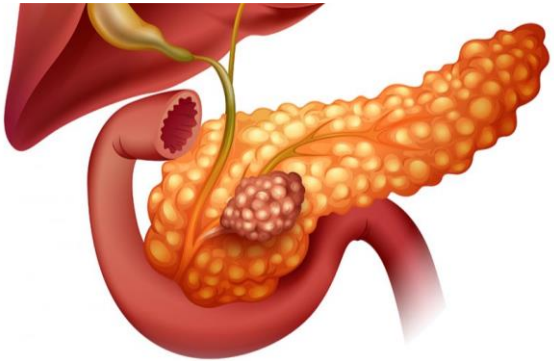
Local stromal targeting via thermosensitive hydrogel to enhance therapy for pancreatic ductal adenocarcinoma.

Remya Valoor, MSc

Pancreatic ductal adenocarcinoma (PDAC)

- PDAC - aggressive solid tumor – 12% survival rate.
- Diagnosed at late stages- chemotherapy remains the standard care of treatment.
- Chemotherapy fails - dense stroma and high resistance- limit drug delivery and effectivenes.
- Stroma composition- CAFs are the key players- Secrete pro-tumorigenic factors, remodel ECM, and orchestrate immunosuppression.
- Limited drug diffusion- increased resistance and immunosuppressive TME.



Local treatment

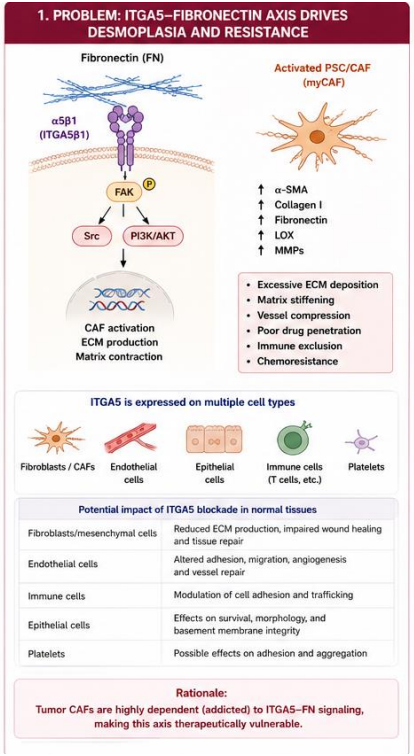
- 10–15% -resectable tumor
- 30–55% -with locally advanced (unresectable)
- Localised tumor can be treated locally with EUS FNI technique.

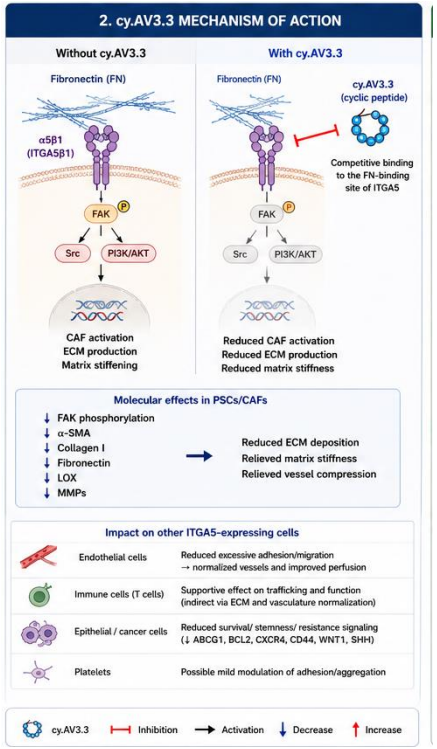
How it works:

