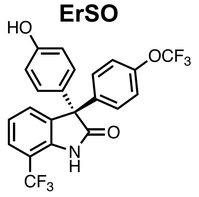
Selective estrogen receptor a-UPR activators (SERA): a novel class of small molecules that eradicate estrogen receptor positive tumors

Michael P. Mulligan[1,2,4], Matthew W. Boudreau[1,2,4], Santanu Ghosh[4], David J. Shapiro[4], Timothy M. Fan[3,4], Paul J. Hergenrother[1,2,3,4], Kerry Barnhart[5], David Azorsa[5], Jeff Kiefer[5], Daniel Von Hoff[5], Spyro Mousses[5]

[1]Department of Chemistry, [2]Carl R. Woese Institute for Genomic Biology, [3]Cancer Center at Illinois, [4]UIUC, [5]Systems Oncology

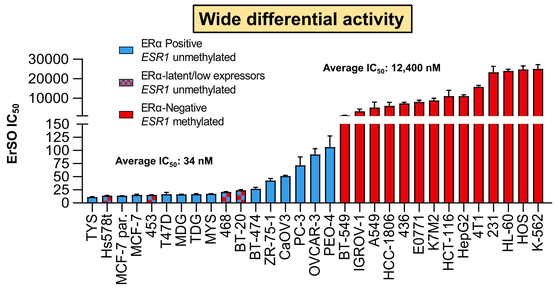
Introduction - ErSO

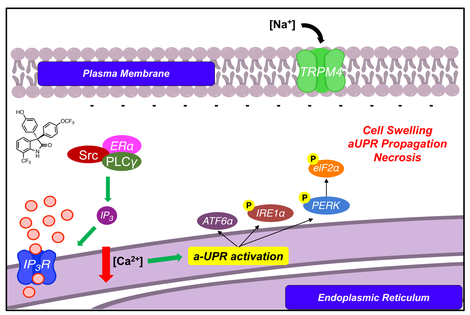
ErSO



cLogD$_{7.4}$ = 6.4

Wide differential activity

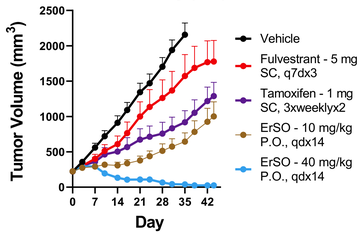




Unique mechanism of action:
Calcium Dysregulation
Endoplasmic Reticulum Stress
Necrosis

Complete tumor regressions

ST941 PDX
ErSO dosed daily (x14)



Excellent oral tolerability, but not IV

Organism	Mouse		Rat
Administration	P.O.	I.V.	I.V.
Compound	**ErSO**	**ErSO**	**ErSO**
MTD (mg/kg)	> 150[a]	20	10
Allometrically Scaled Dose (Humans)	>12 mg/kg	1.5 mg/kg	1.5 mg/kg

[a]: Solubility Limit

Sci. Transl. Med. **2021**, 13 (603), eabf1383.

Acknowledgments

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NCI 1R01CA258746-01A1

Hergenrother Lab

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6. Christensen, M.; et al. "Synthesis and Antitumor Effect in Vitro and in Vivo of Substituted 1,3-Dihydroindole-2-ones". J. Med. Chem. **2010**, 53, 19, 7140–7145.
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Next Generation Derivatives

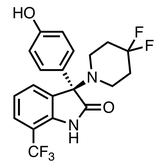
Goals:

- **Versions with even wider selectivity between ERα+ & ERα- cancer cells in culture**
- **Improved animal tolerability**
- **Maintain complete tumor regressions**

Strategy:

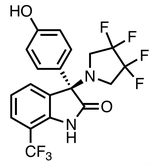
- **Decrease lipophilicity (cLogD) through incorporation of nitrogen**

ErSO-DFP (SERA1)



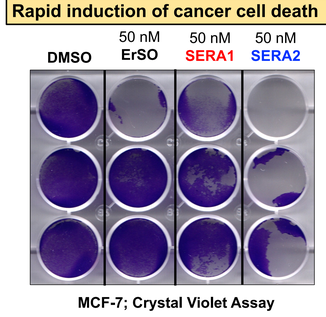
cLogD$_{7.4}$ = 4.4

ErSO-TFPy (SERA2)



