DRUG DEVELOPMENT INSTITUTE (DDI) TECH BRIEF

The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

NASH: A New Approach to Treat Liver Fibrosis With SERMs

Non-alcoholic steatohepatitis (NASH) is projected to affect over 18 million people annually by 2027 and is set to eclipse hepatitis B virus (HBV) as the leading cause of hepatocellular carcinoma. NASH is associated not only with liver cancer but also cirrhosis and multiple other chronic health complications. New selective estrogen receptor modulators (SERMs) selectively agonizing ERβ have been developed by researchers at The Ohio State University. These new compounds have the potential to meet the need for a truly effective drug in this new "epidemic" indication that has so far been nearly untreatable.

Applications

- NASH/Liver Fibrosis
- Follow-on indications – Prostate Cancer, Glioblastoma Multiforme
- Additional indications for these compounds are being explored through internal university collaborations

Advantages

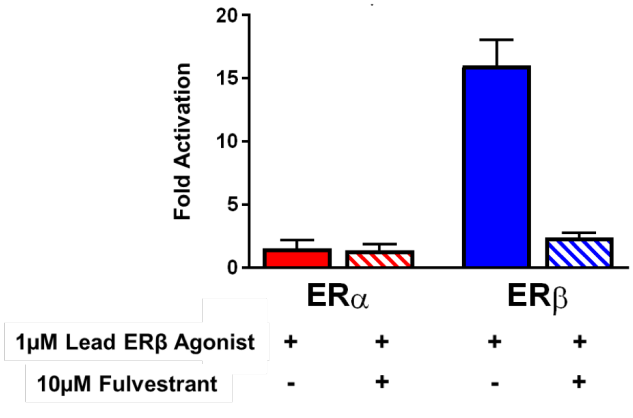
- Novel non-steroidal pharmacophore
- High selectivity for ERβ over ERα
- High oral bioavailability and brain penetrance
- Strong IP position for compound
- Unexplored pharmacophore potentially tunable to desired hormone receptor activity

Stage of Development: Lead Optimization

- **Known Characteristics of Lead Compound:**
  - ERβ Cellular EC_{50} = 32 ± 13 nM
  - ERβ: ERα >200:1
  - Good oral dose response *in vivo* and brain penetrant
  - *In vitro* ADME (no major concerns)
  - No observable toxicity at highest dose tested (300mpk in mice)

- **Next Steps:**
  - More *in vivo* efficacy models
  - Design and synthesize new analogs
  - Profile *in vitro* ADME and PK of follow-on analogs

Lead Compound is ERβ Selective, Steroid Competitive and Reversible.



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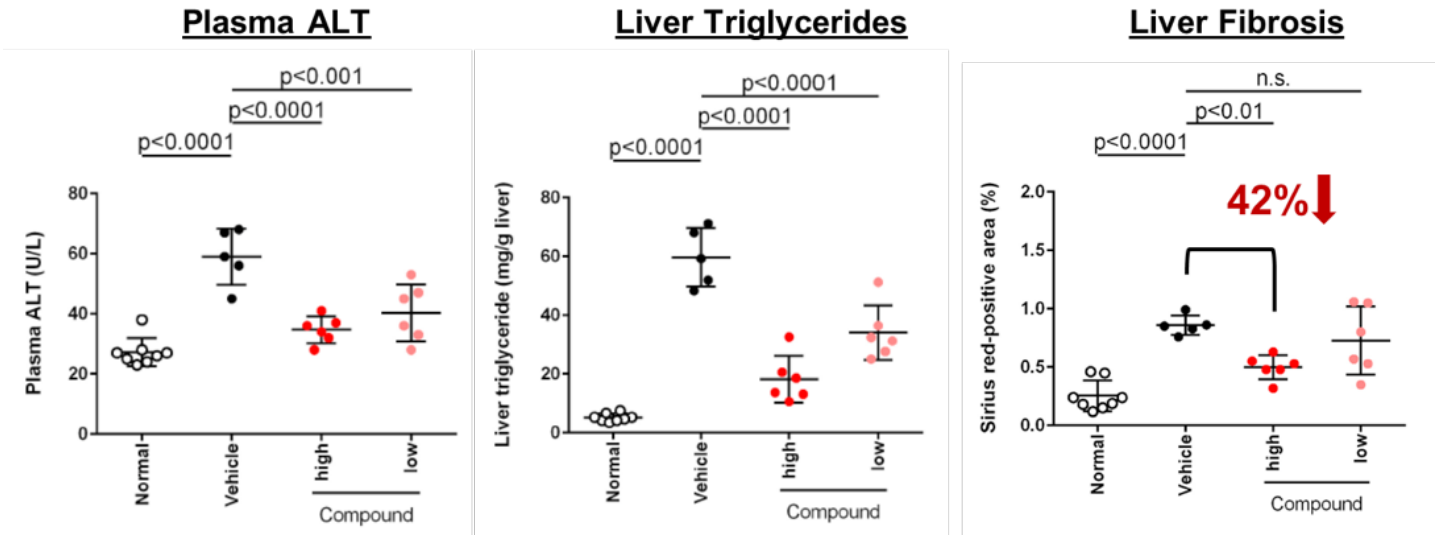
Reduced Fibrosis and Liver Injury after 7 weeks of Daily Oral Dosing of the Lead Compound in a Diet Induced Mouse Model of NASH.



Rationale for Targeting ER

In many cases disease rates differ between men and women, pointing to the potential therapeutic benefits of estrogen pharmacology. As the differences between ERα and ERβ are better defined, selective ERβ agonists hold the promise of providing therapeutic efficacy with greatly reduced risks of ERα-mediated side effects. The endocrine cancers of breast and prostate have been the most widely studied, but recent literature has pointed to beneficial effects of ERβ agonism in glioblastoma and in NASH, a chronic condition of the liver that occurs more frequently in men and is expected to become the leading cause of hepatocellular carcinoma. NASH is part of a disease cascade that begins as non-alcoholic fatty liver disease (NAFLD) and can progress through NASH to cirrhosis and eventually to hepatocellular carcinoma. Multiple lines of evidence support estrogens as protective against diverse aspects of NASH pathobiology. Recent literature suggests that ERβ activation may be central to estrogen action in driving anti-NASH efficacy.

Publications

No information has been published concerning these compounds.

IP Landscape

Patent Application: PCT/US2016/052531
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