

Stage IV Summit 2026: Featured Research



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***Experimental MDM2/X Inhibitors in Combination
with CXCR4 Inhibitors Decrease Metastasis in
Mouse Models of Triple Negative Breast Cancer***

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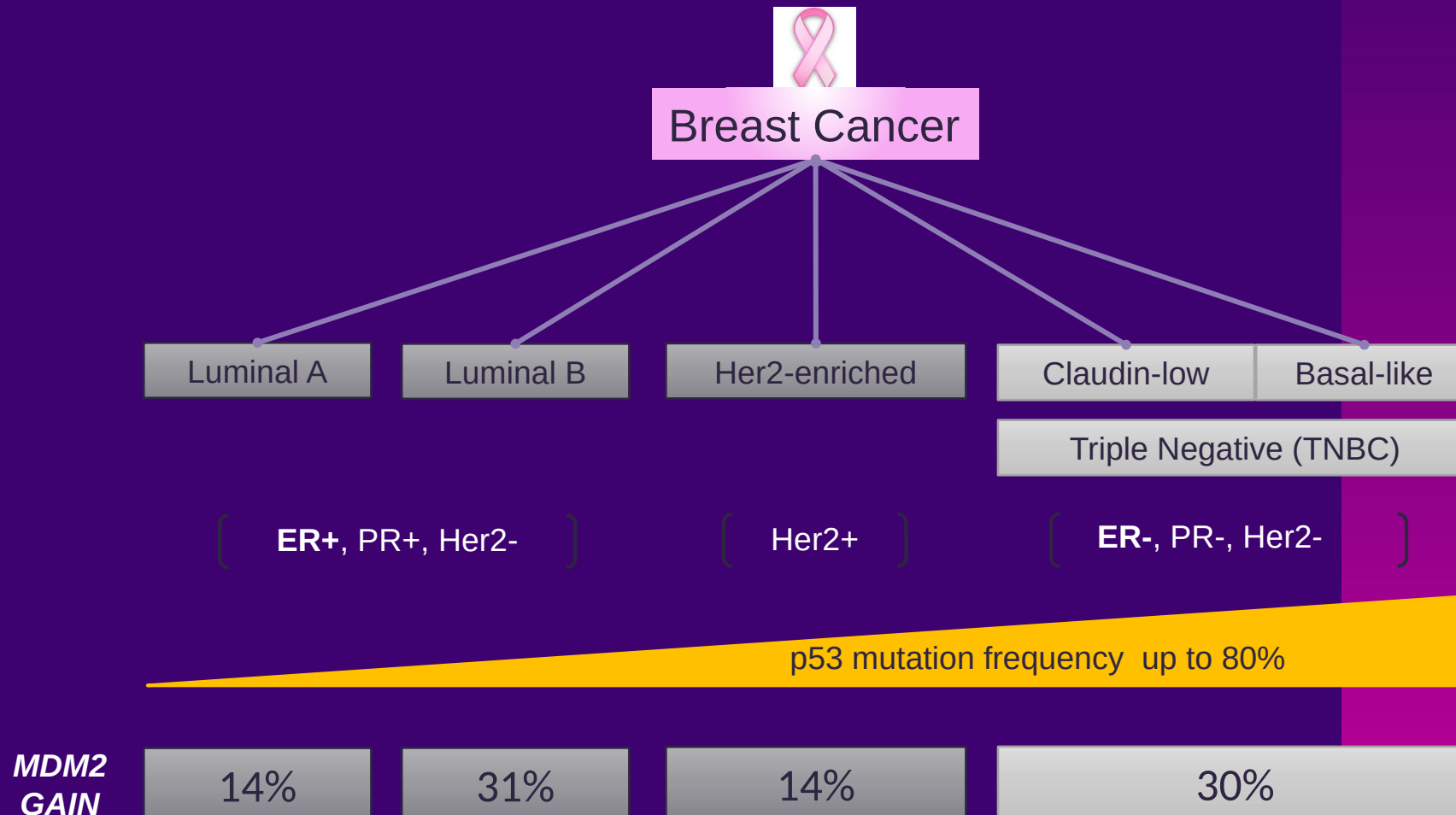
Jill Bargonetti October 5, 2026



Stage IV Stampede & Summit 2026



There is a High p53 Mutation Frequency in Triple Negative Breast Cancers



Adapted From Cancer Genome Atlas, N. (2012).
Comprehensive molecular portraits of human breast tumours.
Nature 490, 61-70.

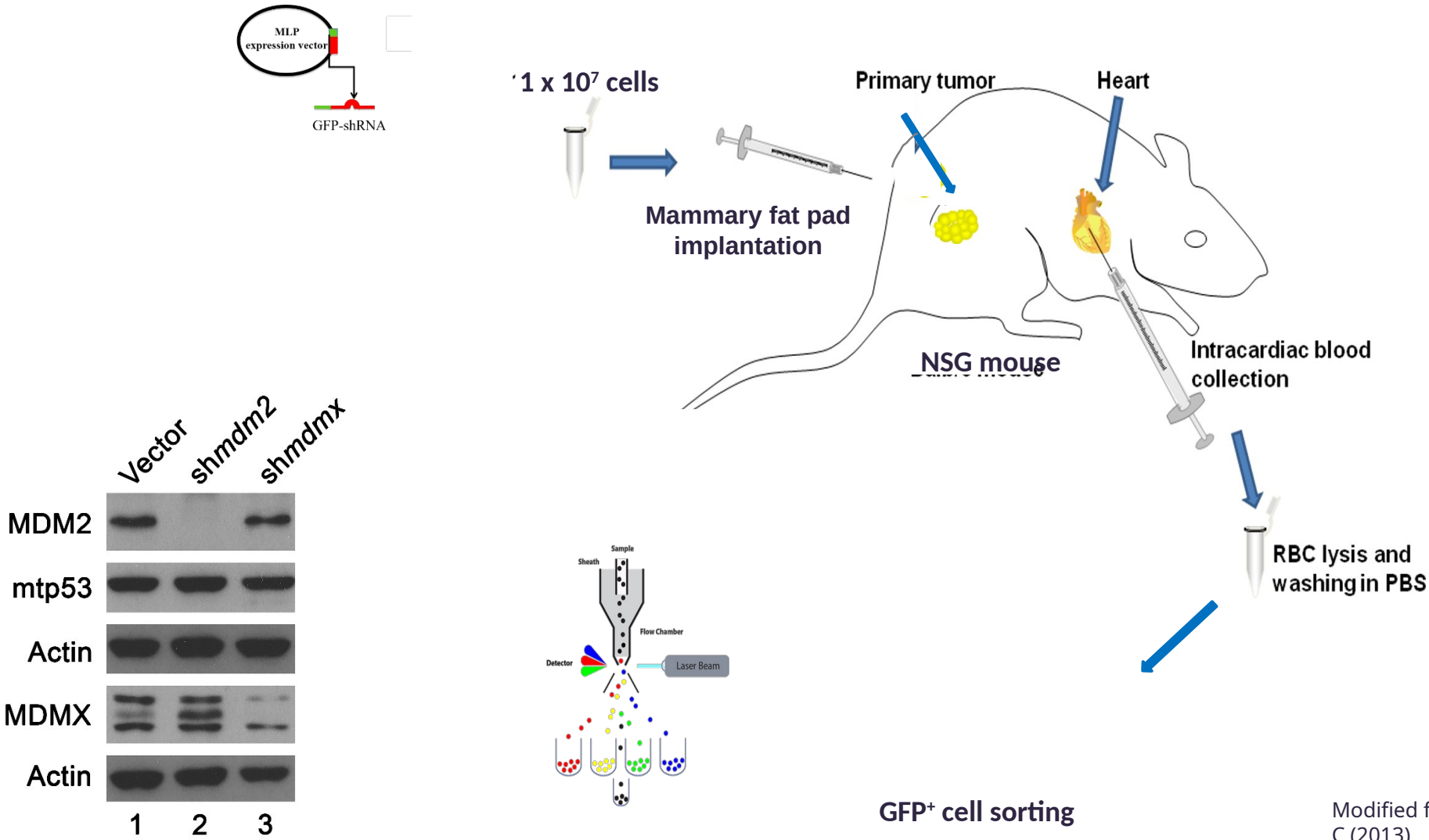
Mutant p53 Drives Triple Negative Breast Cancer

