Controlled Release of Synergistic Drug Combinations for Localized Glioblastoma Treatment

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THE FUTURE OF DELIVERY SCIENCE

OUTLINE

Glioblastoma *multiforme* (**GBM**) background

- Current treatment & therapeutic challenges

In vitro methods for determining **drug-drug synergy**

Drug encapsulation in **acetalated dextran (Ace-DEX)** scaffolds

- Electrospinning & in vitro drug release

In vivo performance upon **localized delivery** in a tumor resection model

- Conclusions & future perspectives

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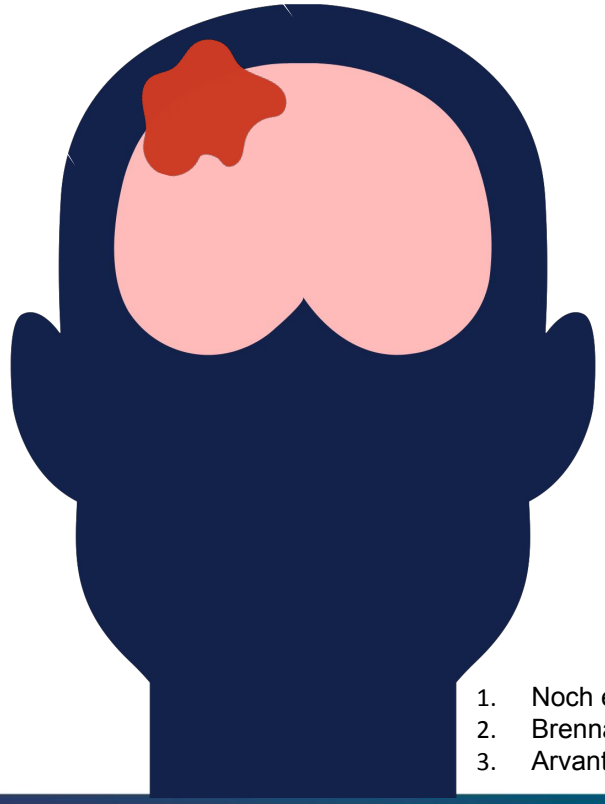
Glioblastoma multiforme (GBM) is the most aggressive form of all central nervous system malignancies

THERAPEUTIC CHALLENGES

POOR PROGNOSIS
~100% mortality rate with 12-15 mo. median survival[1]

STANDARD OF CARE
Resection, oral chemotherapy (Temozolomide), and radiation[1]



HETEROGENEITY
genetic variability promotes therapeutically resistant recurrence[2]

BLOOD BRAIN BARRIER
Prevents drug diffusion to site of tumor[3]

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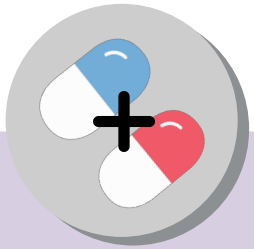
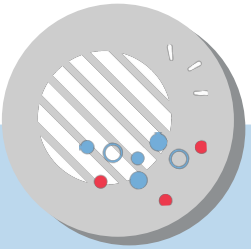
1. Noch et al. *World Surgery,* **2018**
2. Brennan et al. *Cell, **2013***
3. Arvantis et al. *Nature Reviews Cancer,* **2020**

LOCALIZED DELIVERY of SYNERGISTIC DRUG COMBINATIONS can overcome therapeutic challenges



SYNERGISTIC DRUG COMBINATIONS

- Provides a multi-mechanistic attack against tumors
- Mitigates chances of recurrence
- Reduces amount of drug needed for a therapeutic effect



LOCALIZED DELIVERY

- Bypasses the blood brain barrier
- Expands the number of viable therapies for GBM
- Can be administered at the time of surgical resection

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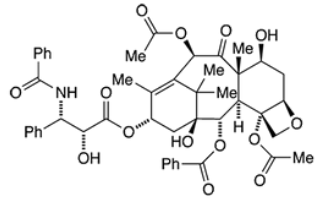
Woodring et al., *ACS Appl Bio Mat,* **2023**

