Drug Development Institute

Non-confidential Projects Deck

June 2019

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DDI Pipeline 2019

SMALL MOLECULE

PP2A Activator for Treatment of AML and Other Hematologic Malignancies
Raj Muthusamy, DVM, PhD; William Kisseberth, DVM, PhD; Mitch Phelps, PhD; John C. Byrd, MD

Selective Estrogen Receptor Modulator (ER-β Agonist) as a New Approach to Targeting Cancer
Werner Tjarks, Dr.rer.nat.

Inhibitors of Mps1 Kinase as Mitotic Regulators for Cancer Therapy
Harold Fisk, PhD, Robert Brueggemeier, PhD; Tom Li, PhD; Michael Darby, PhD

Selective RAL A GTPase Inhibitors as a Cancer Treatment
Steven Sizemore, PhD and Steffen Lindert, PhD

Aryl Hydrocarbon Receptor Inhibition in Hematologic Malignancies
Don Benson, MD, PhD

DHODH Inhibition as a Target in Acute Myeloid Leukemia
Erin Hertlein, PhD, John C. Byrd, MD

DDI Pipeline continued..

BIOLOGICS

Split Delivery and Functional Reconstitution of Immunotoxins via Dual Tumor-Targeted Pathways

Dmitri Kudryashov, MD, PhD

IMMUNOTHERAPY

Modulation of Notch Signaling in Immune Cells for Therapeutic Benefit

Mikhail Dikov, PhD; Thomas Magliery, PhD; David Carbone, MD, PhD

VACCINE

Therapeutic B cell Cancer Vaccine Platform

Thomas L. Cherpes, MD, DVM; Rodolfo Vicetti Miguel, MD; Nirk Quispe Calla, MD

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Ohio State Drug Development Institute (DDI) Portfolio Project

Therapeutic cancer vaccine platform: Activated B cells (ABCs)

Inventors:
Thomas Cherpes, DVM, MD
Rodolfo Vicetti Miguel, MD
Nirk Quispe Calla, MD

DDI Lead: Reena Shakya, PhD

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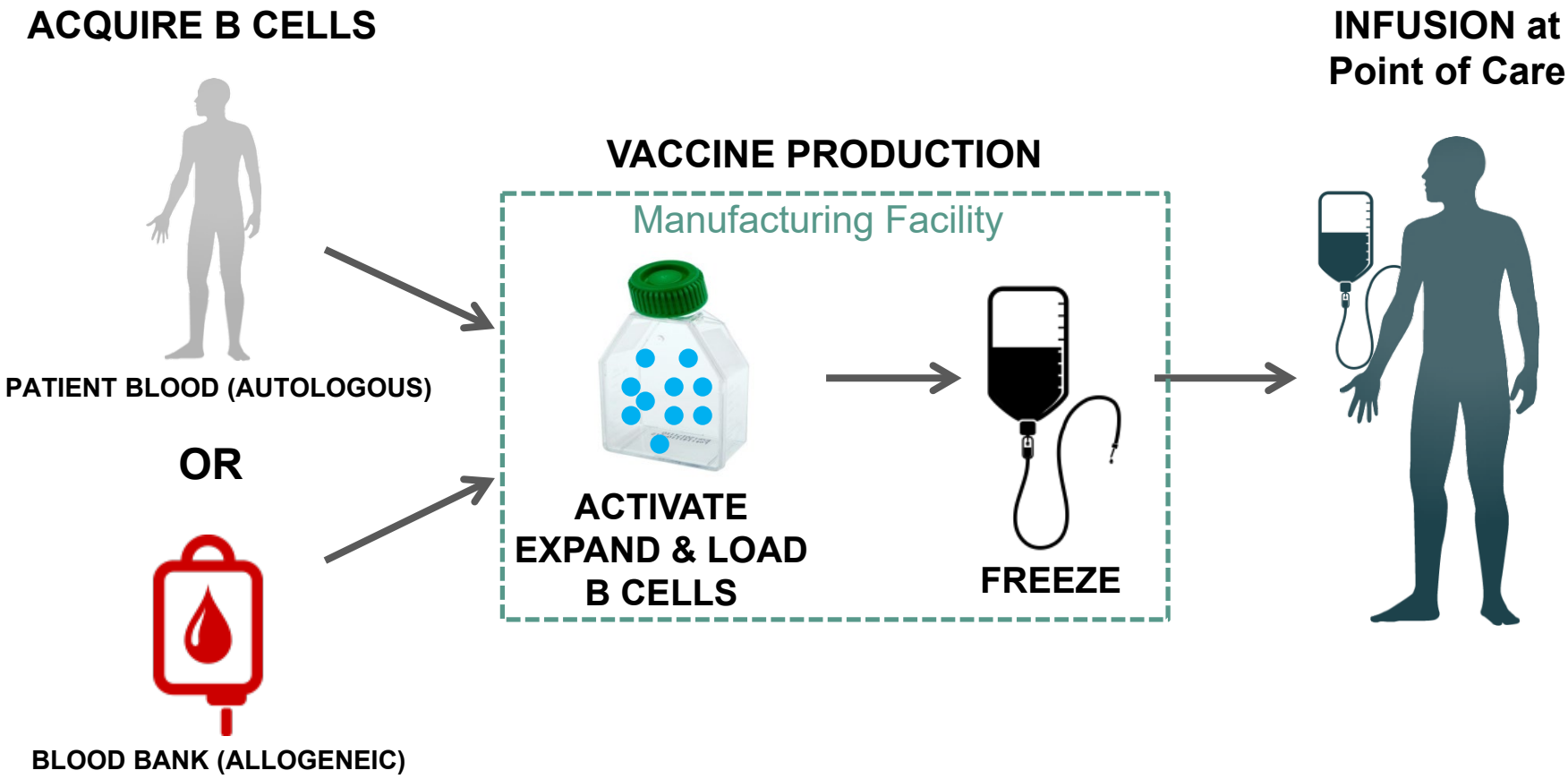
Effective, customizable B cell cancer vaccine



Value propositions:

1. Frozen product stable for shipping and administration at point of care
2. Therapeutic platform customizable to specific tumor antigens
3. Efficacy demonstrated in animal models across multiple tumor types
4. Significant expansion of cells ex vivo eliminating need for leukapheresis

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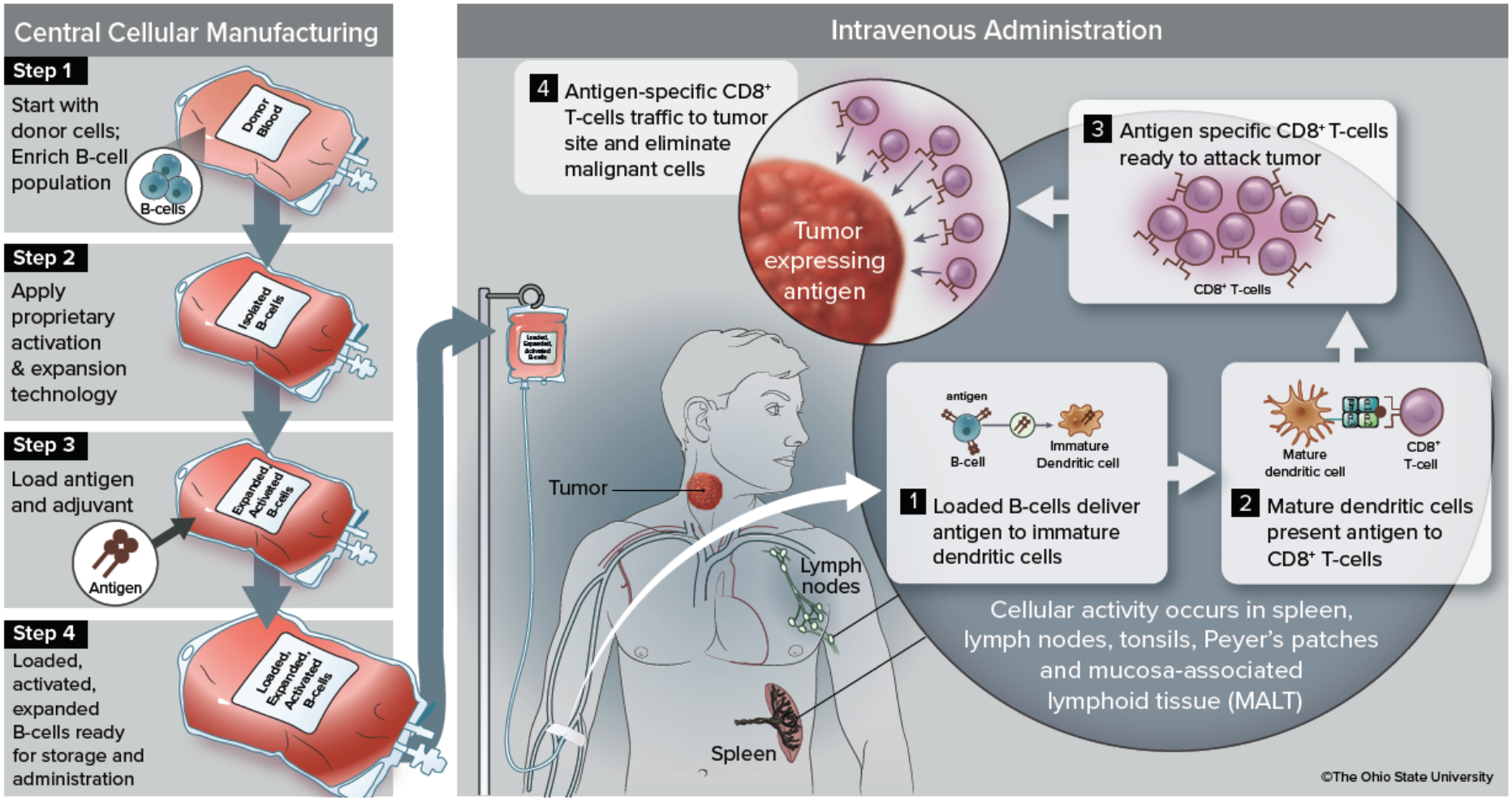
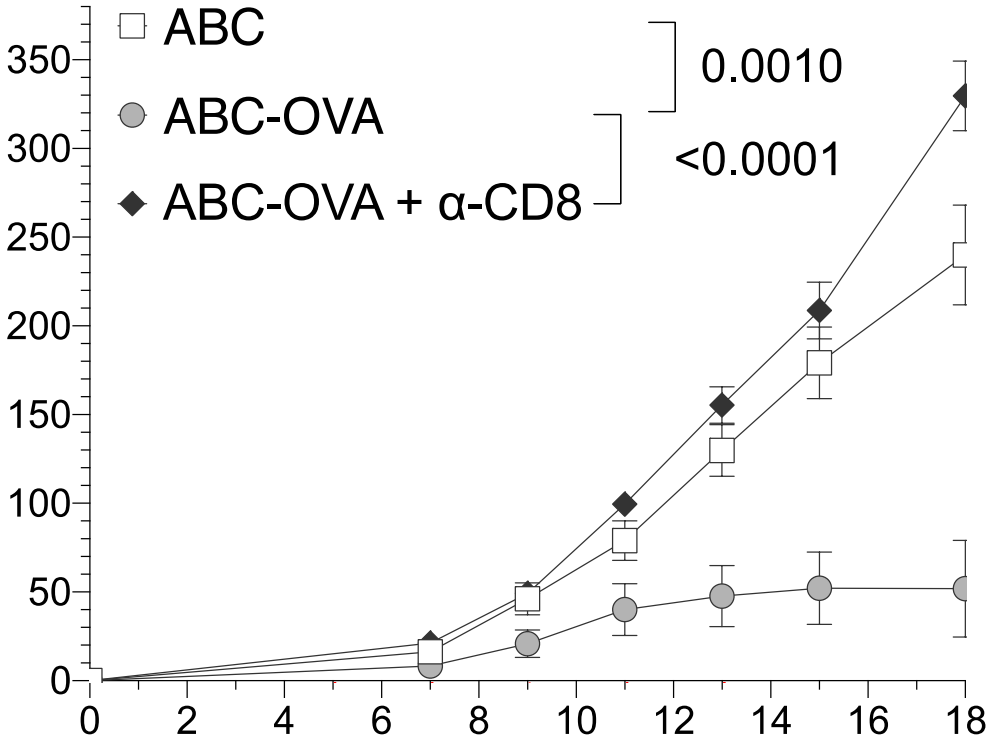
ABCs, *A*ctivated *B*-*C*ells as a therapeutic cancer vaccine

- A **platform** for antigen presentation using activated B-cells
- B cells are activated *in vitro* using a proprietary method and conjugated with tumor antigen to therapeutically target cancer cells
- *In vivo*, the activated B-cells efficiently induce production of antigen-specific CD8+ T cells



