Nanoparticles uptake and distribution

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Enzyme-activatable polymer–drug conjugate augments tumour penetration and treatment efficacy

Quan Zhou[1,6], Shiqun Shao[1,6], Jinqiang Wang[2,3], Changhuo Xu[1], Jiajia Xiang[1], Ying Piao[1], Zhuxian Zhou[1], Qingsong Yu[4], Jianbin Tang[1], Xiangrui Liu[1], Zhihua Gan[4], Ran Mo[5], Zhen Gu[2,3]* and Youqing Shen[1]*

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Nanoparticles promote in vivo breast cancer cell intravasation and extravasation by inducing endothelial leakiness

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24th March 2022

Jessica Merulla

EPR effect and tumour delivery

Most cancer nanotherapeutics are delivered intravenously

Defective tumour vessels and impaired lymphatics on the tissue

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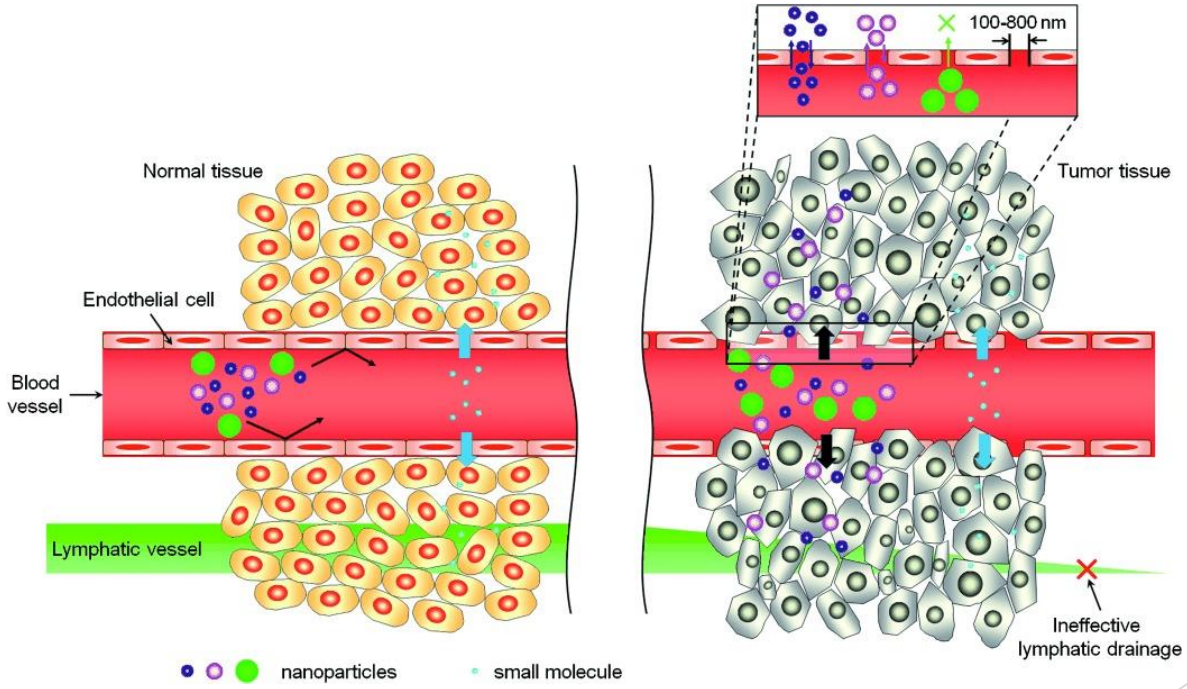
Entry tumour interstitial space and retention



EPR effect and tumour delivery

Oversimplified interpretation of EPR effect

- NPs properties (size, geometry, surface features..) influence EPR effect
- The EPR effect changes within and between different tumours

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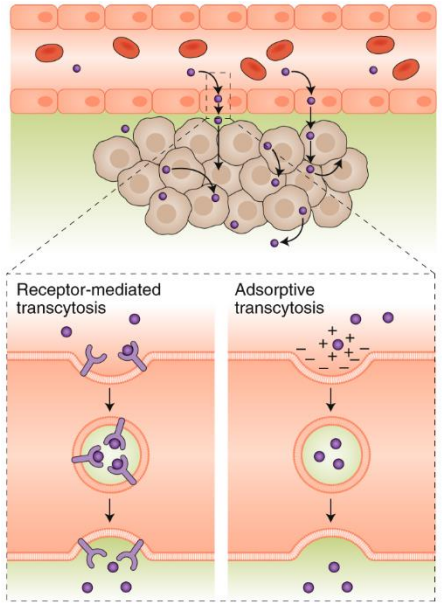
Heterogeneity in vascular leakiness and stromal barriers can became a bottleneck in the efficacy

Transfer NPs through the cells to increase delivery and penetration

Transcellular transfer of nanomedicine

Use paracellular and transcellular transport of endothelial and epithelial cells

Transcytosis



Non-digestive

Caveolae-mediated

Transfer large molecules

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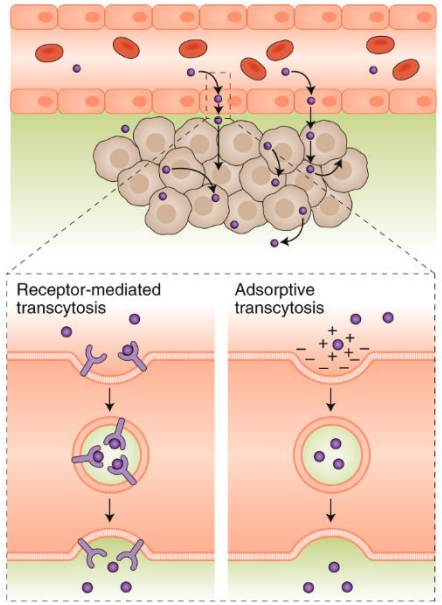
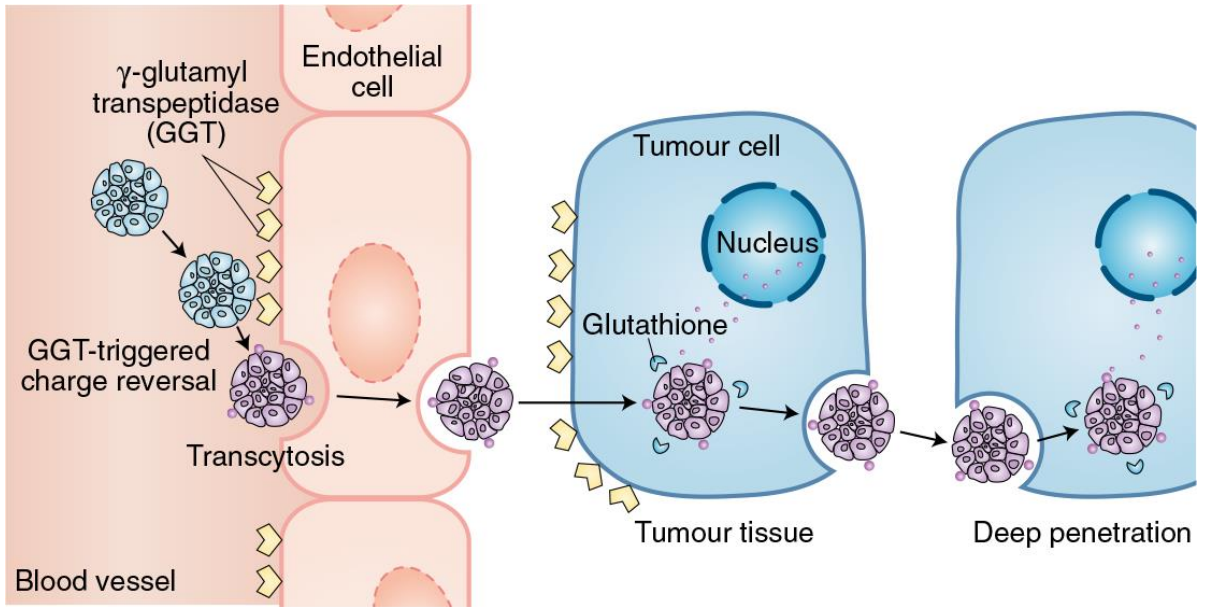
Transcytosis





