Polymeric Nanocarriers for the Delivery of Ionizable Therapeutics: Formulation, Internal Structure, and Large-Scale Process Development

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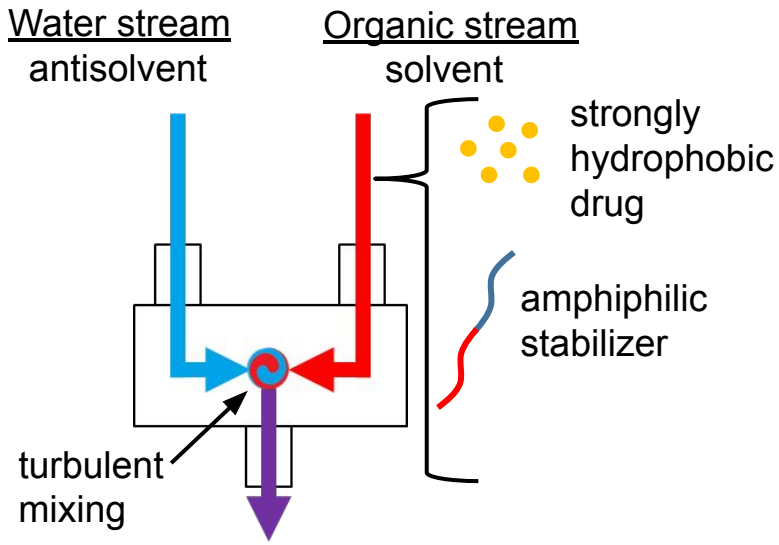
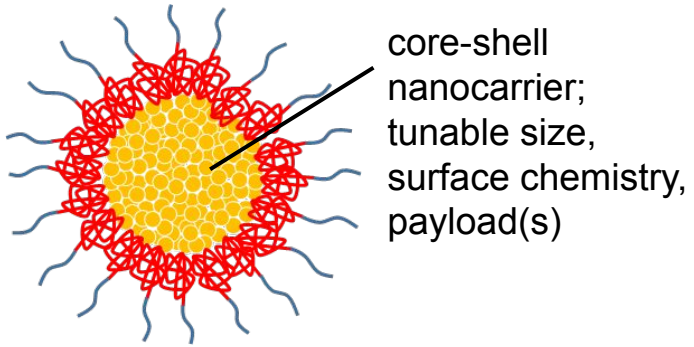
Advisor: Prof. Bob Prud'homme

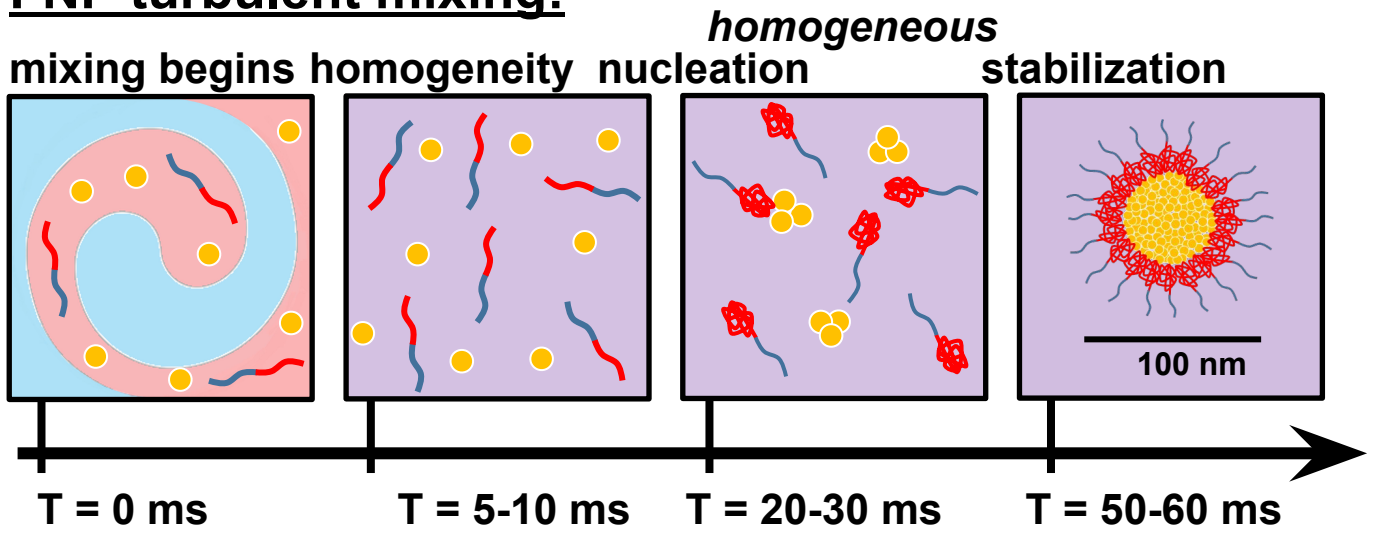
Scalable nanocarrier formulation platform: Flash NanoPrecipitation (FNP)



