Abstract #4452

Liver Selective Acetyl-CoA Carboxylase Inhibition by ND-654 Improves Survival in Cirrhotic Rats with Hepatocellular Carcinoma

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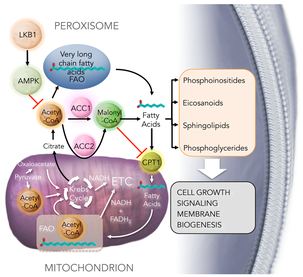
OVERVIEW

- Current treatment options for HCC are limited, and as such, prognosis is extremely poor with a 5-year survival less than 12%
- Metabolic attenuation is a promising approach to cancer therapy, and rate-limiting steps in key biosynthetic pathways are particularly attractive targets. HepaSpecific ND-654 is a potent allosteric inhibitor of Acetyl-CoA Carboxylase (ACC)
- ND-654 demonstrates excellent PK/PD relationships in the target tissue, the liver (exposure vs Malonyl-CoA reduction) and is effective at modifying Cirrhotic and HCC relevant endpoints in the DEN model. **Herein, we report on two rat DEN studies. An 18 week fixed end point study utilizing 10 mg/kg ND-654 PO, QD and a survival study utilizing 10 & 30 mg/kg ND-654 PO, QD.**
- ND-654 demonstrates the ability for tissue targeted ACC inhibition to decrease tumor burden, liver fibrosis and prolong survival in the rat DEN model of HCC

1. ACC: Emerging Tumor Metabolism Target: Tumors Up-regulate ACC to Fuel Cell Growth

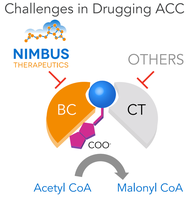


ACC Oncology Validation

- NSCLC: Targeted opportunity via LKB1-AMPK-ACC axis
  - *LKB1 inactivated in Peutz–Jeghers syndrome, NSCLC and cervical carcinoma*
- Breast Cancer: ACC1 knock down causes apoptosis in tumor cells
  - *BRCA1 stabilizes inactive phosphorylated form of ACC*
  - *BRCA1 also implicated in prostate cancer*
- RCC: ACC overexpression
  - *Associated with worse survival in clear cell Renal Cell Carcinoma*
- HCC: ACC overexpression
  - *ACC expression and de novo lipogenesis are increased in HCC*

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

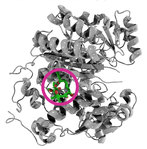
Challenges in Drugging ACC



- Only potent BC domain inhibitor: Soraphen A
- Industry efforts on analoging soraphen proved unsuccessful
- Allosteric binding site implicated in dimerization of ACC
- Highly lipophilic binding site
- Inhibitors bind to active site
- Past programs exhibited poor drug-like properties

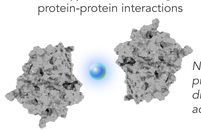
Nimbus Breakthrough

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

3. ND-654: Hepato-Selective ACC Inhibitor

ND-654

Target potency

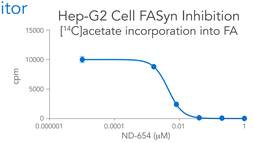
- ACC1 IC_{50} = 3 nM
- ACC2 IC_{50} = 8 nM
- HepG2 EC_{50} = 4 nM (serum free) = 14 nM (10% serum)

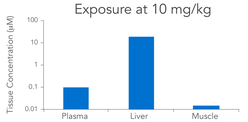
Pharmacology

- 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

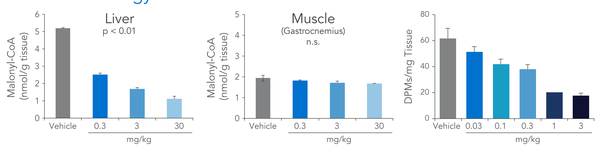
ADME

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



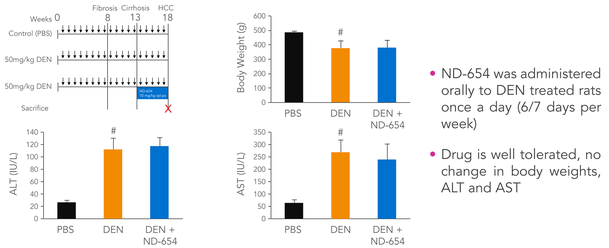


4. ND-654 Demonstrates Liver Tissue Specific Target Engagement and Pharmacology



5. ND-654 is Well Tolerated in Rats Administered DEN Animals on Drug Appear Healthy

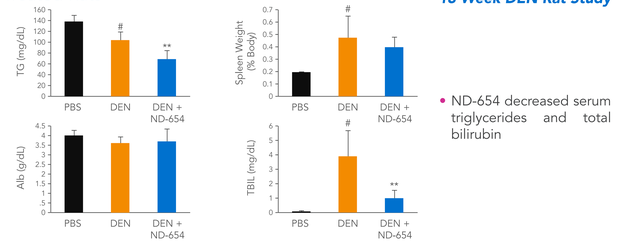
18 Week DEN Rat Study



- ND-654 was administered orally to DEN treated rats once a day (6/7 days per week)
- Drug is well tolerated, no change in body weights, ALT and AST