ABCs induce anti-tumor efficacy via activation of CD8+ T cells *in vivo*



ABC: Activated B-Cells, i.v. administration, 10^7 cells/dose QOD x 5 doses
Control, activated B cells with no antigen
α-CD8, 100ug anti-CD8 depleting antibody administered i.p. QOD from day 4
Tumor Model: EG7.Ovalbumin; 0.75 x 10^6 EG7-OVA tumor cells

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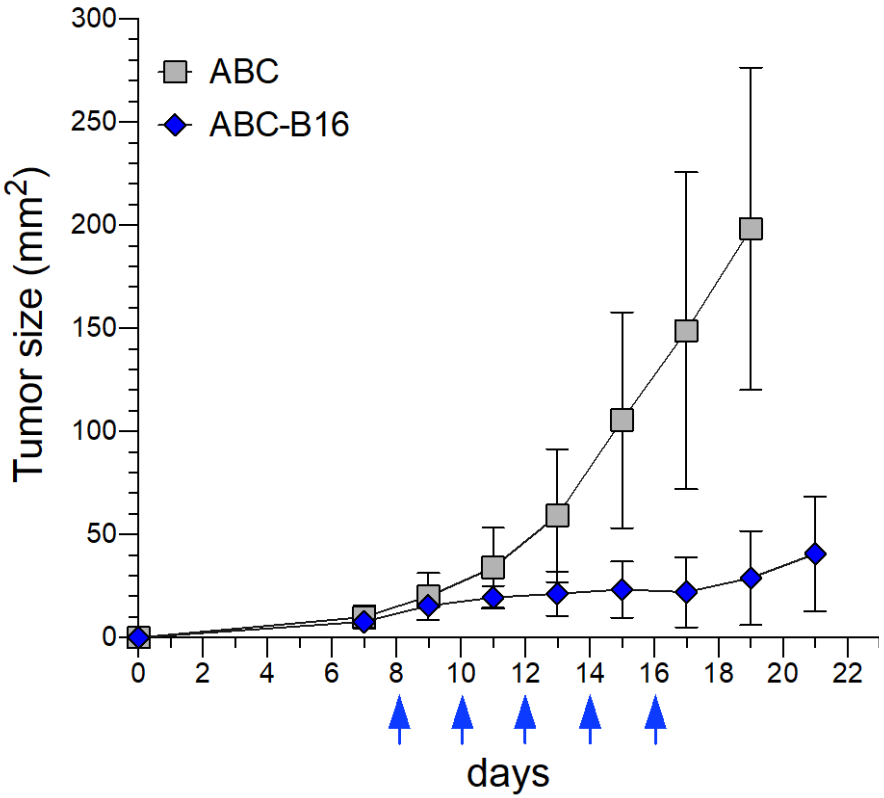
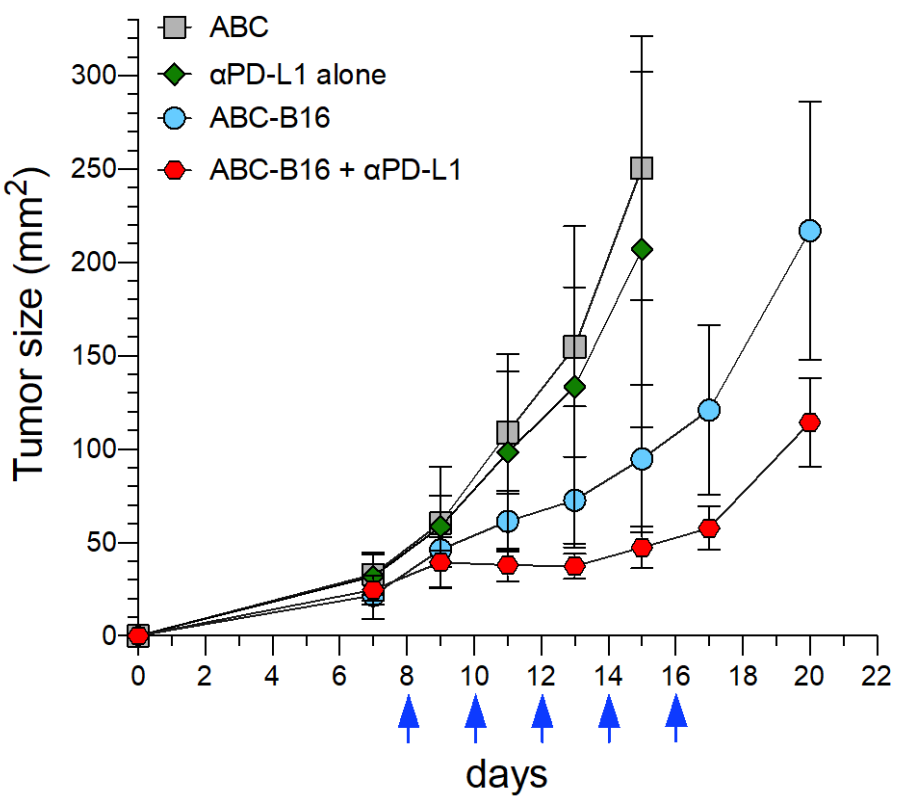
Efficacy in an aggressive, syngeneic melanoma model: mono-therapy or synergy with anti-PD-L1

B16-F10: **2X standard** tumor dose



B16-F10: **4X standard** tumor dose



ABC, optimized activated B cells, i.v. administration, 10^7 cells/dose QOD x 5 doses
B16 indicates B16-F10-specific peptides were conjugated, B16-F10 melanoma model

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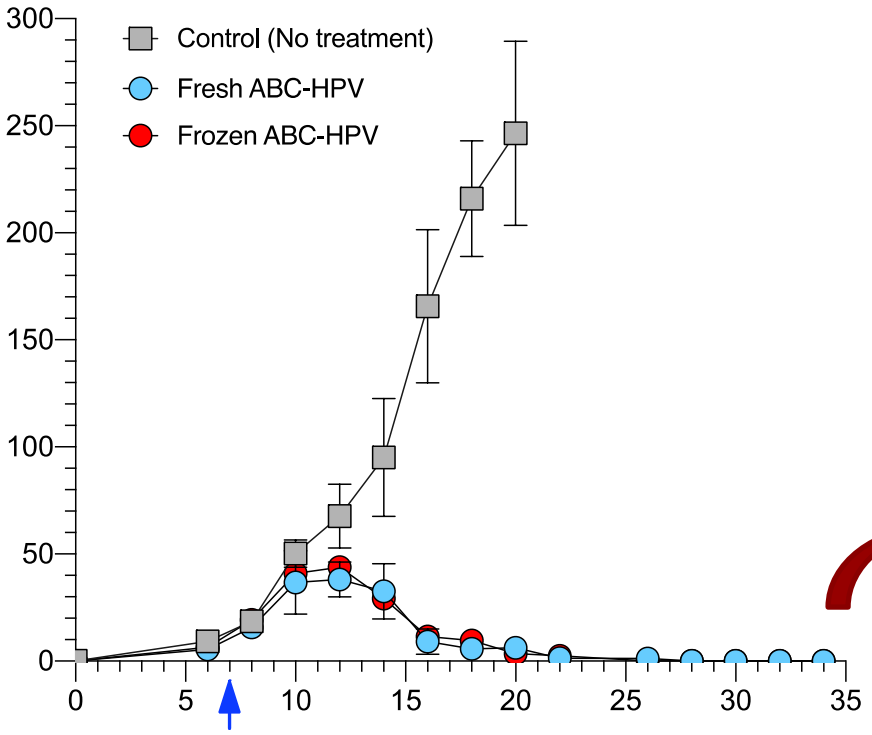
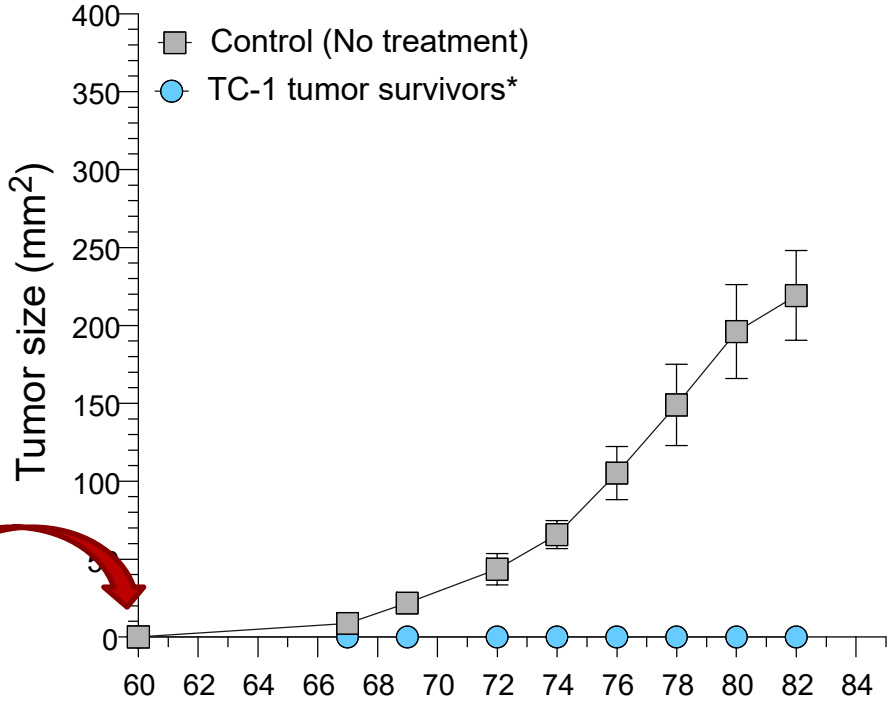
Strong *in vivo* efficacy and generation of memory

(HPV-associated Tumor Model)

Fresh or **Frozen** ABCs are efficacious



Survivors immune to rechallenge after 60 days



*Re-challenge survivors with TC-1 tumor cells 60 days after initial tumor injection

AB, optimized activated B cells, administered as a single dose, 2 x 10^7 cells
Tumor model: TC-1 HPV+ tumor cells (HPV16 E6/E7)

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Platform Research Summary

- **Platform – Customizable to any antigen(s)**
  - Demonstrated efficacy in mouse models of ovalbumin-expressing lymphoid tumor (E.G7-OVA), HPV-associated tumor (TC-1), and Melanoma (B16-F10), [EBV vaccine platform in development]
- **Cryopreservable**
  - Activated B cells, ABCs that had been frozen were as efficacious as fresh in mouse models
- **Robust and memory inducing immune response**
  - Robust $CD8^+$ T cell activation; epitope spreading was observed, and treated mice are immune to re-challenge with tumor cells
- **Off-the-shelf Product**
  - Robust *in vitro* proliferation of naïve T cells was observed in response to human activated B cells
- **Reproducible by third party**
  - *In vivo* efficacy study was successfully replicated by an independent CRO

Intellectual Property

1. Application: PCT/US2016/017338
   Priority Date: Feb. 10, 2015
   Title: CHLAMYDIA-ACTIVATED B CELL PLATFORMS AND METHODS THEREOF
   Inventors: Rodolfo D. Vicetti Miguel; Thomas L. Cherpes
   Status: Published and pending; PCT nationalized in Australia, China (201680009419.0), Canada (2976243), Japan (2017-541938), Europe (16749794.0), and US (15/550,110)

2. Application: PCT/US2016/061062
   Priority Date: Nov. 06, 2015
   Title: METHODS AND COMPOSITIONS RELATED TO ACCELERATED HUMORAL AFFINITY
   Inventors: Nirk E. Quispe Calla; Rodolfo D. Vicetti Miguel; Thomas L. Cherpes
   Status: Published and pending; international coverage reserved

3. Application: PCT/US2017/041948
   Priority Date: July 13, 2016
   Title: PLATFORMS AND METHODS FOR OPTIMIZING HOST ANTIGEN PRESENTATION AND ANTI-TUMOR AND ANTI-PATHOGEN IMMUNITY
   Inventors: Nirk E. Quispe Calla; Rodolfo D. Vicetti Miguel; Thomas L. Cherpes
   Status: Pending; international coverage reserved

4. Application: Provisional filed
   Title: GENERATING RECOMBINANT CHLAMYDIA TRACHOMATIS PROTEINS
   Inventors: Nirk E. Quispe Calla; Rodolfo D. Vicetti Miguel; Thomas L. Cherpes
   Status: Pending; international coverage reserved