Determining SYNERGY in vitro

DRUG A
Chemotherapy

+

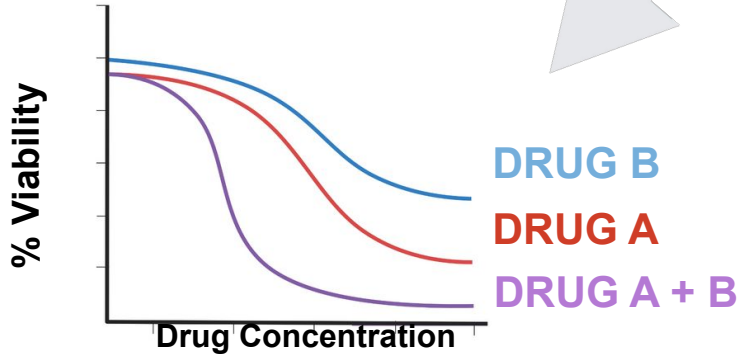
DRUG B
Small Molecule Inhibitor



Paclitaxel (PTX)

Microtubule stabilizing agent

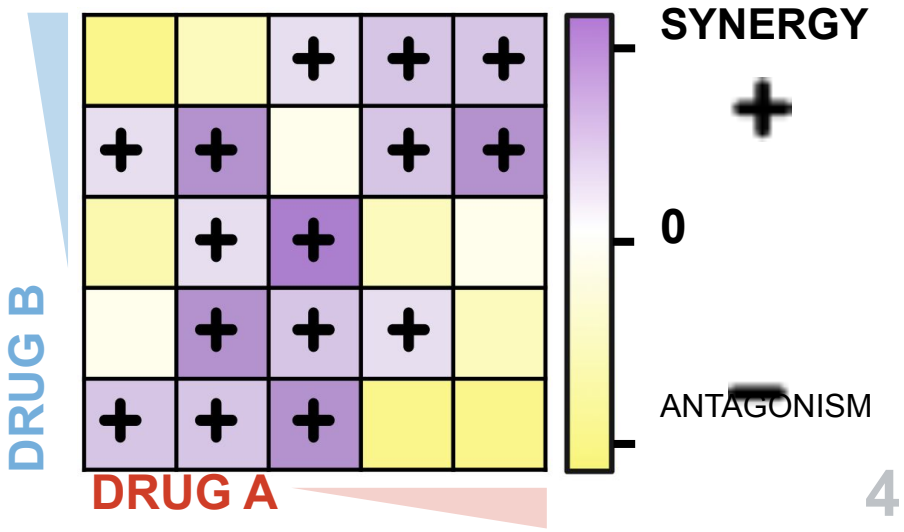
- PDGFR/EGFR inhibitor
- Pan-PI3K inhibitor
- mTOR inhibitor
- BRAF inhibitor
- EGFR inhibitor
- MEK inhibitor



ZIP SYNERGY SCORE

- PTX-drug combinations screened in 5 GBM cell lines
- Viability measured over a 5x5 increasing-dose matrix

Zero-Interaction Potency (ZIP) computational method for determining synergy



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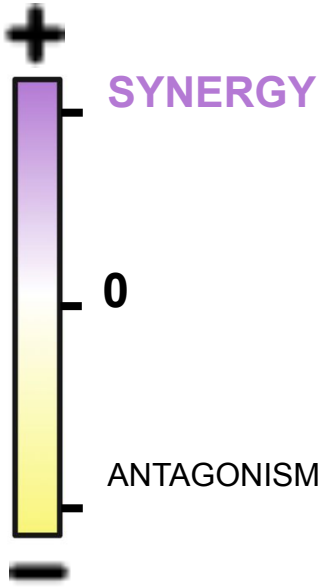
Yadav et al., *Comput Struct Biotechnol J*, **2017**

Paclitaxel (PTX) + Everolimus (EVR)
results in the highest ZIP synergy scores against GBM