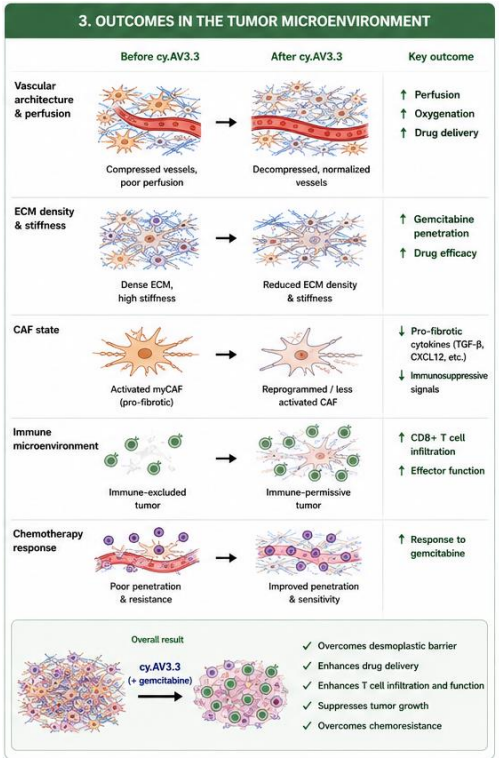
- EUS Localisation: EUS enables detailed visualisation of the pancreas
- FNI Delivery: target area under real-time ultrasound guidance to deliver high doses of drugs

But stroma is still a problem!

Stromal normalisation via ITGα5 targeting with peptide

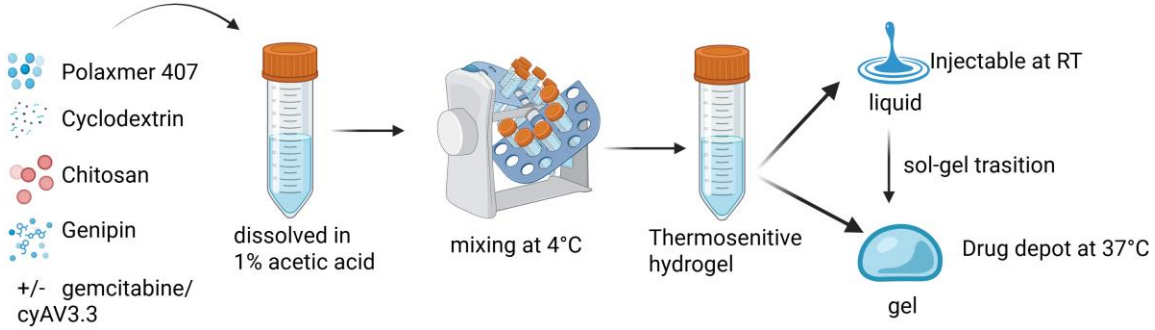






Combine anti-stromal targeting with local therapy to improve drug diffusion

Preparation of ChemoGel



Components/concentration	Gemcitabine (w/w)	cy.AV3.3 (w/w)
ChemoGel	1%	1%
		2%
	2%	1%
		2%

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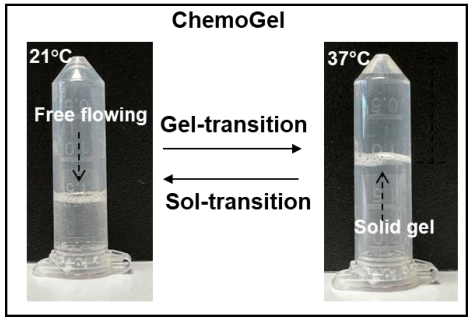
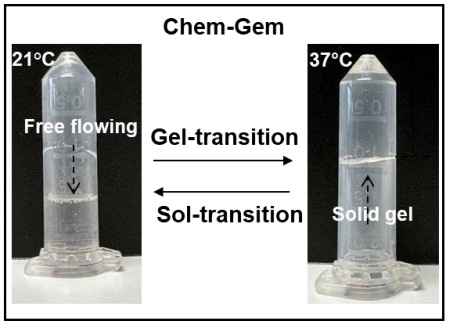
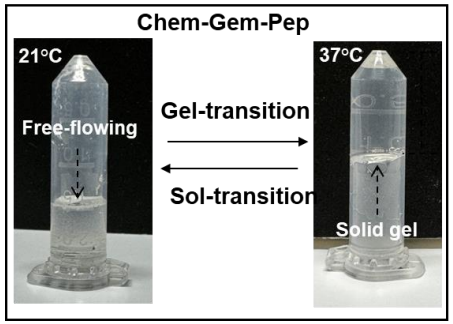
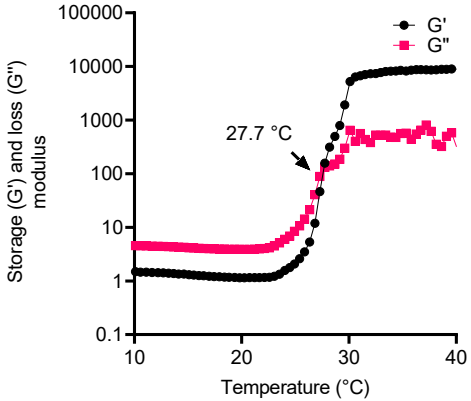
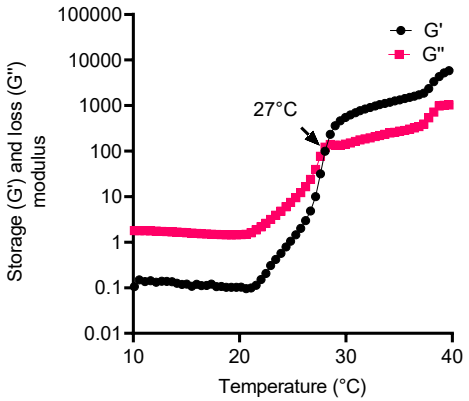
Sol-gel properties - with gemcitabine and peptide

