Short-Chain Brushed PEGylation Evades Anti-PEG Immunity to Enhance Nanomedicine Safety and Efficacy

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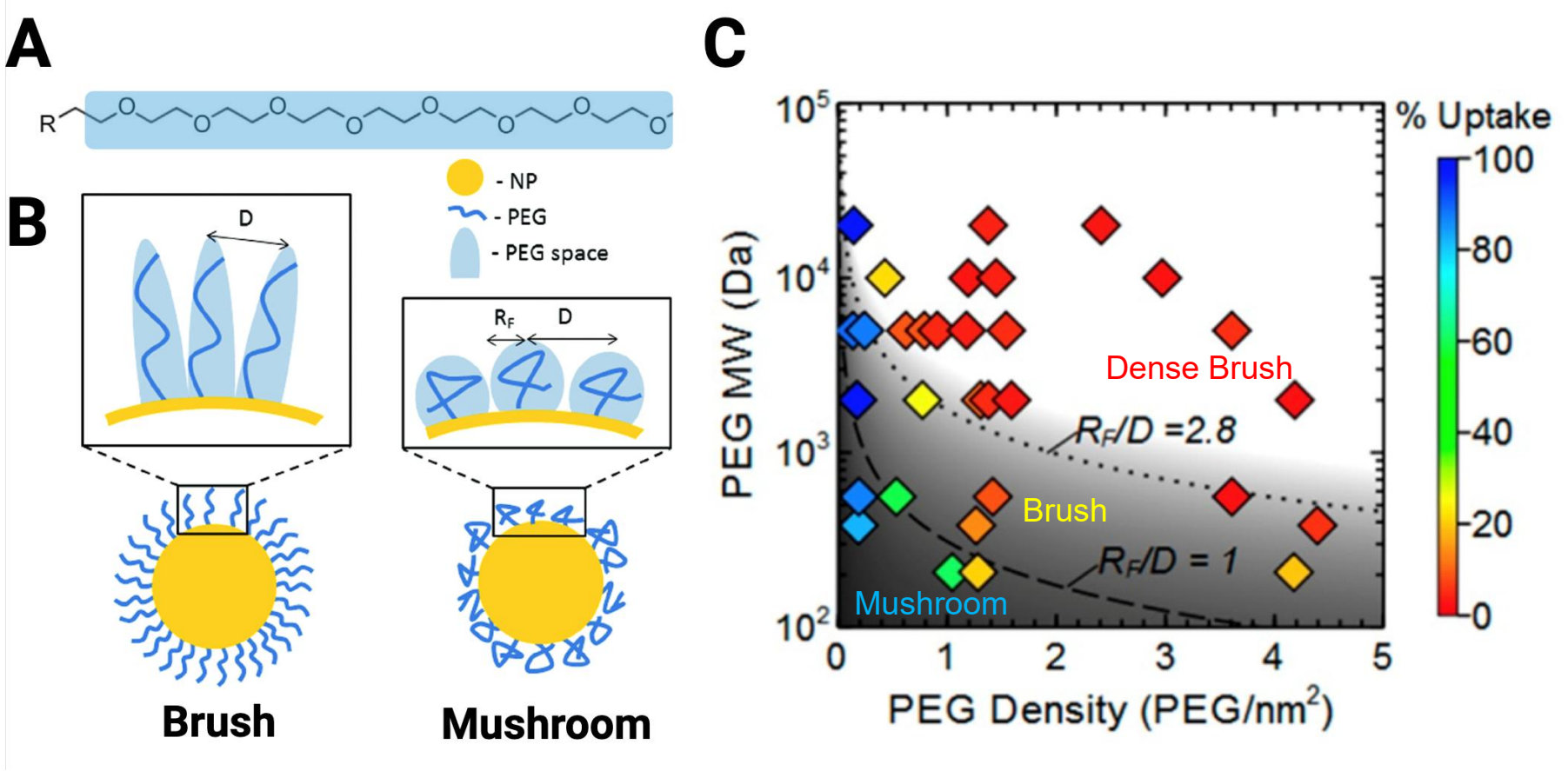
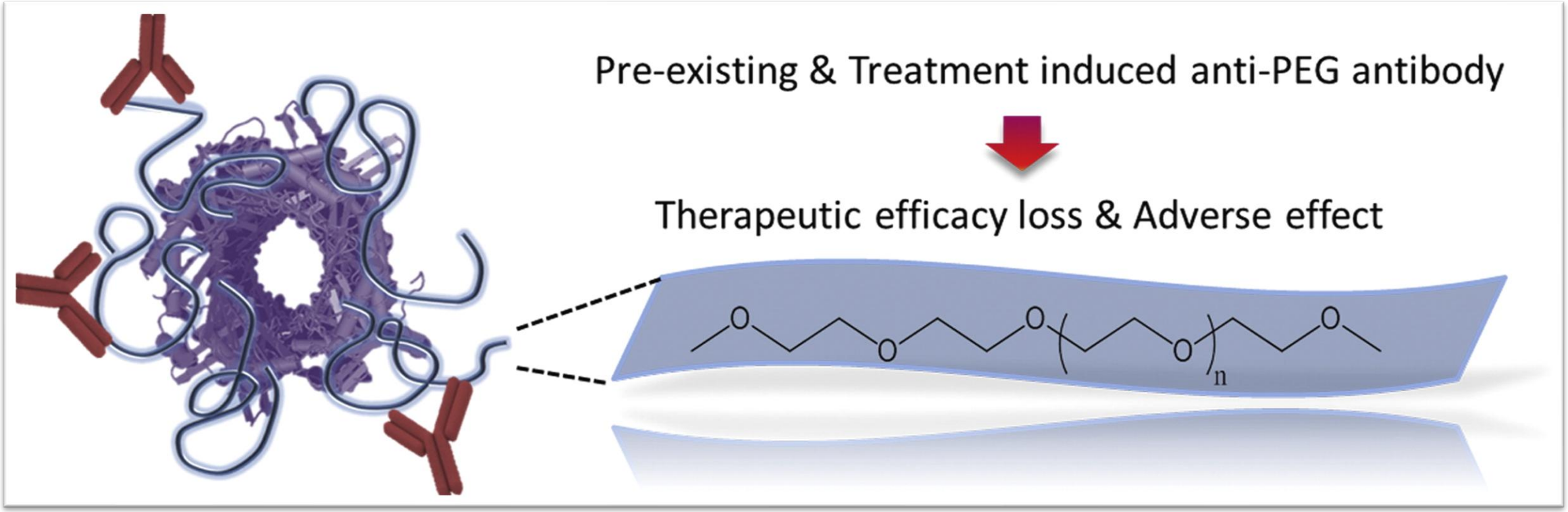
NEXT-GENERATION DELIVERY INNOVATIONS

PEG: From Chain Length to Conformation



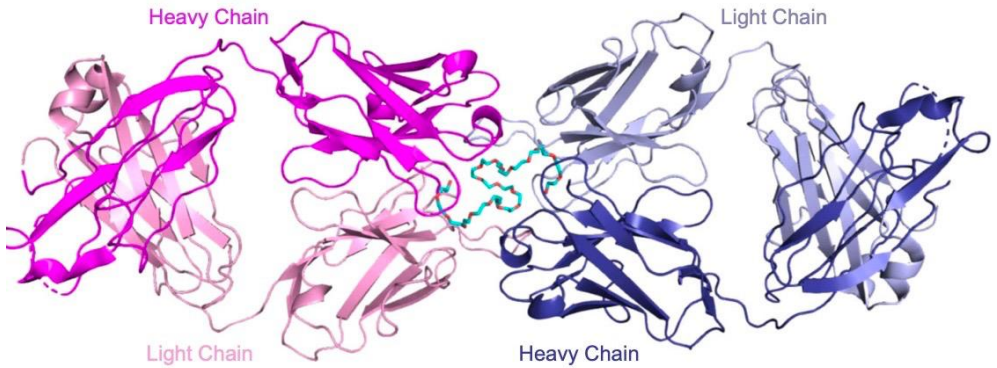
- **PEG conformation depends on chain length (Rf) and spacing (D).**
- **Low-MW PEG requires *higher* density to achieve brush structure.**

