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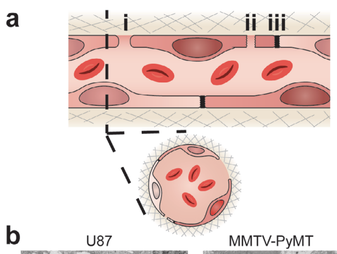
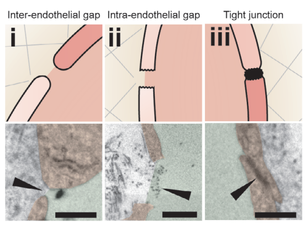
Background

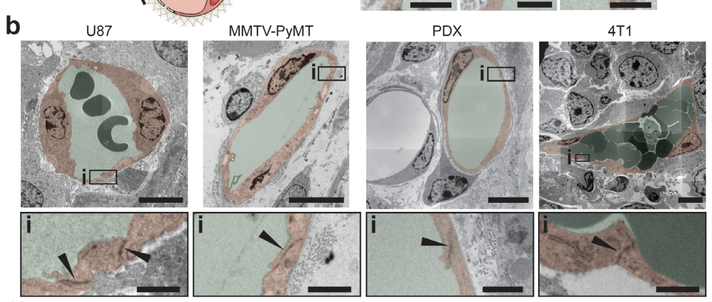
- Nanoparticles have to extravasate from blood vessels and reach tumour to deliver drugs and imaging agents.
- The central dogma of nanomedicine, Enhanced Permeation and Retention (EPR) Effect, postulates that NPs extravasate via inter-endothelial gaps
- Existence of gaps drove researchers to develop nanoparticles for cancer. But, nanoparticle accumulation in tumours remain poor (~1%).
- Thus, we revisted the phenomenon to answer the question: ***How do nanoparticles enter solid tumours?***

Results and Discussion

1. Are there enough gaps to explain accumulation?

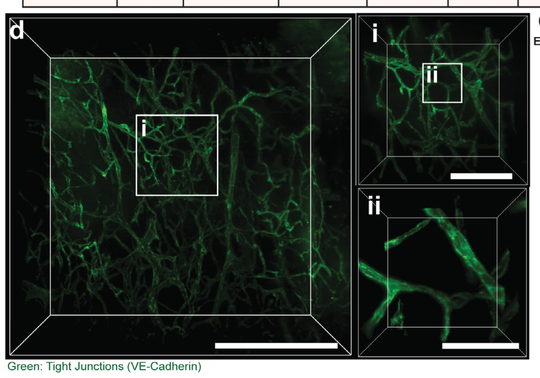






c Vessel characteristics across tumour models

Tumour model	TJ/mm	Fenestrae/mm	Gap Btwn/mm	Gap Wl/mm	# Vessels	Total length (μm)	Total SA (μm²)
U87	154	67	0.8	3.2	161	5366	1197
4T1	161	11	1.7	0.0	27	594	135
MMTV-PyMT	188	93	0.8	0.8	94	2531	634
PDX	131	17	0.0	0.0	17	535	124



Green: Tight Junctions (VE-Cadherin)

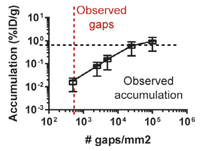
e Equation and Simulation Parameters

$$\frac{\partial n}{\partial t} = D\nabla^2 n(\vec{x},t) + R(n(\vec{x},t),\vec{x},t)$$

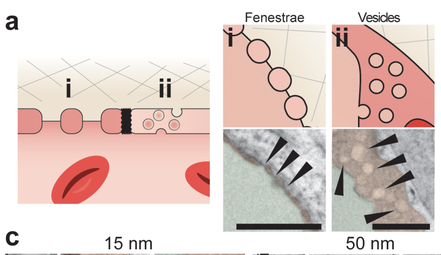
Diffusion Coefficient = 5 X 10^{-15} cm^2/s