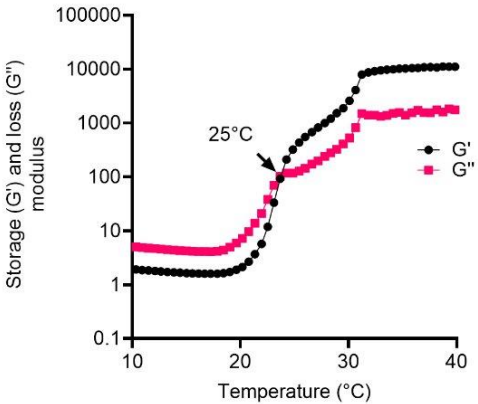




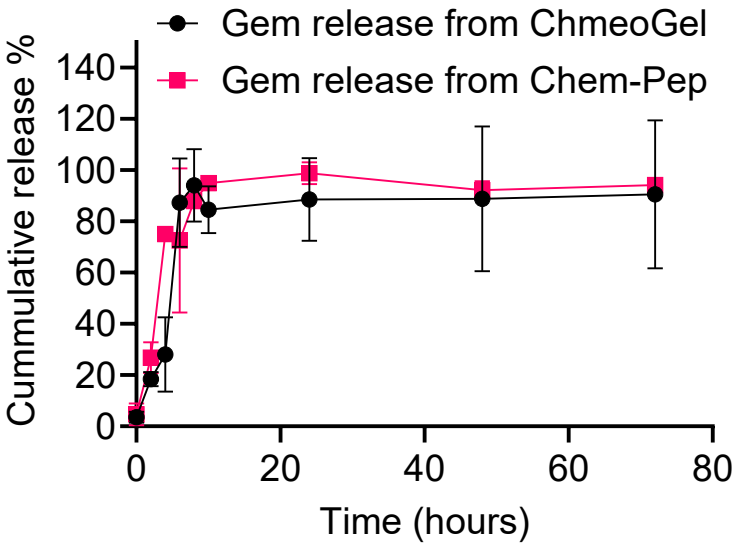


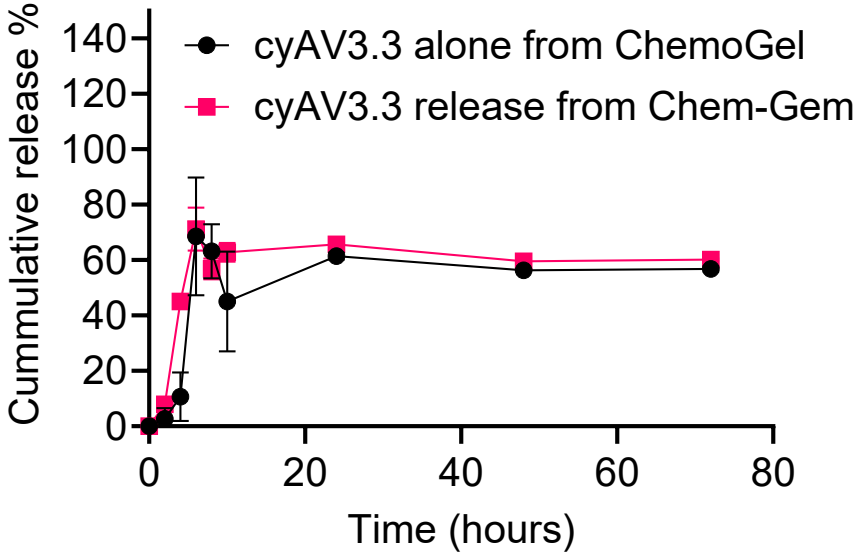






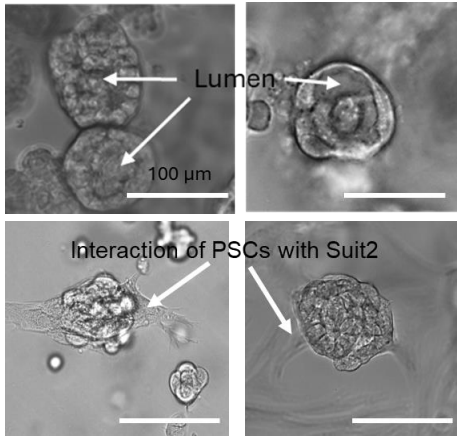
Release properties