Anti-PEG Antibodies: A Growing Concern

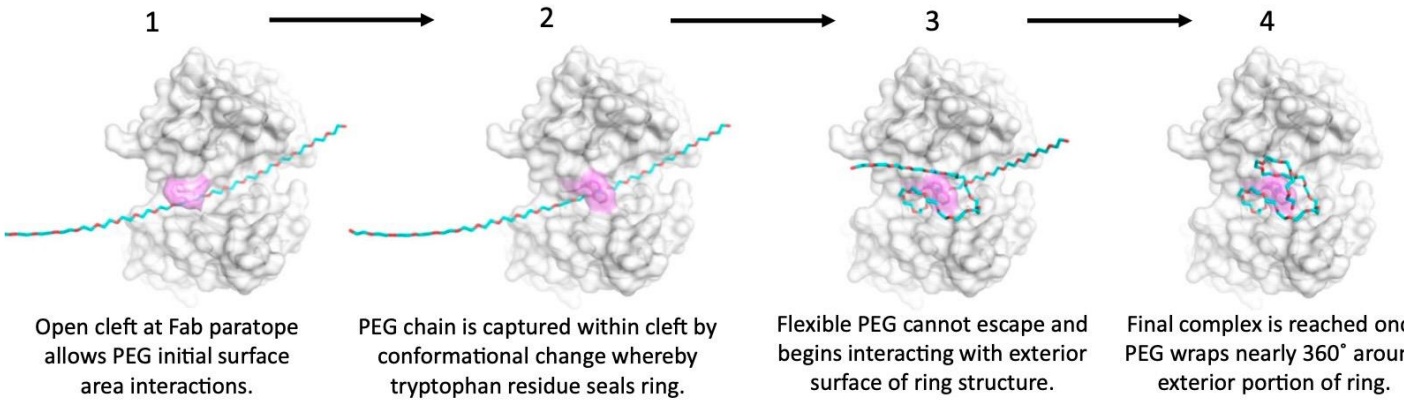


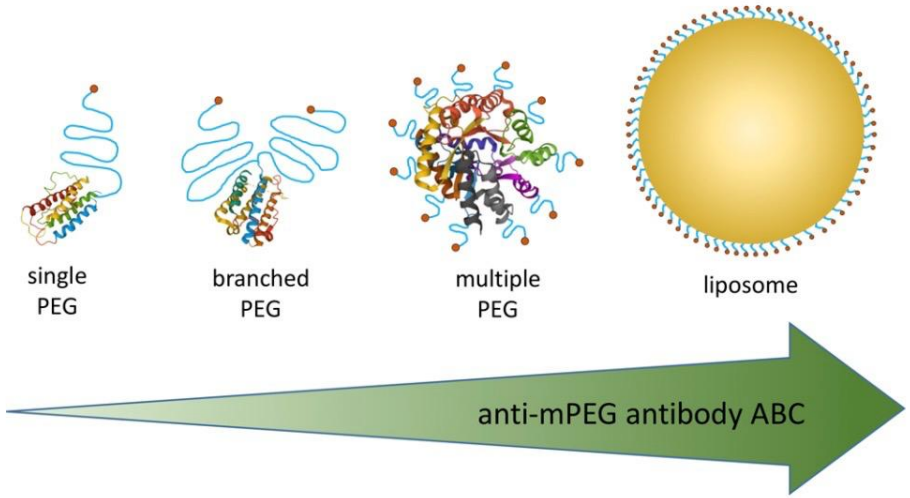
Journal of Controlled Release, 2016, 244, 184-193.

How Anti-PEG Antibodies Recognize PEG



Anti-PEG Fabs bind to PEG as symmetrical dimer complex





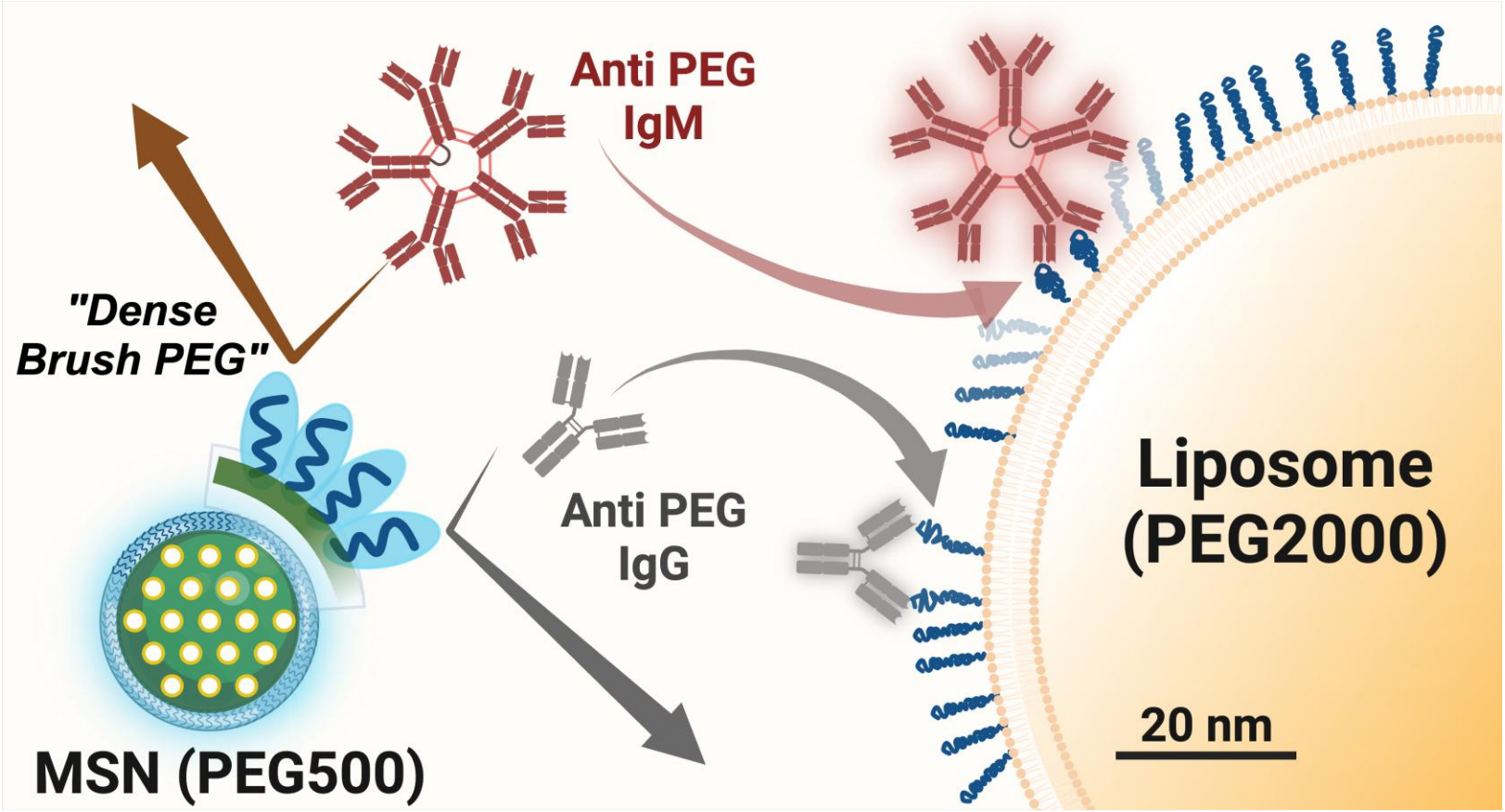
Biol. Pharm. Bull. **35**, 1336–1342 (2012)
Communications Chemistry **3**, 124 (2020)
ACS Nano **15**, 14022-14048 (2021)

- PEG chains ≥**750** Da are sufficient for stable recognition by anti-PEG antibodies. Increasing chain length and flexibility further enhances binding affinity.