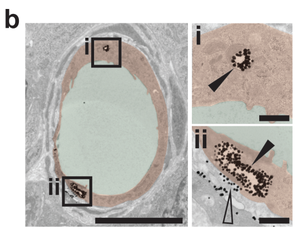
Measured Gap Density = 500 $gaps/mm^2$

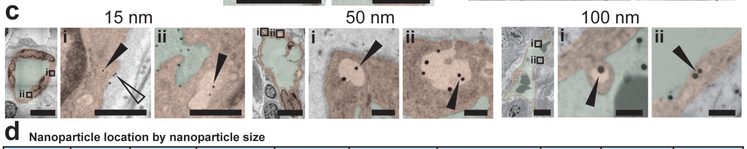
Measured Tumour Accumulation = 0.63% ID/g



2. Can NPs enter tumours through transcytosis?





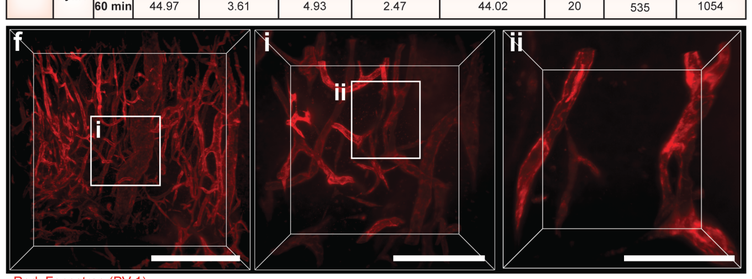


d Nanoparticle location by nanoparticle size

NP size	Model	Lumen (%)	Side wall (%)	Vesicles (%)	Cytoplasm (%)	Extravascular (%)	# Vessels	Length (μm)	Total # NPs
15 nm	U87	35.55	12.70	0.08	3.63	48.04	26	969	2371
	PyMT	77.35	3.60	0.53	3.79	14.73	22	451	8547
50 nm	U87	65.20	4.68	0.00	0.26	29.85	26	653	3052
	PyMT	60.25	7.45	0.62	2.40	29.28	15	394	1127
100 nm	U87	64.43	14.43	0.26	0.52	20.36	20	739	388
	PyMT	92.84	3.46	0.58	0.12	3.00	22	843	866

e Nanoparticle location by time post injection

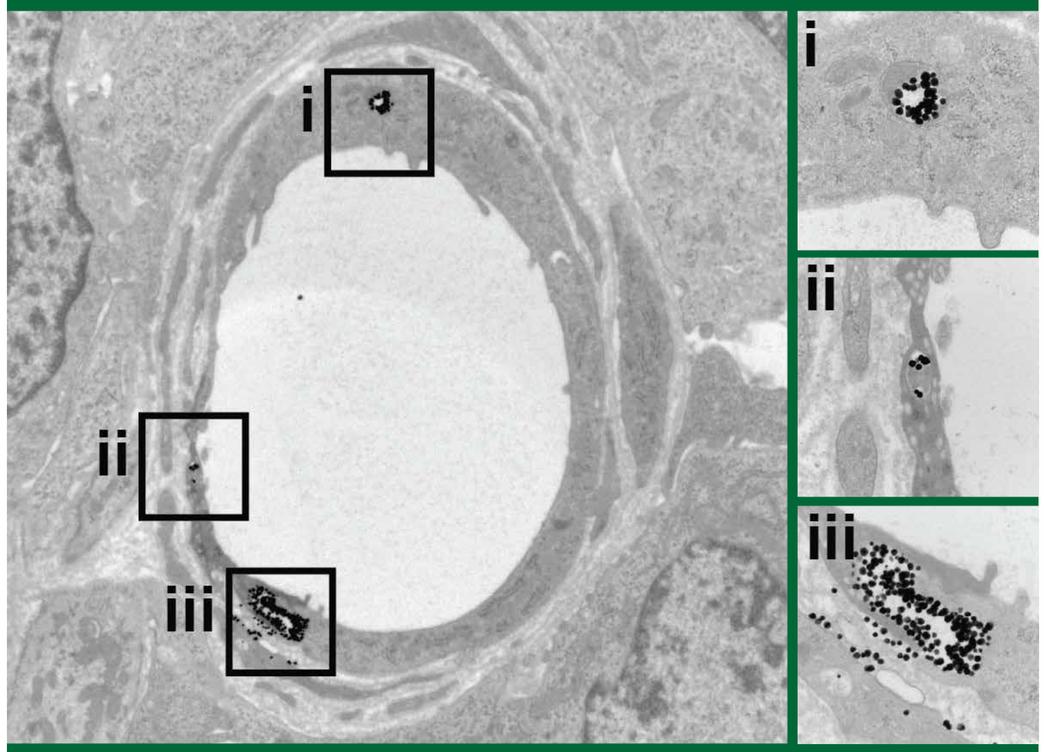
NP size	Model	Time	Lumen (%)	Side wall (%)	Vesicles (%)	Cytoplasm (%)	Extravascular (%)	# Vessels	Length (μm)	Total # NPs
50 nm	U87	15 min	65.20	4.68	0.00	0.26	29.85	26	653	3032
		60 min	49.47	6.99	0.00	3.35	40.19	21	606	1045
	PyMT	15 min	60.25	7.45	0.62	2.40	29.28	15	394	1127
		60 min	44.97	3.61	4.93	2.47	44.02	20	535	1054