Subtype	Luminal A	Luminal B	Basal like	Her2E
ER+ (%)	87	82	10	20
HER2+ (%)	7	15	2	68
TNBCs (%)	2	1	80	9
Gain of MDM2 (%)	14%	31%	14%	30%
TP53 mut (%)	12%	32%	84%	75%

Adapted from Comprehensive molecular portraits of human breast tumours
The Cancer Genome Atlas Network
Nature 490, 61–70 (04 October 2012) doi:10.1038/nature11412

- Targets can be molecules in the driver pathways used by MDM2 proteins and mutant p53 (mtp53) proteins.
 - Our laboratory determines the oncogenic mtp53 pathways and the MDM2/MDMX pathways that work through targets other than inactivation of wild-type p53.
- We are targeting the alternative oncogenic pathways of mtp53, MDM2 and MDMX (MDM4).

Methodology for investigating tumorigenesis and metastasis of 231 cells *in vivo*

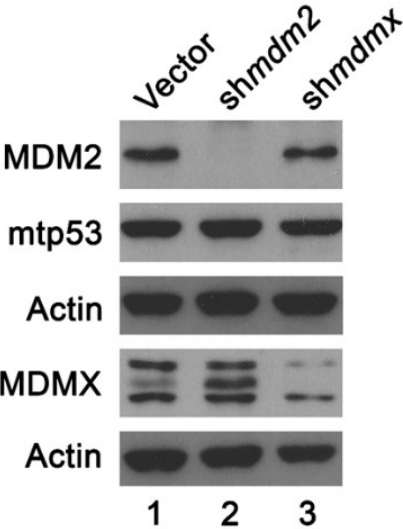


Modified from Ogunwobi OO, Puszyk W, Dong H-J, Liu C (2013)

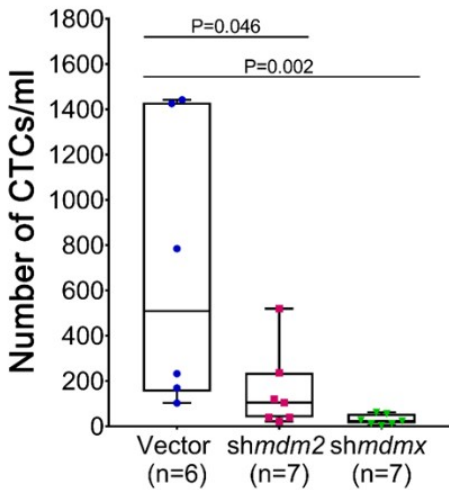
MDMX and MDM2 knockdown in MDA-MB-231 orthotopic transplants

