

Orphagen Pharmaceuticals

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First-in-Class Drugs for Chronic Disease

CDD User Meeting

April 4th, 2013



Who is Orphagen?

- **Privately-held company based in San Diego**
 - Founded in 2001; 8 employees
- **Drug discovery programs for novel drug targets**
 - Fills innovation gap for pharma
- **First-in-class program for autoimmune target partnered in 2008**
 - Three other pre-clinical programs
- **Non-dilutive financing to date: >\$10 M**
 - Partnership and grant funding



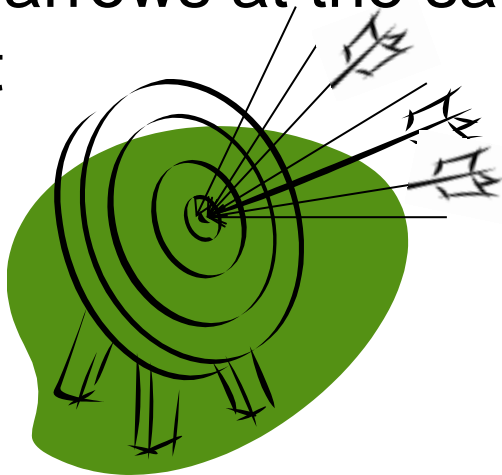
First-in-class Drug Discovery

Only 250 targets in human for **marketed drugs**

- Multiple drugs for the same targets
- **New targets lead to new classes of drug**
 - Transformative therapy for patients

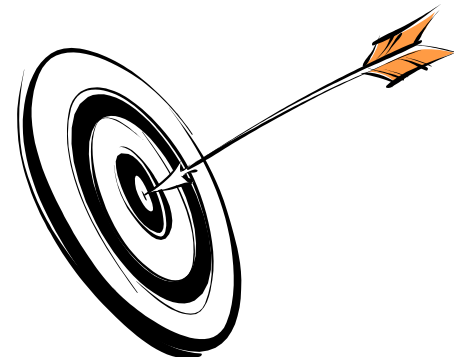
“Follow-on” discovery

- More arrows at the same target



Innovation at Orphagen

- First arrow to target–
“**first-in-class**” drug



Partnering Projections by Program



Innovation Engine at Orphagen

- **Successful target family**
 - Nuclear receptors: osteoporosis, cancer, diabetes, asthma

EVISTA
raloxifene HCl
tablets 60mg

Xtandi
(enzalutamide)
capsules

Actos
pioglitazone

ADVAIR DISKUS[®] 250/50
(fluticasone propionate 250 mcg and
salmeterol 50 mcg inhalation powder)

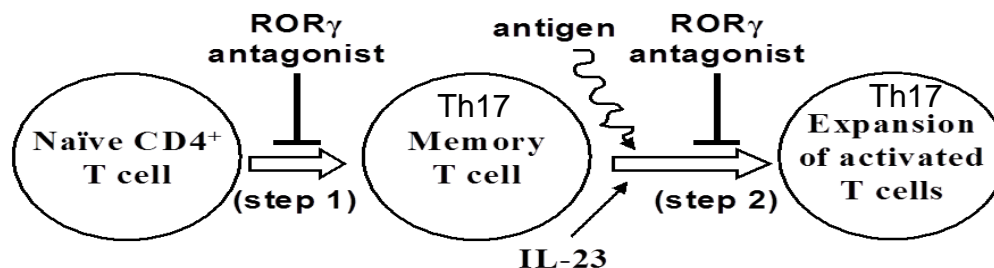


- **Therapeutic area agnostic**
 - Follow unexplored targets
- **Translational research—new targets**
 - First-mover for ROR γ (autoimmune disease)
- **Transformative therapies**
 - Disease-modifying drugs

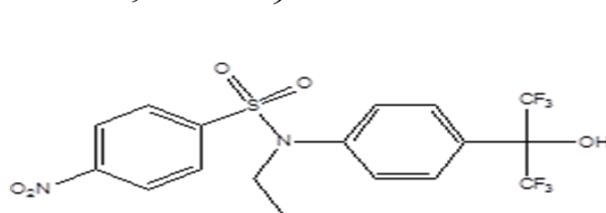


Retinoic Acid-related Orphan Receptor γ (ROR γ)

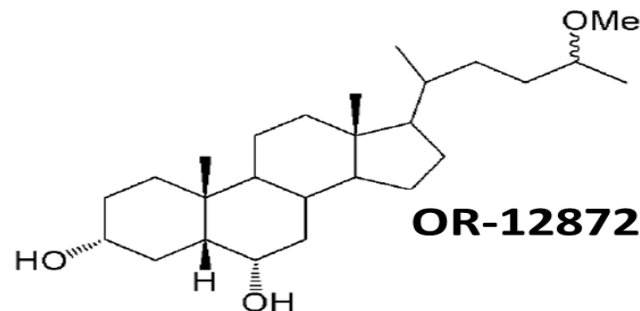
ROR γ (NR1F3) plays a critical role in the differentiation and activation of Th17 T cells, key mediators of immune response in many autoimmune diseases including rheumatoid arthritis, Crohn's disease and psoriasis.