Red: Fenestrae (PV-1)

Q: How do nanoparticles enter solid tumours?

Ans: Nanoparticles enter solid tumours through trans-endothelial pathways, not inter-endothelial gaps



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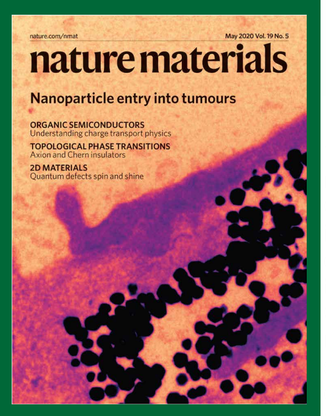
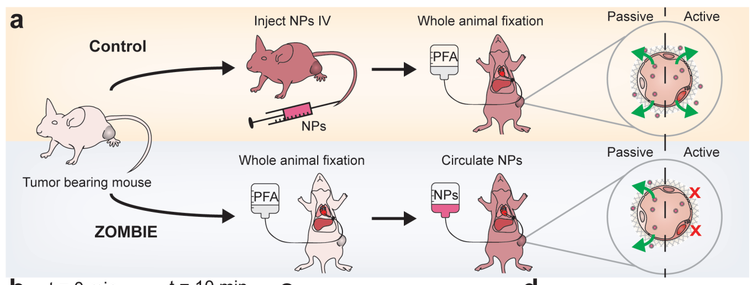
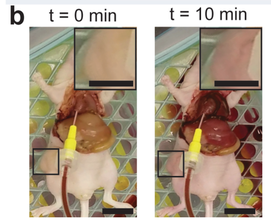
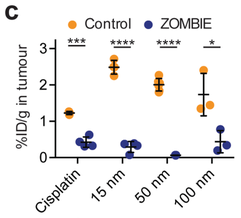


3. What is the dominant mechanism ?

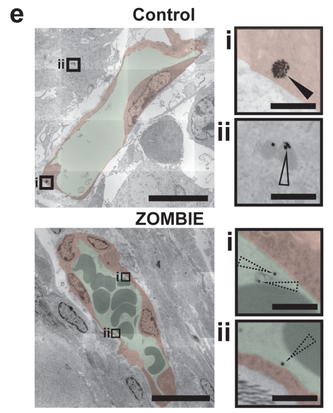


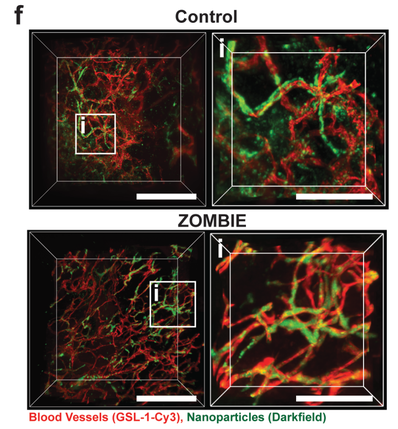




d Relative contribution of gaps

NP Type	% Attributed to gaps
Cisplatin	35%
15 nm	12%
50 nm	3%
100 nm	25%





Blood Vessels (GSL-1-Cy3), Nanoparticles (Darkfield)