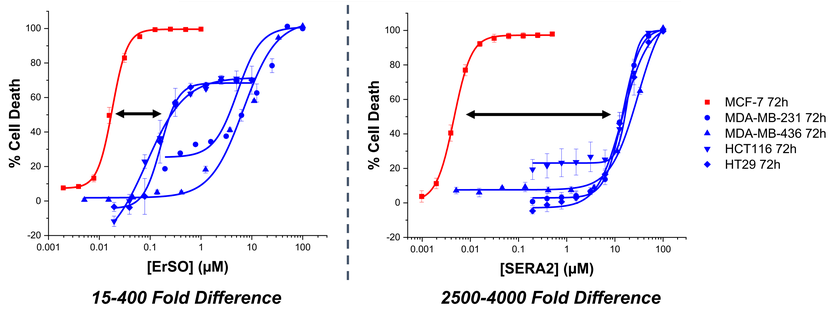
cLogD$_{7.4}$ = 4.5

Rapid induction of cancer cell death



MCF-7; Crystal Violet Assay

SERA molecules have increased selectivity in cell culture



J. Med. Chem. **2022**, 65, 3894-3912.

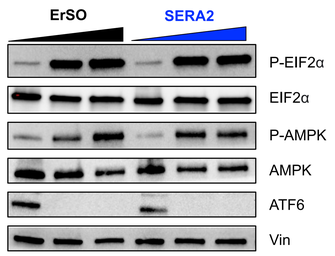
SERA2 is active against breast cancer cells with mutations in ERα

Cell Line	Media Conditions	SERA2 IC$_{50}$ (nM) 24 h	SERA2 IC$_{50}$ (nM) 120h	Amcenestrant IC$_{50}$ (nM) 24h	Amcenestrant IC$_{50}$ (nM) 120h	Camizestrant IC$_{50}$ (nM) 24h	Camizestrant IC$_{50}$ (nM) 120h	Elacestrant IC$_{50}$ (nM) 24h	Elacestrant IC$_{50}$ (nM) 120h	Capivasertib IC$_{50}$ (nM) 24h	Capivasertib IC$_{50}$ (nM) 120h
MCF-7	Unstripped	8 ± 1	5 ± 1	>1000	>1000	>1000	>1000	>1000	>1000	>10000	1772 ± 4
MYS	Unstripped	5 ± 1	4 ± 1	>1000	28 ± 1	>1000	22 ± 9	>1000	>1000	>10000	1128 ± 282
MDG	Unstripped	6 ± 1	6 ± 1	>1000	36 ± 10	>1000	13 ± 1	>1000	>1000	>10000	1163 ± 110
MCF-7	Stripped	7 ± 1	6 ± 1	>1000	796 ± 33	>1000	97 ± 10	>1000	327 ± 67	>10000	539 ± 35
MYS	Stripped	4 ± 1	6 ± 1	>1000	53 ± 9	>1000	12 ± 3	>1000	>1000	>10000	1760 ± 350
MDG	Stripped	5 ± 1	8 ± 1	>1000	46 ± 3	>1000	8 ± 1	>1000	>1000	>10000	1119 ± 333

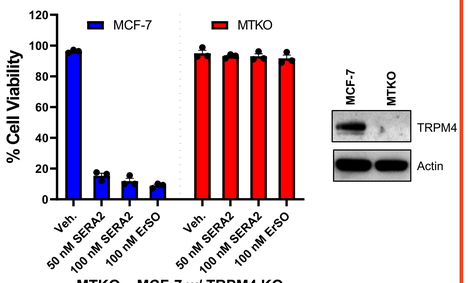
MYS – MCF-7 cells w/ Y537S mutation in ERα, MDG – MCF-7 cells w/ D538G mutation in Erα
n ≥ 2, 24h/72h/120h incubation, 96 well plate, 100 μM Raptinal (dead control), alamar blue fluorescence

Mechanism

ErSO & SERA2 have a shared mechanism of action



MCF-7; 6 hr incubation, [Compound] = 0-450 nM
a-UPR Activation



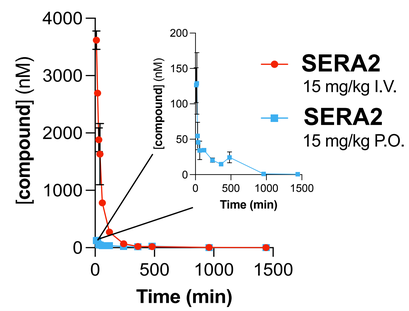
MTKO – MCF-7 w/ TRPM4 KO
Trypan Blue Exclusion, 24 hr incubation

