Selective Estrogen Receptor Modulator (ERβ Agonist) for treating Liver Fibrosis and Cancer

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SME: Chris Coss, PhD

Korea Drug Development Fund - Oct, 2019

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OHIO STATE'S DRUG DEVELOPMENT INSTITUTE (DDI)

Accelerating Innovative Research to Speed Cures to Cancer Patients

The DDI Advantage

- A pipeline of innovative, early-stage therapeutics

- Independently validated technologies

- Rigorous project milestone management by industry scientists

- A network of industry experts to vet projects

- Focus on external partnership and out-licensing

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ERβ Selective Agonist - Overview

Rationale

- ERβ activation may attenuate progression in multiple diseases:

   NASH / Liver Fibrosis   Prostate cancer   Glioblastoma

Technology

- Novel and selective, non-steroidal ERβ agonists

    Lead molecule: ERβ Cellular avg. EC_{50} = 32 ± 13 nM;

    ERβ : ERα >200:1

    ERβ cell-free radio-ligand binding K_i = 2 nM

    High oral bioavailability, brain penetrant

    Good *in vivo* oral dose response
    In vitro ADME completed, no major issues

    - Strong IP position with ability to tune desired SERM activity on novel pharmacophore and expand portfolio
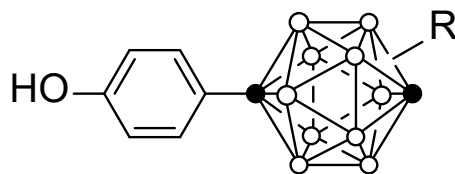
Next Milestones

- Additional *in vivo* efficacy of lead
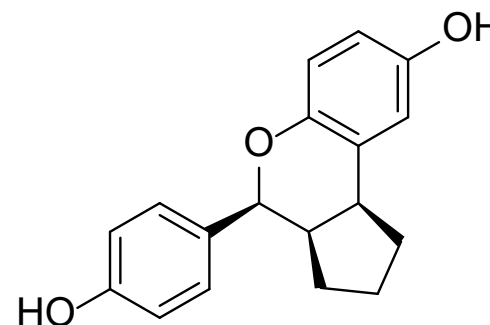- Design and synthesize new analogs

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OSU's Lead vs. LY500307 (Phase II)
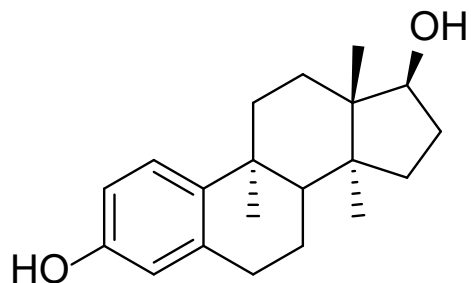
Estradiol (E2)

OSU's Lead*

LY500307

Molecule	ERα EC$_{50}$	ERβ EC$_{50}$	ERα/ERβ
E2	0.14 nM	0.075 nM	2.0
OSU's Lead	>30,000 nM	44.9 nM	>668
LY500307	346 nM	0.6 nM	577

*Black dots are carbon ⟶ ●
White dots represent B-H ⟶ ○

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ER-β Selective Agonist – Lead Molecule

Mouse Acute Tox: No observable tox
(@ 200 mpk PO, highest dose given)

Mouse PK: (10 mg/kg, p.o.)
Plasma AUC = 122 uM-h
$T_{1/2}$ = 5.2 h, C_{max} = 22.0 uM
F = 92%, Brain / Plasma = 0.46

Dog PK: (10 mg/kg, p.o.)
Plasma AUC = 13.0 uM-h
$T_{1/2}$ = 39.8 h , C_{max} = 0.63 uM
F = 16.5%

Solubility:
Kinetic Solubility (pH 7.4) < 1 uM
Sim. Gastric Fluid (pH 1.2) < 1.56 uM
Sim. Intestinal Fluid (pH 6.8) <1.56 uM
Fed State SIF (pH 5.0 + oil) = 1770 uM
Fasted State SIF (pH 6.5) = 336 uM

hERG (Q-Patch): IC_{50} > 30 uM
Plasma Protein Binding: > 99.9%
Caco-2 (Bidirectional): N/A*

Other Human Nuclear Receptors:
Following NHR's screened in agonist and antagonist mode:
AR, GR, PGR, MR, FXR, LXRα, LXRβ, ERRγ, PXR

