Computational Methods for the Design of Macromolecular Therapeutic Agents

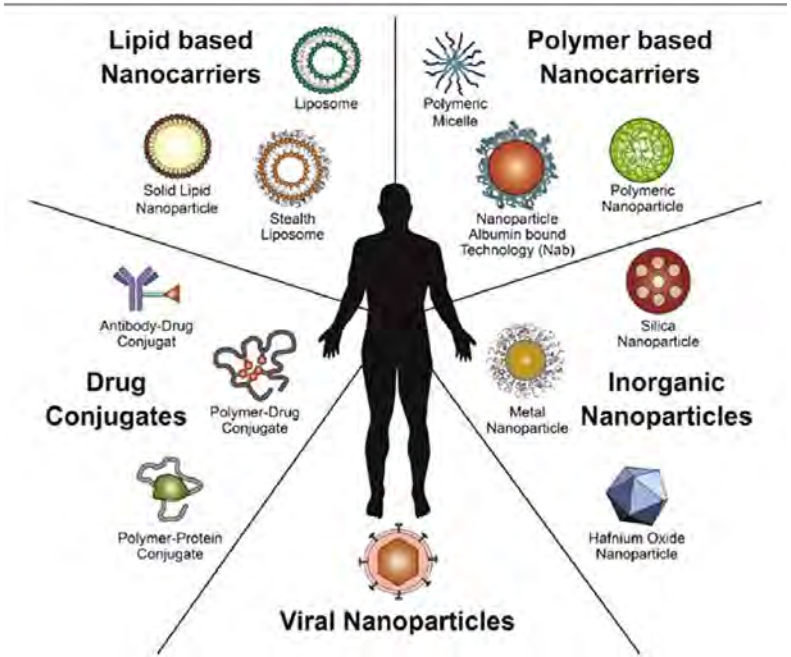
William M. Payne, MS
Department of Pharmaceutical Sciences
Blue Waters Symposium: June 5th 2018

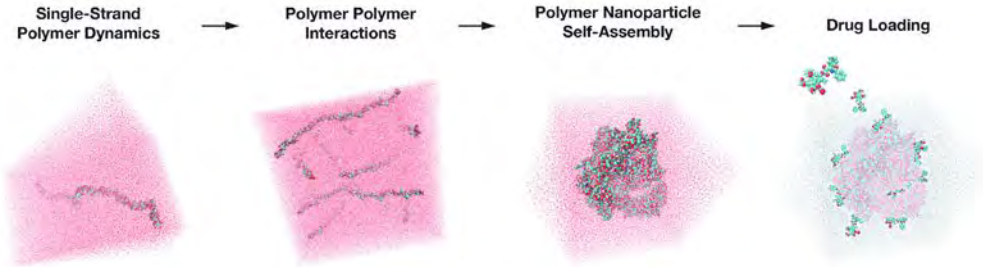
University of Nebraska Medical Center

Introduction

What is nanomedicine?

- How do we improve therapeutic efficacy as an alternate strategy?
- How is this different than traditional formulations?
- **The big question: what is a “good” nanoformulation?**

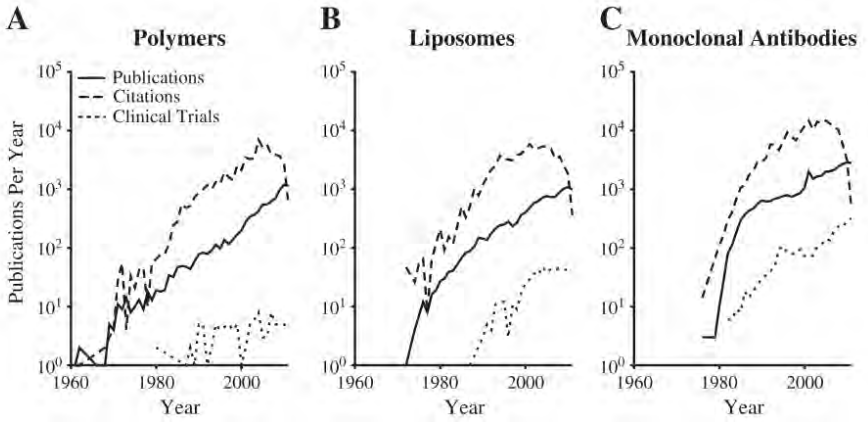




Significance

To move the field forward, we need better formulations.