AVERAGE ZIP SYNERGY SCORES

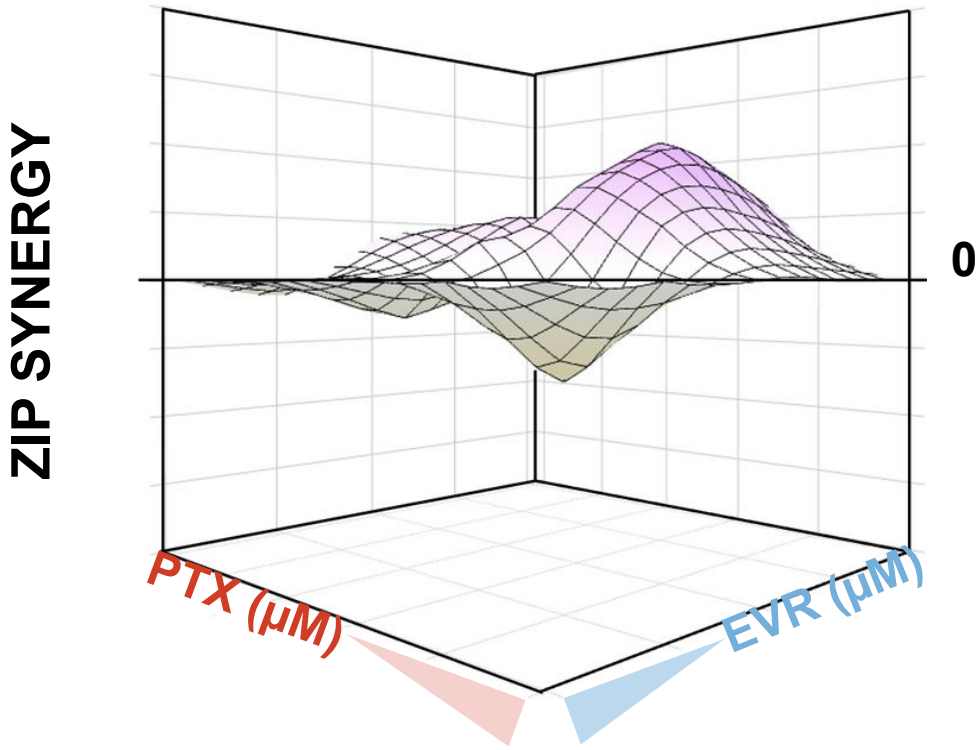
PTX +

GBM Cell Lines	PDGFR/EGFR	Pan-PI3K	mTOR (EVR)	BRAF	EGFR	MEK
U87-MG	-1.89	1.16	3.66	2.63	-9.13	0.80
CT2A	-0.53	-4.68	-4.85	-2.97	-6.25	0.59
3013-PN	-10.33	-12.90	2.02	-5.53	-14.65	-4.06
3017-CL	-3.71	-3.50	0.64	-6.42	-6.86	-8.58
3031-MS	-12.07	-14.73	0.61	-17.89	-12.22	-5.80



U87-MG: PTX + EVR

ZIP Synergy Score = 3.66 ($p < 0.01$)



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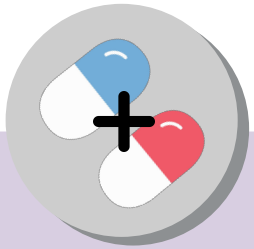

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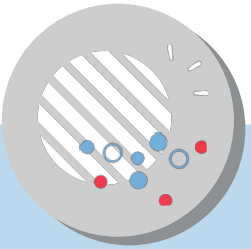

