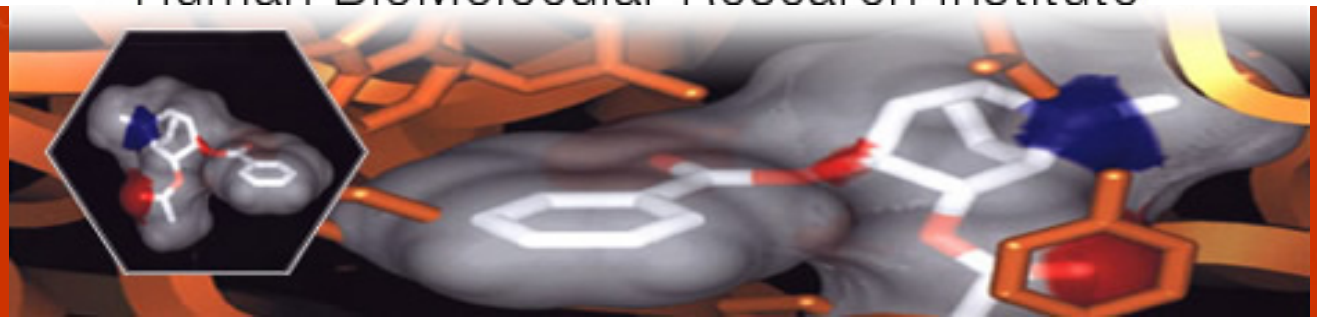
Human BioMolecular Research Institute

HBRI



CANCER THERAPEUTICS: A NOVEL APPROACH

Mary Dwyer, Ph.D.
HBRI and ChemRegen, Inc.

SCDMDG Meeting
October 23, 2012

Outline

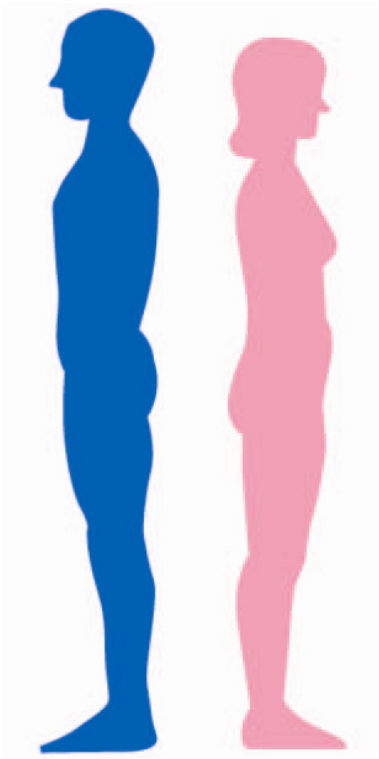
- Introduction
- Hit, HBRI1: identification & characterization
- Leads, HBRI2 & HBRI3: identification & characterization
- Next steps

HBRI

2012 Estimated US Cancer Incidence & Mortality

2012 Estimated US Cancer Deaths

Men 301,820		Women 275,370	
Lung & bronchus	29%	26%	Lung & bronchus
Prostate	9%	14%	Breast
Colon & rectum	9%	9%	Colon & rectum
Pancreas	6%	7%	Pancreas
Liver & intrahepatic bile duct	5%	6%	Ovary
Leukemia	4%	4%	Leukemia
Esophagus	4%	3%	Non-Hodgkin lymphoma
Urinary bladder	3%	3%	Uterine corpus
Non-Hodgkin lymphoma	3%	2%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain/other nervous system
All other sites	25%	24%	All other sites



Current Treatment Approaches, Issues

- Standard Triple Threat
  - Surgery
  - Chemotherapy (fluorouracil)
  - Radiation Therapy
  - Adverse effects on normal tissues

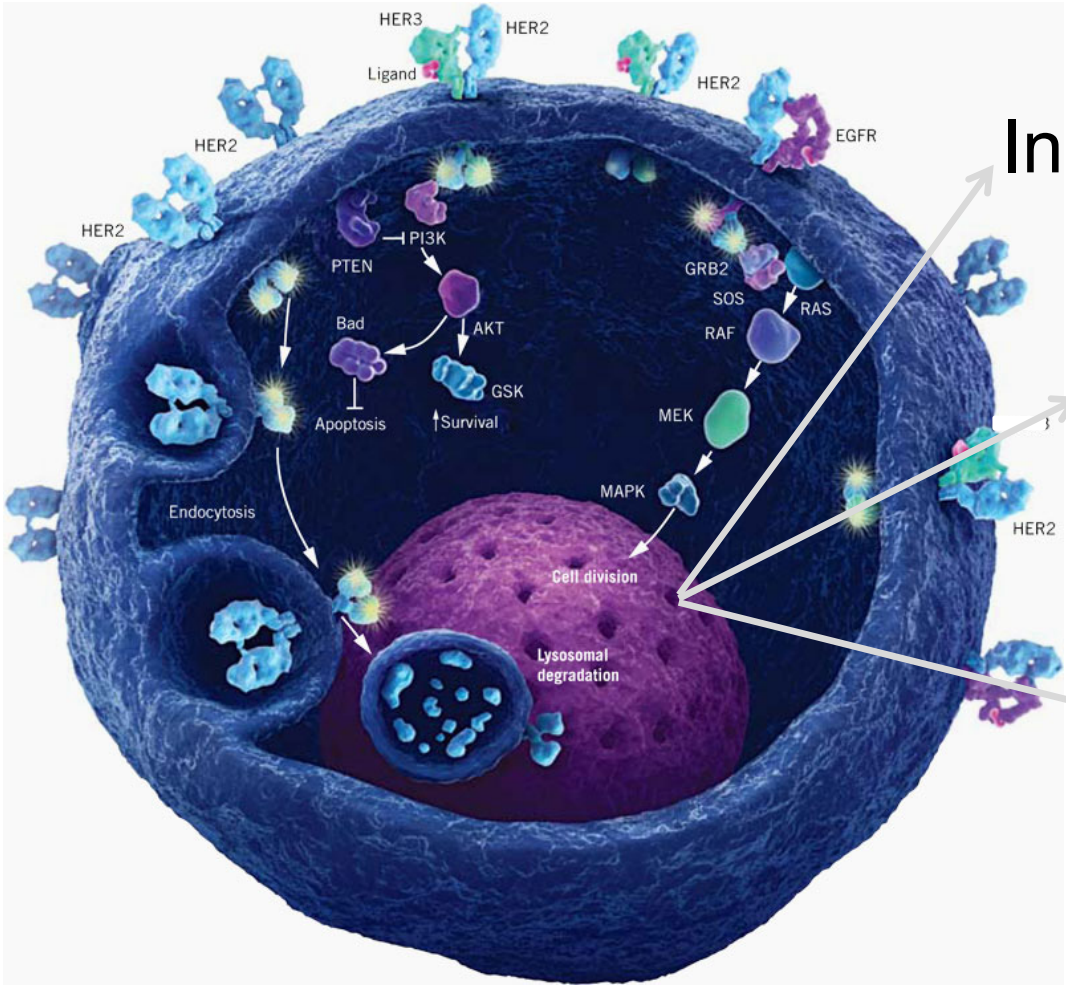
- Targeted Therapies- mAbs & Tyrosine Kinase Inhibitors
  - Avastin®- VEGF-Receptor mAb
  - Sutent®- VEGF-Rs & PDGF-Rs Tyr Kinase inhibitor
  - Costly, Production Limitations, Off-target Effects

HBRI

HBRI Created First-in-Kind Non-Toxic Anti-Cancer Agents

- Breast Cancer
- Prostate Cancer
- Colon Cancer
- Pancreatic Cancer
- Other Cancers