Ohio State Drug Development Institute (DDI) Portfolio Project

Modulation of Notch Signaling in Immune Cells for Therapeutic Benefit

Inventors:
Thomas Magliery, PhD
Mikhail M Dikov, PhD
David Carbone, MD PhD

DDI Lead: Jerry Hilinski, PhD

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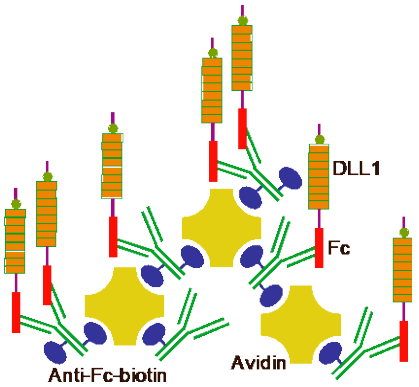
Project Background

- Activation or suppression of the immune system can have therapeutic benefit in a variety of indications
- Selective stimulation of Notch signaling using multivalent DLL1-fragment protein constructs may enhance host tumor immune surveillance and inhibit tumor growth
- Selective inhibition of Notch signaling using monomeric DLL1-fragment protein constructs may enable therapeutic immune suppression in indications such as acute Graft Versus Host Disease (aGVHD)

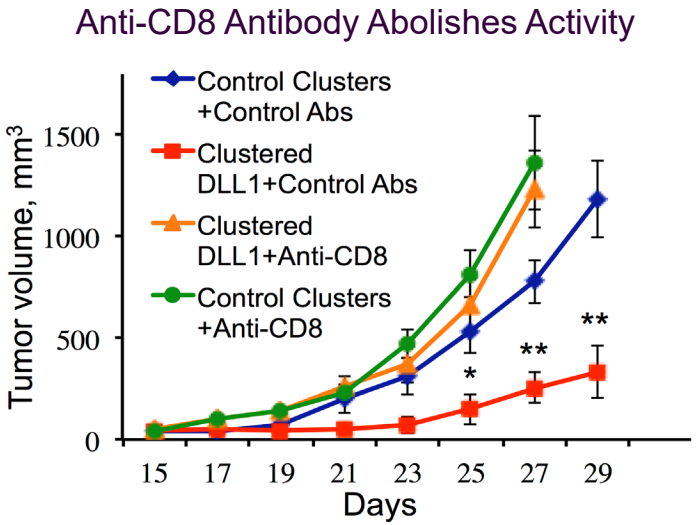
Clustered DLL1 Stimulates T-Cell-Mediated Antitumor Immunity in a Murine Fibrosarcoma (D459) Model



Clustered DLL1

Notch Activation

Tumor Suppression



Ongoing Work:

- Development of Notch ligand analogs that selectively activate or inhibit Notch signaling via specific Notch receptors

Biktasova et al. Cancer Res 2015; 75(22):4728-41
Huang et al. Cancer Res 2011; 71(19):6122-31

Intellectual Property

Application:	PCT/US2018/024343
Priority Date:	March 24, 2017
Title:	Novel Modulators of Notch Signaling and Methods of Using the Same
Inventors:	Thomas Magliery; Mikhail M Dikov; David Carbone; Nicholas Long; Brandon Sullivan; Elena Tchekneva
Assignee:	Ohio State Innovation Foundation

Ohio State Drug Development Institute (DDI) Portfolio Project

Selective RalA Inhibitors

Inventors:
Steve Sizemore, PhD
Steffen Lindert, PhD

DDI Lead: Chad Bennett, PhD

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Selective RalA Inhibitors - Overview

Rationale

- High RalA expression - worse overall survival in patients with certain types of cancer
- High RalB expression - better overall survival in patients with these same types of cancer

Hypothesis

- Selective RalA, small molecule inhibitors should be effective for treating certain types of cancers

Project status

- *In silico* screening has identified a number of potential hits

Next Milestone

- Biochemical screening of *in silico* hits

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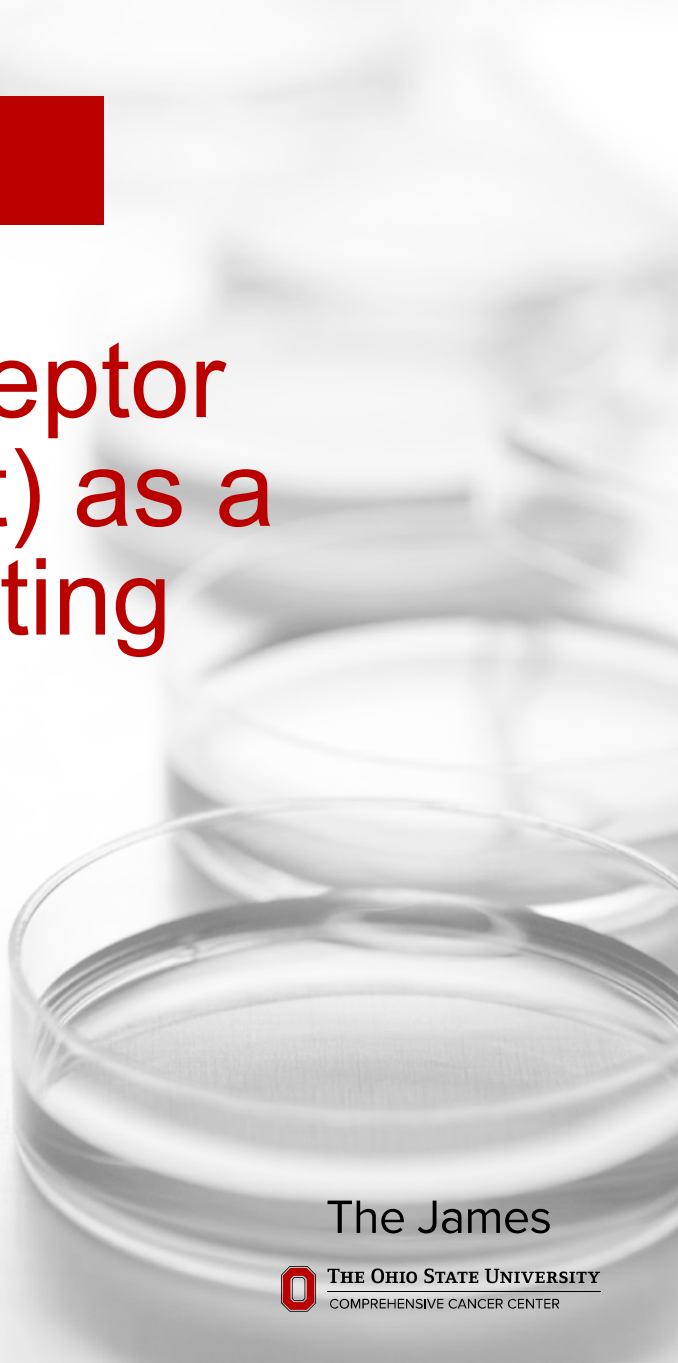
Ohio State Drug Development Institute (DDI) Portfolio Project

Selective Estrogen Receptor Modulator (ERβ Agonist) as a New Approach to Targeting Cancer

Inventor: Werner Tjarks, Dr.rer.nat.

DDI Lead: Chad Bennett, PhD



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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

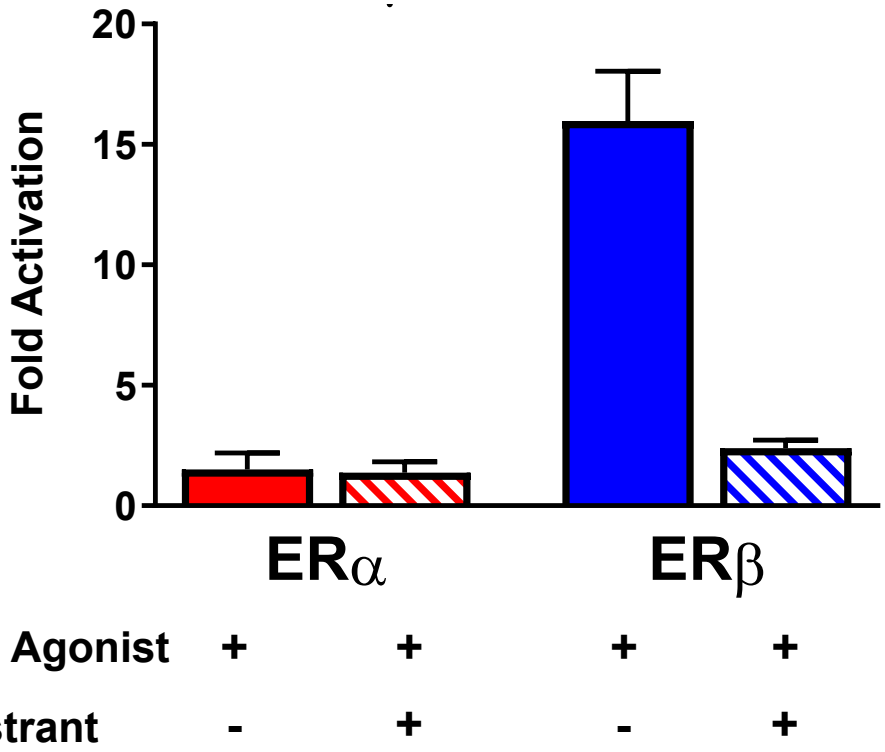
  Lead molecule: ERβ Cellular EC_{50} = 32 ± 13 nM;
  ERβ : ERα >200:1
  Orally bioavailable, brain penetrant
  Good oral dose response *in vivo*
  In vitro ADME completed, no major issues

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

Next Milestones

- Additional *In vivo* efficacy of lead
- Profile in vitro ADME and PK of follow-on analogs
- Design and synthesize new analogs

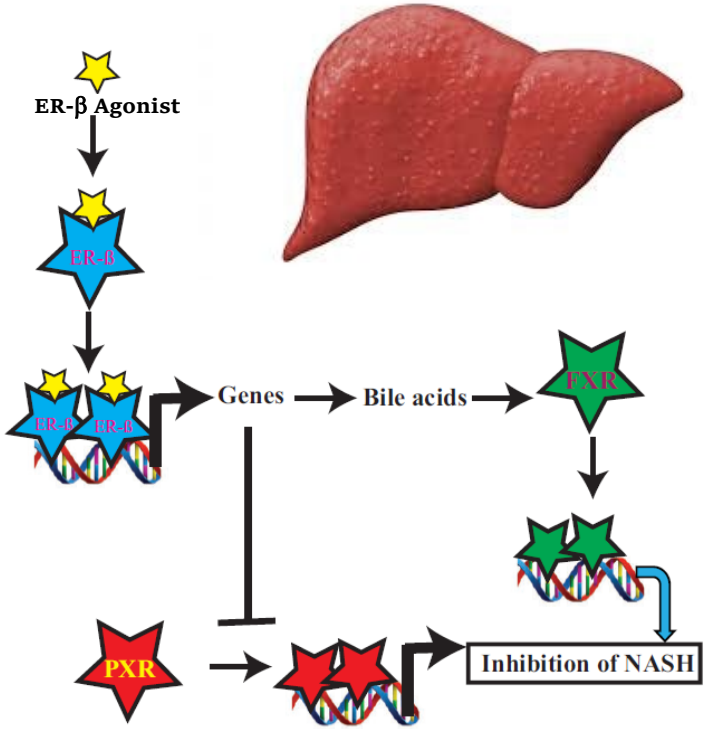
Lead ERβ Agonist is Steroid Competitive and Reversible



- Lead ERβ agonist specifically activates ERβ
- Co-treatment with steroid-competitive antagonist fulvestrant reverses the effect

ERβ Agonist in NASH

- **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)