reduces CTCs

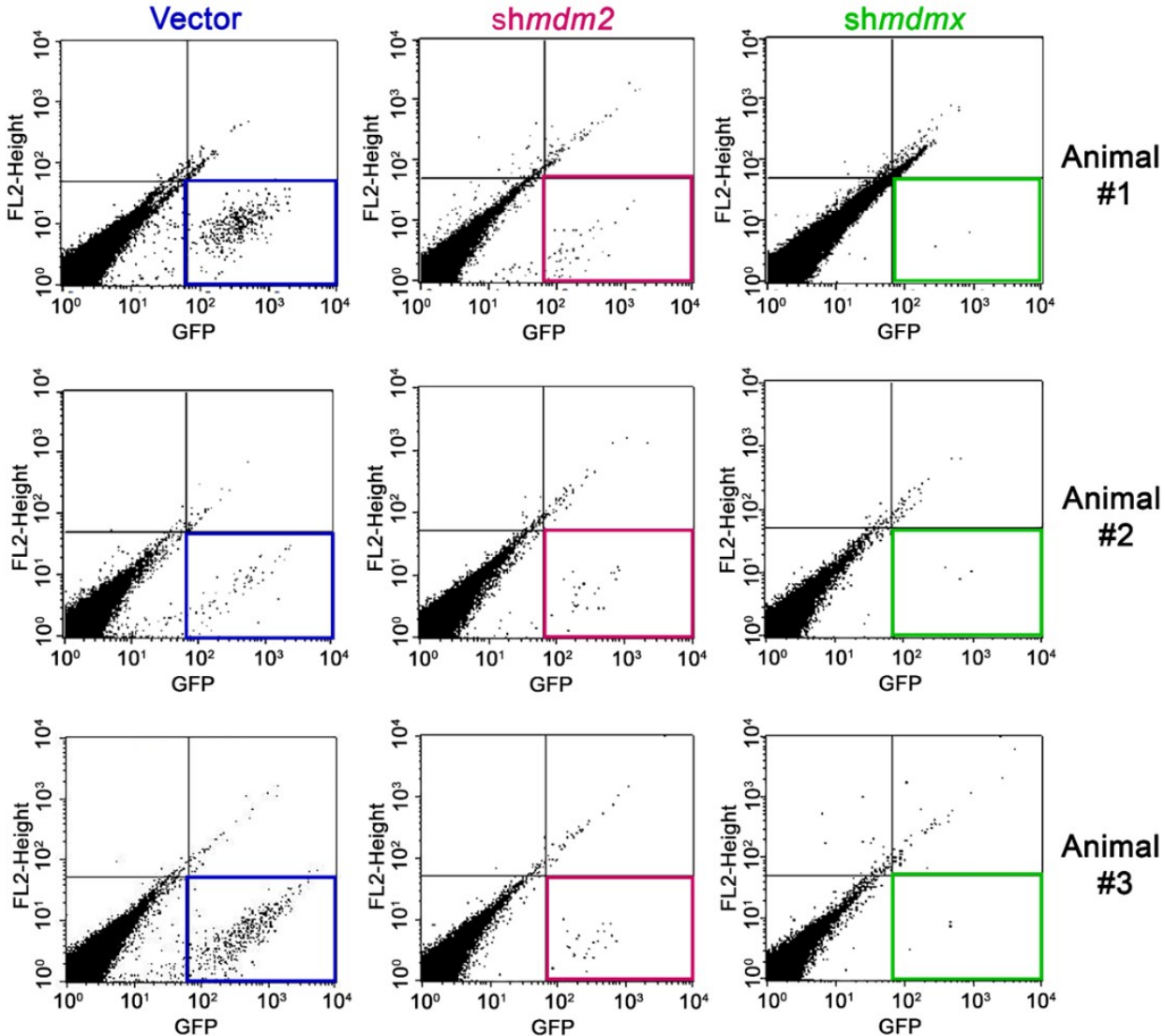
A



B



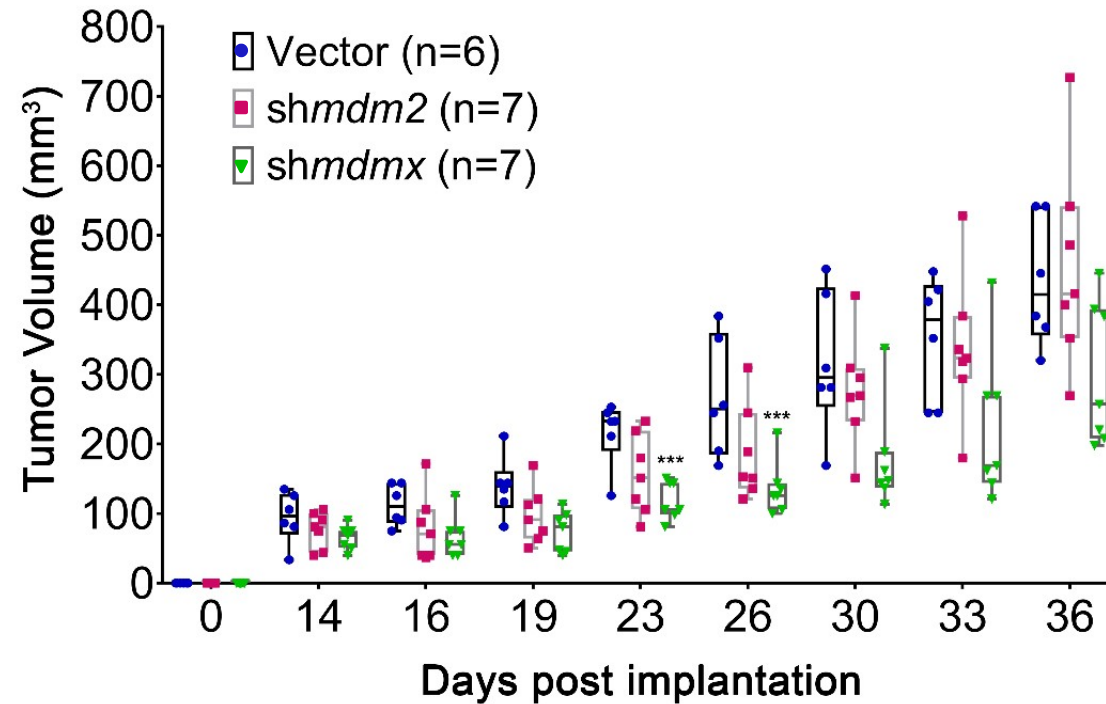
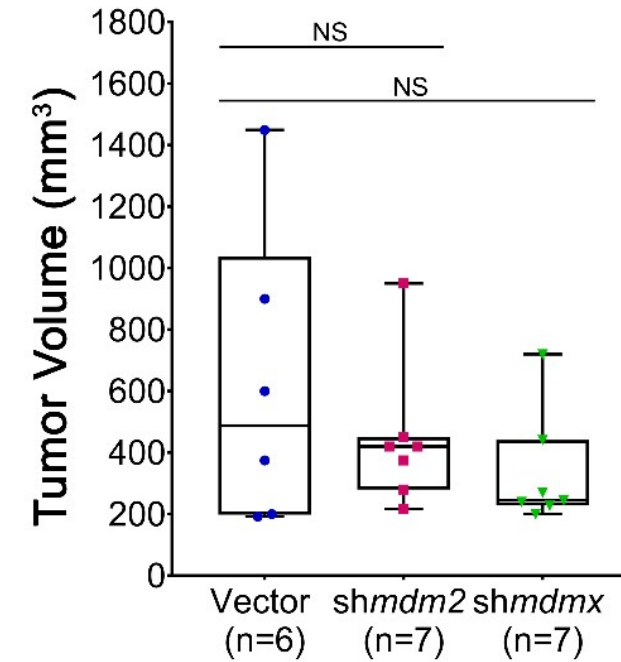
C



Chong Gao et. al. 2019

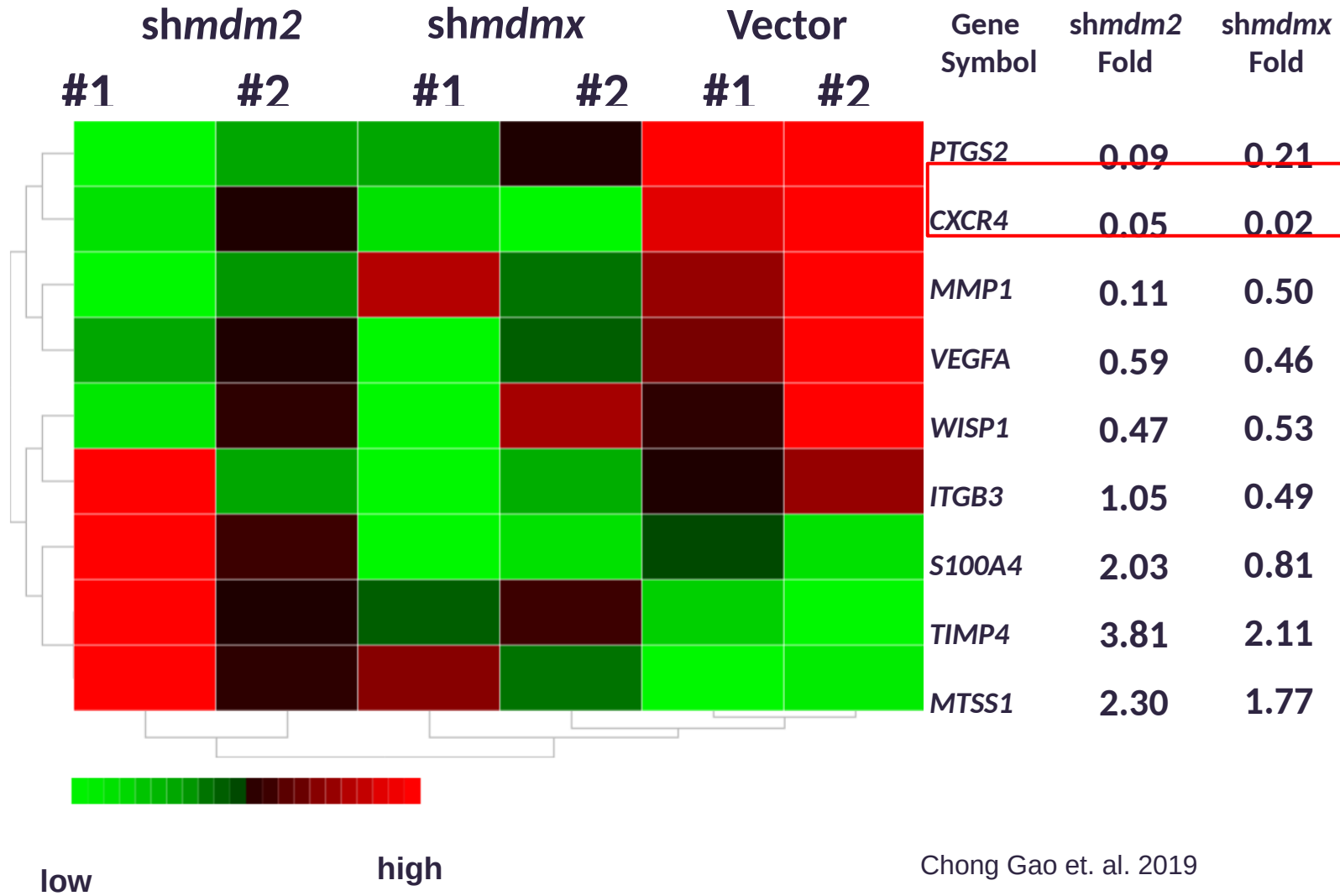


MDM2 and MDMX Knockdown did not show a Sustained Reduction of Primary Tumor Growth