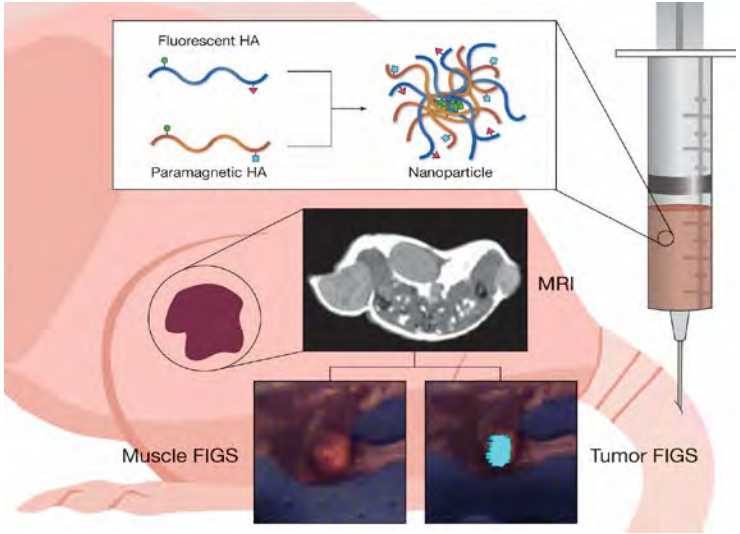
- Many nanoparticle formulations have been developed, but we do not have a way to say what is a “good” formulation.
- Developing metrics for the physical description of nanoformulations will help to invent better formulations

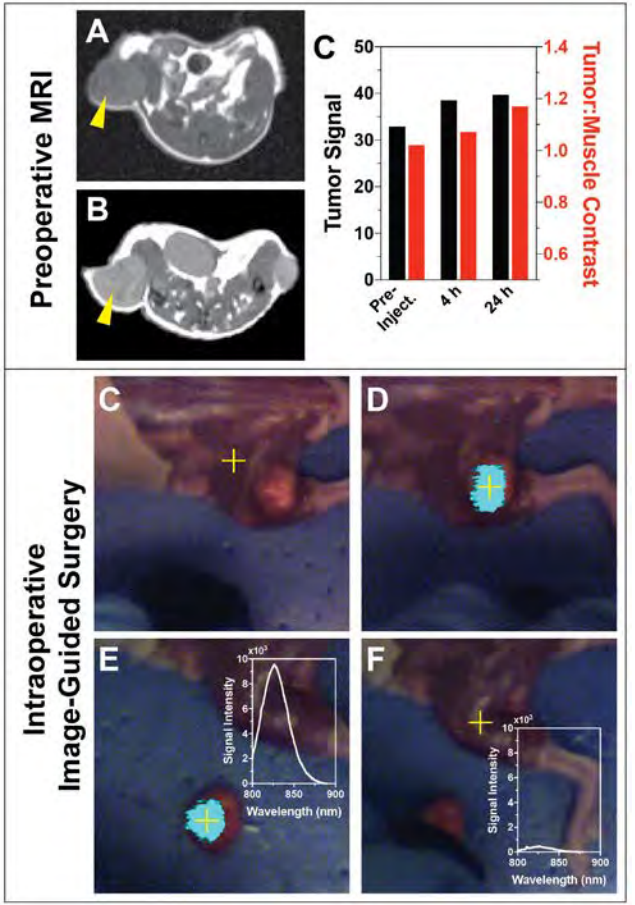


Prior Work

Context on the research

- My research during Blue Waters and for after begins with experimental observations.