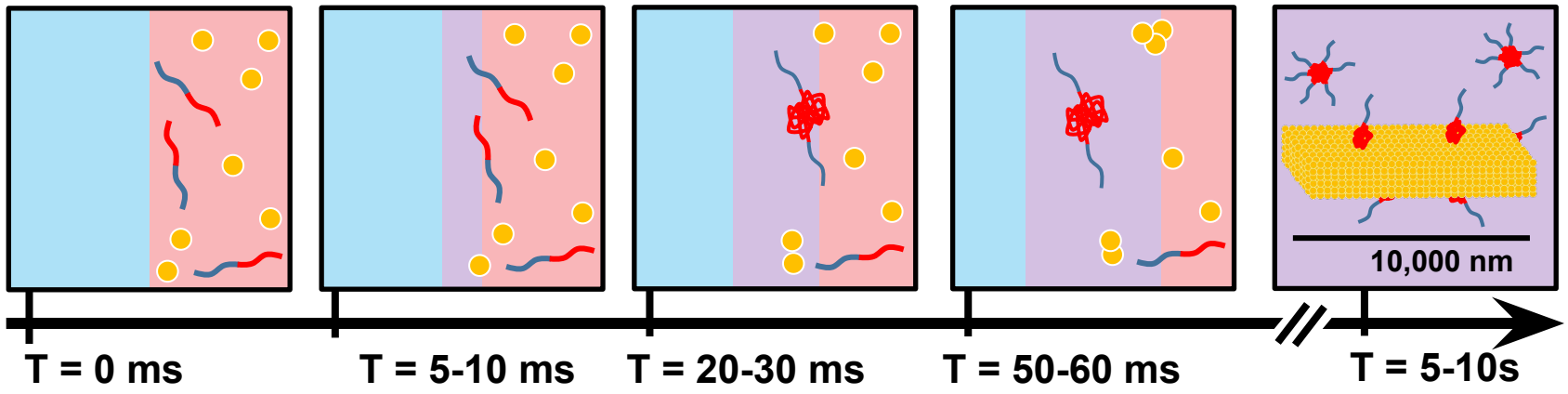


Key challenges for FNP: "intermediate" hydrophobicity & block copolymer cost

FNP turbulent mixing:

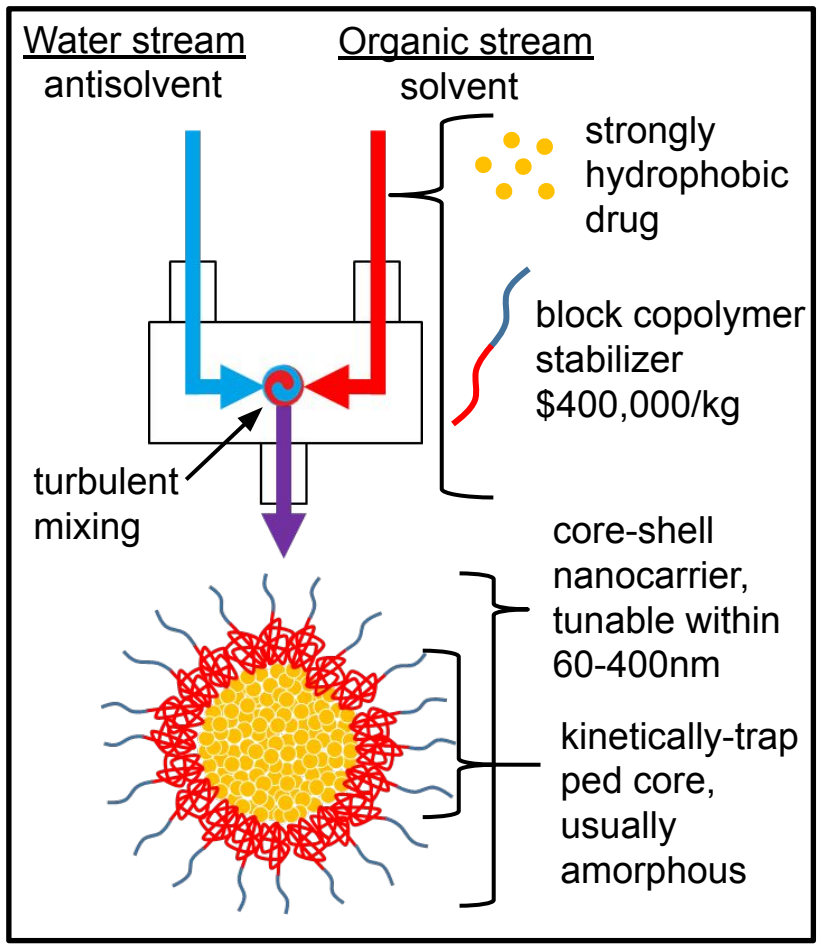


"Bulk nanoprecipitation" poor mixing:

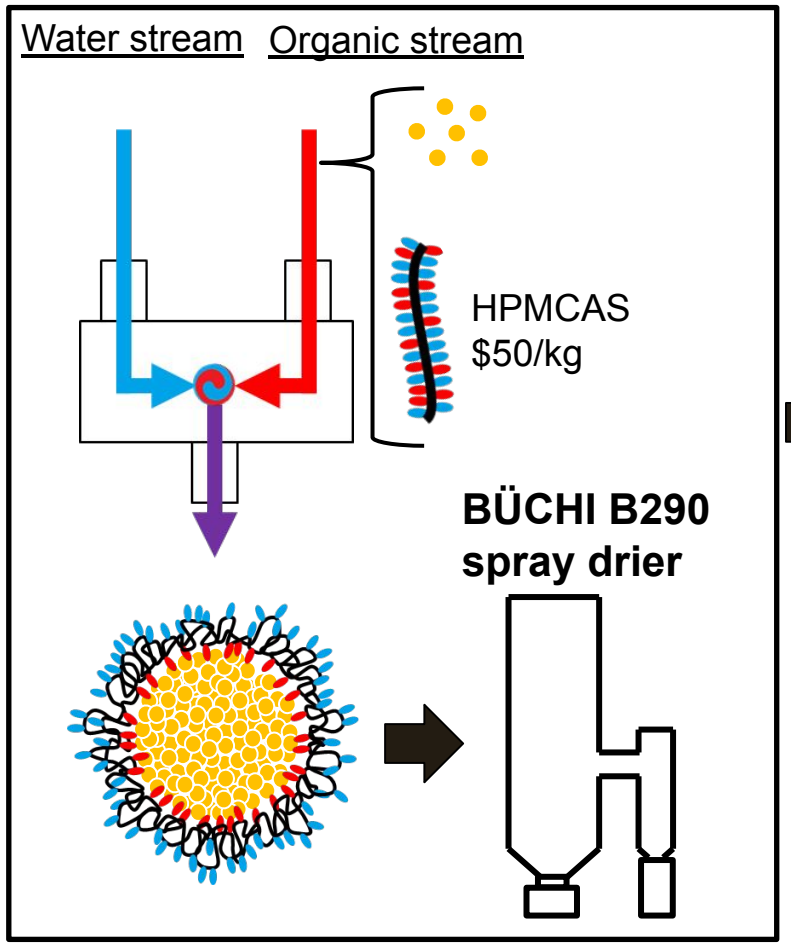


Adapting FNP for use with low-cost stabilizers and continuous drying

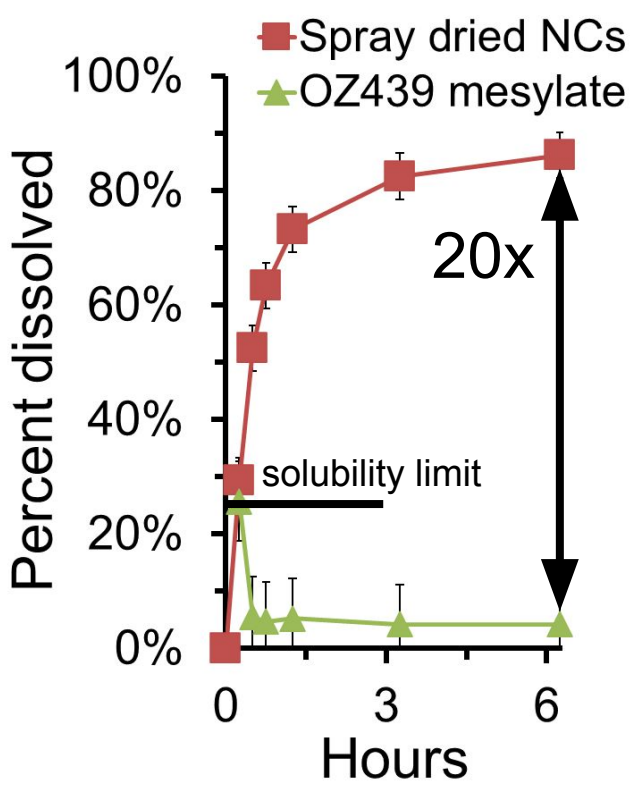
Flash NanoPrecipitation (FNP)
Hydrophobic molecule encapsulation



Low-cost stabilizer
Amphiphilic modified cellulosic



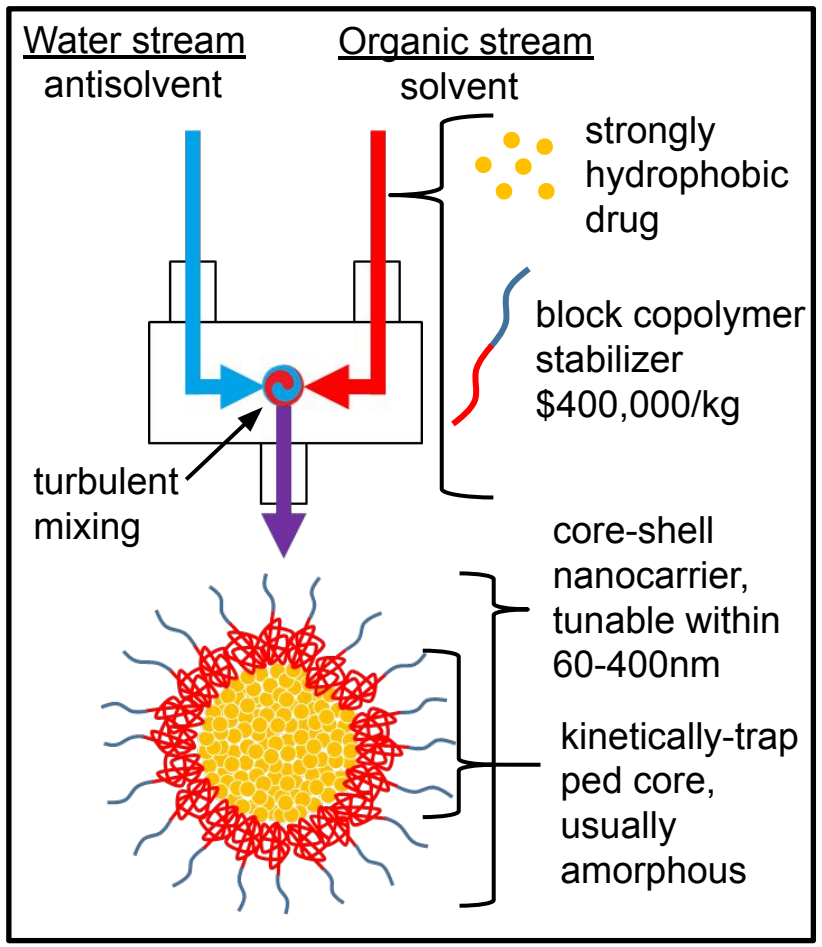
Dissolution kinetics in intestinal fluid