Pathway Dysregulation in Cancer

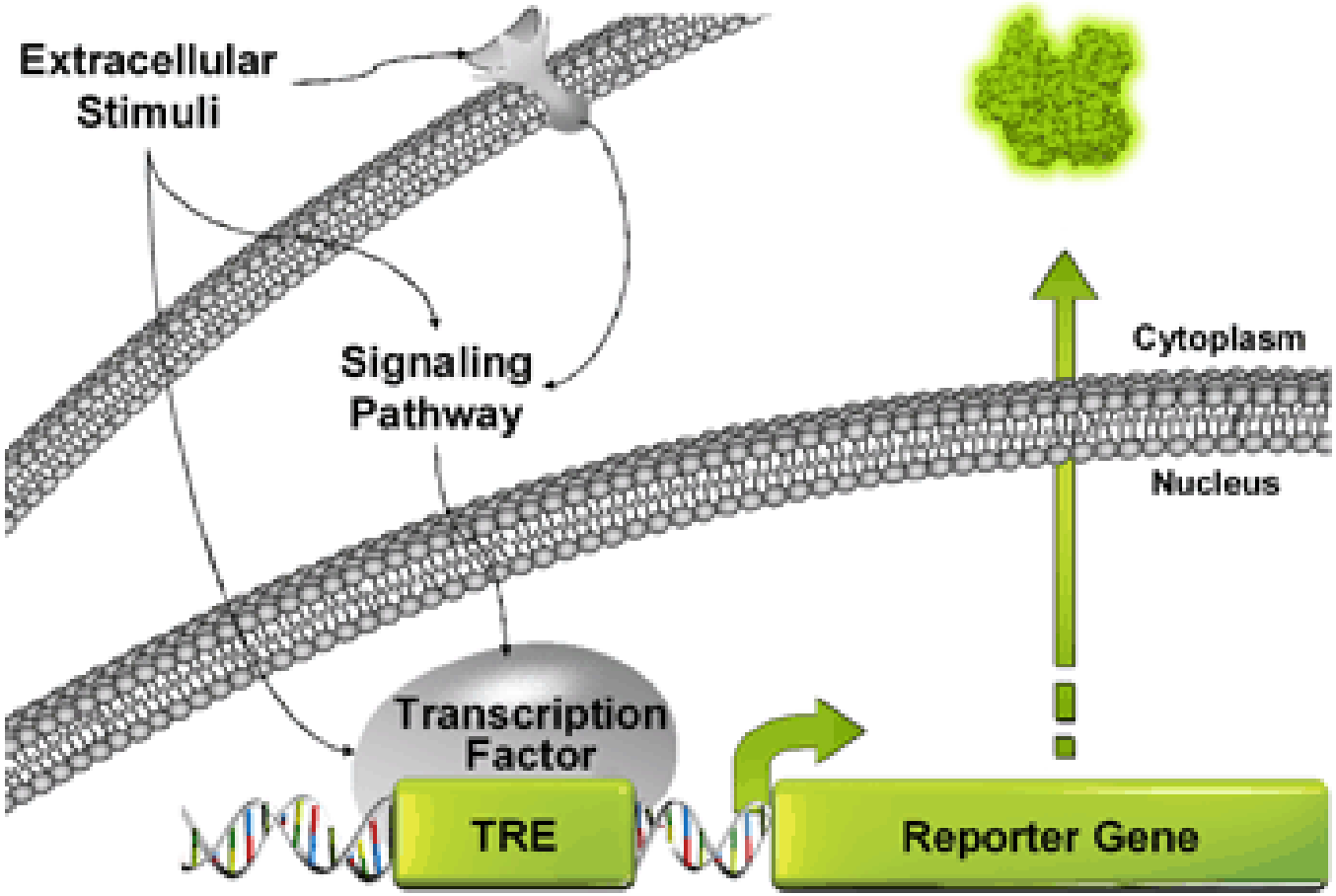


Increased proliferation

Increased metastasis

Resistance to apoptosis

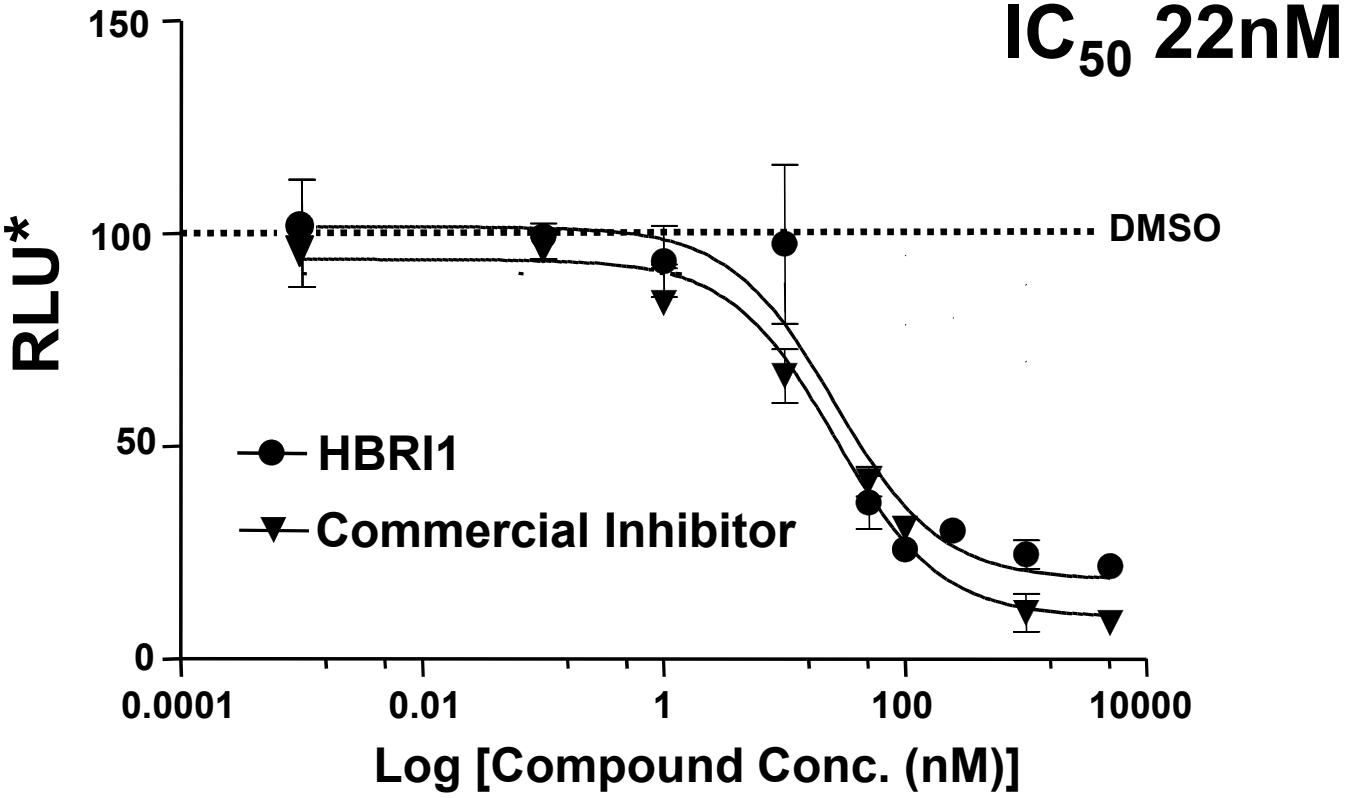
Compound Screen: A Pathway-Selective Inhibitor



Compound Screen: A Pathway-Selective Inhibitor

- Screened 76,000 compounds via a pathway-selective assay
- Identified 181 primary “hits”
- Confirmed 101 “hits”
- 14 pathway-selective “hits”
- 1 potent & reproducible “hit” developed