We identified ROR γ antagonist (e.g. OR-1050) and agonist (e.g. OR-12872) ligands in a Gal4 hybrid transcriptional assay and confirmed activity in a co-activator peptide binding assay (Thacher, 2013).



OR-1050

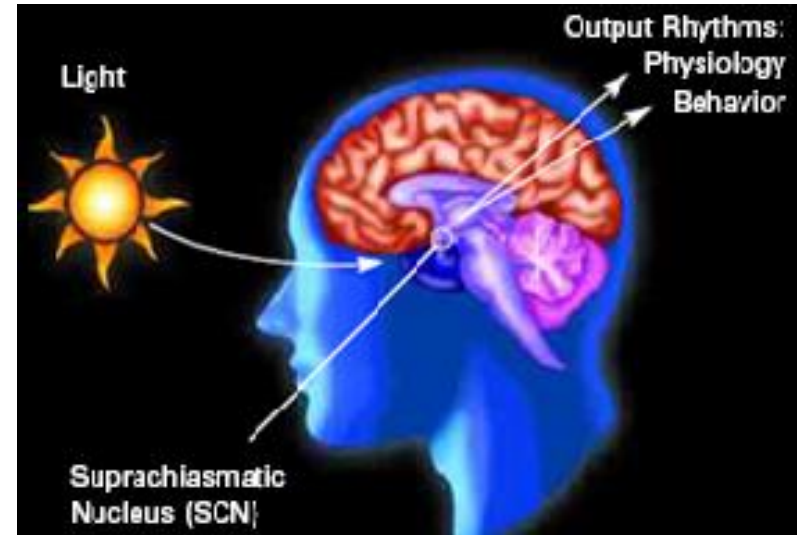


OR-12872



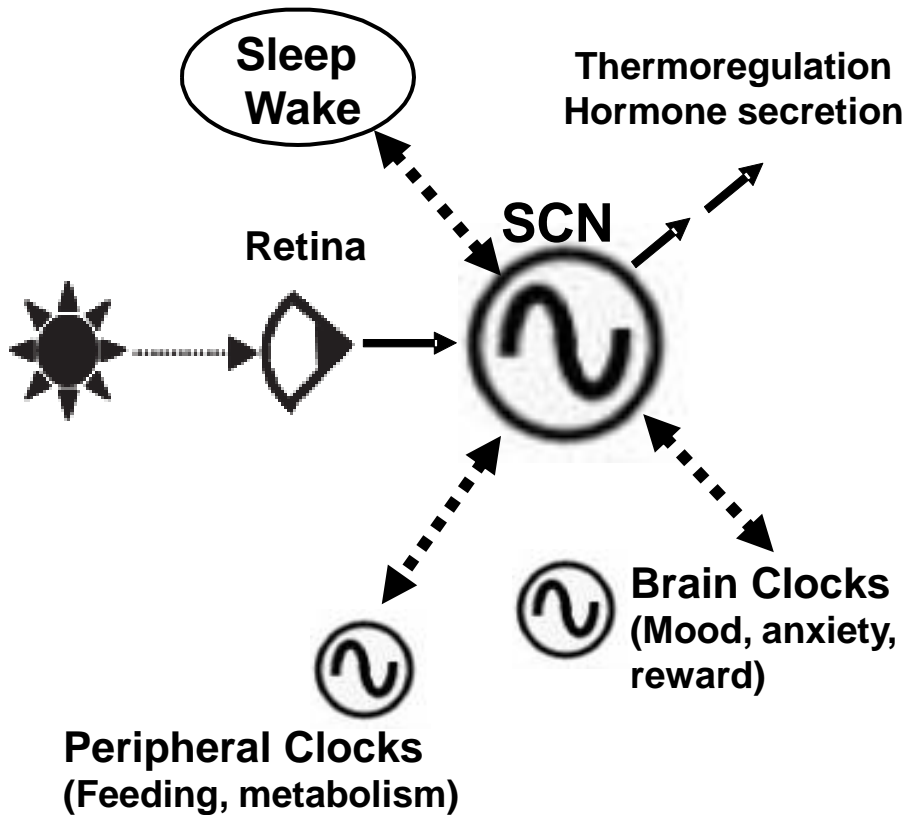
Orphagen's Circadian Target

- Orphan nuclear receptor
- Highly expressed in SCN
 - Knockout mouse has circadian and behavioral phenotype
- Selective, high-affinity ligands
 - Three distinct antagonist chemical series
- *In vitro* efficacy
 - Phase shift in isolated SCN slice culture (electrophysiology)
- PK and *in vivo* efficacy studies ongoing