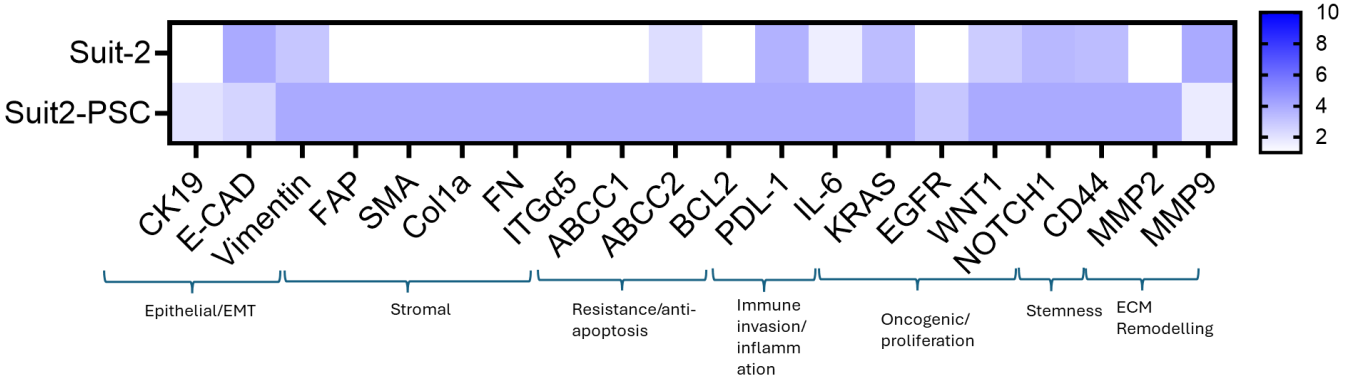


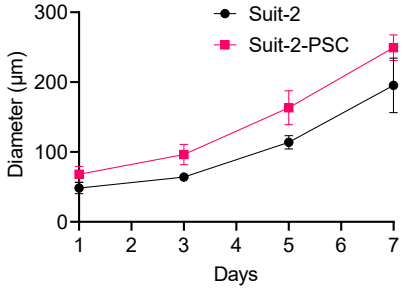


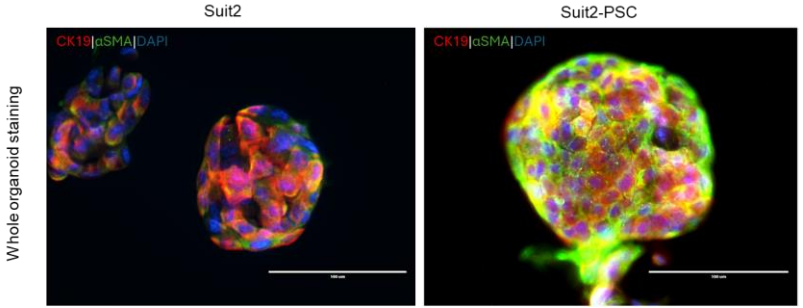
~ 90% of gemcitabine is released by 6h, whereas only ~ 50% of cy.AV3.3 is released at 6h