No EC_{50} / IC_{50} < 10 uM

Microsomal Stability: Stable in human microsomes

Mouse:	$T_{1/2}$ = 47.7 min,	Cl_{int} = 29.1 uL/min/mg
Rat:	$T_{1/2}$ = 15.6 min,	Cl_{int} = 89.0 uL/min/mg
Monkey:	$T_{1/2}$ = 65.9 min,	Cl_{int} = 21.0 uL/min/mg
Human:	$T_{1/2}$ > 145 min,	Cl_{int} < 9.6 uL/min/mg
Dog:	$T_{1/2}$ > 145 min,	Cl_{int} < 9.6 uL/min/mg

CYP Inhibition: (IC_{50}) No significant issues

|	
1A2: 53.2 uM	2B6: 6.3 uM
2B6: 16.3 uM	2C8: 48.4 uM
2C9: 68.8 uM	2C19: 13.1 uM
2D6: 63.5 uM	

3A4 (Testosterone): IC_{50} = 88.4 uM
3A4 (Midazalam): IC_{50} = 18.6 uM

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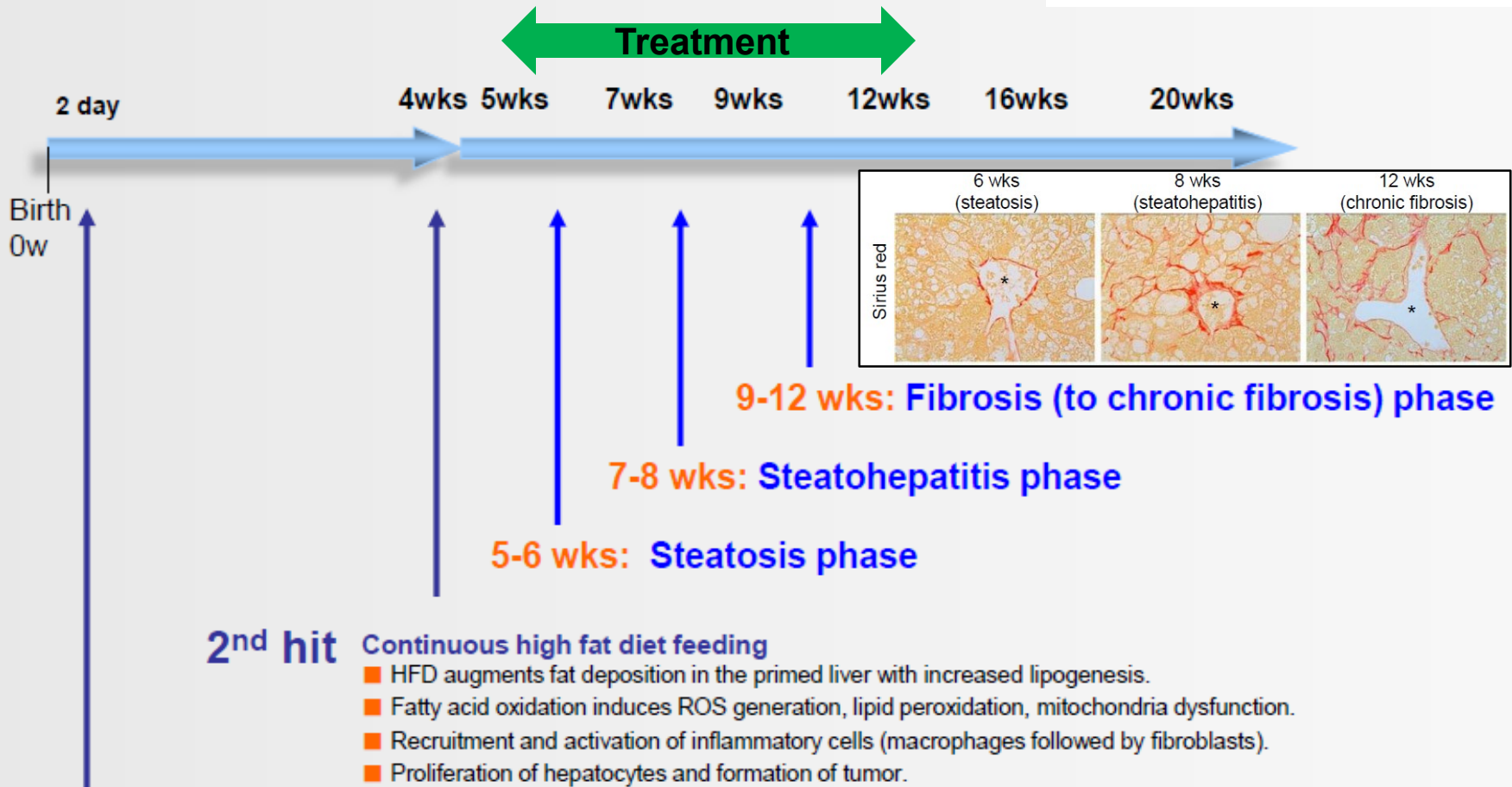
ERβ Agonist in NASH / Liver Fibrosis