HBRI1 Inhibits Pathway-Specific Transcriptional Activity

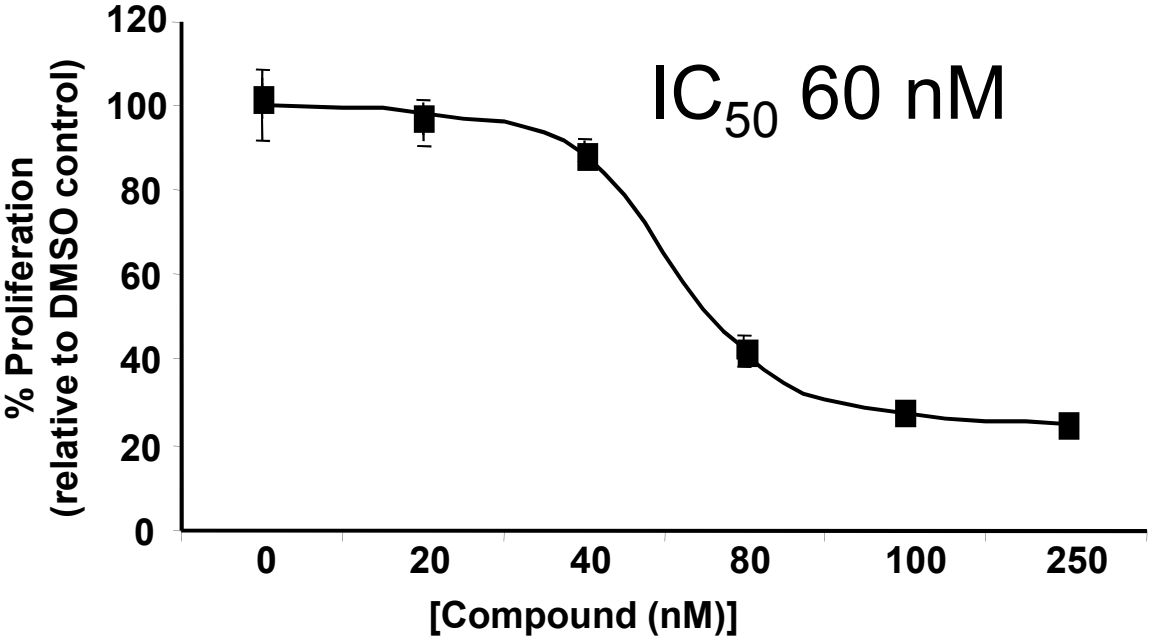


*HEK-293, normalized to DMSO

HBRI

HBRI1 Decreases Prostate Cancer Cell Proliferation & Cytotoxicity

LNCap Proliferation



LNCap Cytotoxicity

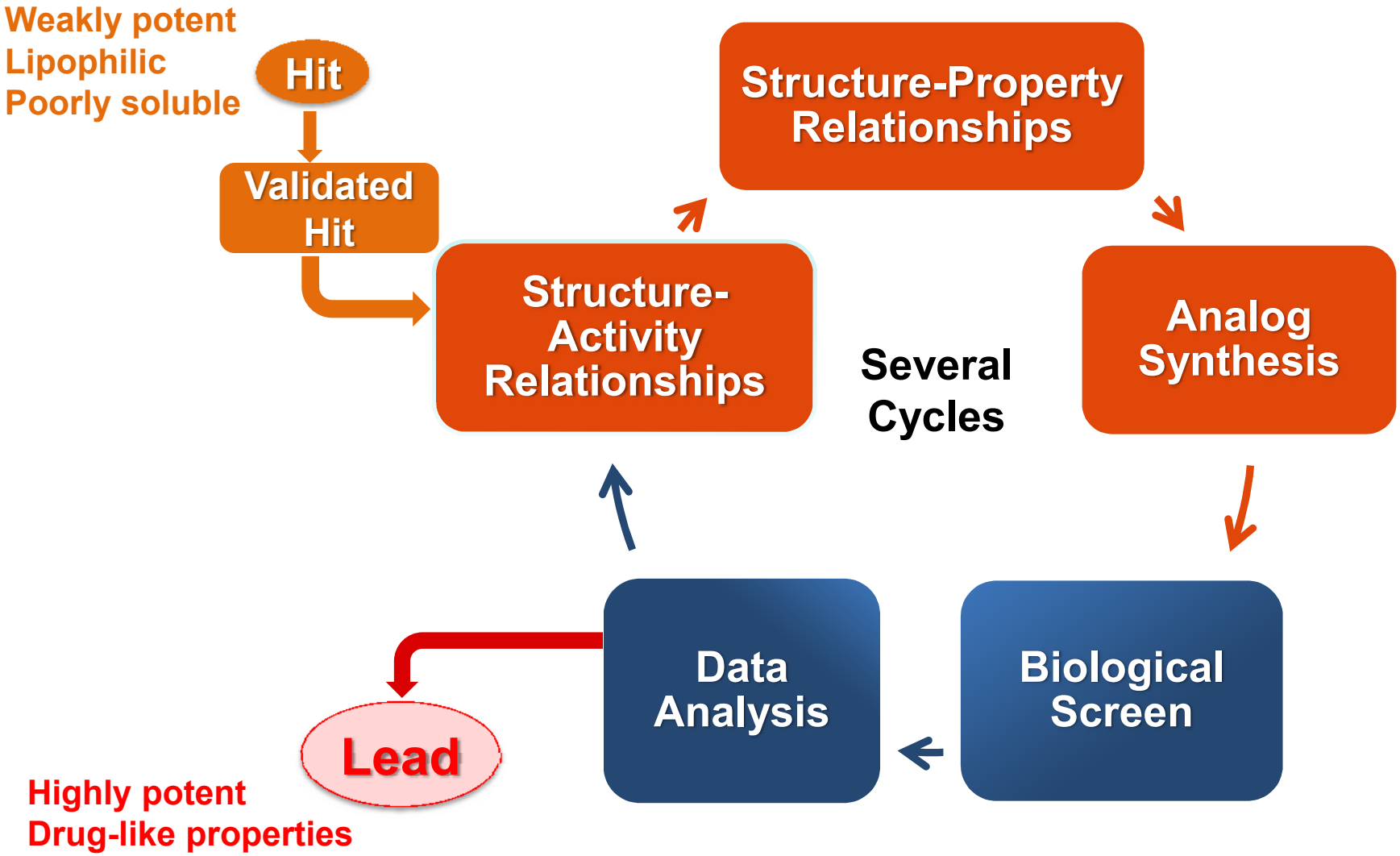
No effect at 5000 nM after 24 hrs

- monitoring GAPDH release

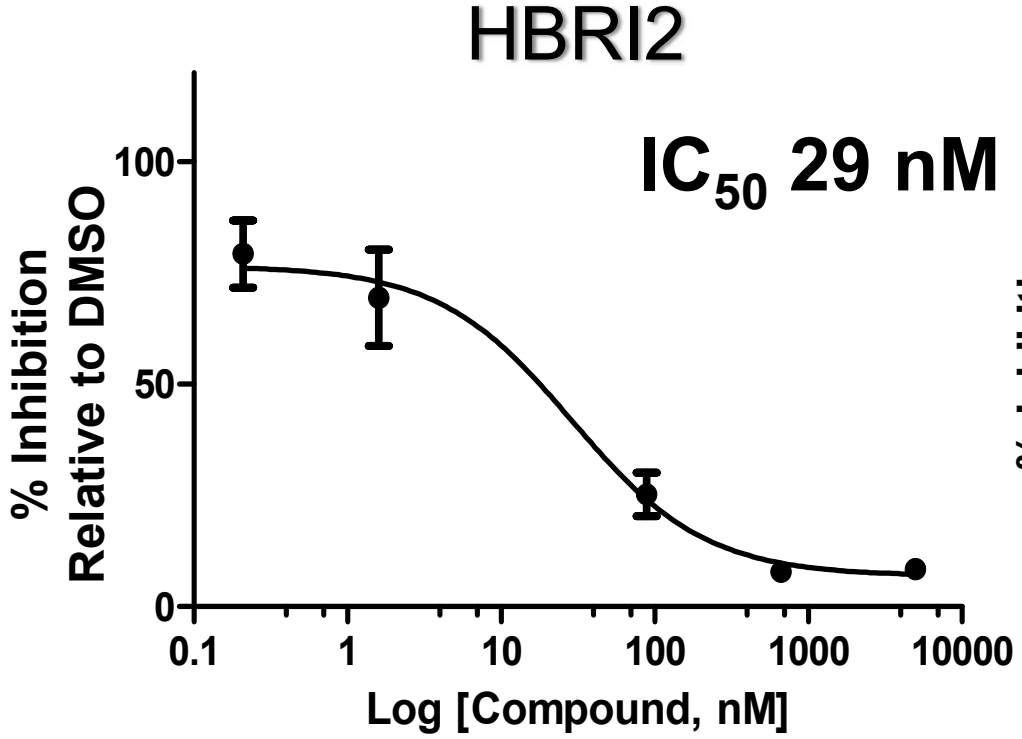
Primary Mouse Fibroblasts

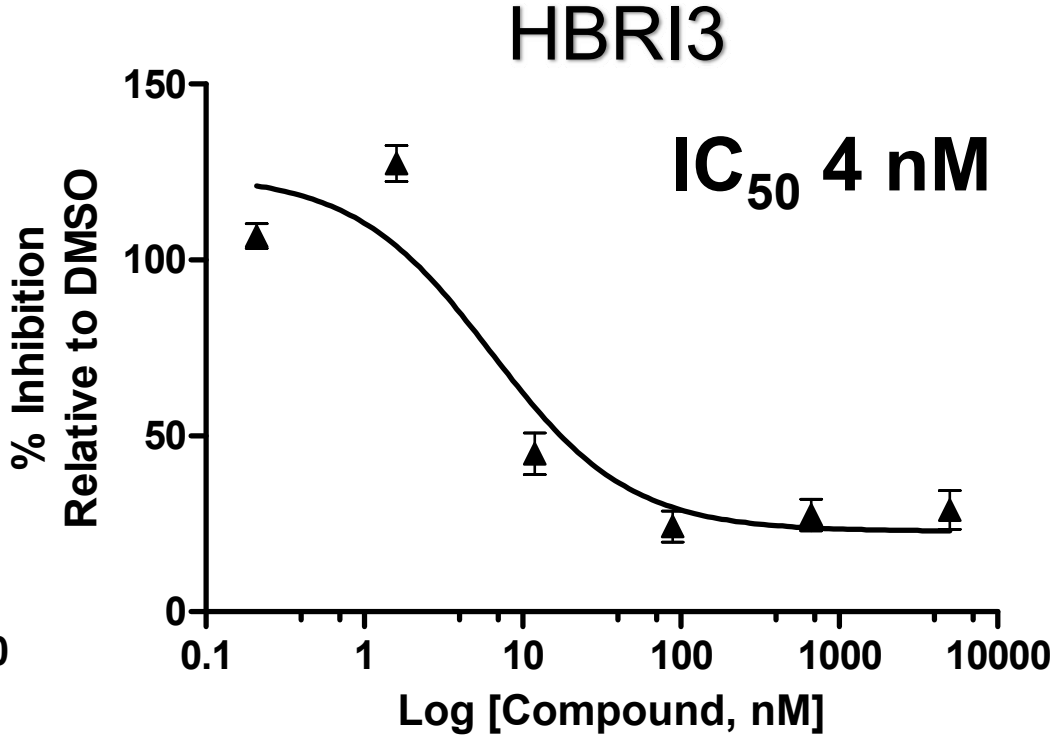
no change in proliferation or viability with 1 week of HBRI1 treatment

