

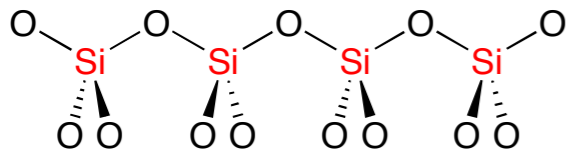
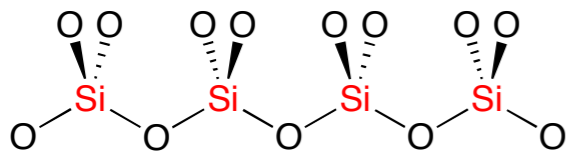
A scanning electron micrograph (SEM) showing a dense collection of spherical, porous silica particles. The particles vary slightly in size and are characterized by a textured, porous surface. They are arranged in a disordered, close-packed manner, filling the entire frame.

Porous Silica Particles in Biology: Studies on Cellular Uptake, Molecular Delivery, and Imaging

Christopher Landry
Department of Chemistry
University of Vermont

Geological Society of America
Bretton Woods, NH
March 19, 2013

Zeolites

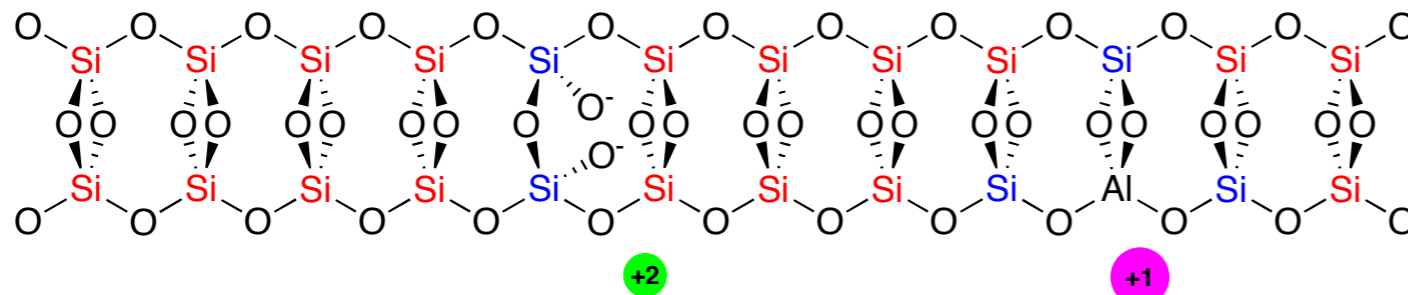
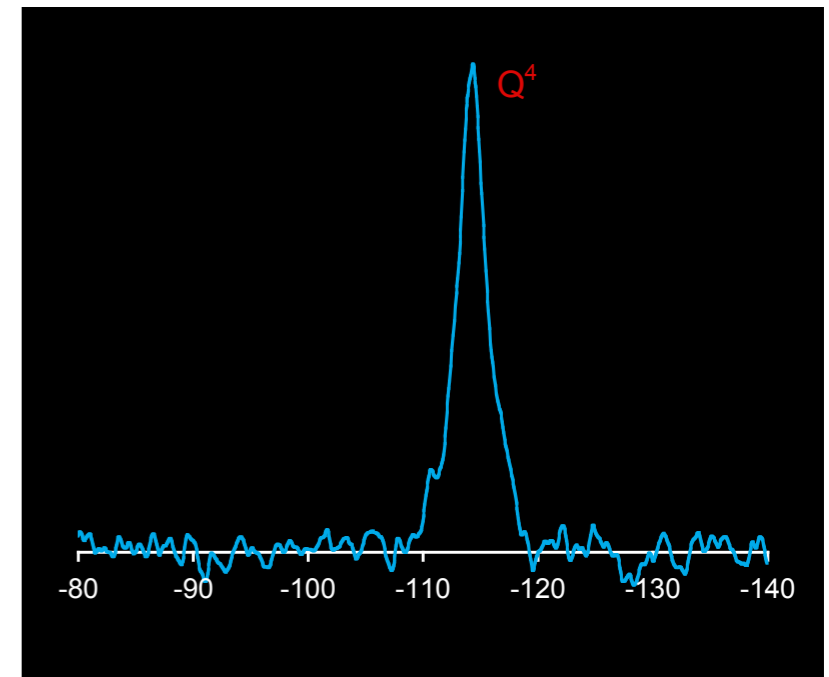


Q^4 = fully polymerized SiO_2

$\delta \approx -110$ ppm in ^{29}Si SSNMR

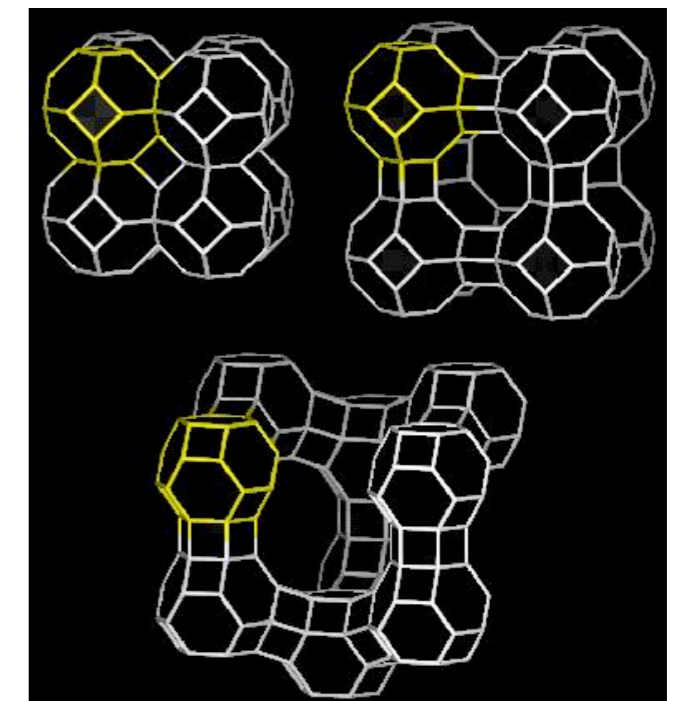
Q^3 = incompletely polymerized SiO_2 (bulk or surface defect)

$\delta \approx -100$ ppm (Si-O^-); -90 ppm (Si-O-M)

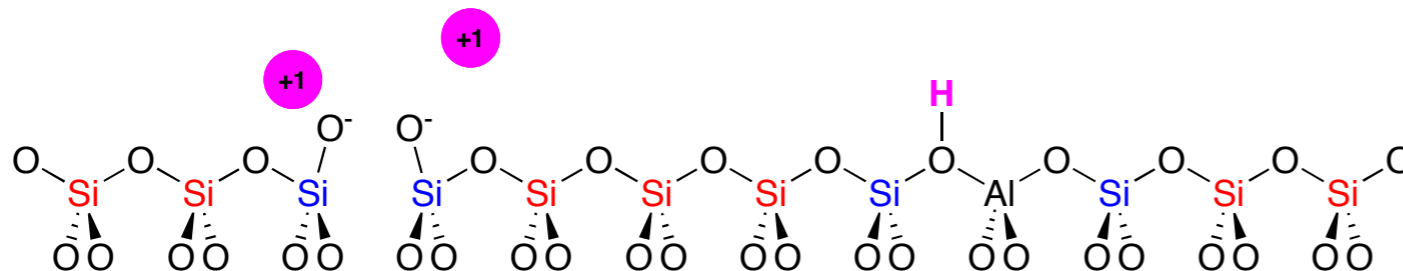


SOD

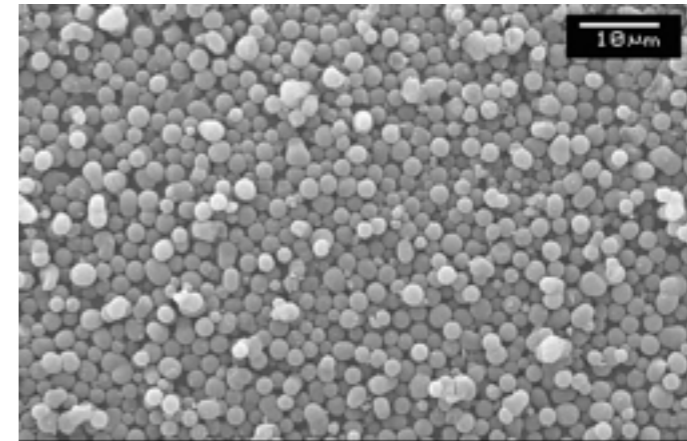
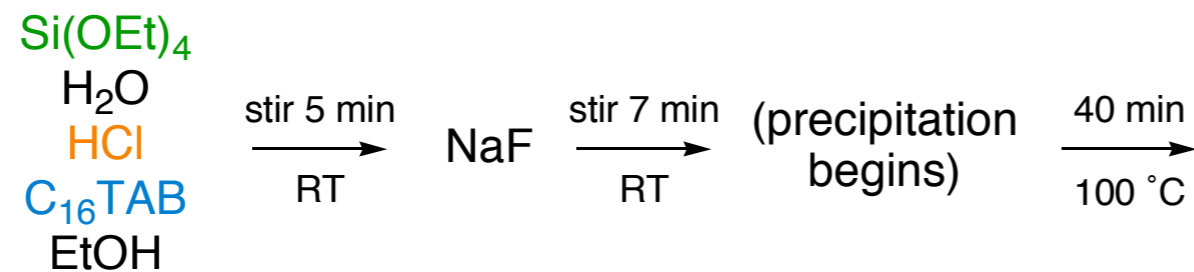
LTA



FAU (LTY)