Dense Short-Chain PEG Brush to Minimize Recognition

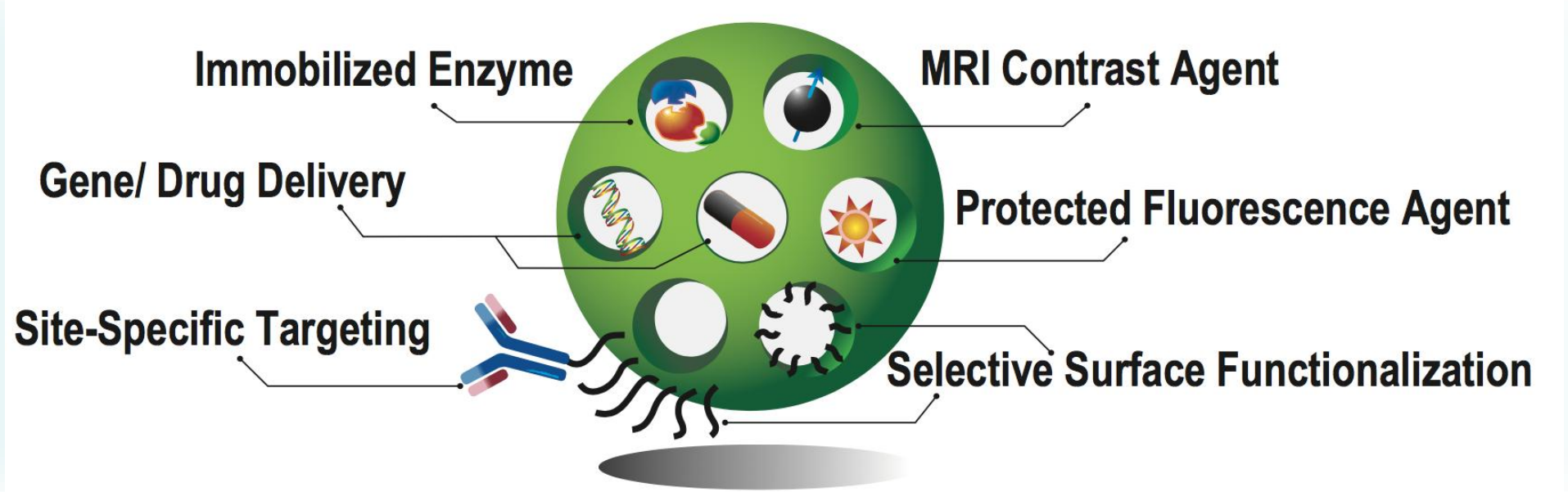
Our Design Strategy

- **PEG500** instead of **PEG2000**
- High grafting density
- Brushed, compact architecture impedes Ab access



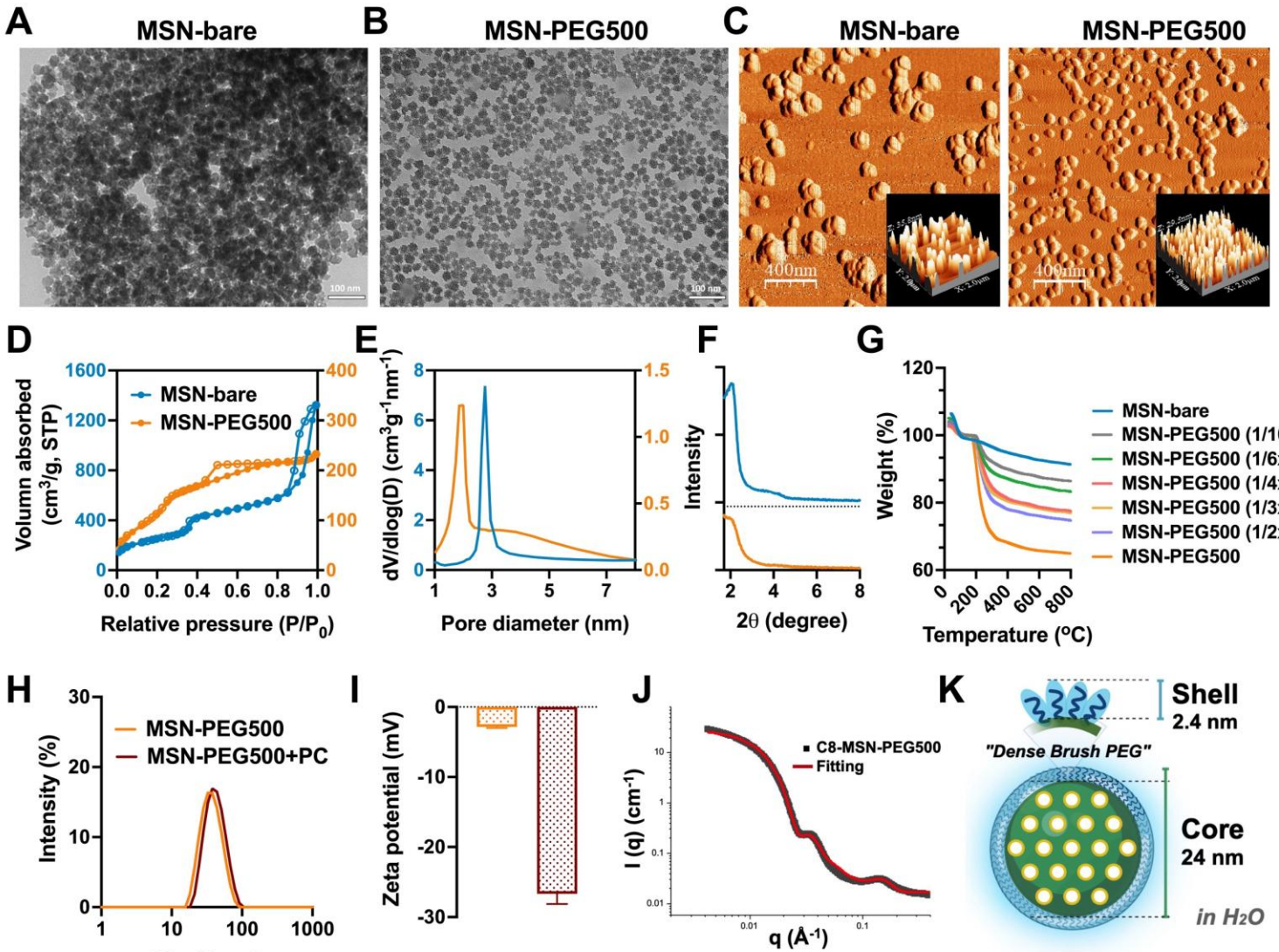
Unpublished data (under revision)

Mesoporous Silica Nanoparticles (MSNs)

