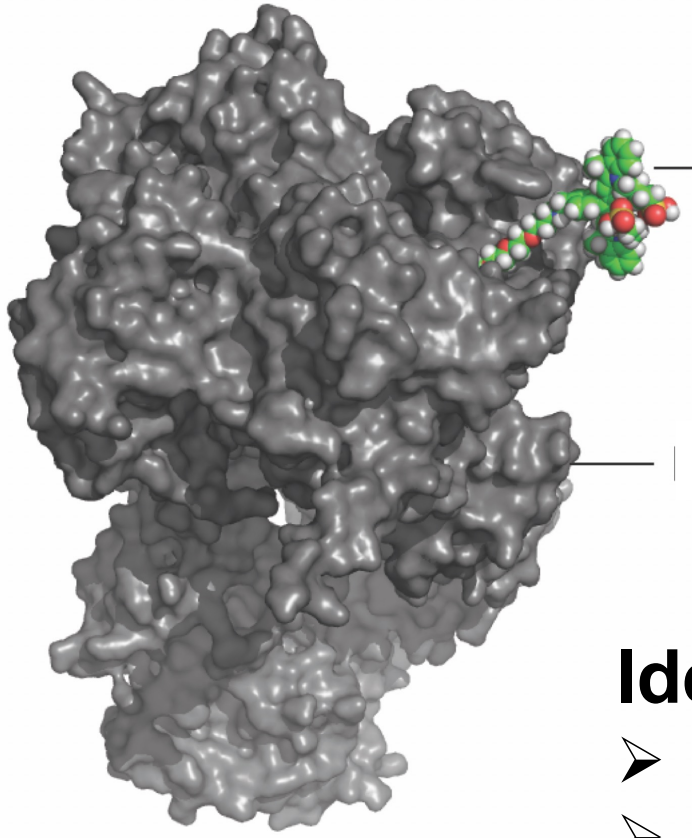
***Targeting the Chaperone Hsp90/HtpG as a theranostic strategy for cancer and infectious disease*.**

Timothy Haystead Ph.D.

Professor of Pharmacology and Cancer Biology Duke University.



Ideal theranostic

- High copy
- Enzymatically non-essential
- Trafficked through cell walls
- Disease specific expression cell surface

Drugs in clinical trials Haystead lab

SNX-5422 oral inhibitor of Hsp90

- Multiple Phase 1 solid tumor
- Progressed through Phase 2
- Approved for phase 3 registration trials 2019

HS-196 – novel imaging agent for the detection of metastatic disease (2017)

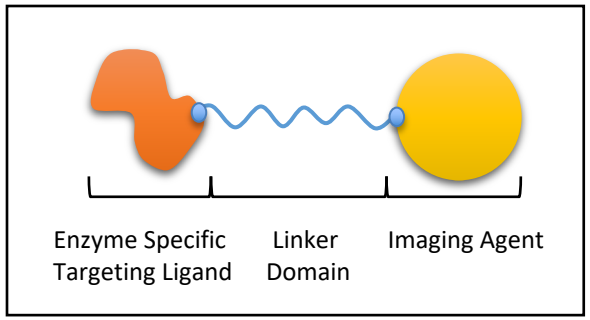
https://clinicaltrials.gov/ct2/show/NCT03333031

HS-201, an HSP90 Inhibitor-linked Verteporfin for Detection of Solid Malignancies (2019)

https://clinicaltrials.gov/ct2/show/NCT03906643

Serenex 2000 – 2008 Durham NC

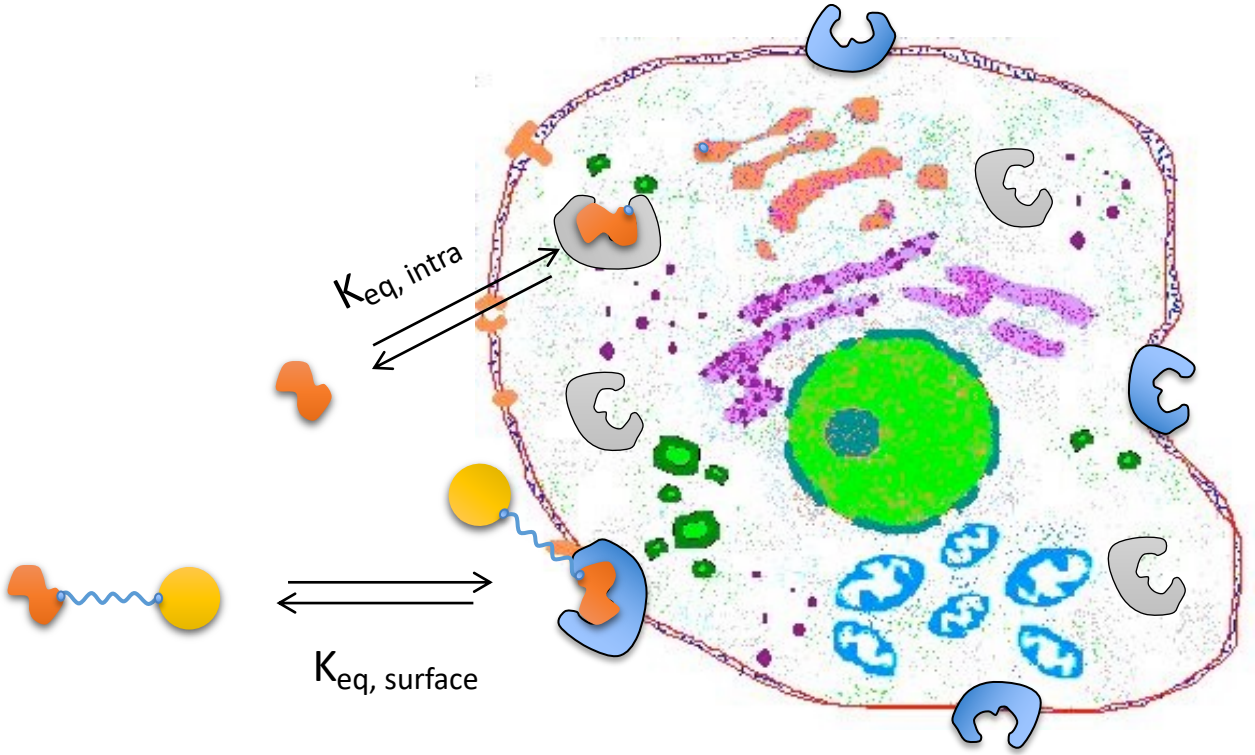
TARGETING PLASMA EXTRACELLULAR HSP90 WITH TETHERED INHIBITORS



