MACKIEWICZ RESEARCH GROUP
LABORATORY OF NANOSTRUCTURED MATERIALS

Portland State UNIVERSITY

The Design of Hybrid Lipid-Coated Superparamagnetic Iron Oxide Nanoparticles for Drug Delivery and MRI Imaging Applications

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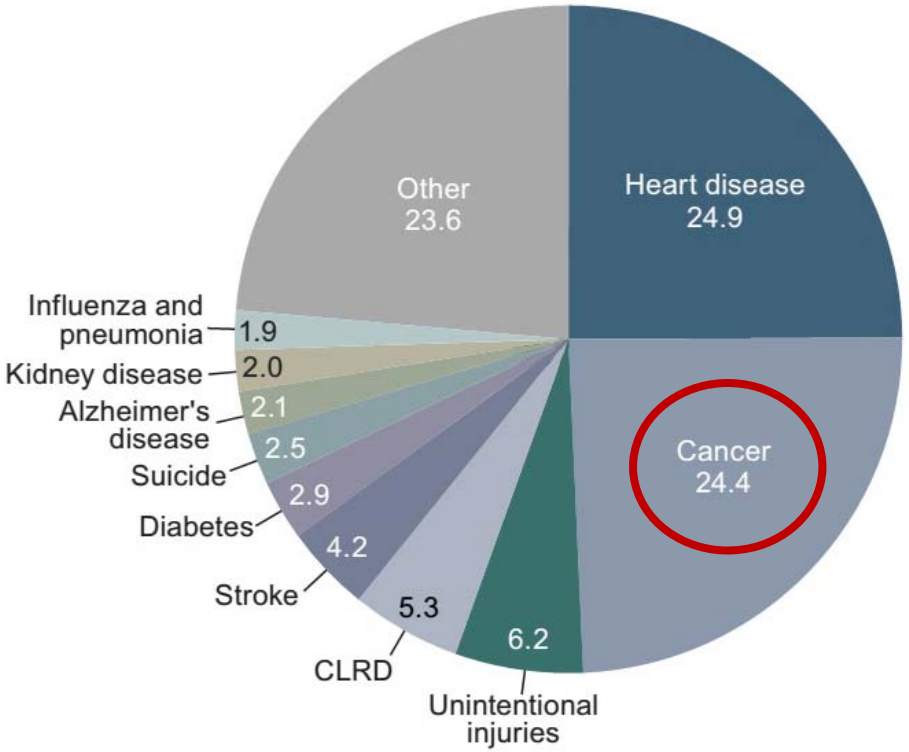
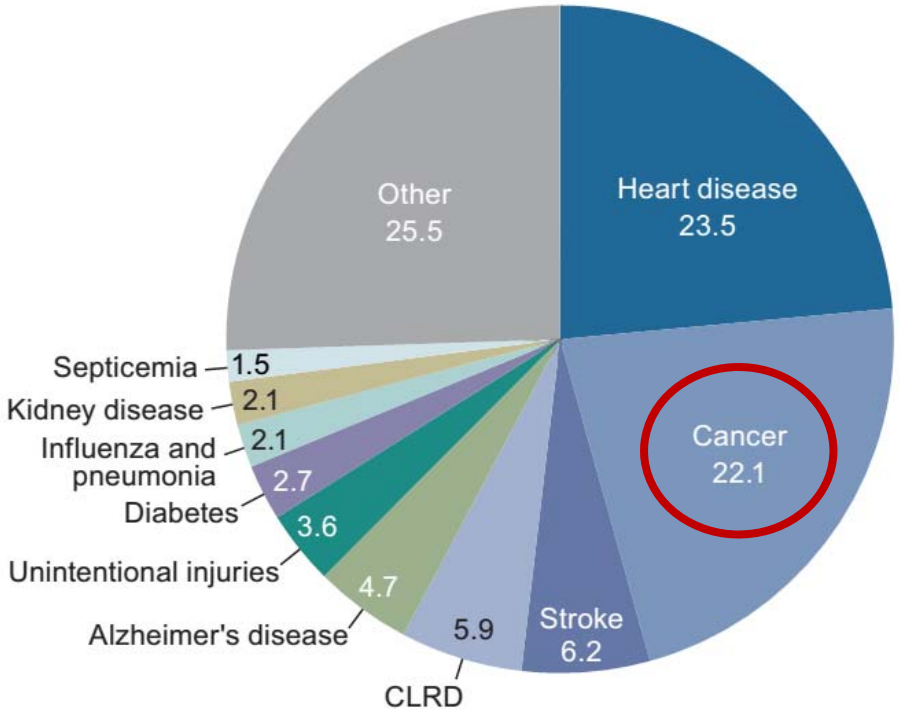
AUGUST 12, 2016

What is the driving force behind our research?

Men



Women



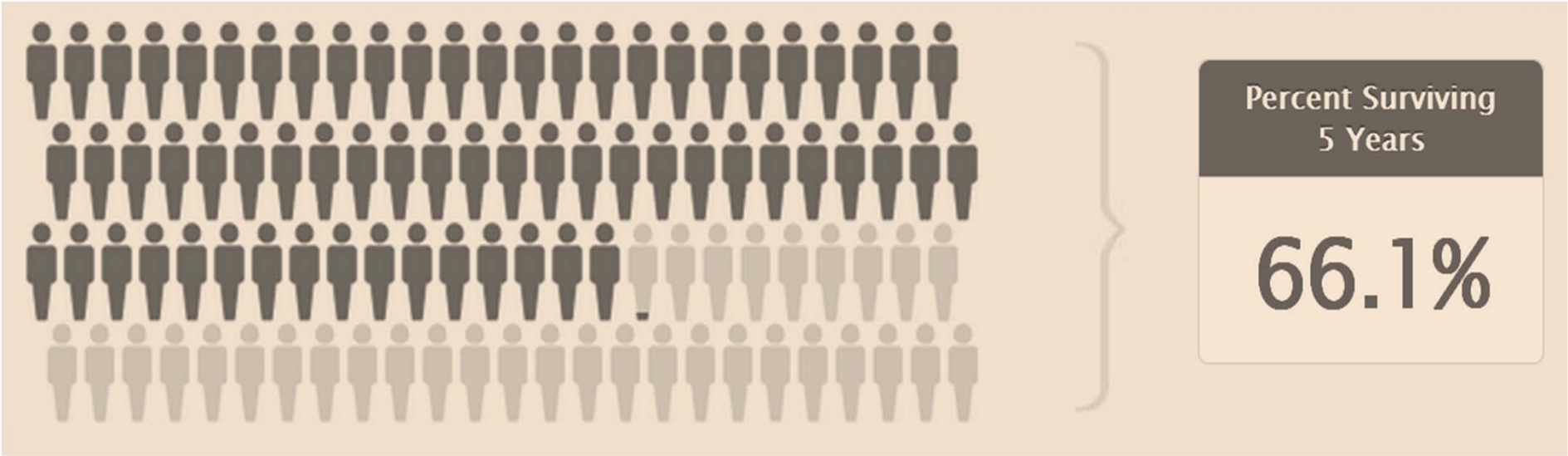
NOTES: CLRD is Chronic lower respiratory diseases. Values show percentage of total deaths.
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.