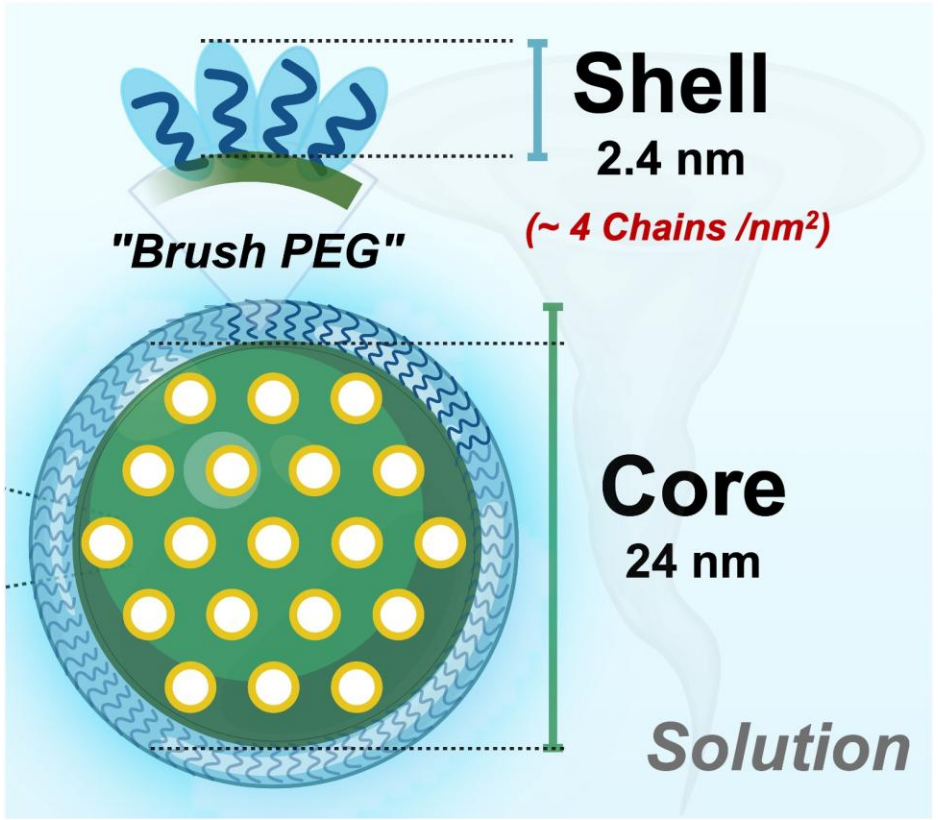


- High surface area (1000 m^2/g)
- Tunable pore size
- Thermal & chemical stability
- Non/Low toxicity
- Large pore volume (2.5-6 nm)
- Easy functionalization
- Controllable degradation rate
- Biocompatibility

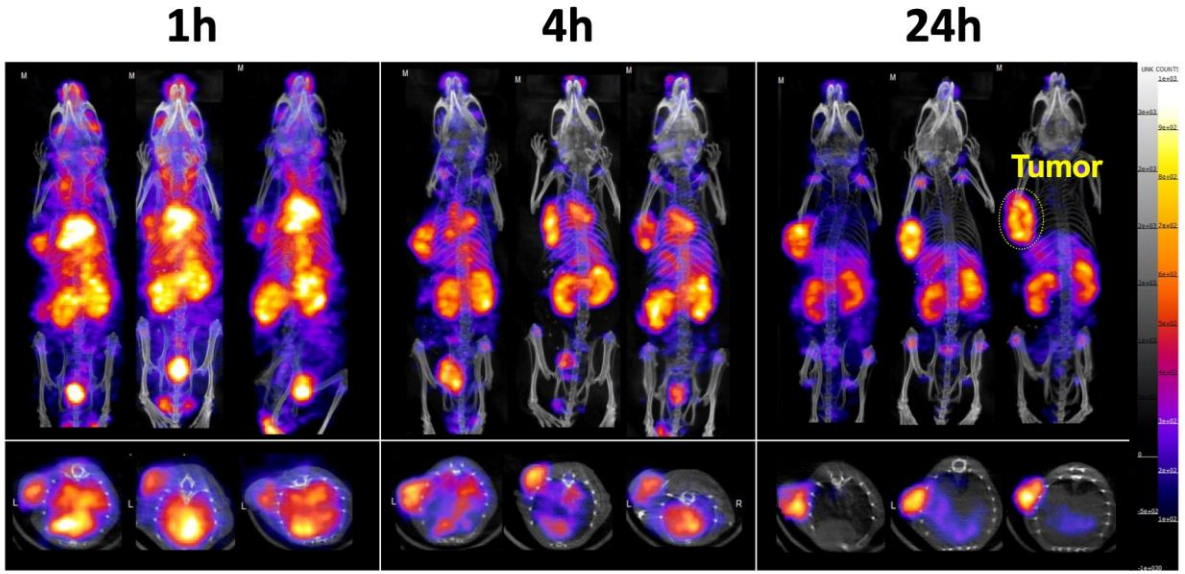
Tunable PEG Brush Thickness and Density on MSN



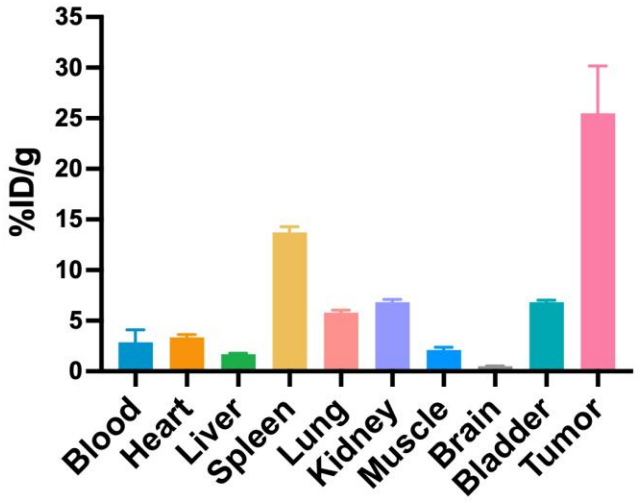
SAXS-confirmed brush PEG

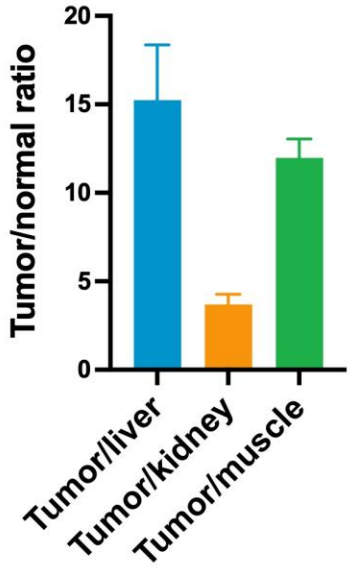


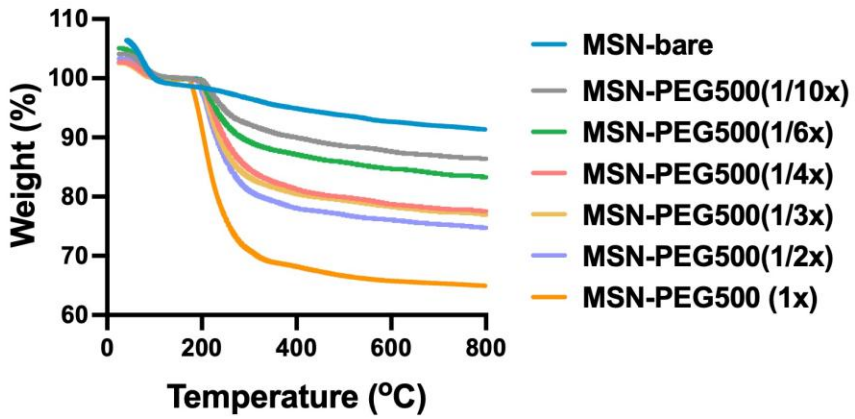
Brushed MSN-PEG500 Enables Superior Tumor Targeting



