

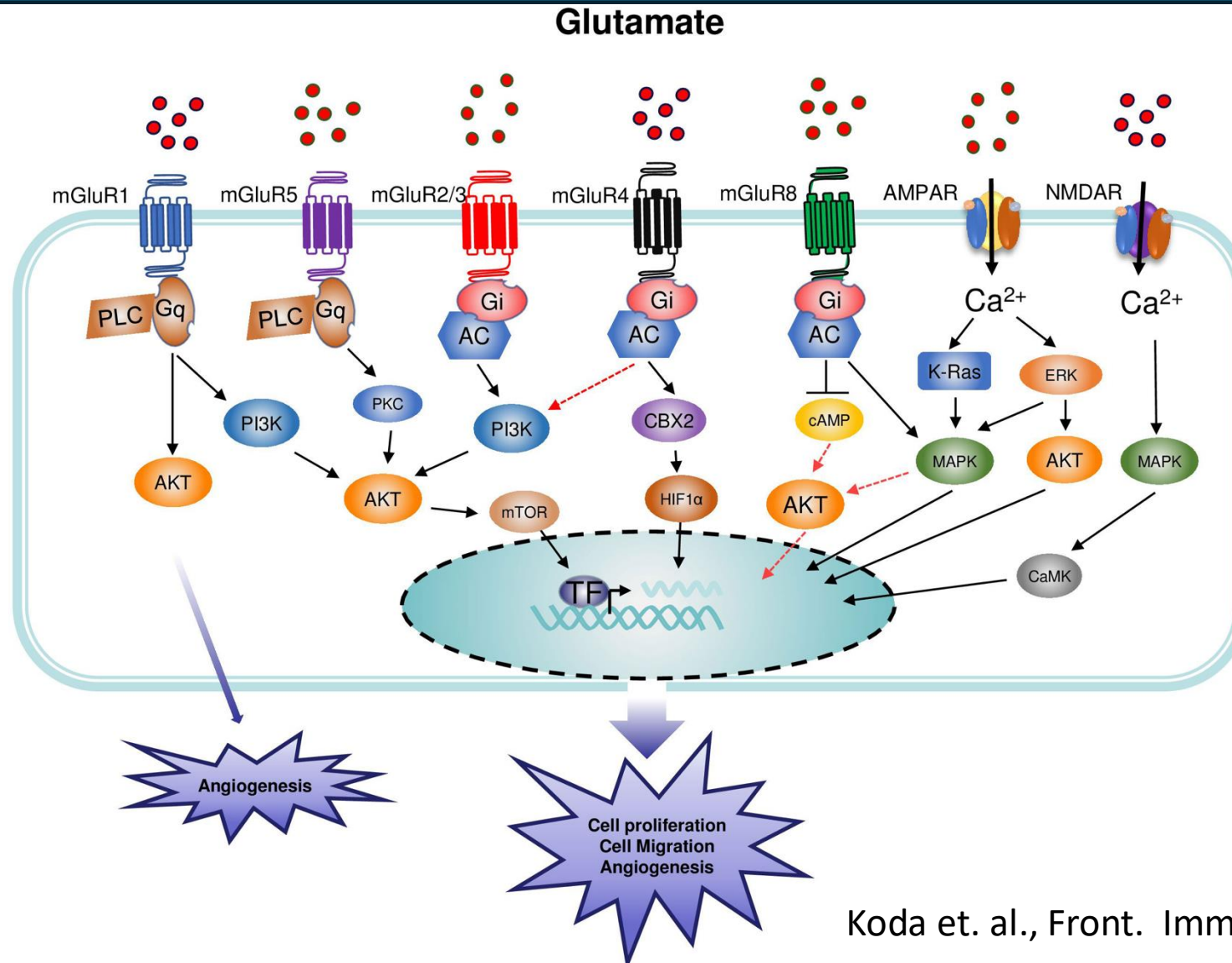
Repurposing Drugs for Osteosarcoma

Shahana S. Mahajan, PhD
June 28, 2025

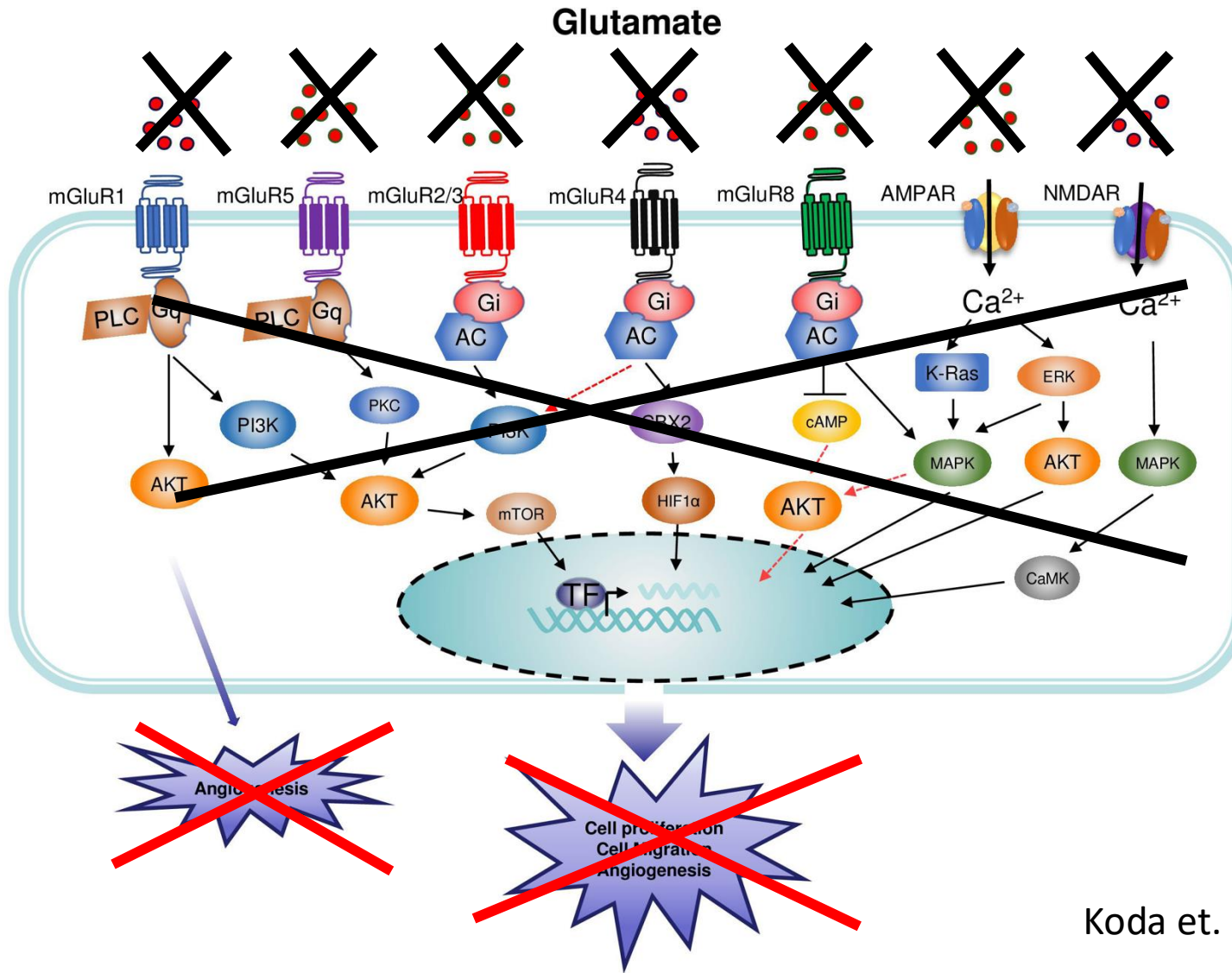
MIB Agents



Glutamate Receptors signal growth in cancer



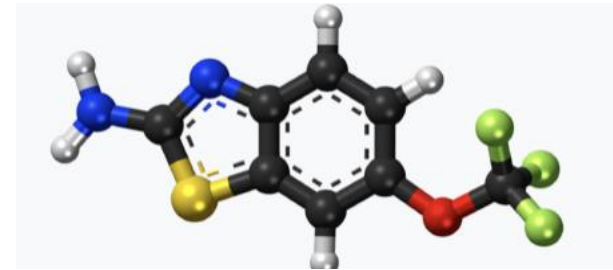
Inhibiting Glutamate-Dependent Growth in Cancer



Riluzole-A Drug Approved for ALS

2-amino 6-(trifluoromethoxy) **benzothiazole**

- FDA approved in 1995 for ALS
Bensimon G et al N Engl J Med. 1994.
delays tracheostomy



