Liver-Directed Allosteric Inhibitors of Acetyl-CoA Carboxylase Reduce Hepatic Steatosis and Improve Dyslipidemia in Diet-Induced Obese Rat Models and Reduce Inflammation and Fibrosis in a Cirrhotic Rat Model

Poster #957

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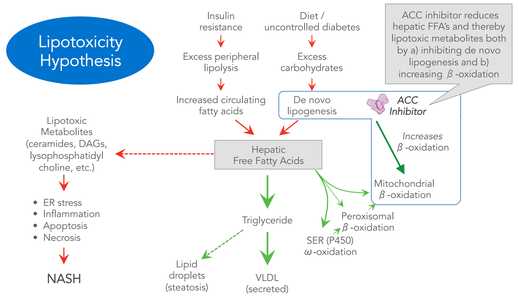
NIMBUS THERAPEUTICS

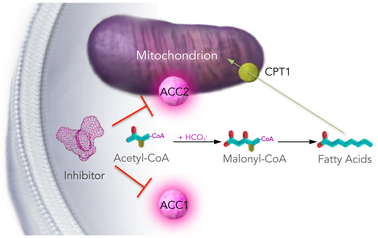
OVERVIEW

- 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-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. Lipotoxicity as a Molecular Cause of NASH: *ACC Inhibition Reduces FFA's & Resulting Lipotoxicity*[1]



2. Acetyl CoA Carboxylase (ACC) Regulates Fatty Acid Synthesis & Oxidation



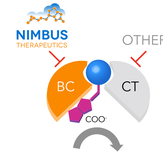
ACC Inhibition Leads to:

- Fatty acid synthesis ↓
- Tissue triglycerides ↓
- Body fat and weight ↓
- Fatty acid oxidation ↑
- Insulin sensitivity ↑

- Beneficial effects on lipids, blood glucose, weight neutral
- Nimbus: first allosteric inhibitor successfully targeting BC domain

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

Challenges in Drugging ACC



BC Domain

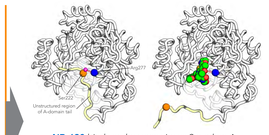
- Only potent BC domain inhibitor: Soraphen A
- Industry efforts on analoging soraphen proved unsuccessful
- Allosteric binding site implicated in dimerization of ACC

CT Domain

- Highly lipophilic binding site
- Inhibitors bind to active site
- Past programs exhibited poor drug-like properties

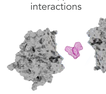
Nimbus Breakthrough

1. Novel class of ACC inhibitors



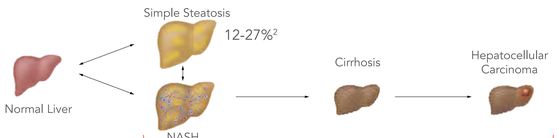
ND-630 *binds to the same site as Soraphen A*

2. Prototype for modulating protein-protein interactions



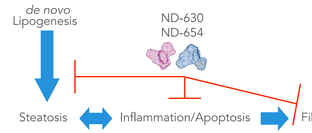
Nimbus inhibitors prevent ACC dimerization and activation

4. Liver Health: Unmet Need in Nonalcoholic Steatohepatitis



ND-630
Liver: Muscle
100:1

ND-654
Liver : Muscle
2700:1



- ACC inhibition directly addresses causative and perpetuating biological steps in NASH

5. ND-630: Hepatotropic ACC Inhibitor

ND-630

Target potency

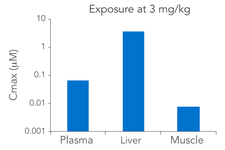
- ACC1 IC_{50} = 2 nM
- ACC2 IC_{50} = 7 nM
- HepG2 EC_{50} = 9 nM (serum free)
  = 66 nM (10% serum)
- C2C12 FAOxn stim. = 2x @ 200 nM

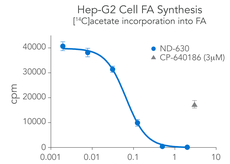
Pharmacology

- 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)