Setup 3D in vitro cell-line-derived organoid model

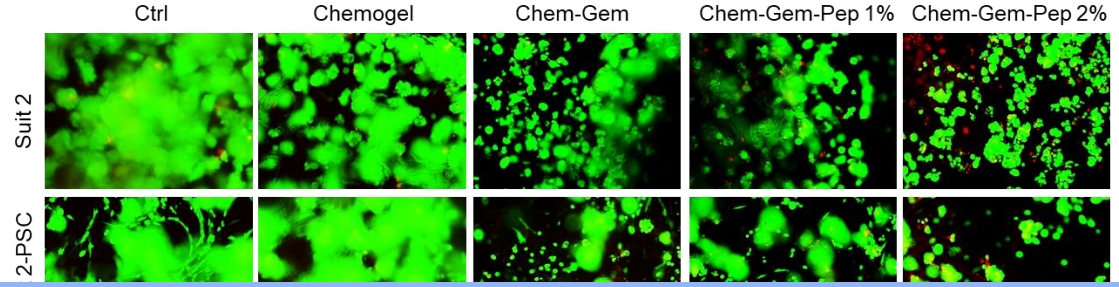




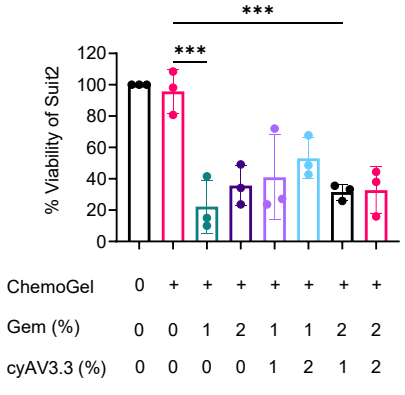


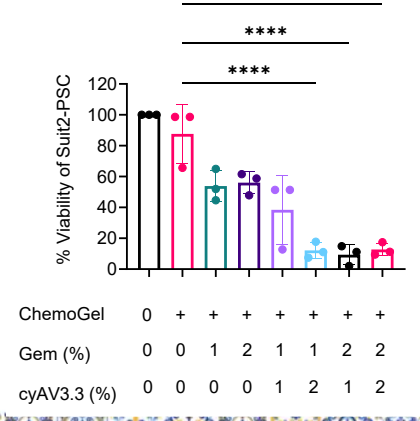


Testing local therapy on 3D invitro model

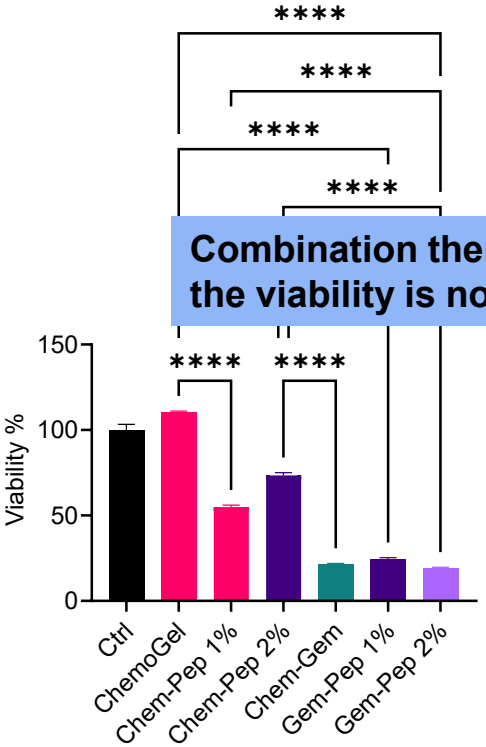


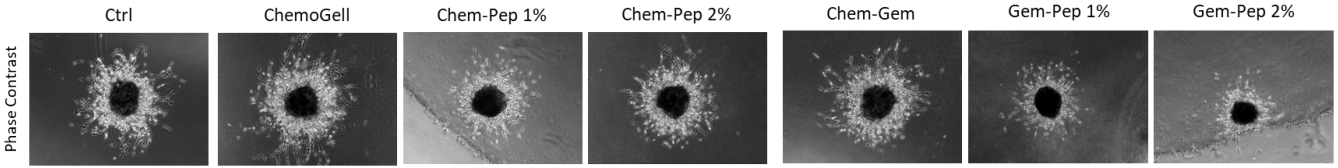
Peptide blocks α5β1 → less FN fibrillogenesis → less TGF-β sequestered in ECM → less TGF-β