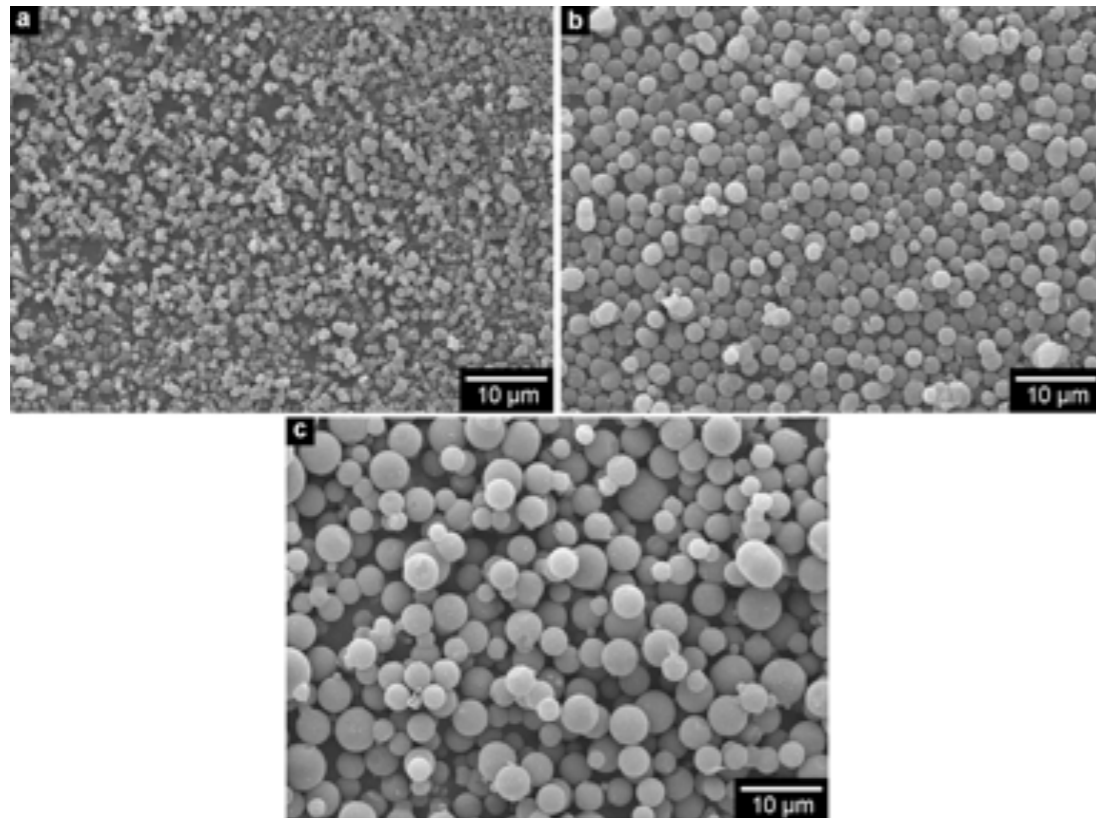


Acid-Prepared Mesoporous Spheres (APMS)



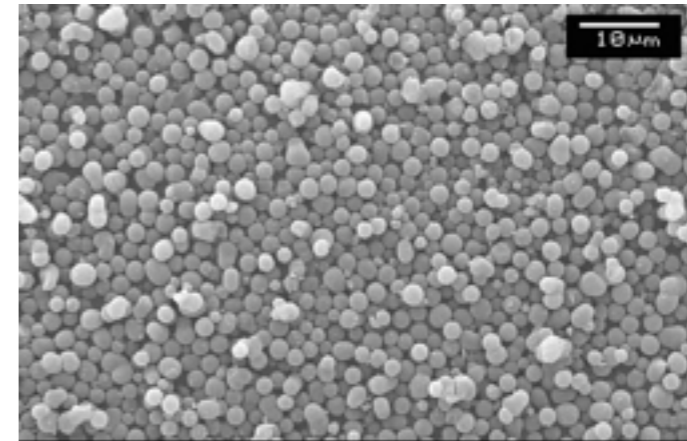
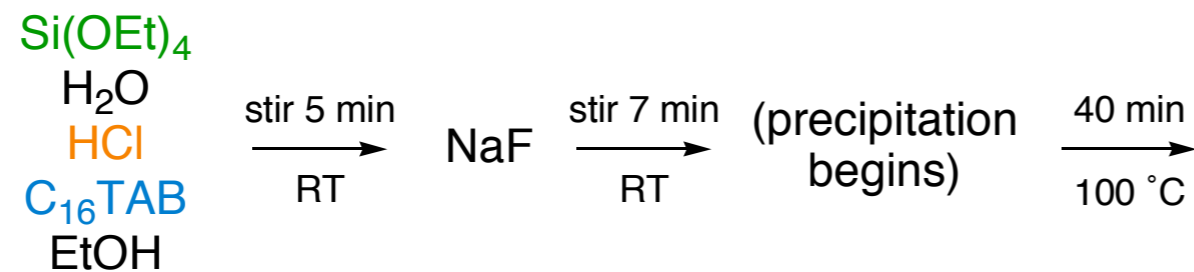
EtOH: slows polymerization rate of Si(OEt)_4
 F^- : increases number of nucleation sites
 heat: increases polymerization rate

} adjusting variables relative to each other
 allows control over diameter of spheres



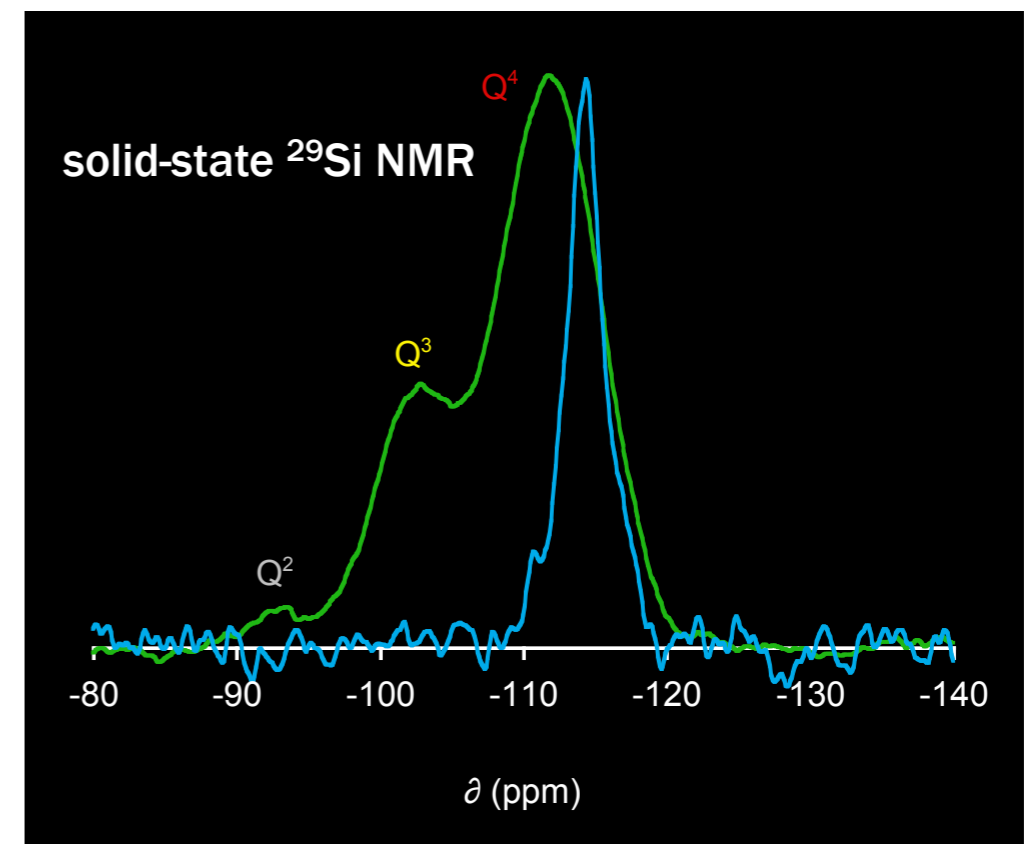
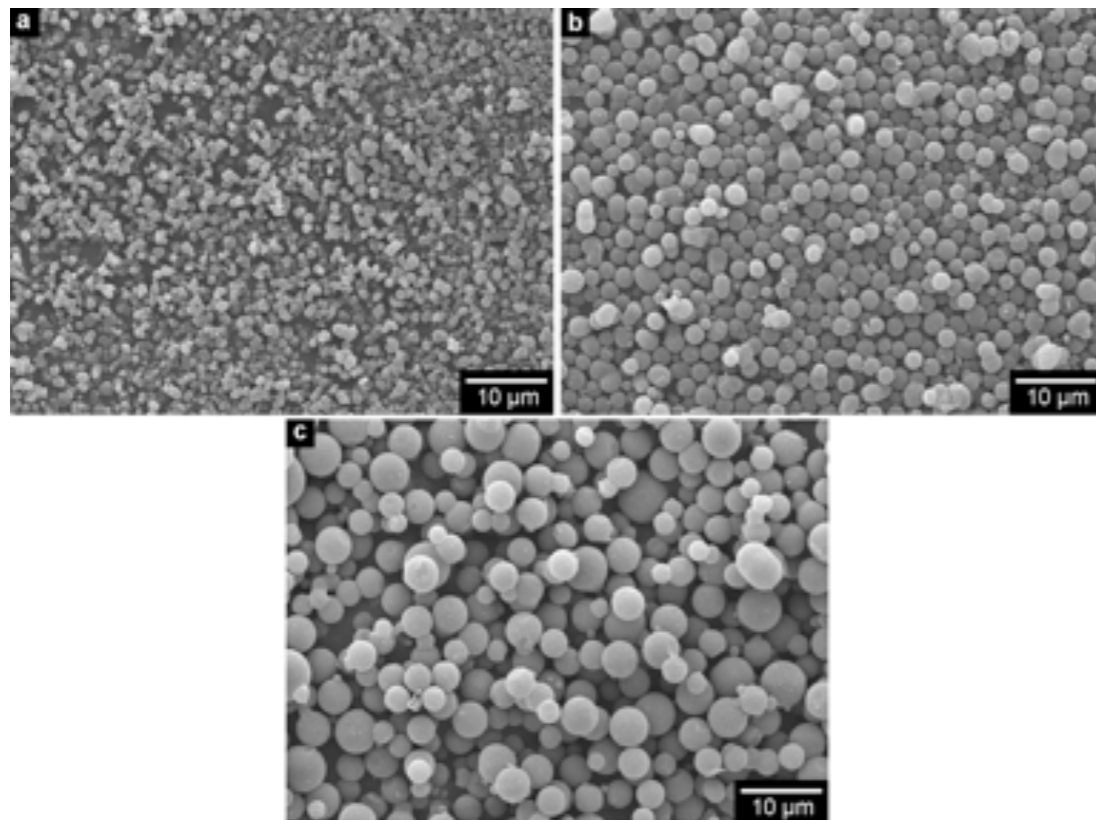
	particle diameter (μm)	NaF (mg)	EtOH (wt %)	S_{BET} (m ² /g)	V_{pore} (cm ³ /g)	d_{pore} (nm)
a	0.5 - 1.0	200	30	1022	1.35	3.9
b	1.5 - 2.5	100	20	894	1.20	4.8
c	2.5 - 5.0	50	10	672	1.15	6.6

