SAND2018-2745C

CINT

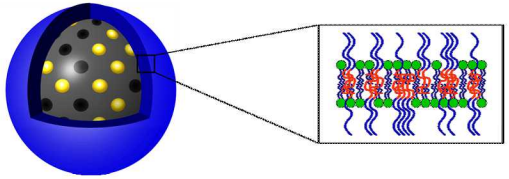
The Center for Integrated Nanotechnologies

Nanomaterials

Integration

A U.S. DOE Nanoscale Science Research Center

Mesoporous Nanoparticle-Supported Hybrid Bilayers for Drug Delivery



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Center for Integrated Nanotechnologies (CINT)
Sandia National Laboratories

255th ACS National Meeting
March 21st, 2018

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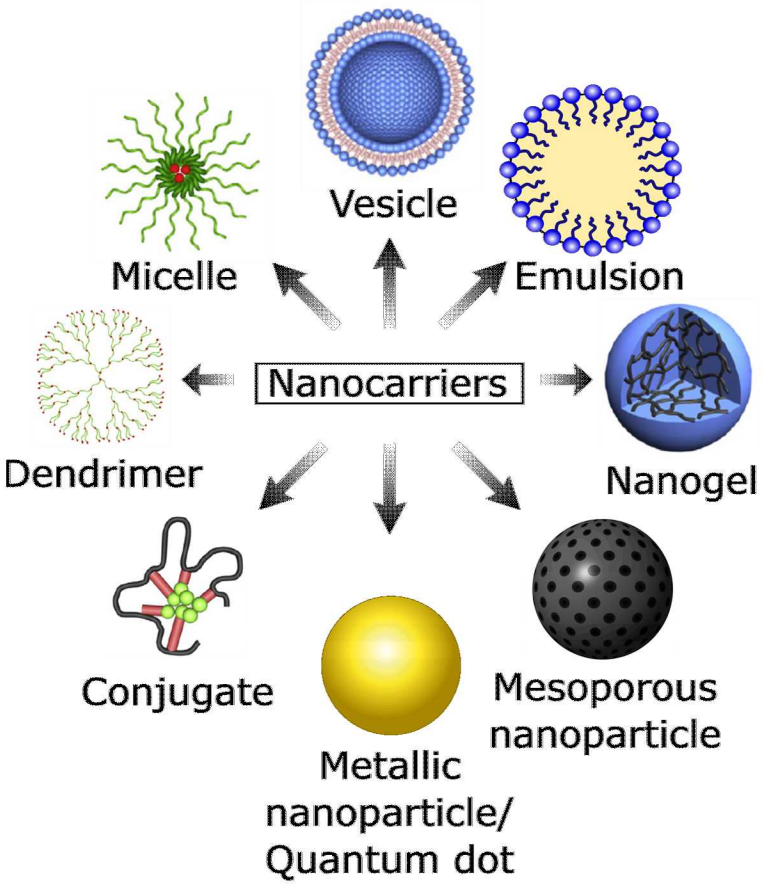
Smart Delivery Vehicles



Ideal nanocarriers

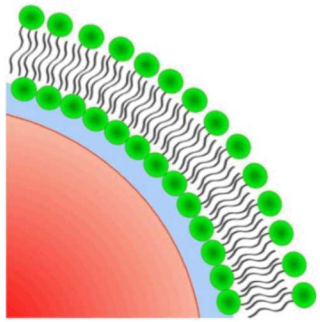
- High capacity for cargos
- High specificity to targets
- Precise release of cargos
- High colloidal stability
- Low cytotoxicity
- Long circulation time

Li et al. *Nanomed. Nanotech. Biol. Med*. **2015**, *11*, 769-794

Mesoporous Silica Nanoparticles (MSNP)

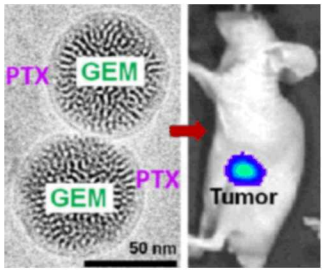
- High internal surface area (>1000 m^2/g)
  → high loading capacity
- Controllable size, shape, pore size, and surface chemistry
- Biodegradable
- **Often require coatings**
  - Cargo encapsulation
  - Colloidal stability
  - Blood circulation time
  - Potential toxicity of unmodified silica

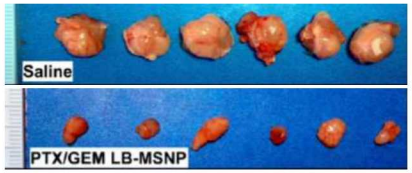
Lipid Bilayers vs Polymer Bilayers



Michel et al. *Int. J. Mol. Sci.* **2012**, *13*, 11610-11642

- Lipid bilayers
  - Low cytotoxicity and immunogenicity
  - Poor physical and chemical stability
- Polymer bilayers
  - Superior mechanical stability
  - Chemical versatility





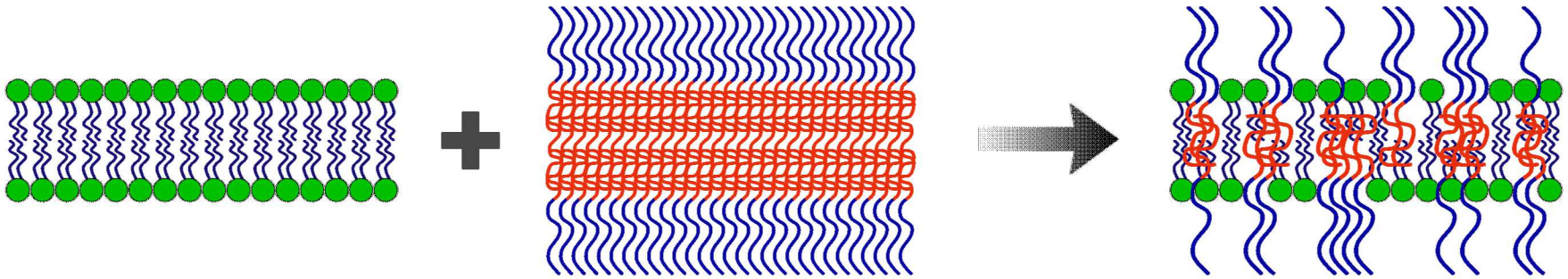
Meng et al. *ACS Nano* **2015**, *9*, 3540-3557

	Liposomes	Polymersomes
Bending modulus (kT)	11 – 30	40 – 460
Surface shear viscosity (mN/ms)	10^{-5}	1.5×10^{-2}
Water permeability (μm/s)	15 – 150	0.7 – 10

Le Meins et al. *Eur. Phys. J. E.* **2011**, *34*, 14-31

Hybrid Bilayers

Let's take advantages of their strengths!