^{111}In-labeled MSN-PEG500



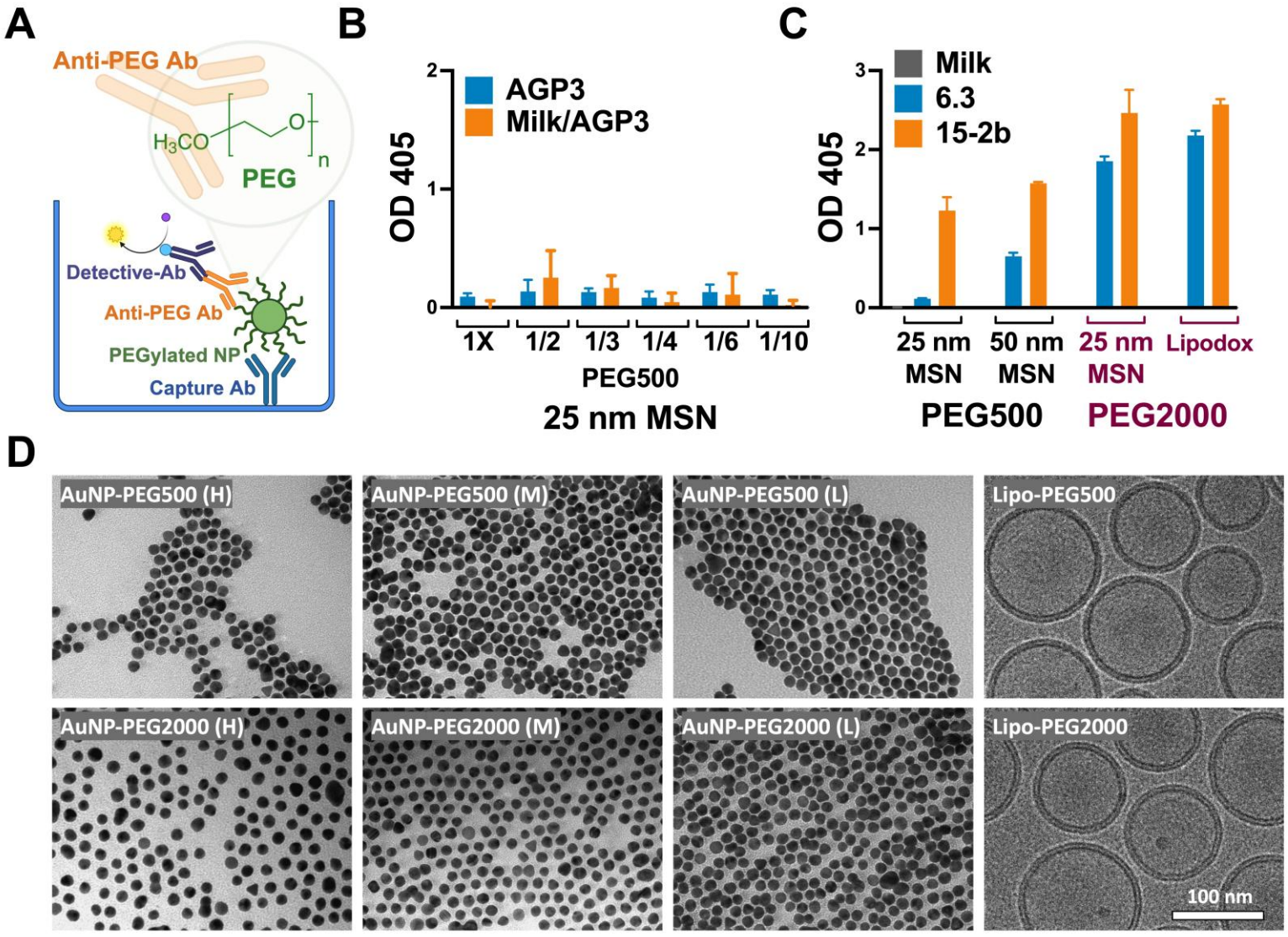


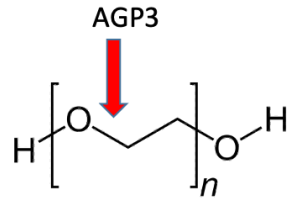


MSN-PEG500	TEM (nm)	D_h in PBS Z-average (d.nm) / PDI	Weight lost (%), TGA*	PEG density (#/nm²)
1x	26.0 ± 4.5	38.7 / 0.090	36.05 (27.89)	4.43
1/2x	19.7 ± 2.8	70.8 / 0.244	24.41 (16.25)	1.68
1/3x	21.0 ± 3.6	104.3 / 0.219	22.43 (14.27)	1.54
1/4x	20.2 ± 3.0	707.5 / 0.346	21.97 (13.81)	1.43
1/6x	23.6 ± 4.0	1310 / 0.685	15.88 (7.72)	0.87
1/10x	23.3 ± 3.0	1721 / 0.709	13.13 (4.97)	0.54

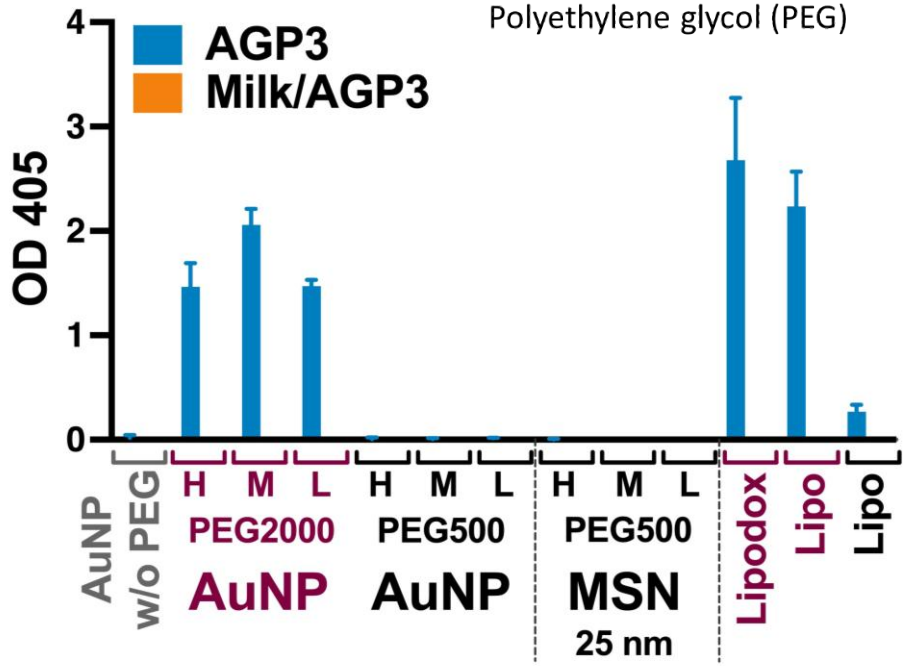
PEG500 Brush Drastically Reduces Antibody Recognition

Immunological Evasion in Vitro



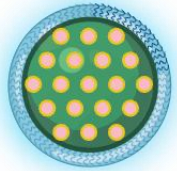


Polyethylene glycol (PEG)



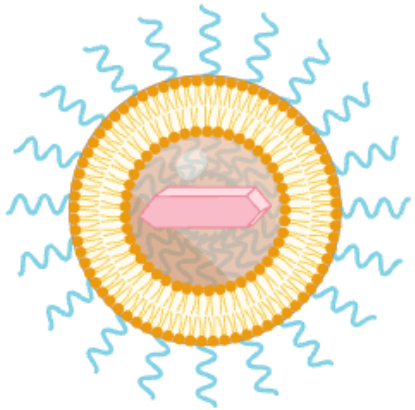
PEGylation Determines Toxicity and Efficacy in Immunized Hosts

In Vivo: Tumor-bearing Mice with Controlled Anti-PEG Antibody Titers: **(I) *Naïve* vs. *Strong responder group***