Tablets



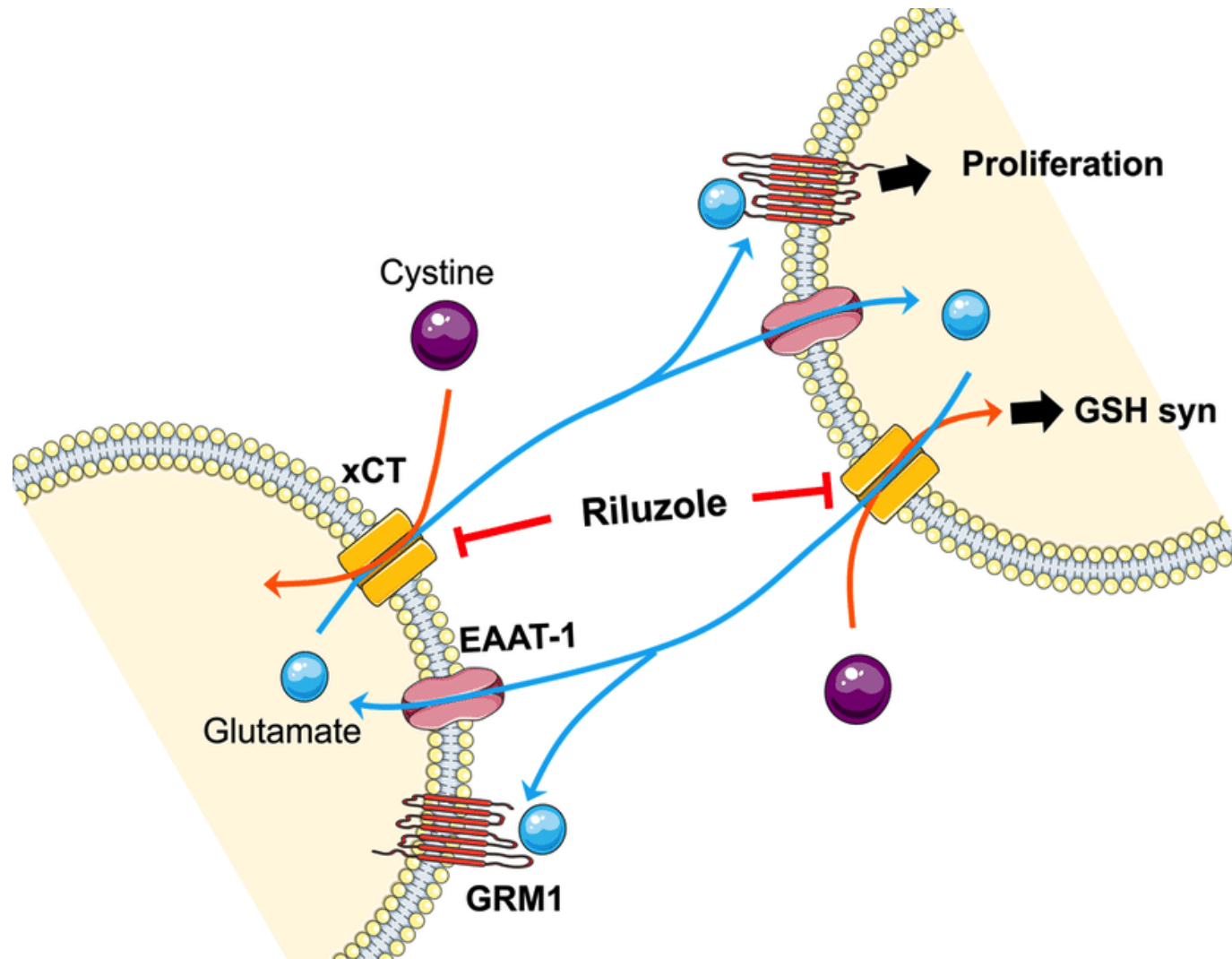
Oral suspension **2018**



Oral film **2021**

Exservan™
(riluzole) oral film

Inhibitory effect of Riluzole in cancer



1. Release of glutamate-xCT
2. Enhances clearance of glutamate- EAAT-1
3. Inhibits activation of Glutamate receptor

Why Riluzole?

The New England Journal of Medicine

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Volume 330

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Number 9

A CONTROLLED TRIAL OF RILUZOLE IN AMYOTROPHIC LATERAL SCLEROSIS

G. BENSIMON, L. LACOMBLEZ, V. MEININGER, AND THE ALS/RILUZOLE STUDY GROUP*

Original Article



Pharmacokinetics, Bioavailability, and Swallowing Safety With Riluzole Oral Film

Clinical Pharmacology
in Drug Development
2023, 12(1) 57–64
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Pharmacology in Drug Development*
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on behalf of American College of
Clinical Pharmacology.
DOI: 10.1002/cpdd.1168

**FDA approved
3 decades ago**

**Toxicity, tolerance and
pharmacokinetics**

James Wymer¹, Stephen Apple², Antoinette Harrison², and Bryan Alan Hill²

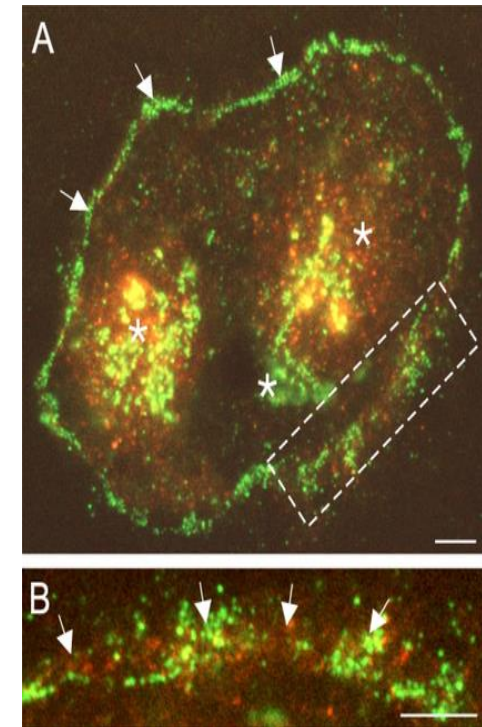
Osteosarcoma (OS) express glutamate receptors

- Glutamatergic system exist in osteoblast like MG63 cells
- Spontaneous release of glutamate
- Glutamate release blocked by Riluzole

The FASEB Journal, V15, 19 Jul
2001, 1586-1588

- GWAS study showed mGluR4 is expressed

Nat Genet. 2013 Jul; 45(7): 799-803



NMDAR1 glutamate
receptor subunits (green)
SaOS-2 osteoblast-like
cells

Previous studies in our lab



RESEARCH ARTICLE

Osteosarcoma cell proliferation and survival requires mGluR5 receptor activity and is blocked by Riluzole

Sally Liao¹, Yuleisy Ruiz¹, Hira Gulzar¹, Zarina Yelskaya¹, Lyes Ait Taouit¹, Murielle Houssou¹, Trisha Jaikaran¹, Yuriy Schvarts¹, Kristina Kozlitina¹, Upal Basu-Roy², Alka Mansukhani², Shahana S. Mahajan^{1,3*}