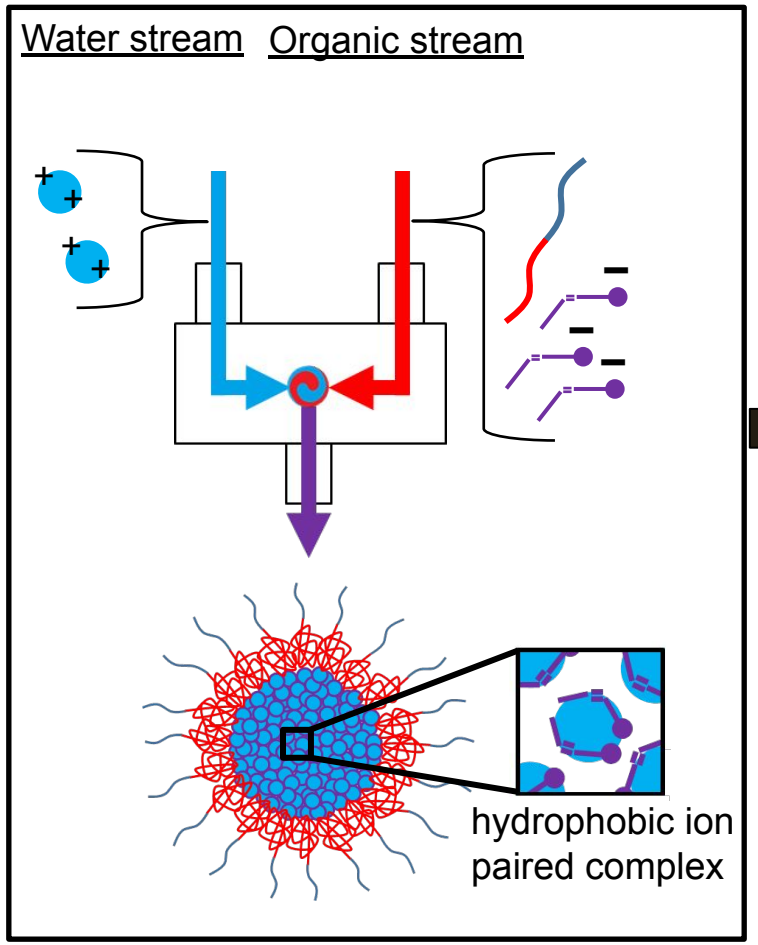
Ristroph et al., *J. Trans. Med.* 2019

Adapting FNP to encapsulate hydrophilic biologics

Flash NanoPrecipitation (FNP)
Hydrophobic molecule encapsulation

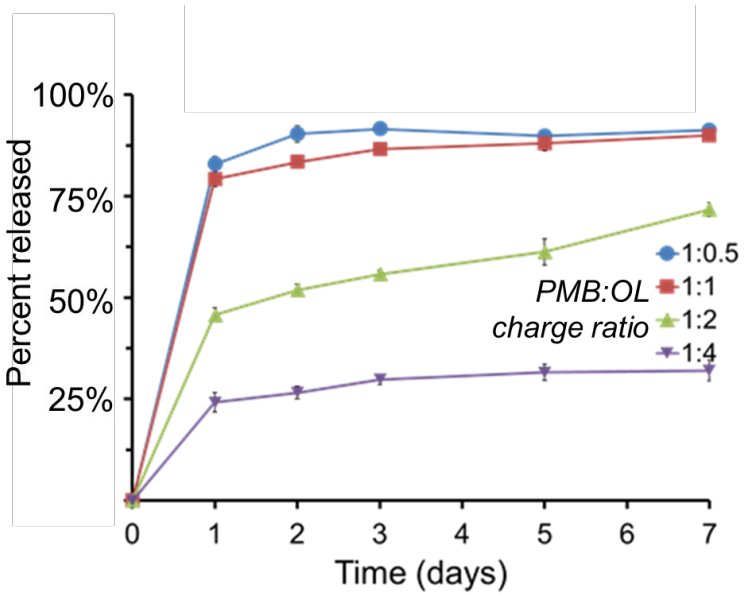


Hydrophobic ion pairing (HIP)