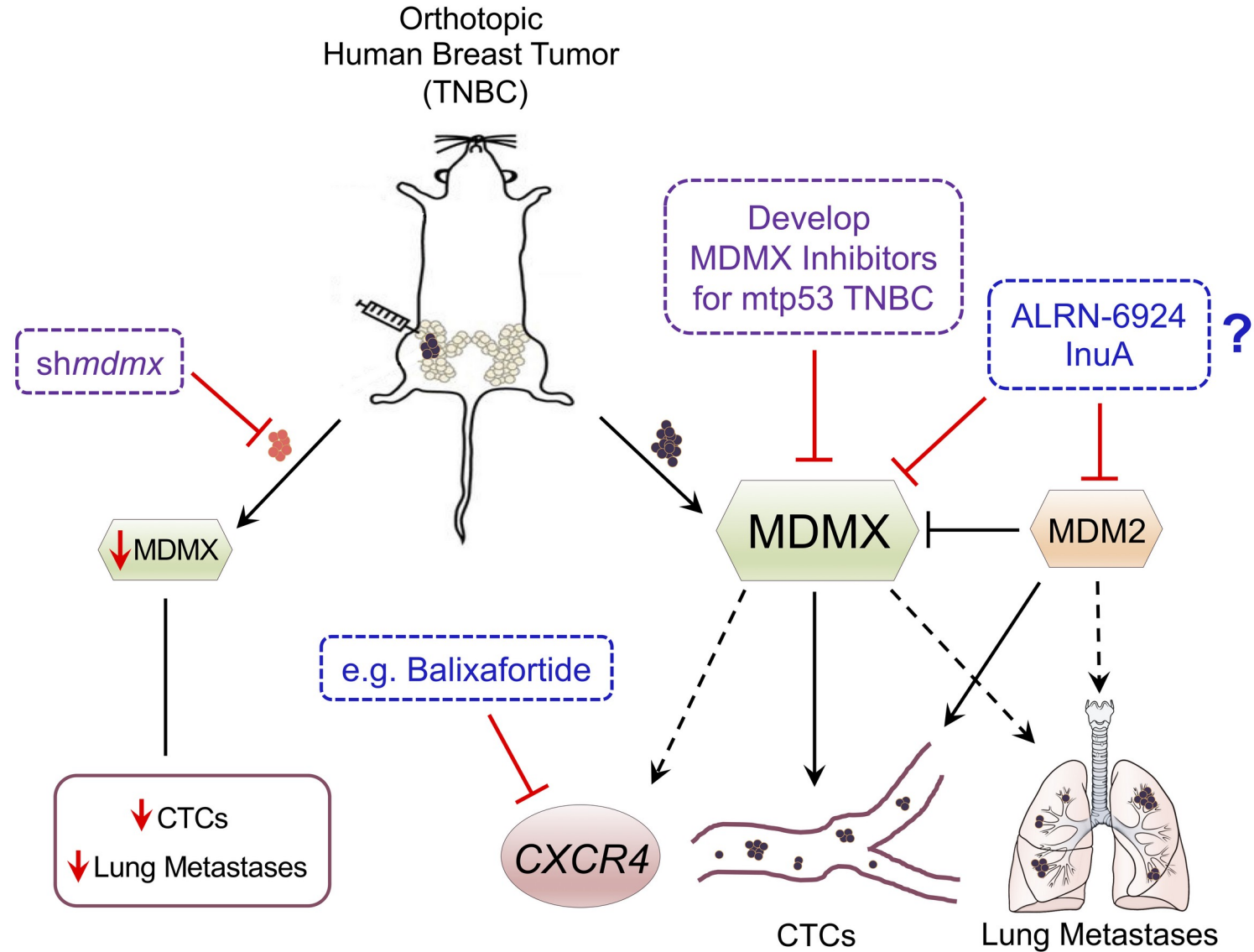


Chong Gao et. al. 2019

Human Metastasis Microarray Identified MDM2 and MDMX target genes *COX2* and *CXCR4*



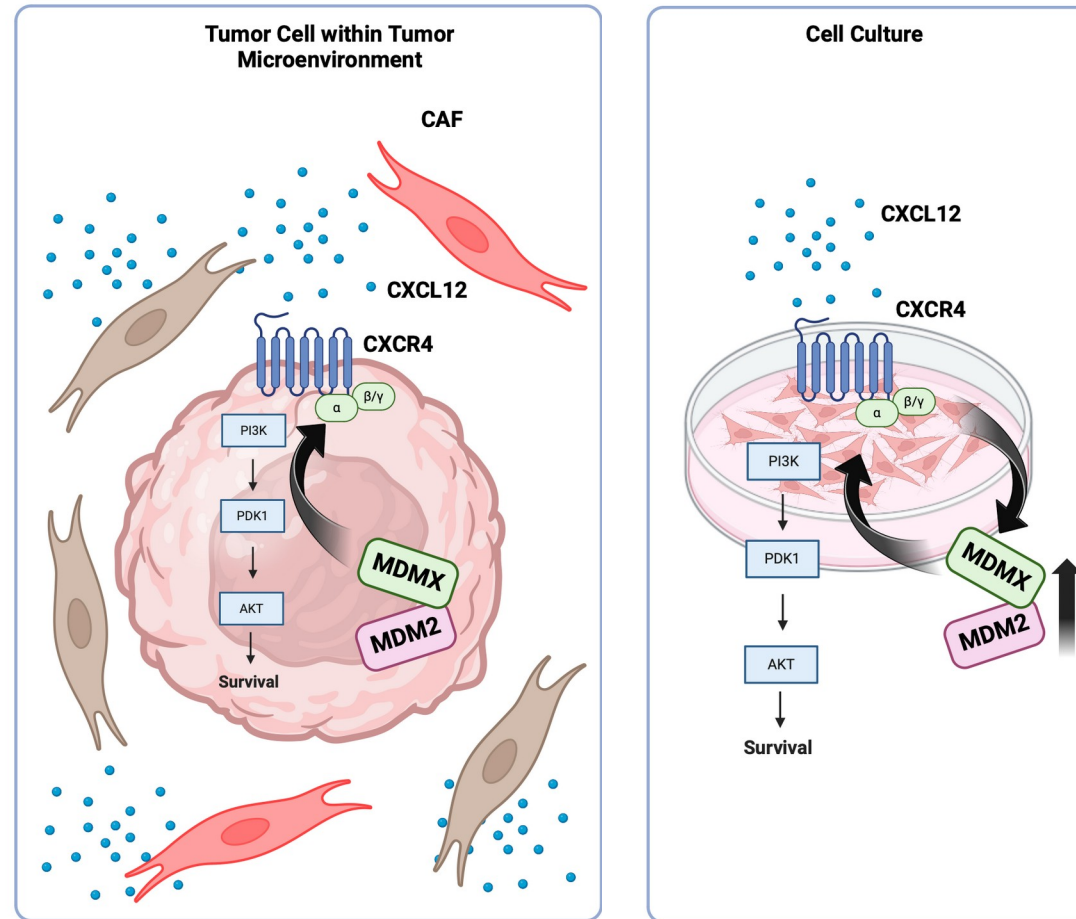
Potential Targeting of MDMX to Reduce Circulating Tumor Cells



What is the CXCL12-CXCR4 Pathway?