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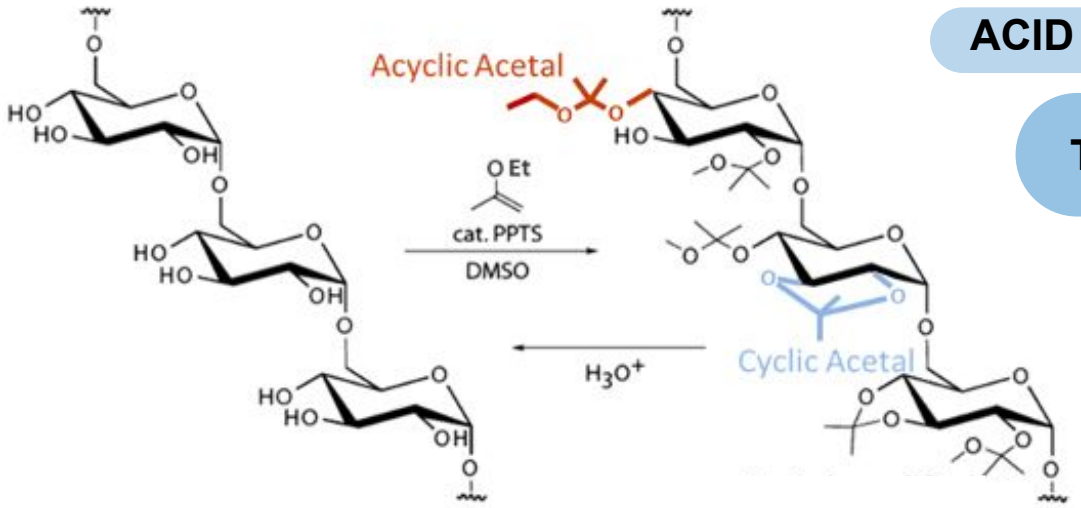
Woodring et al., *ACS Appl Bio Mat,* **2023**

Encapsulation of PTX and EVR in **acetalated dextran (Ace-DEX) Scaffolds**

Ace-DEX SYNTHESIS

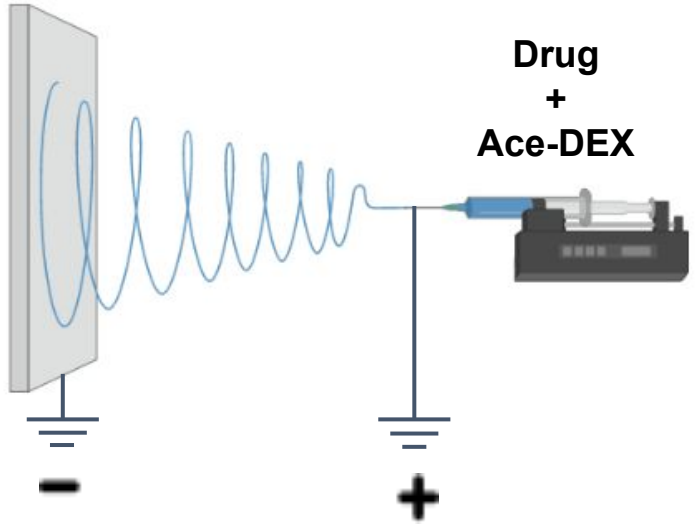


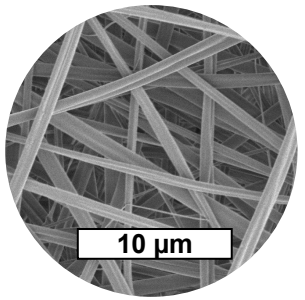
Dextran (**DEX**)

Acetal-modified Dextran (**Ace-DEX**)

- **BIOCOMPATIBLE**
- **ACID SENSITIVE**
- **TUNABLE DEGRADATION**
- **CYCLIC ACETAL COVERAGE (%CAC)**
  - **45% CAC** - Fast Degradation
  - **50% CAC** - Medium Degradation
  - **60% CAC** - Slow Degradation