I. Efficacy of Riluzole in osteosarcoma cells lines and PDX

11 cell lines

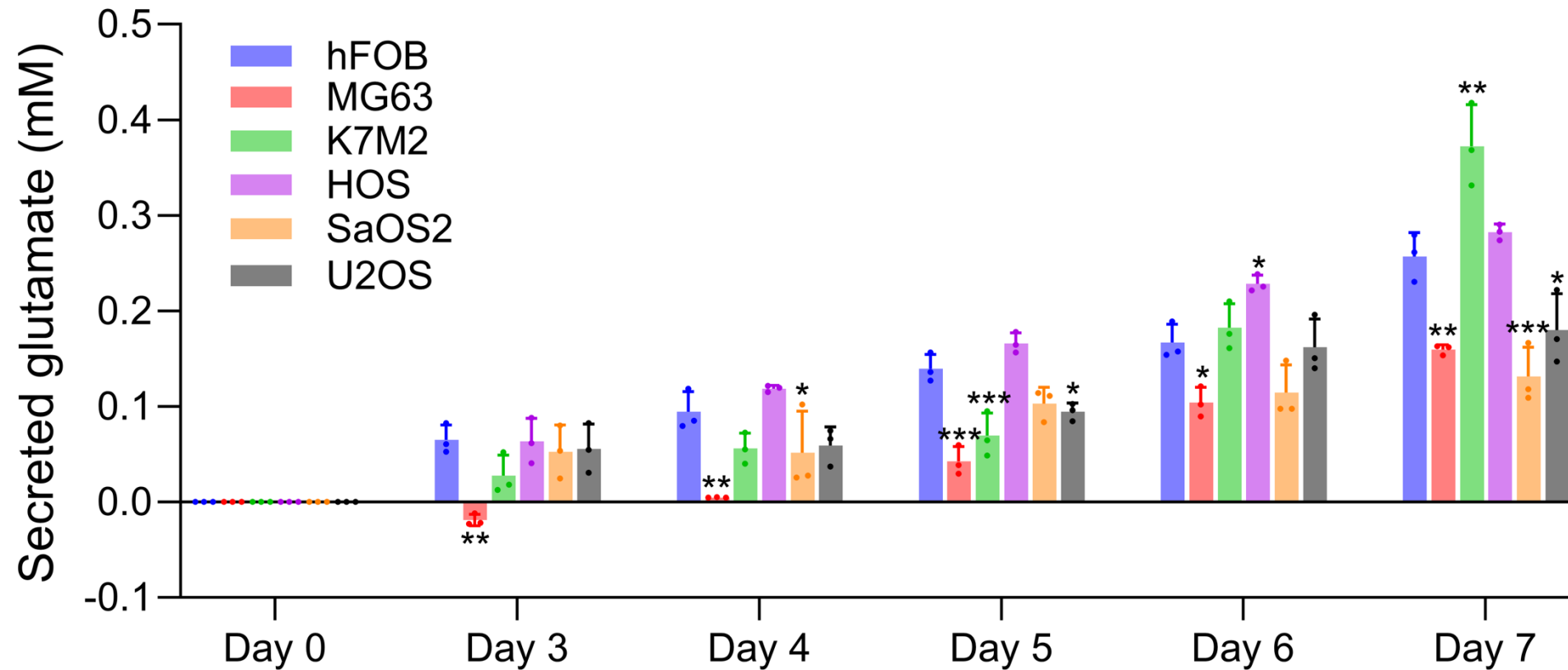
5 Patient-Derived Xenograft cell lines

Efficacy of Riluzole in Osteosarcoma cell lines and PDX

Cell Line	Species	Metastatic	Characteristics
SaOS2	Human	No	Mature Osteoblast, p53 null, mutant Rb
SaOS2-LM7	Human	Yes	Mature Osteoblast, p53 null, mutant Rb
MG63	Human	No	Immature Osteoblast, p53 null, CDKN2A null
MG63.3	Human	Yes	Immature Osteoblast, CDKN2A null
HOS	Human	No	Osteolytic, mutant CDKN2A, Mutant p53
HOS/MNNG	Human	Yes	Osteolytic, Mutant p53 with high expression, wild type Rb
HOS/143b	Human	Yes	Osteolytic, Mutant p53 with high expression, wild type Rb, KRAS oncogene G12S, A59T)