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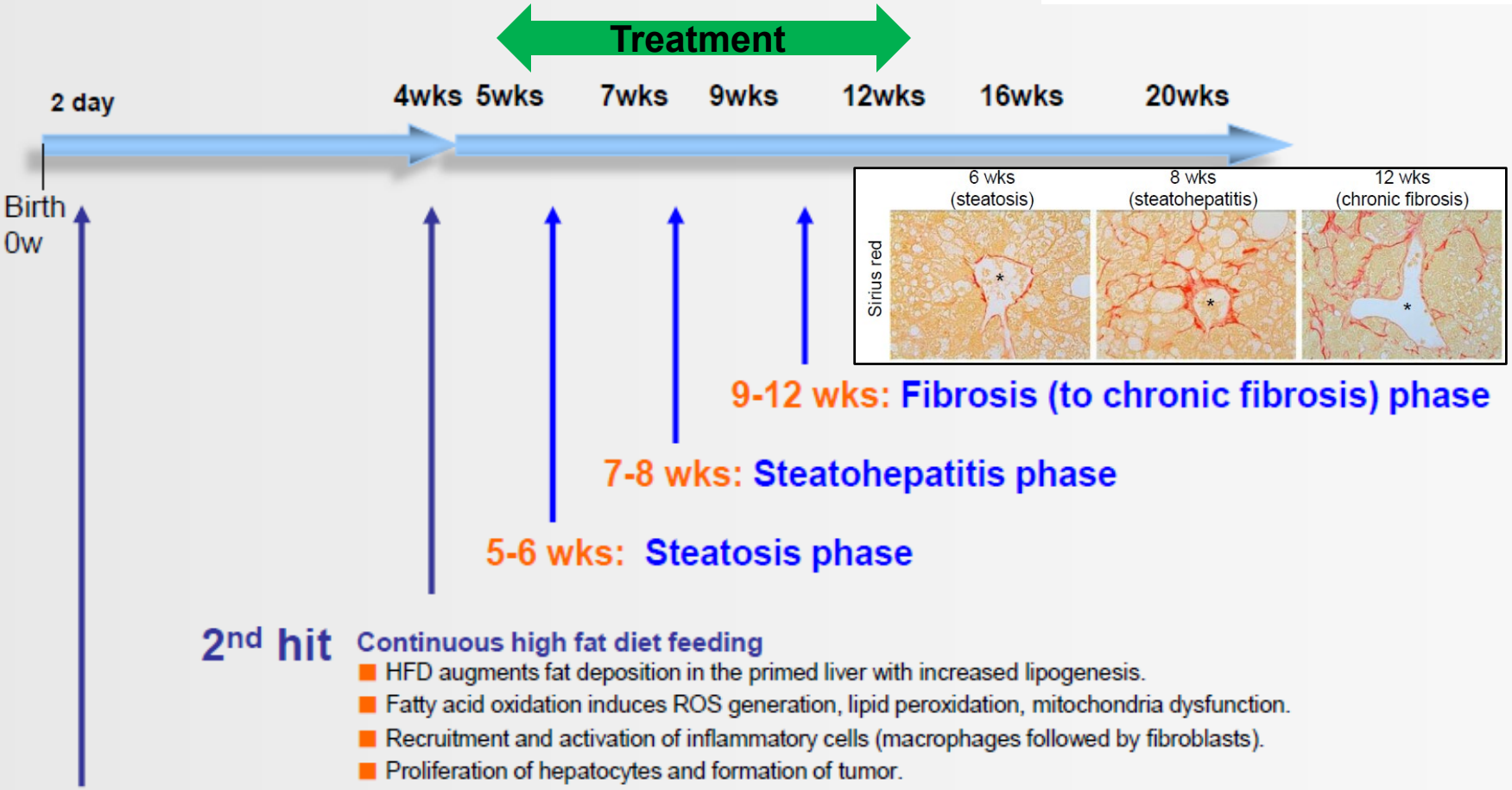
Exp Biol Med (Maywood). 2017 Mar;242(6):606-616. Int J Mol Med. 2018 Mar;41(3):1357-1364.

STAM™ NASH-Fibrosis-HCC Model

SMC Laboratories, Inc.



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.

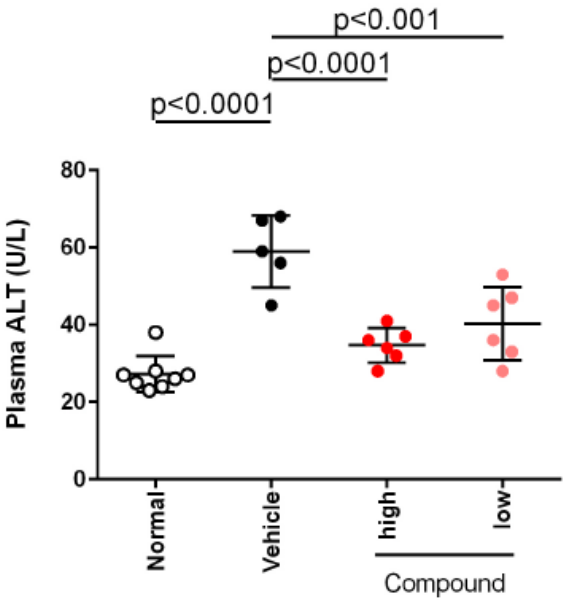
1st hit Inhibition of O-GlcNAc-β-N-acetylglucosaminidase of β-cell (STZ)

- 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").

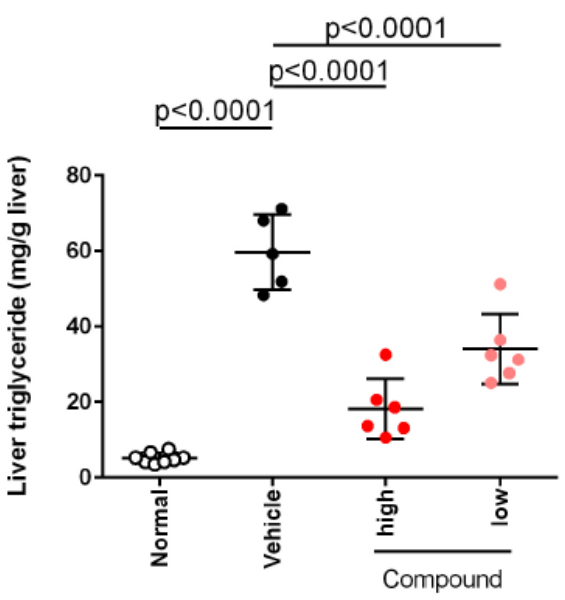
Decrease in Liver Fibrosis by Lead ERβ Agonist

Daily oral dosing

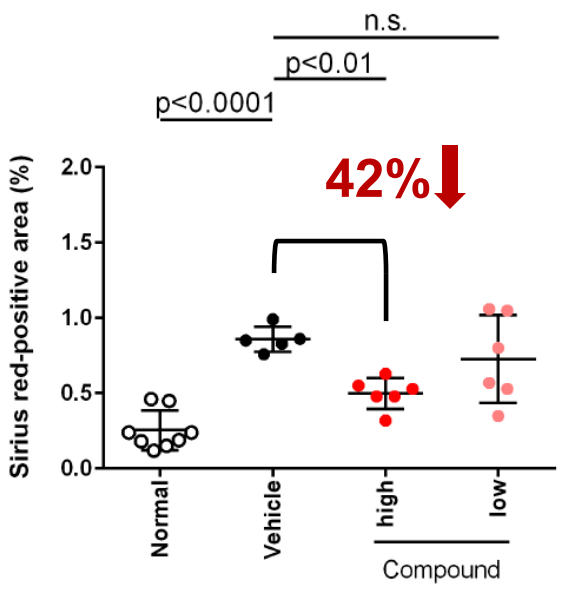
Plasma ALT



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 fibrotic liver area, comparable to 36% reduction following FXR agonist Tropifexor (LJN452) administration in same model[1]. Single agent LJN452 currently in Phase II for NASH.

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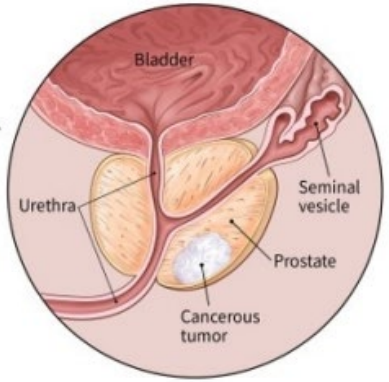
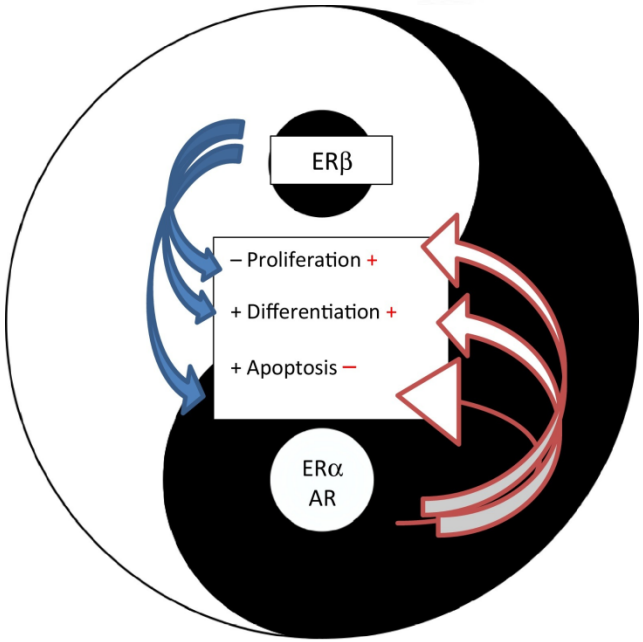
[1] https://doi.org/10.1002/hep.29501, AASLD Abstract #2052

ERβ Agonist in Prostate Cancer



- Prostate Cancer (PCa)
  - **1 in 9 men** will be diagnosed with prostate cancer during his lifetime
  - **165,000** new diagnoses/year in US
  - **30,000** PCa deaths/year in US

- Targeting ERβ in Prostate Cancer
  - Prevent proliferation of prostate epithelium
  - Antagonize AR-mediated oncogenic signaling
  - Prolong hormone sensitive disease status
  - Avoid ERα-mediated cardiovascular effects
  - Improve side-effect profile compared to ADT as first-line for low grade disease



- ERβ expression confirmed in human PCa samples
  - In vitro potency to be evaluated: 2Q 2019
  - Transgenic PCa Mouse Model: To start mid-2019

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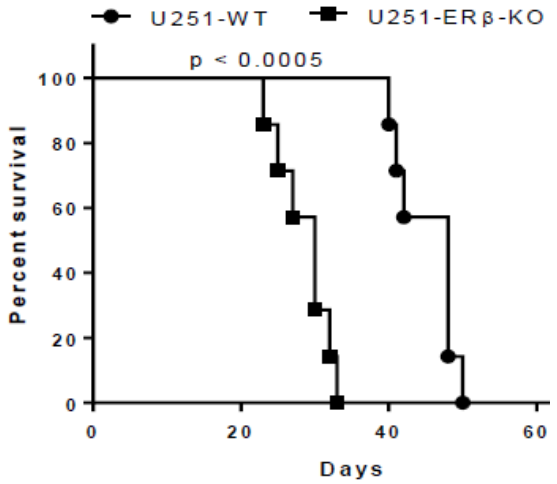
Trends Pharmacol Sci. 2017 Jan;38(1):92-99.

ERβ Agonist in Glioblastoma

- Glioblastoma Multiforme (GBM)
  - Most common and deadly primary brain tumor
  - **35%** 1-year survival rate
  - **13,000** new diagnoses/year in US

- Targeting ERβ in GBM
  - Estrogen signaling in brain is cancer-protective
  - ERβ *but not* ERα expressed in GBM tissue/cells
  - ERβ expression inversely associated with tumor stage
  - ERβ agonism can synergize with temozolomide (TMZ)
  - Critical brain penetrant PK already demonstrated

- Survey of primary GBM tissue and PDX lines
  - ERβ expression
  - *in vitro* Sensitivity to ERβ agonists (+/- TMZ) – on going



GBM orthotopic xenograft

Liu *et al.*, Cancer Res. 2018 Apr 16.