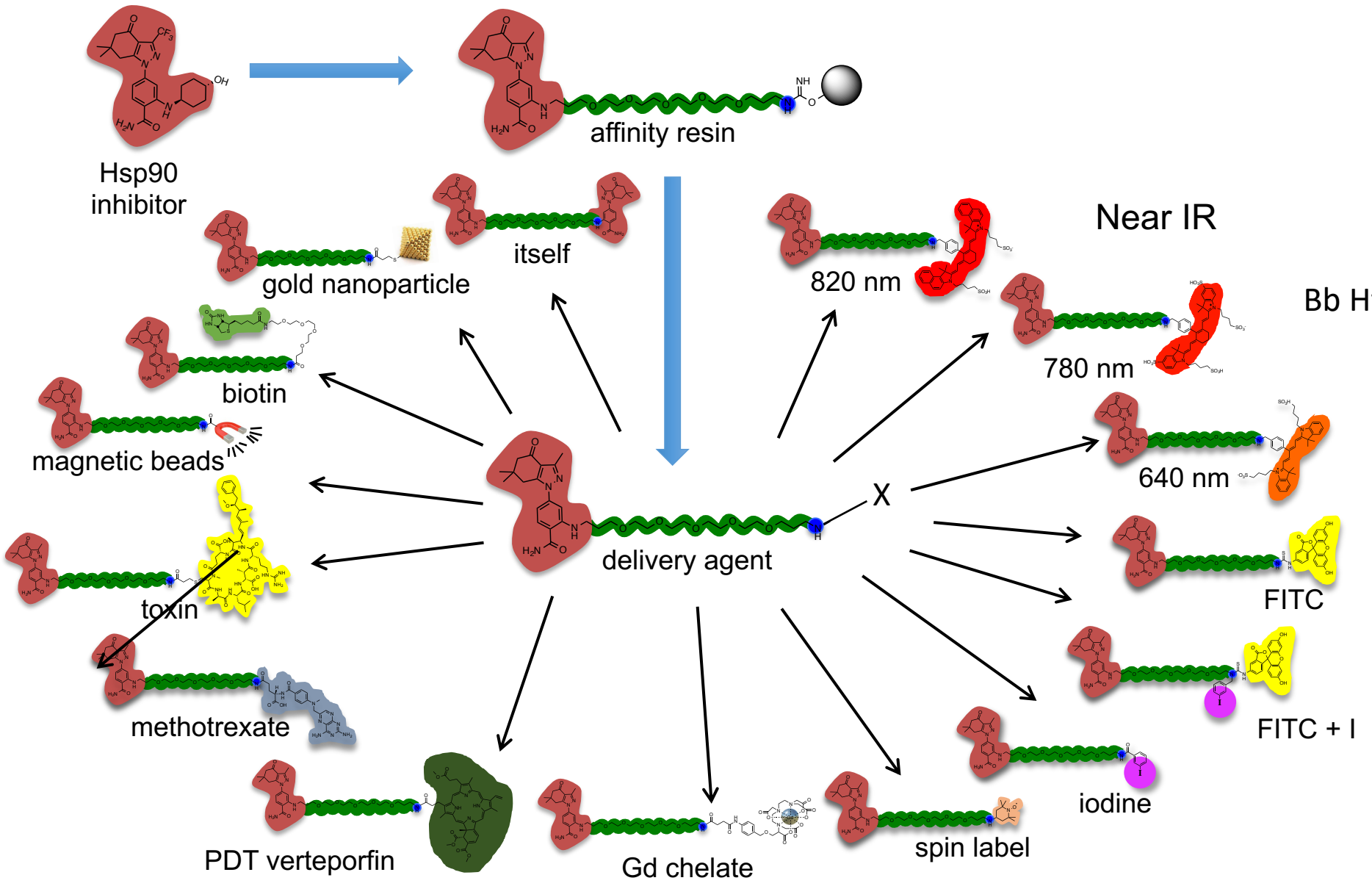
Ectopic Hsp90

- Associated with malignancy
- Antibodies to Hsp90 block migration

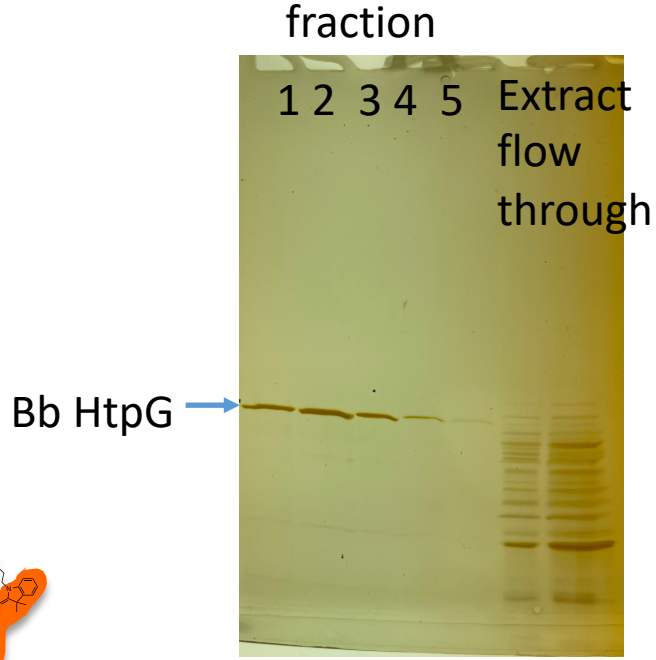
Tsutsumi S, Neckers L. Extracellular heat shock protein 90: a role for a molecular chaperone in cell motility and cancer metastasis. Cancer Sci. 2007;98(10):1536-9.



CHEMISTRY PLATFORM



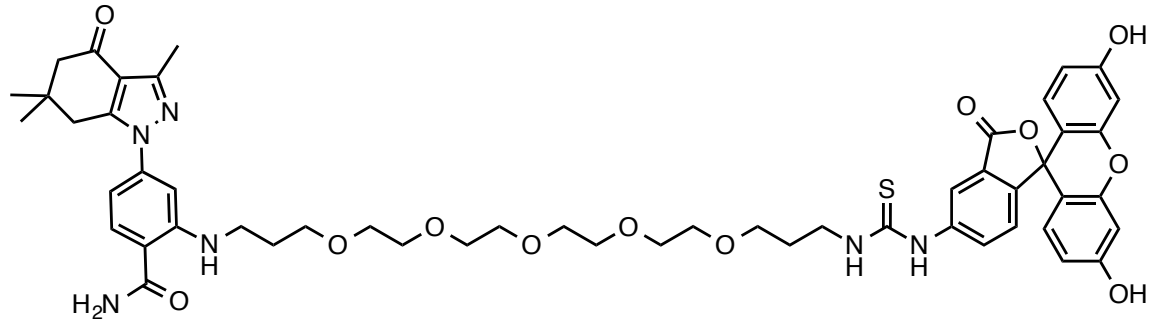
BX-2819 affinity resin

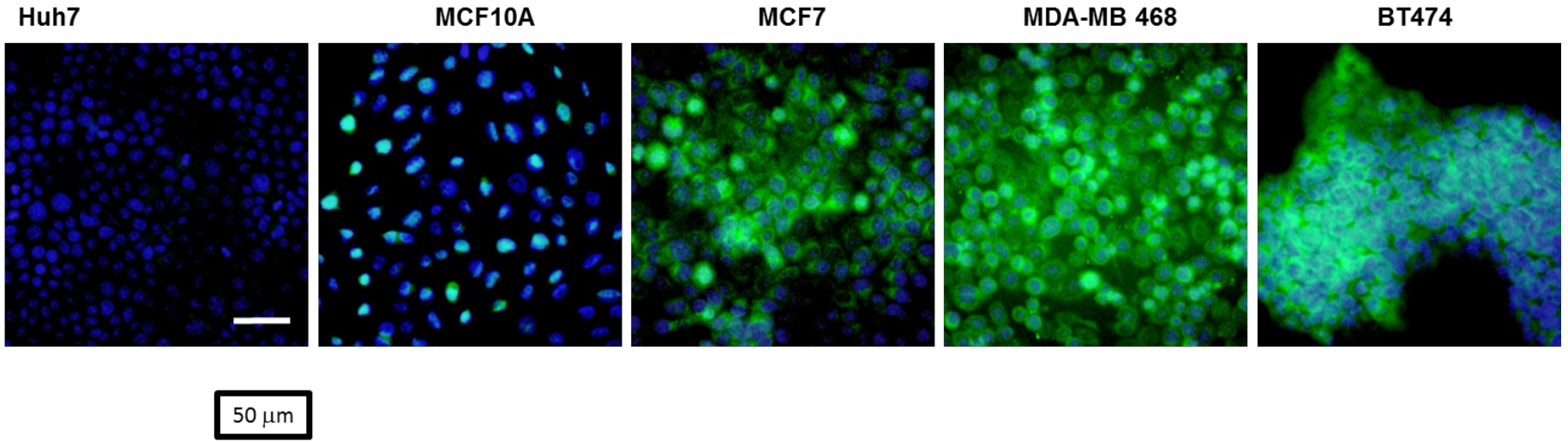


Fluor-tethered Hsp90 Inhibitors Discriminate Various Tumor Lines

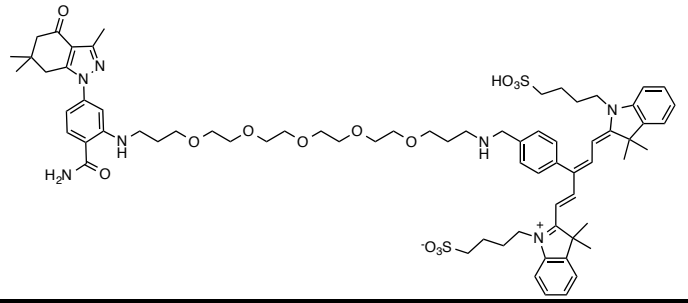
Jarred Barrott (*Cell Chem Bio. 2013*).