available to CAF → less collagen produced → stroma remodelled → cytotoxicity



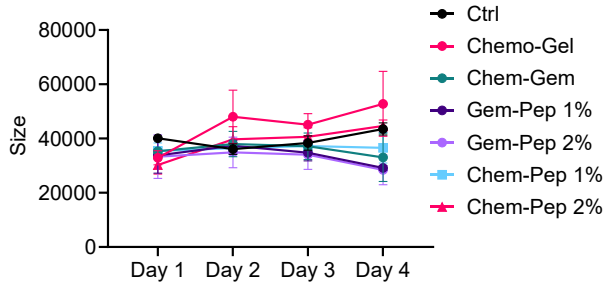


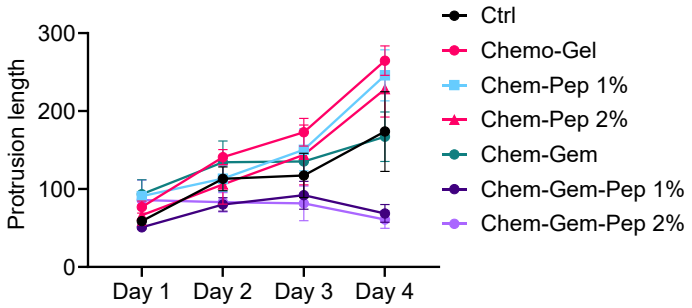
One step ahead: testing in PDOs



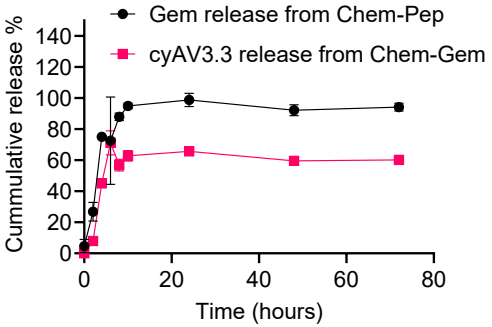


Combination therapy suppresses tumour expansion and invasive morphology; however, the viability is not reduced → slow release of pep → pretreatment with peptide