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

Ohio State Drug Development Institute (DDI) Portfolio Project

Inhibitors of Mps1 Kinase as Mitotic Regulators for Cancer Therapy

Inventors:
Harold Fisk, PhD
Bob Brueggemeier, PhD
Michael Darby, PhD
Tom Li, PhD

DDI Lead: Jerry Hilinski, PhD

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Mps1 Kinase Inhibitors as Cancer Therapeutics

Rationale

- Mps1 is overexpressed in both solid and hematological tumors and genetic or chemical inhibition suppresses tumor growth

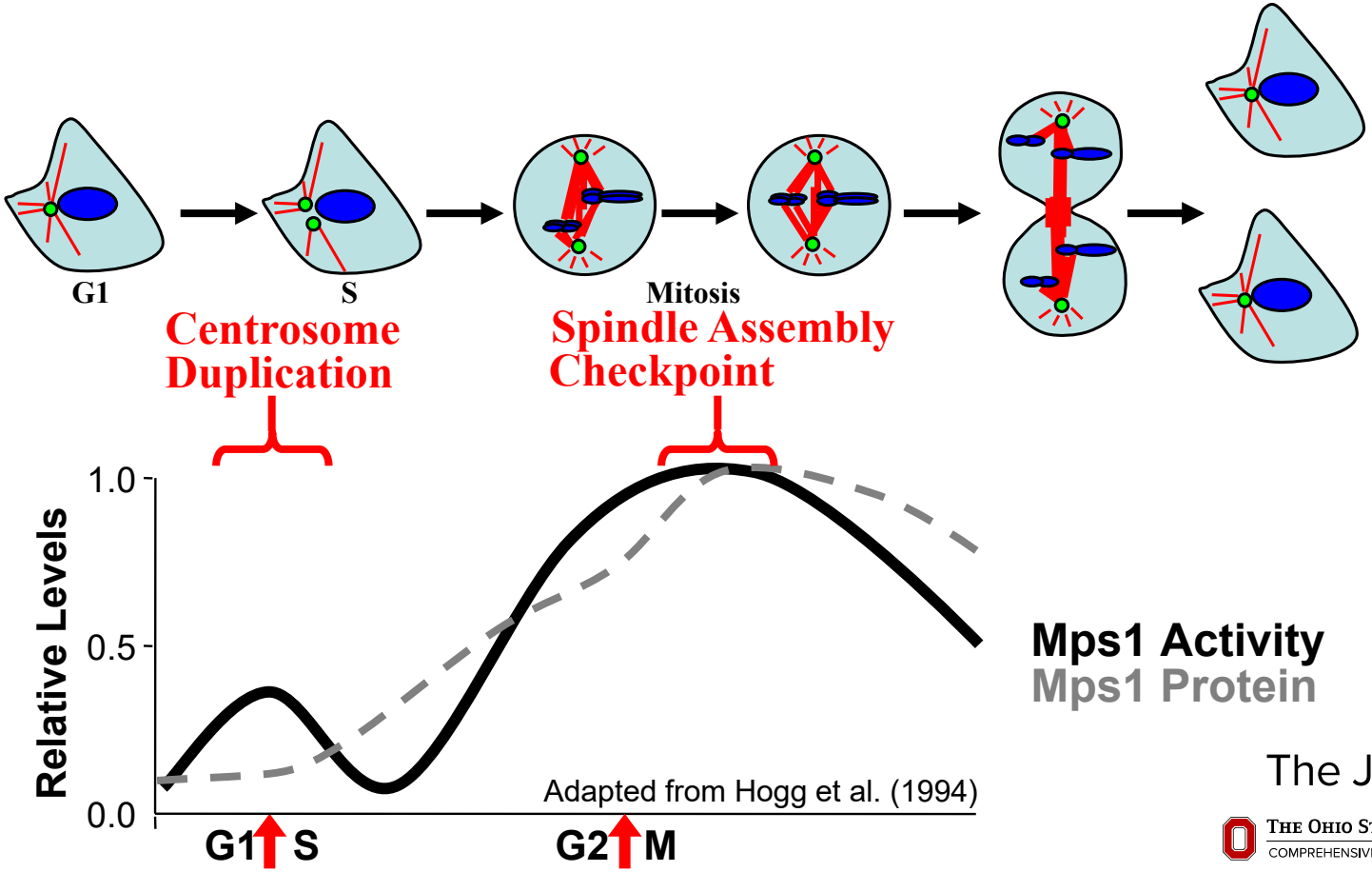
Technology

- Novel small molecule Mps1 inhibitors have been patented
  - The lead molecule controls tumor growth without weight loss when given IP daily for 6 weeks in a TNBC xenograft model[1]
  - The lead molecule is orally bioavailable and brain penetrant
  - Preliminary in vitro efficacy in hematologic malignancy

[1] Sugimoto et al. Bioorg Med Chem 2017; 25:2156-66

Mps1 is Critical for Genomic Integrity

- Mps1 activity is critical in regulating centrosome duplication and spindle assembly checkpoint (SAC)
- Highly aneuploid cells are susceptible to targeting by Mps1
- TNBC is highly aneuploid and therefore treatable by Mps1 inhibition



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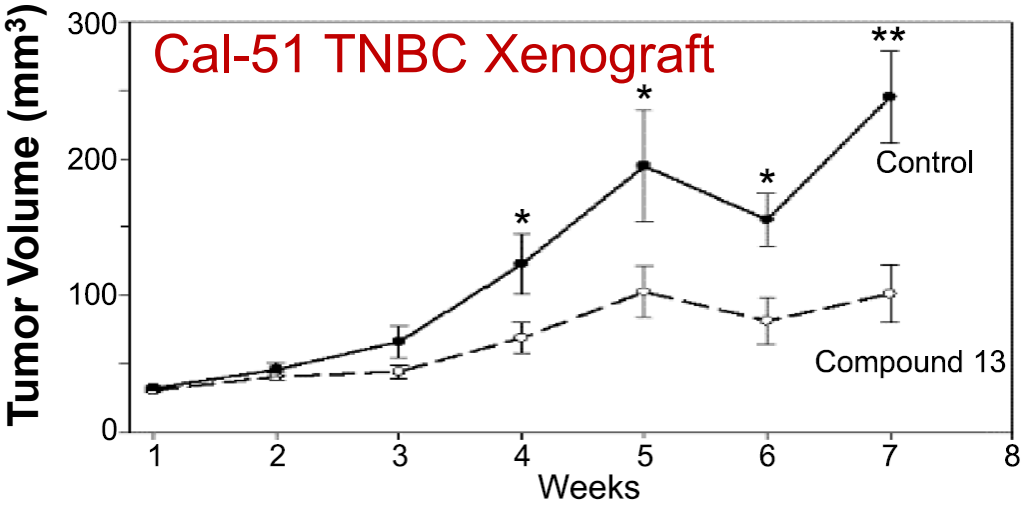
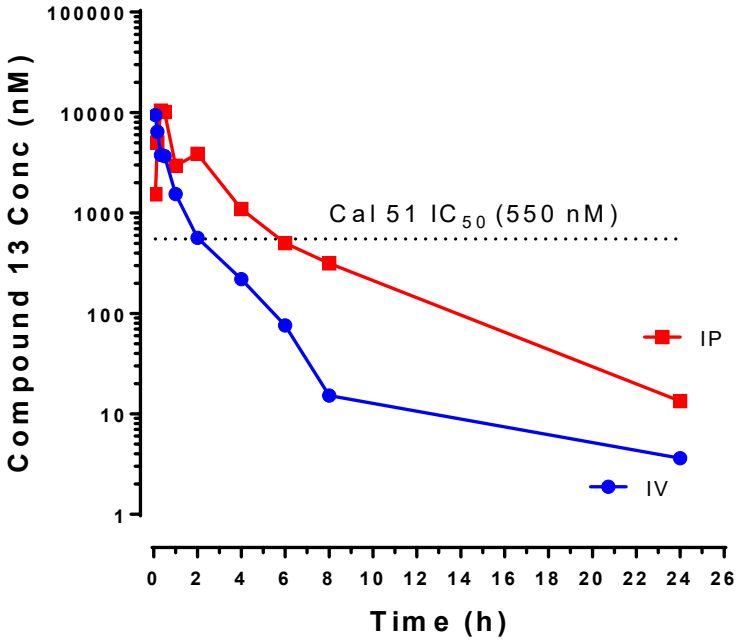
Lead Molecule Controls Tumor Growth in a TNBC Xenograft Model





DMSO or Lead Molecule (10 mg/kg) given
IP daily for 6 weeks
Mean ± SEM, * $P < 0.05$ ** $p < 0.01$
No significant body weight reduction

IV – 20 mg/kg single dose
IP – 50 mg/kg single dose

Mps1 IC_{50} = 123nM (Eurofins Mps1 Turnover Assay)

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Sugimoto et al. Bioorg Med Chem 2017; 25:2156-66

Lead Molecule is Orally Bioavailable and Brain Penetrant

- IV (10 mg/kg) and PO (50 mg/kg), 3 ICR mice per time point
- Brain harvested and compound exposure determined at each time point

	Plasma IV	Plasma PO	Brain IV	Brain PO
Dose (mg/kg)	10	50		
HL_Lambda_z (min)	61.1	387	60.7	264
Tmax (min)	5.00	60.0	5.00	60.0
Cmax (nM)	7900	4776	*1662	*1338
AUCINF_pred(hr*nmol/L)	7733	22700	*1817	*4450
AUClast (hr*nmol/L)	7700	13250	*1340	*3133
Vz_pred (L/kg)	4.50	28.4		
Cl_pred (L/min/kg)	0.0510	0.0510		

*Brain concentrations expressed in molar units; assumes 1mg brain tissue = 1uL volume

Oral Bioavailability = 58.7% (based on AUCinf_pred)

Intellectual Property

Application:	US Patent Application 15/524,606
Priority Date:	November 6, 2014
Title:	Pyrrolopyrimidine Derivatives as Mps1/TTK Kinase Inhibitors for Cancer Therapy
Inventors:	Robert Brueggemeier, Harold Fisk, Pui-Kai Li, Chenglong Li, Yasuro Sugimoto
Assignee:	Ohio State Innovation Foundation
Filing:	USA only
Description:	Composition of matter

Ohio State Drug Development Institute (DDI) Portfolio Project

PP2A Activator for Treatment of AML and Other Hematological Malignancies

Inventors:
Natarajan Muthusamy, DVM, PhD
Mitch Phelps, PhD
John Byrd, MD
William Kisseberth, DVM, PhD

DDI Lead: Chad Bennett, PhD

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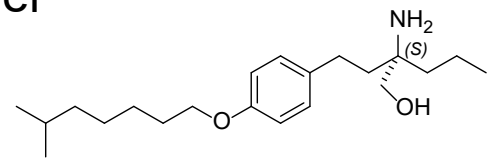
OSU-2S for AML and Other Hematological Malignancies

Rationale

- Protein phosphatase 2A (PP2A) is frequently inactivated in AML and restoration of its activity has anti-leukemic effects in both KIT-positive and KIT-negative AML

Technology

- OSU-2S is a patented small molecule activator of PP2A
  - Demonstrates cell death in AML cell lines
  - Induces differentiation in AML cell lines and primary AML blasts
- OSU-2S increases survival in a murine AML xenograft model
- Good oral bioavailability in mice and dogs
  - Dose linear PK dogs
- 4-week oral dosing in dogs completed, no significant issues
- ADME, Met ID, Kinome and Cerep screening completed



OSU-2S

Next Milestones

- Further assessment in patient-derived xenograft and transplantable murine models of AML
- Confirmation of *in vivo* efficacy at CRO – on going

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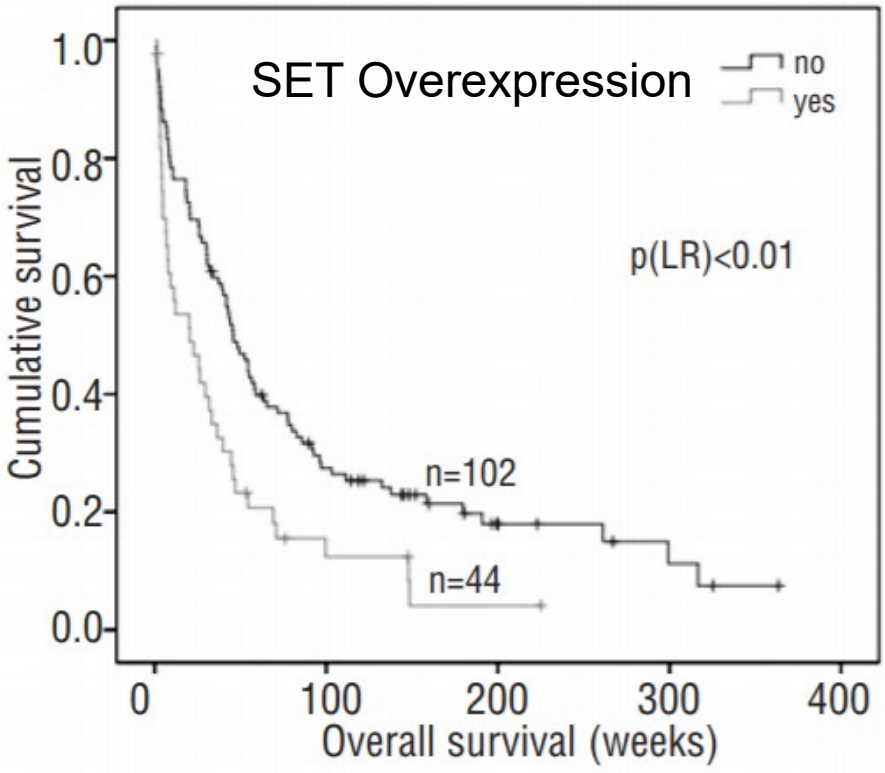
SET is Overexpressed in AML and is Associated with Poor Survival

Acute Myeloid Leukemia (AML)

- Heterogeneous disorder of hematopoietic progenitor cells
  - abnormal proliferation of undifferentiated cells or blasts
- About 25% of all leukemias in adults in the western world
- Standard chemotherapy is Daunorubicin and Cytarabine
- Most cases are elderly adults
  - Less than 5% overall 5-yr survival rate for those over 65 yr
  - Median survival < 1 year