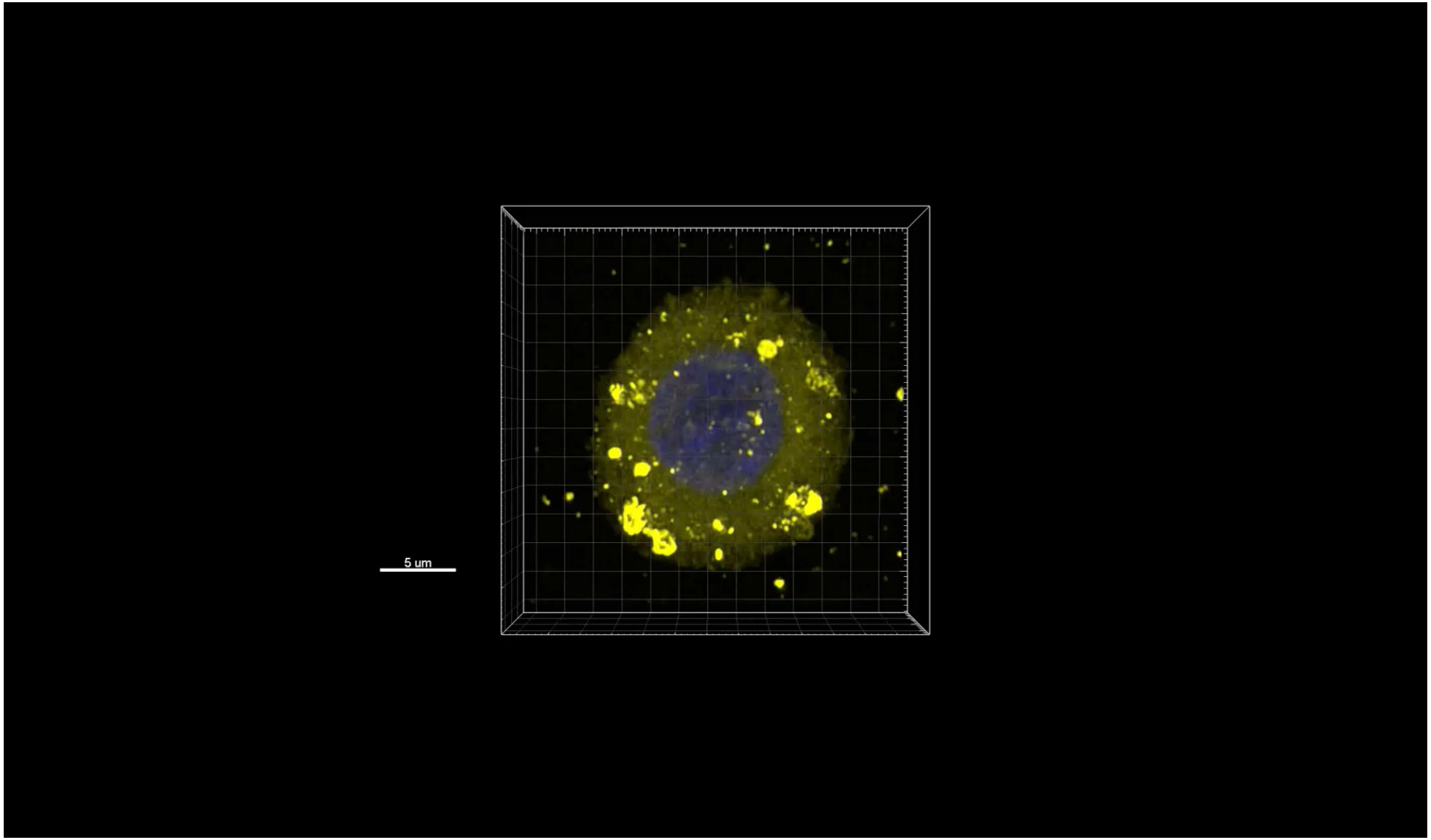
HS-27





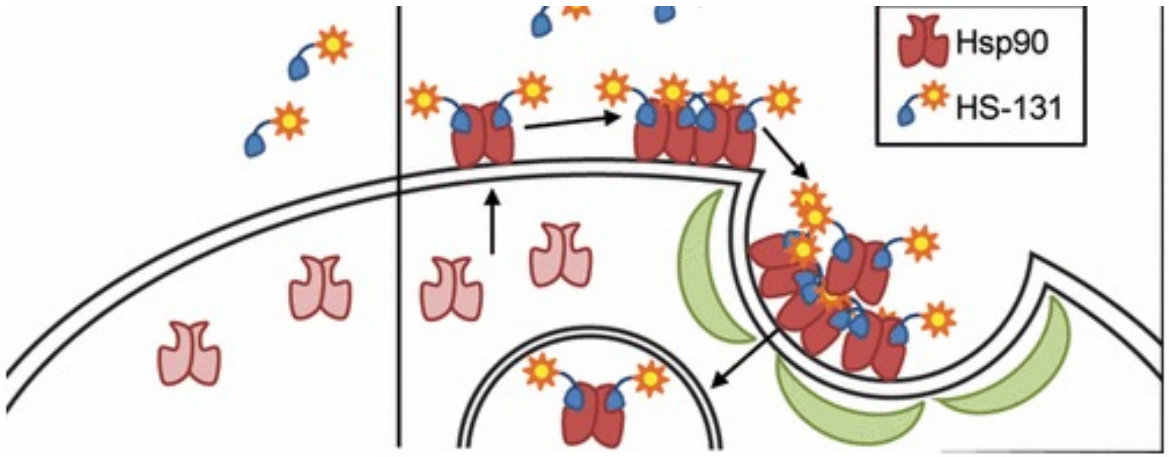
Video shows 3D confocal analysis of HS-131 uptake BT474 and then MDA-MB 468 cells