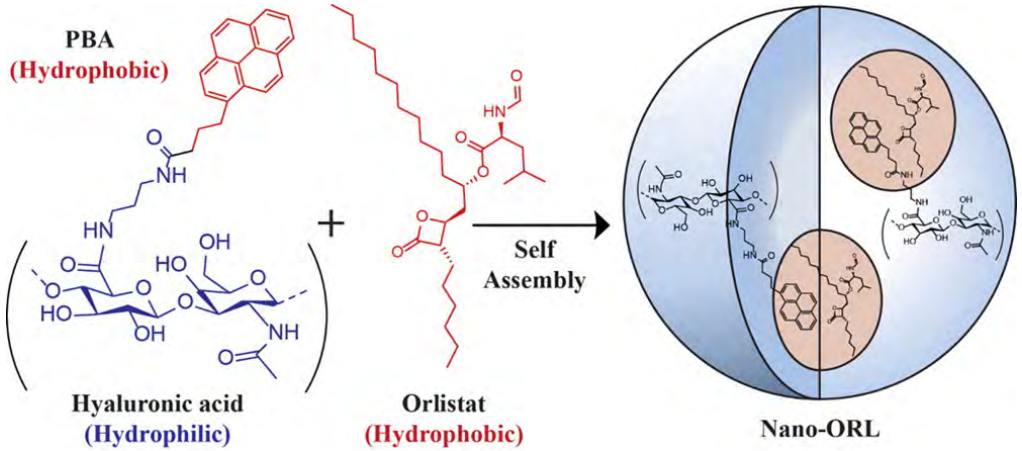




Prior Work

More context

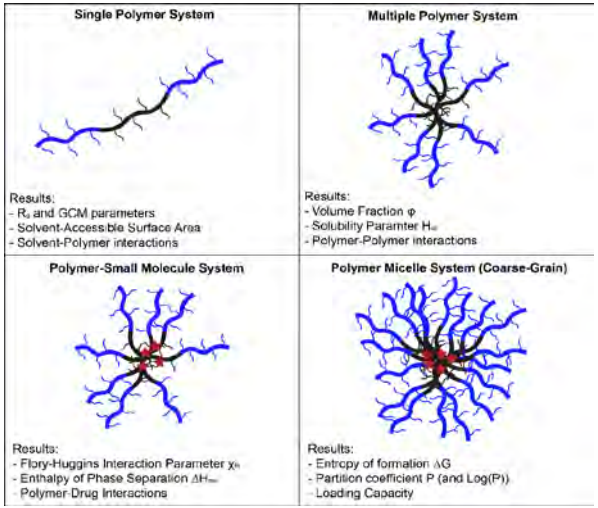
- Drug delivery: freely encapsulated vs. covalent modification
- Active targeting vs. passive targeting

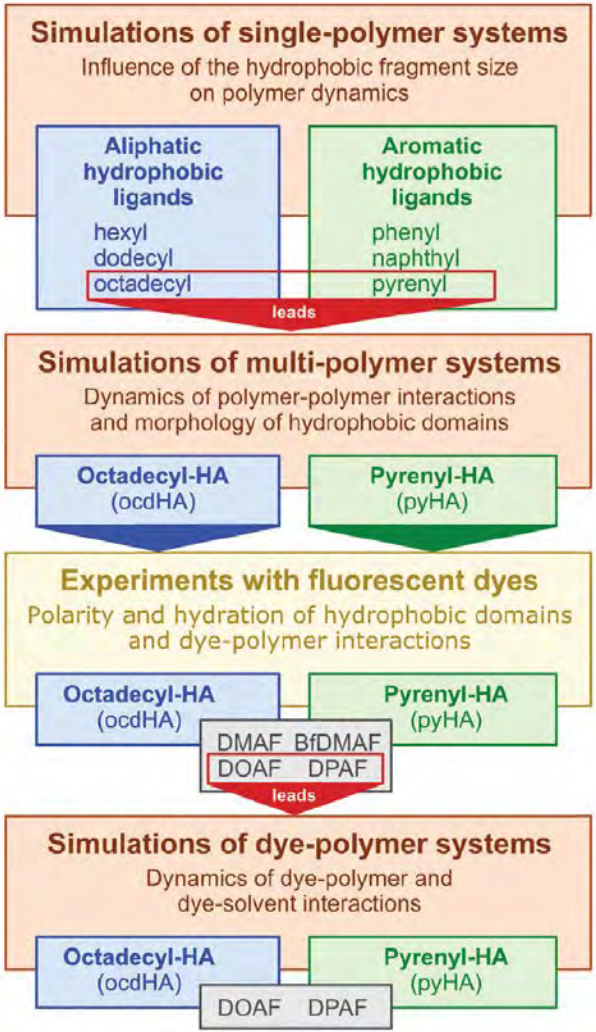


Experimental Design

Informing wet-lab science with theoretical insights

- I needed a way to relate simulations to experimental processes.
- Measurable interactions are key!