Non-digestive

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Transfer large molecules

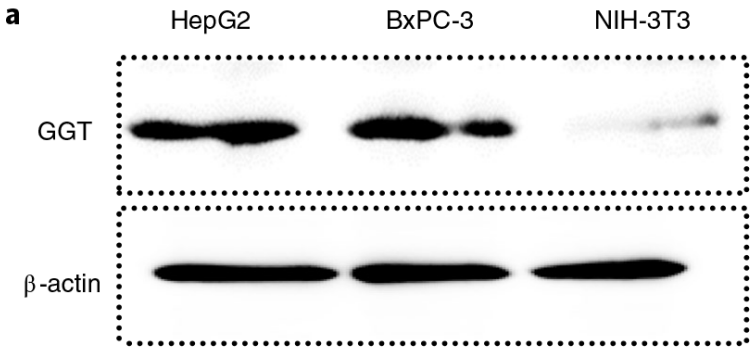
The nanomedicine is polymer PBEAGA-CPT (Camptothecin)

Neutrally charged in blood, positively charged by GGT

Cationization triggers fast endocytosis and transcytosis

Cell cytotoxic assays

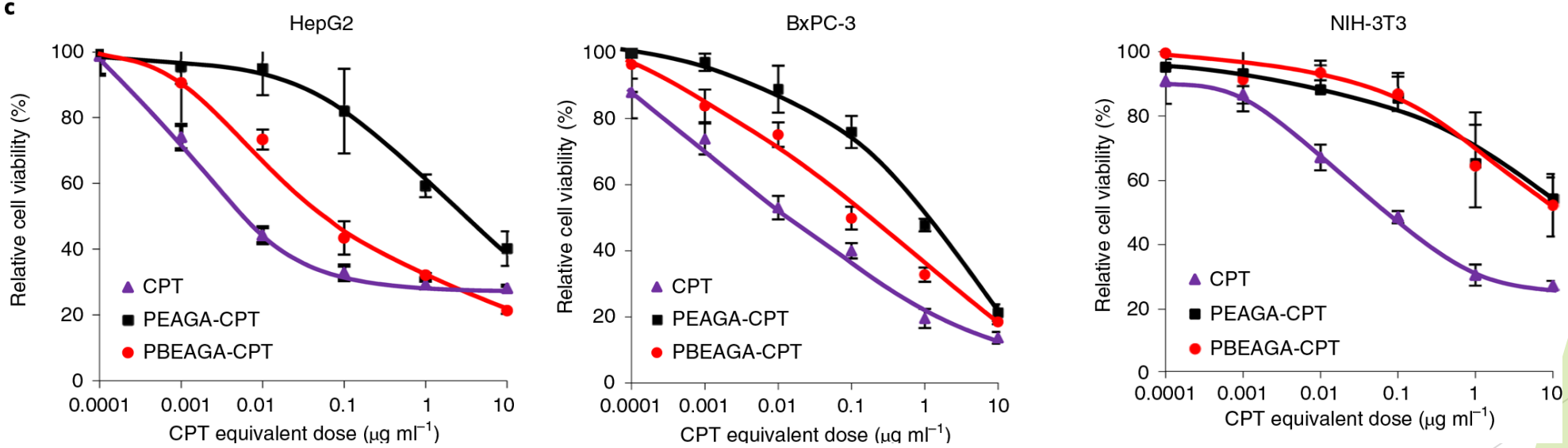
a



b

Cell lines	IC_{50} values (ng ml^{-1})				
	CPT	PBEAGA-CPT	PEAGA-CPT	PBEAGA-CPT (GGsTop)	PEAGA-CPT (GGsTop)
HepG2	24	32	126	560	637
BxPC-3	54	156	756	856	902
NIH-3T3	50	286	283	298	295