Cancer is 2nd deadliest disease in America

Heron, M. *Natl. Vital Stat. Reports* **2013**, *62*.

What is the driving force behind our research?

1600 Americans die from cancer every day

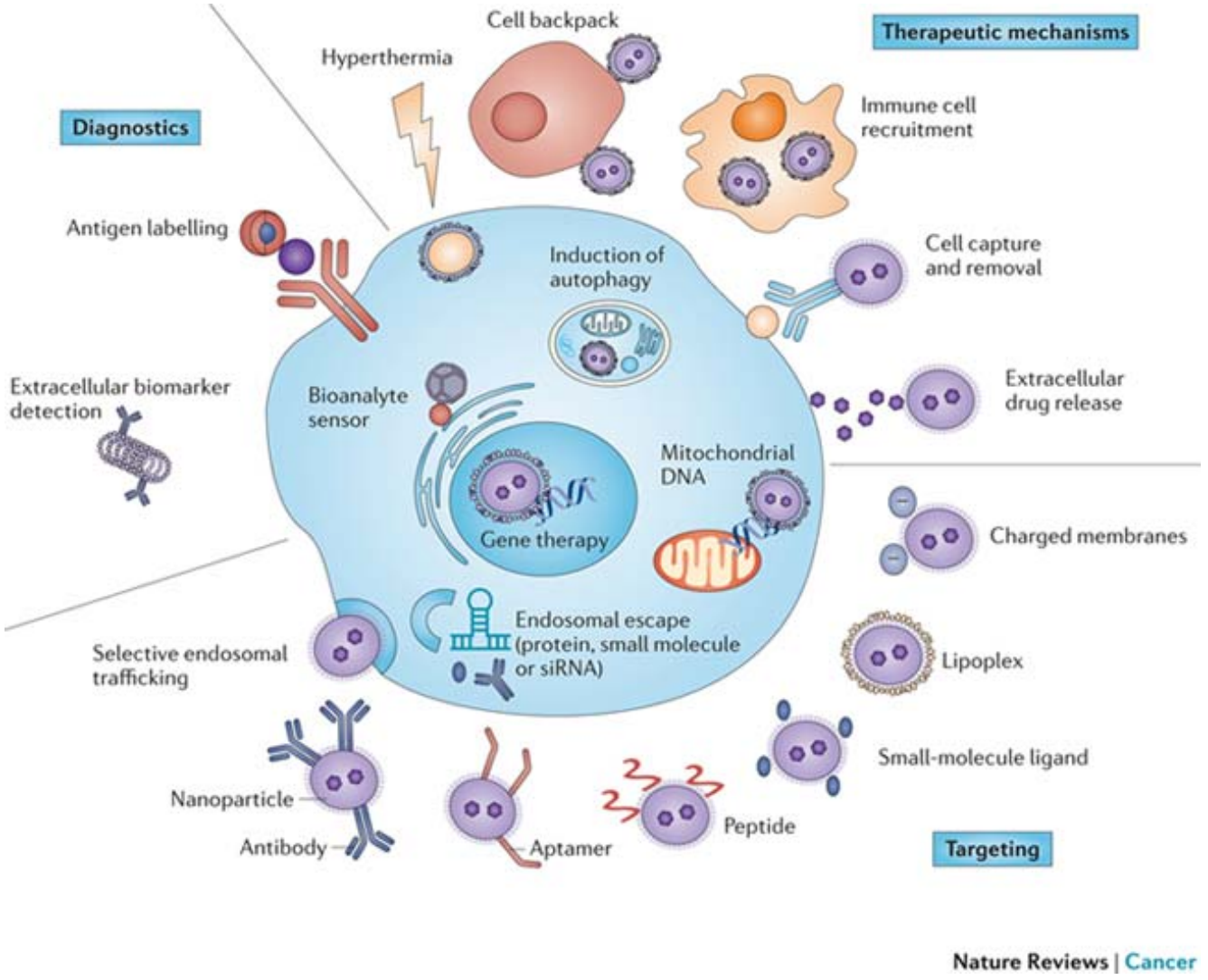


Critical Need

Early detection and improved treatments

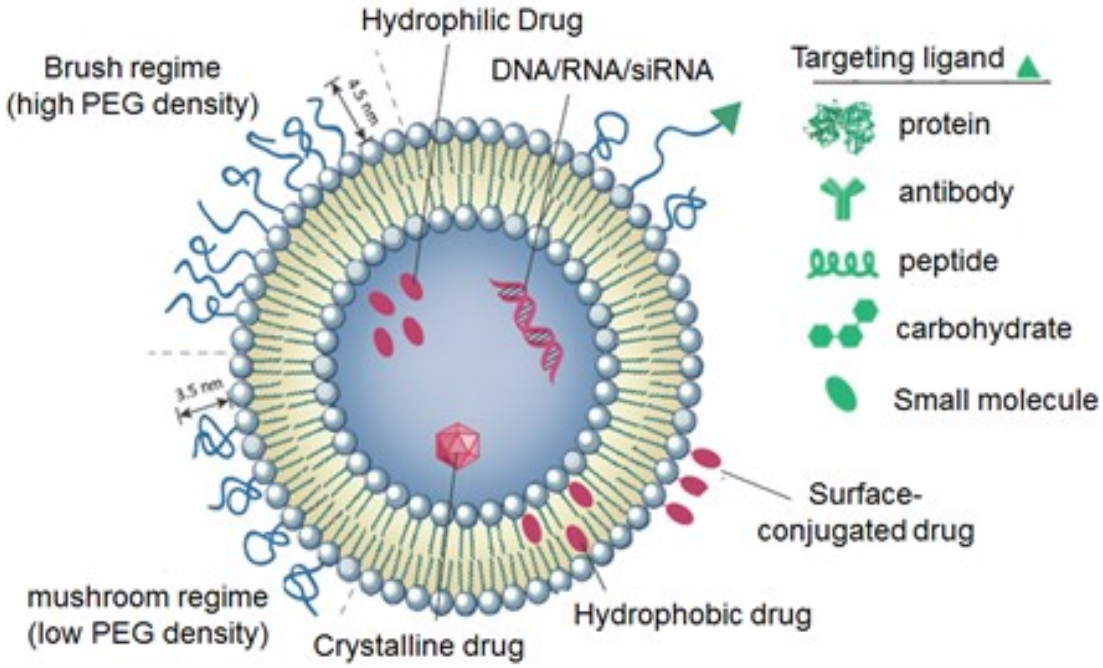
http://seer.cancer.gov/statfacts/html/all.html