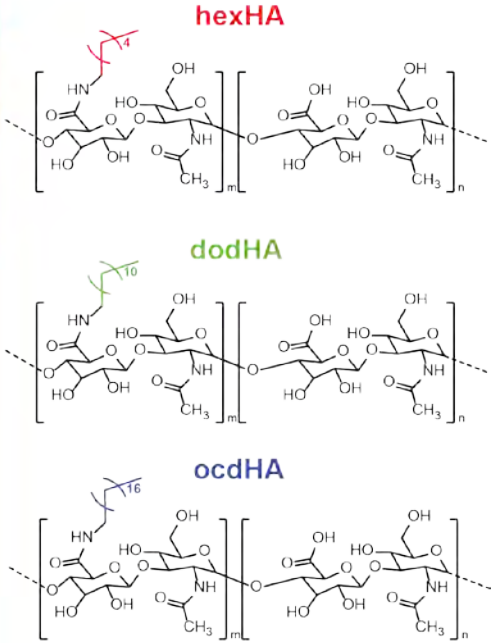


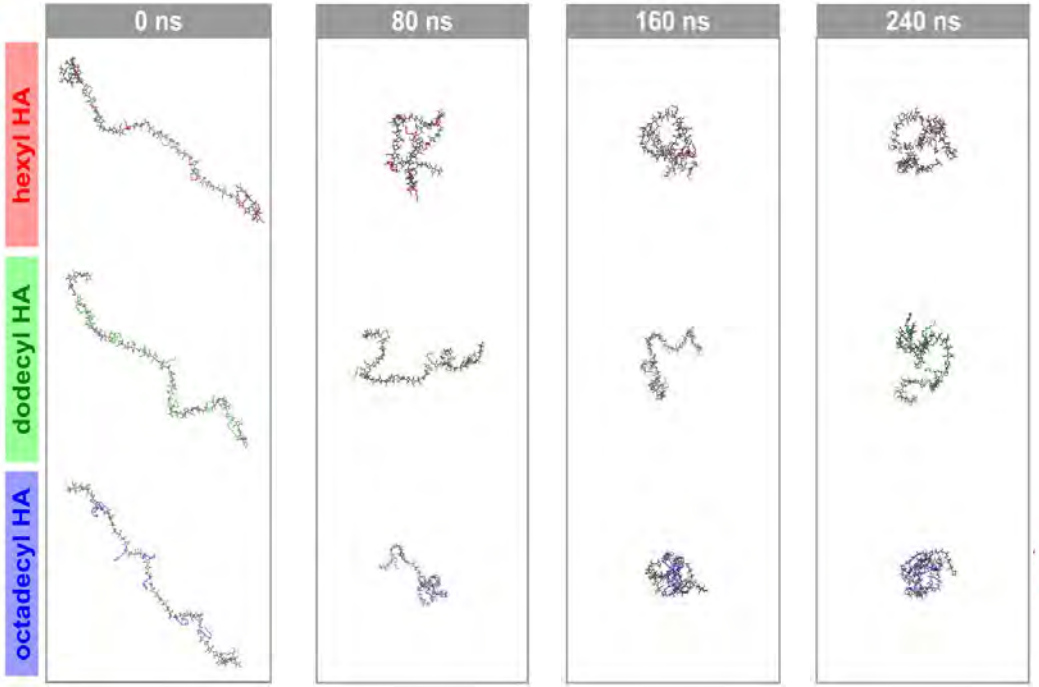


Learning simulations

As an experimentalist, I had to learn everything

- My first simulations were of very simple polymer conjugates to learn how to perform simulations

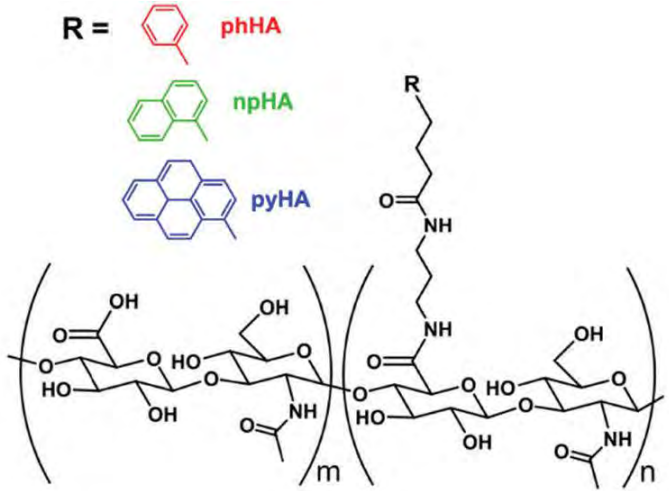


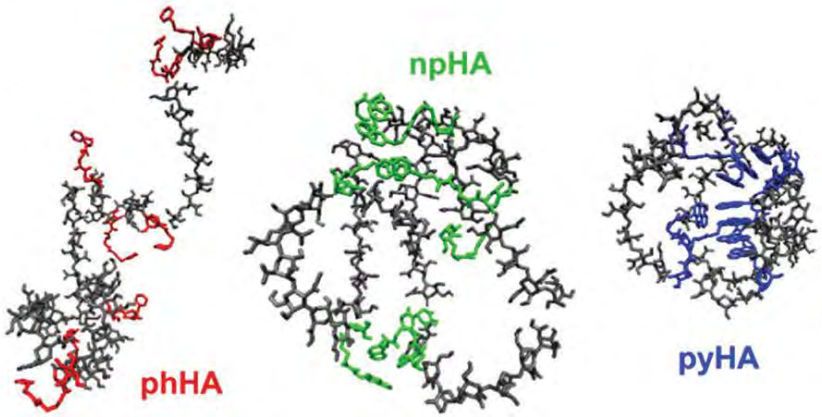


New Polymers

Looking at aromatic substitutins

- We increased the “library” of polymer models we use to include aromatic compounds