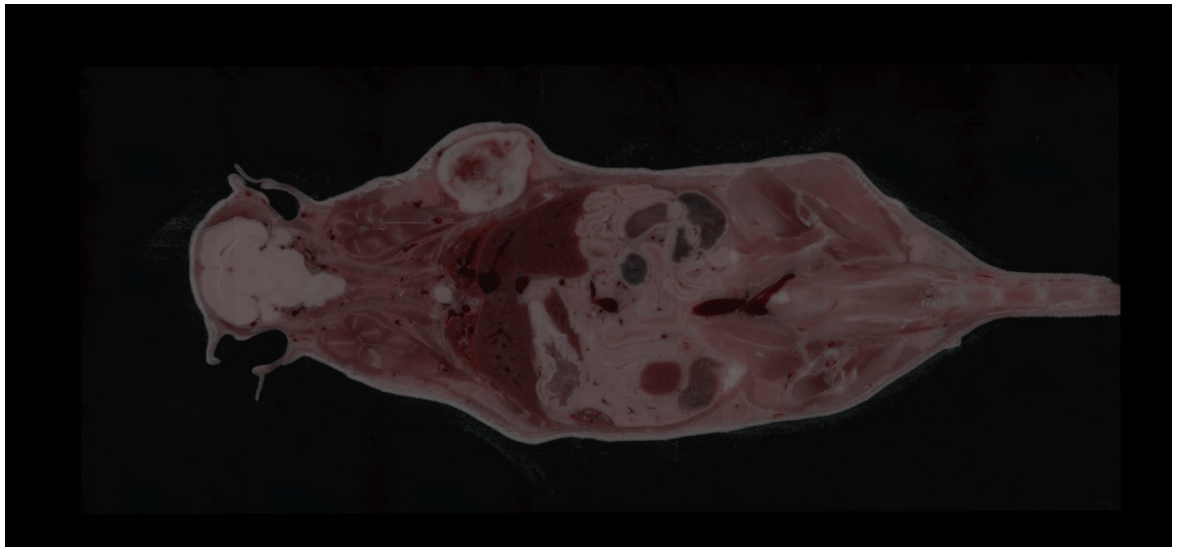
Normal cells

Tumor cells

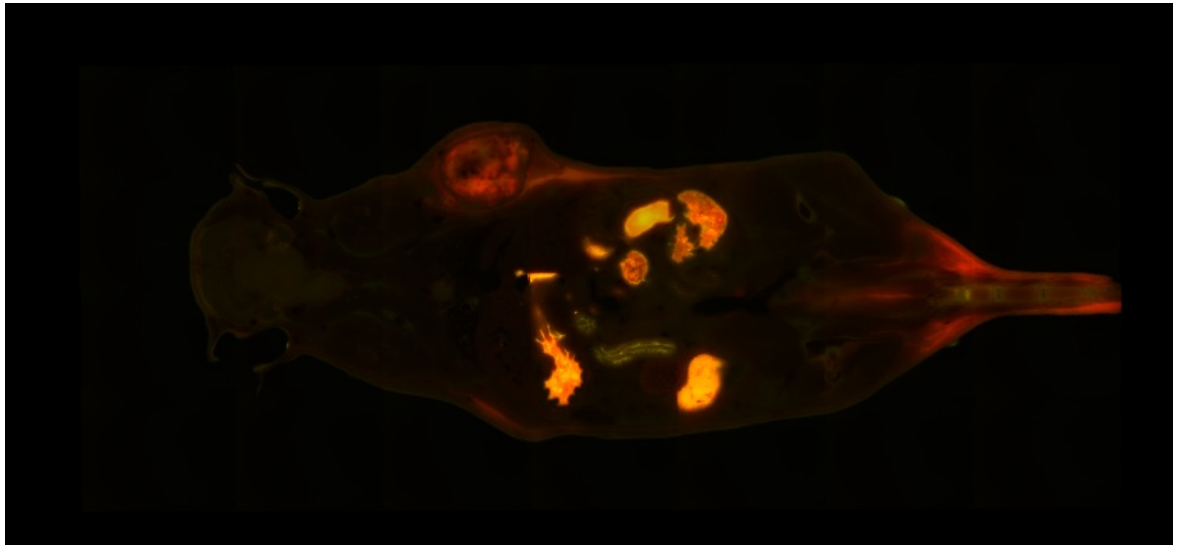


Bright field and fluorescence (em640nm) cryo-sectioned mouse bearing flank tumor

Brightfield

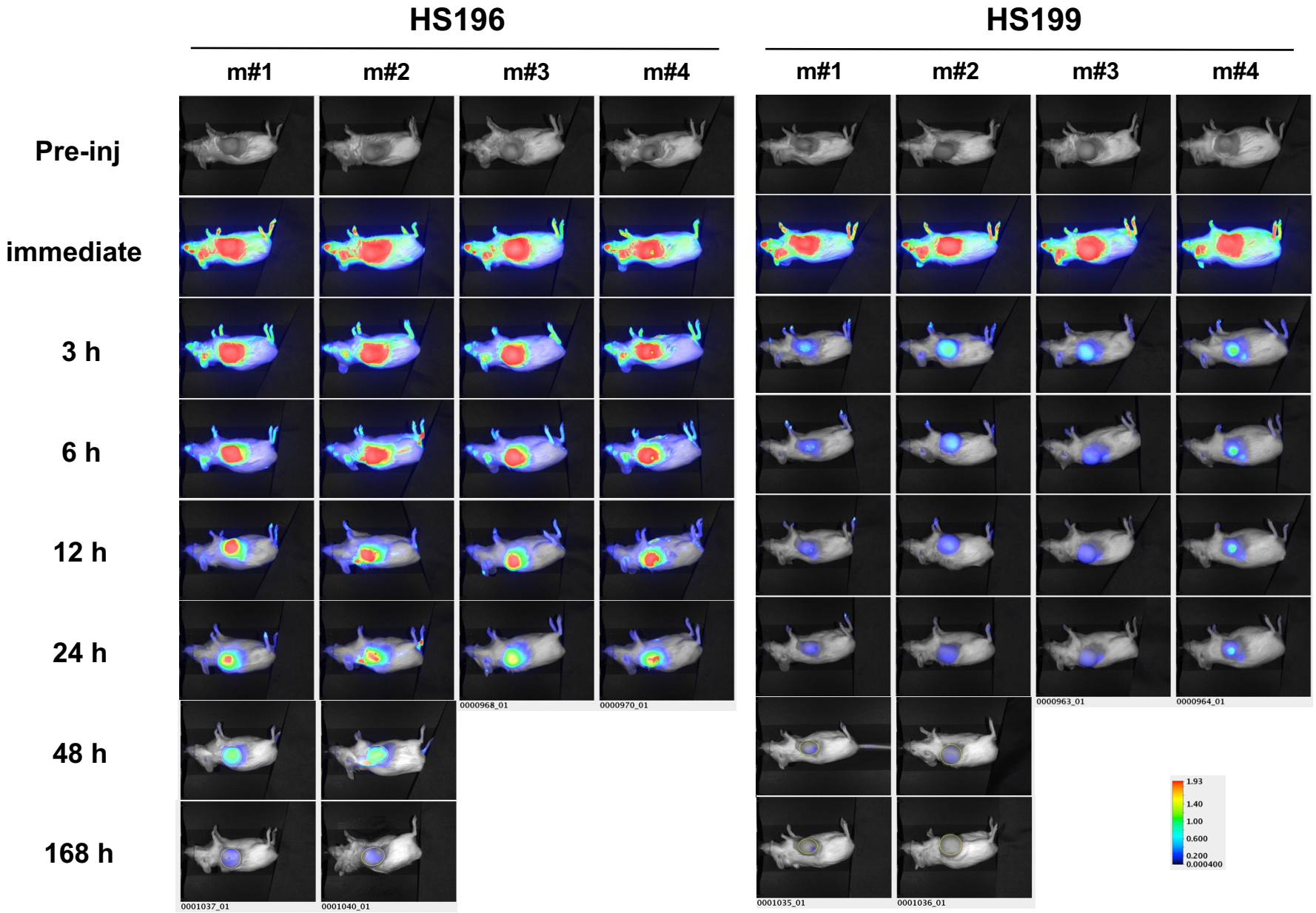


Fluorescence (exp = 2000 ms)

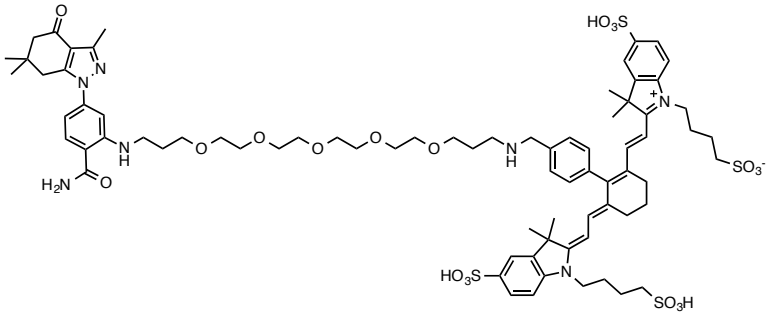


MDA-MB-231 Tumor Imaging with nIR-Hsp90 Inhibitor: HS196 vs. HS199

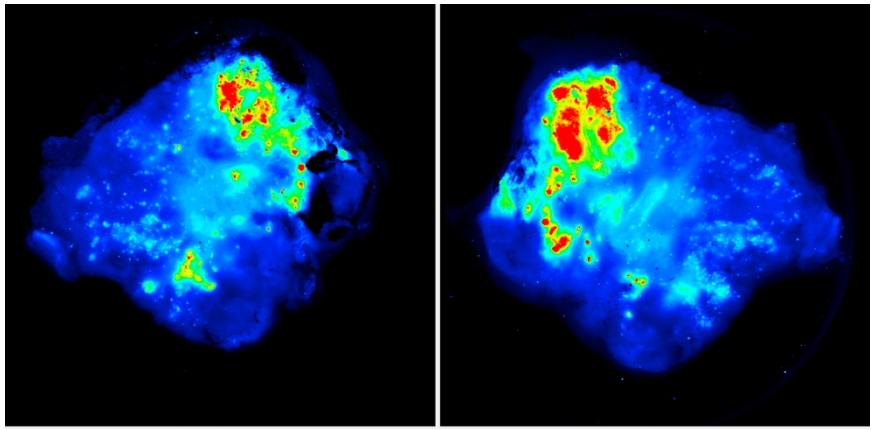
Images provided by Takuya Osada Duke University)