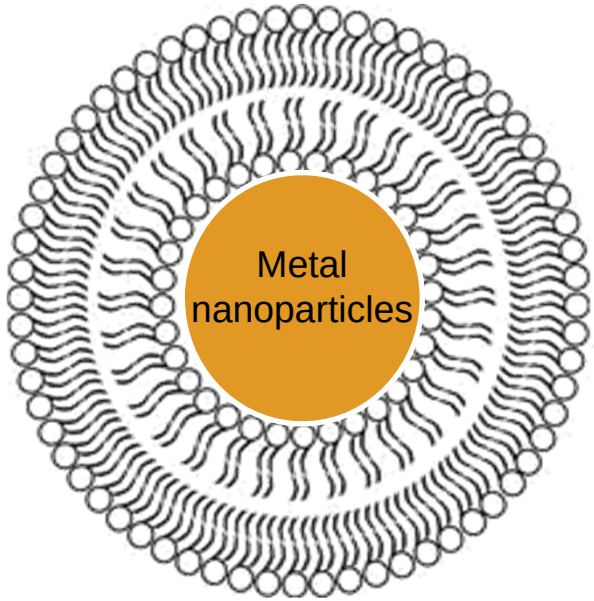
Treating Metastatic Cancer with Nanotechnology



- Feridex is the only iron oxide nanoparticle that is FDA approved
  - Used for imaging liver cancer
  - Difficult to remove from liver

Liposomes as Drug Delivery Vehicles





- **Liposome Based Drug Delivery**
  - Biomimetic and widely used FDA approved technology
  - Carry targeting molecules and drugs

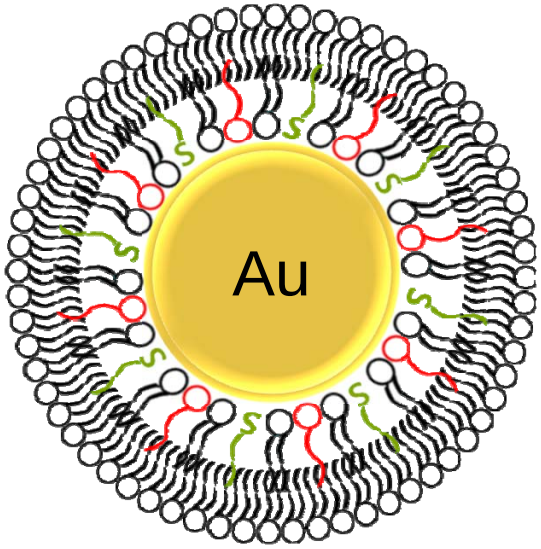
- **Challenge**
  - Prone to rearrangement
    - Instability
      - Drug leakage

How can we stabilize liposome drug delivery platforms?

Previous work: Preparation of Hybrid Lipid-Coated Metal Nanoparticles as Drug Delivery Vehicles

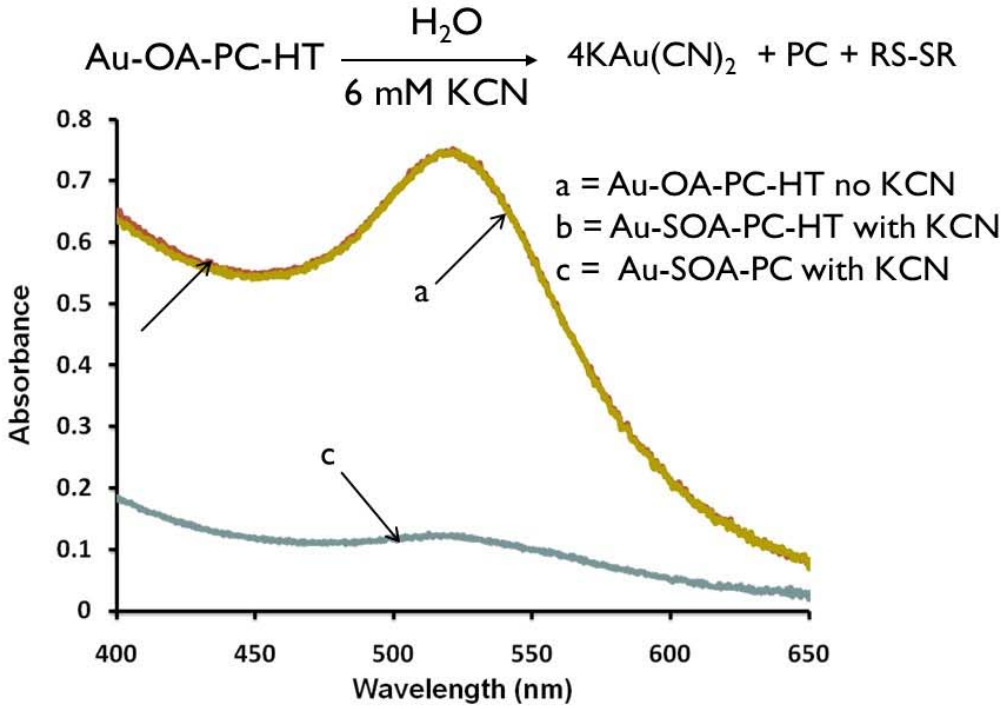
A

Hybrid Membrane-coated Gold Nanoparticles (Au-SOA-PC-HT)



B

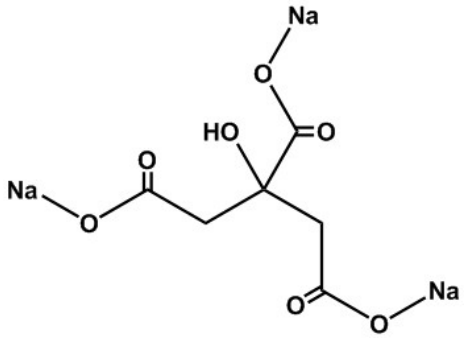
KCN Etch Test for Surface Coverage



- **Metal nanoparticles**
  - Thiol anchors lipid-membrane and pulls it close to the surface for complete coverage
  - Stable under oxidant conditions
  - Serves to prevent uncontrolled liposome reorganization, fusion, and aggregation

First Stage: Synthesis of Citrate-Capped Superparamagnetic Fe_3O_4 Nanoparticles (SPIOS)

Step 1:



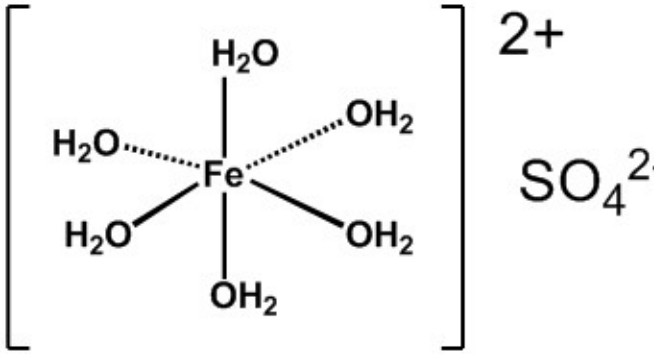
Trisodium citrate (capping agent)