Medicinal Chemistry Development of HBRI1:



HBRI1 SAR Yields Potent Inhibitors, HBRI2 & HBRI3





- HBRI3 is 5-fold more potent than HBRI1
- HBRI3 is 10-fold more water soluble than HBRI1

HBRI1-3 Stimulate Prostate Cancer Cell Apoptosis & Regulate Target Gene Expression

Apoptosis

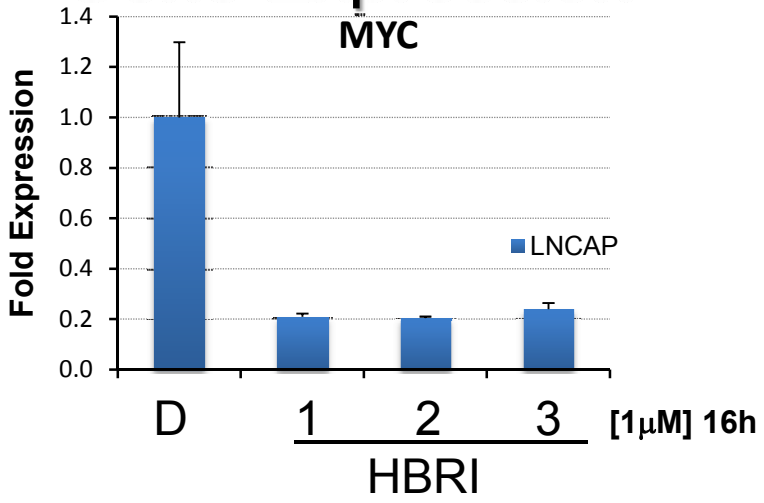
- HBRI1 induces apoptosis:
  - HEK-293

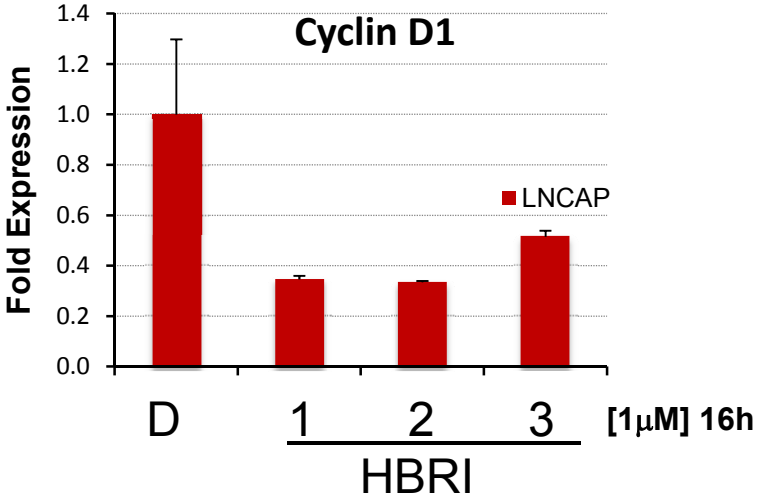
    Caspase-Glo (dose dependent increase)

  - HCT-116 (Colon Cancer)

    PARP cleavage observed (1μM, 16h)