The suprachiasmatic nucleus (SCN), is a tiny region located in the hypothalamus, situated directly above the optic chiasm. It is responsible for controlling circadian rhythms.

SCN: The Central Circadian Clock



- Uses only ~20,000 neurons
- Primarily regulated by light signals from retina and the only light regulated pace maker
- Synchronizes sleep-wake cycle and many other physiological rhythms
- Coordinates other clocks in brain and periphery
- Important target for chronotherapy: light has been used clinically

Target Profile of New Drug Class

- Chronotherapy: shifts circadian phase
 - Efficacy is time of day dependent
- Target core transcriptional clock in SCN
- Brain-penetrating with short half-life
- Oral dosing
 - Better compliance than bright light therapy
- Non-sedating, chronic therapy
 - Circadian entrainment for sleep-wake cycle

Major Therapeutic Areas

Circadian Dysfunction and/or Sleep-Wake Cycle Disruption are Salient Characteristics of Many CNS Disorders

Psychiatric

- Seasonal Affective Disorder (SAD)
- Major Depressive Disorder (MDD)
- Bipolar Disorder
 - Autism

Neurodegenerative

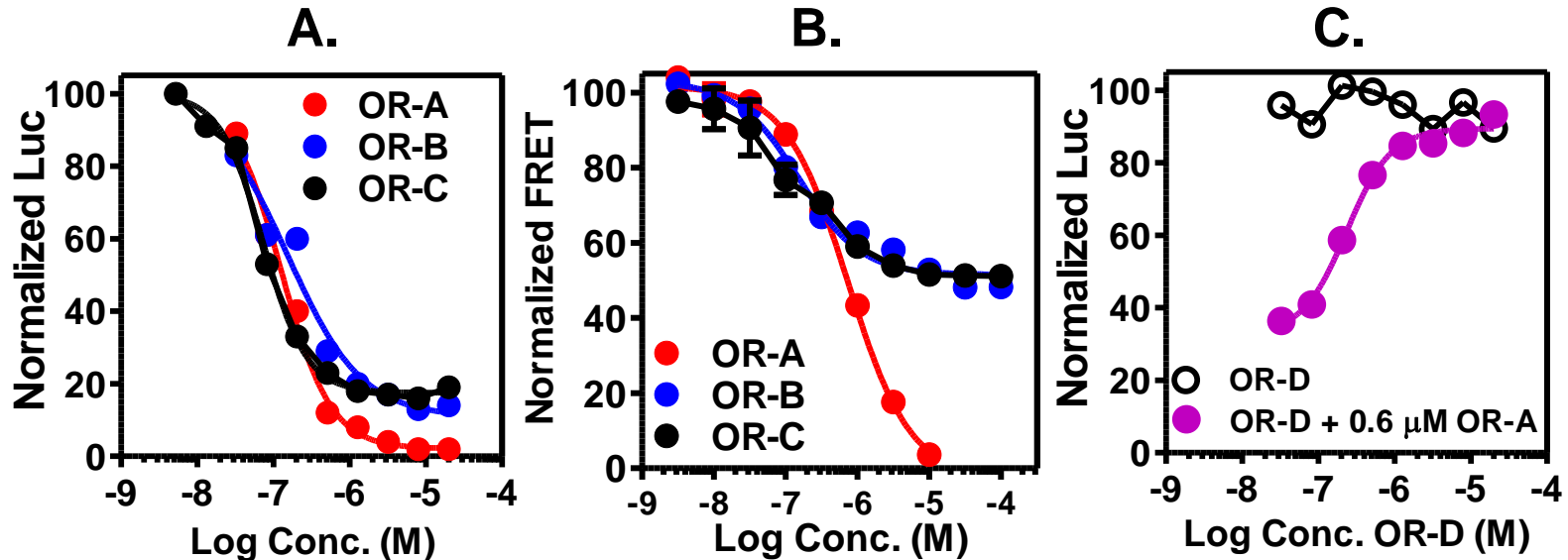
Alzheimer's Disease

Trauma

- PTSD
- Traumatic Brain Injury (TBI)