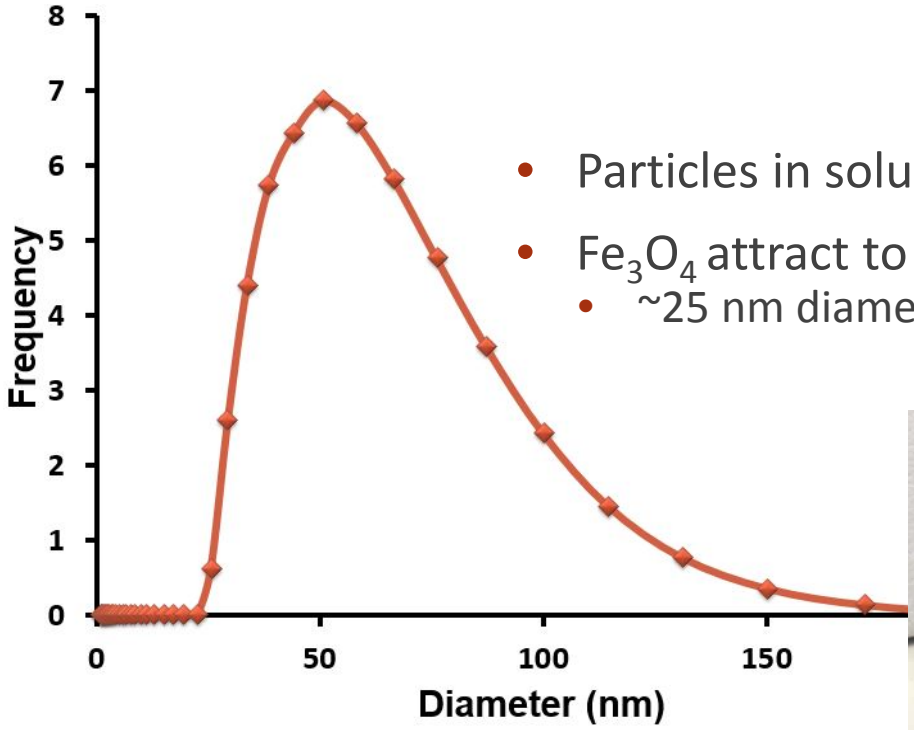
+ NaOH + $NaNO_3$

Controls size of NPs

Step 2:
Heat to 100°C

Step 3:





- Particles in solution
- Fe_3O_4 attract to each other
  - ~25 nm diameter

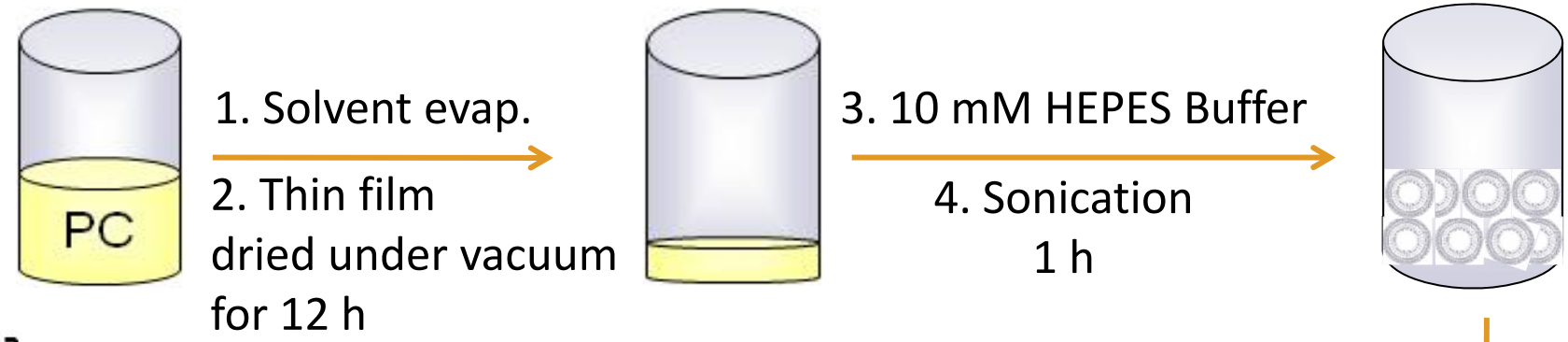
Superparamagnetic iron oxide nanoparticles

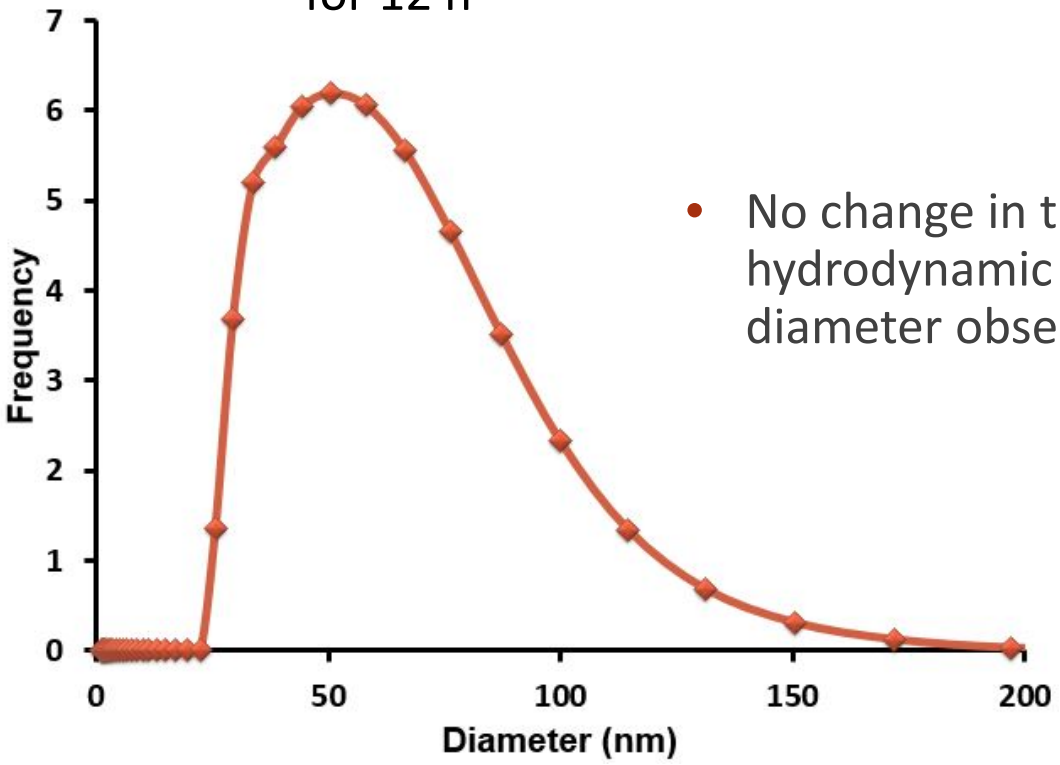
Step 4:
Heat at 100°C for 1 hour

Fe_3O_4

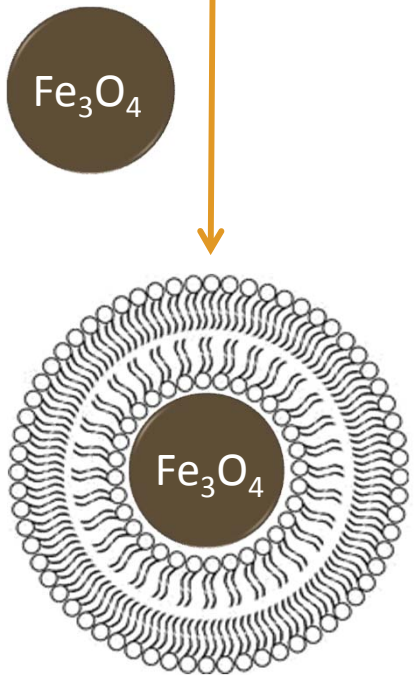
Hui, C., Shen, C., Yang, T., Bao, L., Tian, J., Ding, H., ... & Gao, H. J. (2008), *The Journal of Physical Chemistry*