- **N**on-**A**lcoholic **S**teato**H**epatitis
  - Affects 10 million people within US
  - 3-5 million NASH patients progress to **fibrosis**
  - Will overtake viral hepatitis as primary cause of **Hepatocellular Carcinoma** in US by 2040
  - No approved therapy

- Targeting ER-β in NASH
  - Promote FXR-mediated lipid clearance
  - Block PXR-mediated lipid accumulation
  - Reduce oxidative stress induced hepatic stellate cell activation
  - Avoid ERα-mediated pro-thrombotic and HPG-axis effects
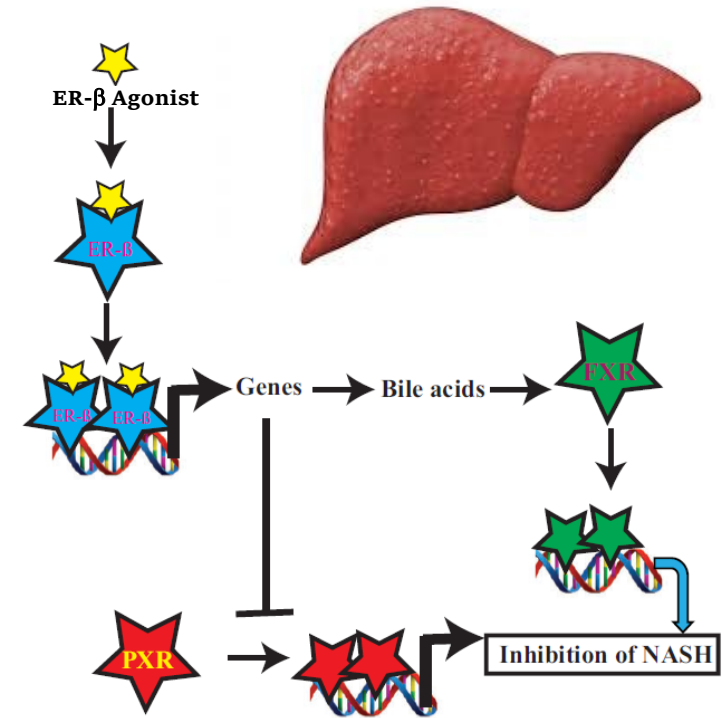
- Comprehensive NASH/Fibrosis Prevention Study by SMC Labs
  - 10 and 100 mg/kg dose levels
  - Study readouts:
    - Serum liver damage markers (ALT, triglycerides)
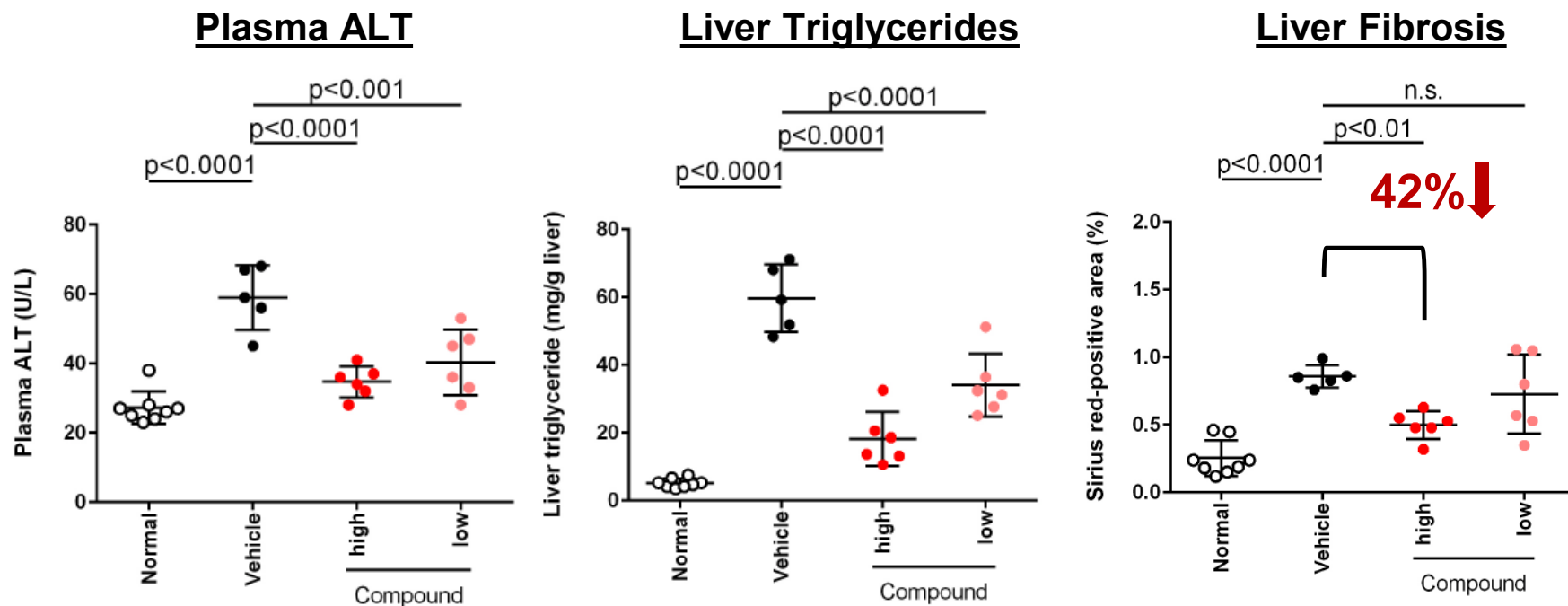   - Fibrosis Area (sirius red staining)