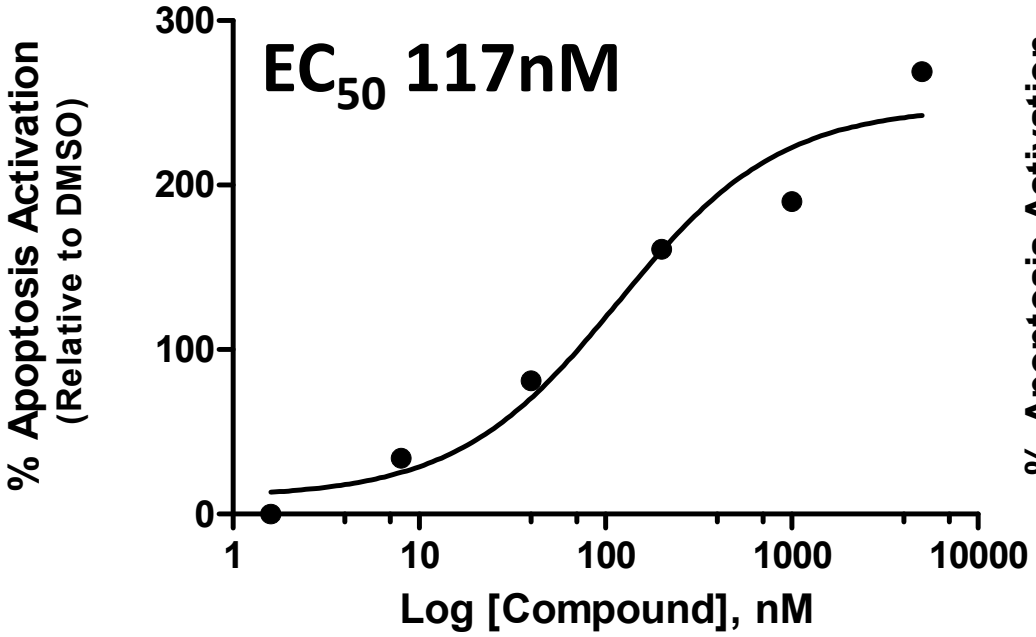
Gene Expression



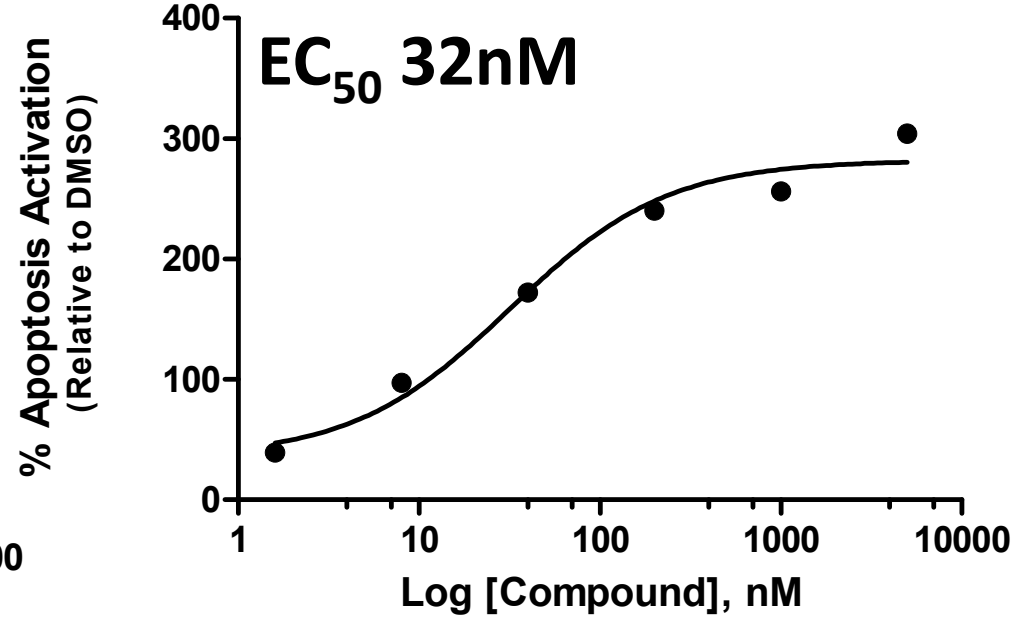


HBRI2 & HBRI3 Stimulate Prostate Cancer Cell (PC-3) Apoptosis

HBRI2



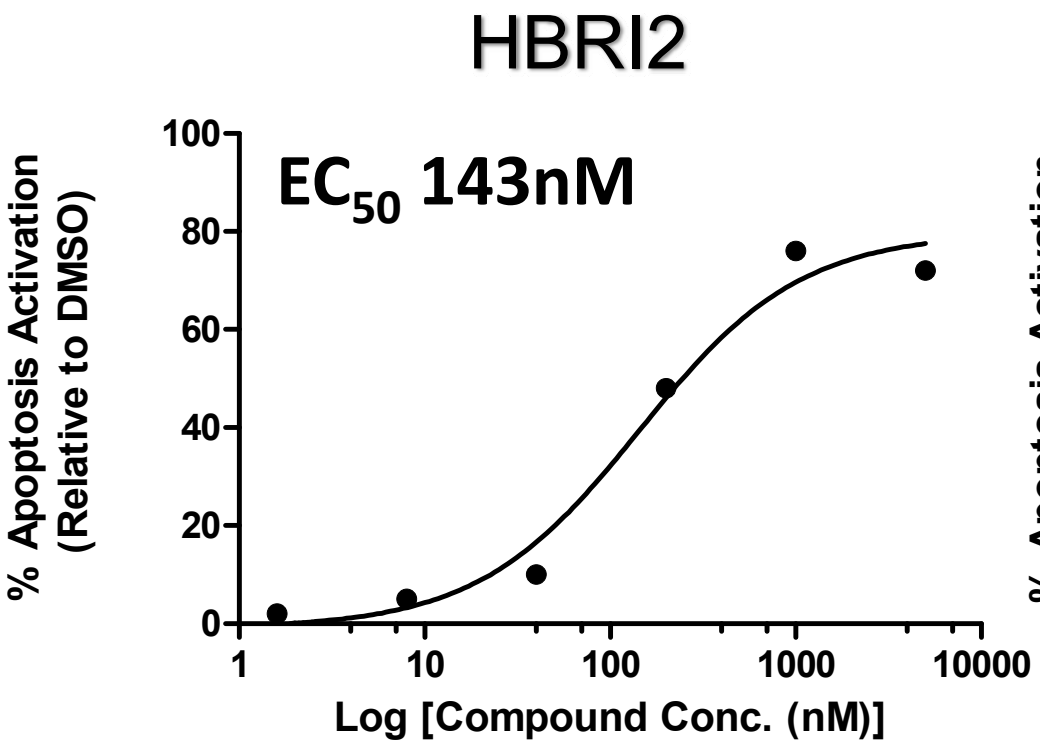
HBRI3

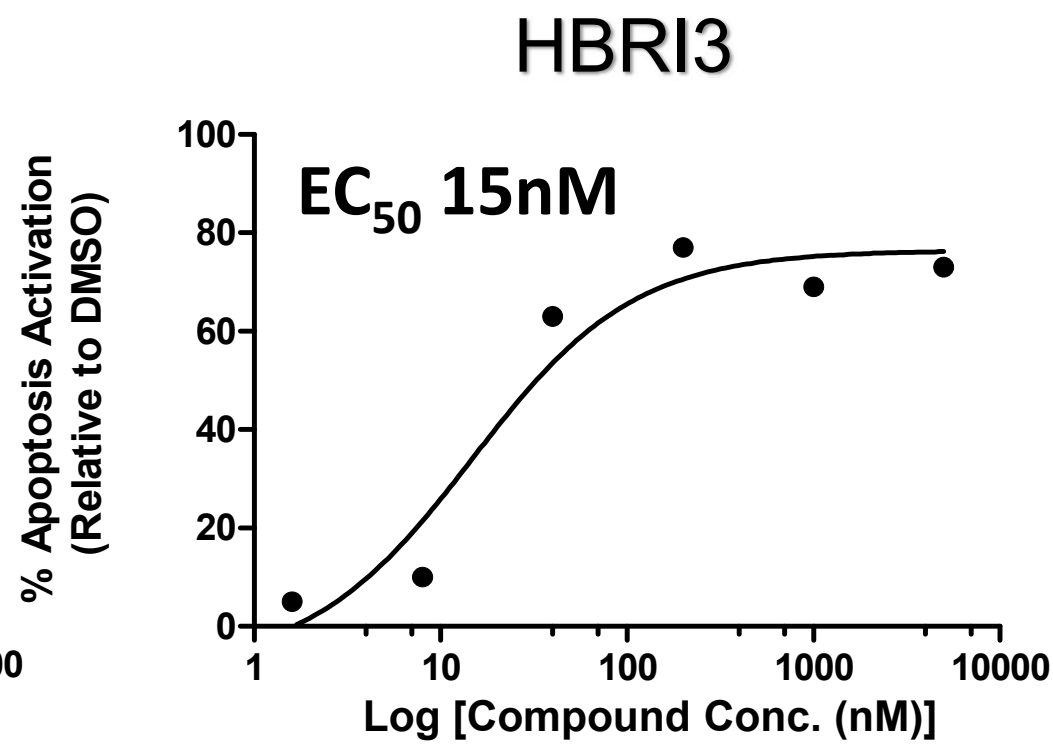


- Apoptosis monitored by Caspase Activation.