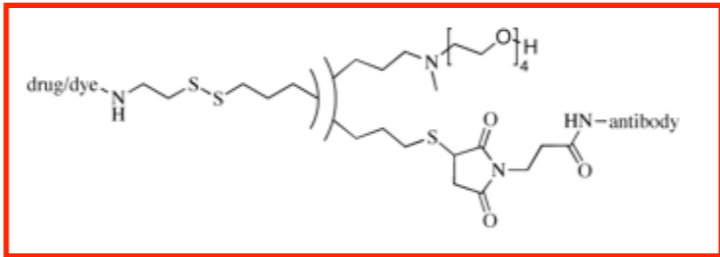
Acid-Prepared Mesoporous Spheres (APMS)



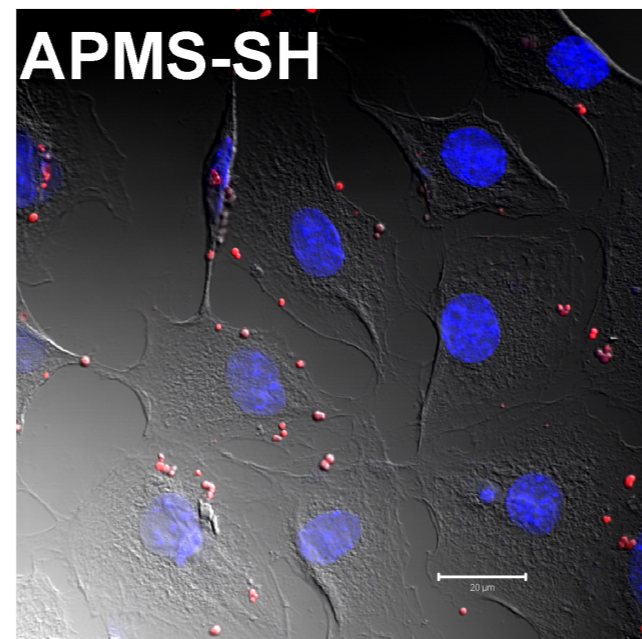
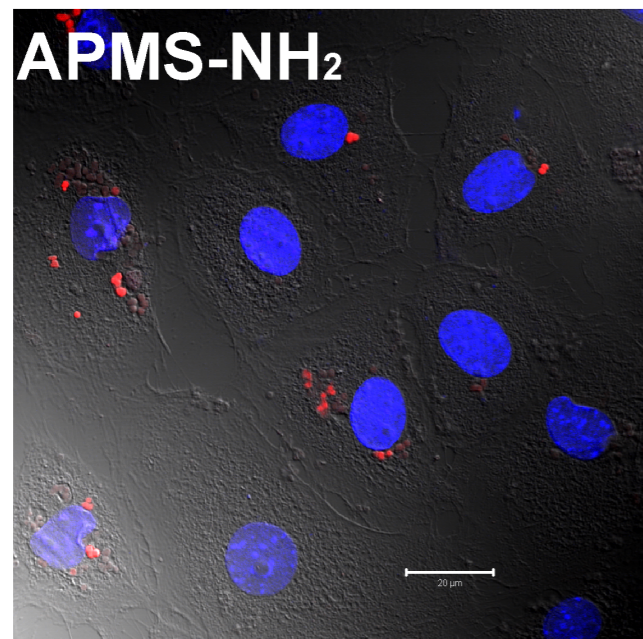
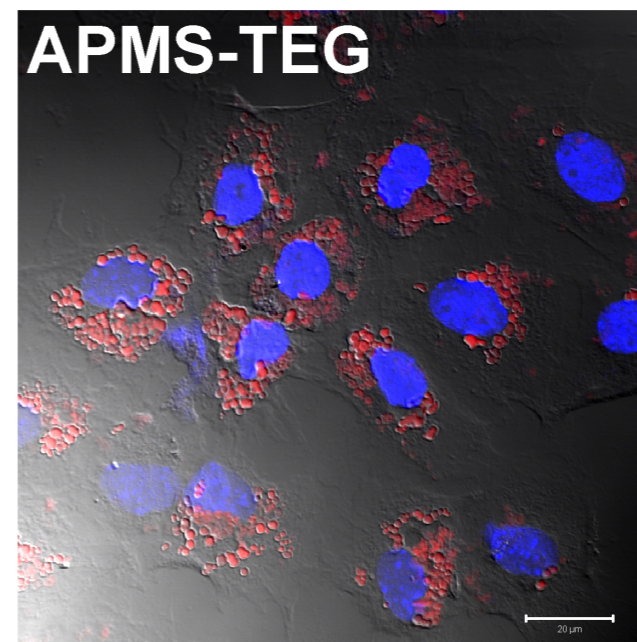
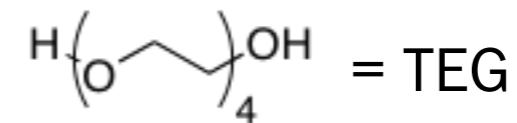
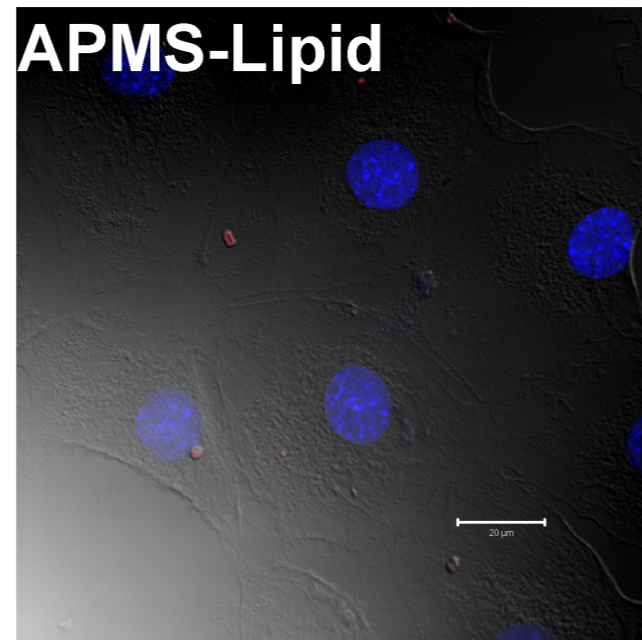
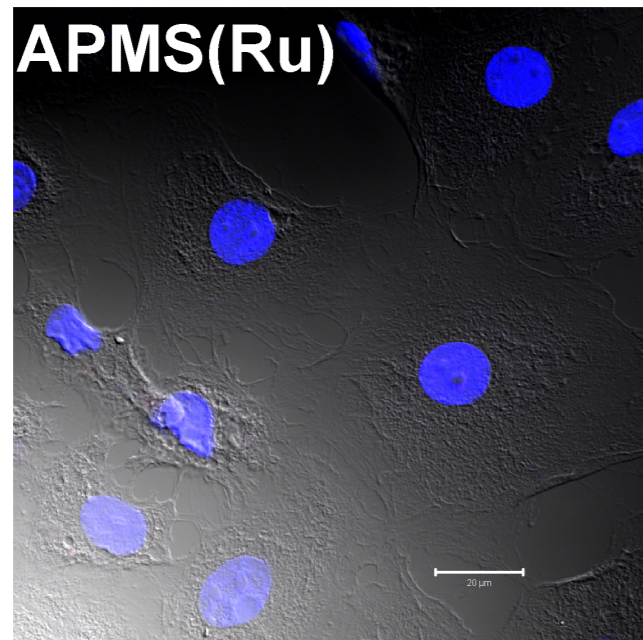
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TEG-APMS Are Endocytosed By Lung Epithelial Cells