Lipid bilayer

Polymer bilayer

Hybrid bilayer

Fluidity, Biocompatibility

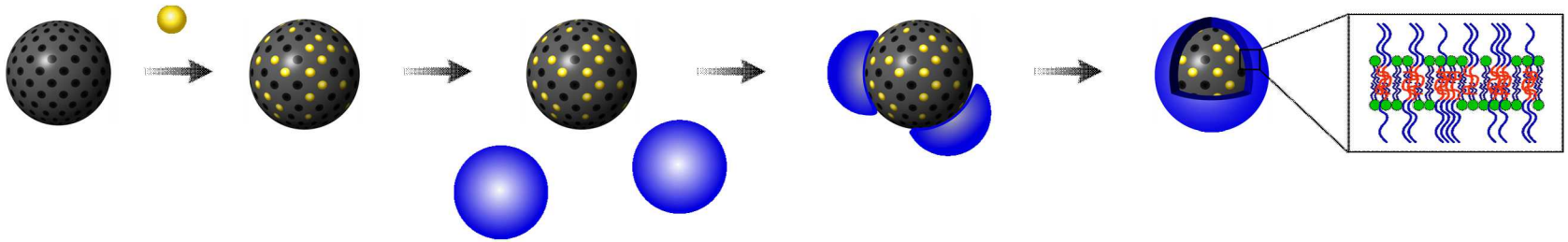
Stability, Robustness, Versatility

Synergistic membrane properties

Research Objective

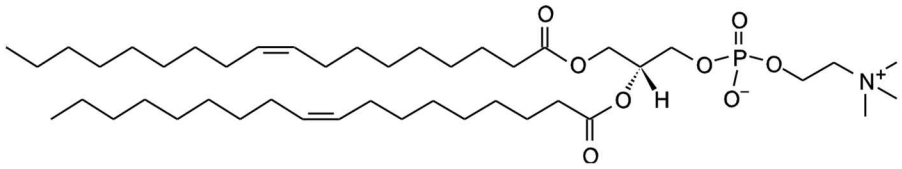
Objective : To design prophylactic and therapeutic delivery vehicles based on MSNPs coated with hybrid bilayers

Approach :
1. MSNP-supported bilayers
2. Drug loading and release
3. Cell interaction

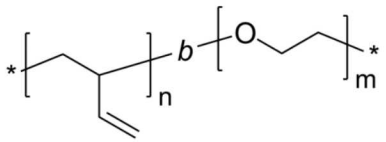


Preparation of Hybrid Bilayers

- Lipid : 1,2-Dioleoyl-*sn*-glycerol-3-phosphocholine (DOPC)



- Polymer : Poly(ethylene oxide)-b-polybutadiene (PEO-PBd)

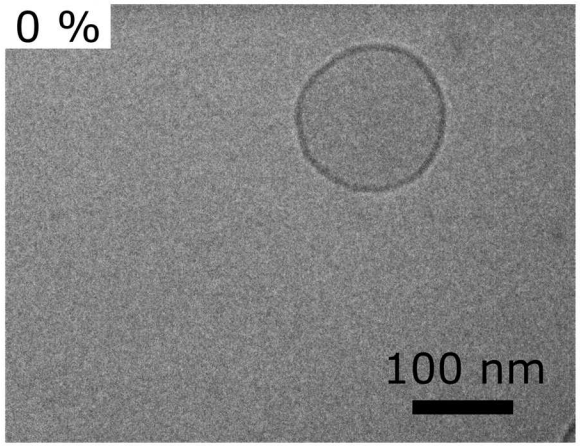


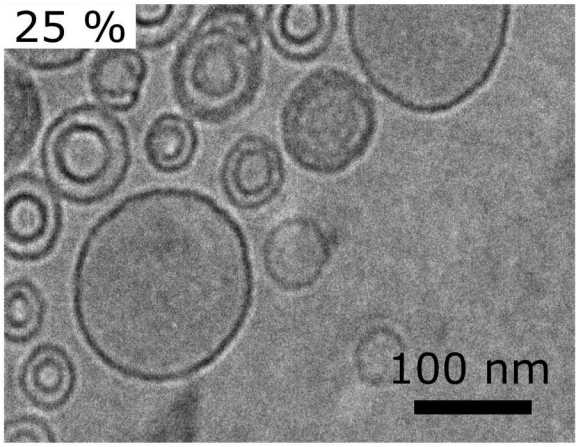
n=33, m=21

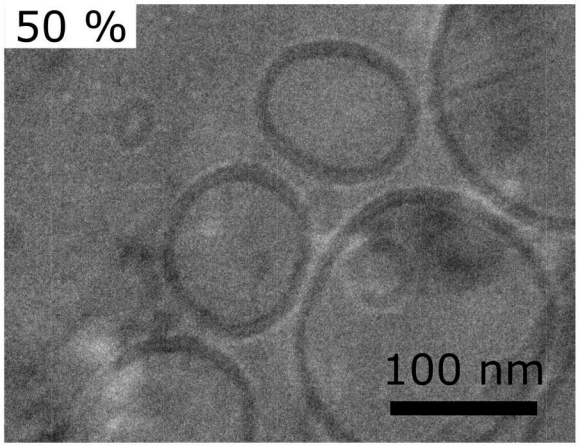
Sample	DOPC (mol%)	PEO-PBd (mol%)
0%	100	0
25%	75	25
50%	50	50
75%	25	75
100%	0	100

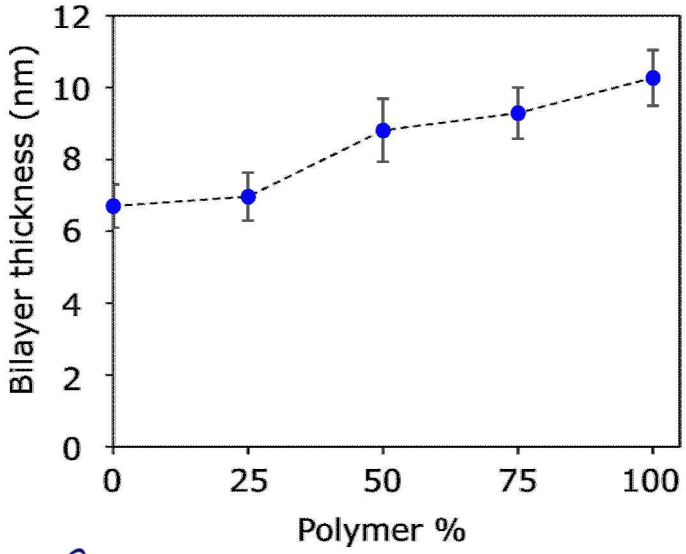
Characterization of Hybrid Bilayers

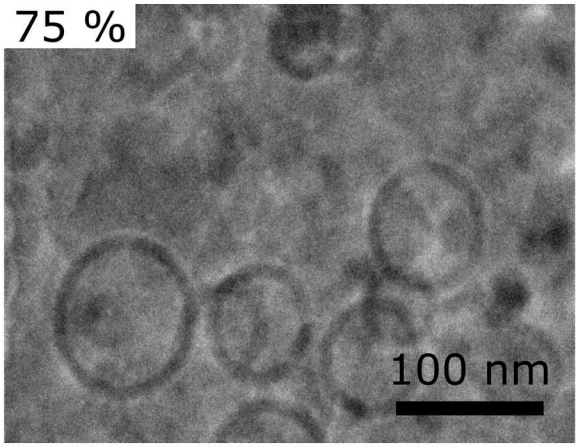
- Cryo-electron microscopy images of vesicles