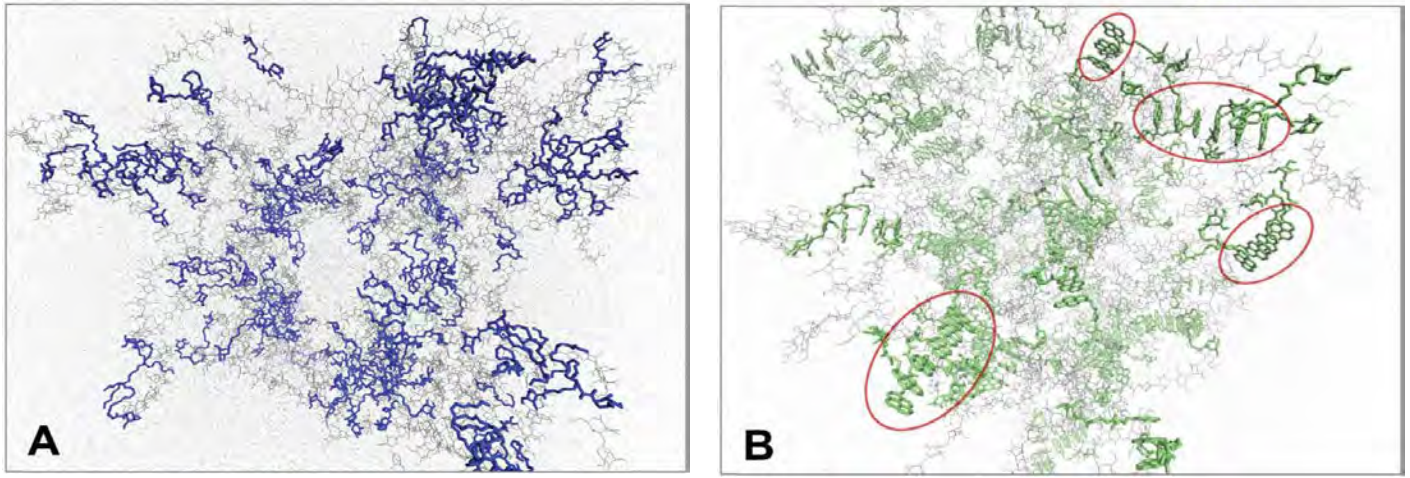




New Models

Moving to multi-polymer systems

- Systems were simulated containing multiple polymer strands to observe self-assembly



Deeper-level measurement

Using dyes to probe the internal environment

- Fluorescent dyes can reveal information on their immediate environment

Parent dye to provide reference response

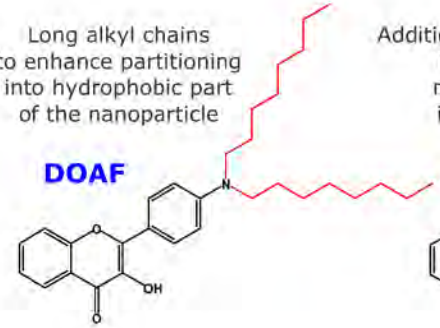
DMAF

Shielded carbonyl group to decrease influence of specific interactions on ESIPT

BfDMAF

Long alkyl chains to enhance partitioning into hydrophobic part of the nanoparticle