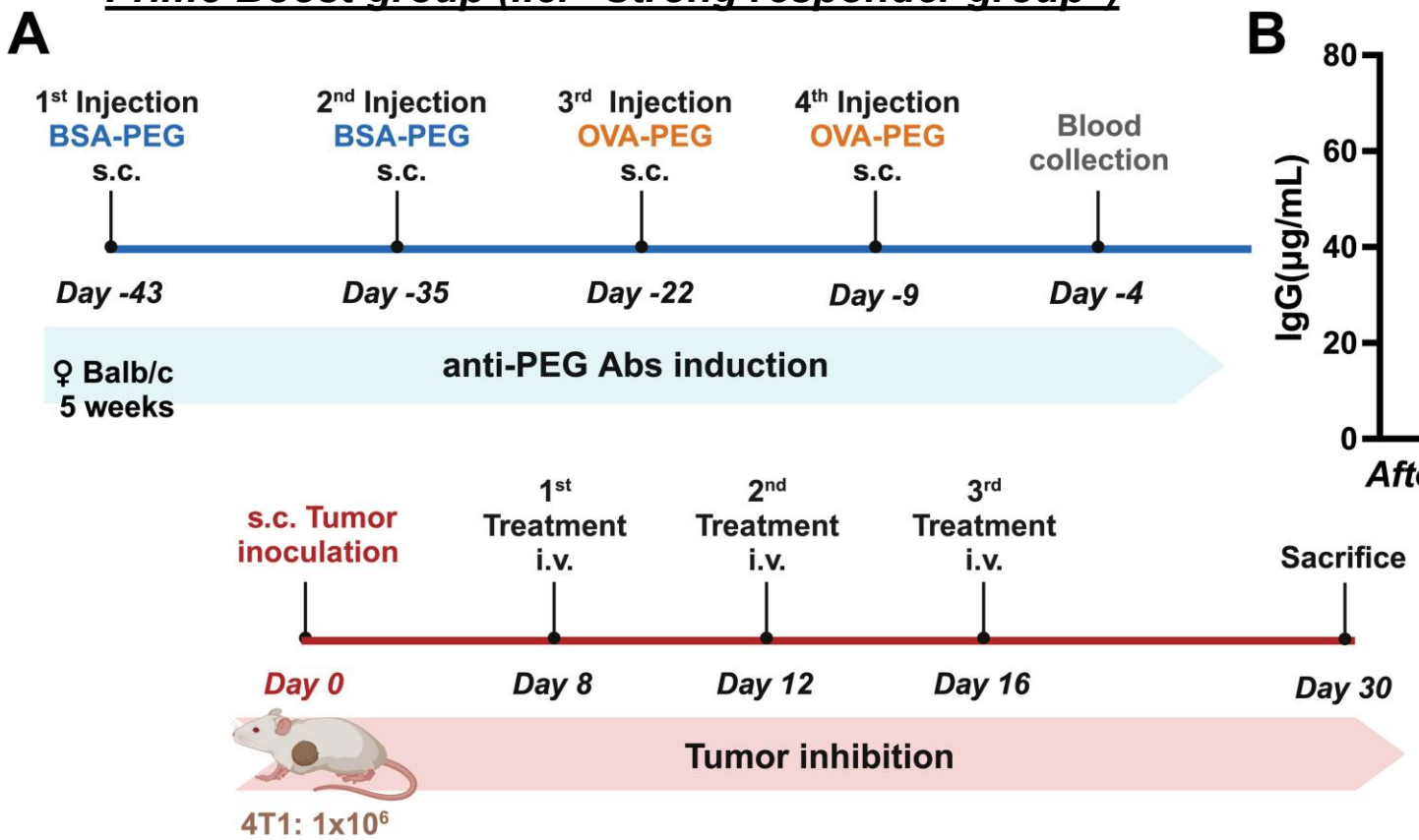
DOX@MSN-PEG500

VS.



Lipodox (PEG2000)

Prime-Boost group (i.e. "Strong responder group")



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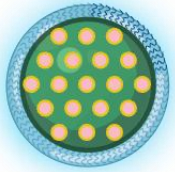
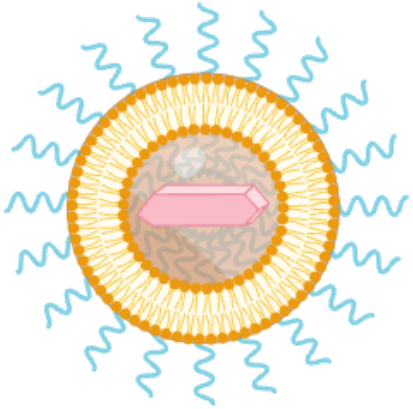
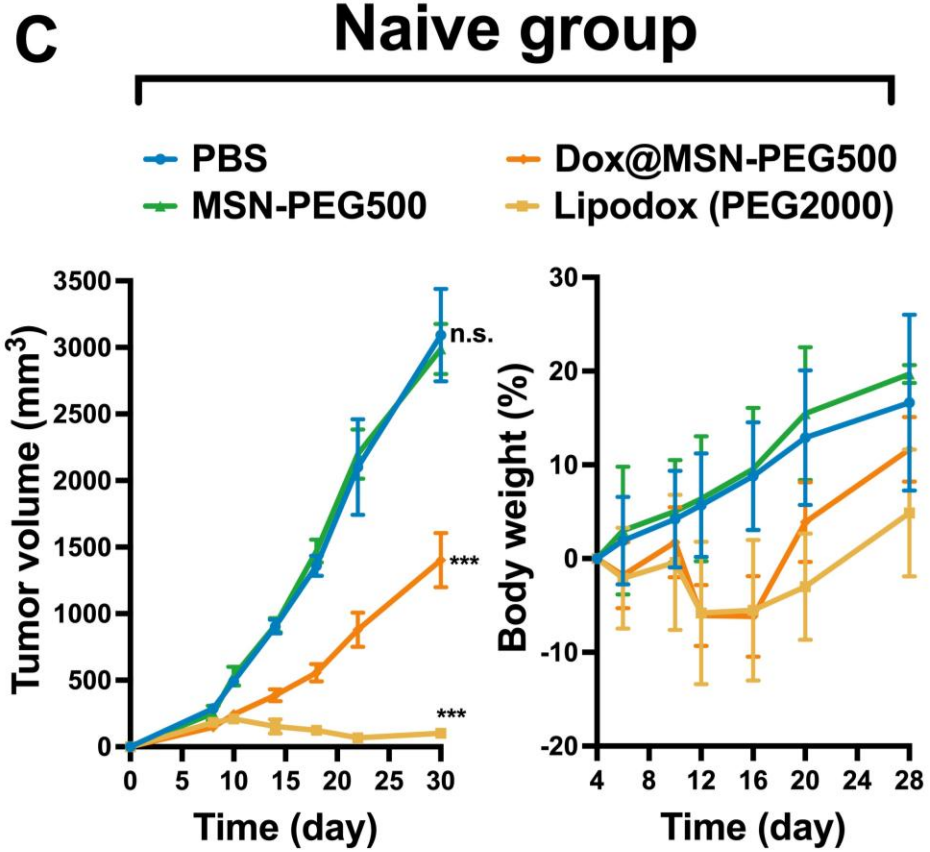


DOX@MSN-PEG500

VS.