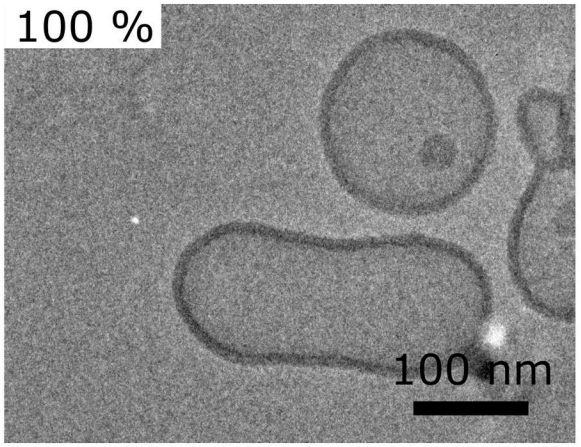






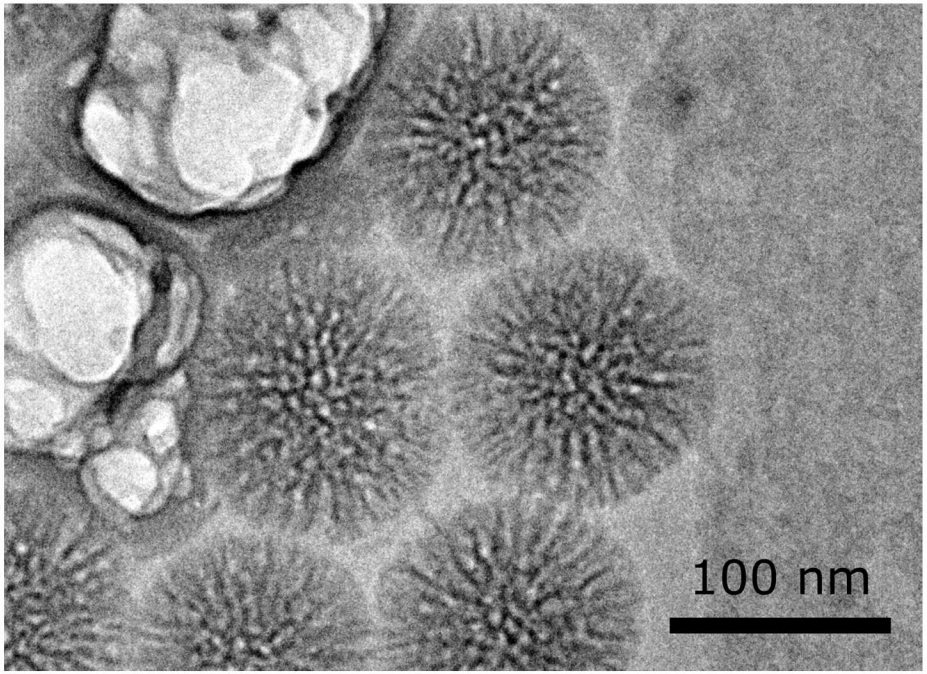






Large Pore MSNPs

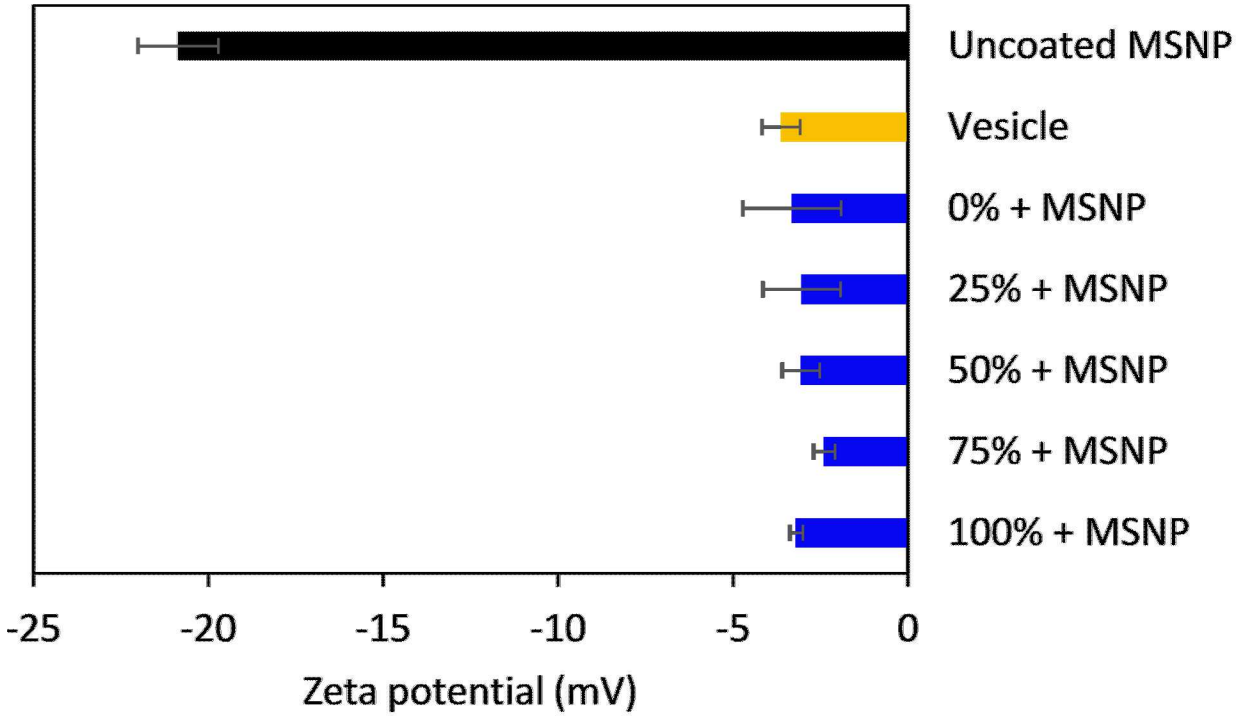
- Pore size: 8 nm
- Dendritic pore morphology



MSNPs were synthesized by Achraf Noureddine, Ph.D. (University of New Mexico)

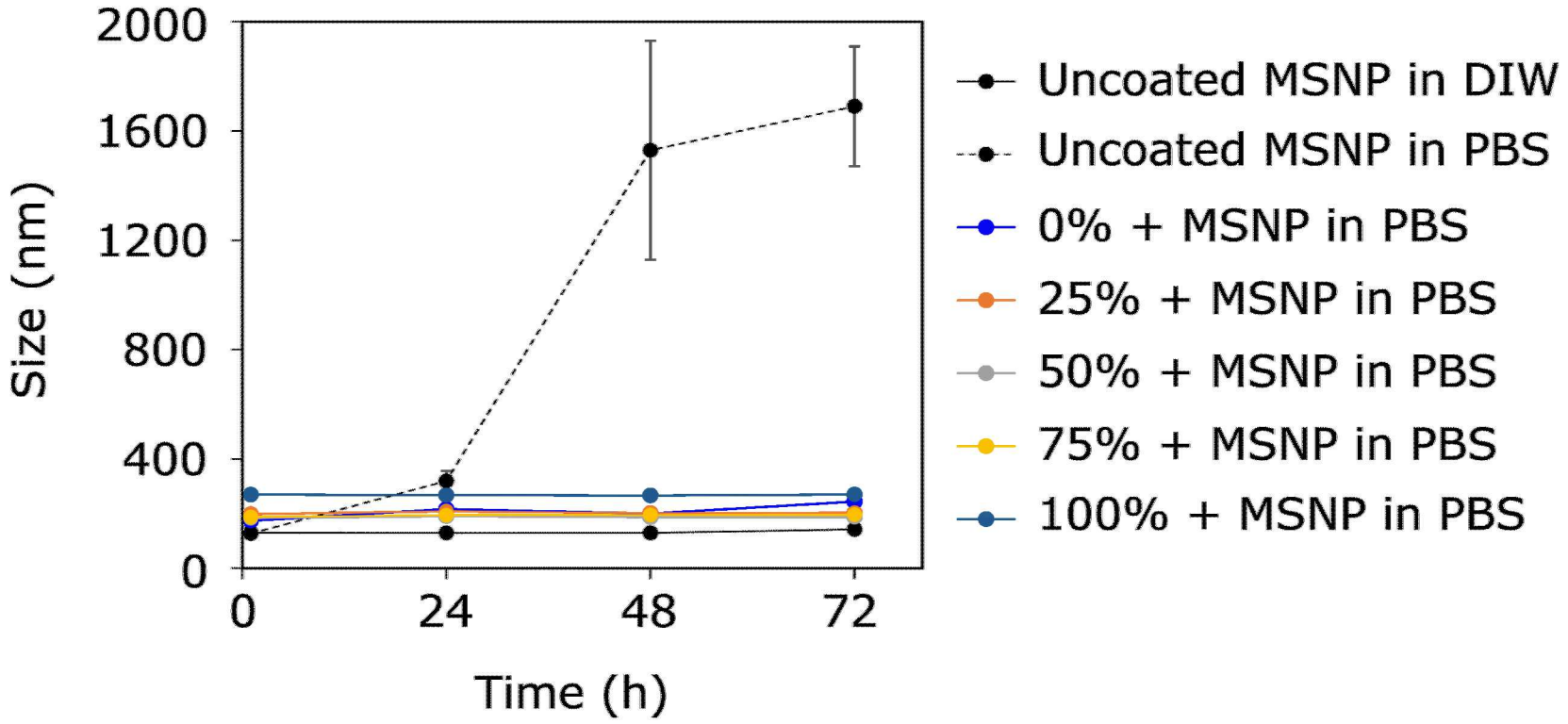
MSNP-Supported Hybrid Bilayers

- Change in zeta potential of MSNP after vesicle fusion, indicating formation of bilayer coating on the MSNP