DOAF

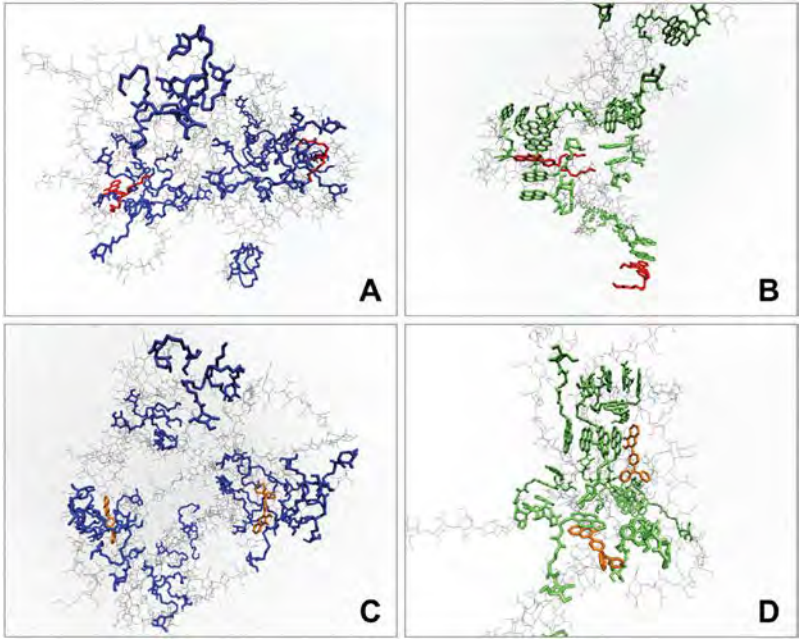


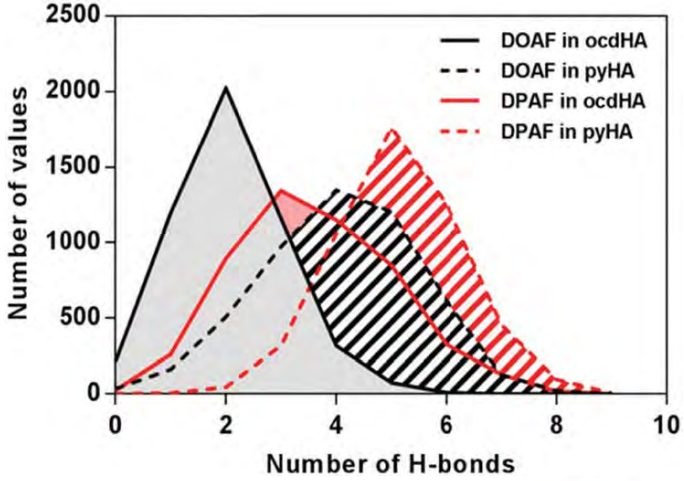
Additional phenyl rings to enhance π-π stacking interactions

DPAF

Simulating Dye-Polymer Systems

- We can measure interactions between dyes and polymers to explain experimental observations
- Aromatic vs. Aliphatic interactions