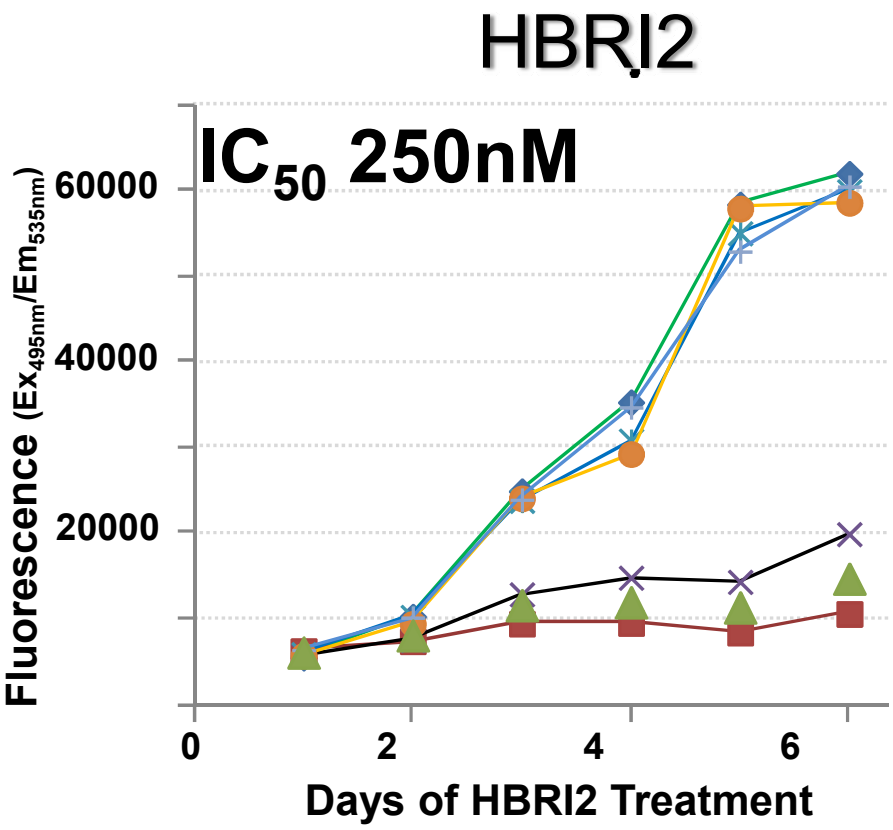
HBRI

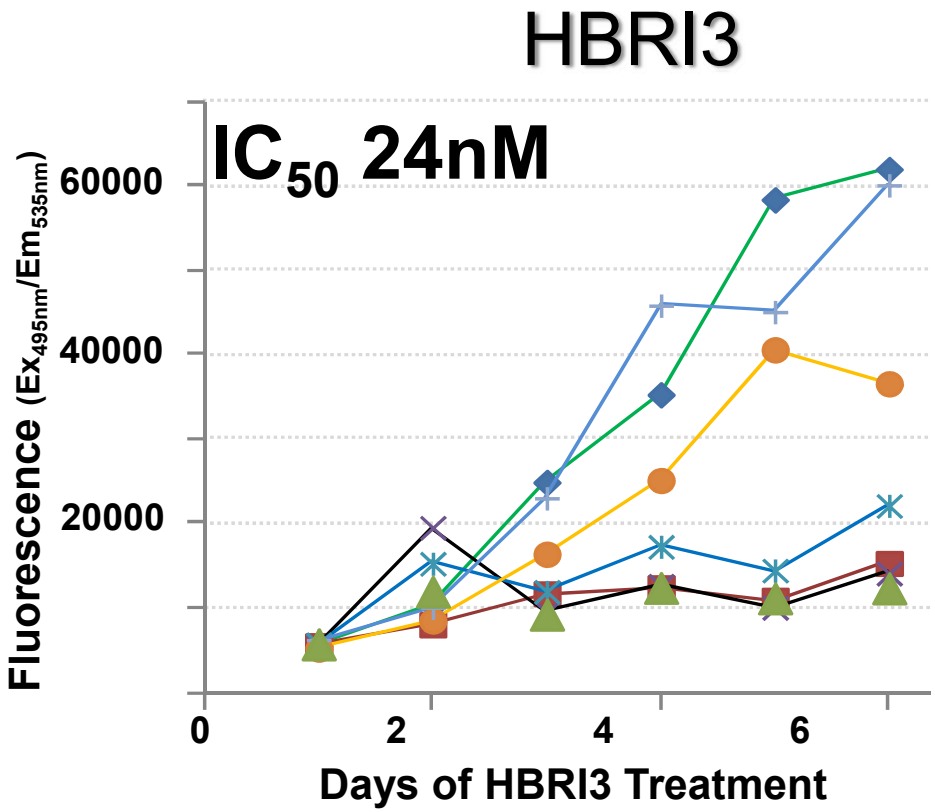
HBRI2 & HBRI3 Stimulate Colon Cancer Cell (HCT-116) Apoptosis