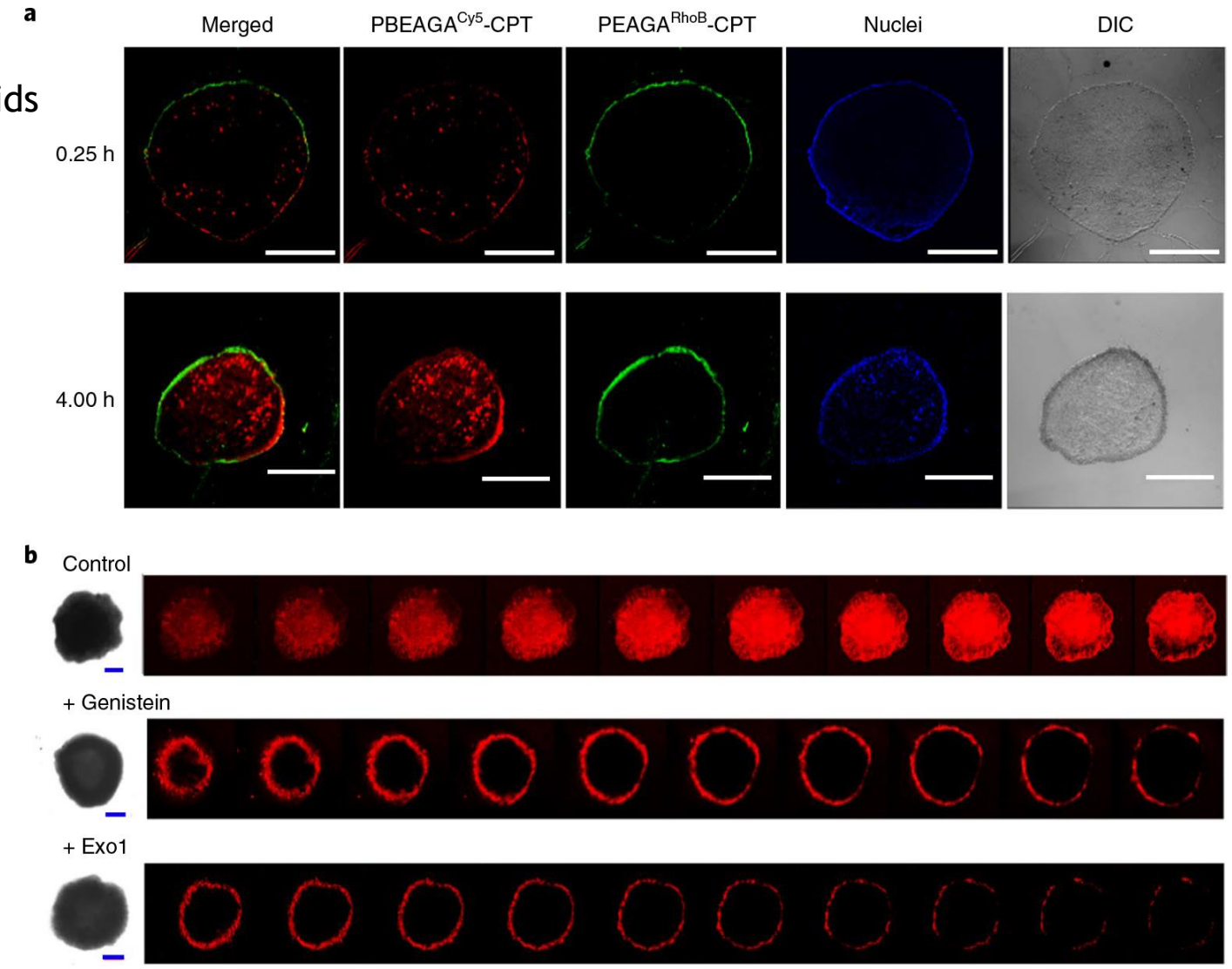
c



PBEAGA-CPT toxicity depends on GGT activity

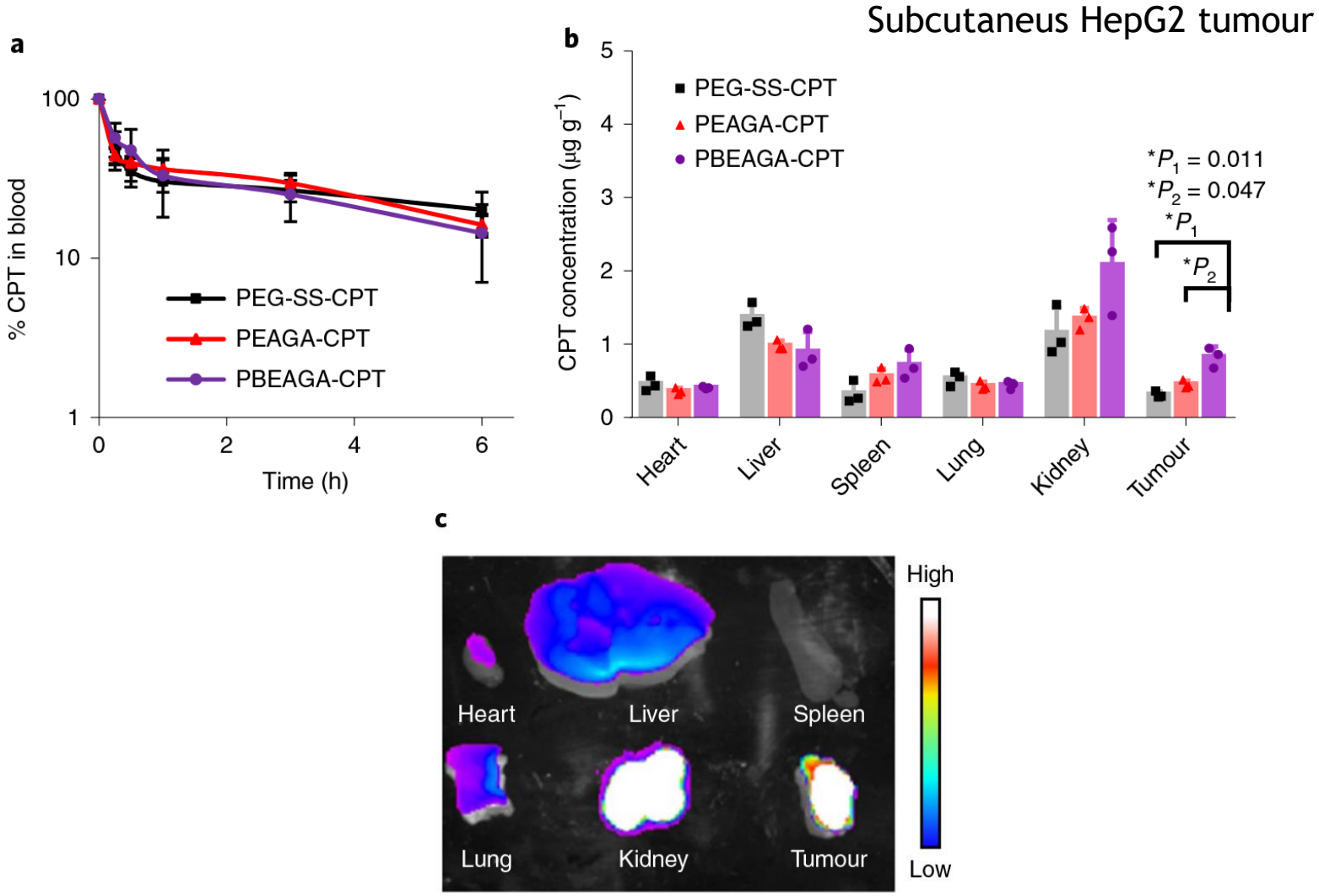
In vitro penetration of polymer-drug conjugates