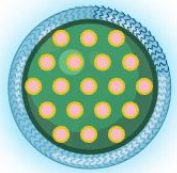
Lipodox (PEG2000)



- **Doxorubicin dose: 8 mg/kg**
- **Formulation-derived PEG dose:**
  - Lipodox (PEG2000): ~12.7 mg PEG/kg
  - Dox@MSN-PEG500: ~35.4 mg PEG/kg

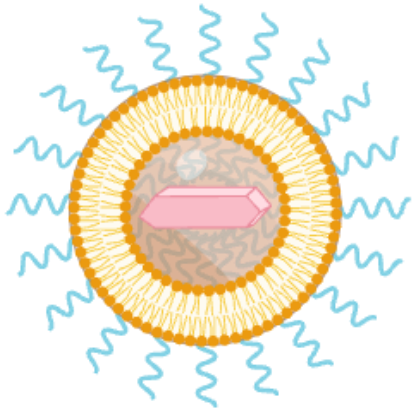
Mild Responders Reveal Subtle Efficacy Impairment

In Vivo: Tumor-bearing Mice with Controlled Anti-PEG Antibody Titers: **(II) *Weaker responder group***



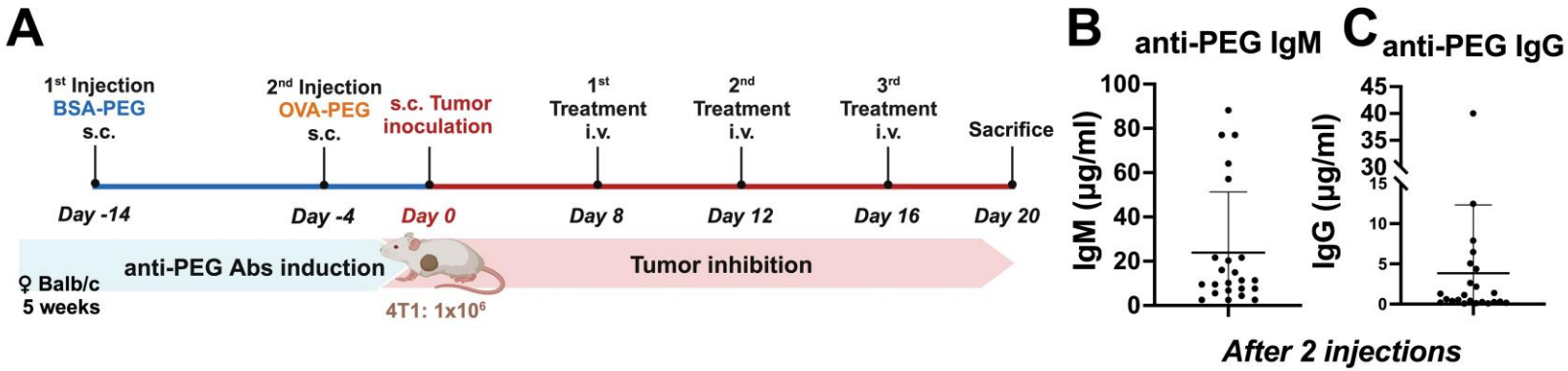
DOX@MSN-PEG500

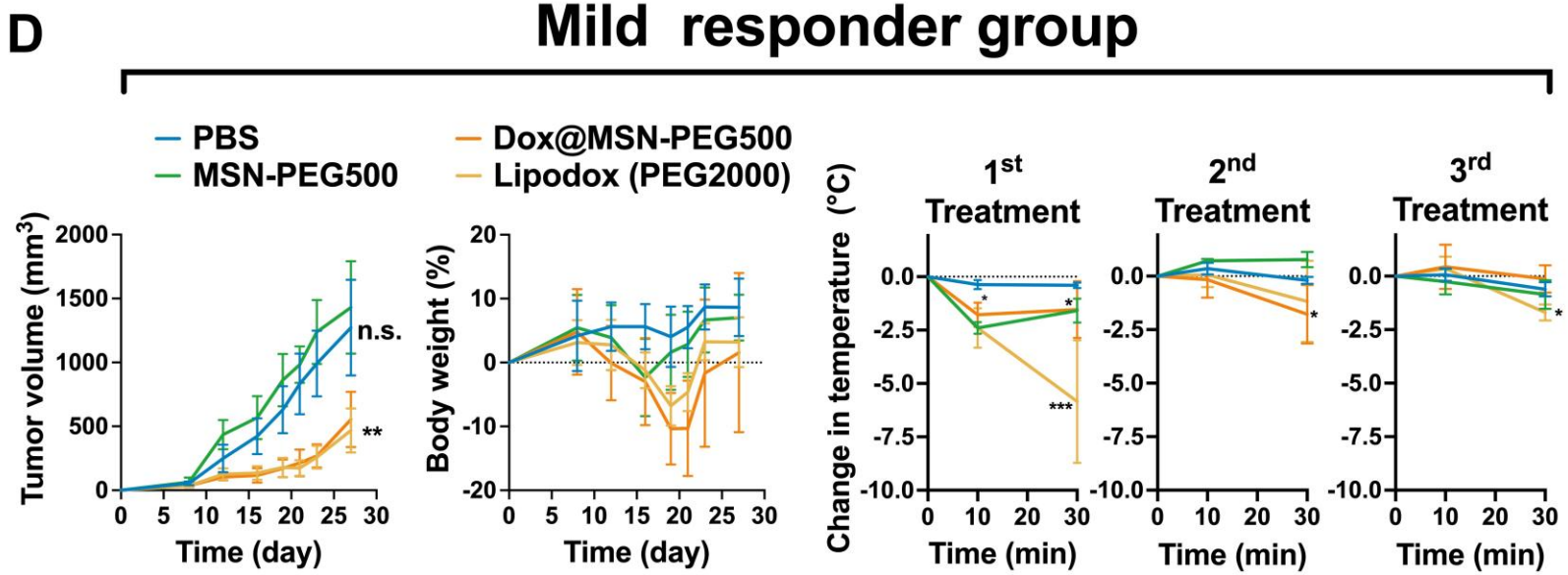
VS.



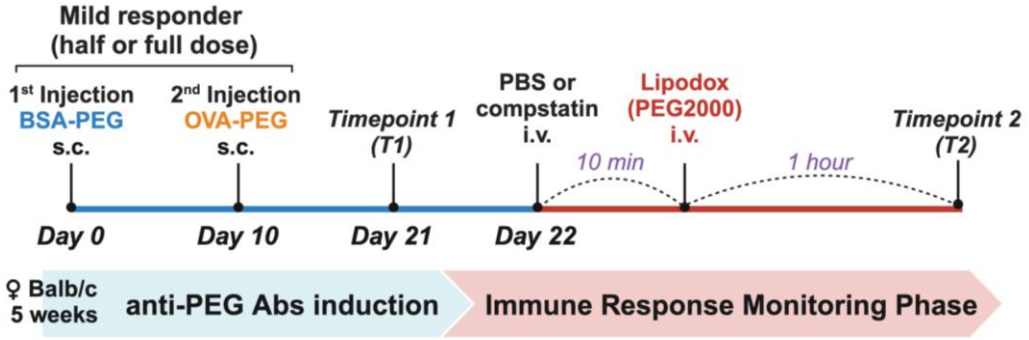
Lipodox (PEG2000)

Primed only (i.e. "Weaker responder group")