Neviani & Perrotti Clin Cancer Res 2014; 20(8):2026-8
Cristóbal et al. Haematologica 2012; 97(4):543-550

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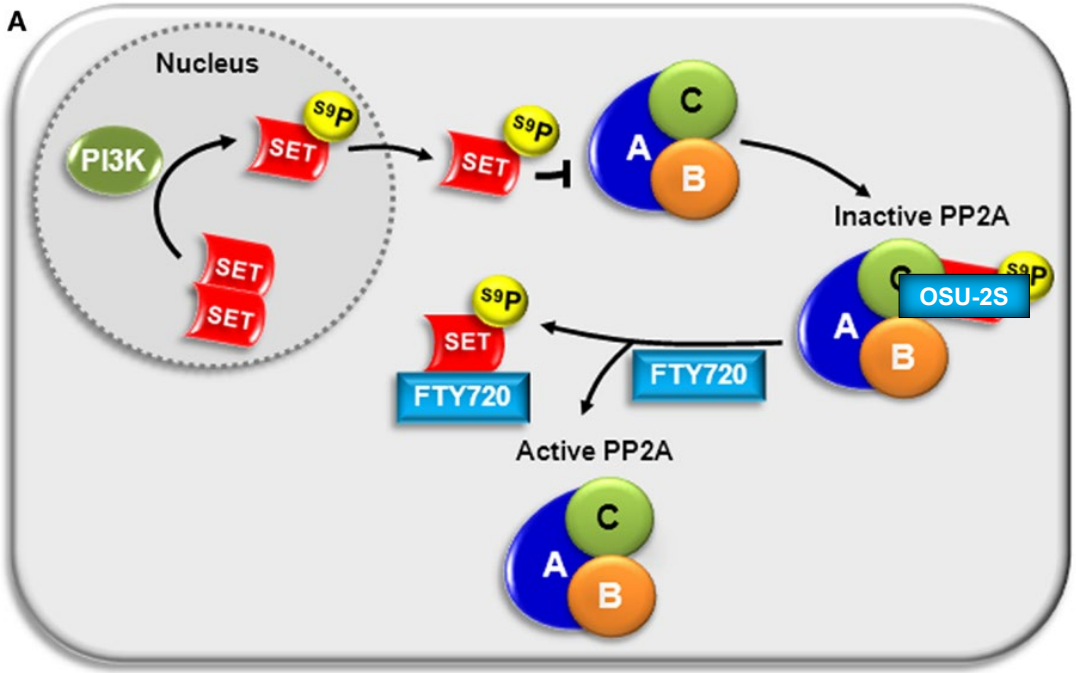
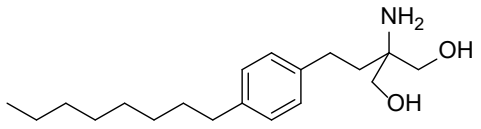
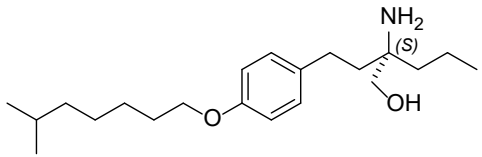
SET Protein Inhibits PP2A Activity – FTY720 and OSU-2S Bind to SET and Re-activate PP2A





FTY-720



OSU-2S

Arriazu et al. Front Oncology 2016; 6: 1-21

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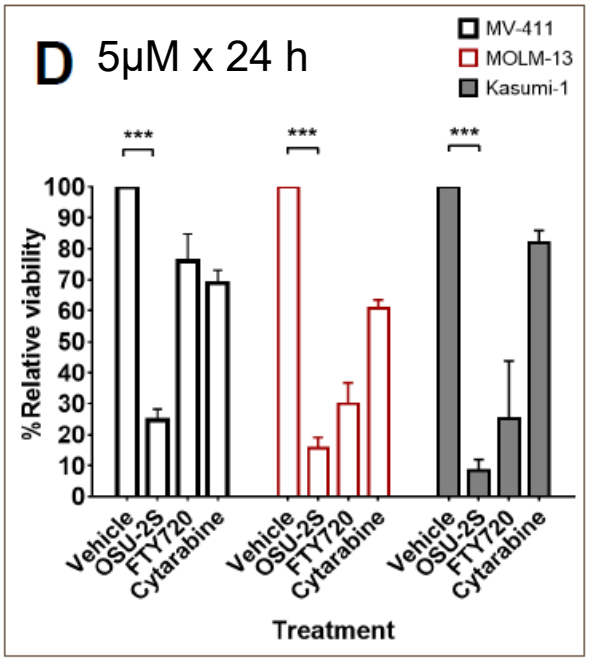
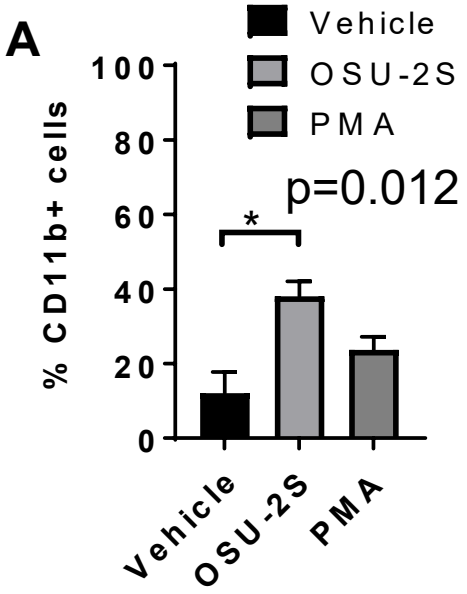
OSU-2S: More Potent than Cytarabine & Induces Differentiation in AML Cell Lines & Primary Cells

OSU-2S Compared with FTY-720 and Cytarabine

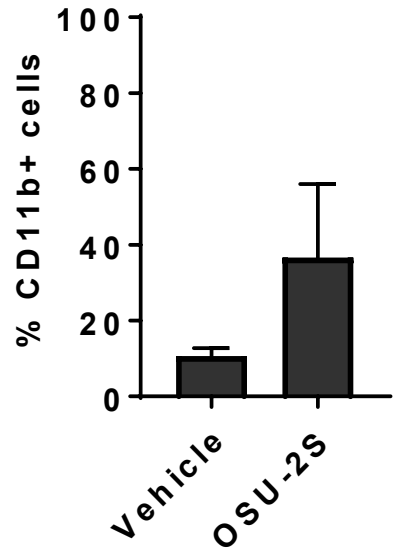


Enhanced Differentiation

AML HL-60 Cell Line



Primary AML Cells



OSU-2S 3.5uM (Primary AML and 5uM) for HL-60- 24hrs

PMA - Phorbol 12-myristate 13-acetate; potent PKC activator

Goswami et al. Blood 2016 128:2748

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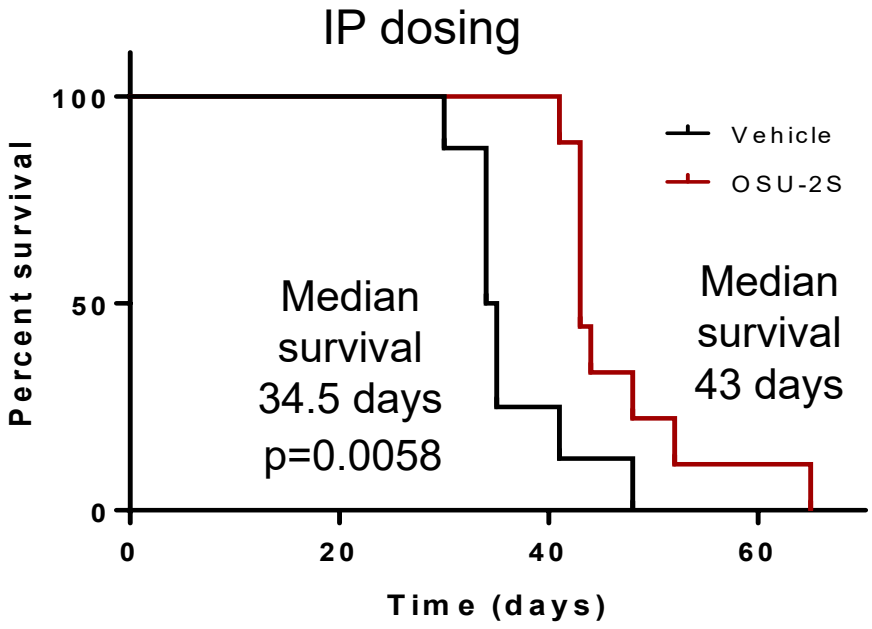
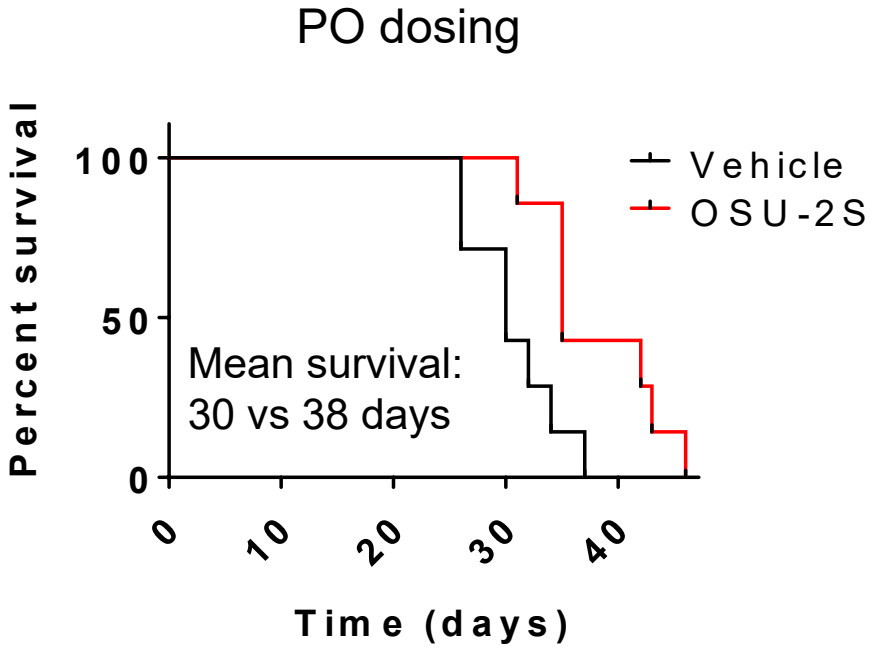
OSU-2S Enhances Survival in a Murine Model of AML

MV4-11 xenograft





12.5 mg/kg IP, 3 doses / week (MWF) x 4 weeks
Dosing started on Day 6 post inoculation.

60 mg/kg PO, 5 doses / week (MTWThF) x 4 weeks
Dosing started on Day 6 post inoculation.