U2OS	Human	No	Wild type p53, Wild type Rb, epithelial morphology, no osteoblastic markers
hFOB 1.19	Human	Immortalized	Fetal Osteoblast
K7M2	Mouse	Yes	Osteolytic
OS482	Mouse	Yes	p53 null, mouse model based on LM7
<u>Patient derived lines</u>			
OS24		Yes	Mutations in NCOR1 (X361_splice), DOT1L (K97R), and FGFR3 (K501M
OS29		No	Amplifications in NBN1, CCND3, VEGFA, and NOTCH4
OS33		No	Deletion of GAP, a negative regulator of RAS (RASA1)
OS69		No	Missense mutation in p53 (R337C)
OS39		No	MYC amplification,MCL1 amplification, RB 18-19 exons,NUF2 amplification

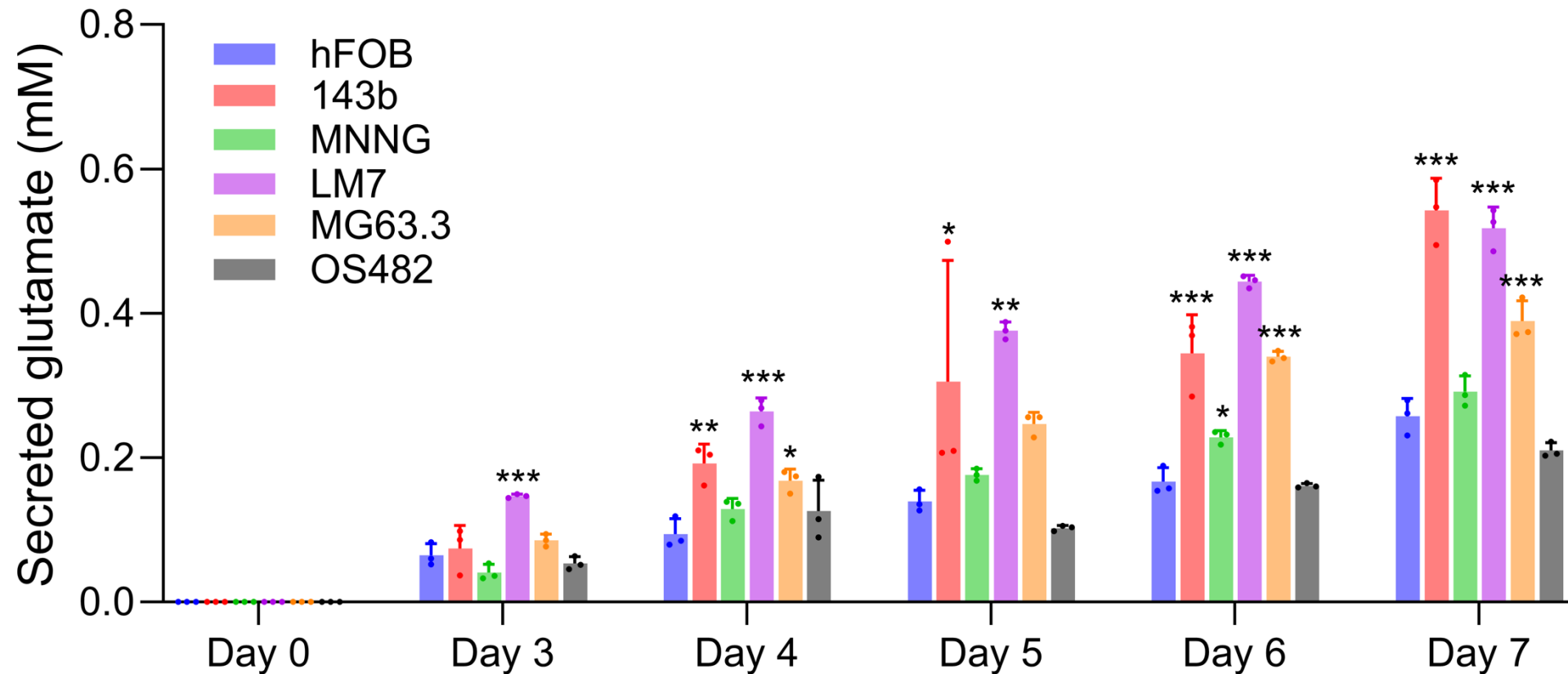
Primary osteosarcoma cells secrete glutamate