Solubility engineering for hydrophilic APIs



- Forms ~100nm NCs, tunable
- 90-100% EE
- 30-40% API loading

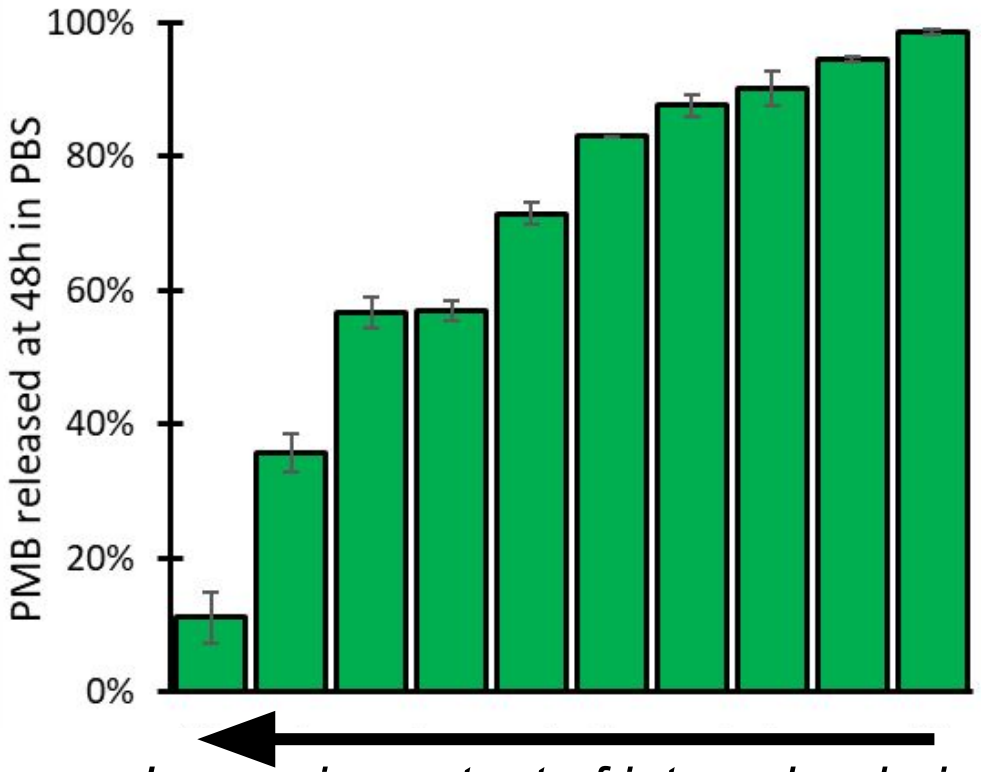
- *Release rate varies with counterion chemistry and quantity; why?*



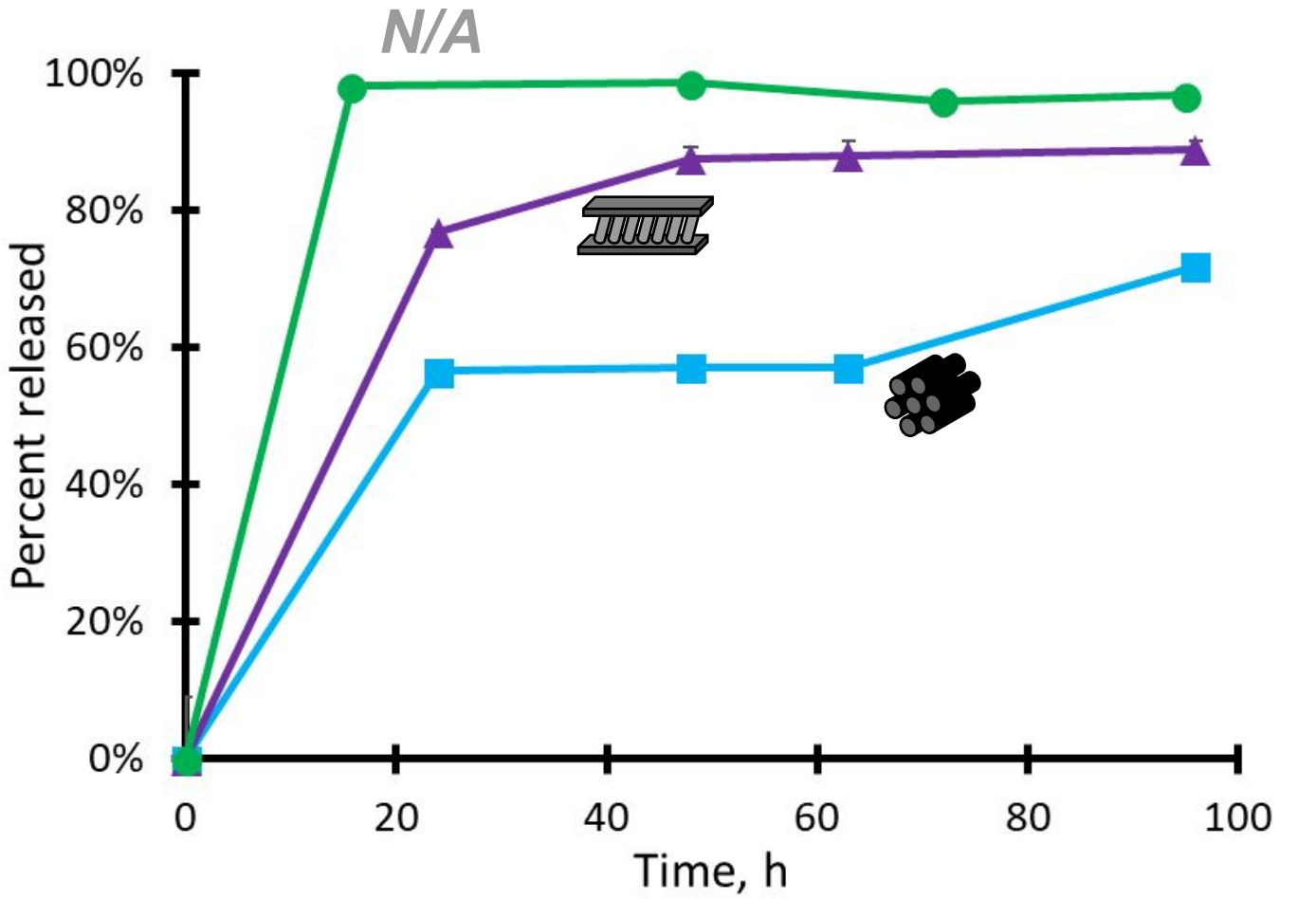
Ristroph et al., *Nanoscale Advances 2020*