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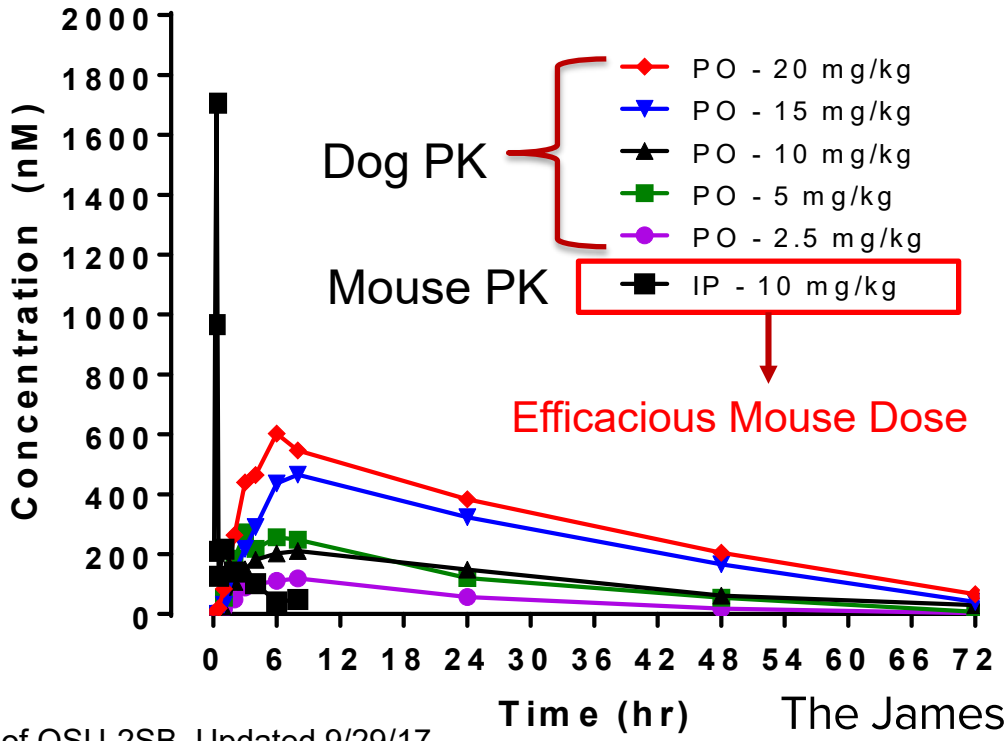
Comparative Dog Exposures Exceed Efficacious IP Exposure in Mice – Dose Linear Dog Exposures

- Exposures at the 10 mg/kg IP dose in mice are:
  - Cmax = 1,705 nM
  - AUC = 1,378 h•nM
- Dog exposure exceeds Mouse efficacious exposure by >15x

Dog Dose	C_{max} (nM)	AUC_{∞} (hr·nM)
2.5 mg/kg	118.7	3043
5 mg/kg	272.8	7151
10 mg/kg	210.63	8369
15 mg/kg	465.91	17122
20 mg/kg	602.73	22132



PhASR0088 Project "Pharmacokinetic (PK) Study of OSU-2SB, Updated 9/29/17

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Intellectual Property Status

IP Summary:

US Patent: 8,309,768
Priority Date: 29 November 2010
Title: FTY720-derived Anticancer Agents

Inventors: Cheng-Shih Chen, Samuel Kulp, Dasheng Wang, John Byrd, Natarajan Muthusamy
Assignee: Ohio State Innovation Foundation
Filing date: 29 November 2010
Filing: US
Description:
Use Claims = 0
Composition of matter Claims = 16

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Inventor: Don M Benson, Jr, MD PhD, FACP

Aryl Hydrocarbon Receptor Inhibition in Hematologic Malignancies

Inventor: Don Benson, MD

DDI Lead: Jerry Hilinski, PhD

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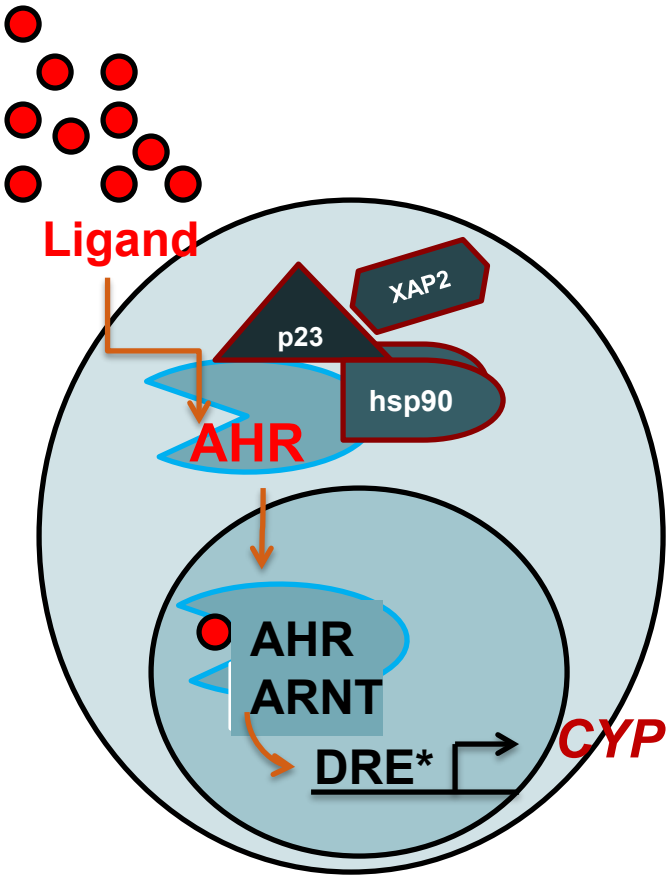
AHR Plays a Critical Role in Hematopoiesis and Cancer

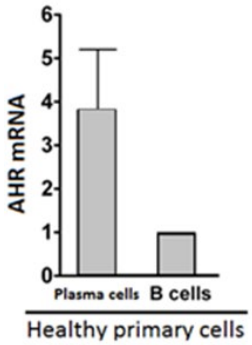


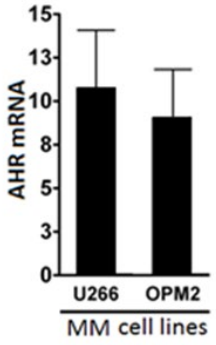
- Aryl hydrocarbon receptor (AHR): a ligand-binding transcription factor regulating xenobiotic-metabolizing enzymes[1]
- AHR has an important role in hematopoiesis and lymphocyte development[2]
- AHR roles in cancer:[3]
  - Initiation, promotion, progression, metastasis

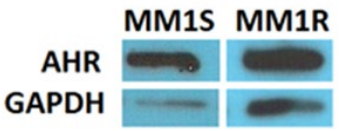
1. ***Chem Biol Interact*** 2002;141:3 2. ***Cell Reports*** 2014;8:150 3. ***Nat Rev Cancer*** 2014;14:801

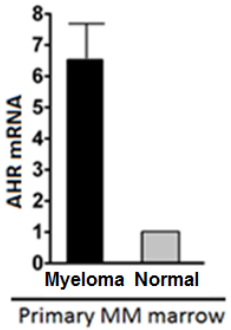
AHR is expressed in healthy plasma cells and myeloma

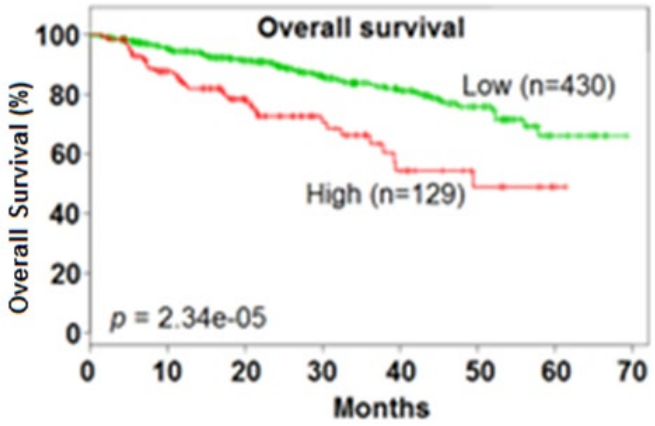
- Endogenous ligand levels correlate with disease burden and clinical stage
- AHR transcribes cytokines integral to myeloma biology
  - IL-21, TGF-β, IL-6
- AHR cooperates with other transcription factors implicated in myeloma
  - c-Maf, c-Myc, NFκB members







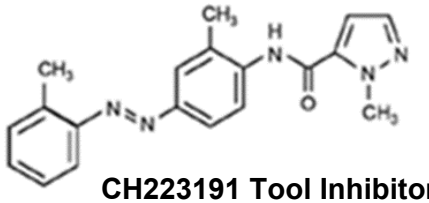




AHR is preferentially expressed by myeloma tumor cells and expression level correlates with overall survival.

AHR Antagonism with Off-Patent Tool Inhibitor Induces:

- Direct cell death of myeloma stem cells and tumor cells
  - Including cytogenetically “high risk” myeloma, plasma cell leukemia and dexamethasone-resistant myeloma cells



CH223191 Tool Inhibitor

- Favorable immunomodulatory effects:
  - Expansion, enhanced activation, and increased cytotoxicity of immune effector cells
  - Increased susceptibility of myeloma cells to immune mediated recognition and lysis

The Drug Development Institute is designing novel candidate AHR inhibitors and further developing assays to interrogate their biology

Ohio State Drug Development Institute (DDI) Portfolio Project

HOSU-3 for Acute Myeloid Leukemia (AML) and Transplant for Hematological Malignancies

Inventors:
Erin Hertlein, PhD
Thomas Goodwin, PhD
John Byrd, MD

DDI Lead: Chad Bennet, PhD

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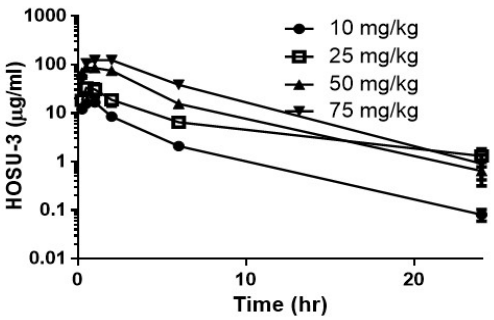
DHODH Inhibitors for treatment of AML

Rationale

- DHODH inhibition has been shown to induce differentiation in AML cells and prolong survival in AML animal models
- AML cure rates:
  - With transplant: 35-40% for ages <60 years 5-15% for ages >60 years
  - Without transplant: 6.6% for ages <60 years 2.4% for ages >60 years

Technology

- Novel DHODH inhibitors developed collaboratively by OSU and Hendrix College – provisional application filed
- HOSU-3 induces cell death and differentiation primary AML blasts
- HOSU-3 exhibits sustained, dose linear oral bioavailability in mice
- *In vitro* ADME was completed with no major concerns
- Established *in vivo* efficacy of HOSU-3 in a xenograft model



Next Milestones

- Assessment of additional *in vivo* efficacy in xenograft (cell line or patient-derived) and spontaneous murine models of AML
- New analogs being evaluated for cellular potency, *in vivo* efficacy, and *in vitro* ADME
- Additional analogs being designed

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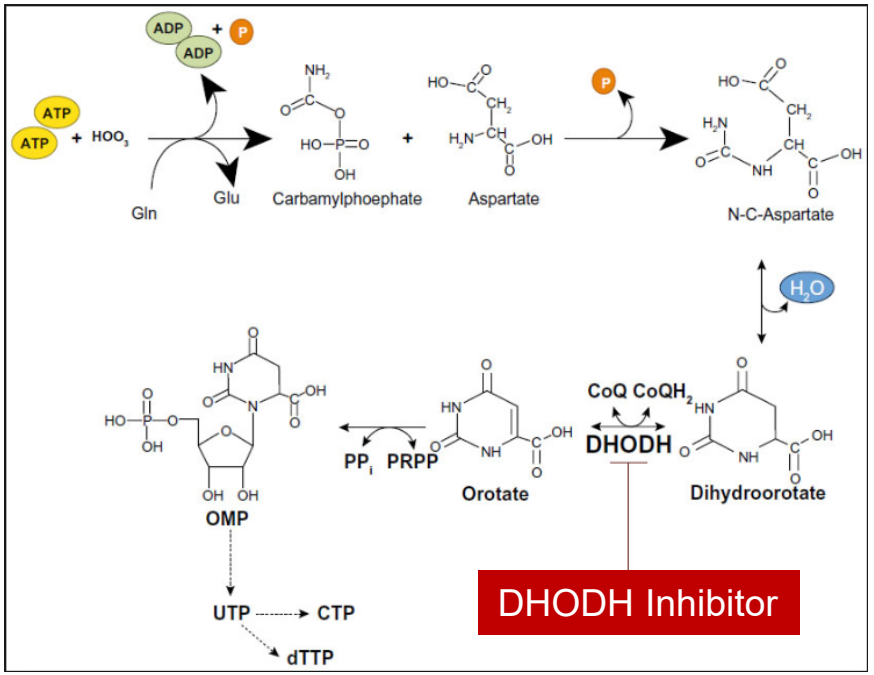
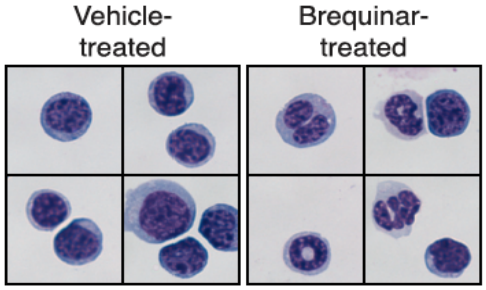
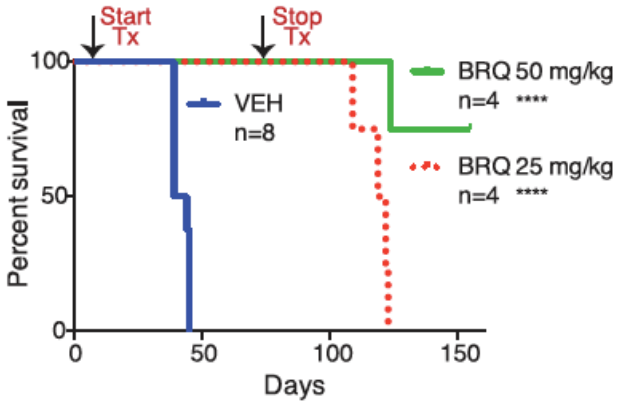
Role in DHODH inhibition in Cancer

- DHODH is critical for *de novo* pyrimidine biosynthesis
- Inhibiting DHODH with brequinar (BRQ) has been shown to
  - induce differentiation in AML
  - prolong survival in AML animal models.
- Brequinar (BRQ) was unsuccessful clinical development in solid tumor cancers
- Targeting DHODH in AML represents a promising new treatment strategy with the potential to have a broad impact.