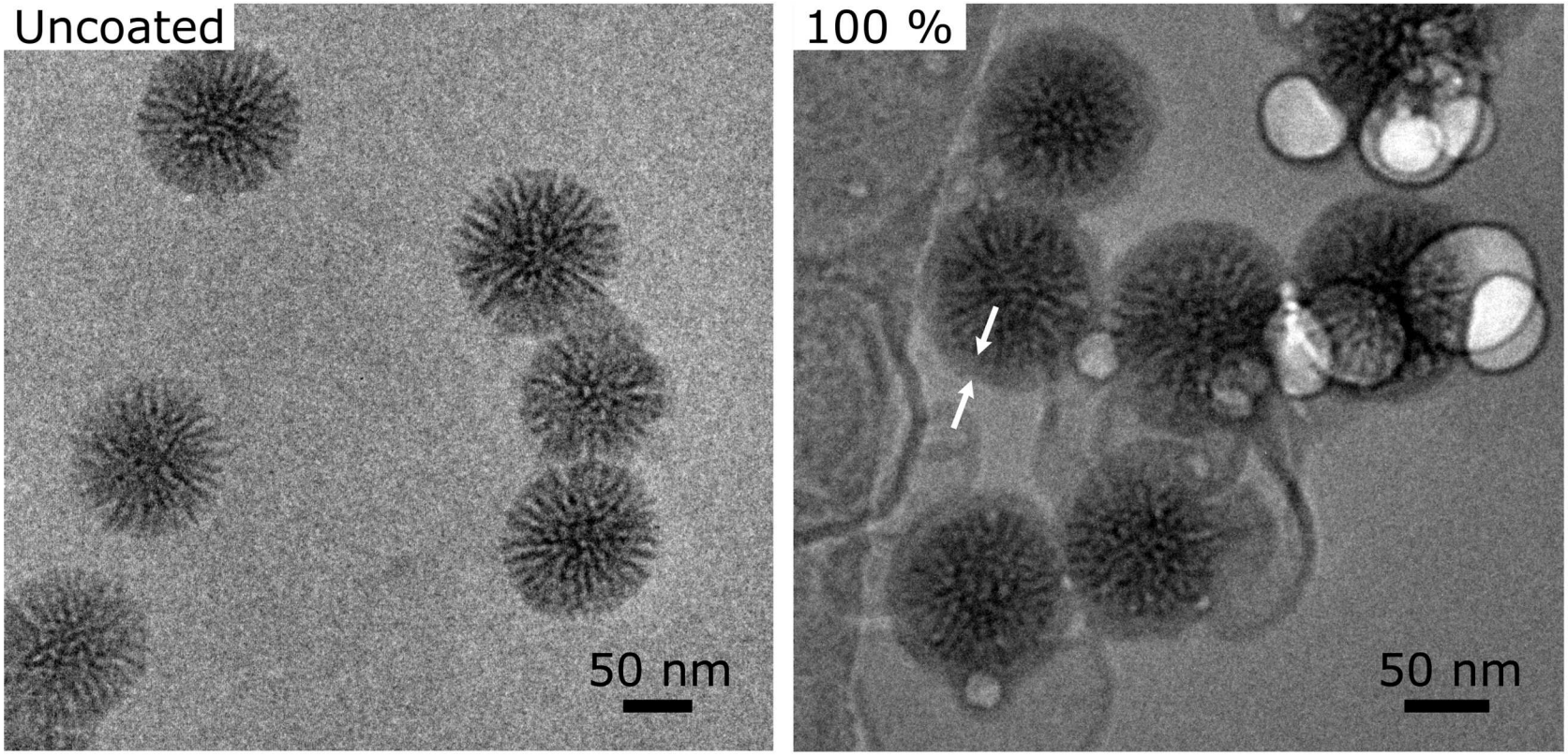
MSNP-Supported Hybrid Bilayers

- Stable MSNP suspensions in PBS buffer after vesicle fusion, indicating enhanced colloidal stability in buffer



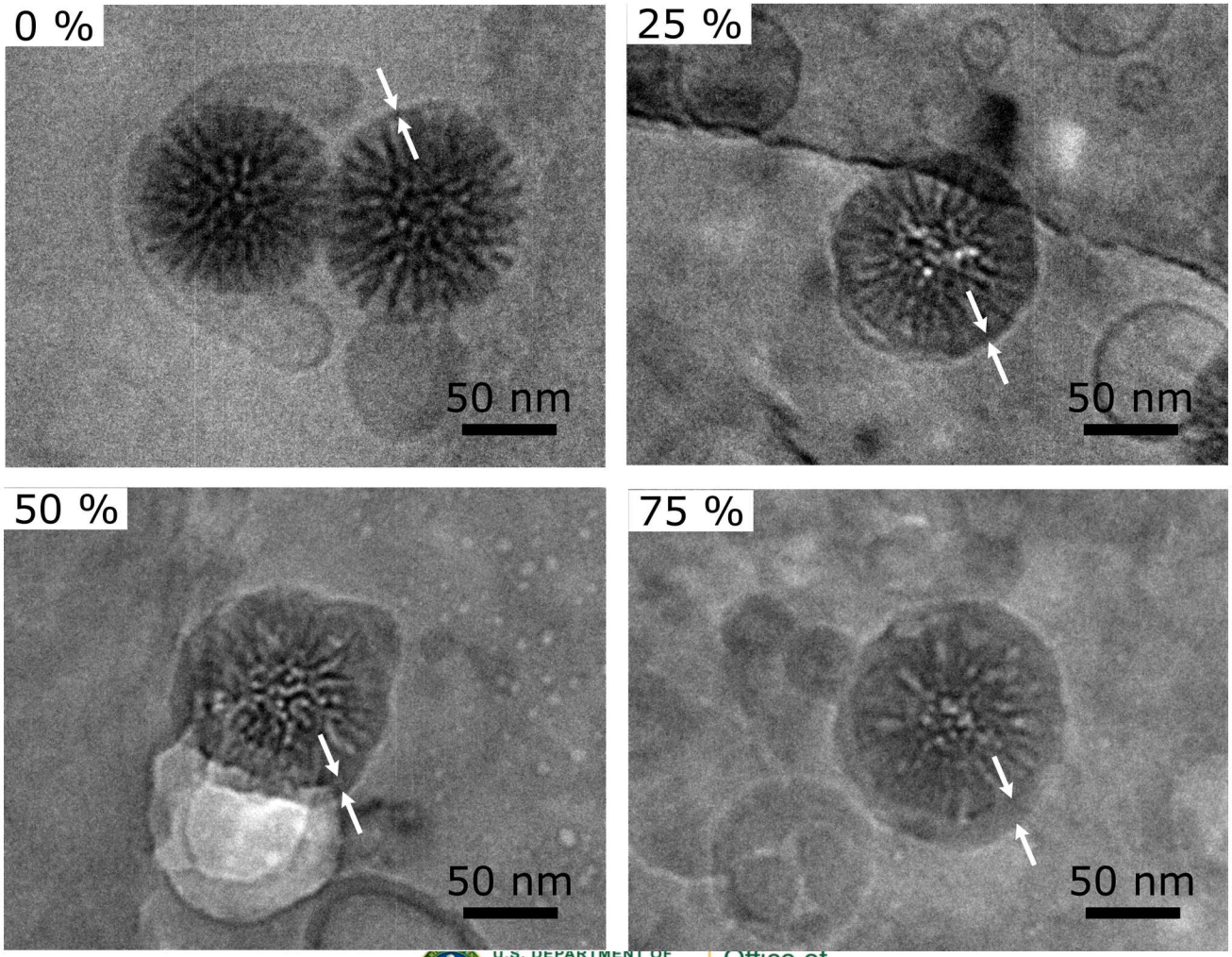
MSNP-Supported Hybrid Bilayers

- Bilayer coating on MSNP (white)