Primary OS cell lines

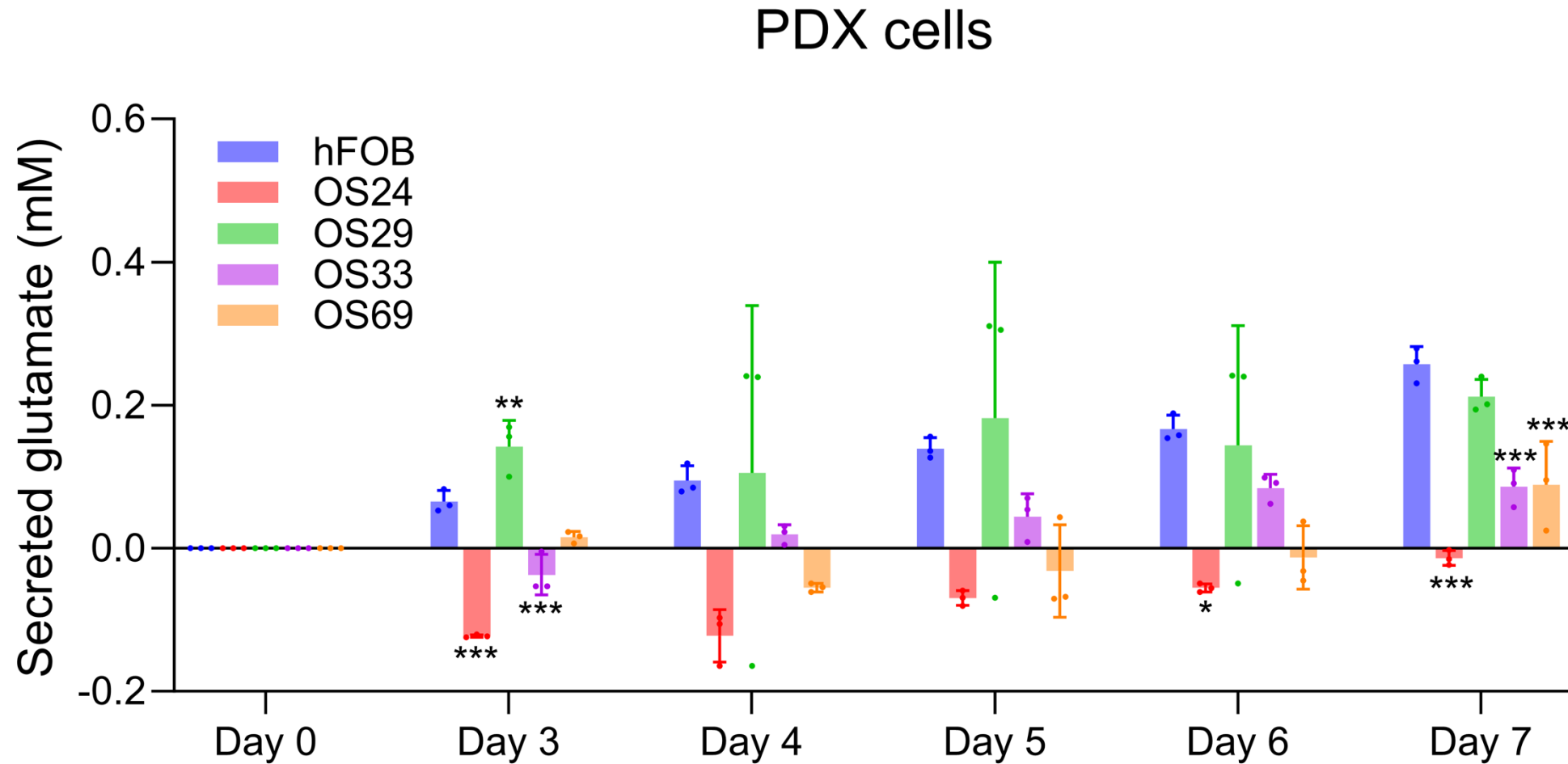


Metastatic osteosarcoma cells secrete glutamate

Metastatic OS cell lines