HepG2 spheroids



Caveolar and Golgi dependent transport

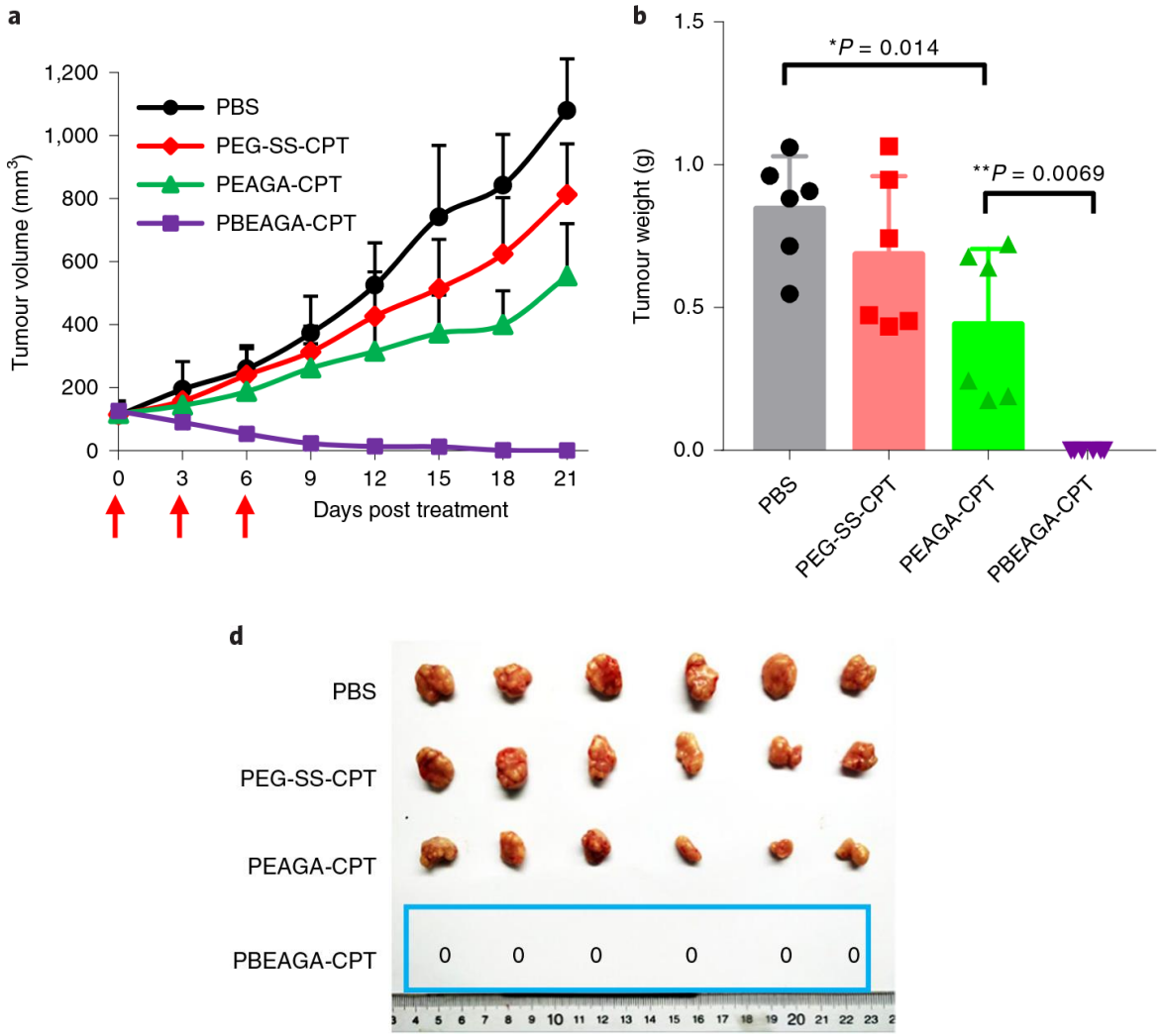
Blood clearance, biodistribution and in vivo penetration