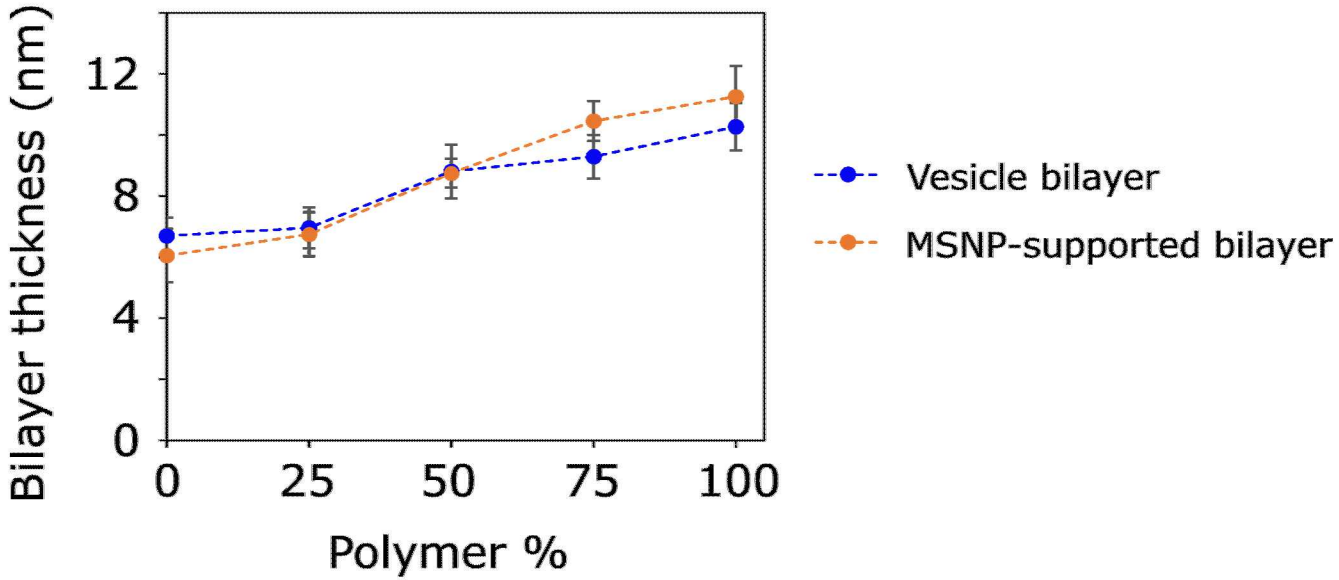
MSNP-Supported Hybrid Bilayers

- Bilayer coating on MSNP (white)