Liquid crystalline structures in NC cores control release rate (poster 300)

PMB release from NC formulations



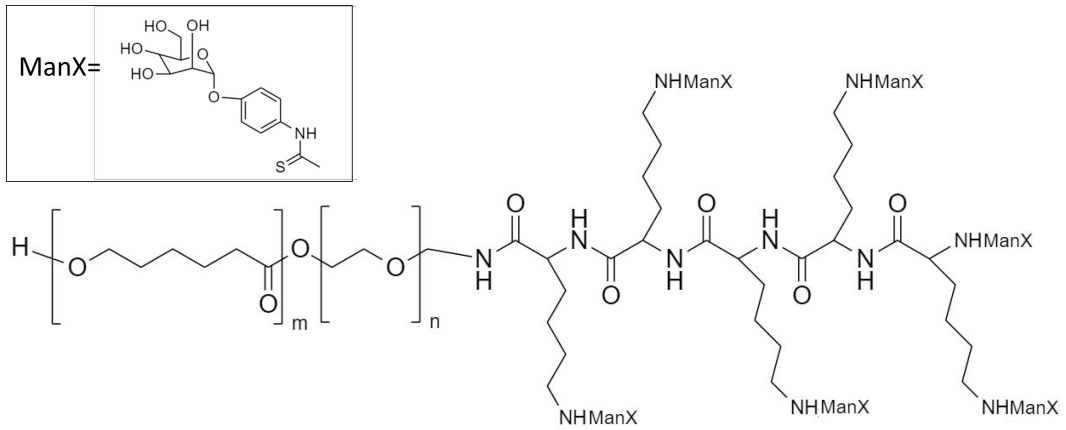
Increasing extent of internal ordering (various counterions, charge ratios)



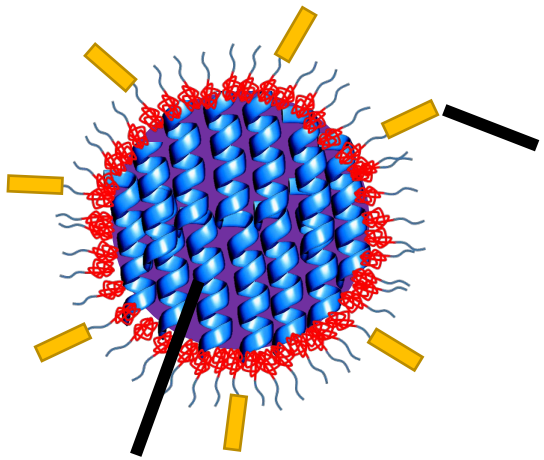
- Phase behavior can be controlled with choice and quantity of counterion.
- Allows straightforward method of tuning release rate.