Orphagen Circadian Target: *In Vitro* Pharmacology



- A. Transcriptional activity in cultured cells (luciferase readout)
- B. Coactivator peptide interaction with partially purified receptor is regulated by ligand binding, detection by FRET
- C. Neutral Antagonist OR-D reverses the inhibitory effect of antagonist (**OR-A**, 0.6 μM) in transcriptional assay

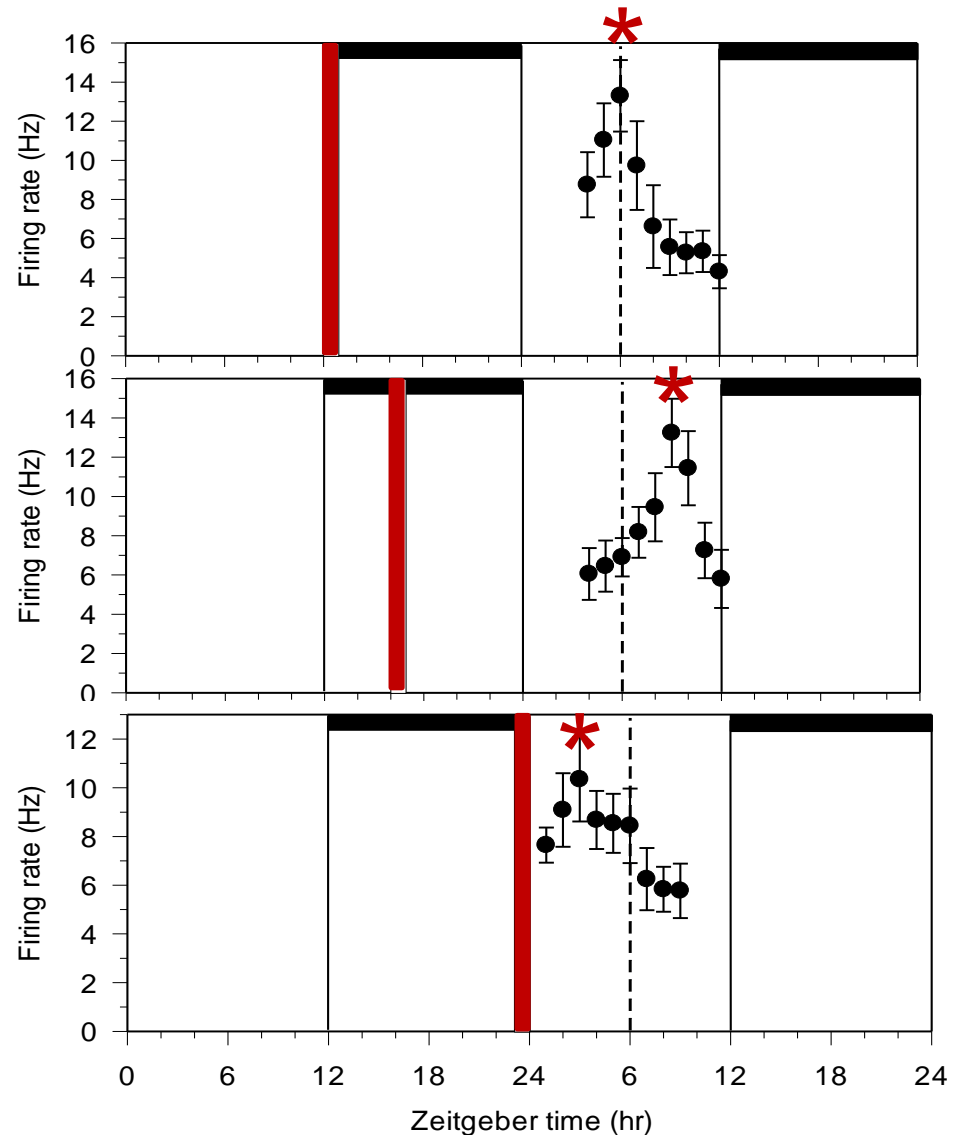


OR-B (3 μ M, 1 hr) Shifts the Phase of SCN Firing Activity at ZT 16 and 23

Time of Addition	Result
ZT 12 (6 pm)	No phase shift

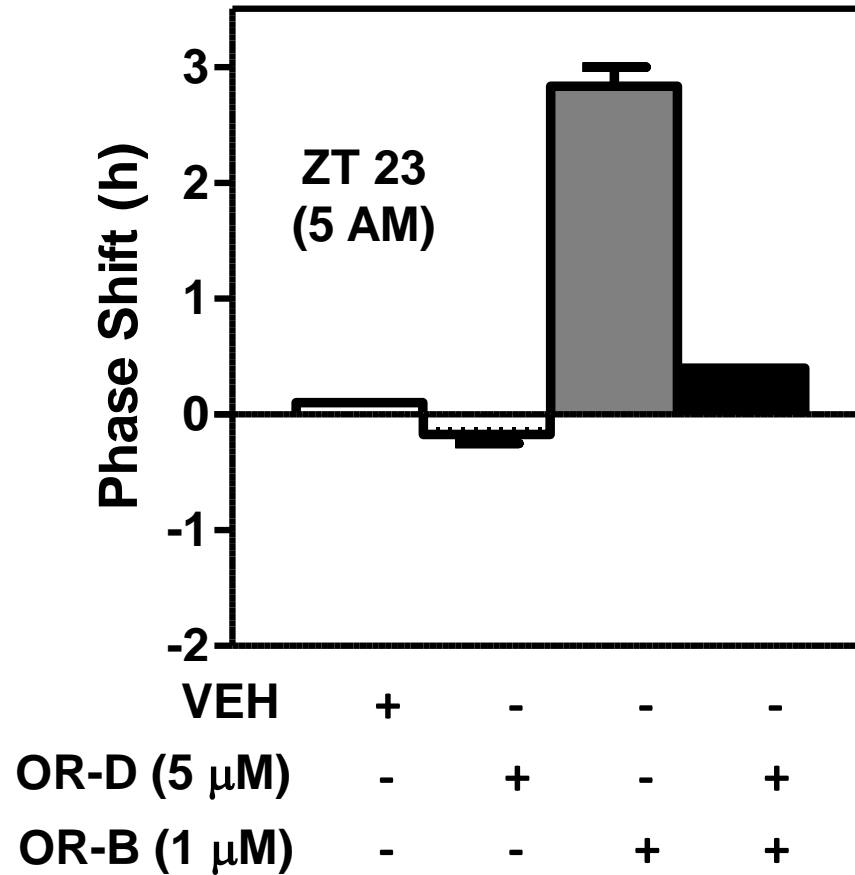
ZT 16 (10 pm)	2.5 hr delay
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ZT 23 (5 am)	2.5 hr advance