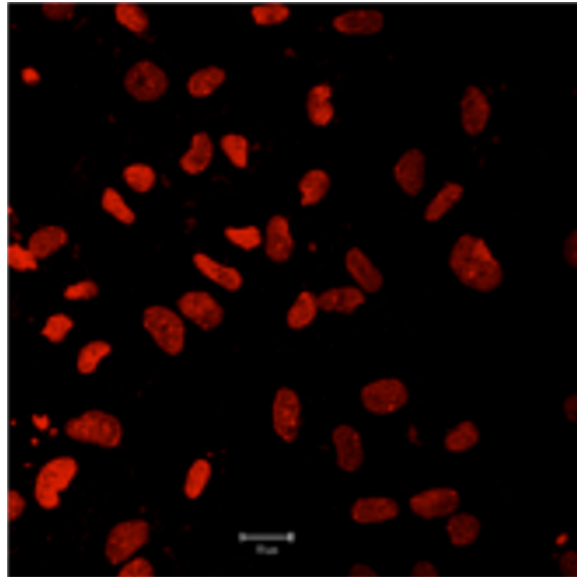


TEG facilitates uptake
of APMS by C10 cells

- Label with **Alexa 568** or doped with **Ru(bpy)₂**
- Incubate with C10 cells for 24 h *in vitro*
- Fix, stain nuclei with **DAPI**

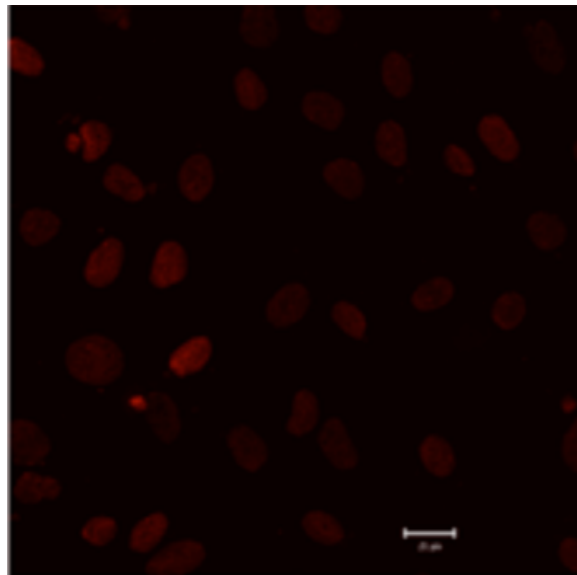
Doxorubicin Is Delivered To MM Cells

APMS+Dox



.....

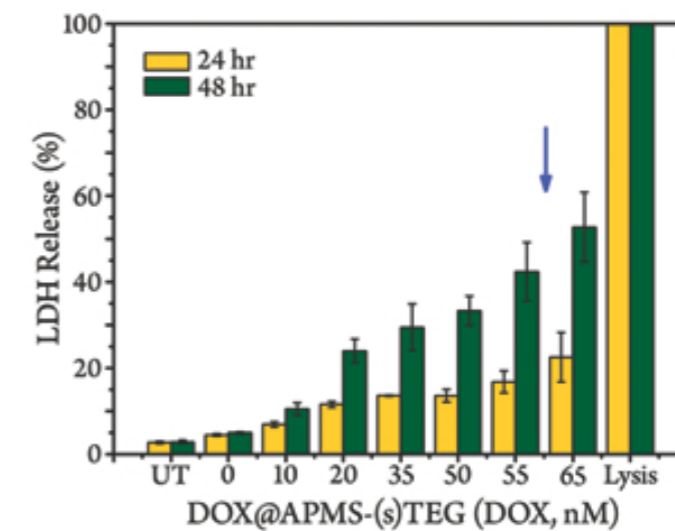
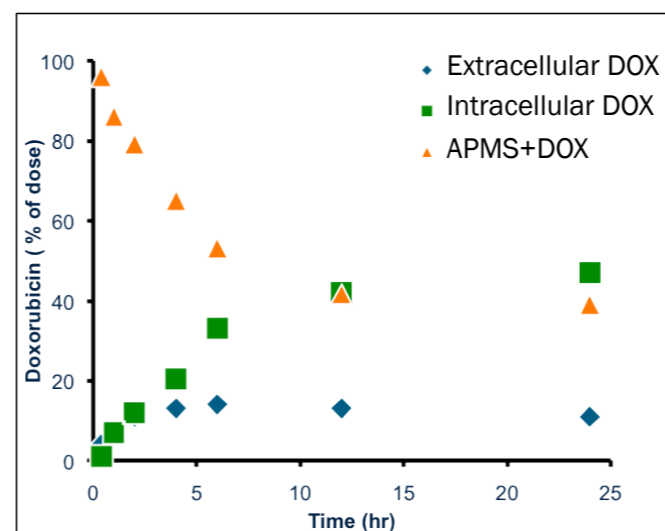
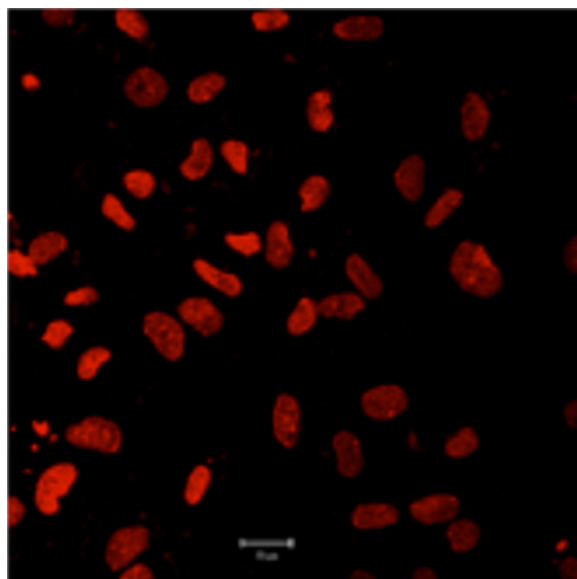
Dox alone