ER-β Agonist
ER-β
ER-β ER-β
Genes → Bile acids → FXR
PXR
Inhibition of NASH

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STAM™ NASH-Fibrosis-HCC Model

SMC Laboratories, Inc.

Treatment

2 day	4wks	5wks	7wks	9wks	12wks	16wks	20wks

Birth
0w

Sirius red
| 6 wks (steatosis) | 8 wks (steatohepatitis) | 12 wks (chronic fibrosis) |

9-12 wks: Fibrosis (to chronic fibrosis) phase

7-8 wks: Steatohepatitis phase

5-6 wks: Steatosis phase

2ⁿᵈ hit **Continuous high fat diet feeding**
- HFD augments fat deposition in the primed liver with increased lipogenesis.
- Fatty acid oxidation induces ROS generation, lipid peroxidation, mitochondria dysfunction.
- Recruitment and activation of inflammatory cells (macrophages followed by fibroblasts).
- Proliferation of hepatocytes and formation of tumor.

1ˢᵗ hit **Inhibition of O-GlcNAc-β-N-acetylglucosaminidase of β-cell (STZ)**
- β cell-injury early after birth drives regenerative response with islet inflammation.
- Accumulation of macrophages in the islet and adipose tissue.
- Induction of mild diabetic condition.
- Up-regulation of scavenger receptors and TNF-α in the liver ("priming").

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Decrease in Liver Fibrosis by Lead ERβ Agonist
Daily oral dosing