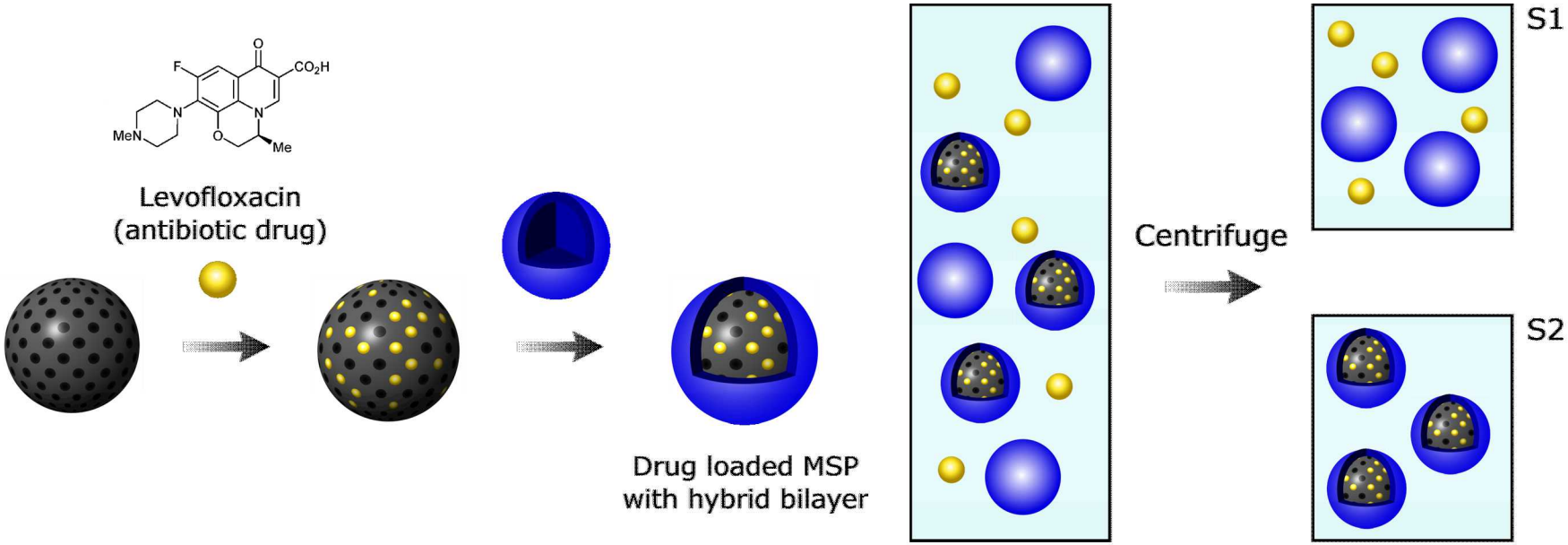


Bilayer Thickness

- Thickness of MSNP-supported bilayer is similar to thickness of vesicle bilayer



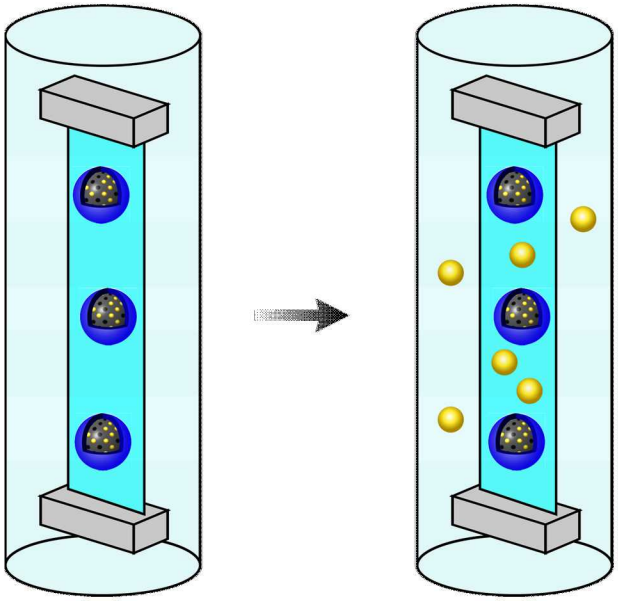
Loading Drug into MSNPs

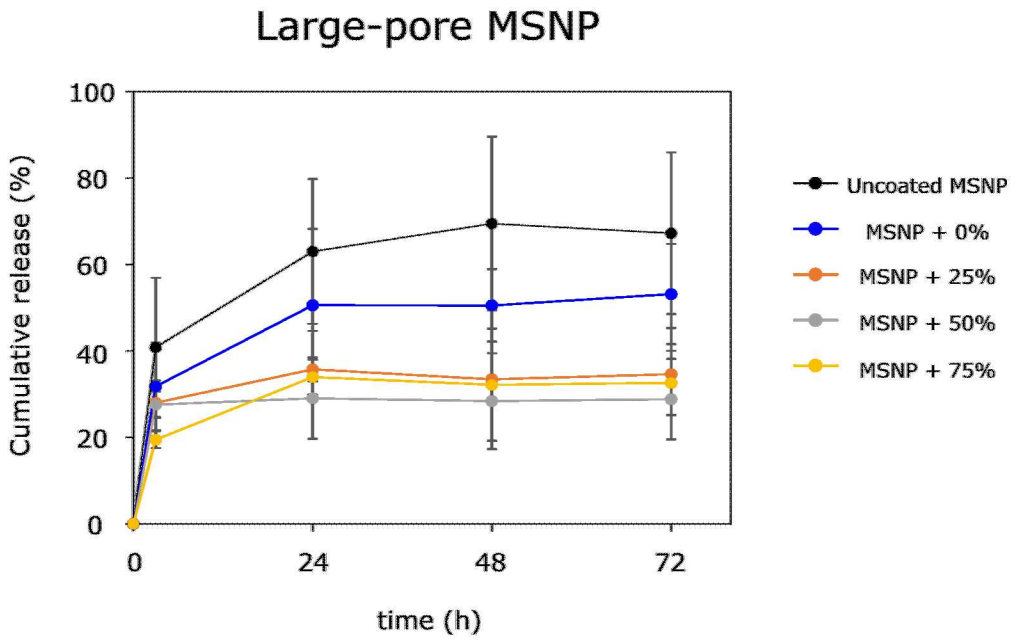


$$\text{Encapsulation efficiency (\%)} = \frac{\text{Drug added (mg)} - \text{Drug left in S1 (mg)}}{\text{Drug added (mg)}} \times 100$$

Averaged encapsulation efficiency (%) = 12.5 ± 1.3

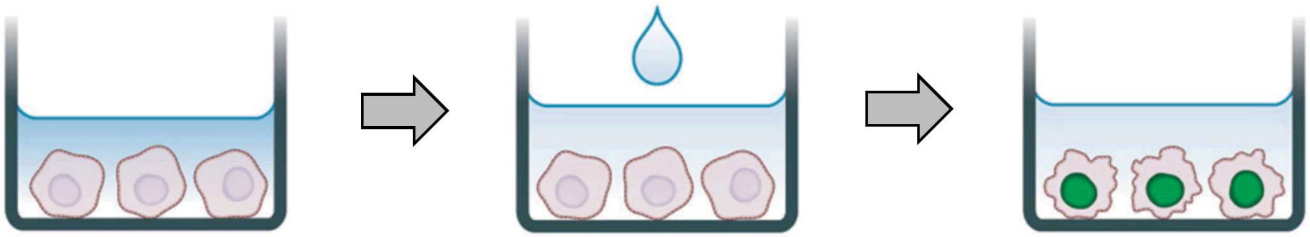
In Vitro Drug Release





- MSNPs with hybrid bilayer coating (32 %) release drug less than MSNPs with lipid bilayer coating (53 %) or uncoated MSNP (67 %) in PBS

Cell Cytotoxicity



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1. Cultivate target cells
   A549 (adenocarcinomic human alveolar basal epithelial cell)

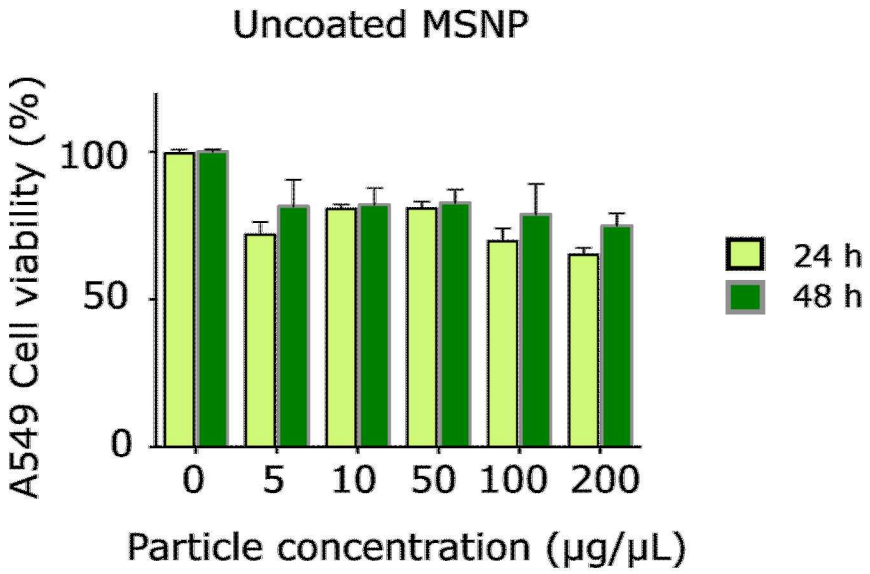
2. Treat cells with cytotoxicity reagents
   Uncoated MSNPs
   Hybrid vesicles
   MSNPs with bilayer coating

3. Monitor cell viability for 48 h by measuring luminescence

Cell experiments were conducted by Amber McBride, Ph.D. (Sandia National Laboratories)

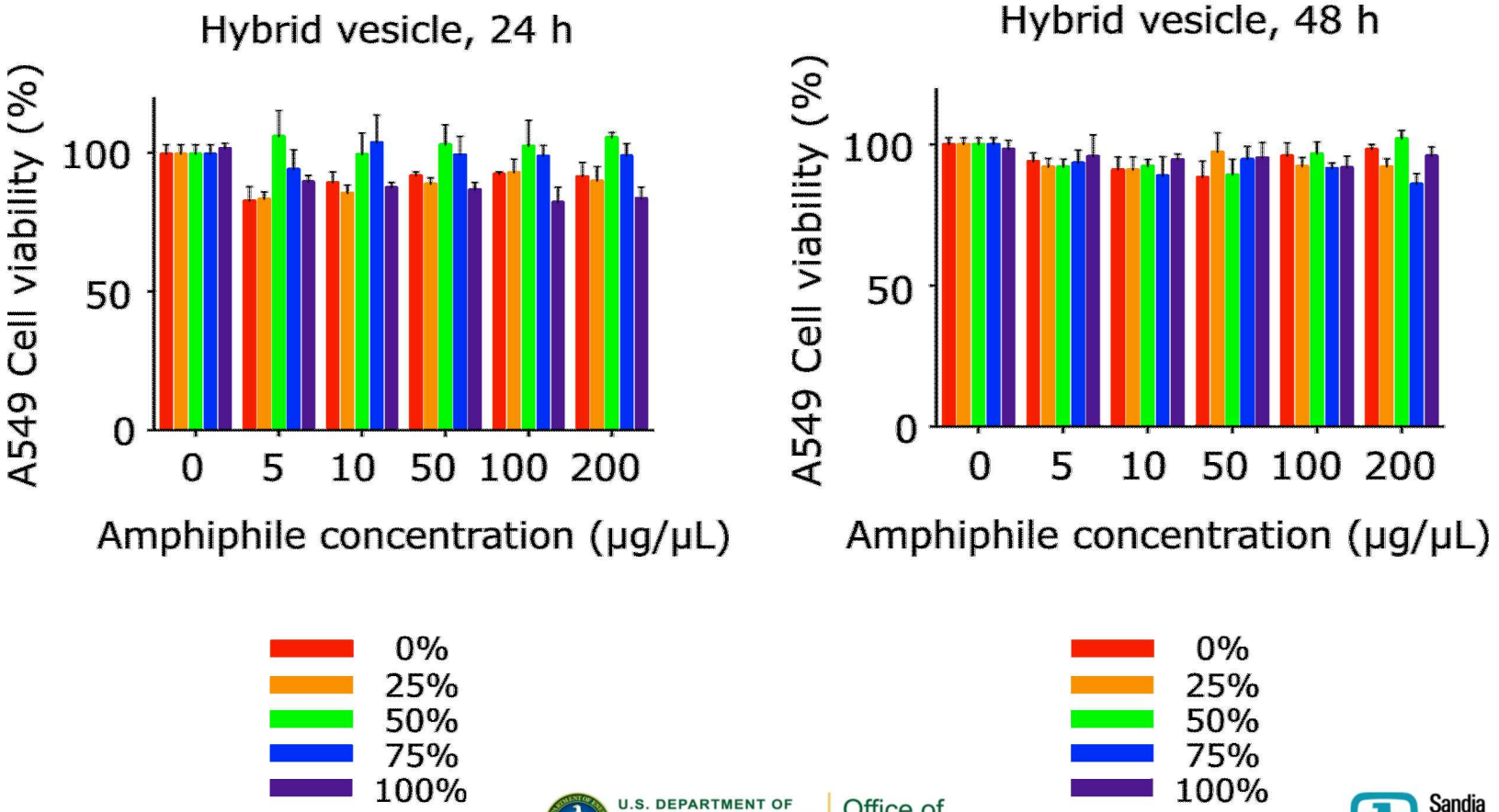
Cell Cytotoxicity – Uncoated MSNPs

- The viability of A549 cells with exposure to uncoated MSNPs is 70–80 % after 48 h