Conjugates are stable in blood and accumulate in tumor

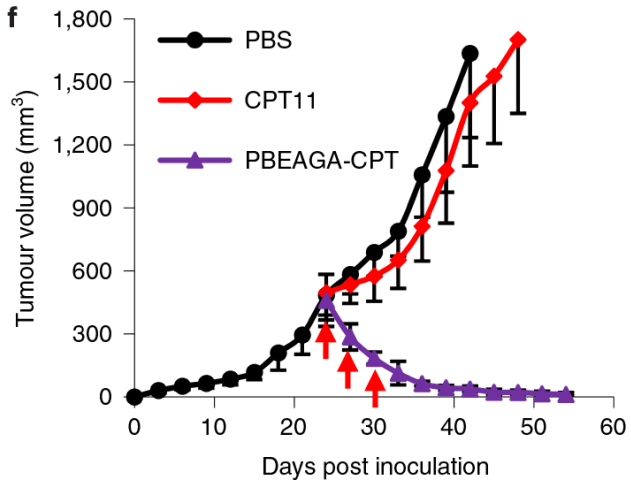
In vivo antitumor efficacy

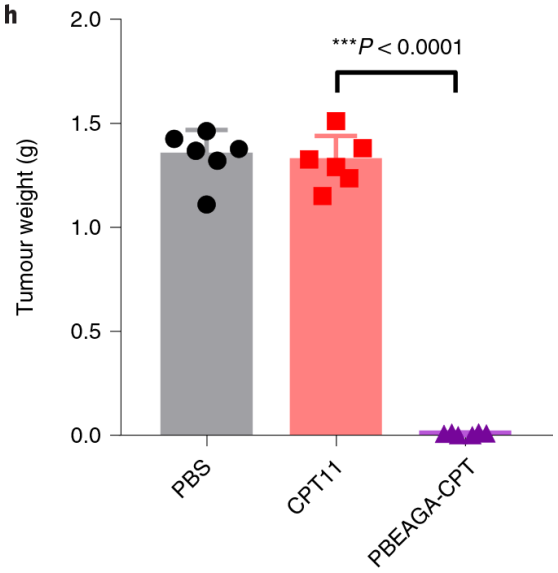
Subcutaneus HepG2 tumour

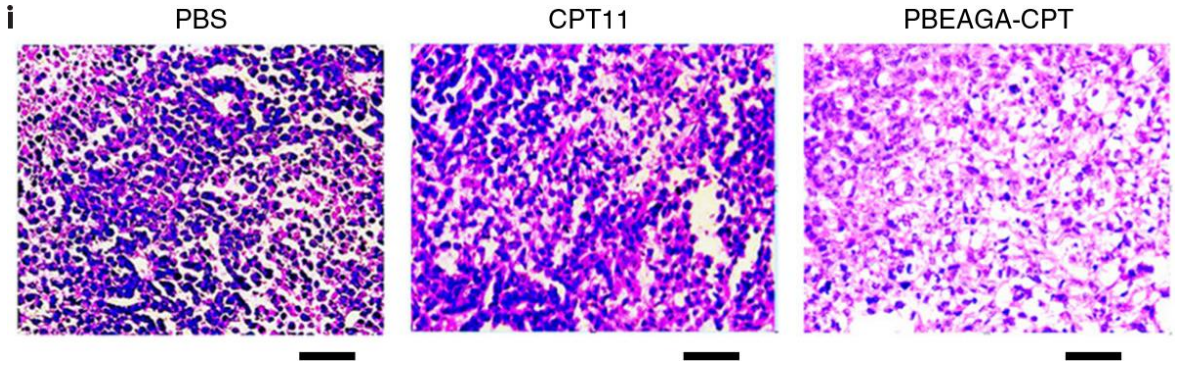


PBEAGA-CPT showed the higher tumour inhibition

In vivo antitumor efficacy

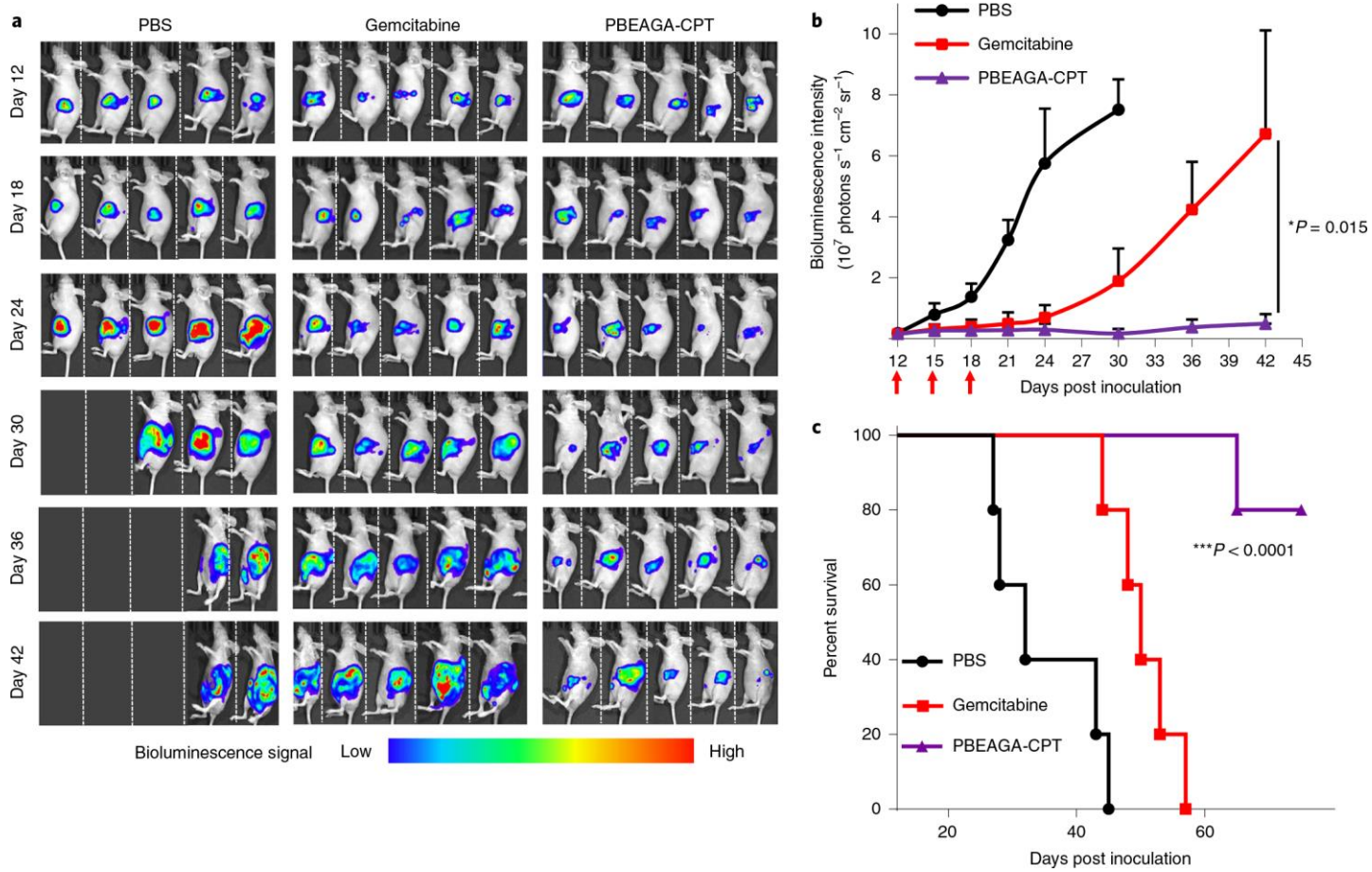






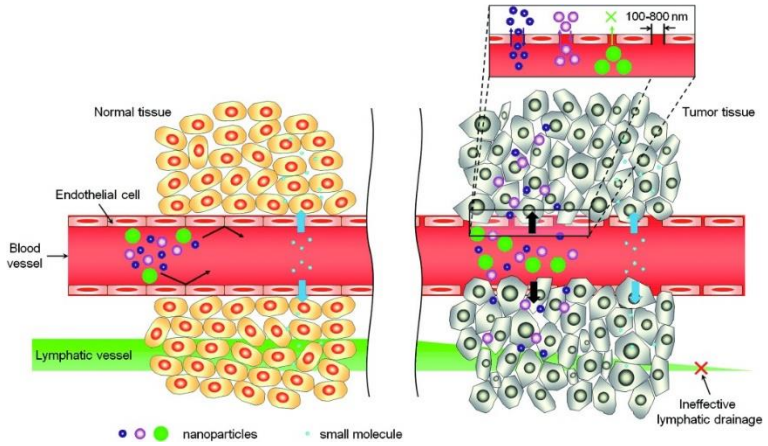
PBEAGA-CPT has high efficacy in large/inoperable tumours

Antitumour activity against orthotopic pancreatic tumour



PBEAGA-CPT is active in orthotopic pancreatic tumour (high GGT activity)

Opening the vascular gate (NanoEL)



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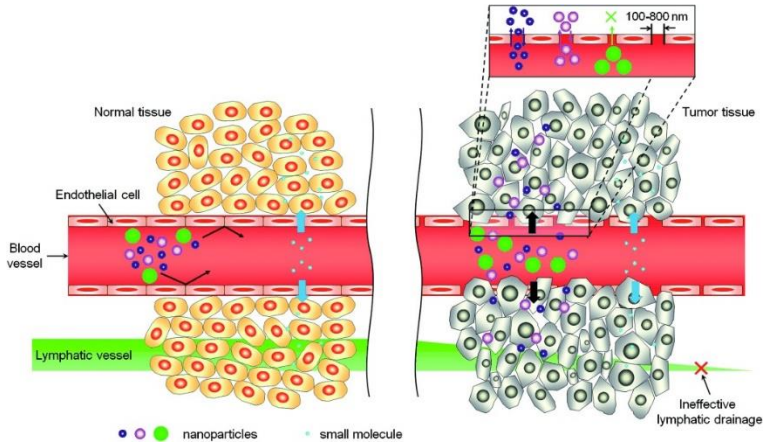