Plasma ALT   **Liver Triglycerides**   **Liver Fibrosis**

Following 7 Weeks of PO QD Treatment, Lead ERβ Agonist Demonstrates:
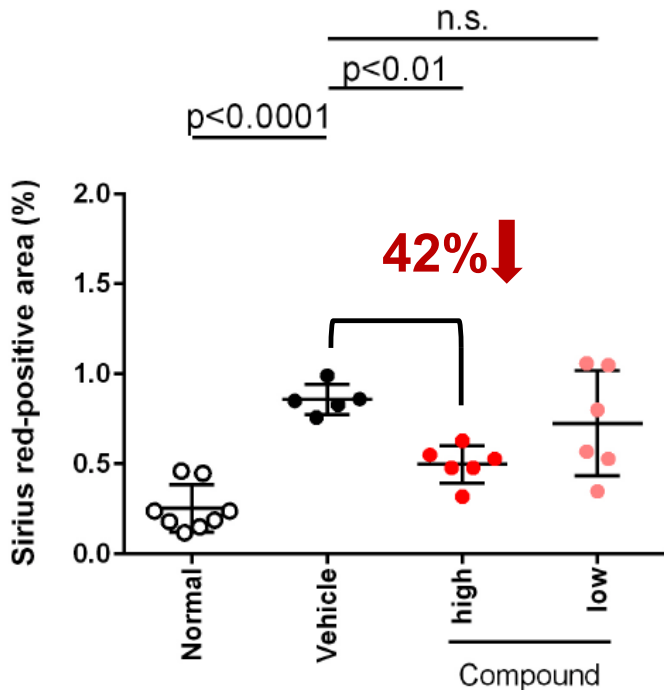
- Large dose dependent reductions in liver injury marker serum ALT.
- Large dose dependent reductions in liver triglycerides.
- 42% reduction in fibrotic liver area for high dose group.
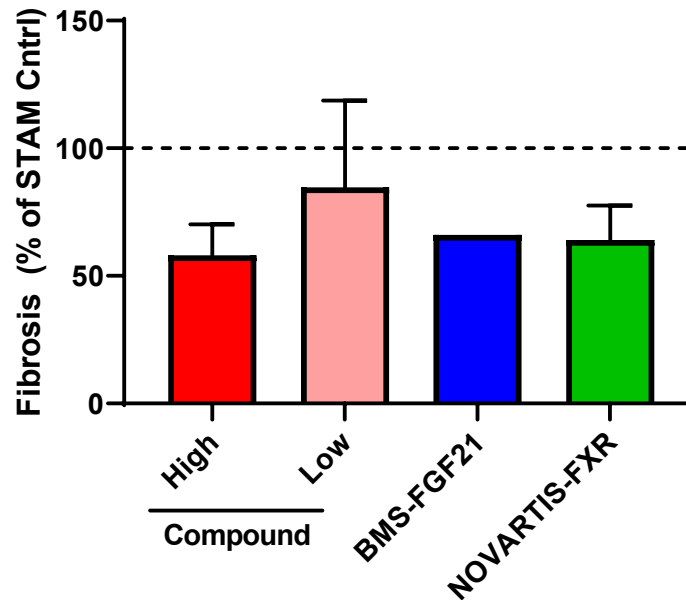
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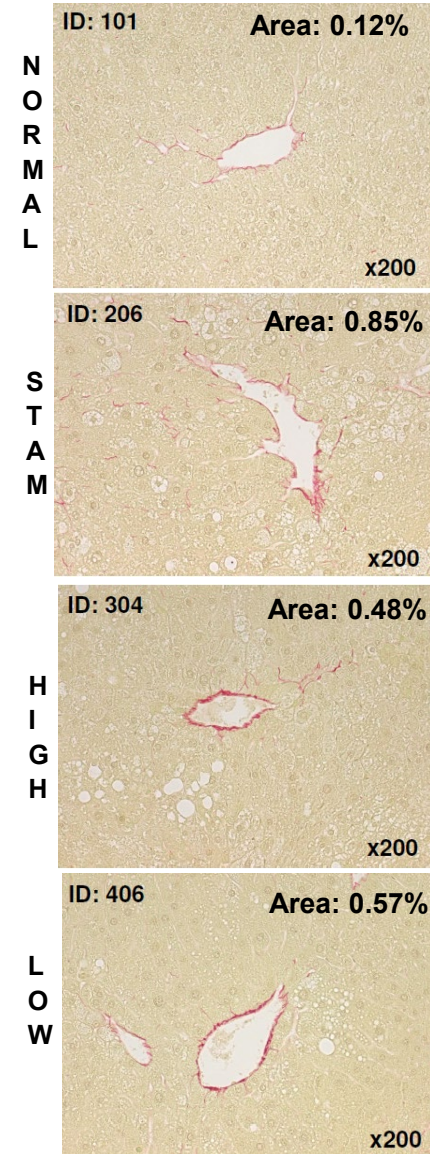# Reduction in Fibrosis with ER-β Agonist Similar to Other Phase II NASH Agents

Fibrosis Area

Fibrosis Area

Liver H&E

- High dose level significantly reduced fibrotic area with an anti-fibrotic effect similar to published STAM data for BMS-FGF21 and NOVARTIS-FXR.

Intellectual Property

Application: PCT/US2016/052531
Priority Date: Sep. 17, 2015

Title: CARBORANE COMPOUNDS AND METHODS OF USE THEREOF
Inventors: Werner Tjarks, David Sedlak, Petr Bartunek
Assignee: Ohio State Innovation Foundation & Institute of Molecular Genetics of the ASCR

Filing: Provisional (Sep 17, 2015), PCT (Sep 19, 2016),
              National Phase (Mar 17, 2018)

Description: Compositions of matter as well as methods of use

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