6. Liver Directed ND-654 Improves Markers of Liver Health in DEN Treated Rats

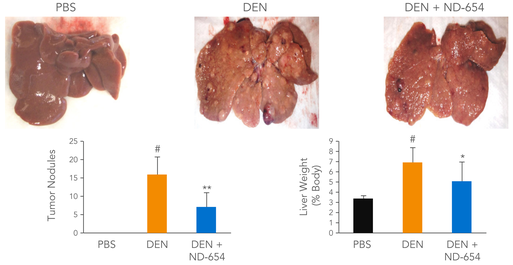
18 Week DEN Rat Study



- ND-654 decreased serum triglycerides and total bilirubin

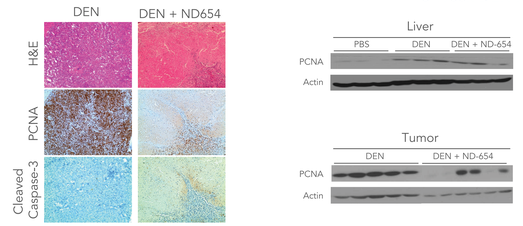
7. Treatment with 10 mpk ND-654 QD Results in Marked Reduction of Tumor Nodules

18 Week DEN Rat Study



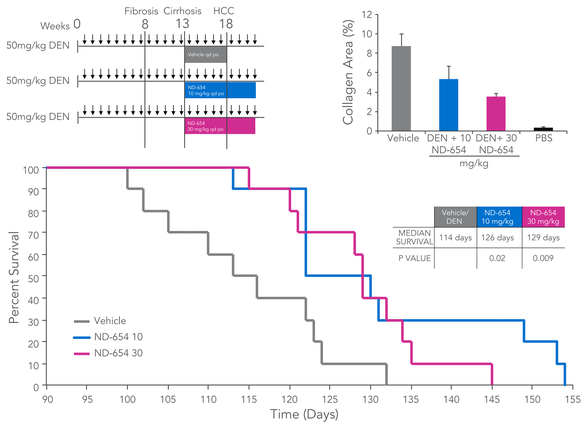
8. ND-654 Decreases PCNA Expression in Tumors and Results in Tumor Necrosis

18 Week DEN Rat Study



9. ND-654 Significantly Improved Survival in the Aggressive DEN HCC Model

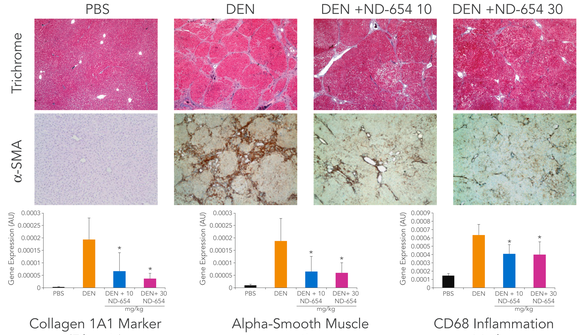
DEN Rat Survival Study



	Vehicle/ DEN	ND-654 10 mg/kg	ND-654 30 mg/kg
MEDIAN SURVIVAL	114 days	126 days	129 days
P VALUE		0.02	0.009

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

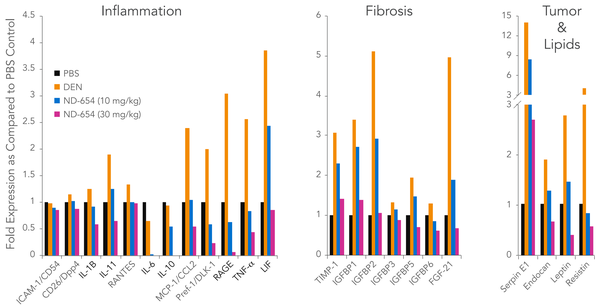
DEN Rat Survival Study



Collagen 1A1 Marker (Fibrosis) | Alpha-Smooth Muscle Actin | CD68 Inflammation Marker

11. Quantitative Liver Adipokine Array From ND-654 Treated DEN Rats Demonstrates Modulation of Fibrosis, Inflammation and Tumor Markers in the Liver

DEN Rat Survival Study



CONCLUSION

- ND-654 preferentially biodistributes to the liver where it inhibited ACC activity but did not increase liver toxicity.
- ND-654 inhibits HCC development by decreasing tumor proliferation and causing tumor necrosis.
- ND-654 reduces markers of inflammation and fibrosis and improves overall survival in the DEN rat model.
- Our results therefore provide further evidence that de novo lipogenesis is an important mediator of hepatic carcinogenesis.
- Selective inhibition of hepatic ACC is a potential therapeutic strategy for HCC

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