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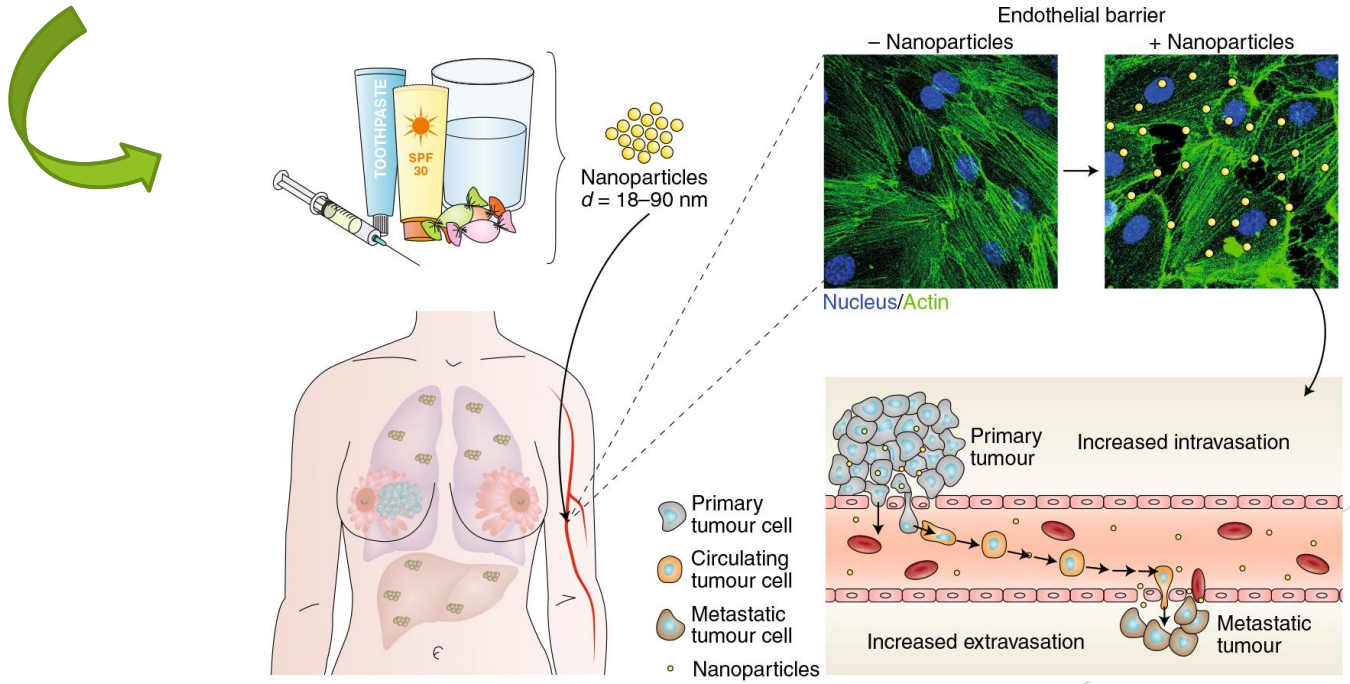
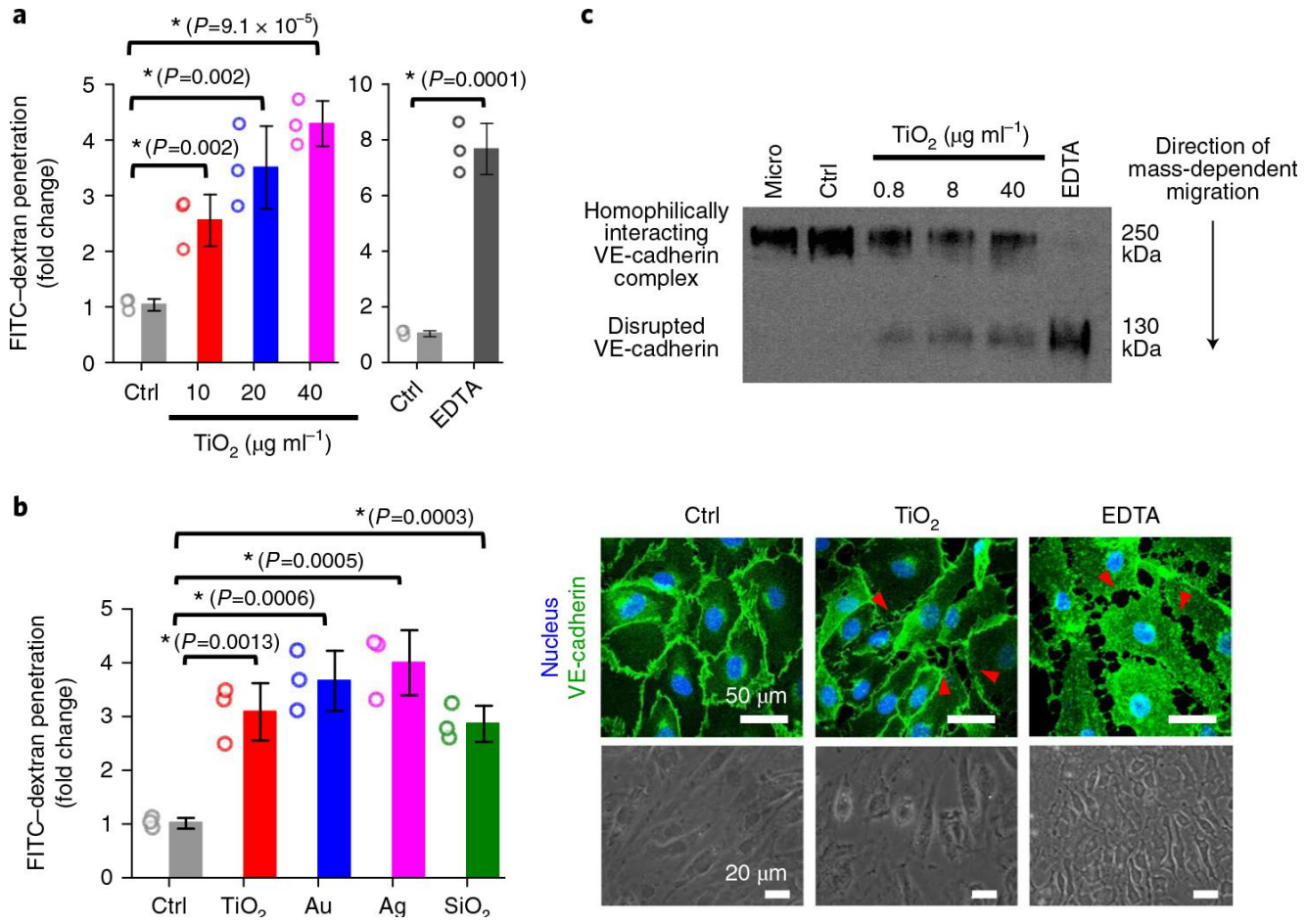
NPs strongly distrupts vascular endothelial barrier and promotes tumour metastasis (NanoEL)