- CXCR4 (40 kDa): a g-protein coupled receptor which when overexpressed is critical for to tumor growth, angiogenesis, and metastasis
- CXCL12 (10.6 kDa): aka SDF-1, a chemokine expressed in many tissues and subtypes, the ligand for CXCR4 and CXCR7
- CXCR4/CXCL12 axis has a variety of roles, but most relevant is the “cross-talk” between tumor cells and their microenvironment
- One theory involves utilization of a chemokine gradient to travel from primary to secondary tumor sites
- AKT (56 kDa): aka protein kinase b, roles include glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration.
- p70s6K (56 kDa): a kinase required for cell growth and G1 cell cycle progression

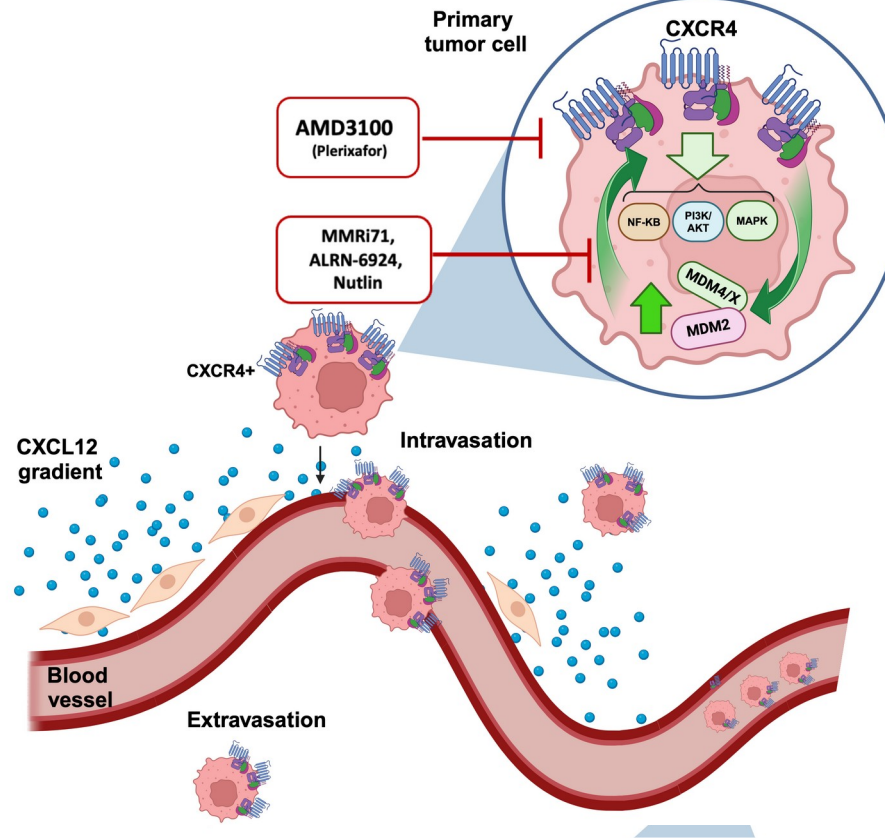
Positive feedforward loop between CXCL12-CXCR4 axis and increased MDMX protein levels



- CXCL12 addition increases MDM2 and MDMX protein levels and activates PI3K/AKT signaling pathway
- MDMX knockdown impedes CXCL12-CXCR4/AKT pathway

Created by BioRender

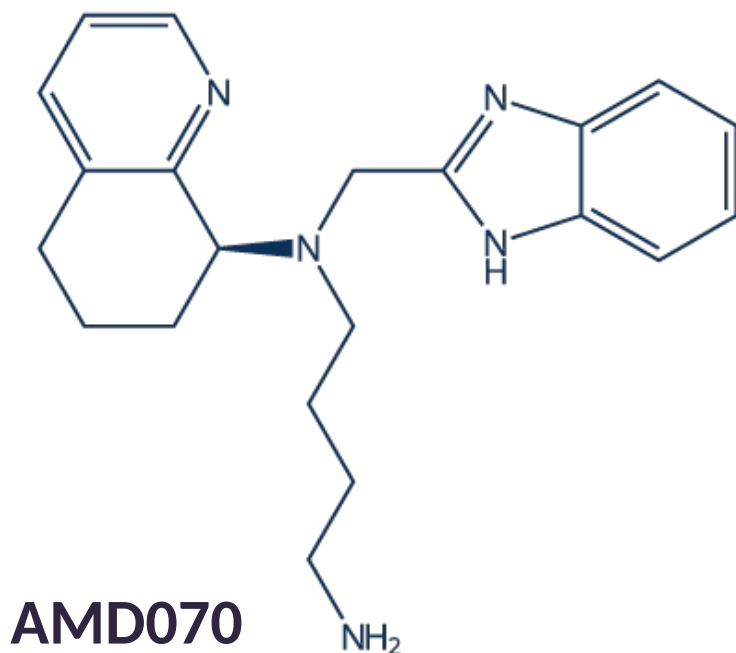
Targeting CXCR4 and MDM2/MDMX to Reduce Metastasis



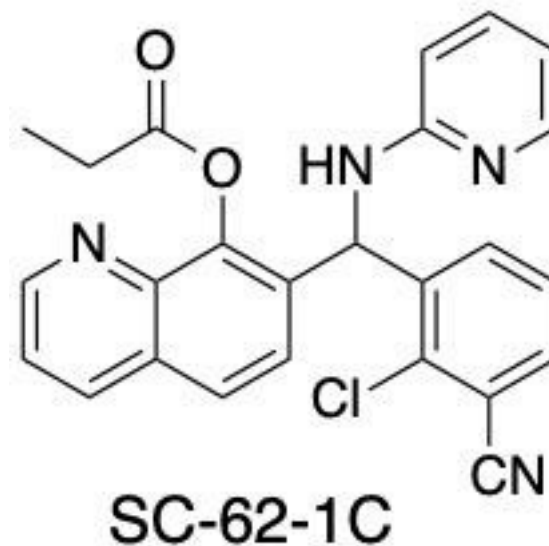
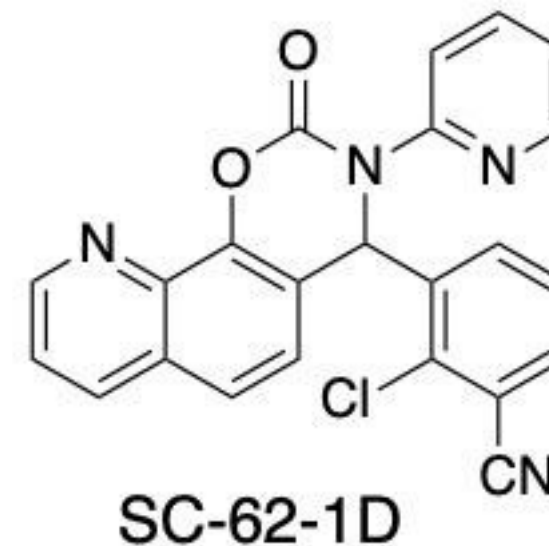
- CXCL12 treatment activates PI3K/Akt signaling pathway and increases MDM2 and MDMX protein in parental and CTC cells
- *Mdmx* knockdown impedes CXCL12-CXCR4/Akt pathway
- *Mdmx* knockdown CTC cells do not exhibit CXCL2-CXCR4/MDMX feedforward loop
- The upregulation of CXCR4 in CTCs is not a MDMX-dependent pathway