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In collaboration with R. Prosser, UT Knoxville

Phase Advance by OR-B is Reversed by Neutral Antagonist OR-D



Summary

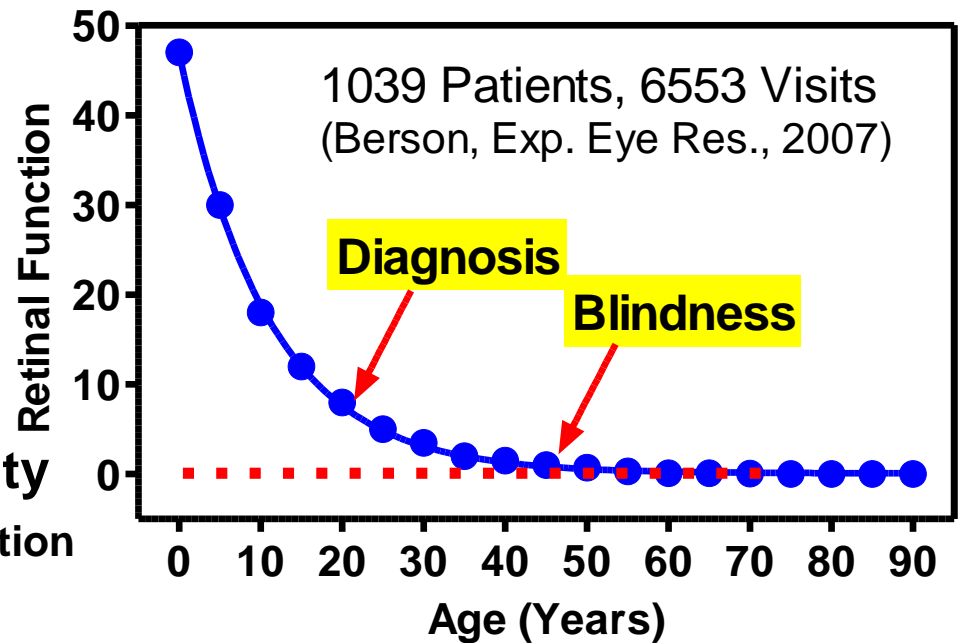
- **Novel ligands discovered for SCN target**
- ***In vitro* POC: advances & delays**
 - 2.5 h phase advance at ~5 am (ZT 23)
 - 2.5 h phase delay at ~10 pm (ZT 16)
 - No phase shift at noon or at 6 pm
- **Strong pharmacological validation**
 - Two distinct series with activity in SCN
 - Antagonist phase advance blocked in presence of neutral antagonist
- **Probe Compounds: Cross BBB ($t_{1/2} = 1$ h)**