Images of a patient prostate tumor administered 2 mg HS-196

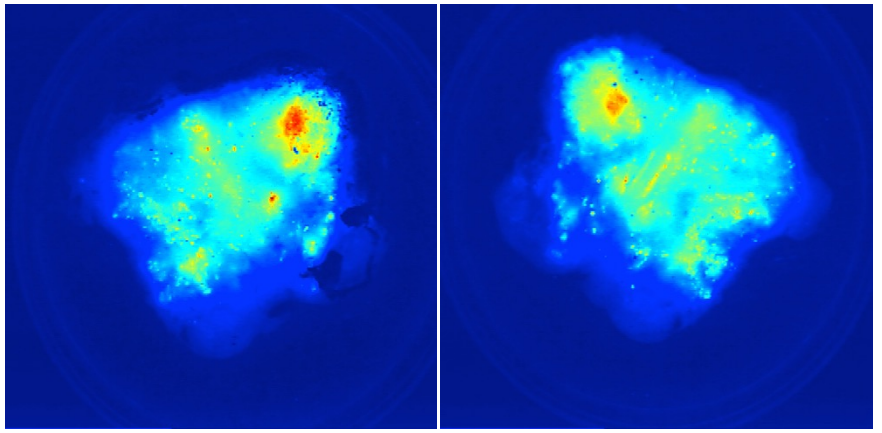


Side 1 | Side 2



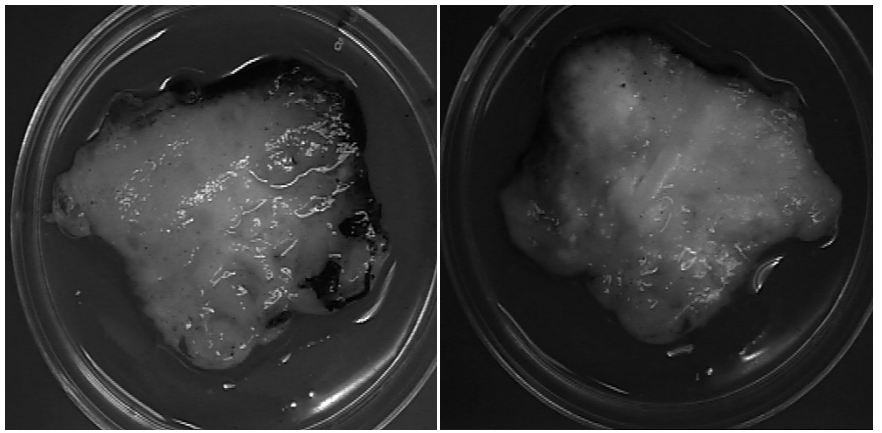
LI-COR Pearl

Image analyzed by
Image Studio software



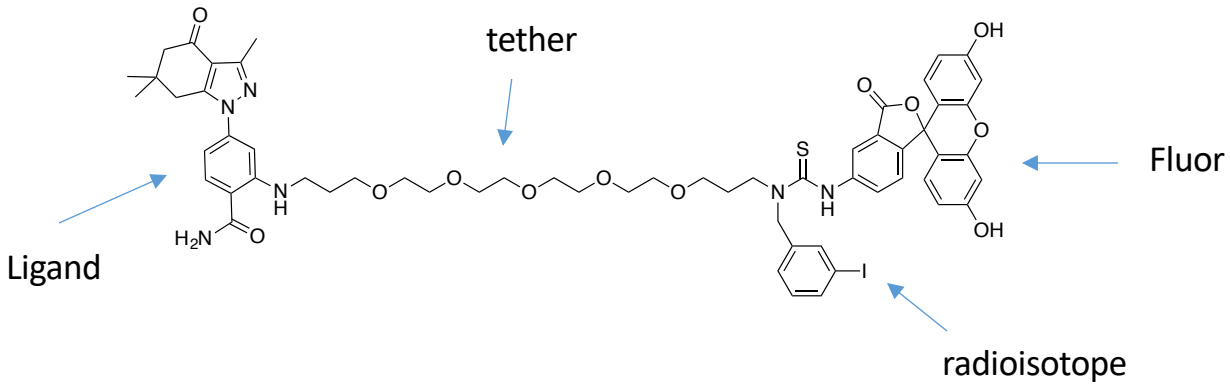
FLUOBEAM

Image analyzed by
Image J software

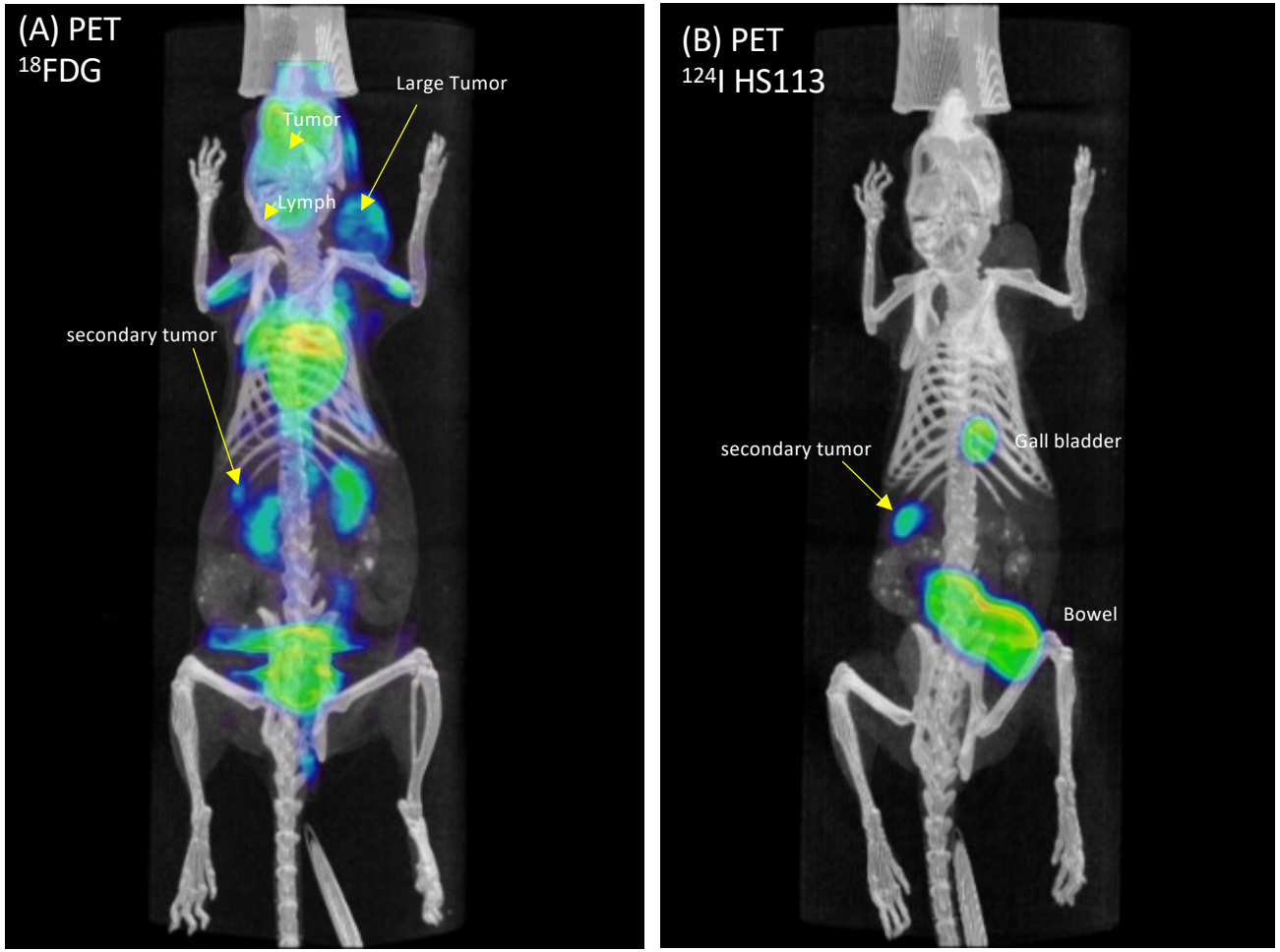


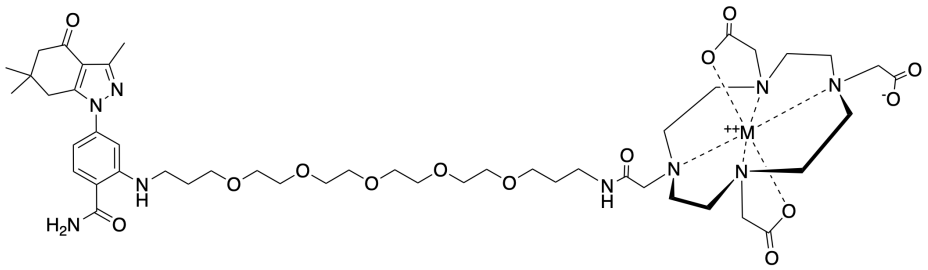
Photograph

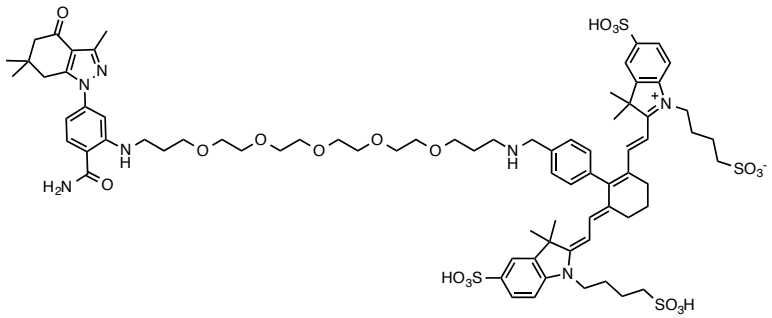
Structure of HS-113, fluorophore - a PET enabled Hsp90 inhibitor.



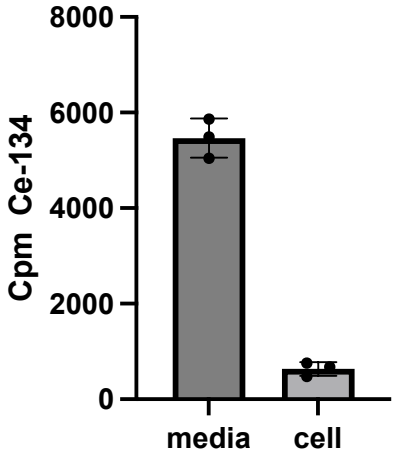
PET images comparing the biodistribution ^{18}FDG and ^{124}I labeled HS-113 in the MMTV model of HER2+ breast cancer.