Created by BioRender

Targeting Breast Cancer Metastasis by Combination Inhibition of CXCR4 and MDM2/MDM4

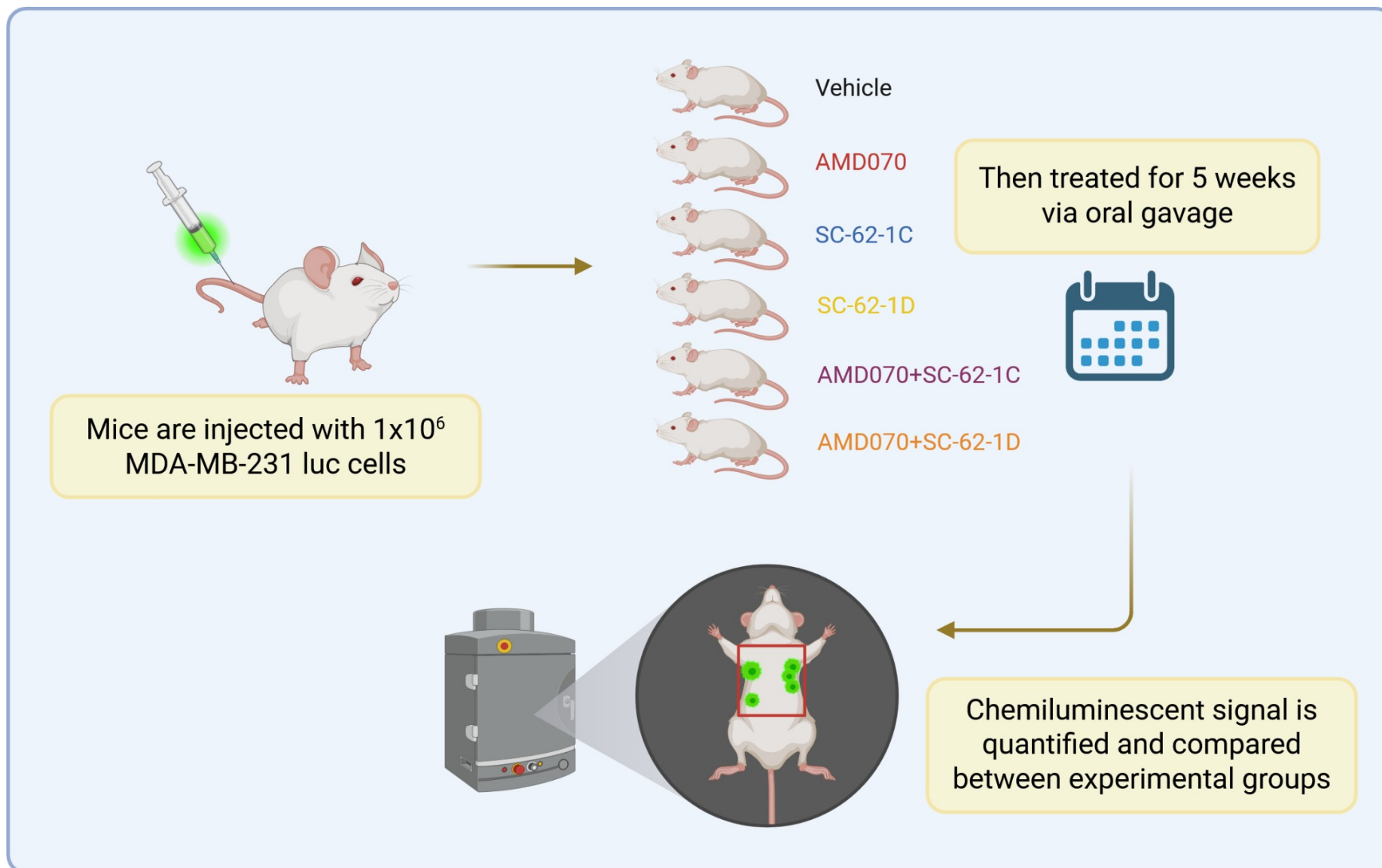


Mavorixafor (AMD-070) is a potent, selective CXCR4 antagonist, with an IC₅₀ value of 13 nM against CXCR4 125I-SDF binding.

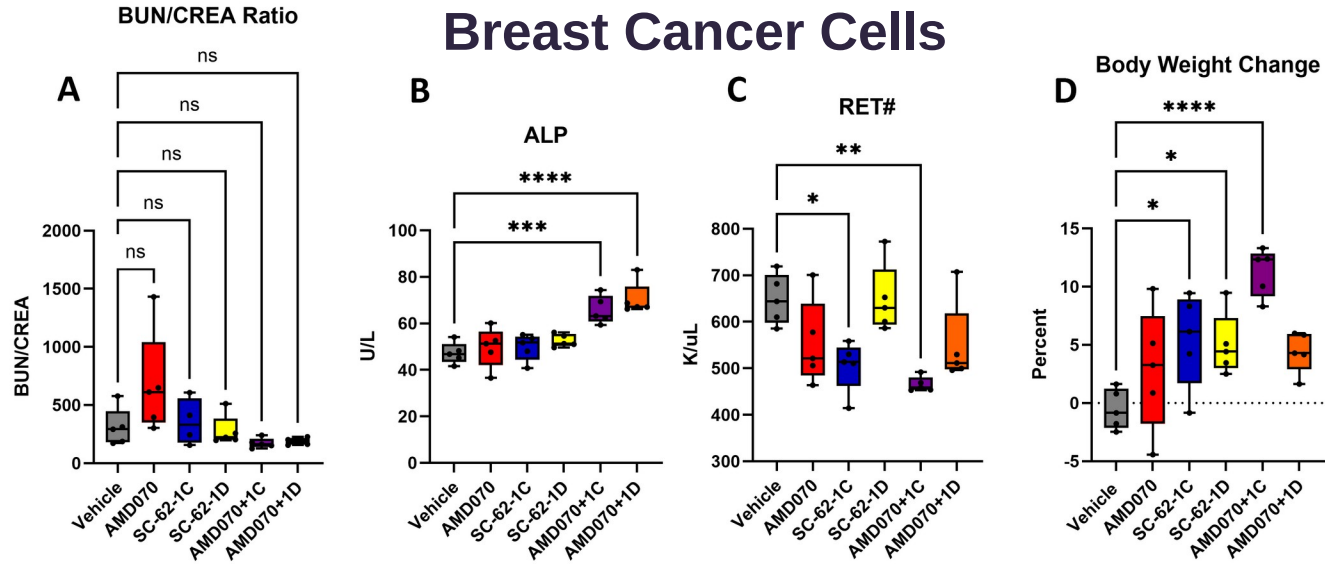


SC-62-1C is an ester. 1D is a cyclic carbamate. While esters like 1C are readily hydrolyzed by both chemical and enzymatic methods, cyclic carbamates are known to be more resistant to hydrolysis, thereby allowing for greater oral and in vivo stability. While both 1C and 1D are prodrugs with activity expected primarily from their hydrolyzed, phenolic forms, it is hypothesized that the cyclic carbamate of 1D allows for greater in vivo stability and sustained release, and less rapid clearance, thus allowing it to act on its target(s) more effectively.