Preparation of Lipid-Coated SPIOS



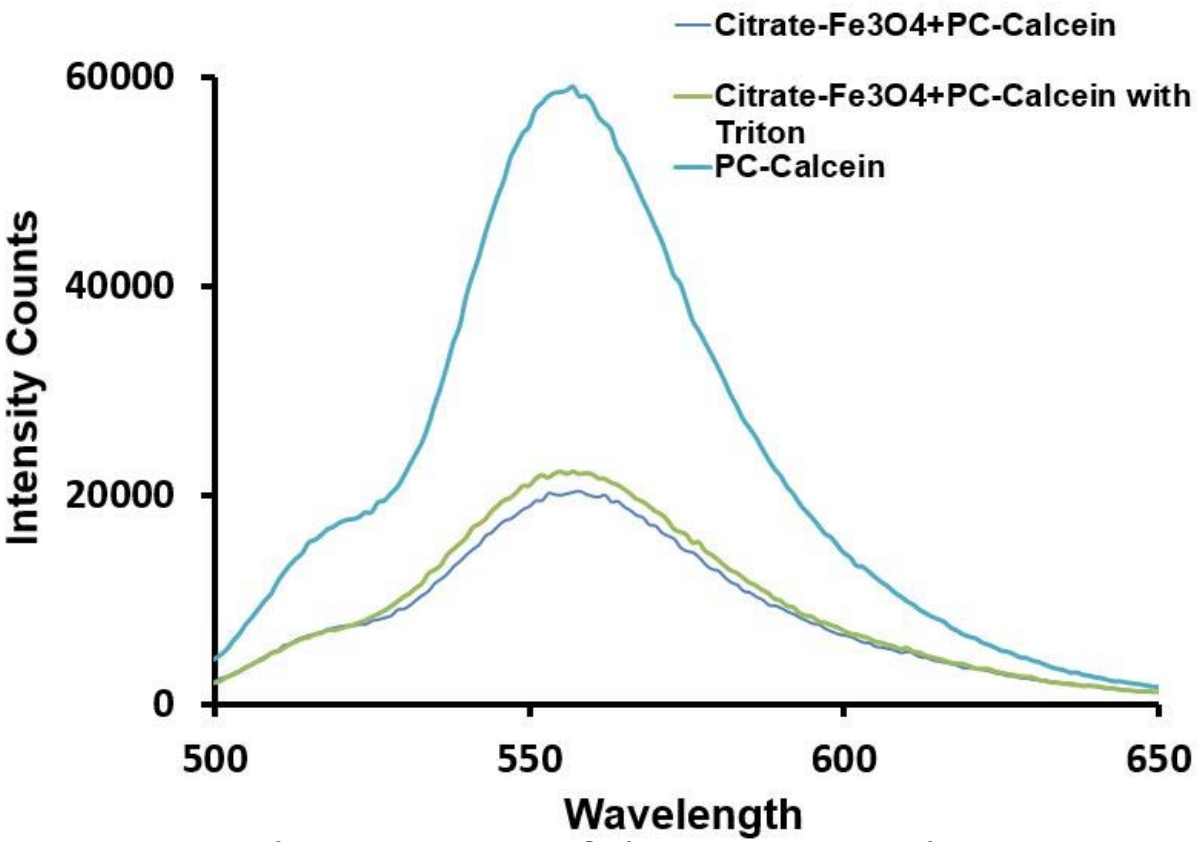


- No change in the hydrodynamic diameter observed



How do we know if the membrane is around the Fe_3O_4 core?

Citrate-Capped SPIOS with PC-Calcein Membrane

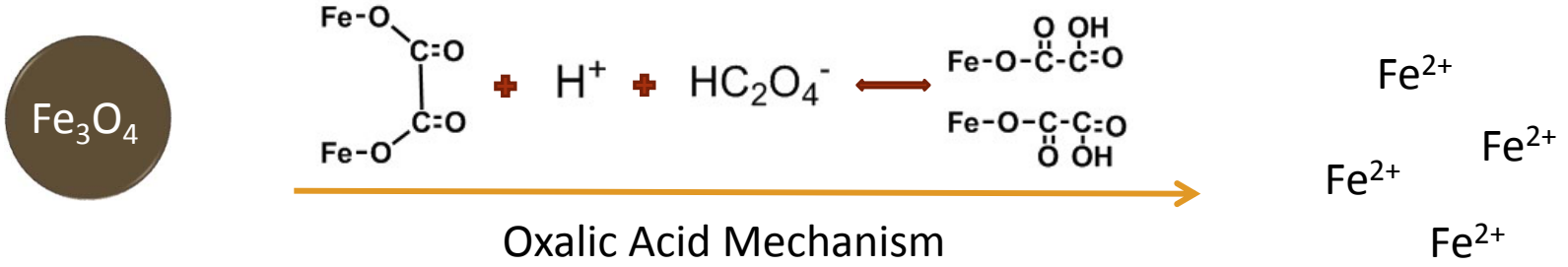


- Decrease in the Calcein fluorescence in the presence of the nanoparticles
- Increase in the fluorescence in the presence of Triton X-100a membrane disrupting agent
- Suggest the PC membrane is around the iron core

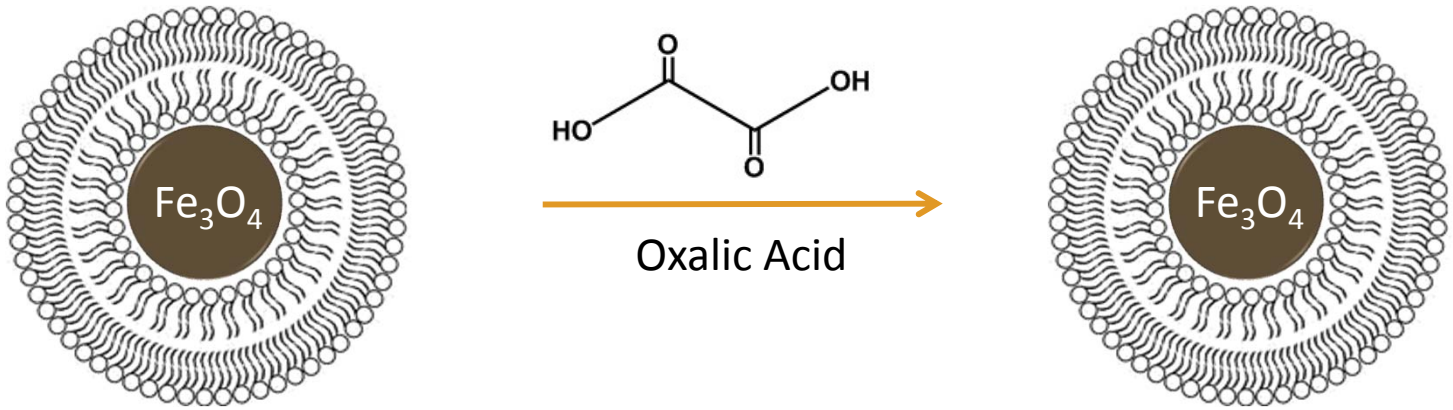
Do we have complete membrane coverage and how tightly packed is it?

