466 SERDs with Brain Penetration for Advanced Breast Cancer

Asset Overview

Product Type	Small Molecule
Indication	Oncology
Current Stage	Lead identification / optimization
Target(MoA)	Targeting the estrogen receptor
Brief Description	• Next generation Selective Estrogen Receptor Degraders (SERDs) developed from core compound G1T48 (L/O to G1 therapeutics, Phase 1/2) to deliver next generation SERD with brain penetration • Treatment for TAM/AI-resistant breast cancer • Strong potential for treatment in ER+ metastatic breast cancer • Opportunity for combination with CDK4/6 inhibitors and PI3K inhibitors
Organization	University of Illinois at Chicago

Differentiation

□ **Unmet need**

- Approximately 70% of breast cancer patients have estrogen receptor positive (ER+) tumors; and despite the success of endocrine therapy, 50% will progress to metastatic disease with resistance to tamoxifen (TAM) and aromatase inhibitors (AIs)
- Fulvestrant (FUL), a selective estrogen receptor degrader (SERD) able to ablate ER, was introduced to clinical practice in 2002 for advanced ER+ metastatic breast cancer. In August 2017, FUL was added to first-line therapy after demonstrating superiority to first-line AI therapy
- Acquisition of FUL resistance in first-line setting (and in combination with CDK4/6I, i.e palbociclib) has arisen in many patients, which may be associated with the poor pharmacokinetics of FUL leading to sub-maximal dosing
- 10-15% endocrine-resistant breast cancer patients have brain metastasis
- Neither FUL, nor oral SERDs in current clinical trials address brain metastases

□ **SERD pipelines**

- Fulvestrant (Faslodex, AstraZeneca): Marketed, intramuscular administration, 1US$b in 2018
- Elacestrant (RAD-1901, Radius Health): Phase III for metastatic breast cancer (2^{nd}/3^{rd} line), significant ability to penetrate the blood-brain barrier, oral administration
- G1T48 (lerociclib, G1 Therapeutics): Phase II for breast cancer, oral administration
- SAR-439859 (Sanofi): Phase II for metastatic breast cancer, oral administration
- ARV-471 (Arvinas): Phase I for metastatic breast cancer, oral administration
- AZD-9496 (AstraZeneca): Phase 1 for breast cancer, oral administration
- LSZ-102 (Novartis): Phase 1 for metastatic breast cancer, oral administration
- SHR-9549 (Hengrui): Phase 1 for breast cancer, oral administration

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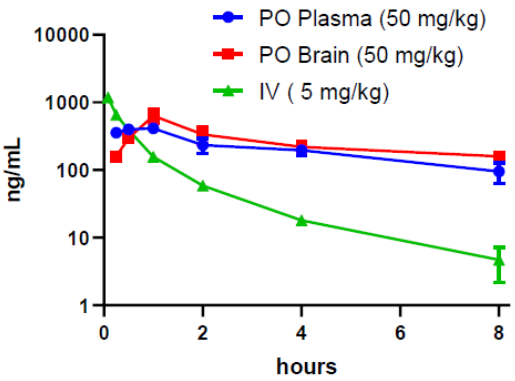
Key Data

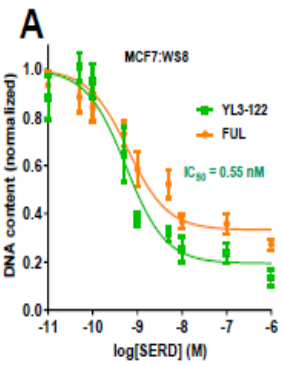
B-SERD Optimization

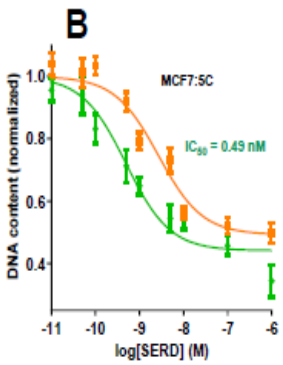


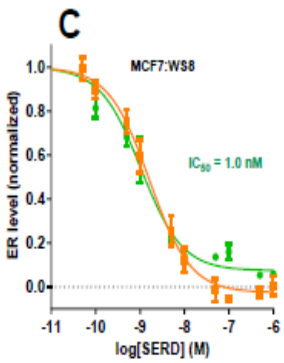
YF3-122 (50 mg/kg p.o.) pharmacokinetic parameters	
Oral bioavailability (F)	22%
$T_{1/2}$ (h)	4.48
C_{max} Ratio (Brain/Plasma)	1.54
C_{max} (ng/ml)	413
AUC_{Last} Ratio (Brain/Plasma)	1.26
AUC_{Inf} h*ng/mL	2292
T_{max} (h)	1.0

Data normalized to vehicle (1.0) and no cells (0.0); ER level following treatment for 24hr by In-Cell-Western.

