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Mission Statement:

To advance small molecule inhibitors of the Oligosaccharyltransferase (OST) for the treatment of cancer and other diseases.
Research Program:

Why Support this Research?
1. Novelty: a new target/biologic effect previously uninvestigated in human biology
2. We identified a new class of inhibitors
3. Demonstrated anti-tumor activity
4. Designed and implemented key assays for \textit{in vitro} and \textit{in vivo} advancement of drug discovery
5. No competition in this space
Initial Market:

EGFR driven tumors

*Lung Cancer
Colon Cancer
Head and Neck Cancer

FDA approved EGFR inhibitors

Gefitinib: 518
Erlotinib: 538
Afatinib: 610
Osimertinib: 1,860
Cetuximab: 159
Panitumumab: 168

> $3.8 billion/year
The Problem: EGFR inhibitor resistance

Hercules vs. the Hydra

Inhibitor

MEK  PI3K

MAPK  AKT

Proliferation  Survival
The Solution:

**Oligosaccharyltransferase (OST) targeting:**

- Enzyme that adds glycans to EGFR and other receptors
- Partial loss of glycans impairs receptor function
- Our HTS identified first in class inhibitors
OST Inhibitors:

Drug Discovery Venture

- Collaboration with New England Discovery Partners, supported by NIH STTR grant

- 46 analogs with activity ≥ initial lead (NGI-1)

- analogs with IC\textsubscript{50} of 60-90nM
  - in intact cells
  - \textit{true} IC\textsubscript{50} likely <10nM

- Solubility improved by 25X
  - \textit{room to improve}

- Allosteric inhibitor with partial effect- no toxicity

Confidential – Not for distribution
OST inhibitors: Efficacy

EGFR mutant NSCLC Xenografts

Treatments:
- 1. Vehicle
- 2. Osimertinib 5mg/kg
- 3. NGI-155 10mg/kg
- 4. NGI-155 + Osimertinib

NHI-155 delivered *i.p.* for a total of 6 doses over 2 weeks

Osimertinib delivered *p.o* daily for 2 weeks

2 week Tx

3 mice cured with NGI-155 alone
OST Inhibitor Development:

Three year Goals:

• Improve in vivo pharmacokinetics of OST inhibitors - formulations and improved analogs
• Expand IP for OST inhibitors
• Complete preclinical testing of a clinical candidate: tumor efficacy and dosing in mice and primates
• Submit an IND application to the FDA
• Initiate a phase I trial in NSCLC