Characterization of Membrane Coverage: Oxalic Acid Etch Test

Without membrane coverage:

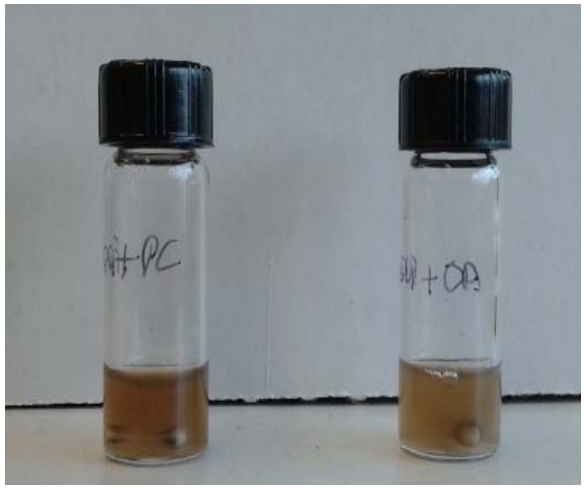


With full membrane coverage:



- Goal is to have no color or quality change

Determining Membrane Coverage of SPIOS: Oxalic Acid Etch Test



Initial shot

15 minutes

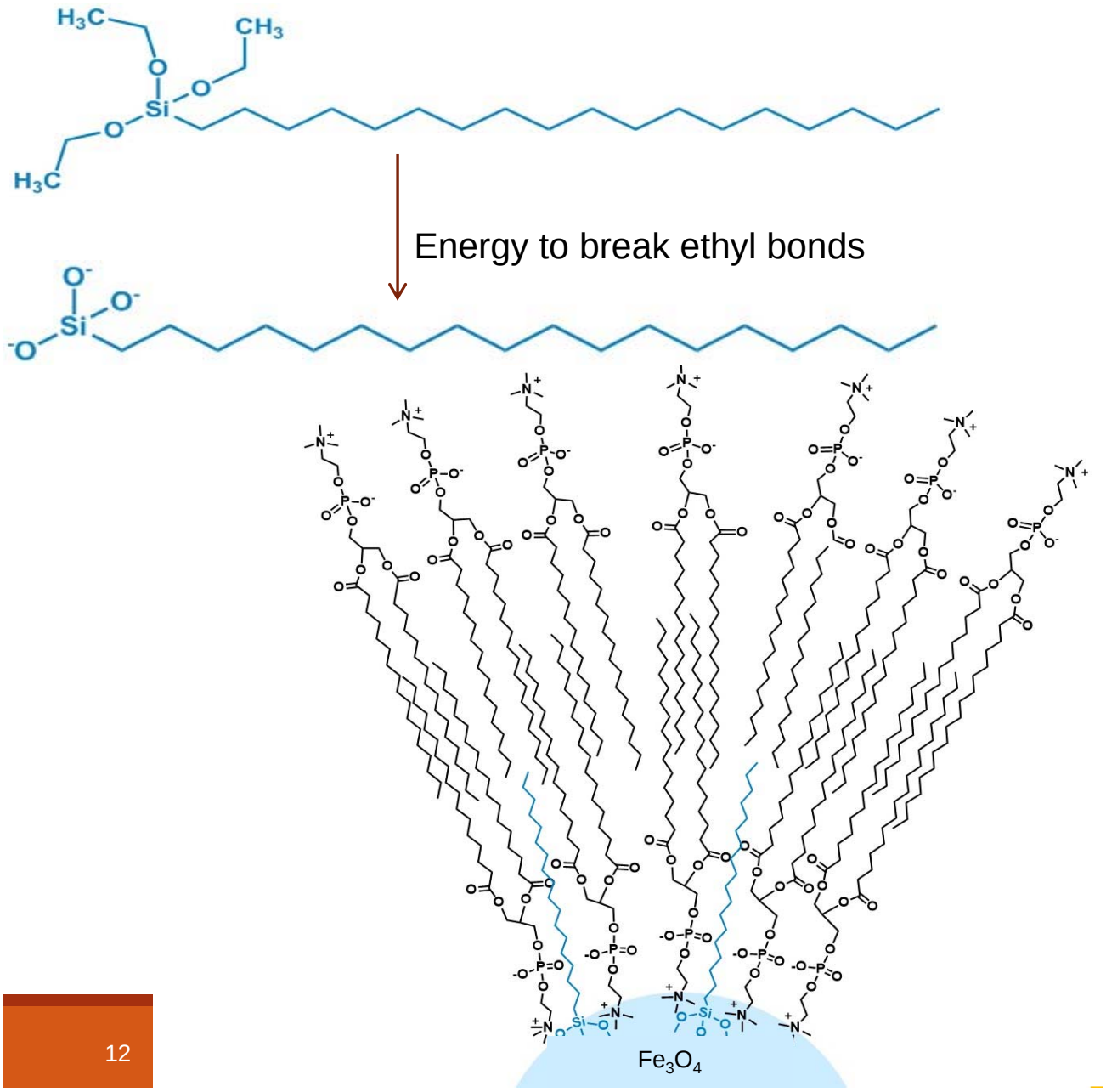
30 minutes

- Left vial: Citrate-capped SPIOS and PC
- Right vial: Citrate-capped SPIOS and oleic acid

- **Observations**
  - Different etch rates
    - Fe_3O_4-OA acid SPIOs etched much faster than the Fe_3O_4-PC
  - Loss of superparamagnetic quality
  - Pale green indicates Fe^{2+} oxidation state

How can we further stabilize the membrane around the Fe_3O_4 core?

Stage 2: Preparation of Hybrid Lipid-Coated SPIOS

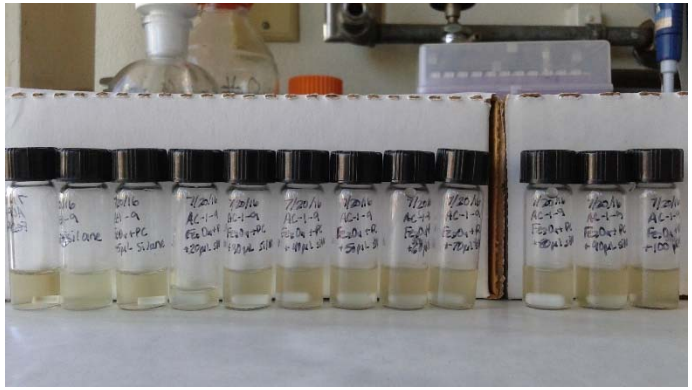


- PC lipid used for stability
- Expect the silane polar head to attach to iron oxide NP to anchor the membrane closely to the nanoparticle core