In Vitro Activity







	TAM	AI	FUL	PALB
WS8	✓	✓	✓	✓
PKCα	✓	-	✓	✓
TAM1	×	×	✓	✓
TAMR	×	-	✓	✓
5C	×	×	✓	✓
CFR	×	×	×	✓
CPR	×	×	✓	×
WFR	×	×	×	✓

Data normalized to vehicle (1.0) and no cells (0.0); ER level following treatment for 24hr by In-Cell-Western.

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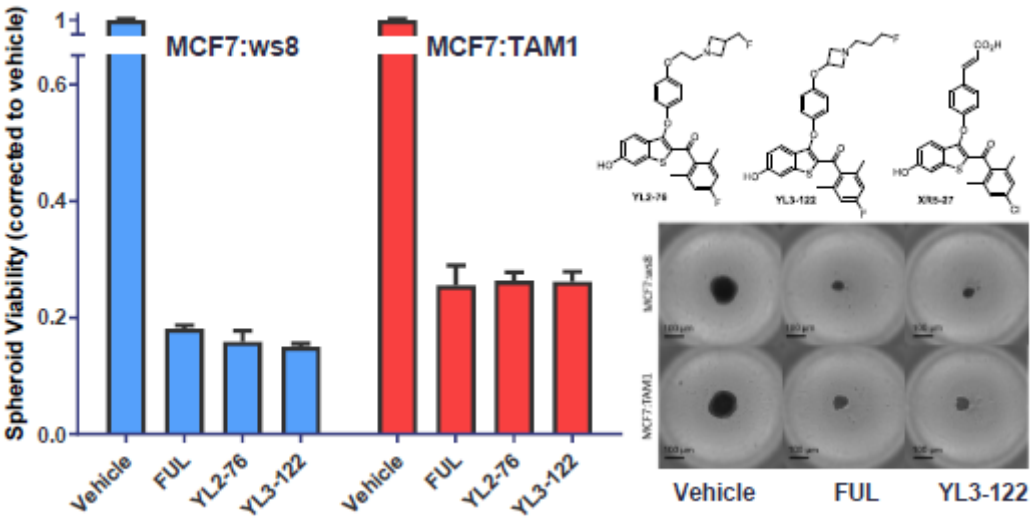
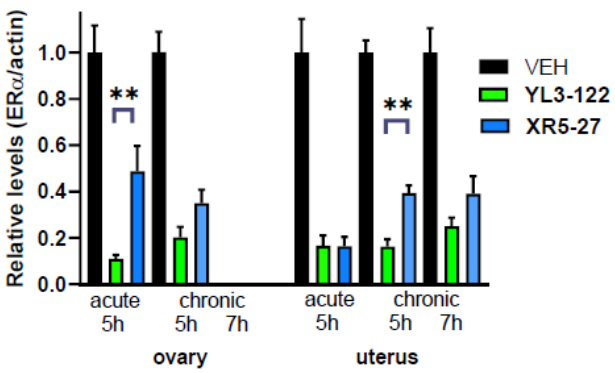
In Vitro Activity in 3D Spheroids Modeling



Spheroid viability following treatment (10 nM) with representative images on day 10 of treatment. Luminescence normalized to vehicle/control (1.0) and background (0.0)

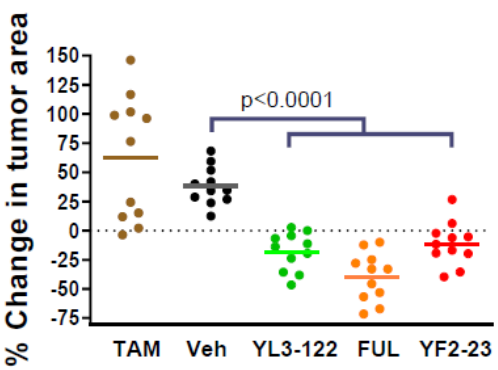
In Vivo Activity

ERα degradation



ERα degradation after oral dosing of female mice with vehicle, YL3-122, or XR5-27 (50 mg/kg) measured by western blot of tissues, with representative immunoblots shown from individual mouse uteri

MCF:TAM1 xenograft



MCF7:TAM1 xenografts grown to 0.3 cm2 before treatment with FUL (5 mg s.c.), BETi (30 mg/kg), BSERD (100 mg/kg) Individual tumor % area change after 4 weeks treatment: one-way ANOVA stud

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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