microscopy, 8 hr

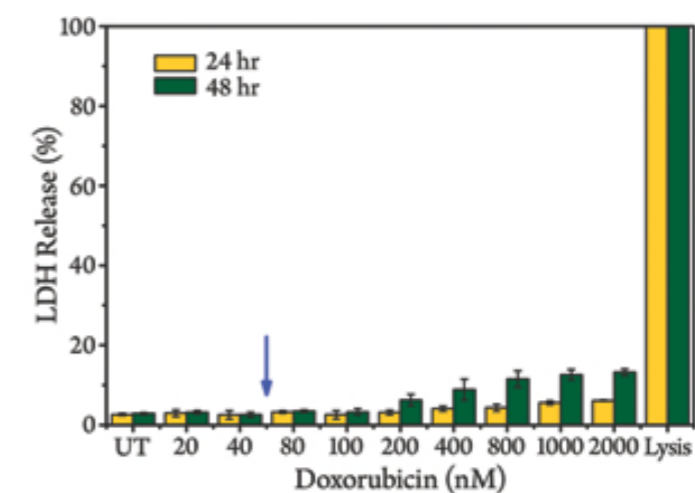
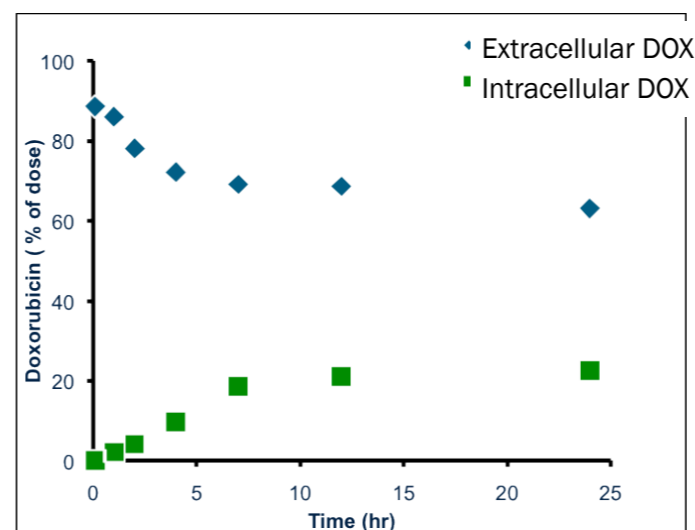
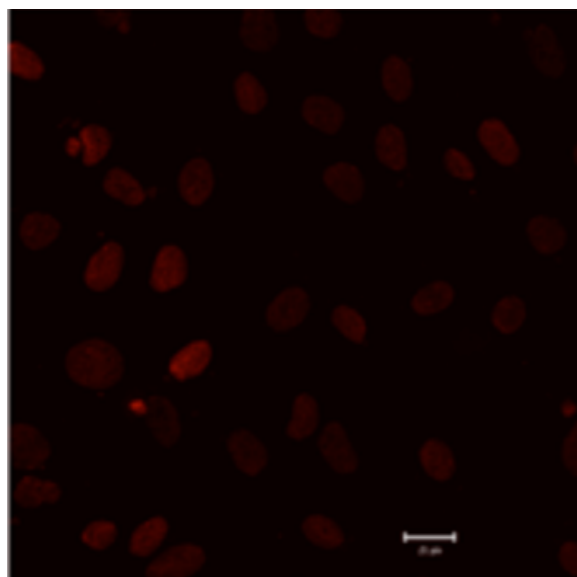
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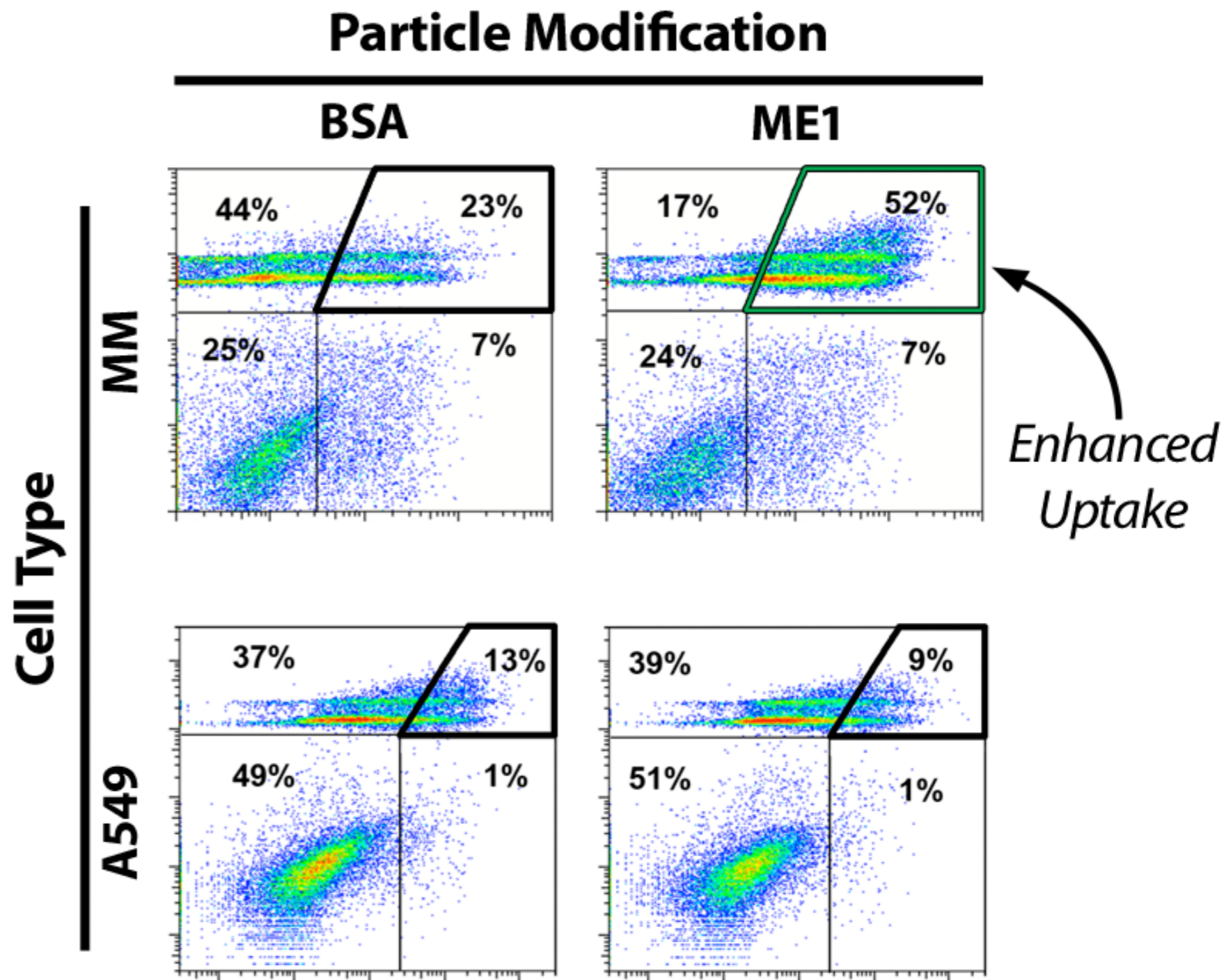
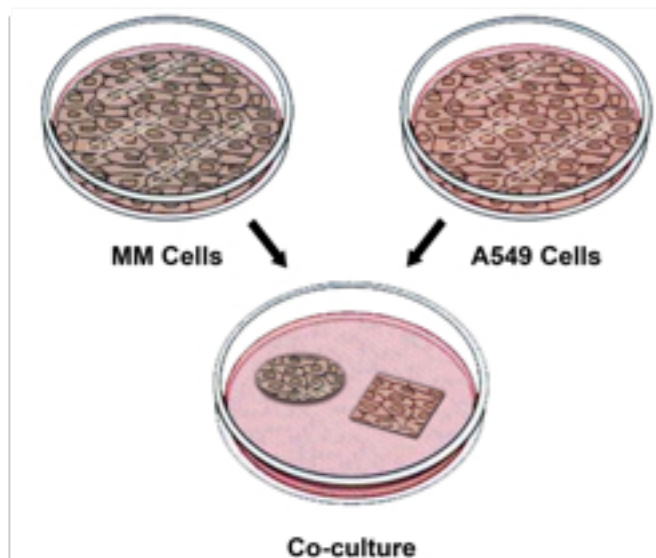
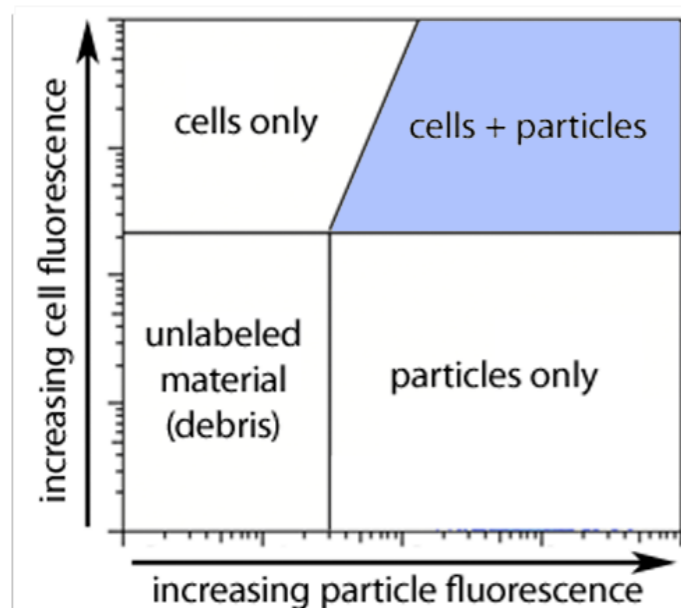