New Drug Class for Hereditary Blindness

- **Retinitis Pigmentosa (RP)**
 - RP is usually diagnosed in early adulthood
- **100,000 affected in U.S.**
 - No preventive therapy
- **Local delivery to eye**
 - Intravitreal or topical
- **Market Expansion Opportunity**
 - Dry age-related macular degeneration

Loss of Vision in RP Patients

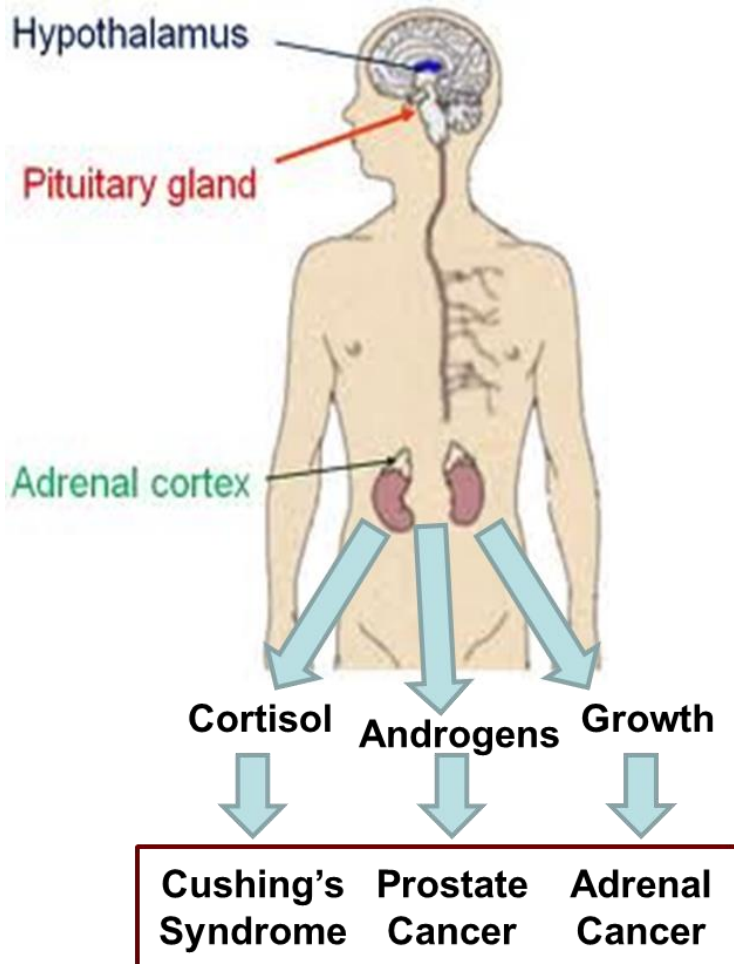


Therapeutic goal: treatment at diagnosis that doubles visual lifetime (e.g., for a 20-year old patient, extend from 40 years of age to 60)



Endocrine Target: Steroidogenic Factor-1

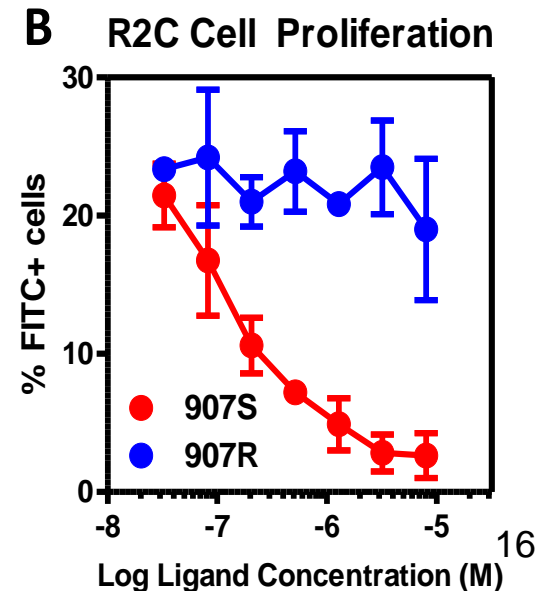
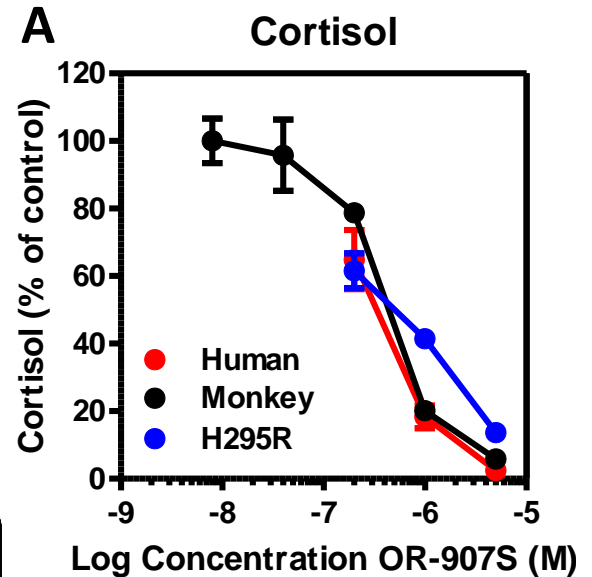
Endocrine Cancers