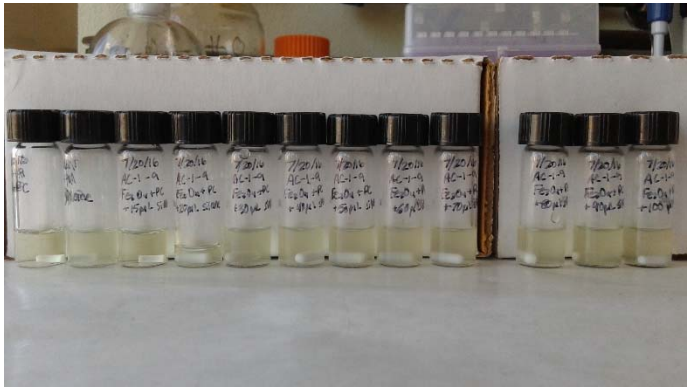
Oxalic Acid Etch Test with Hybrid Lipid-Coated SPIOS

Initial shot

20 minutes



40 minutes

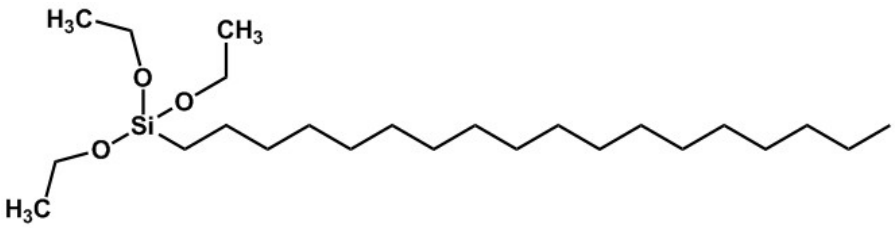


60 minutes

- Variations from 15-100 µL of silane (with 100 µL PC)
- We proposed that the ethyl groups on the silane were not breaking, therefore, there was no attachment to the nanoparticle surface

Alternative Approach to Hybrid Lipid-Coated Fe_3O_4 Nanoparticles (SPIOS)

Step 1:



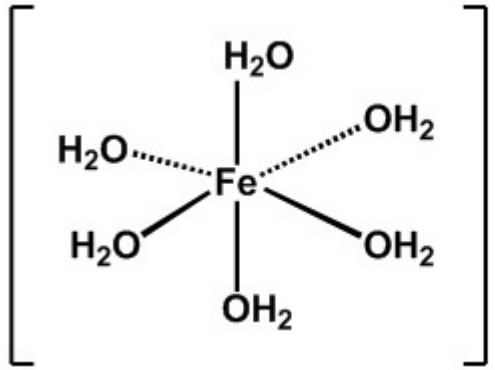
Octadecyltriethoxysilane (capping agent)

+ NaOH + $NaNO_3$

Controls size of NPs

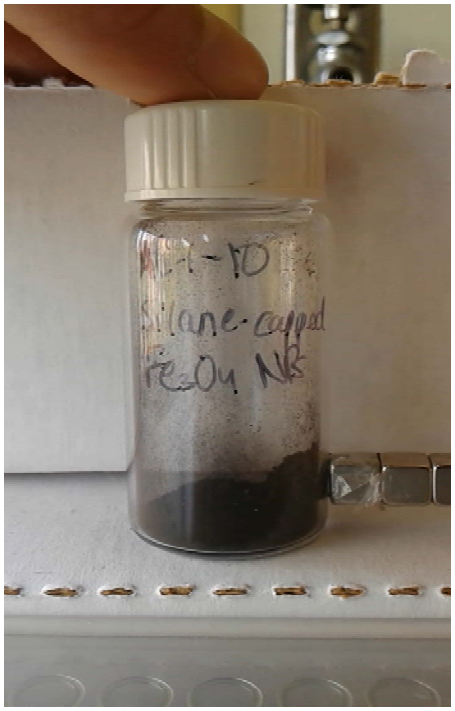
Step 2:
Heat to 100°C

Step 3:



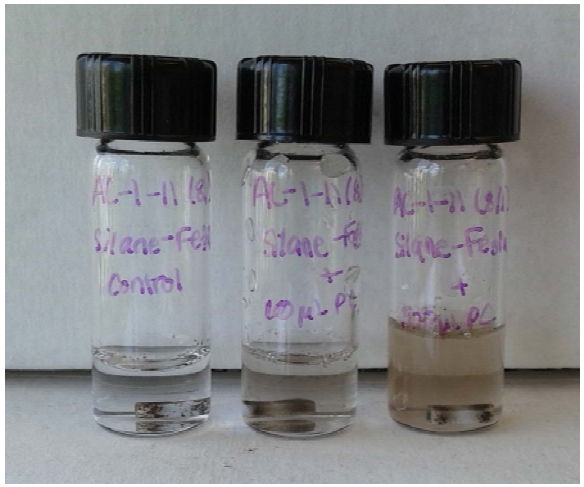
Step 4:
Heat at 100°C for 1 hour

Fe_3O_4

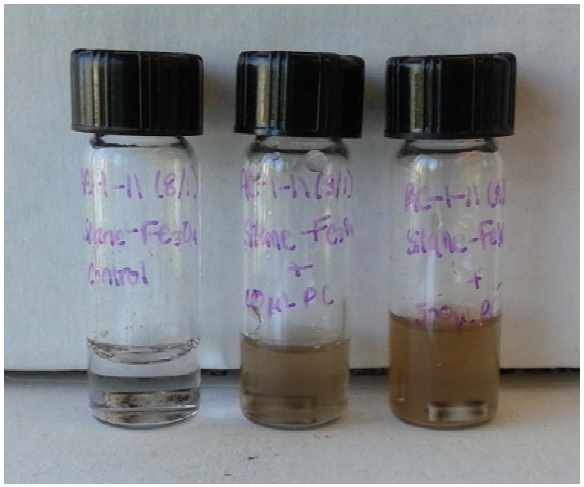


Superparamagnetic iron oxide nanoparticles

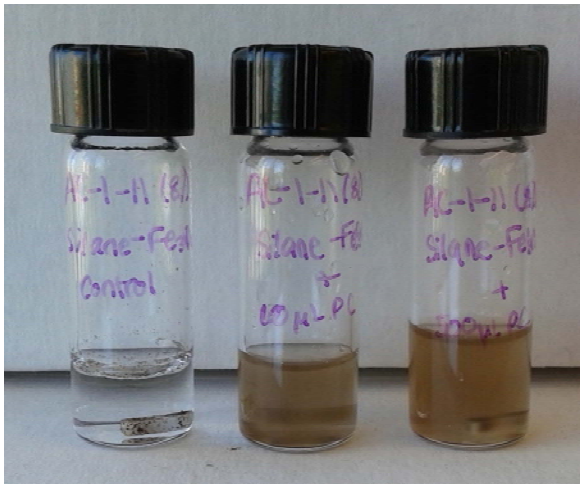
Oxalic Acid Etch Test with Hybrid Lipid-Coated Silane-SPIOS