microscopy, 8 hr

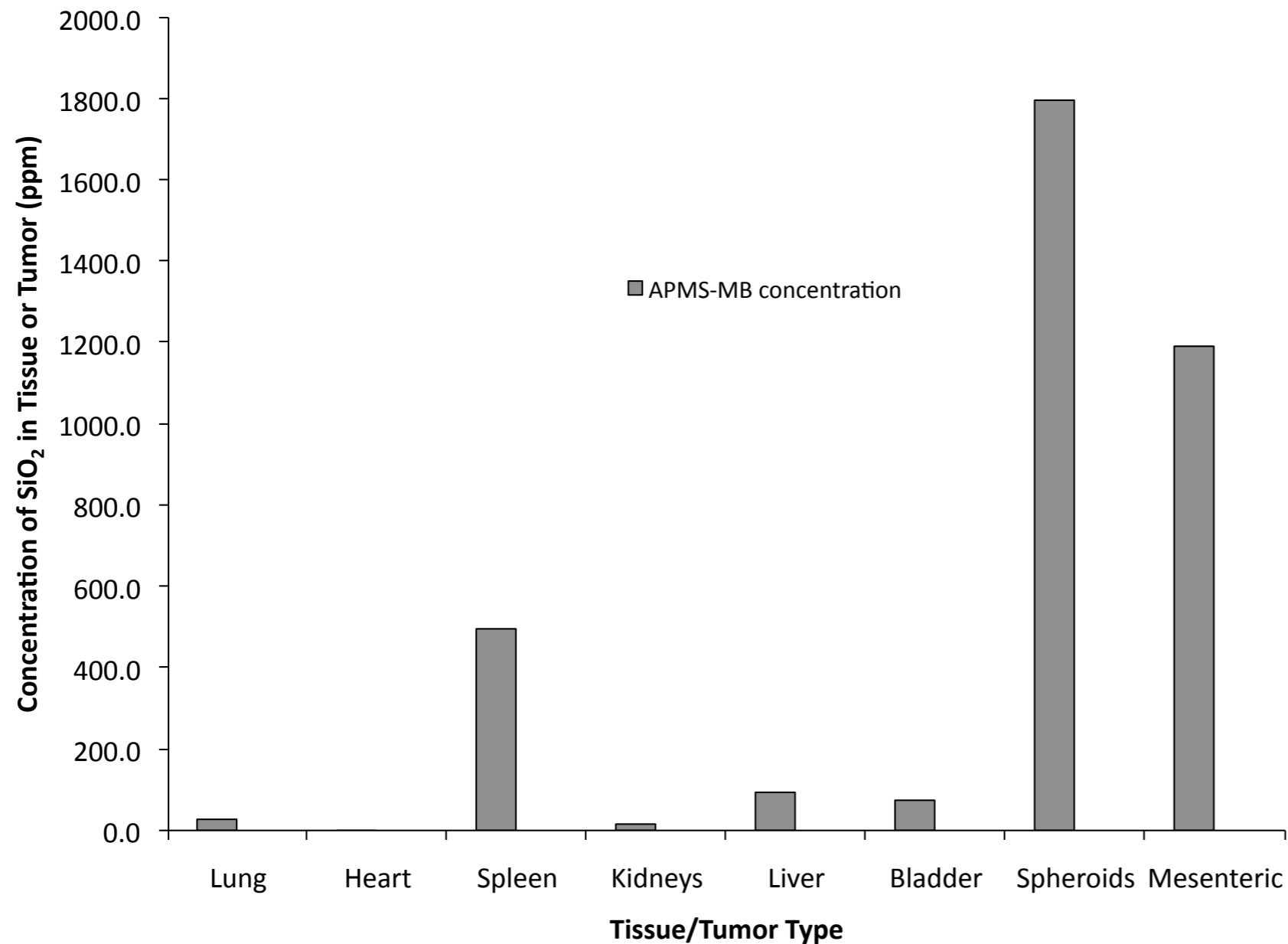
HPLC, 24 hr

dose-response

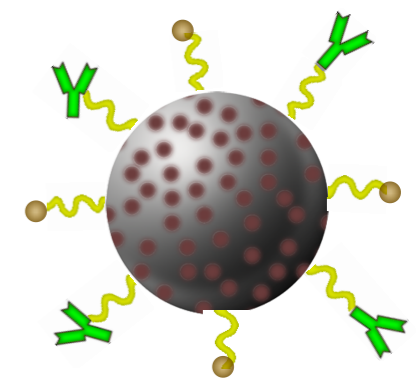
APMS-TEG-Ab Is Selectively Endocytosed



Targeted Particles Are Non-Immunogenic



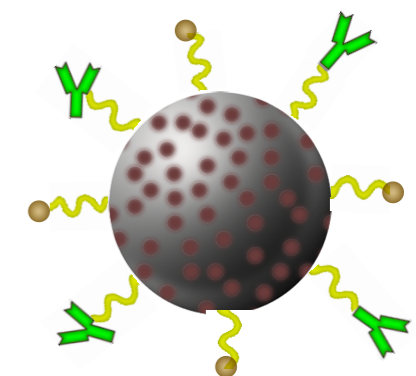
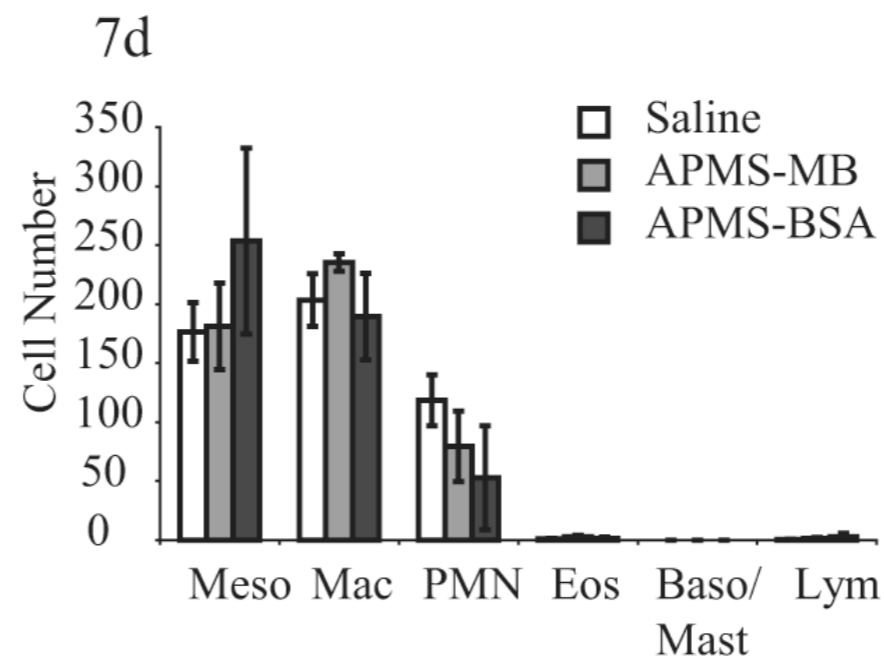
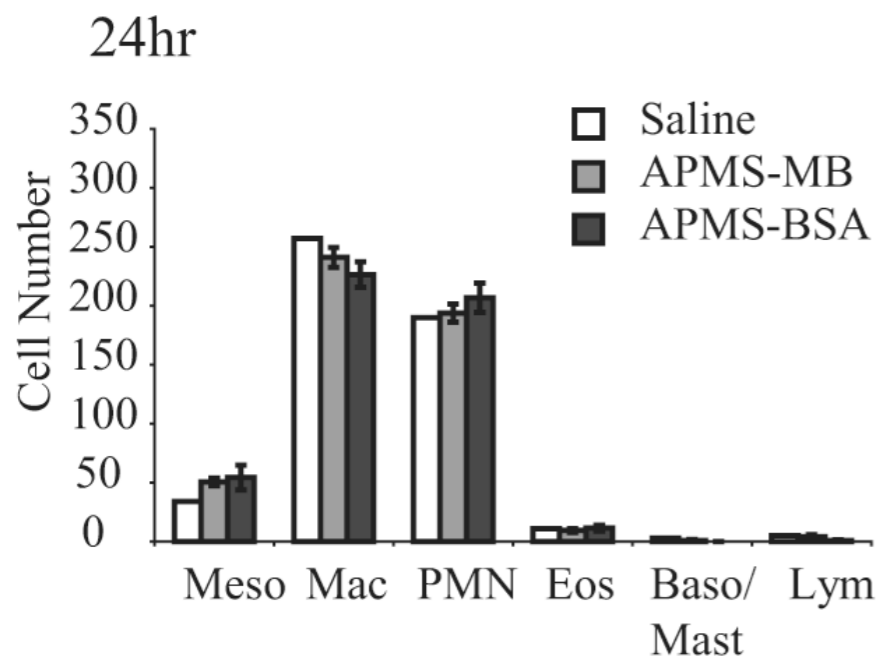
- Human MM tumors grown in mouse IP cavity
- After 4 weeks, **APMS-TEG-MB** (targeted) or **APMS-TEG-BSA** (control) injected into IP cavity
- Euthanasia after 24 h, organs and tumors collected
- Digestion in (CH₃)₄NOH followed by ICP-MS (Dartmouth)



APMS-TEG-MB

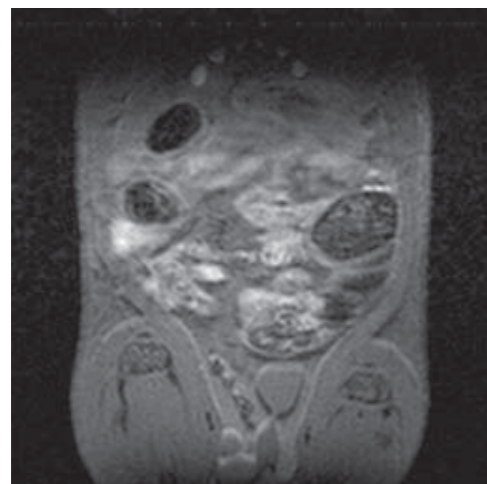
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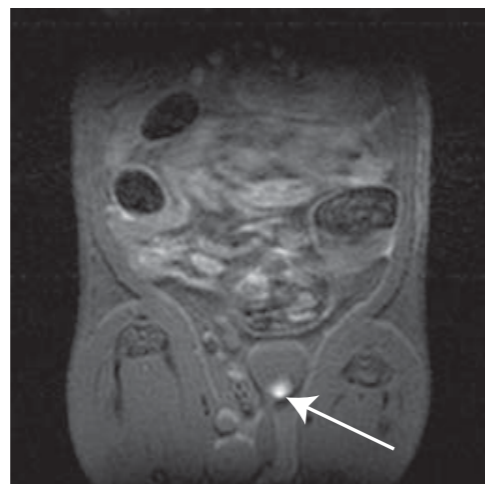


APMS-TEG-MB

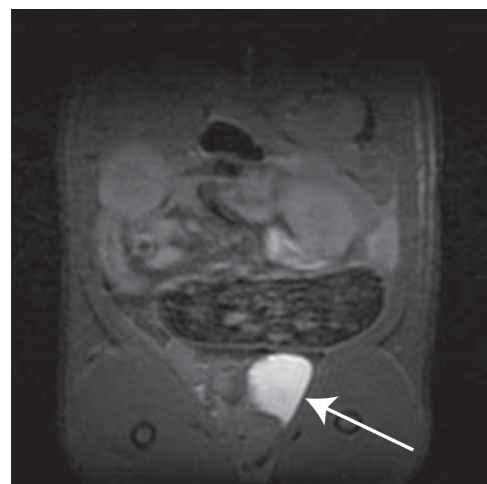
Excretion Of Microparticles Followed By MRI