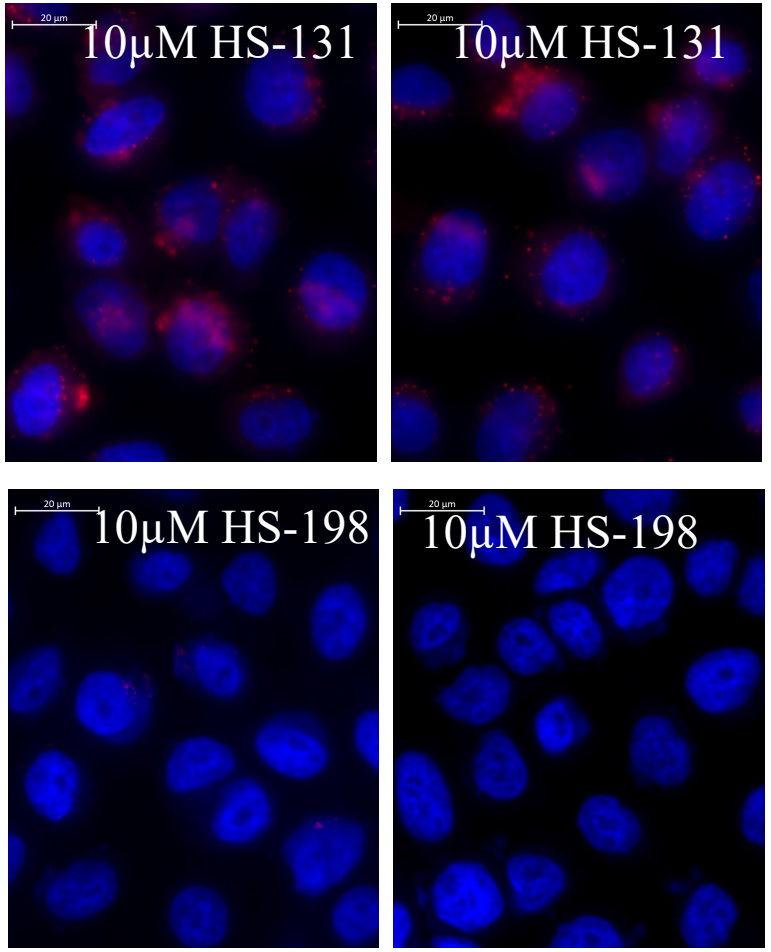




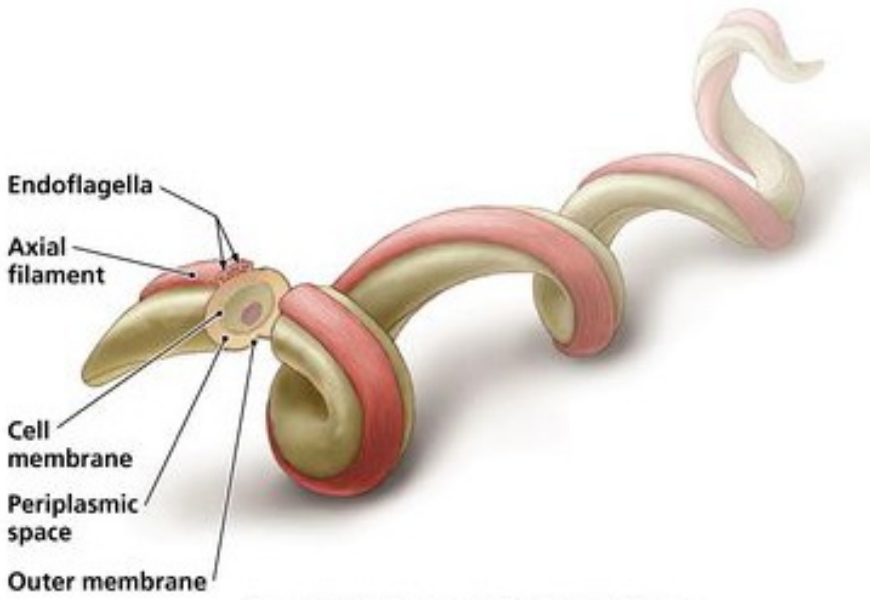


Uptake DOTA-Tethered Hsp90 inhibitor into MDA-231 cells

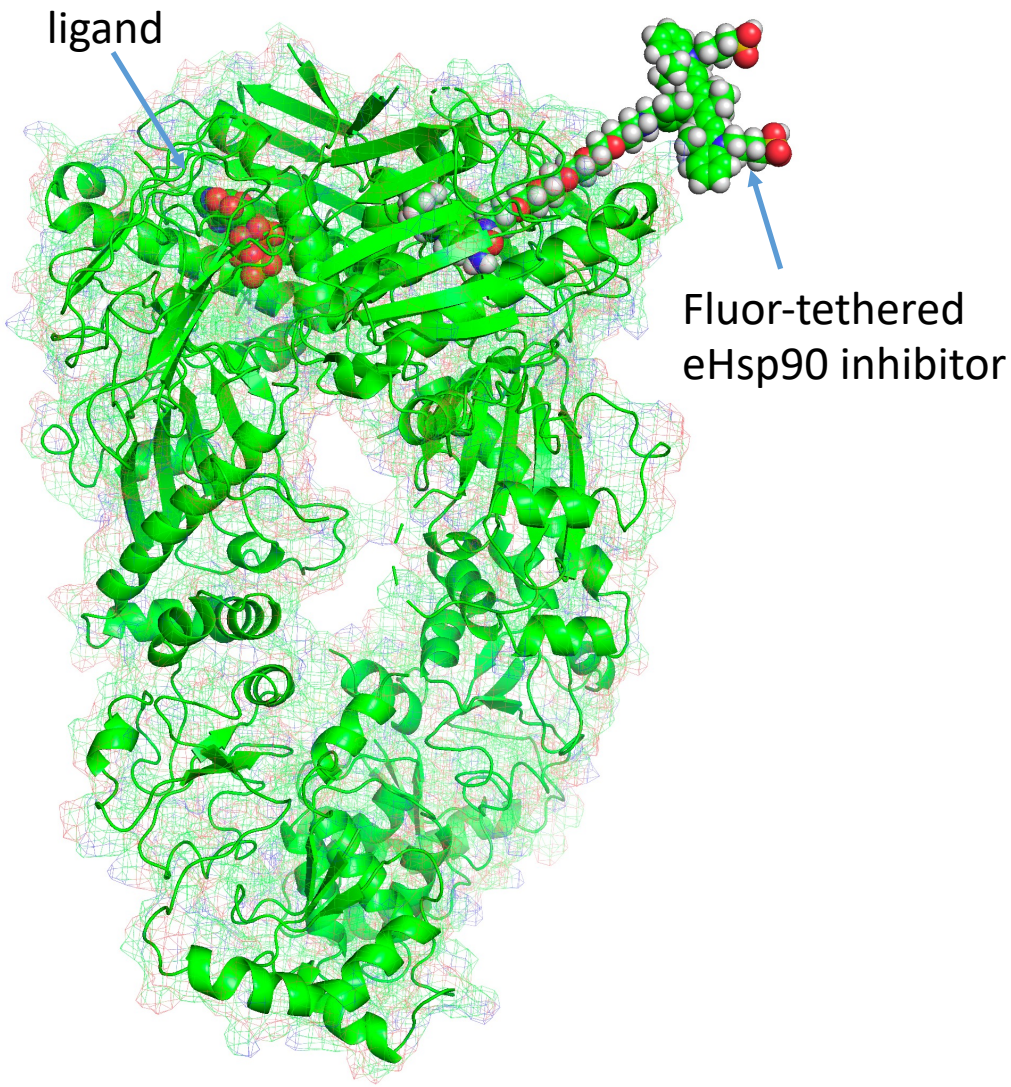




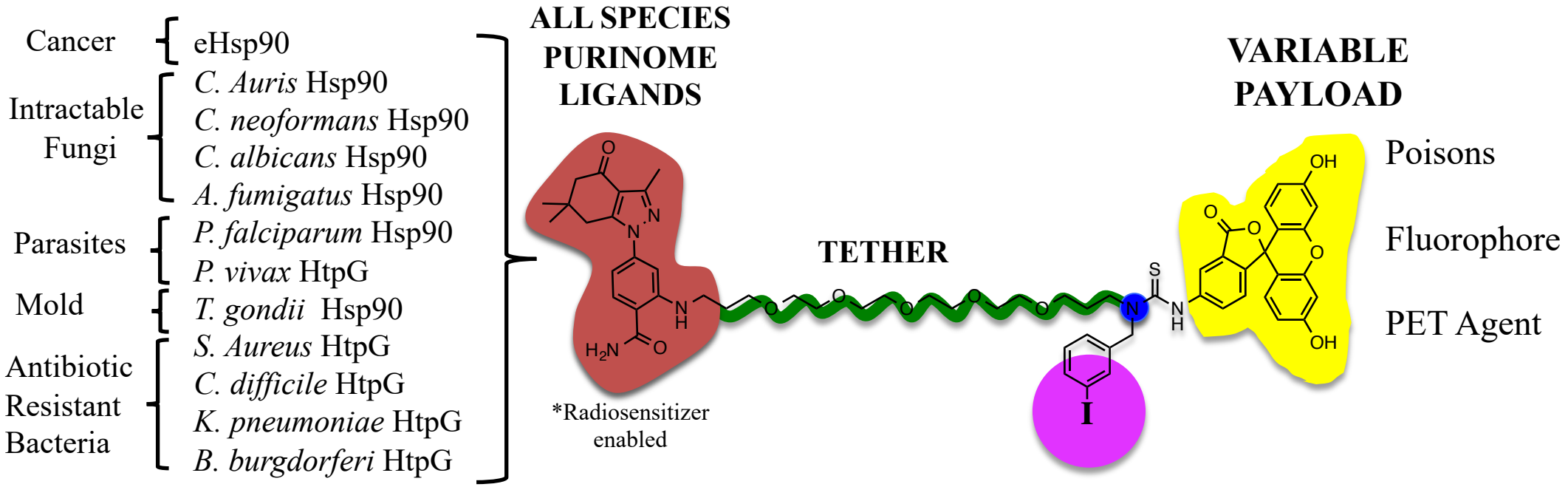
Targeting Borrelia HtpG

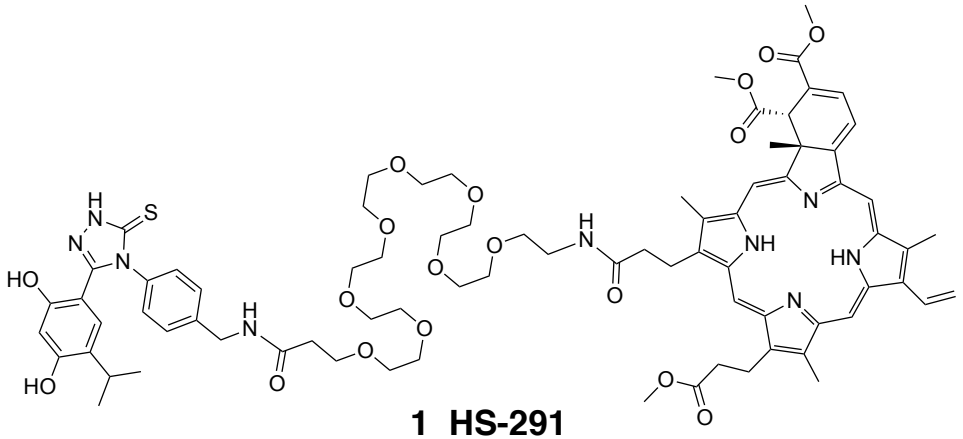


Carlson et al. Cell Chem Bio 2023 in press



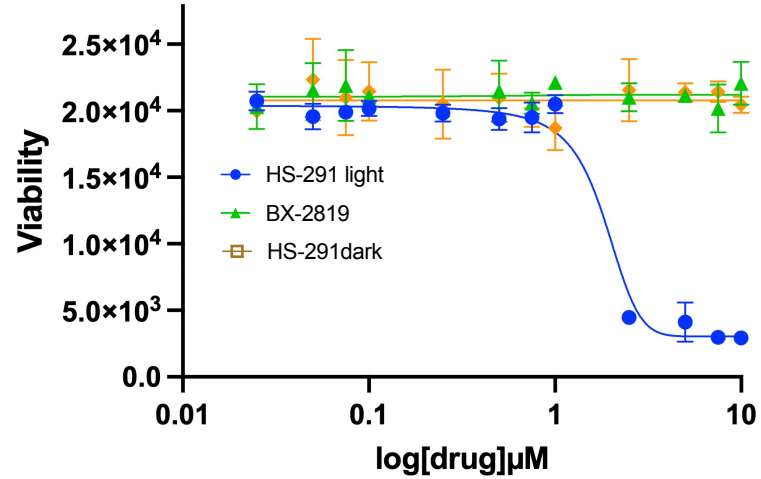
Molecular model of tethered inhibitor bound to Hsp90.