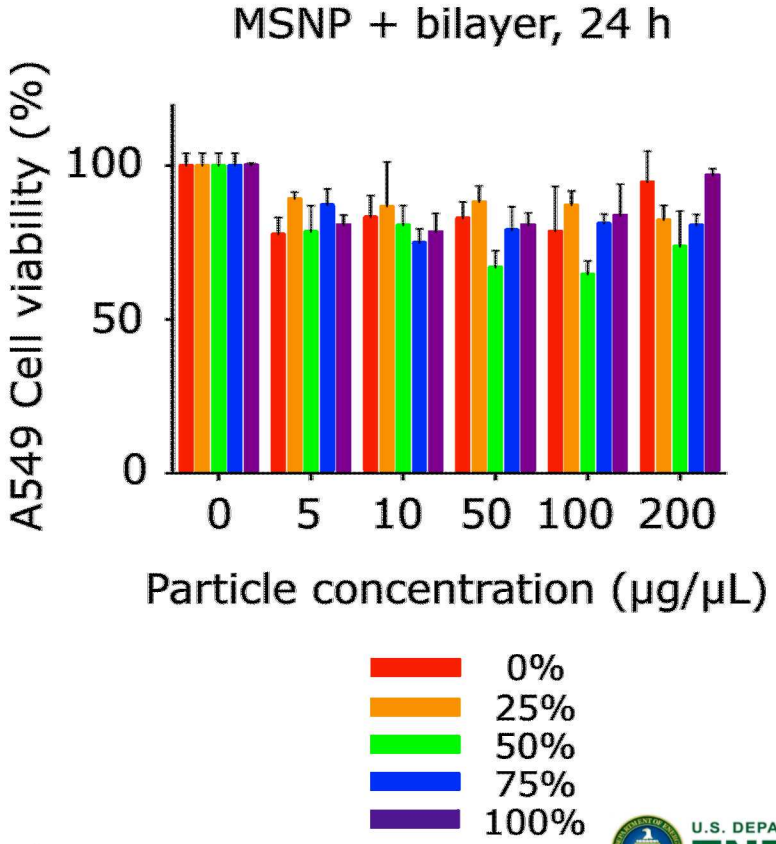
Cell Cytotoxicity – Hybrid Vesicles

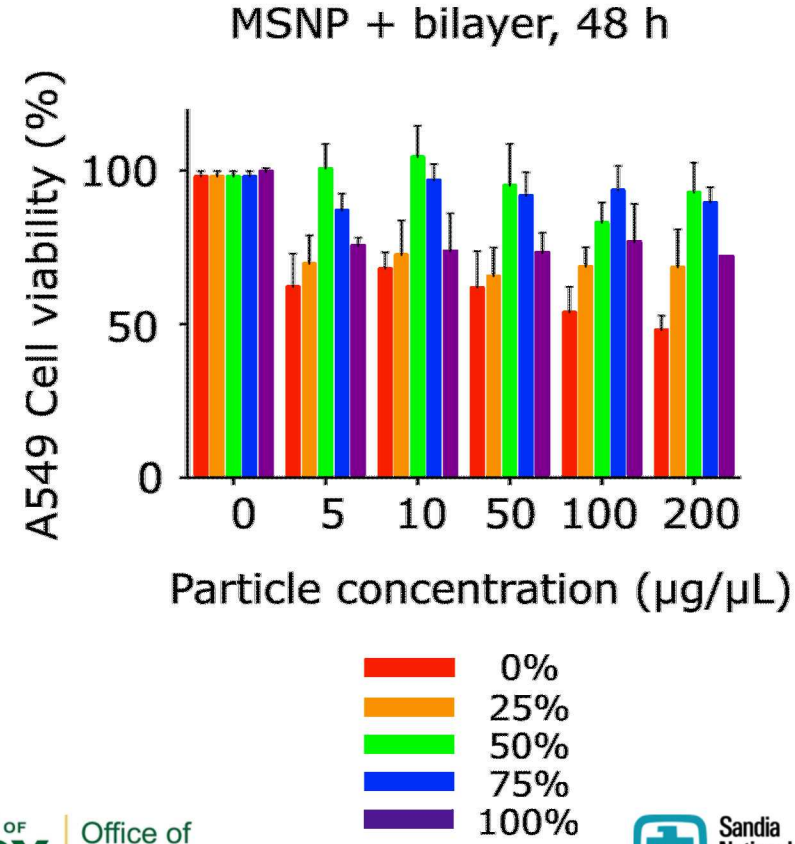
- The viability of A549 cells with exposure to hybrid vesicles is higher than 90% after 48 h



Cell Cytotoxicity – MSNP+Bilayer

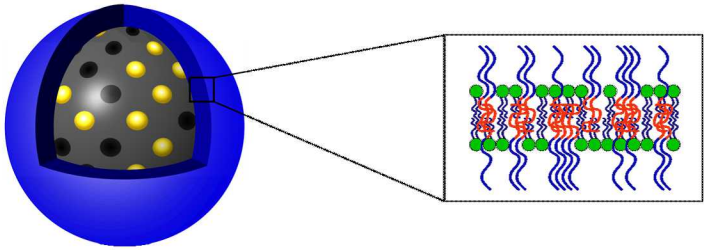
- The viability of A549 cells with exposure to hybrid lipid-polymer coated MSNPs is higher than lipid or polymer coated MSNPs after 48 h
- Supported lipid bilayer becomes unstable after 48 h while hybrid lipid-polymer bilayer remain stable.





Summary and Conclusion

- We confirm formation of supported hybrid bilayers on MSNPs with large (8 nm) pore size.
- *In vitro* release of drug from MSNPs coated with hybrid bilayers shows decreased permeability of hybrid bilayers compared to lipid bilayers.
- The viability of A549 cells with exposure to hybrid bilayer coated MSNPs is higher than lipid or polymer coated MSNPs after 48 h
- Hybrid lipid-polymer bilayers are promising membranes that can offer synergistic membrane properties in the development of artificial organelles



Acknowledgements

- **Principal Investigator**: Walter Paxton, Ph.D. (SNL)
  Student Intern: Haley Monteith (SNL)

- **MSP synthesis**
  Achraf Noureddine, Ph.D.; Jeffrey Brinker, Ph.D. (Univ. of New Mexico)

- **Cytotoxicity study**
  Amber McBride, Ph.D.; Kim Butler, Ph.D. (SNL)

