} = 4 nM (serum free)
  = 14 nM (10% serum)

Pharmacology
- Rat FASyn ED_{50} = 0.3 mg/kg PO
- Rat Malonyl-CoA ED_{50} = 0.3 mg/kg (liver)
- Rat DEN HCC MED = 10 mg/kg

ADME
- Moderate multispecies intrinsic clearance (human, mouse, rat, dog, monkey)
- P450 inhib >50 μM
- Highly selective across broad panel (>1000x)

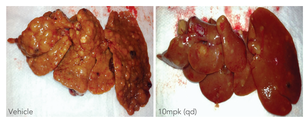
Exposure at 10 mg/kg



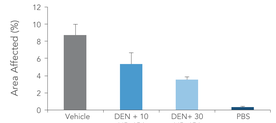


9. *In vivo* Efficacy of Hepatospecific ACC Inhibitor in Model of Cirrhosis and Hepatocellular Carcinoma

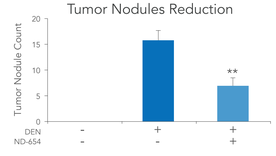
Tx-Mode DEN (diethylnitrosamine) HCC Model (Rat)



Sirius Red Staining

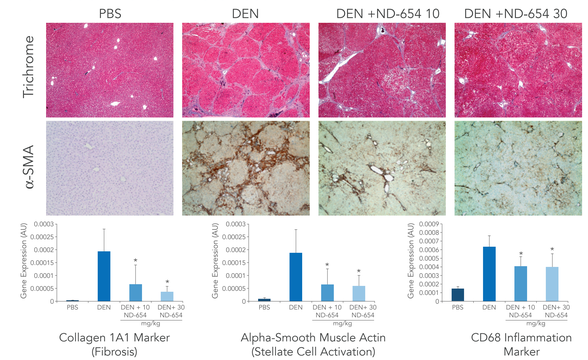


Tumor Nodules Reduction

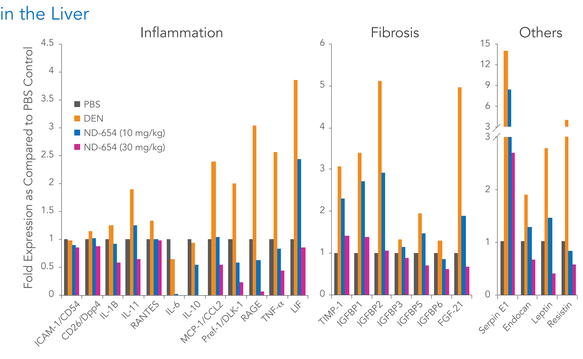


Marked improvement in liver health:
- Reduced…
  - Tumor burden (>60%)
  - Fat accumulation, serum TG & total bilirubin
  - Fibrosis
- Improved survival

10. ND-654 Shows Improvements in Fibrosis, Stellate Cell Activation and Inflammation Markers in the Rat DEN Model



11. Quantitative Liver Adipokine Array From ND-654 Treated DEN Rats Demonstrates ACC Inhibition Modulates Fibrosis and Inflammation in the Liver



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Notes:

1. Graphic adapted from Neuschwander-Tetri et al. *Hepatology*, 2010; 52:774-788; modified from slides presented by B. Neuschwander-Tetri at 2015 Keystone Symposia: Liver Metabolism and Nonalcoholic Fatty Liver Disease
2. Arthur J. McCullough, Cleveland Clinic at the AASLD - FDA Workshop on NASH, Sep 5, 2013
2. AASLD Practice Guidelines for NAFLD, 2012
3. Schuppan et al., *Liver International*, 2010
4 US Census Bureau, 2013 estimate: 317 million
5. Venook et al. *The Oncologist*, 2010;15(suppl 4):5–13
6. Will develop NASH-related HCC over time
7. Graphic adapted from Cohen et al. *Science*, 2011; 332(6037): 1519–1523