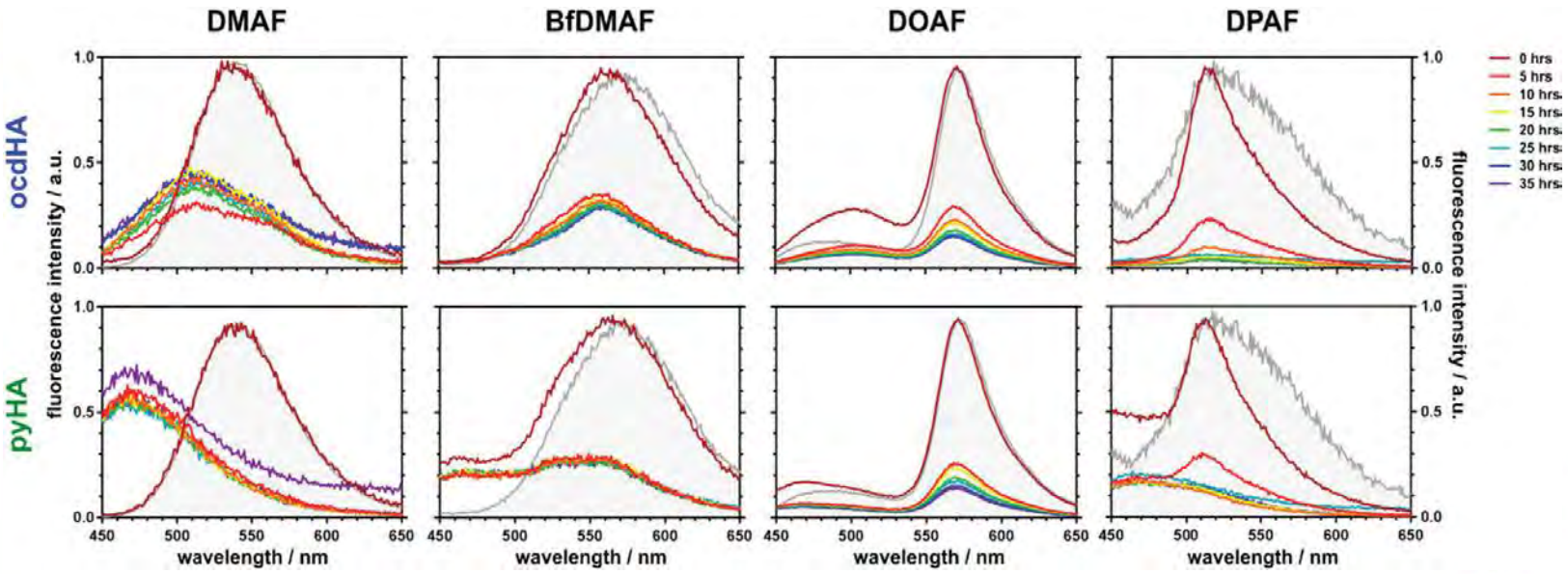




Experimental Analysis

Fluorescence spectroscopy to validate simulations

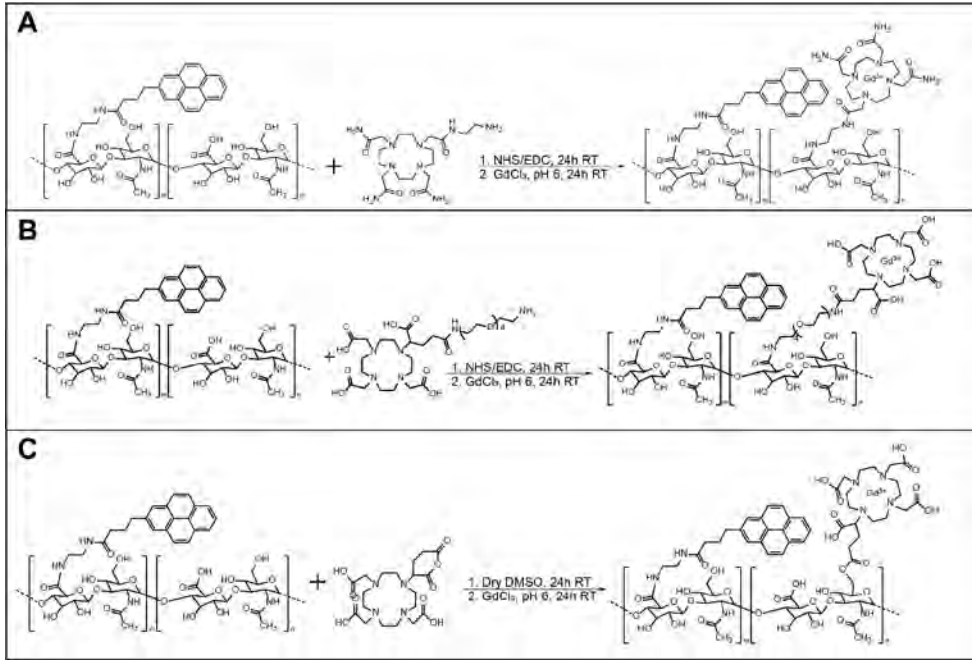
- We can perform spectroscopic measurements to gain more information on self-assembly



Back to the original problem

How to improve the contrast obtained from polymer conjugates?

- Moving to different polymers to improve imaging efficacy

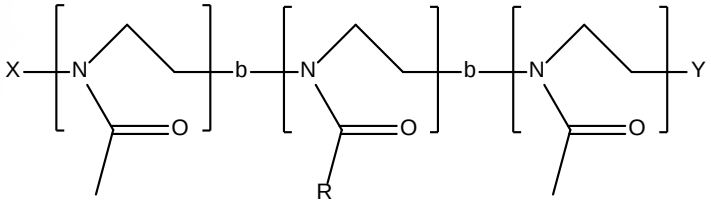


Future Work

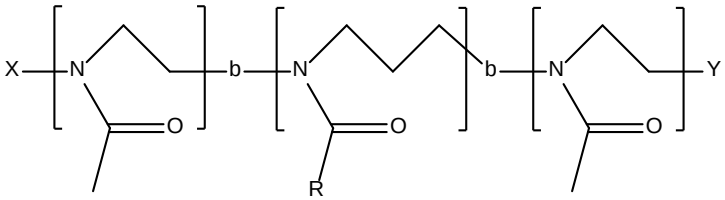
Generalization and abstraction

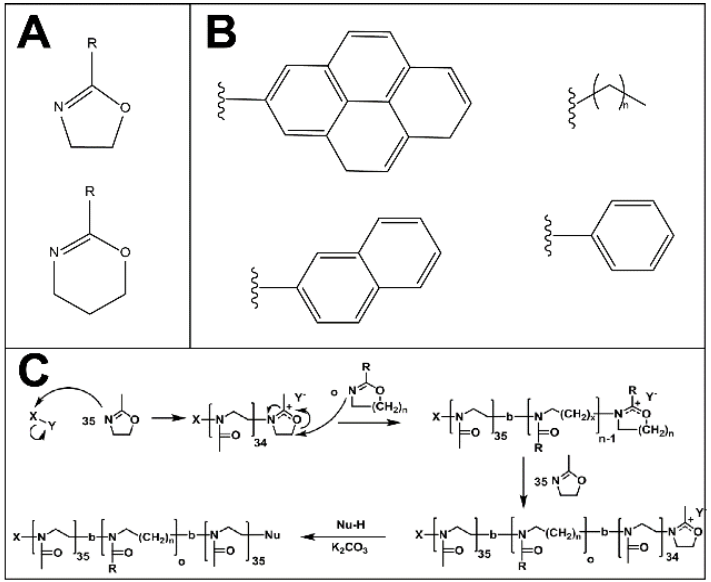
- HA is not a suitable model polymer.
- Widespread applicability to the nanomedicine field is necessary for real impact.