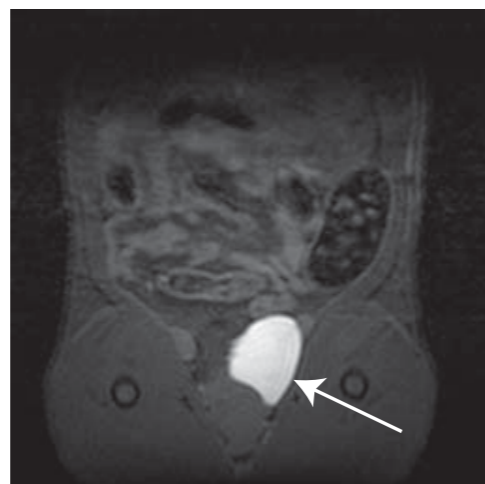
No APMS-Gd



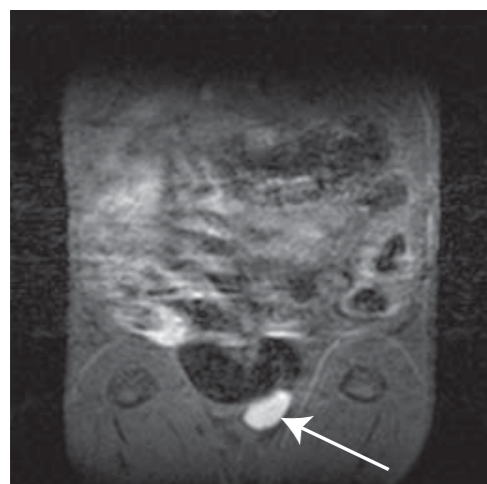
0.5 hr



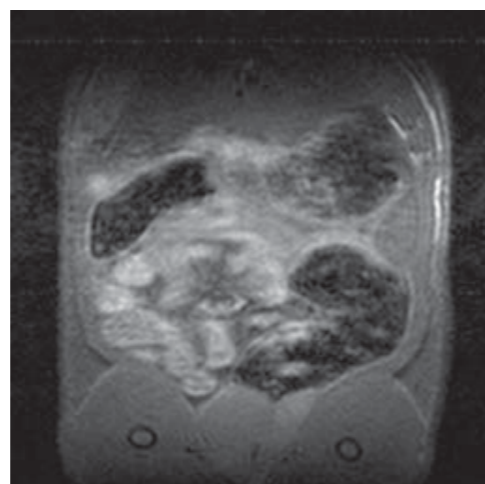
2 hr



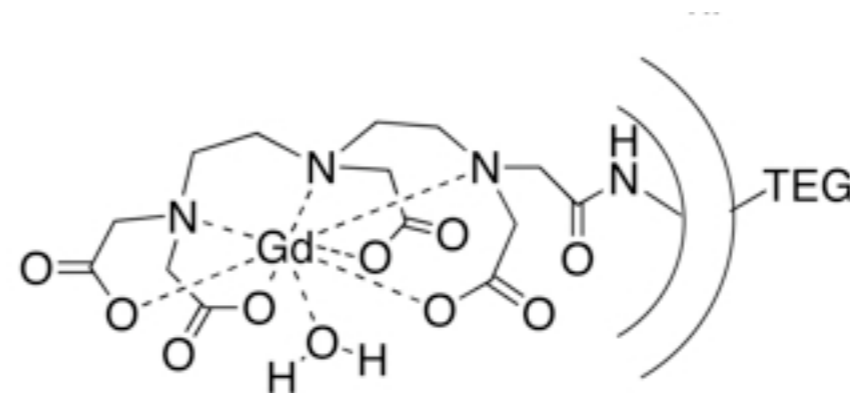
4 hr



24 hr



144 hr (6 days)

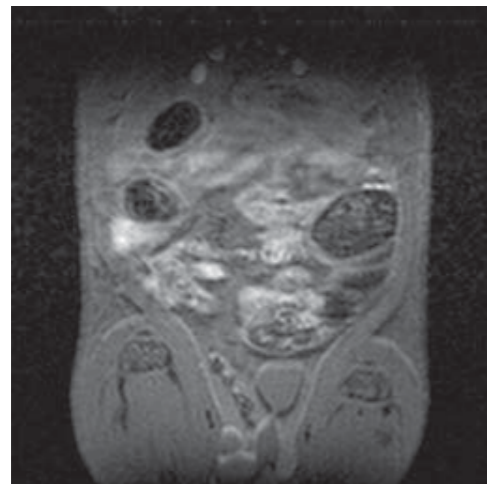


MRI shows that APMS-TEG is excreted in the urine by 24 hr. The bladder has returned to normal intensity after 6 days, indicating that APMS-TEG has been excreted.

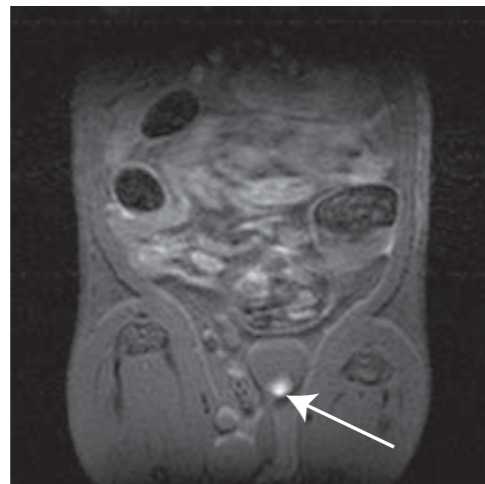
Relaxivities ($\text{mM}^{-1}\text{s}^{-1}$) at 1.5 T suspended in agar.

Sample	r_1 (per Gd)	r_1 (per particle)	r_2 (per Gd)	r_2 (per particle)
APMS/Gd	$2.8 \pm .1$	$\sim 3 \times 10^9$	23 ± 1	$\sim 2 \times 10^{10}$
DTPA/Gd _(aq)	$2.9 \pm .2$	-	$2.9 \pm .2$	-

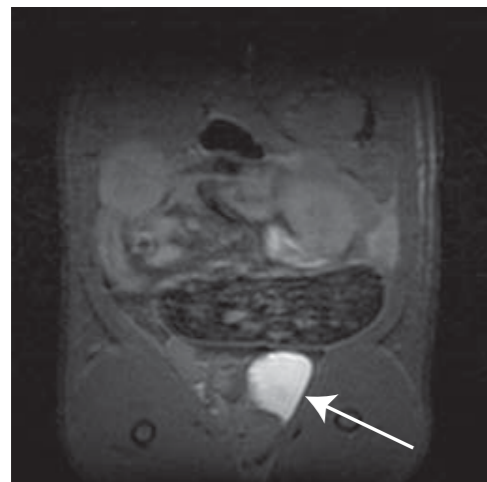
Excretion Of Microparticles Followed By MRI



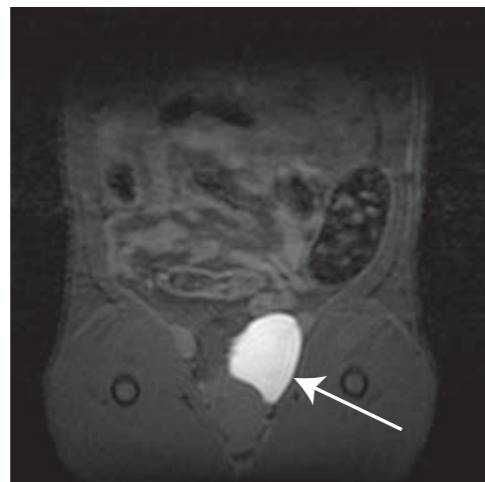
No APMS-Gd



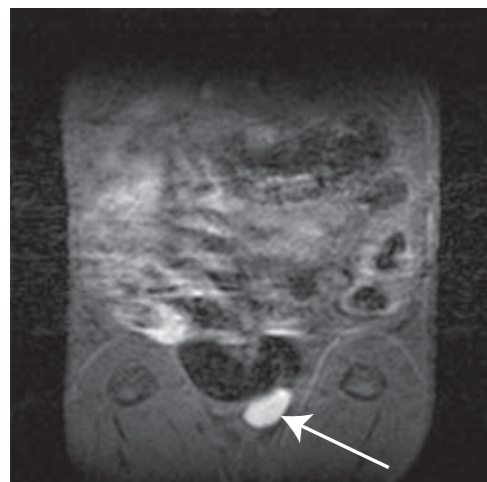
0.5 hr



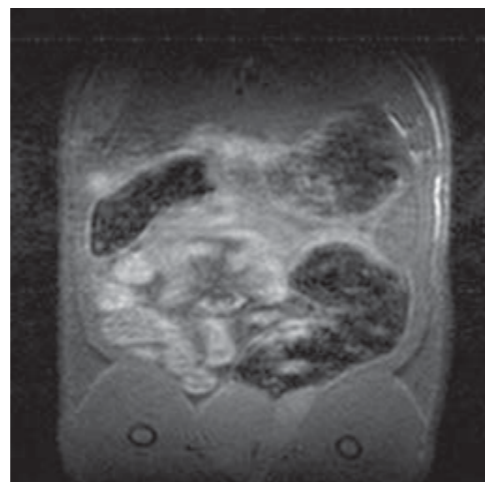
2 hr



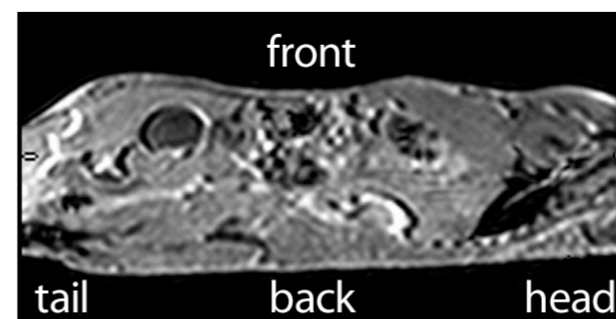
4 hr



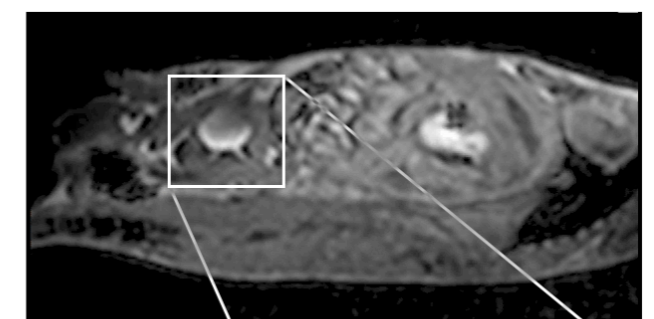
24 hr



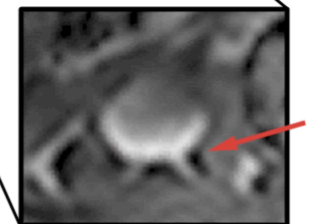
144 hr (6 days)