Cancer
eHsp90
Intractable Fungi
C. Auris Hsp90
C. neoformans Hsp90
C. albicans Hsp90
A. fumigatus Hsp90
Parasites
P. falciparum Hsp90
P. vivax HtpG
Mold
T. gondii Hsp90
Antibiotic Resistant Bacteria
S. Aureus HtpG
C. difficile HtpG
K. pneumoniae HtpG
B. burgdorferi HtpG
ALL SPECIES PURINOME LIGANDS
*Radiosensitizer enabled
TETHER
I
VARIABLE PAYLOAD
Poisons
Fluorophore
PET Agent

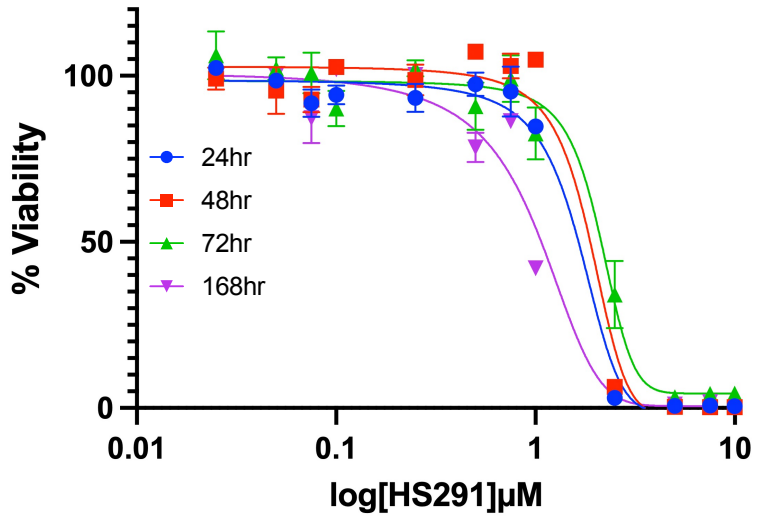


1 HS-291

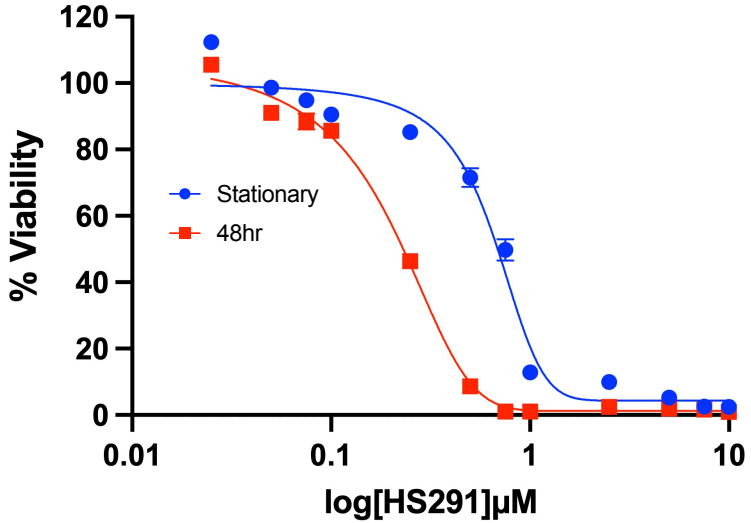
A. HS-291 ± light (670nm) and BX-2819 stationary phase 24hr.

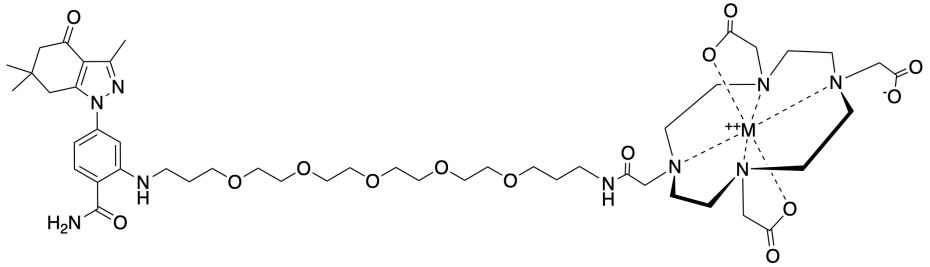


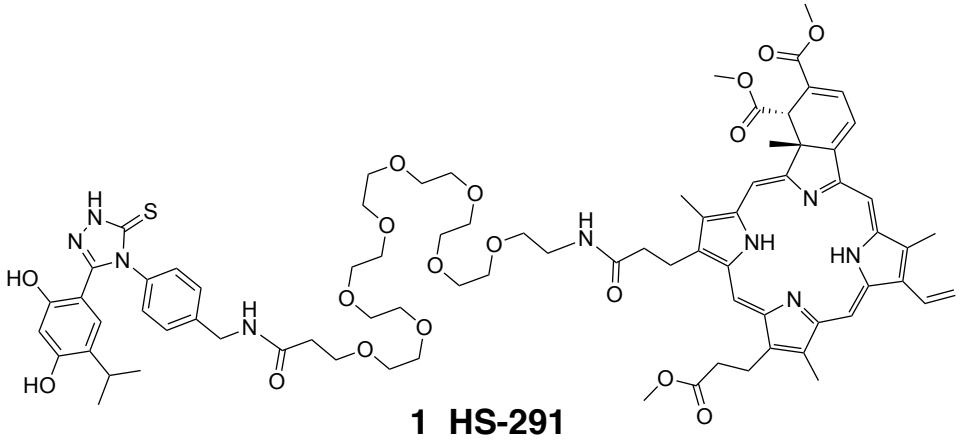
B. HS-291 post light (670nm) log phase 24 to 168hr