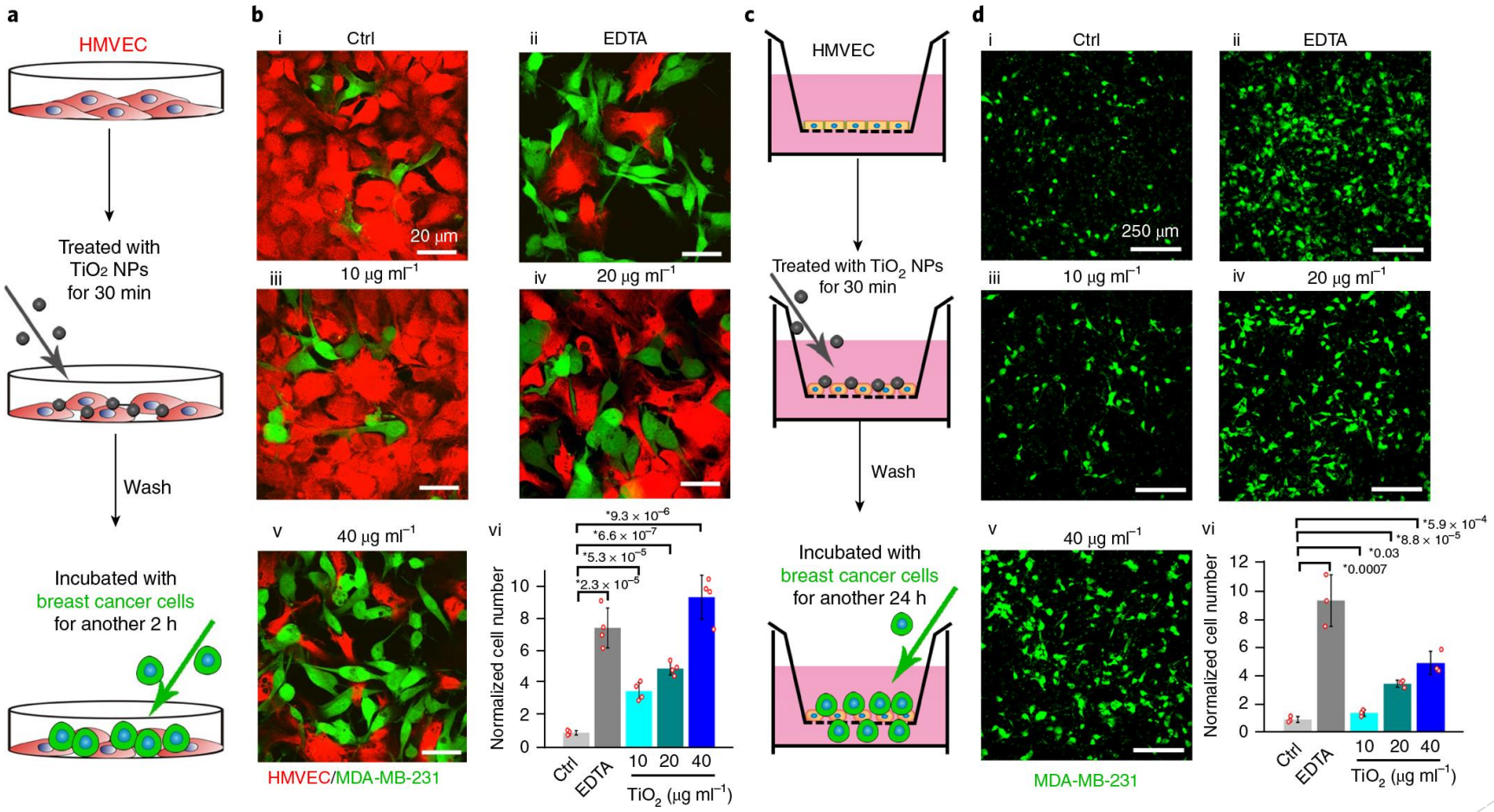


TiO_2 NPs disrupted endothelial cell barrier integrity



Dose dependent damage of endothelial cells barrier depending on VE-cadherin

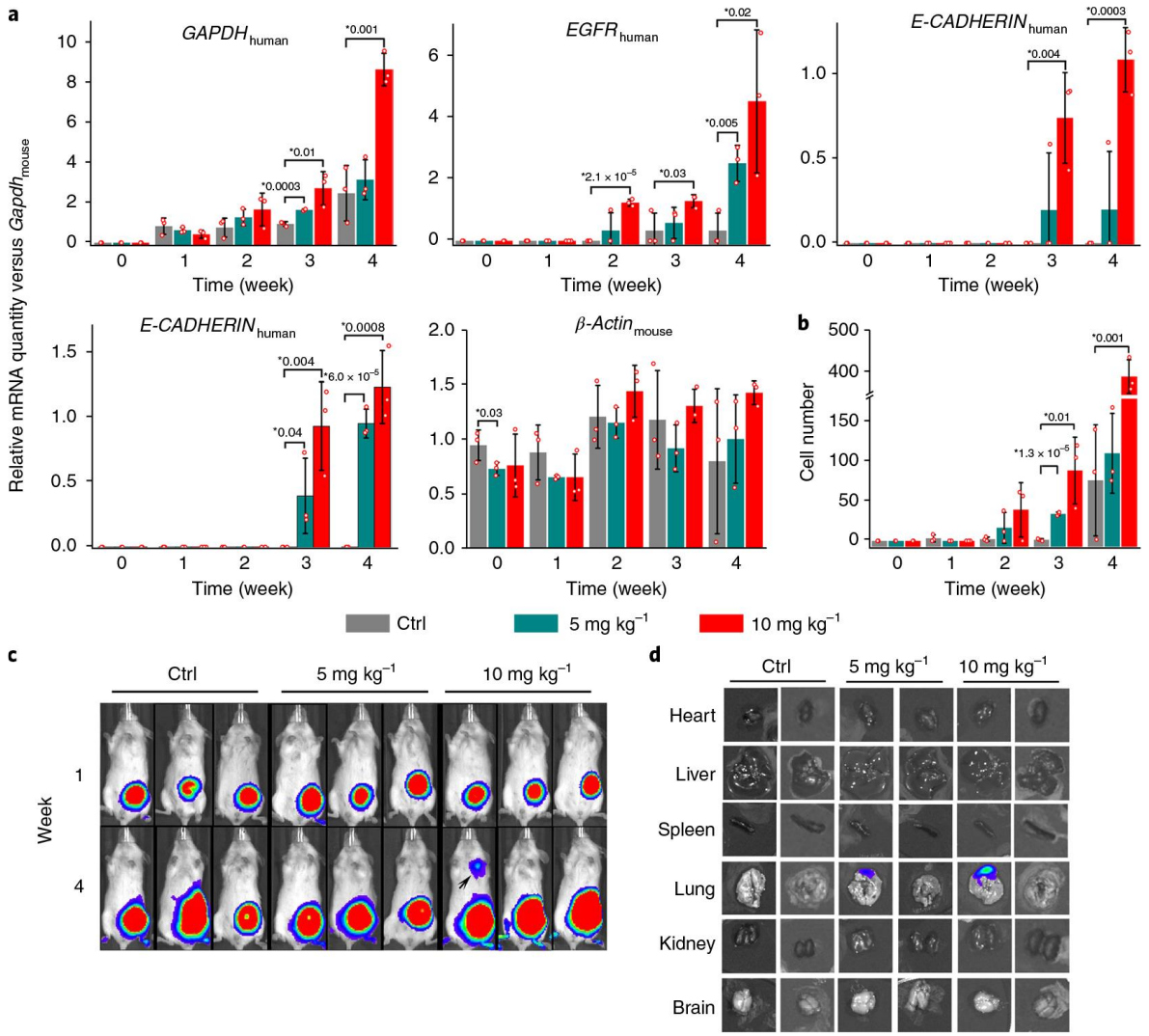
NanoEL increases endothelial permeability of MDA-MB-231