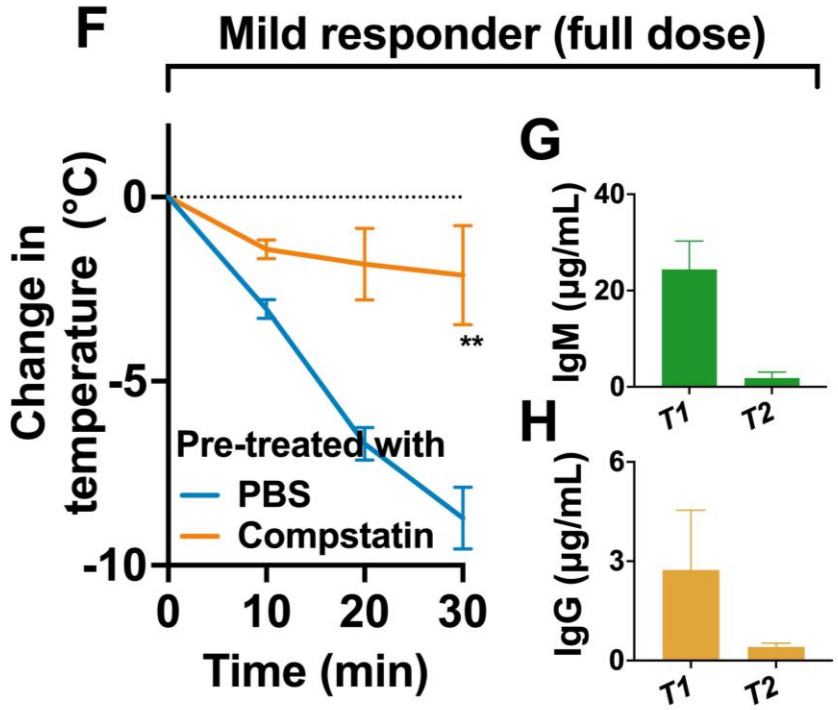


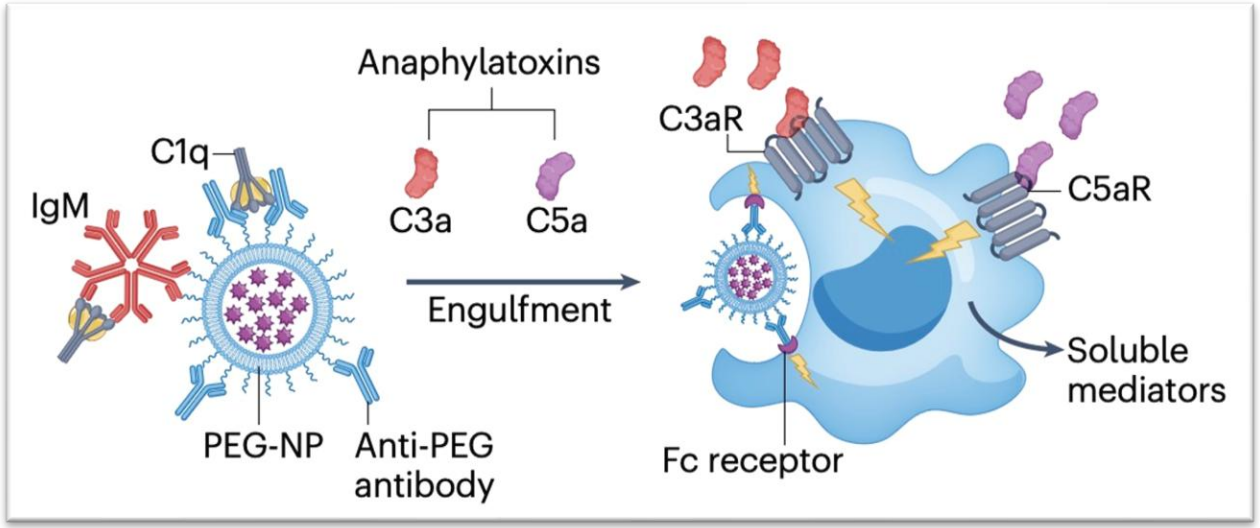


Hypersensitivity induced by Lipodox Is Complement-Driven



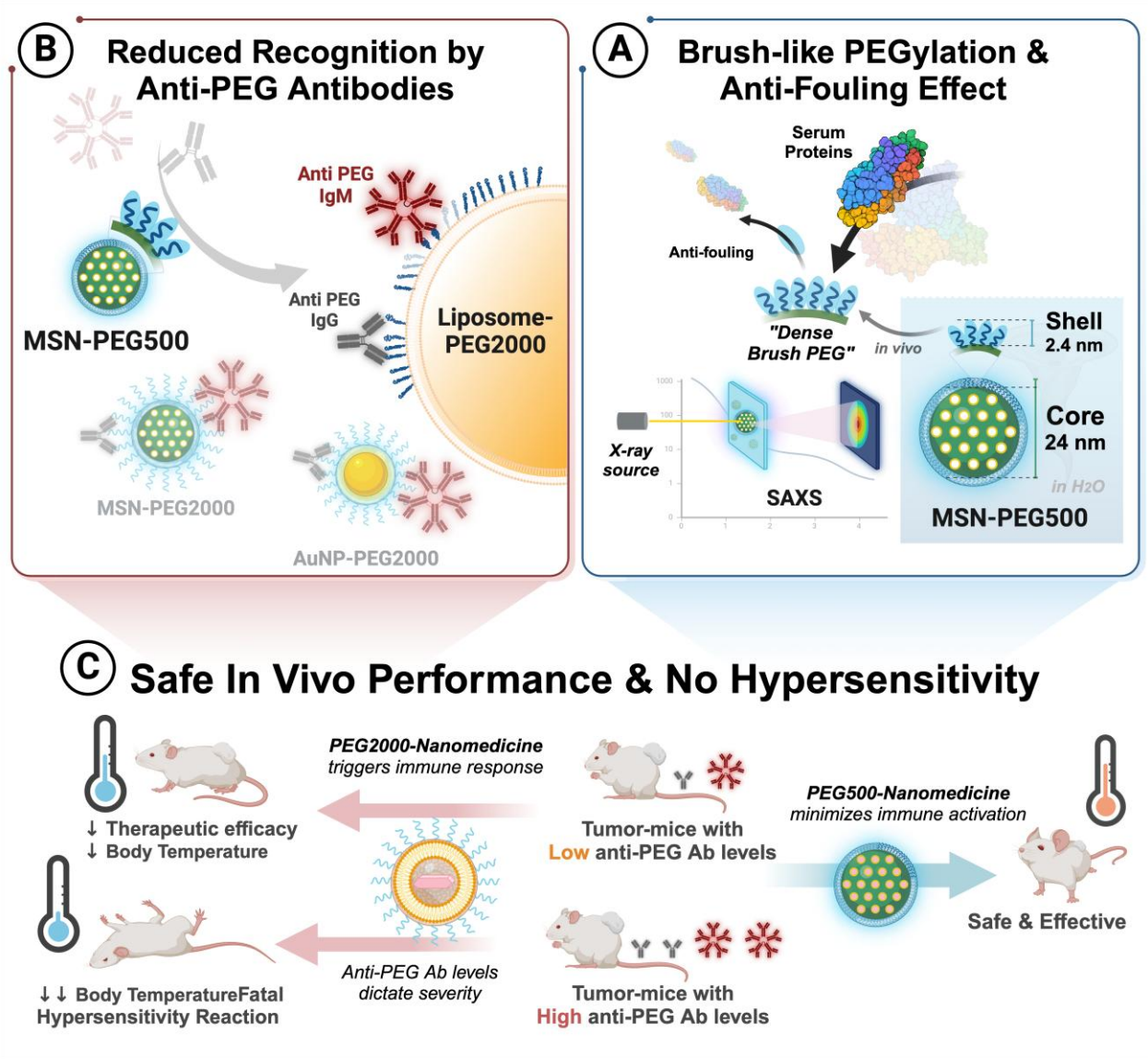
1. **Anti-PEG IgM/IgG binding initiates CARPA in PEGylated systems.**
2. **C3 blockade (Compstatin) reduces the severity, but doesn't solve the root cause.**





Nature Reviews Bioengineering, 2025

Concluding Perspective



1. PEG needs re-design, not retreat.
2. Anaphylaxis = Anti-PEG Ab titer × PEG accessibility

PEG: Not the end, but a new beginning!

Acknowledgement

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Thank you

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