Initial shot



20 minutes



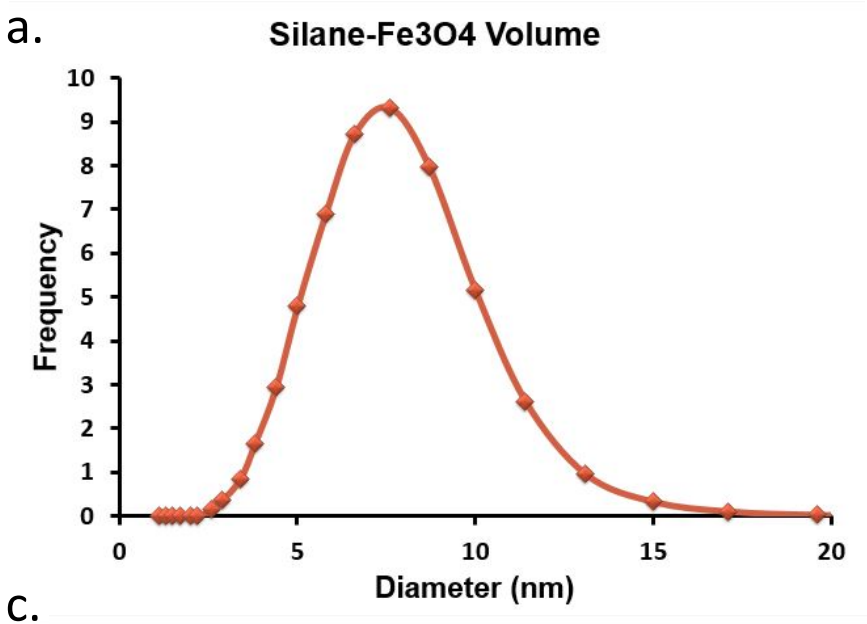
60 minutes

- Left: Silane-SPIOS in PBS
- Middle: Silane-SPIOS with 100 µL PC in PBS
- Right: Silane-SPIOS with 500 µL PC in PBS

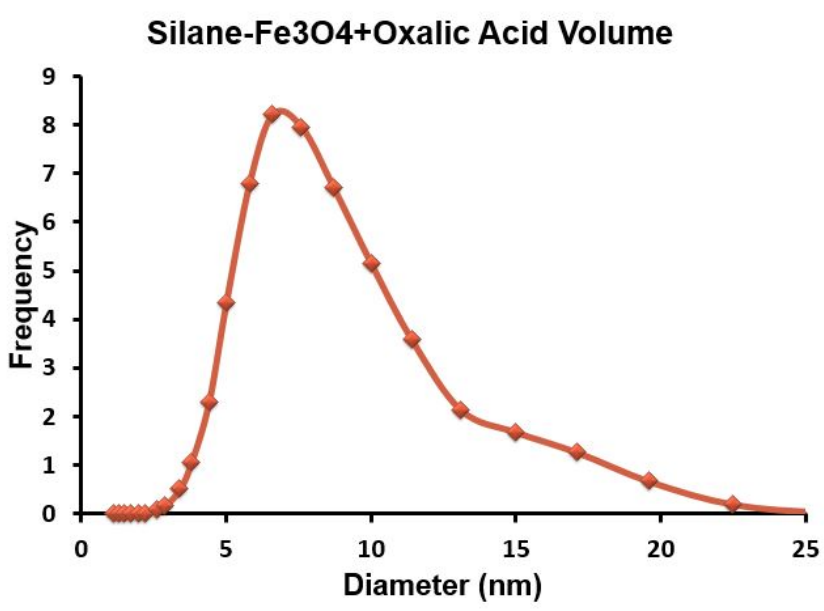
- **Observations:**
  - Addition of PC liposome to nanoparticles led to more soluble in water
    - Indicates the membrane is around the nanoparticle
  - No etching occurred for all three samples

Confirming the Existence of a Hybrid Membrane Coverage by Dynamic Light Scattering

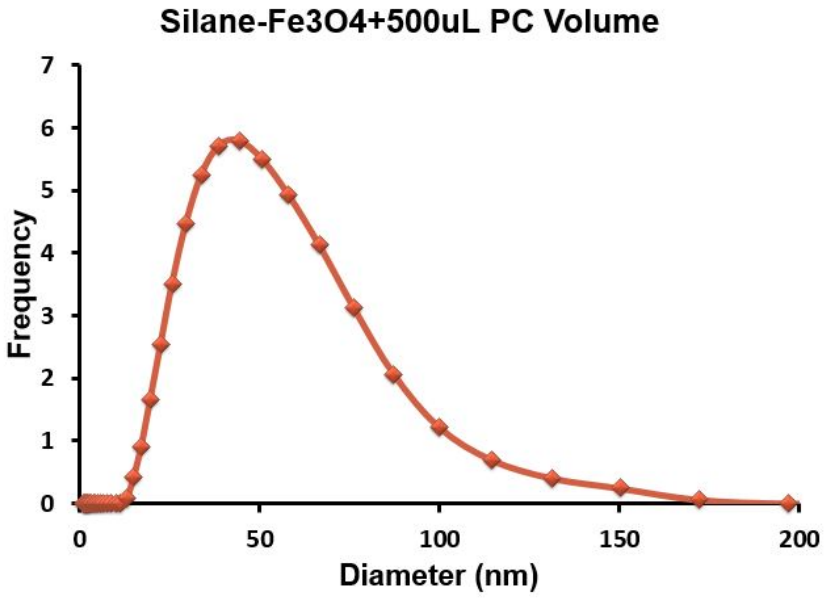
a.



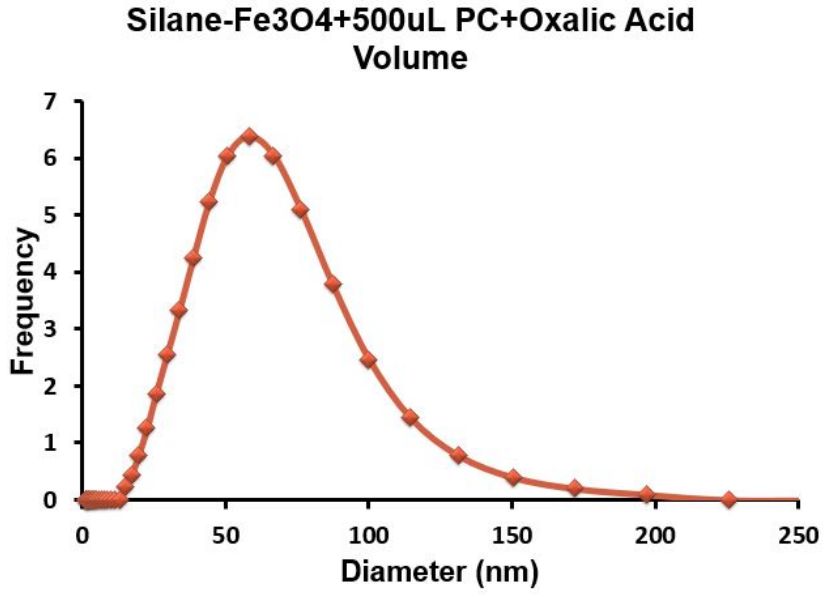
b.



c.



d.



Summary

- Overall, we have successfully prepared membrane coated silane-capped and citrate capped iron oxide nanoparticles
- We have shown they are very magnetic and water soluble
- We can tune the membrane stability on the surface

Future Directions

- Determine amount of silane needed to cover nanoparticles
- SEM microscopy to determine size and shape of nanoparticles
- Cell uptake studies to test nanoparticle acceptance
- Test new ways of synthesizing the nanoparticles to help with lipid membrane coverage

Acknowledgements

Mackiewicz Research Group:

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