ELECTROSPINNING





Drug-loaded Ace-DEX Scaffold

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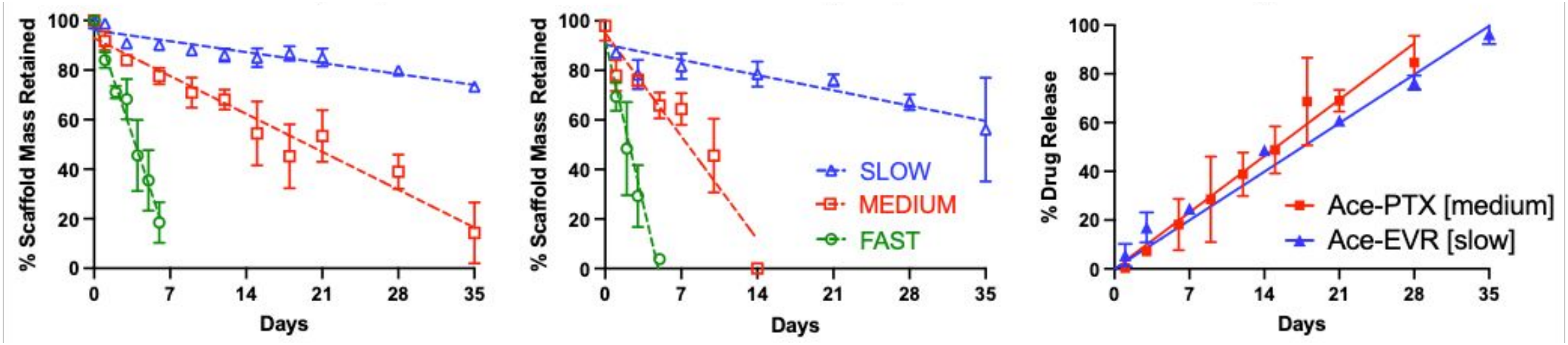
Kauffman et al., *ACS Appl Mater Interfaces*, **2012**

In vitro Ace-DEX degradation and drug release

Ace-PTX
20% wt. PTX

Ace-EVR
5% wt. EVR

Drug Release
37°C, PBS



Ace-PTX [medium, 50% CAC] & **Ace-EVR** [slow, 60% CAC] have correlating release kinetics in vitro

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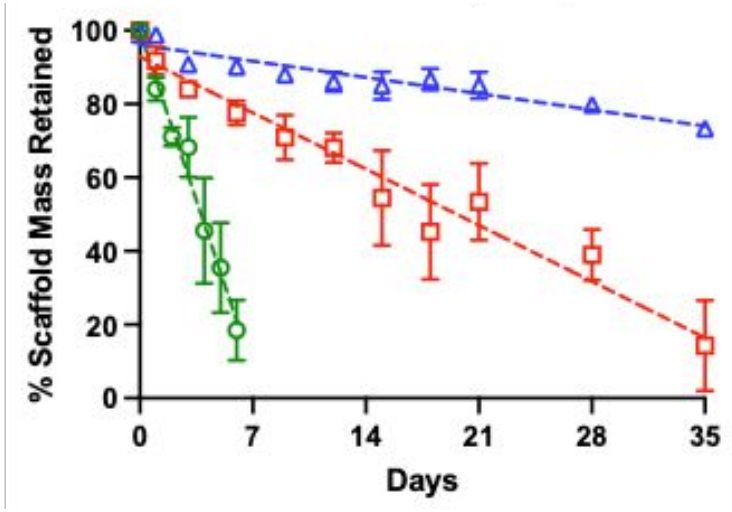
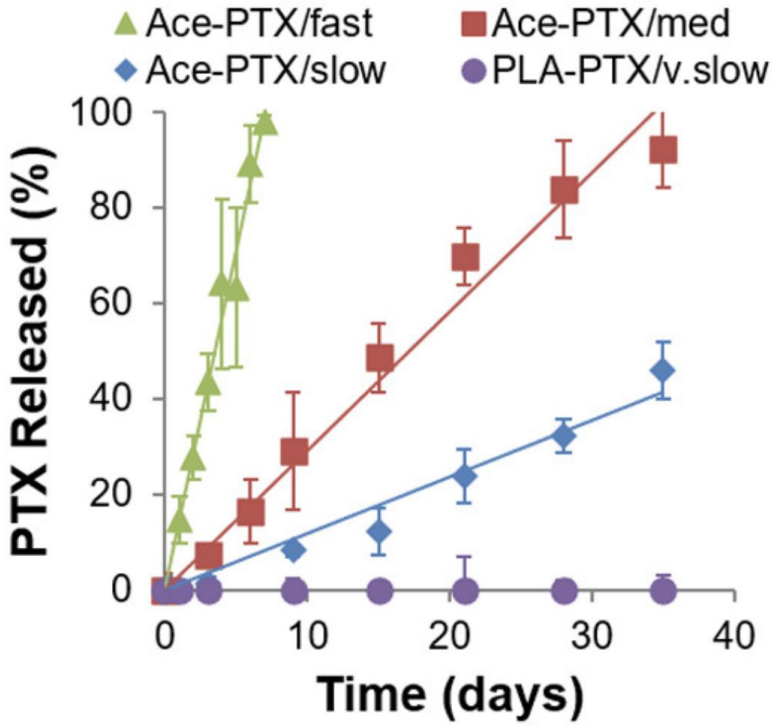
Gurysh et al. *J. Control Release*, **2020**
Gurysh et al. *ACS Appl. Mater. Interfaces*, **2020**