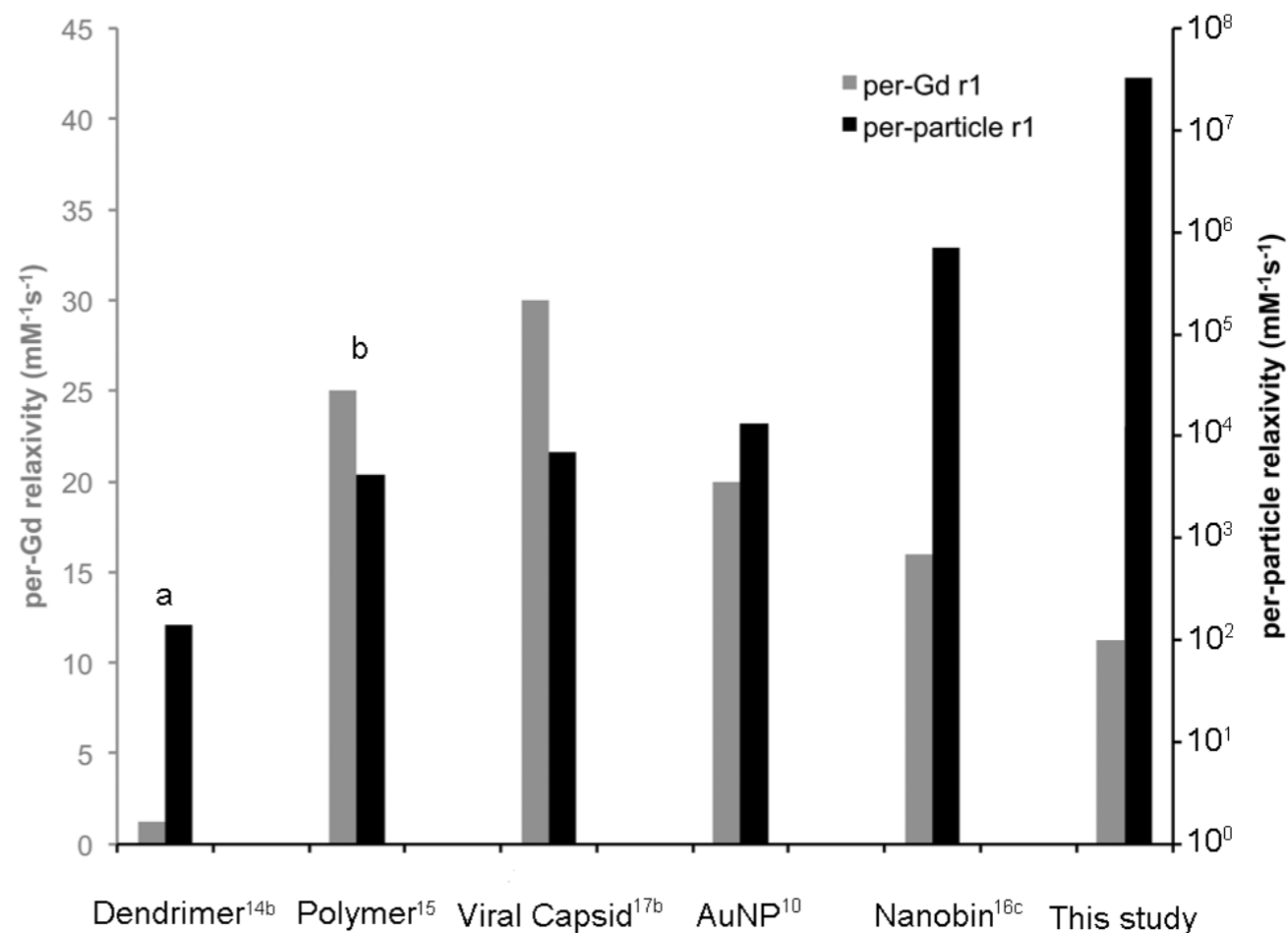
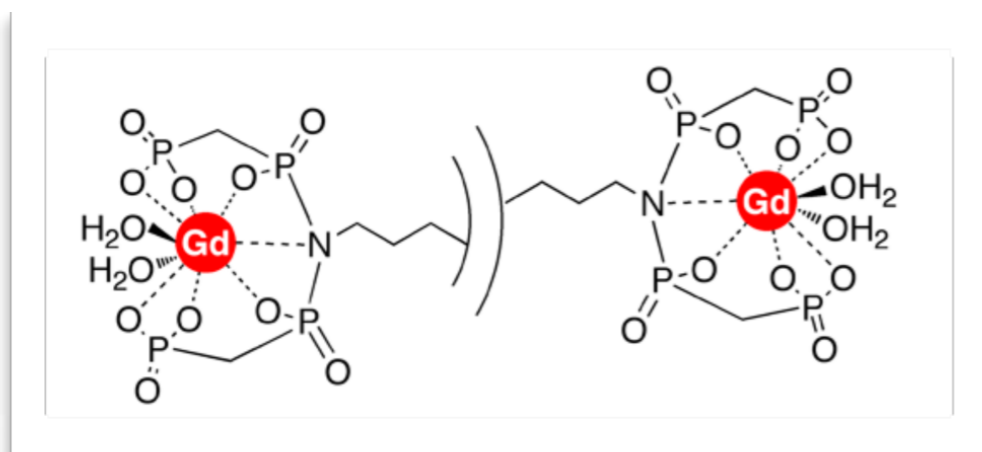
Pre-Injection



30 minutes



New Gd Chelates Have High Relaxivities



standard synthesis

rehydroxylated

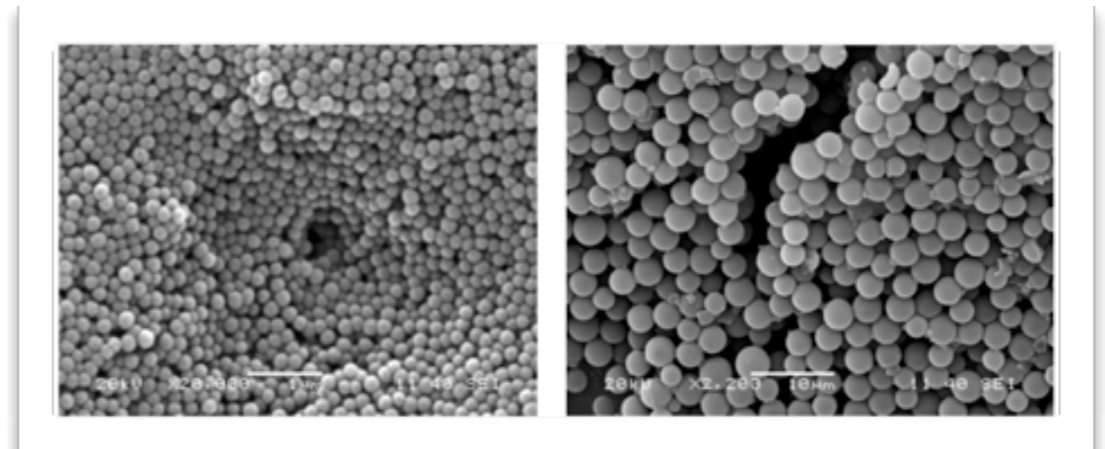
pore-expanded

Sample	as-made			functionalized			per-Gd relaxivity		per-particle relaxivity	
	d_{pore} (Å)	SA_{BET} (m ² /g)	V_{pore} (cm ³ /g)	d_{pore} (Å)	SA_{BET} (m ² /g)	V_{pore} (cm ³ /g)	r_1 (mM ⁻¹ s ⁻¹)	r_2 (mM ⁻¹ s ⁻¹)	r_1 (mM ⁻¹ s ⁻¹ × 10 ⁷)	r_2 (mM ⁻¹ s ⁻¹ × 10 ⁷)
1	36	790	0.87	33	380	0.41	4.6	15	3.3	11
2	39	780	0.65	34	350	0.35	6.0	17	1.7	5.0
3	55	690	0.97	45	380	0.56	10	23	2.4	5.4
Gd-DOTA²	-	-	-	-	-	-	3.0	3.3	-	-
Gd-DTPA²	-	-	-	-	-	-	3.5	3.9	-	-

Ongoing Studies

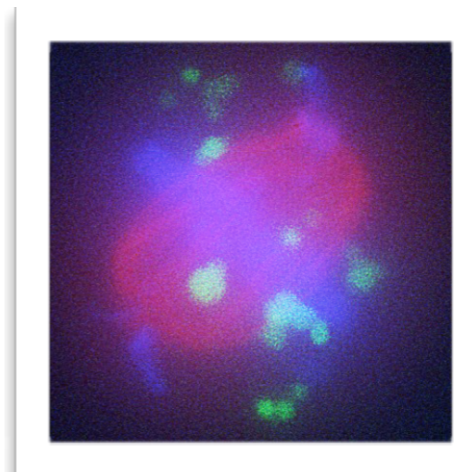
1. Effect of particle size on rate of uptake and trafficking of particles

- 200 , 1000, 3000 nm
- 0 - 100 % ethylene glycol
- Vesicular, mitochondrial, and microtubule staining



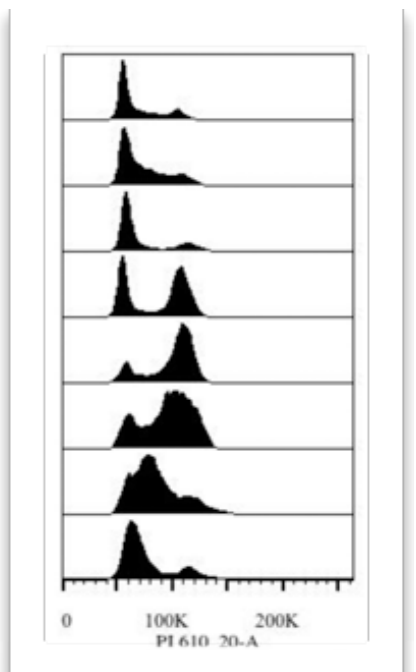
2. Trafficking of particles during mitosis

- DNA and microtubule staining
- Live cell imaging over 2 to 8 hours



3. Delivery of CDK inhibitors through cleavable covalent bonds

- Cell viability assays
- Flow cytometry analysis of cell cycle progression



Acknowledgements

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Sherrill Lathrop

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ITQ:

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Dr. Pablo Botella Ascunción

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FULBRIGHT
España