Sykes et al., Cell 167, 171–186, September 22, 2016

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HOSU-3 is a potent inhibitor of DHODH and has anti-proliferative activity in AML

DHODH inhibition		
Compound	% inhibition	IC50, uM
HOSU-3	97	0.043 (0.039 - 0.047)
HOSU-5	95	0.099 (0.092 - 0.11)
HOSU-6	99	0.076 (0.07 - 0.083)
HOSU-17	8	ND*

Cell free enzymatic assay for several derivatives indicate potent DHODH inhibitory activity.

IC50 (uM) at 96 hours					
Compound	MOLM-13	MV4-11	THP1	HL-60	OCI-AML3
HOSU-3	0.4	0.67	1.1	0.28	0.61
HOSU-4	5.38	13.1	17.82	5.94	6.19
HOSU-5	3.02	6.96	7.84	20.9	3.37
HOSU-6	6.91	6.48	10.39	3	6.25
HOSU-8	6.76	7.54	11.56	3.57	4.99
HOSU-9	6.98	8.17	13.45	3.3	3.58
HOSU-14	8.63	13.99	21.4	9.48	11.2
HOSU-16	3.42	6.23	6.7	1.69	2.9
HOSU-18	6.76	6.86	9.34	2.4	4.01
BRQ.Na	0.48	0.49	1	0.23	0.4
ATRA	3.06				0.09

IC50 values for the 9 most highly active derivatives based on MTS assays in AML cell lines.

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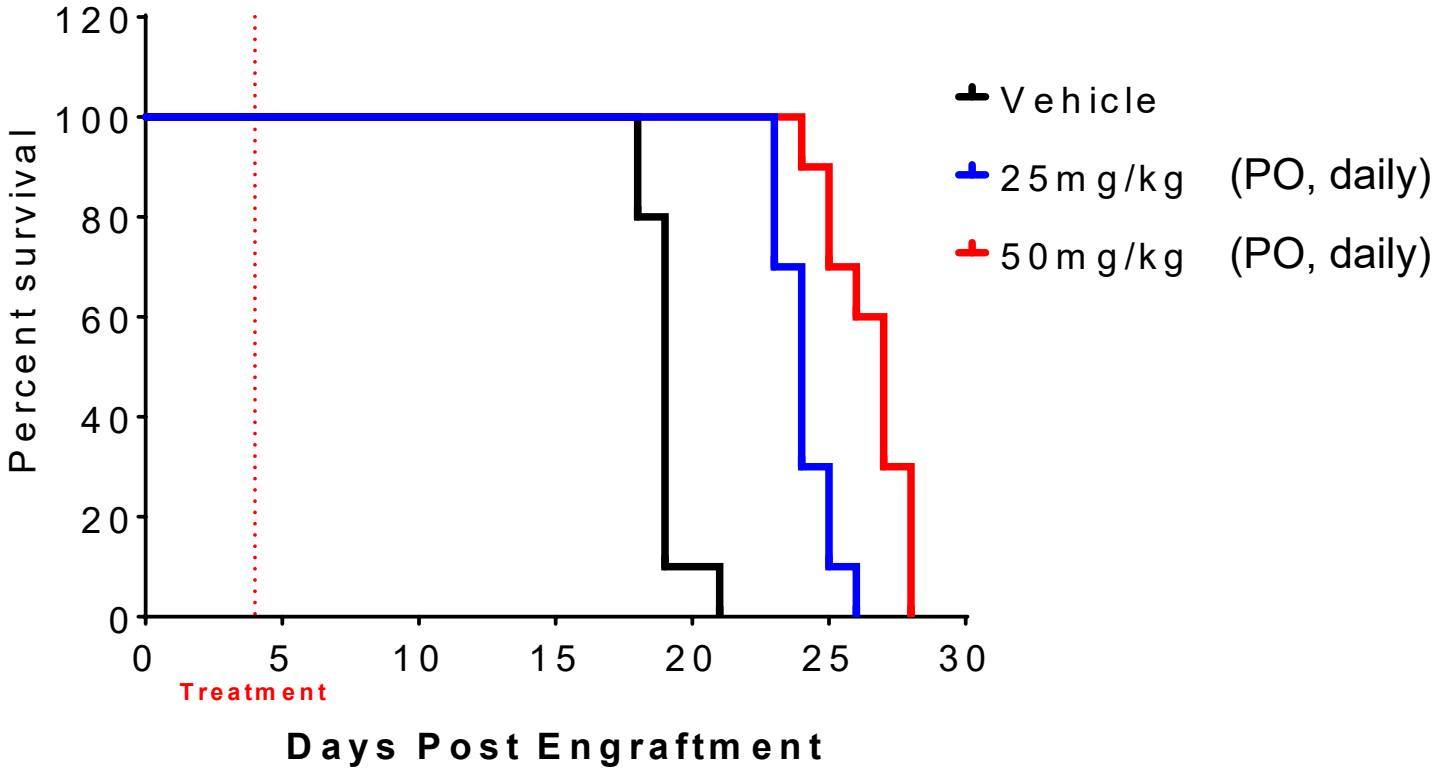
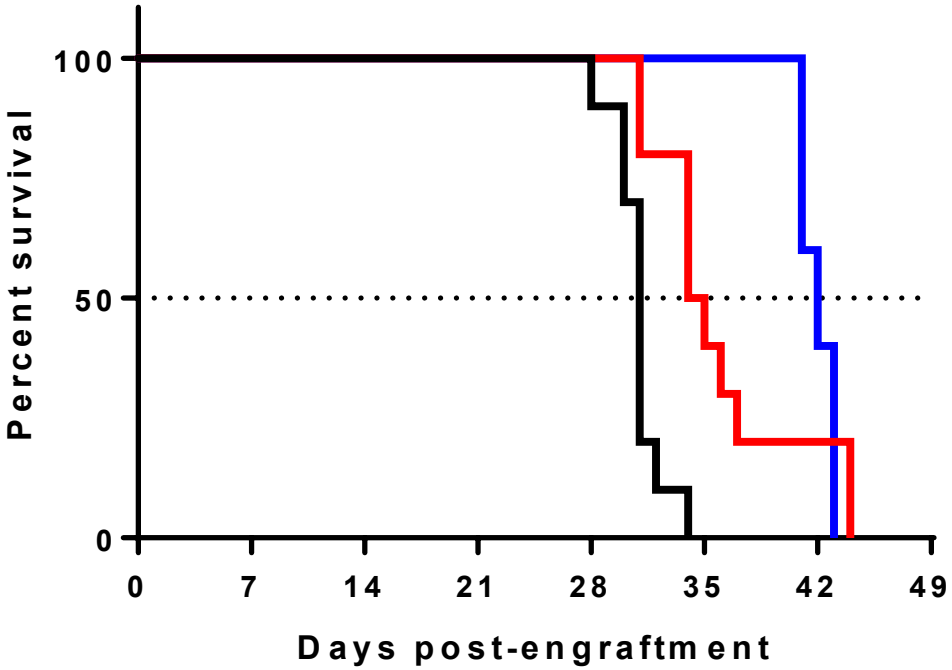
In vivo efficacy of HOSU-3 in MOLM13 Disseminated xenograft mouse model



Group	N	Median survival time (days)
Vehicle	10	19
25mg/kg HOSU3 QD PO	10	24
50mg/kg HOSU3 QD PO	10	27

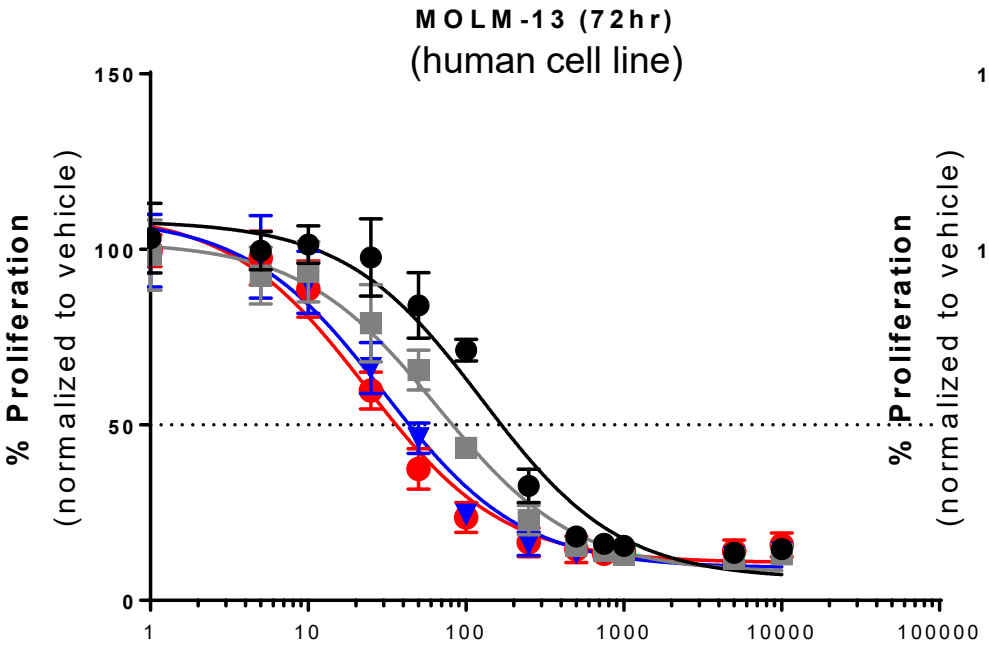
In vivo efficacy in syngeneic mouse model
Idh2^{R140Q}/Flt3-ITD murine leukemia



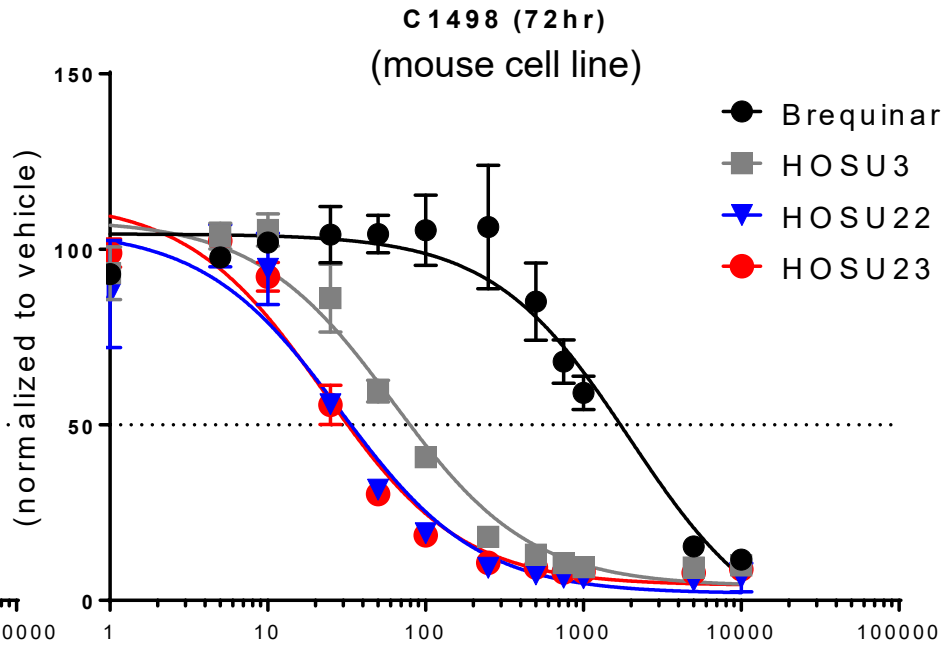
Treatment	N	Median survival (days)
Vehicle	10	31
Enasidenib	10	34
HOSU-3	10	42

Treatment began 7 days post-engraftment (daily oral gavage).

New analogs have increased cellular potency



DHODHi	IC_{50} (nM) in MOLM-13
Brequinar	167.73
HOSU3	82.15
HOSU22	43.81
HOSU23	36.12



DHODHi	IC_{50} (nM) in C1498
Brequinar	1719.2
HOSU3	79.7
HOSU22	33.7
HOSU23	32.1

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For more information about the DDI or DDI projects, please contact:

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Website: cancer.osu.edu/ddi

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