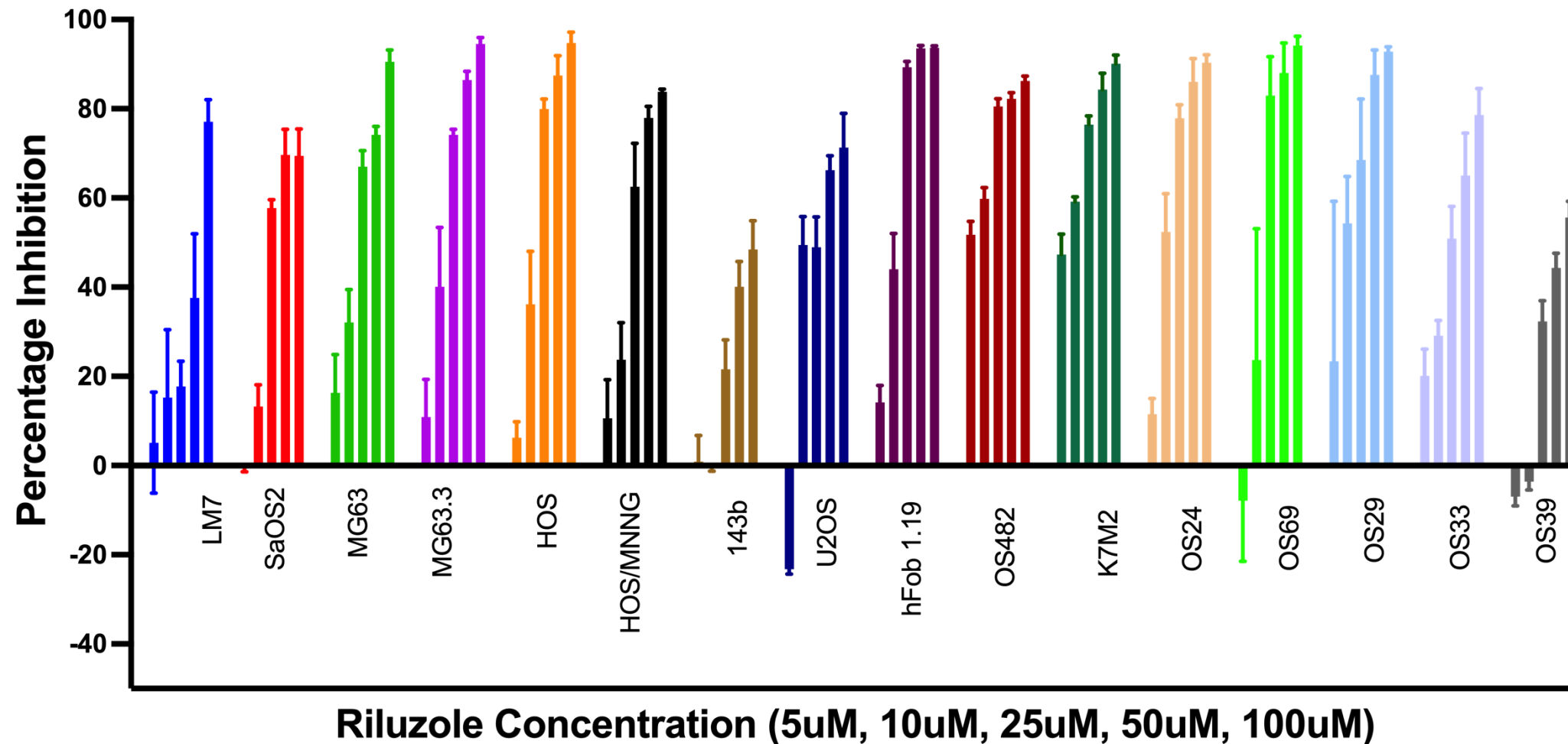


PDX cell lines secrete glutamate

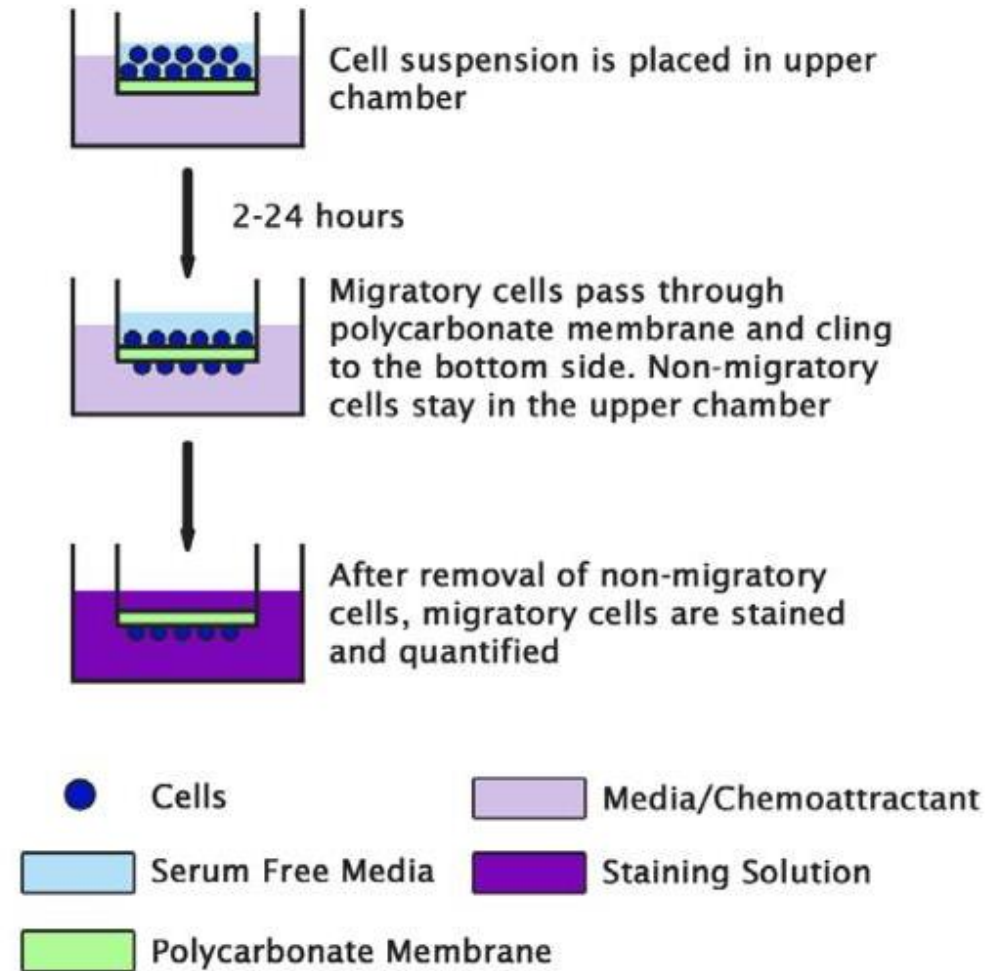
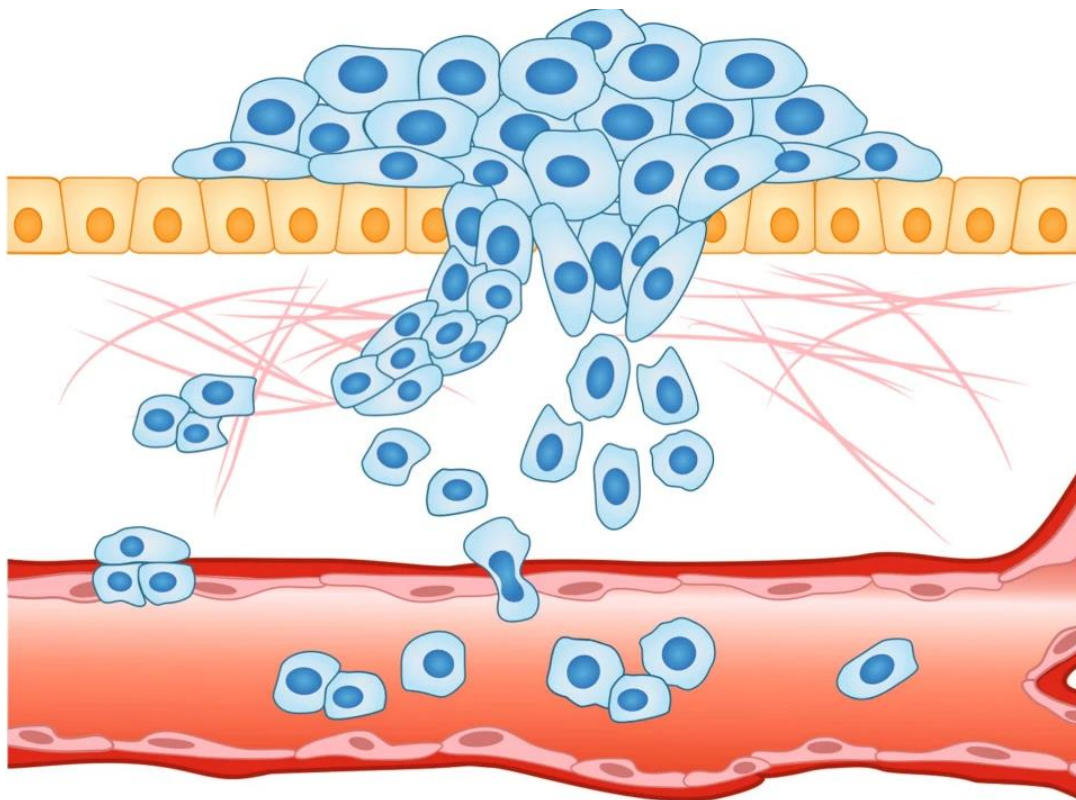