C. *Bb* Strain 5297 HS291.

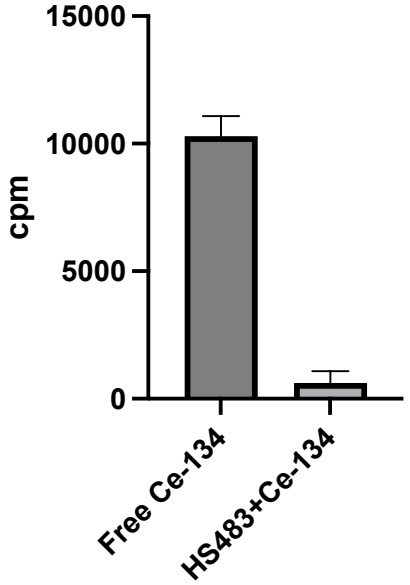




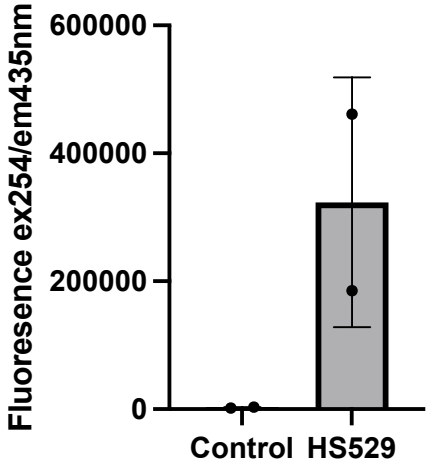


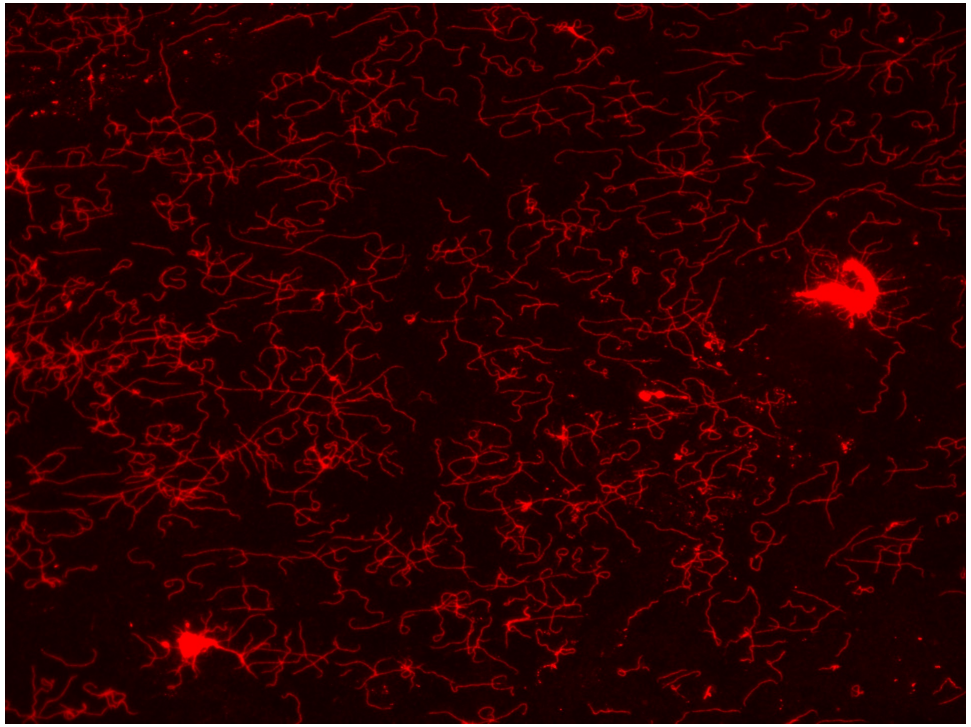
1 HS-291

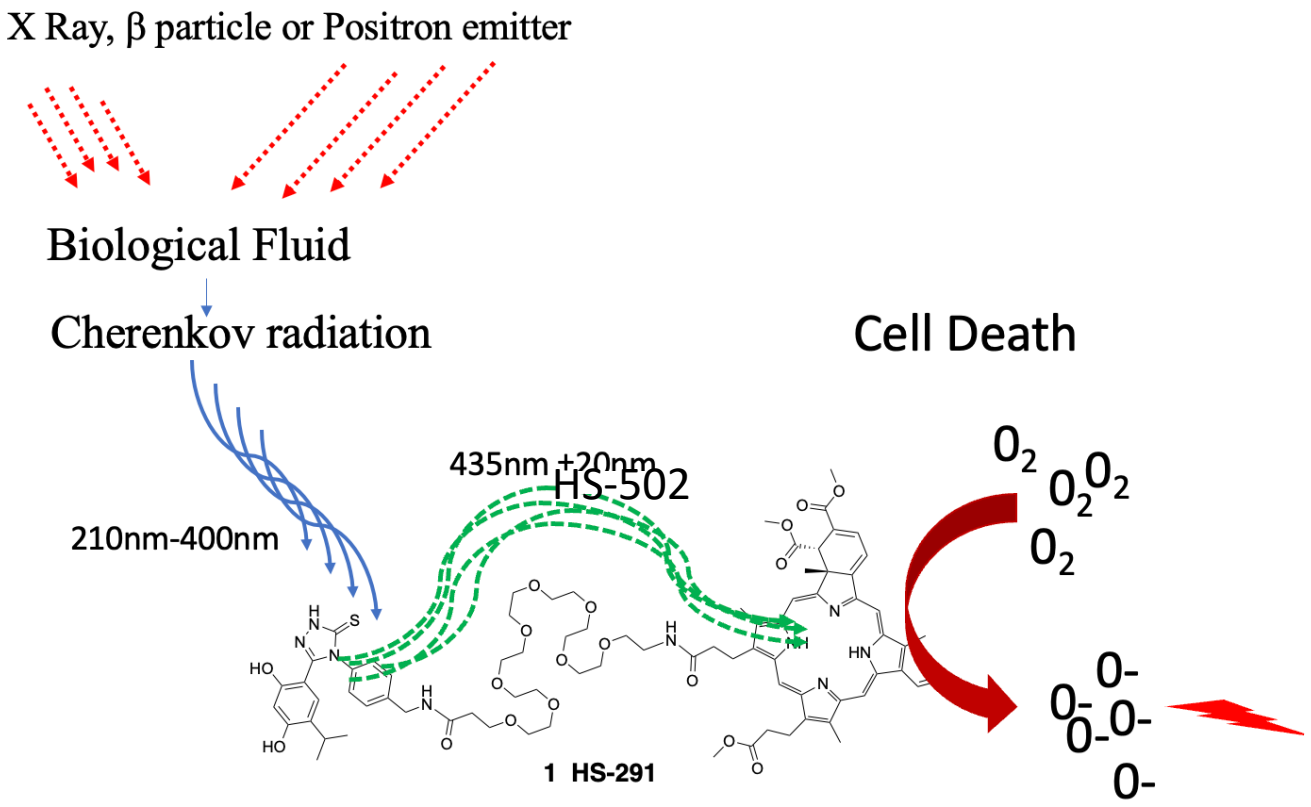
Uptake of HS483 into B31 Bb

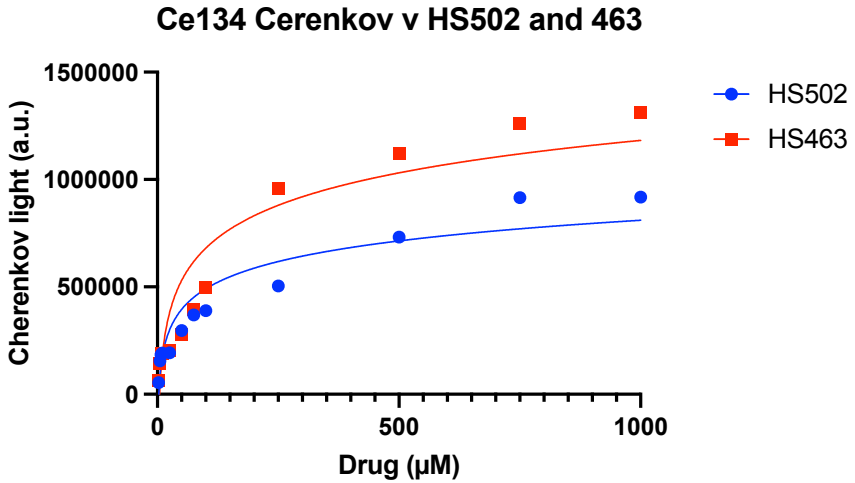


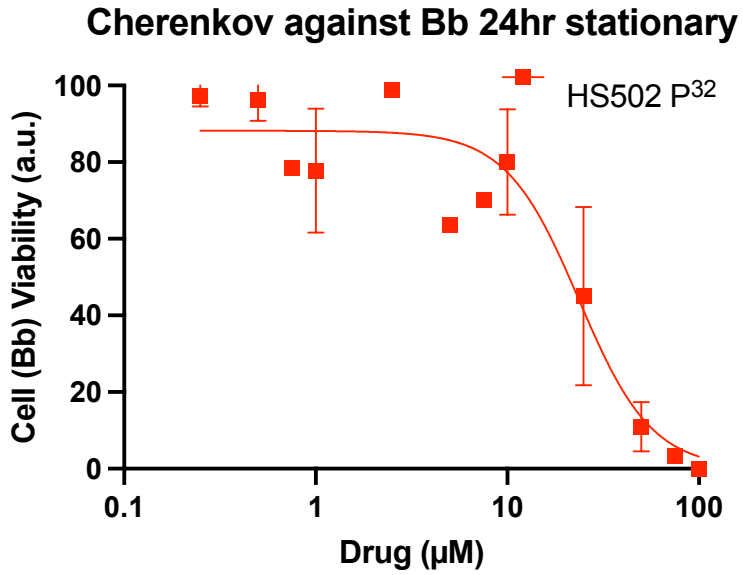
Uptake 10μM HS529 Cu chelate into Bb






X Ray, β particle or Positron emitter
Biological Fluid
Cherenkov radiation
Cell Death
435nm +20nm
HS-502
210nm-400nm
1 HS-291


Ce134 Cerenkov v HS502 and 463
Cherenkov light (a.u.)
1500000
1000000
500000
0
0
500
1000
Drug (μM)
HS502
HS463


Cherenkov against Bb 24hr stationary
Cell (Bb) Viability (a.u.)
100
80
60
40
20
0
0.1
1
10
100
Drug (μM)
HS502 P32

ACKNOWLEDGEMENTS

Haystead Lab (Duke)
Philip Hughes
David Carlson
David Alcorta
David Gooden
Khaldon Bodoor
Lauren Crowe
Jared Barrott
David Loiselle
Isaac Lutz
Kelly Yang
Lucas Dingman
Sawyer Lyons
Zoe Dingman
MaryBeth Nedrud

Neil Spector

Collaborators.
UNC
Matt Redinbo
Hong Yuan

Tulane
Monica Embers

Stanford
Christine Jacobs Wagner

Duke
Kim Lyerly
Takuya Osada

U. Delaware (TEM/Storm)
Shannon Modla
Jean Ross
Jeff Caplan

UC Davis
Emir Hodzic

Funding.

NIH
DOD
Openphilanthropy.org
Cohen Foundation
Bill & Marian Cook Foundation
Bay Area Lyme
OpenPhilantropy