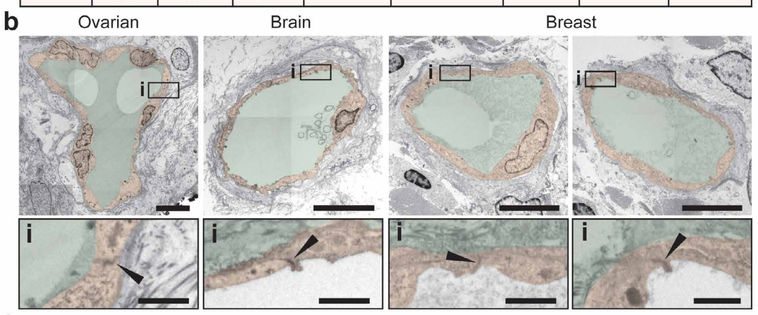
g Location of nanoparticles from TEM imaging

Model	Lumen (%)	Side wall (%)	Vesicles (%)	Cytoplasm (%)	Extravascular (%)	# Vessels	Length (μm)	Total # NPs
Control	21.1	2.5	16.7	20.3	39.4	22	596	2281
ZOMBIE	68.1	30.8	0.0	1.1	0.0	6	191	91

4. What is the likely mechanism in humans?

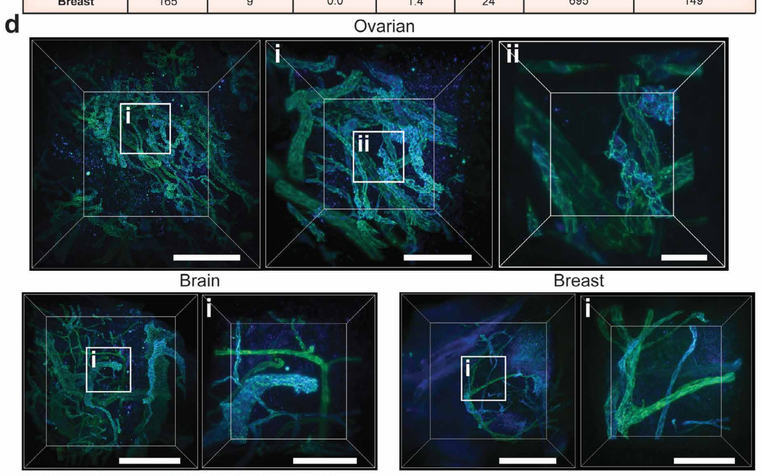
a Nanoparticle location by tumour type

Model	Lumen (%)	Side wall (%)	Vesicles (%)	Cytoplasm (%)	Extravascular (%)	# Vessels	Length (μm)	Total # NPs
U87	65.20	4.68	0.00	0.26	29.85	26	653	3032
PyMT	60.25	7.45	0.62	2.40	29.28	15	394	1127
4T1	41.36	5.72	6.19	6.00	40.73	27	594	3165
PDX	3.78	3.85	1.47	3.78	87.13	17	535	1430



c Frequency of human tumour vessel features

Tumour type	TJ/mm	Fenestrae/mm	Gap Btwn/mm	Gap Wl/mm	# Vessels	Total length (μm)	Total SA (μm²)
Ovarian	130	5	0.0	0.0	29	941	205
Brain	228	61	0.0	0.0	14	289	79
Breast	165	9	0.0	1.4	24	695	149



VE-Cadherin (Tight junctions), PV-1 (Fenestrae)

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