PK and Tolerability

SERA molecules have increased tolerability *in vivo*

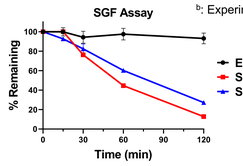
[a]: Solubility Limit

Organism Administration	Mouse P.O.			Mouse I.V.			Rat I.V.			Dog I.V.		
Compound	**ErSO**	**SERA1**	**SERA2**	**ErSO**	**SERA1**	**SERA2**	**ErSO**	**SERA1**	**SERA2**	**ErSO**	**SERA1**	**SERA2**
MTD (mg/kg)	> 150[a]	n.d.	n.d.	20	95	150	10	> 50[a]	> 50[a]	n.d.	n.d.	> 5
Allometrically Scaled Dose (Humans)	>12 mg/kg	--	--	1.5 mg/kg	8 mg/kg	12 mg/kg	1.5 mg/kg	>8 mg/kg	>8 mg/kg	--	--	>3 mg/kg



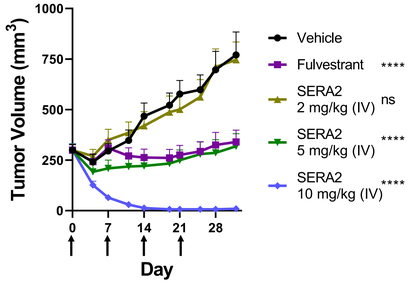
Parameters	ErSO (20 mg/kg IV)	SERA1 (20 mg/kg IV)	SERA2[b] (15 mg/kg IV)
C_{max} (ng/mL)	7700	14700	1700
AUC (h*ng/mL)	10,100	6300	1400
half life ($t_{1/2}$, min)	55	18	34
MRT (h)	5.1	0.9	1.3
CL (mL/min/kg)	33	52	183

[b]: Experiment was not head to head

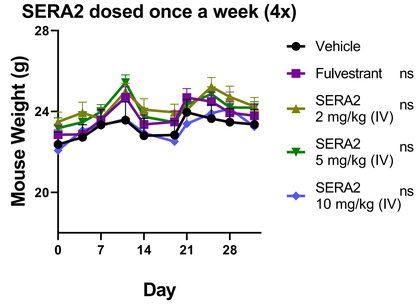


Xenografts

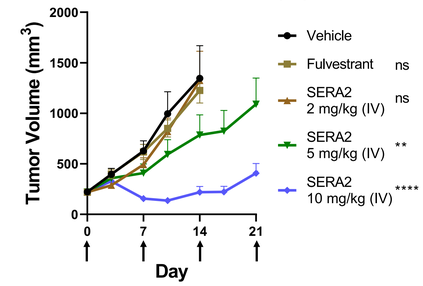
MCF-7 Xenograft
SERA2 dosed once a week (4x)



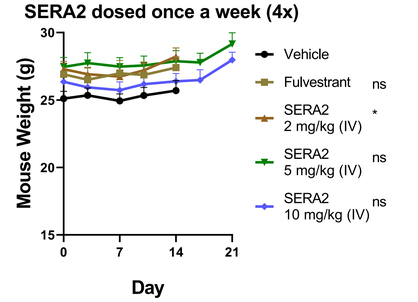
MCF-7 Xenograft
SERA2 dosed once a week (4x)



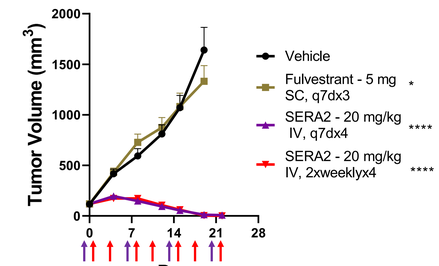
ST941 PDX
SERA2 dosed once a week (4x)



ST941 PDX
SERA2 dosed once a week (4x)



ST941 PDX
SERA2 dosed once or twice a week



ST941 PDX Waterfall
SERA2 dosed once or twice a week