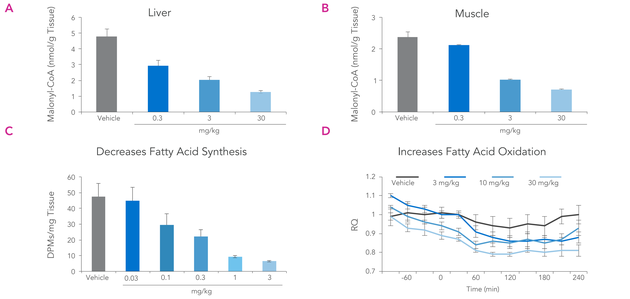
ADME

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





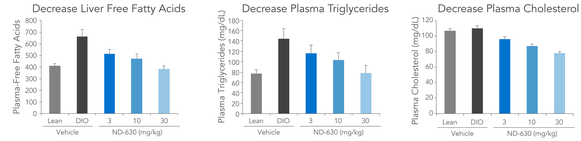
6. ND-630 Modulates Key Metabolic Parameters In Liver and Muscle



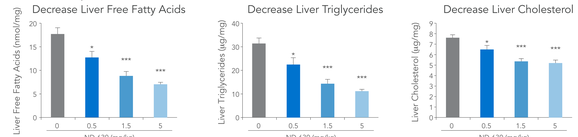
ND-630 was evaluated in three rat models of target engagement. (**A**,**B**) ND-630 shows a dose-dependent reduction in the formation of the enzymatic product of acetyl coA carboxylase, malonyl coA. This reduction occurs in both the liver and muscle tissues. In alignment with the hepatoselective nature of the bio-distribution of ND-630, the ED_{50} is 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).

7. ND-630 Favorably Modulates Key Plasma and Liver Lipids *in-vivo*

28d HS DIO Rat Endpoints



37d ZDF Rat Endpoints



Data are mean values for n=8 animals DIO, n=10 animals ZDF ± SEM

8. ND-654: Hepatoselective ACC Inhibitor

ND-654

Target potency

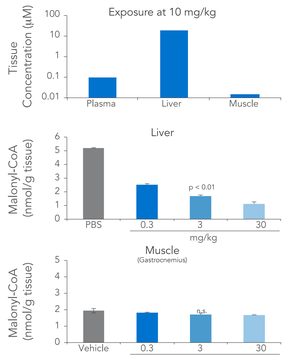
- ACC1 IC_{50} = 3 nM
- ACC2 IC_{50} = 8 nM
- HepG2 EC_{50} = 4 nM (serum free)
  = 14 nM (10% serum)

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

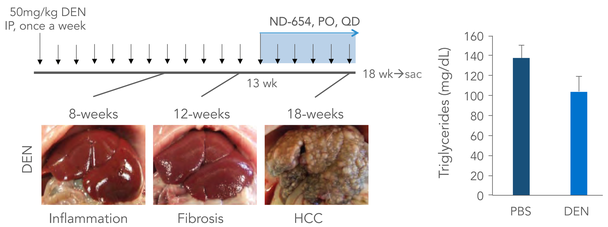
ADME

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

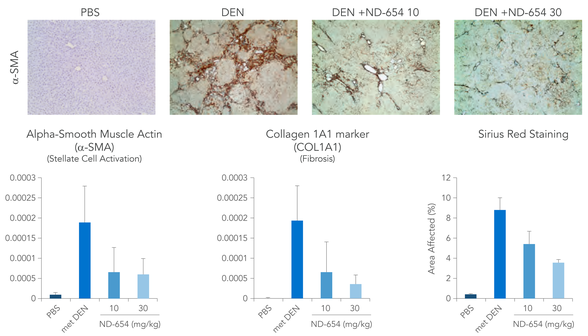


9. DEN-Induced Model of Cirrhosis in Rat

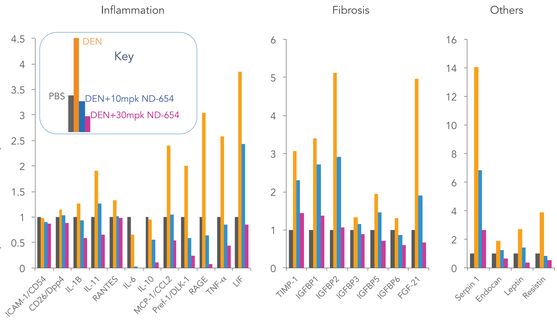
- Diethyl-nitrosamine (DEN): powerful inducer of injury-repair process, inflammation, fibrosis, and oncogenesis in rodents
  Recapitulates the histological changes of human NASH
- Weekly administration of DEN in rats causes progressive inflammation and fibrosis followed by development of cirrhosis by 18 weeks



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



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