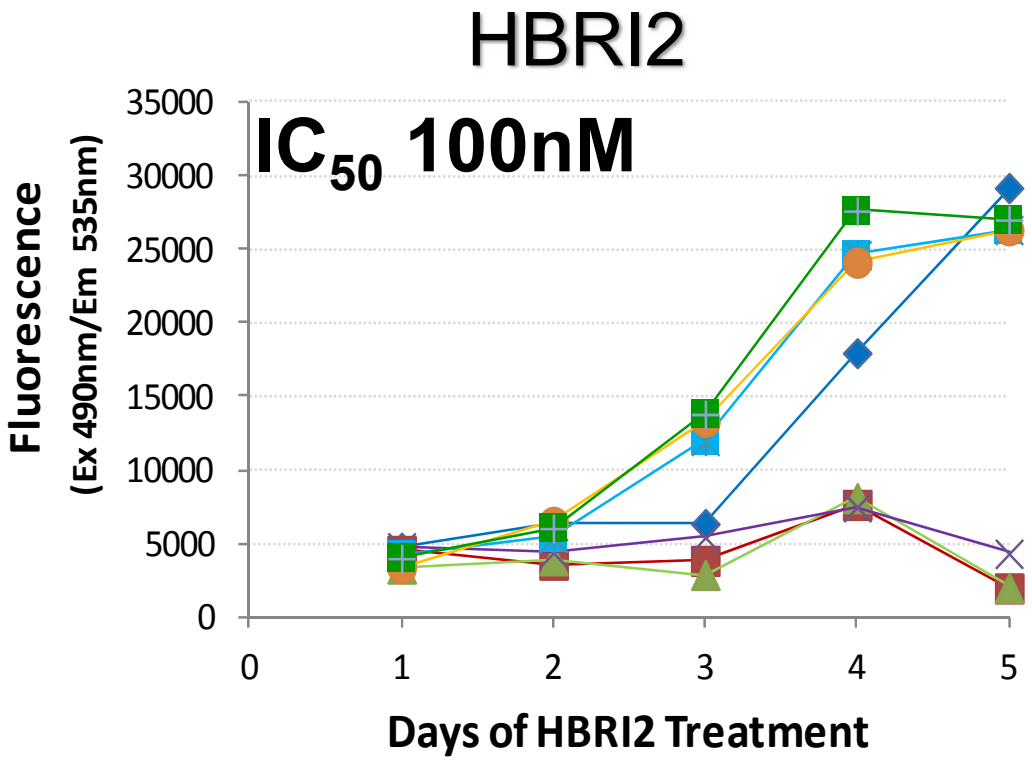


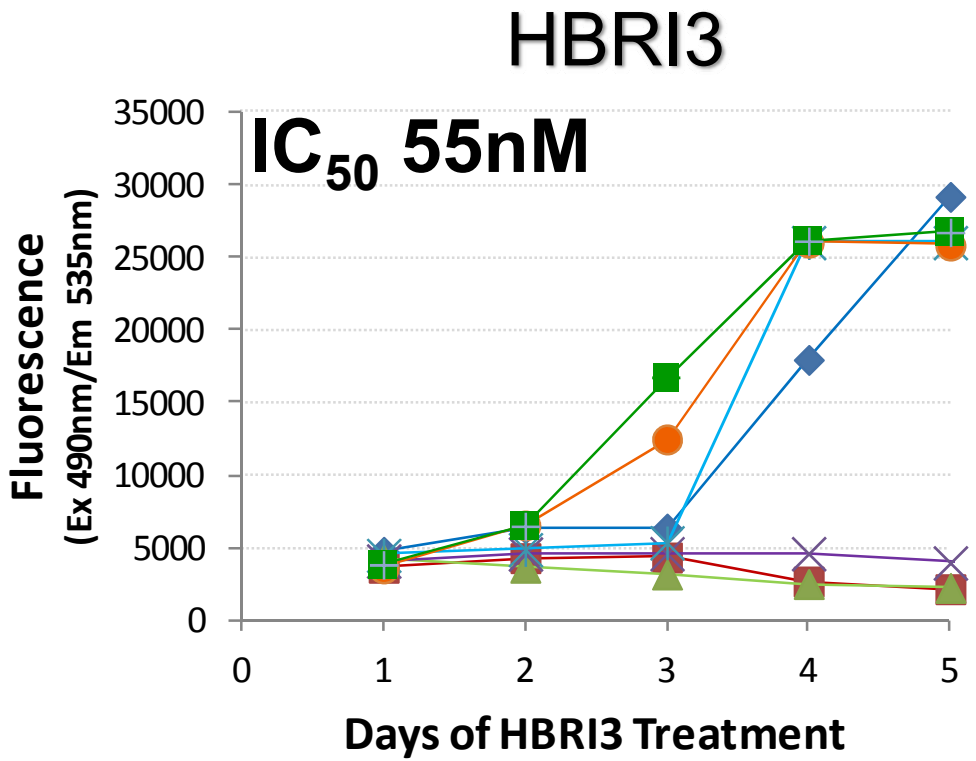
HBRI2 & HBRI3 Inhibit Breast Cancer Cell (MDA-MB-231) Proliferation





HBRI2 & HBRI3 Inhibit Pancreatic Cancer Cell (Mia-PaCa) Proliferation





- Similar decreases in proliferation of prostate & colon cancers were observed.

HBRI2 & HBRI3: Initial Pharmacokinetic Studies

Chemical & Metabolic Stability

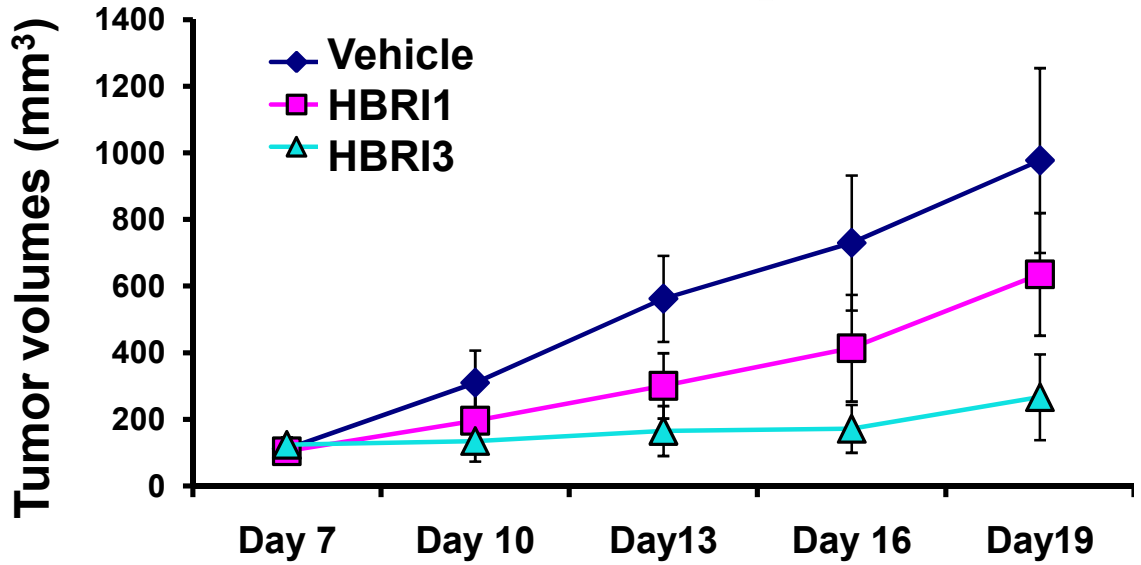
	Chemical Stability (h)	Metabolic Stability ($t_{1/2}$, min)		
		Human	Mouse	Rat
HBRI 1	120	NA[1]	NA[1]	NA[1]
HBRI 2	NA[1]	NC[2]	30	102
HBRI 3	NC[2]	77	382	65

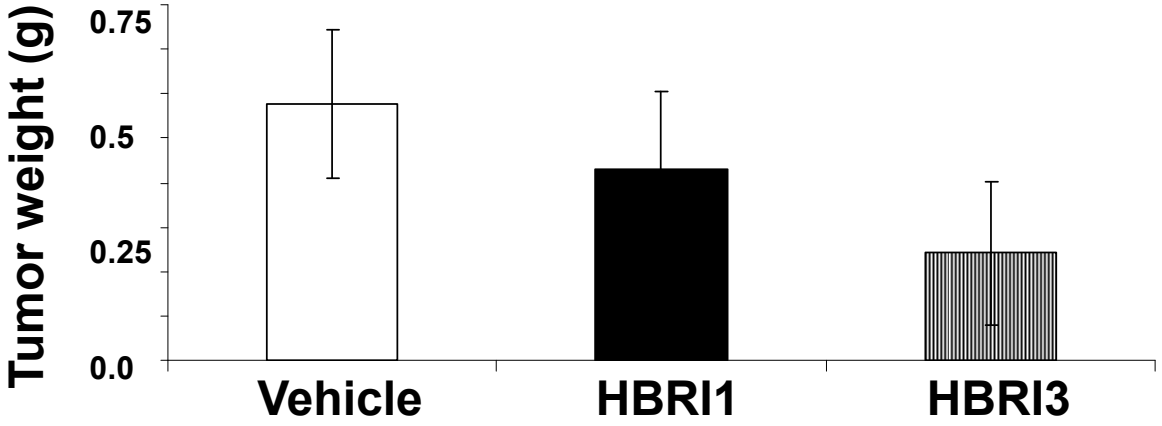
[1]NA = Not Tested
[2]NC = No Change

Rat *in vivo* studies: no acute toxicity of HBRI3

- Single dose at 200 mg/kg
- 7-days of daily dosing at 30 mg/kg:
  no effect on weight gain compared to vehicle-treated animals