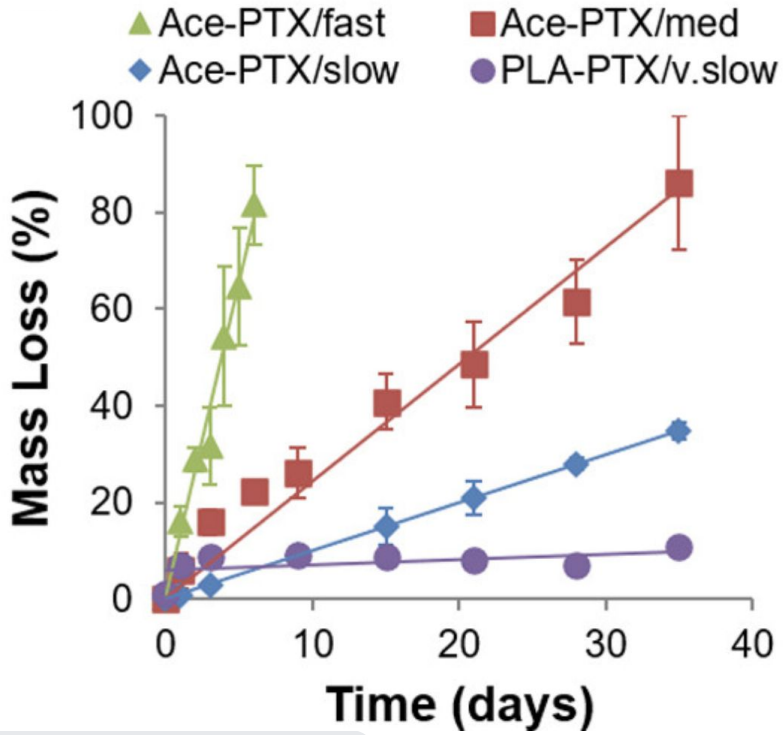
Error Bars = ± SD

In vitro Ace-DEX degradation and drug release

Ace-PTX
20% wt. PTX







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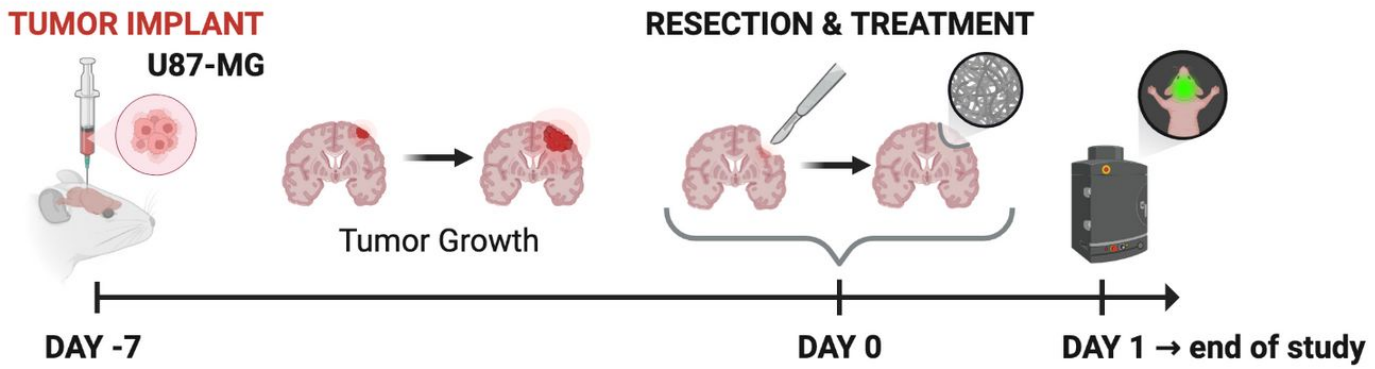