Poly(oxazoline)



Poly(oxazine)





Conclusions

- Simulations show promise in helping to inform the search for better formulations
- Quantitative methods afforded through molecular dynamics and similar methods may help to define what is a “good” formulation
- Using simulations in attempt to improve the formulation and original problem in polymeric contrast agents

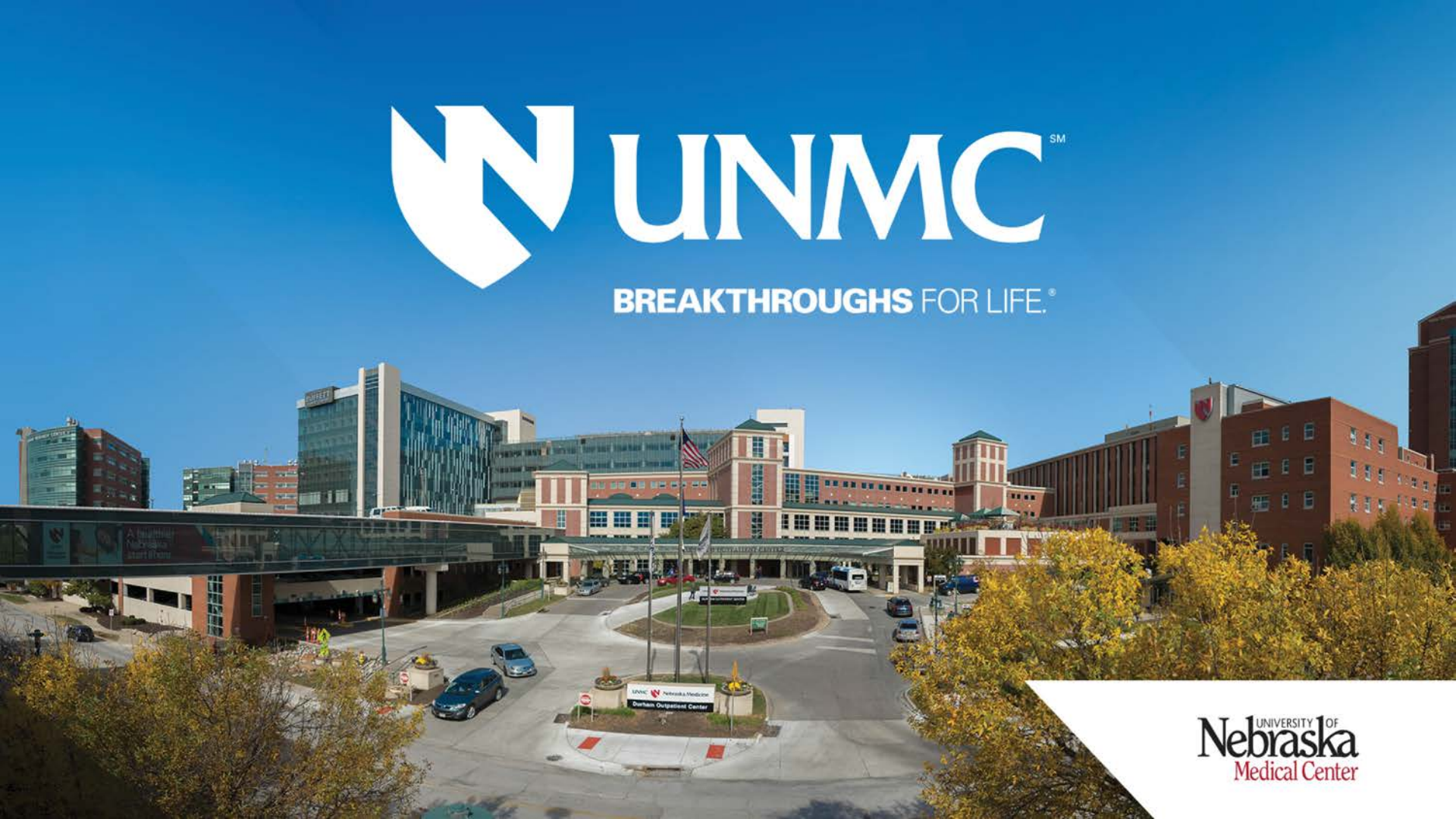
Acknowledgements

- PI: Aaron Mohs, PhD
- Lab Members
  - Denis Svechkarev, PhD
  - Megan Holmes
  - Josh Souchek, PhD
  - Deep Bhattacharya, MPharm
  - Bowen Qi, MS
  - Nick Wojtynek
- Collaborator:
  - Alexander Kyrychenko, PhD Karazin Kharkiv National University, Ukraine
- Blue Waters:
  - PoC: Robert Brunner
  - Blue Waters Support Staff

Funding:

- NIH R01 EB019449
- Nebraska Research Initiative
- Holland Computing Center

BLUE WATERS
SUSTAINED PETASCALE COMPUTING


UNMC
SM
BREAKTHROUGHS FOR LIFE.®
UNMC Nebraska Medicine
Durham Outpatient Center
UNIVERSITY OF
Nebraska
Medical Center