**Inhibit
adrenal
steroid
secretion**

**SF-1
antagonists**

**Block
SF-1+
cell
growth**



New Ligand Discovery & Potential New Programs

- **Novel assays developed at Orphagen**
 - Orphan nuclear receptors with no proven ligands
- **Sickle Cell Anemia**
 - Induction of fetal hemoglobin by orphan receptor
- **Stage IV glioblastoma**
 - Specific neural stem cell proliferation factor, expression correlated with poor clinical outcome
- **Metabolic Disease**
 - Energy expenditure, glucose sensitivity
- **Oncology**
 - Angiogenesis, cell differentiation



NR Assay Services

- **The steroid hormone receptors (ER, AR, PR, and GR)**
- **Metabolic receptors (PPAR α,δ,γ ; LXR α , FXR, and ERR α,β,γ)**
- **Retinoid receptors (RAR α and RXR α)**
- **New orphan targets (ROR α,β ; SF-1 and LRH-1)**
- **Unexplored targets**
- **Custom receptor assay development upon request.**



CDD at Orphagen

- **Compound registration**
- **Assay protocols and results**
- **Functional assay results**
- **In vitro ADME**
- **In vivo PK**
- **Brain penetration studies**
- **Data sharing**



Compound Registration

AA-003

[Edit](#) - [Delete](#)

Salt: No Salt, free base or acid


Amount: 300mg

Solvent:

FW: 487.406 g/mol

Concentration
mM:

position:

External Identifier: 

Volume uL:

Volume:

Date: 2012-05-10

Purity: >95%

Appearance: Brown soild

Person: Feixiong Zhang

PlateID:

Store_condition:

Place: 10mM stock solution = Freezer #4, Shelf #4, Box #W70. Powder = Freezer #4, Shelf #3, Box: Sundia 134897A-

Well:

Emolecules ID:

Vendor: Sundia

Column:

Emolecules Barcode:

VendorID: S25550

Row:

Orphagen Notebook ID: Orp-22-92-001

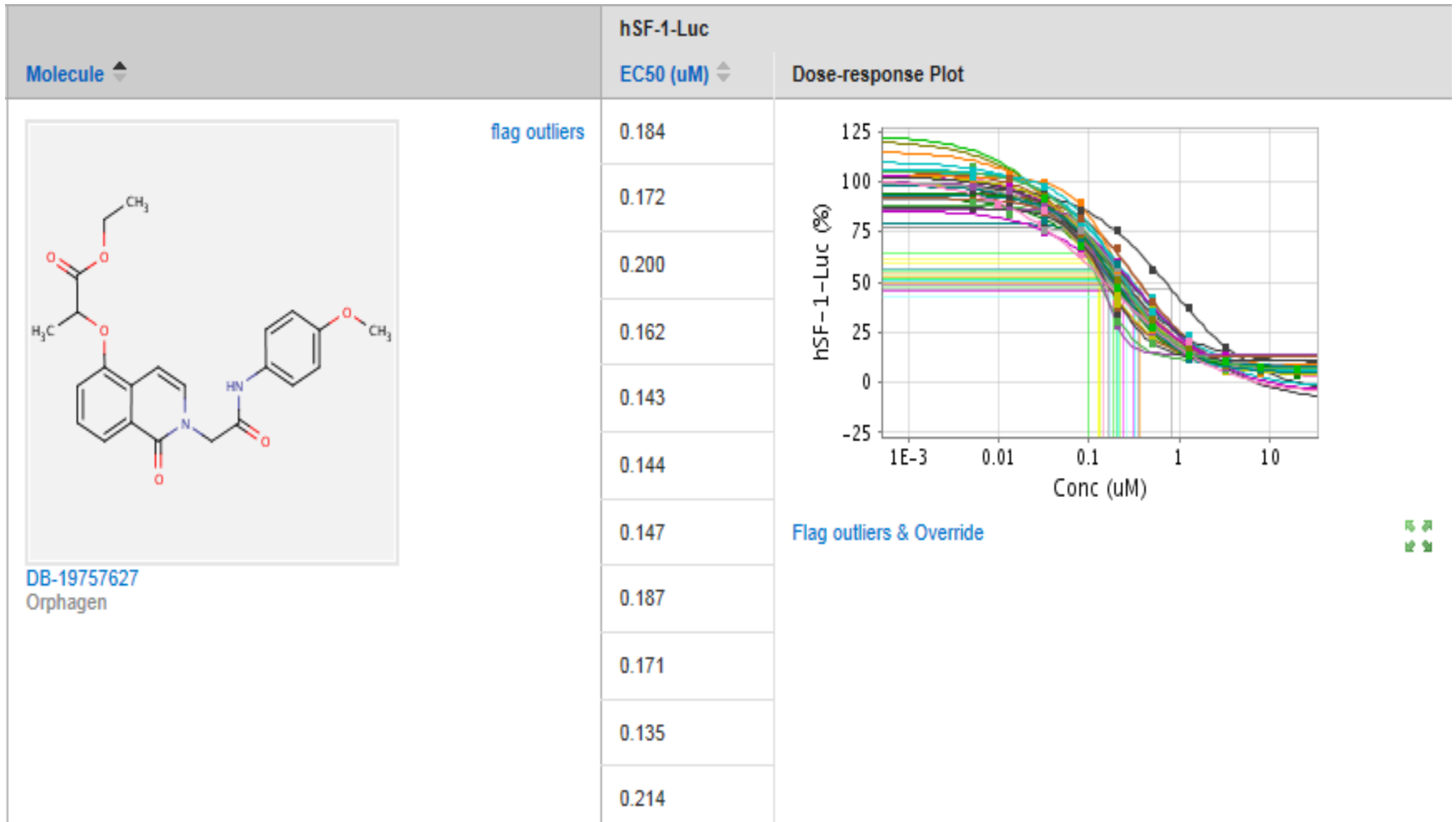
Lot ID: E766-4511-40

Plate Barcode:

Note:



Assay Results



In Vitro ADME

Molecule ▲	Liver Microsome Stability Summary ✎			Protein binding-equilibrium dialysis ✎	
	Species ▲	T1/2 (minutes) ▲	CLint (mL/min/kg) ▲	Species ▲	Bound Fraction (%) ▲
DB-19934603 ✎ Orphagen	flag outliers				
	Rat	178.6	23.0	human	99.4
	Human	386.1	6.5		
	mouse	151.5	41.2	human	98.4

Molecule ▲	Permeability and Pgp substrate-1					
	PGP inhibitor ▲	Papp A->B (cm/sec x 10-6) ▲	Papp B->A (cm/sec x 10-6) ▲	Efflux Ratio ▲	Permeabilit...ssification ▲	PGP sub
DB-19934603 ✎ Orphagen	flag outliers					
	No	14.4	29.4	2.0		
	Cyclosporine A	26.9	21.3	0.8	high	no



In Vivo PK

in vivo PK-1						
Species	Dosing route	Dose (mg/kg)	Vehicle	Tmax (hrs)	Cmax (ng/mL)	T1/2 (hrs)
Mouse	IV	1.0	DMAC/Solutol HS 15/20% HP-?-CD (10%/6%/84%)	0.08	534.8	1.64
Mouse	PO	50.0	DMAC/Solutol HS 15/20% HP-?-CD (10%/6%/84%)	2.17	1327.1	8.97

AUC (0-inf) (ng x hr/mL)	MRT (hrs)	Vd (L/kg)	CL (mL/min/kg)	F (%)	Relative IV study
545.8	1.59	4.4	30.83		20130428
24401.1	5.58	14.3	22.61	61.4	20131014



In Vivo BBB Results

In Vivo Brain Penetration					
Species	Dosing route	Dose (mg/kg)	Plasma Conc.@0.5h (ng/mL)	Brain Conc.@0.5h (ng/g)	B/P@0.5h
Mouse	IV	1.0	191.6	171.2	0.89



The People