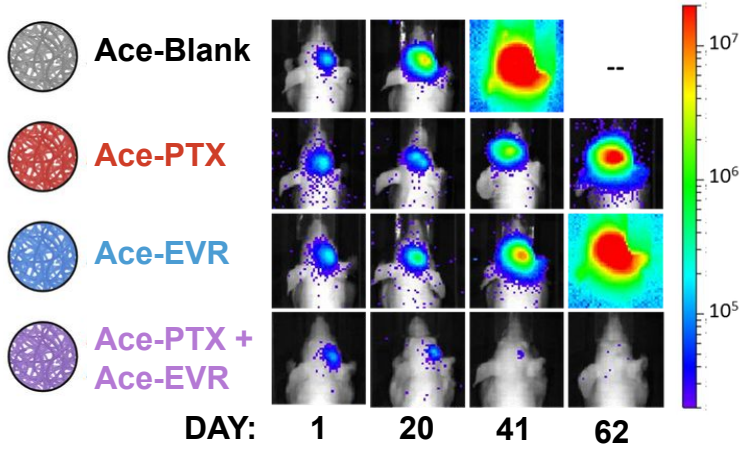
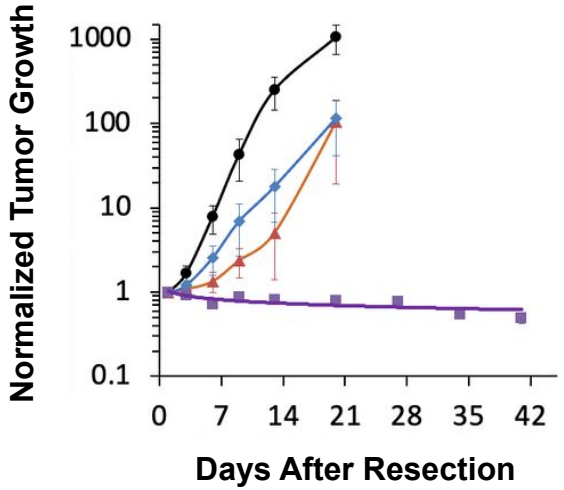
Gurysh et al. *ACS Appl. Mater. Interfaces*, **2020**

Error Bars = ± SD

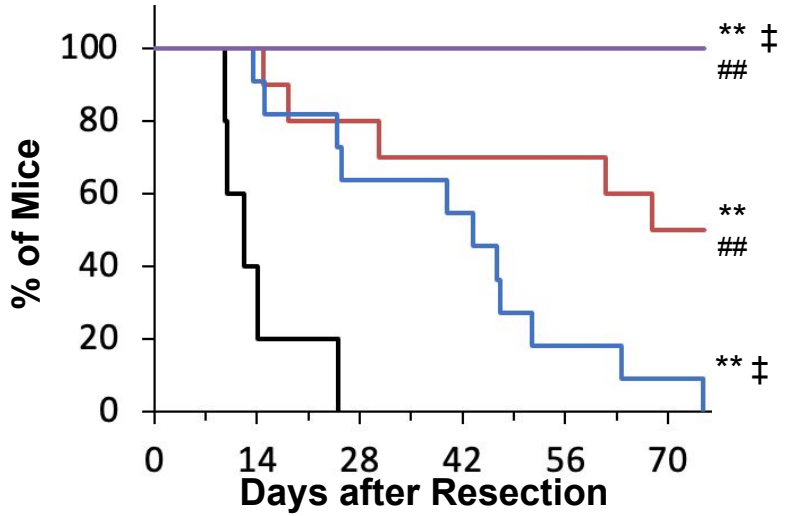
In vivo performance of Ace-PTX + Ace-EVR