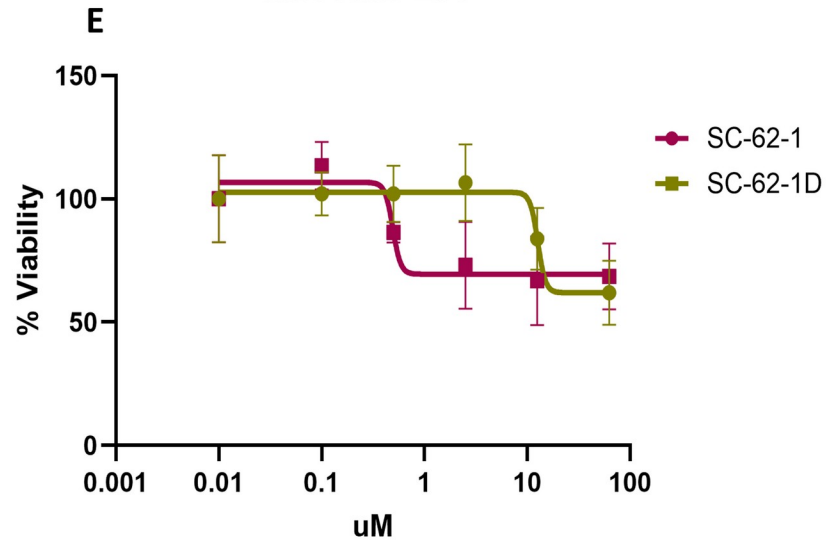
Targeting Breast Cancer Metastasis by Combination Inhibition of CXCR4 and MDM2/MDM4



CXCR4 Plus MDM Drugs Are Not Toxic to Whole Animals but are Toxic to Cultured Breast Cancer Cells