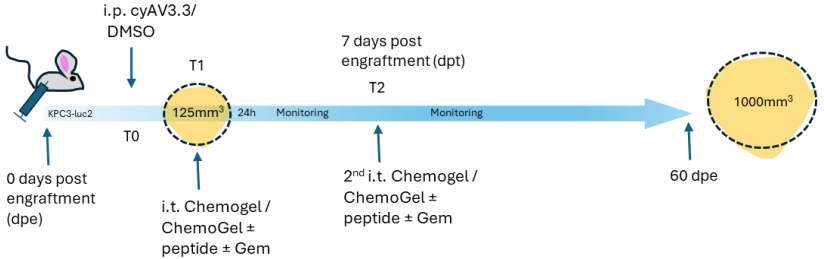


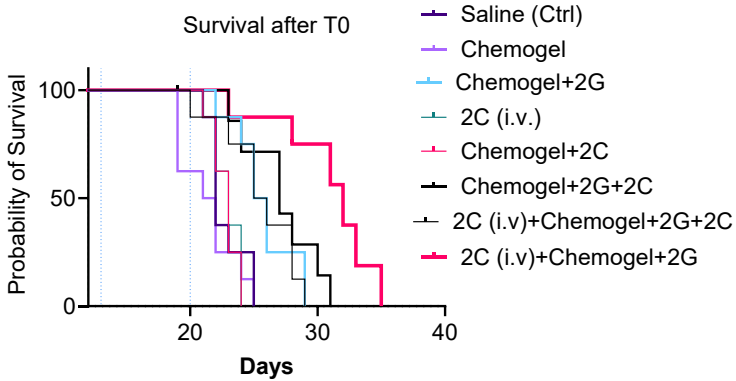


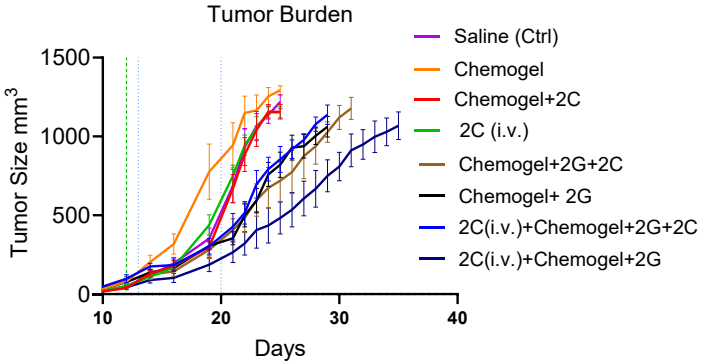
Invivo efficacy



Based on the release study, we included a pretreatment group for in vivo efficacy





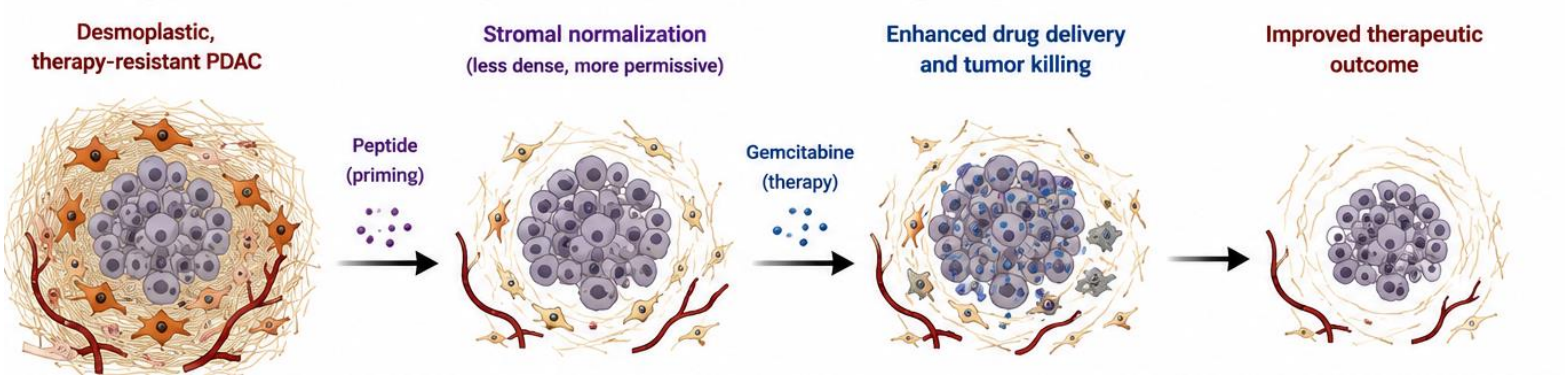


Outlook

Ongoing in vivo experiments and analysis of tumour-stromal crosstalk

Take away message

The peptide alone does not directly suppress tumor growth, but instead functions as a stromal-normalizing/sensitizing agent that enhances gemcitabine efficacy in a context- and timing-dependent manner



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Thank you for your time.
I’m happy to take questions!