Prostate Cancer Xenograft Study in Mice





- **HBRI3** reduced PC3 tumor volume by 80%

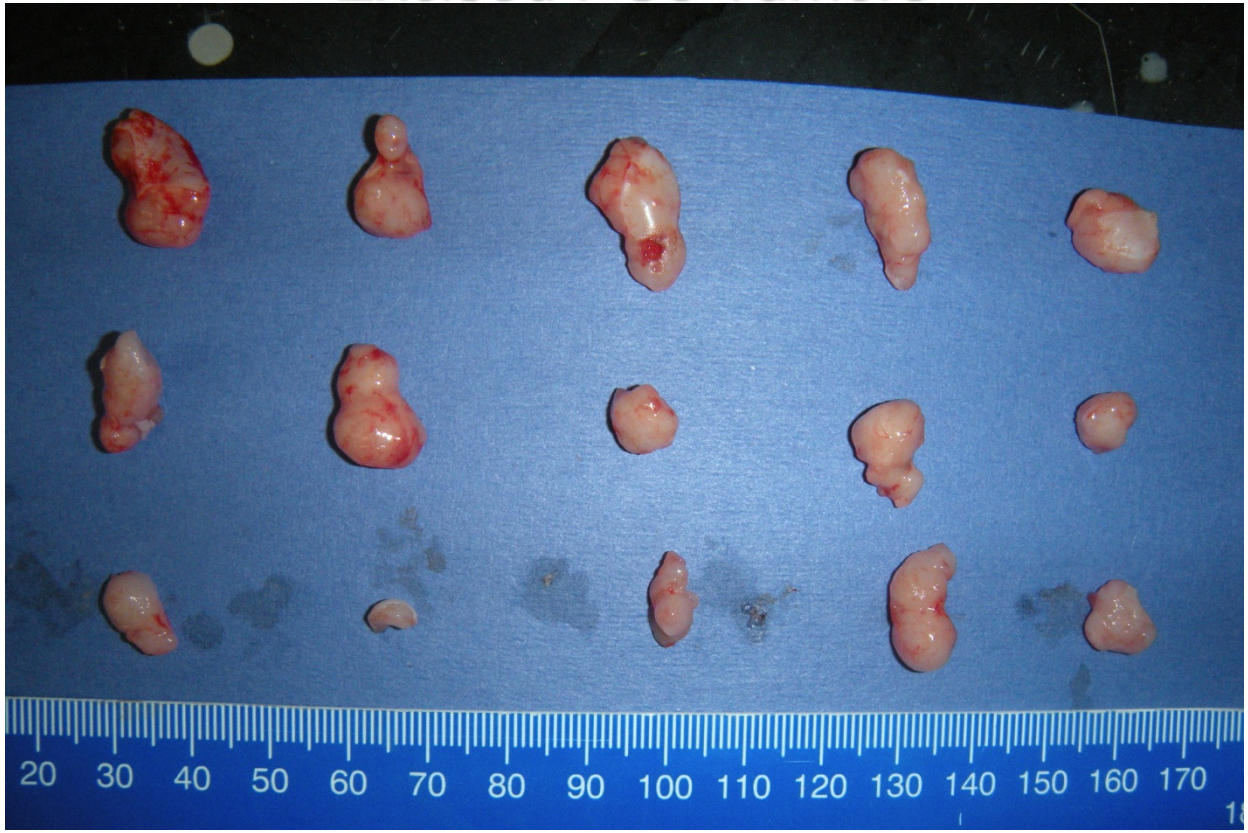
Prostate Cancer Xenograft Study in Mice

Excised PC3 Tumors

Vehicle

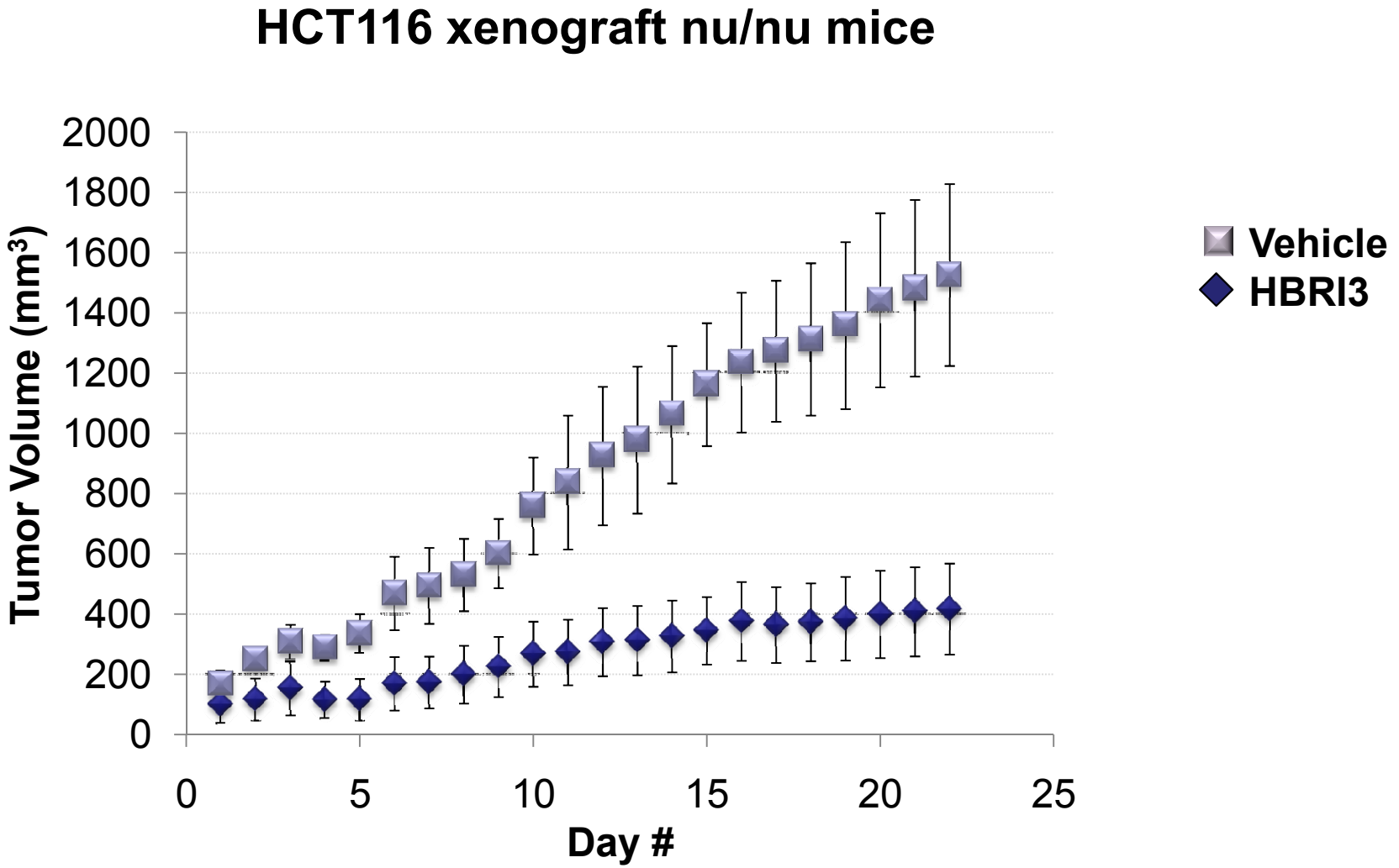
HBRI1
(original hit)

HBRI3
(the lead)



- **HBRI3** decreased PC3 tumor size in 80% of animals

Colon Cancer Xenograft Study in Mice



Summary

- **HBRI3 is a novel anti-cancer agent widely useful against a number of cancers**

- In the presence of other anti-cancer drugs, HBRI3 may be useful as a synergist to increase the potency and decrease the toxicity or off-target action of anti-cancer drugs.

- HBRI3 appears to work on cycling cells such as cancer cells and does not appear to affect normal cells, hence the non-toxicity.

- HBRI3 may be useful for hypoxic tumors (solid tumors)

Acknowledgements

- John Cashman Ph.D., HBRI and CR
- Mark Mercola Ph.D., Sanford-Burnham (SB) and CR
- Chemists
  - Karl Okolotowicz Ph.D., HBRI and CR
  - Dennis Schade Ph.D., HBRI, SB, and CR
  - Daniel Ryan, HBRI and CR
- Biologists
  - Masanao Tsuda Ph.D., SB and CR
  - Mary Dwyer Ph.D., HBRI and CR
  - Erik Willems Ph.D., SB and CR
  - Sigeng Chen Ph.D., HBRI and CR