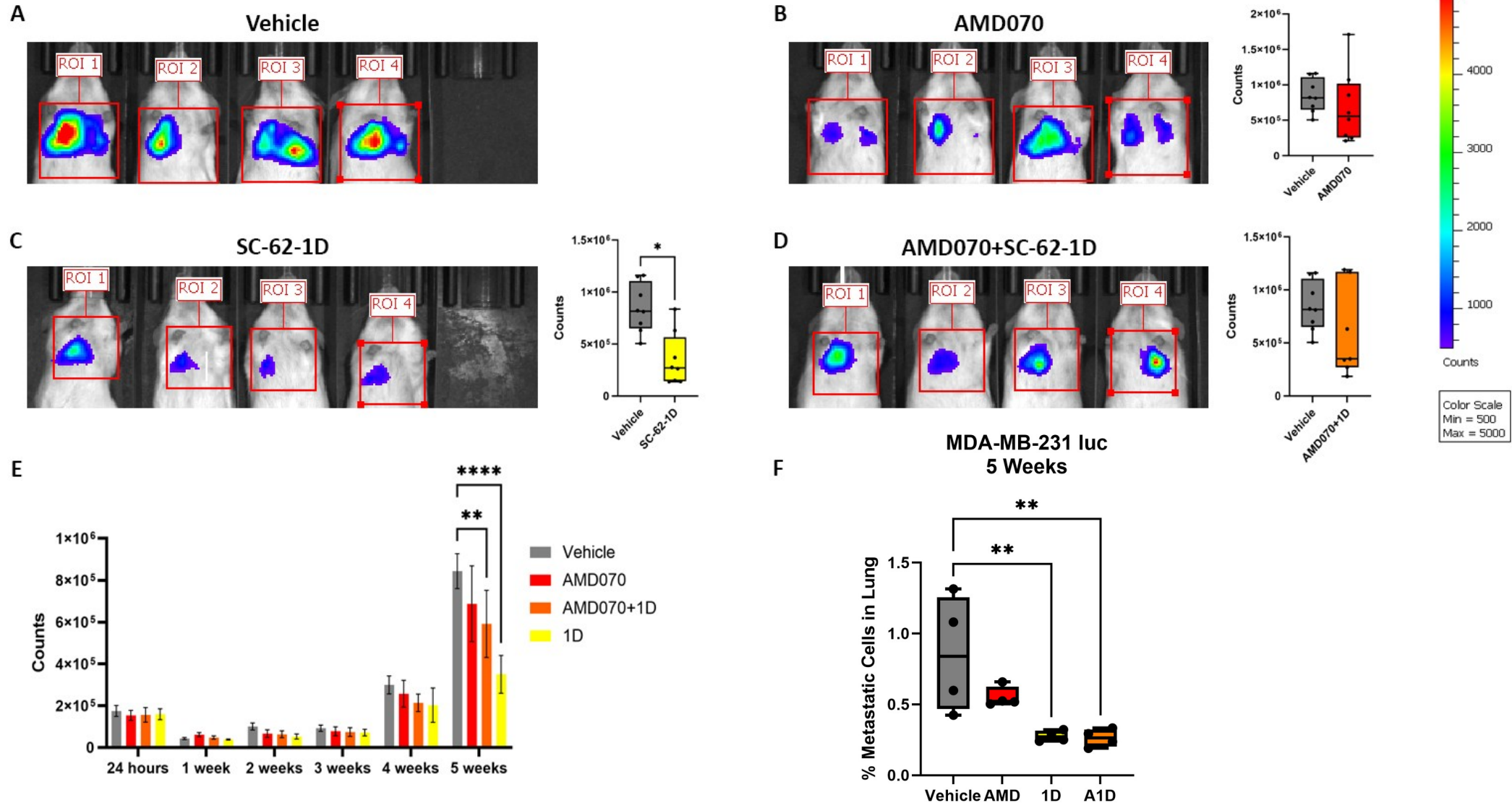
MDA-MB-231



24h Treatment

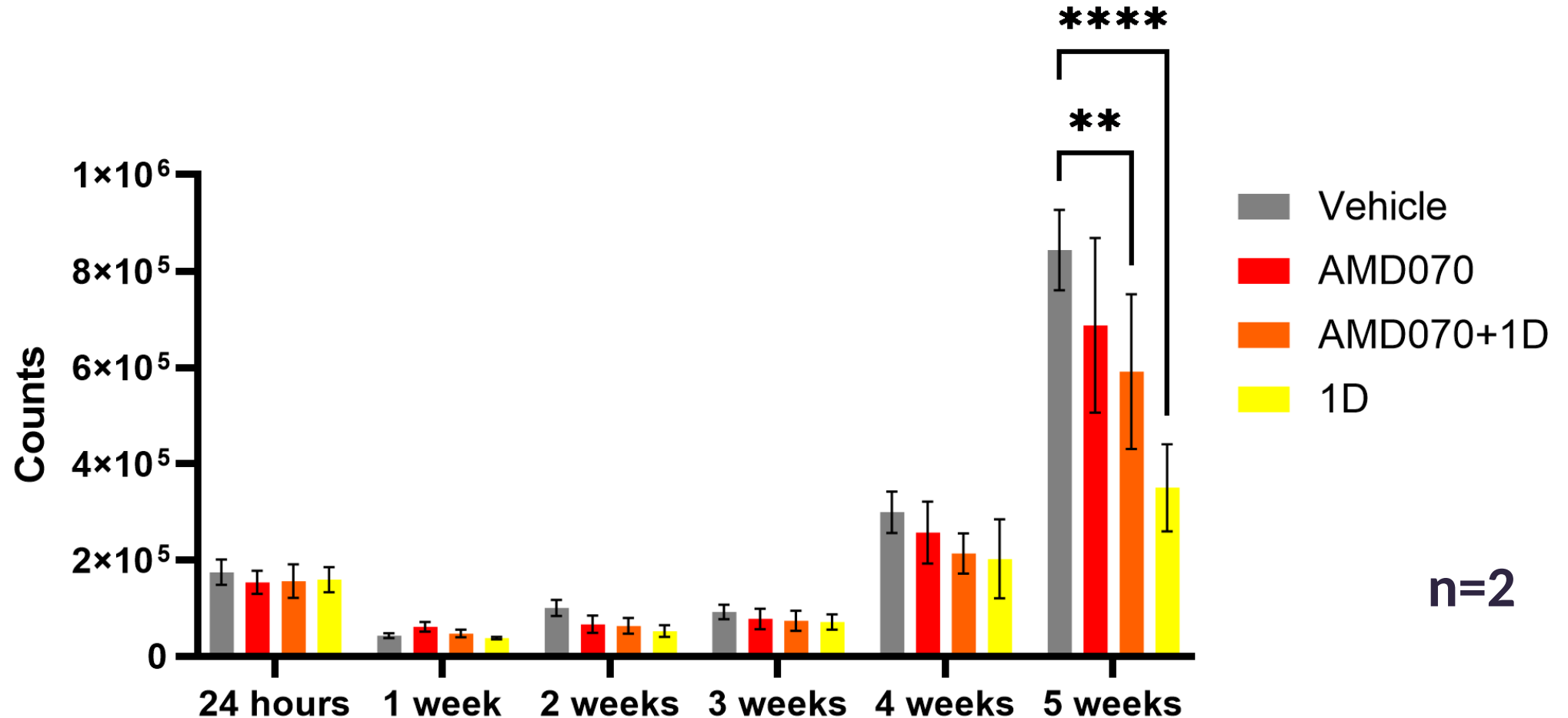
CXCR4 Plus MDM Drugs Reduce Triple Negative Breast Cancer Cell Metastasis

MDA-MB-231



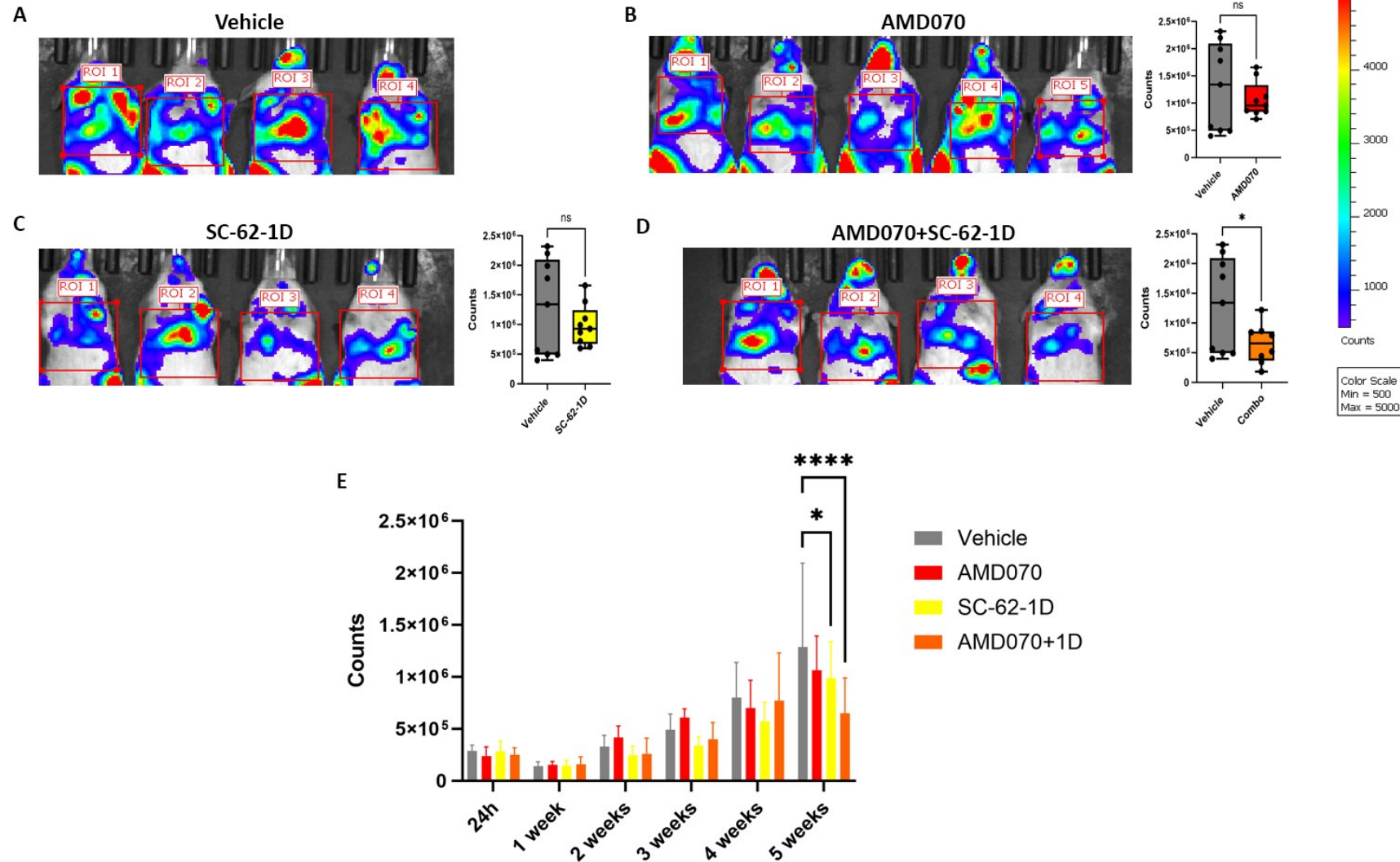
Experimental MDM2/X Inhibitors in Combination with CXCR4 Inhibitors Decrease Metastasis in Mouse Models of Triple Negative Breast Cancer

MDA-MB-231 luc



CXCR4 Plus MDM Inhibition Drugs Reduce Mutant p53-Estrogen Receptor Positive Breast Cancer Cell Metastasis

T47D



CXCR4 Plus MDM Inhibition Drugs DO NOT Reduce Wild-type p53-Estrogen Receptor Positive Breast Cancer Cell Metastasis



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