Error Bars = ± SEM



Ace-PTX + Ace-EVR
displays synergy in vivo

** p < 0.001 w.r.t. Ace-Blank
p < 0.001 w.r.t. Ace-EVR
‡ p < 0.05 w.r.t. Ace-PTX

Gurysh et al. *J. Control Release*, **2020**

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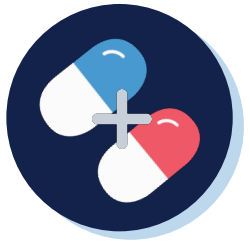
Conclusions & Future Perspectives



Paclitaxel (PTX) + **Everolimus (EVR)** displayed positive ZIP synergy scores across a panel of relevant GBM cell lines

- highest score for U87-MG

Acetalated dextran (Ace-DEX) provides tunable release of PTX and EVR for a localized delivery platform

- Correlating drug release rates from Ace-PTX medium and Ace-EVR slow

In vivo delivery of **Ace-PTX + Ace-EVR** upon surgical resection significantly improved progression free survival in a U87-MG model

FOR THE FUTURE

Expand drug library and combination screens

Characterize relationship between Ace-DEX degradation, % CAC, and drug release rates for optimal delivery of future synergistic drug combinations

Explore the pharmacokinetics of drug in vivo following release from Ace-DEX scaffolds

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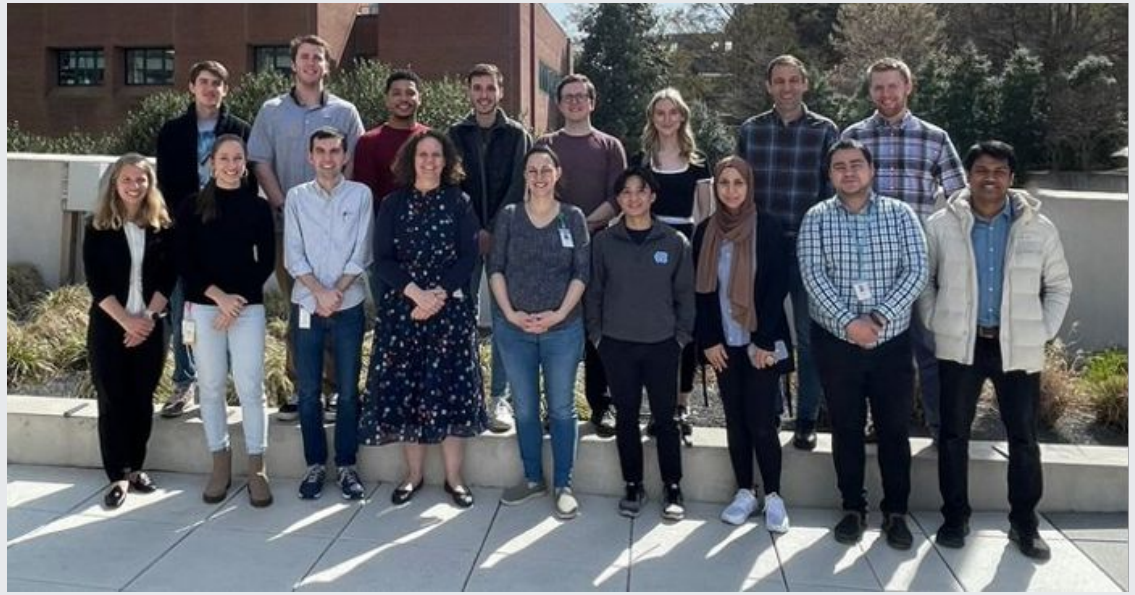

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