Breast cancer cells migrate across the endothelial barrier

NanoEL facilite metastasis of cancer cells

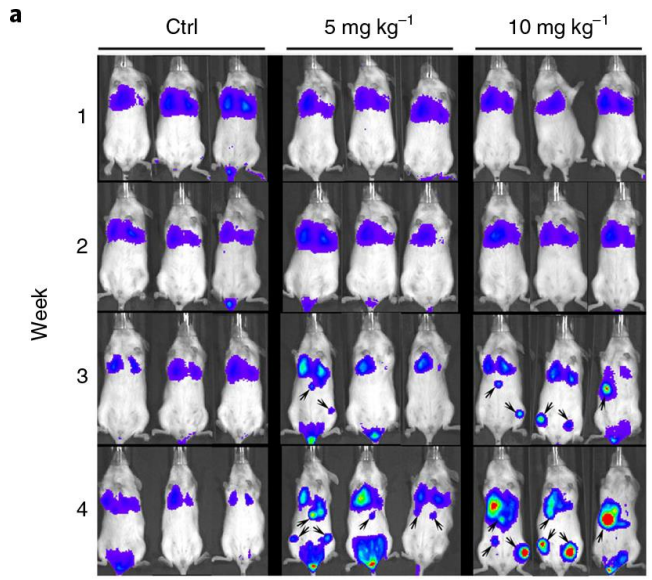
MDA-MB-231 xenograft

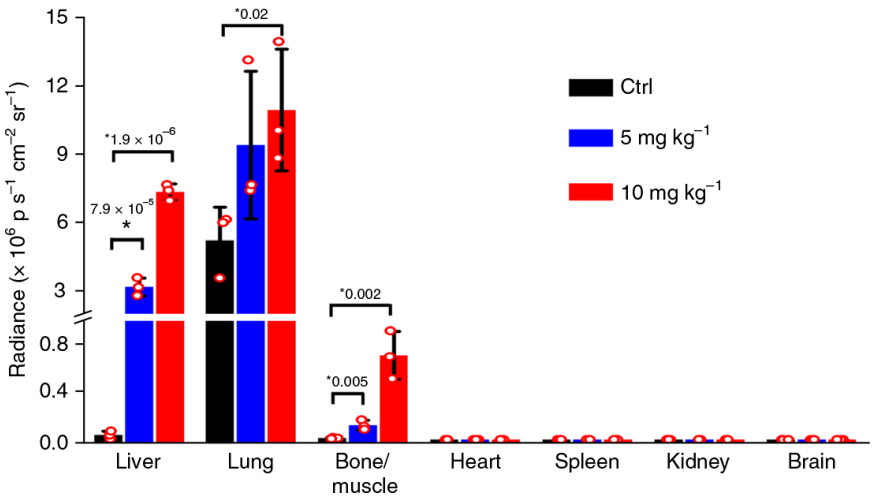


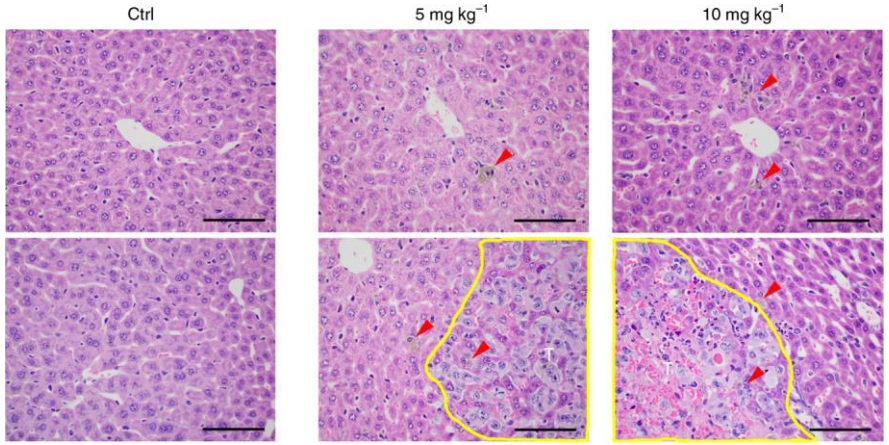
Increased intravasation of tumor cells in the blood circulation

Higher extravasation of circulating breast cancer cells

MDA-MB-231 circulating cells



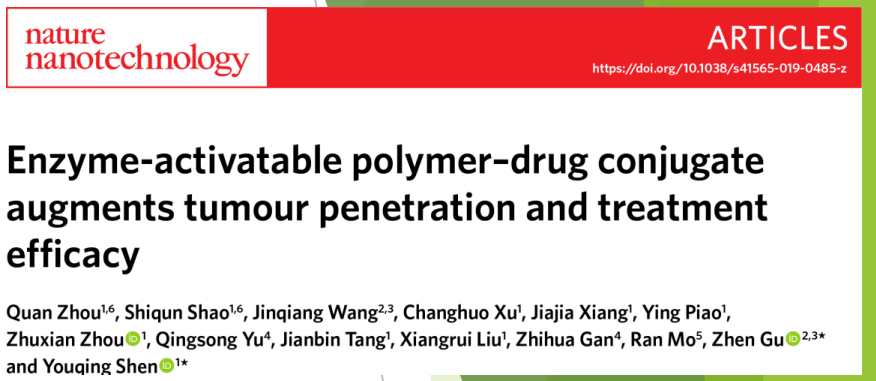




Presence of metastasis in lung and not lung-sites

Conclusion and Discussion points

- Transcytosis can potentially used to reach tumour cells located aware from blood vessel and enhance anticancer drug efficacy
- Rigorous toxicity testing is necessary to confirm the selectivity towards tumours and asses its affect on other organs
- Is charge-switching the only property for nanoparticles that trigger transcytosis?
- NPs in analogy to inflammatory agonists, may destabilize endothelial junctions facilitating migration of cells through the vessel wall
- The work raises interesting issues for nanomedicine design suggesting the direction of therapeutic strategies aimed to normalize tumour vasculature
- Risk of nanomaterials present within the environment (food, paints, cosmetics..)



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