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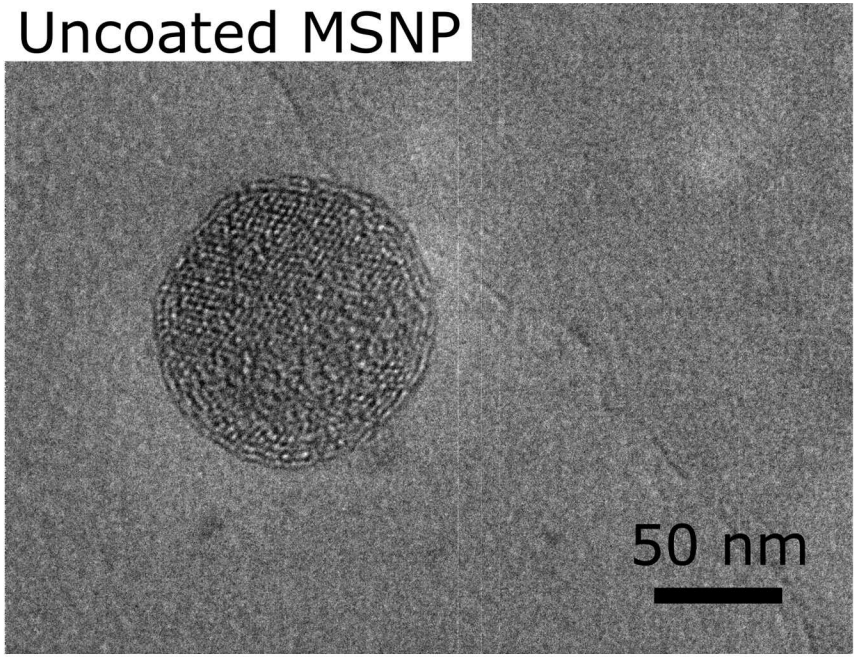
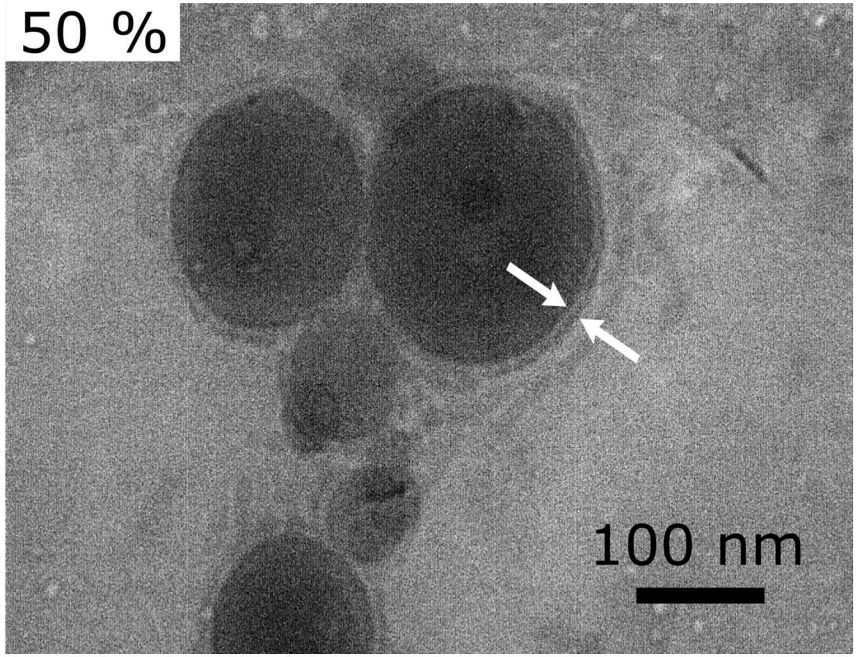
  This work was performed in part, at the Center for Integrated Nanotechnologies, an Office of Science User Facility operated for the U.S. Department of Energy (DOE) Office of Science (project number 2017BC0053). Research was supported by the Laboratory Directed Research and Development program at Sandia National Laboratories, a multi-mission laboratory managed and operated by National Technology and Engineering Solutions of Sandia, LLC, a wholly owned subsidiary of Honeywell International, Inc., for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-NA-0003525.

Supplementary Slide: Small Pore MSNPs

- Pore size: 2.5 nm
- Hybrid bilayer coating on small pore MSNPs

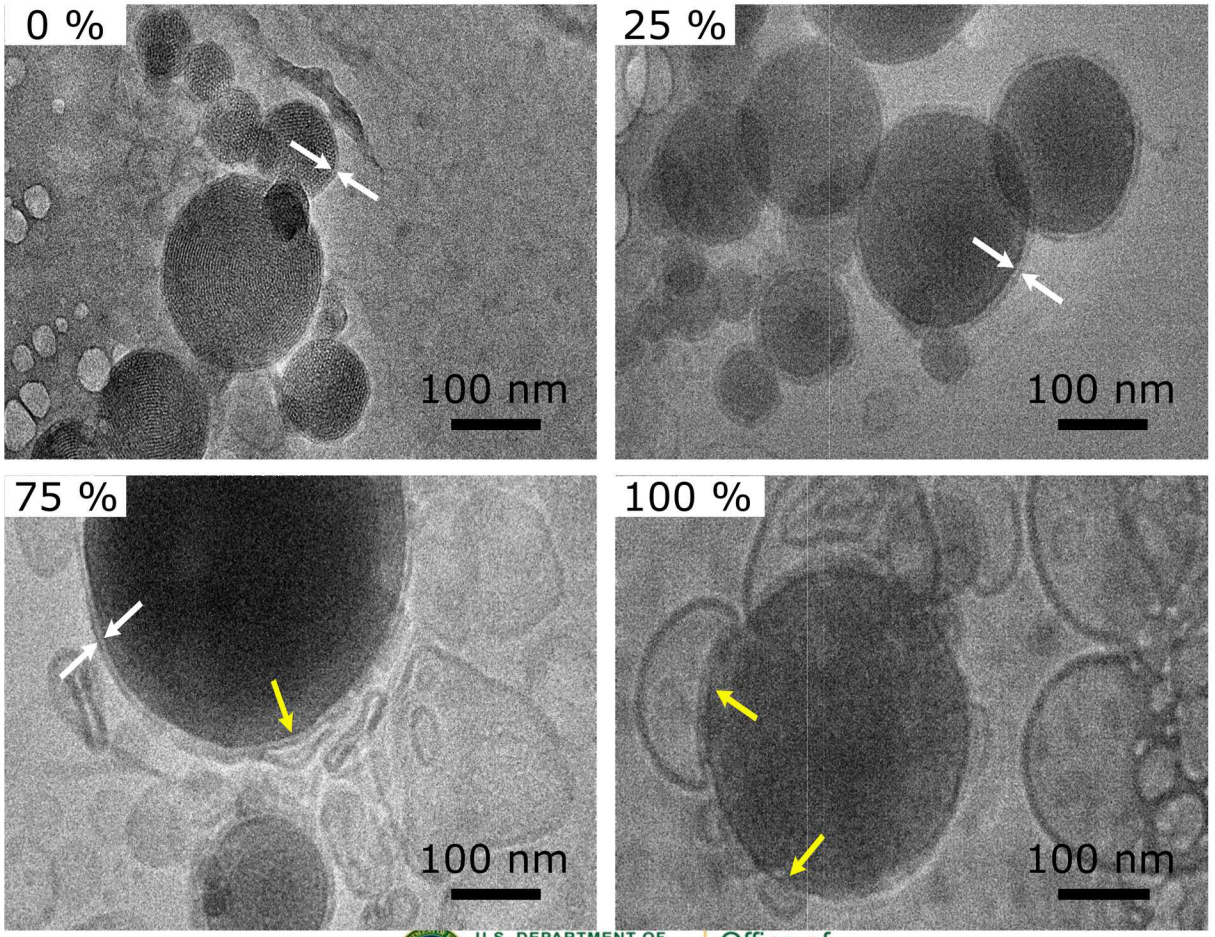




MSNPs were synthesized by Brandon Slaughter, Ph.D.
(Advanced Materials Laboratories)

Supplementary Slide: Small Pore MSNPs

- MSNP-supported hybrid bilayers (white)
- Deformed vesicles with higher polymer content (yellow)



Supplementary Slide: Encapsulation Efficiency