Inhibition of Cell Growth by Riluzole

MTT Assay

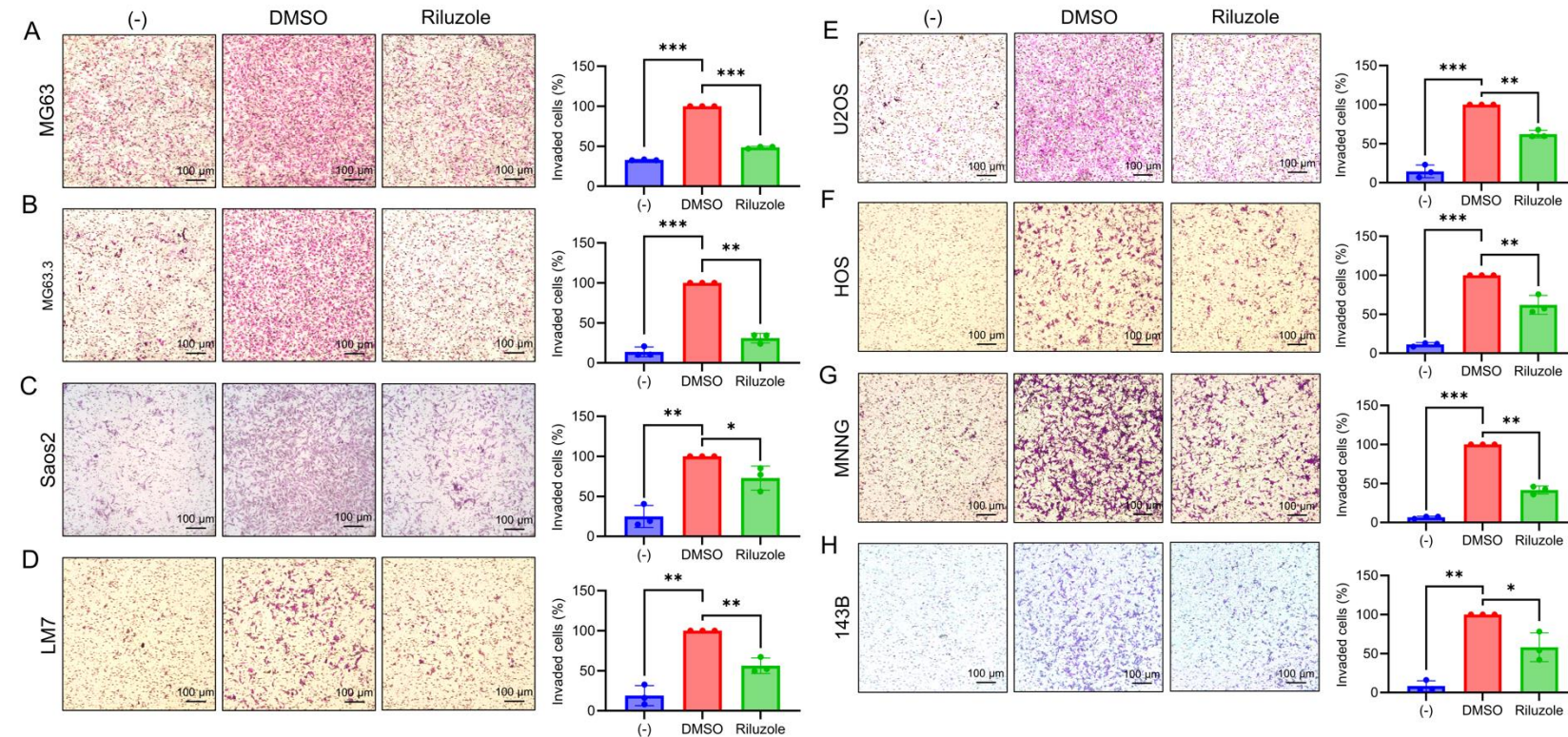


Boyden Chamber assay to measure cell invasion

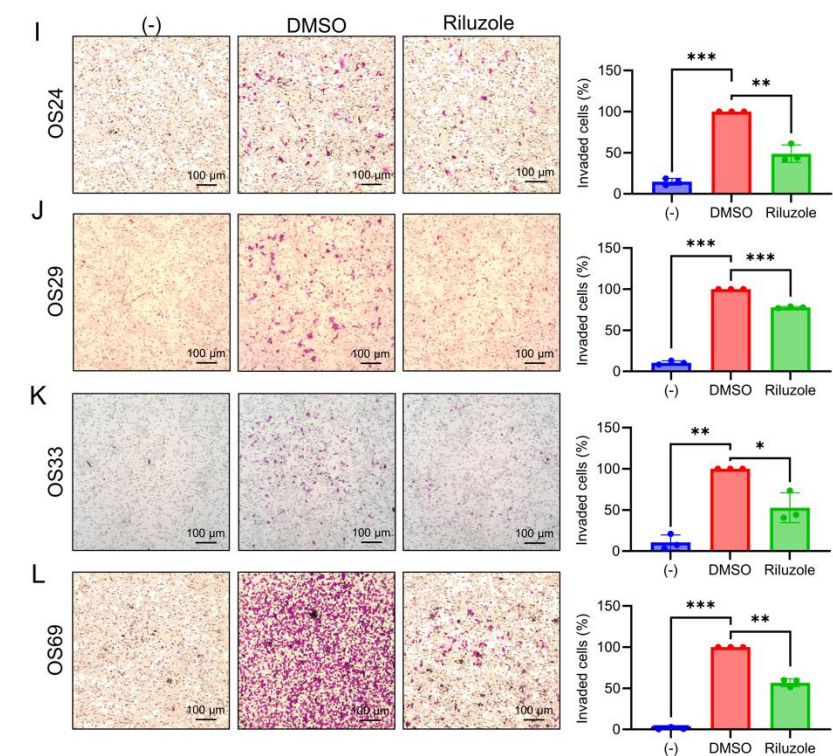


Riluzole inhibits invasive ability of osteosarcoma

OS cell lines



PDX cell lines



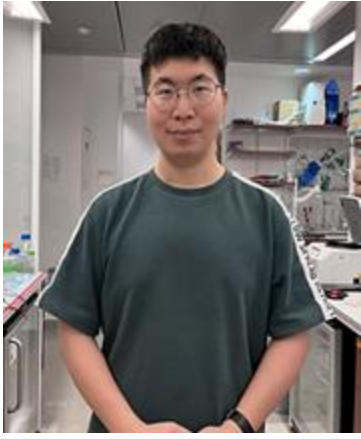
Clinical trials with Riluzole

Cancer Type	Clinical Trial	Riluzole Dosage	Reference
Melanoma	Phase 0 (single)	100mg x2	Clin. Cancer Res 2009;15(11) June 1, 2009
	Phase II (single)	100mg x2	Pigment Cell Melanoma Res. 2018 July ; 31(4): 534–540. plasma levels 8.16-294.4 ng/ml
Colorectal cancer	Phase I (mFOLFOX6 +bevacizumab)	50-100mg x2	J Clinical Oncology 2024, 42 (3)
Solid tumors	Phase I (sorafenib)	100mg x2	Oncotarget 2023, 14, 302-315
	Phase I (prodrug)+nivolumab	420 mg	European Journal of Medical Research (2022) 27:107

Summary

Riluzole blocks
growth in
osteosarcoma cell
lines and PDX lines

Riluzole prevents
invasive ability of
osteosarcoma cell
lines and PDX lines



Okkeun Jung



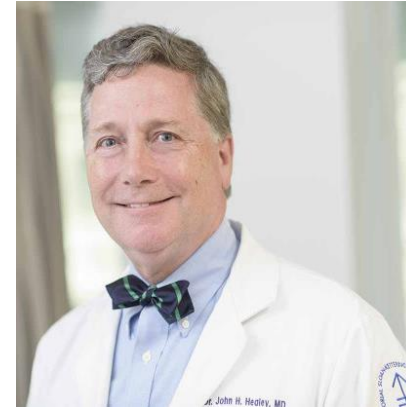
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Raisa Munira
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Elena Garay

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MIB Agents for Outsmarting OS



Hunter College

Dr. Andy Wolfe (Biological Sciences)
Shlomo Pallas (undergraduate student)

Thank you!!