Ristroph et al., *JCIS 2020*
Ristroph et al., *Mol. Pharm 2021*

Nanocarrier targeting: macrophage-targeted antitubercular NCs (poster 301)

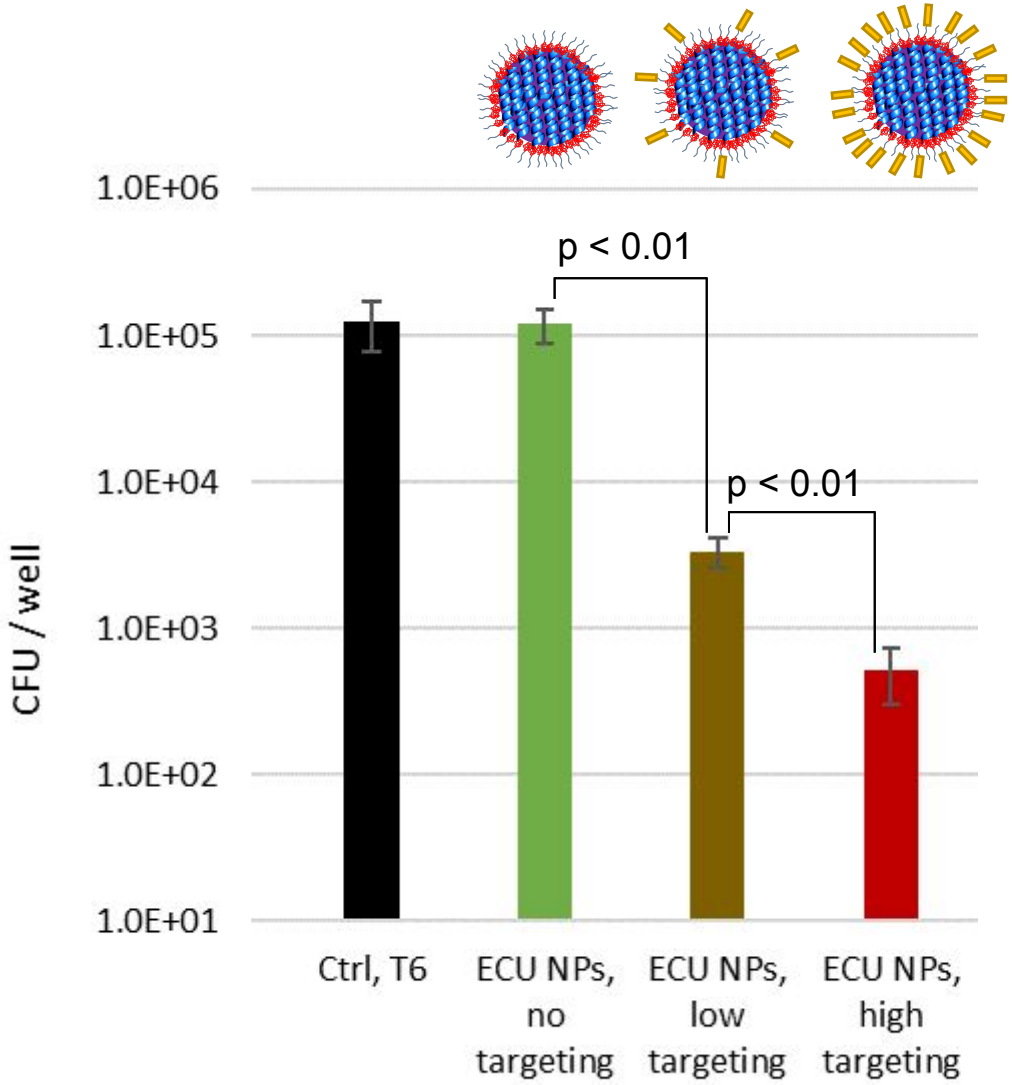


PCL-*b*-PEG-HM



hexamannose targeting moiety for macrophages

ecumicin core

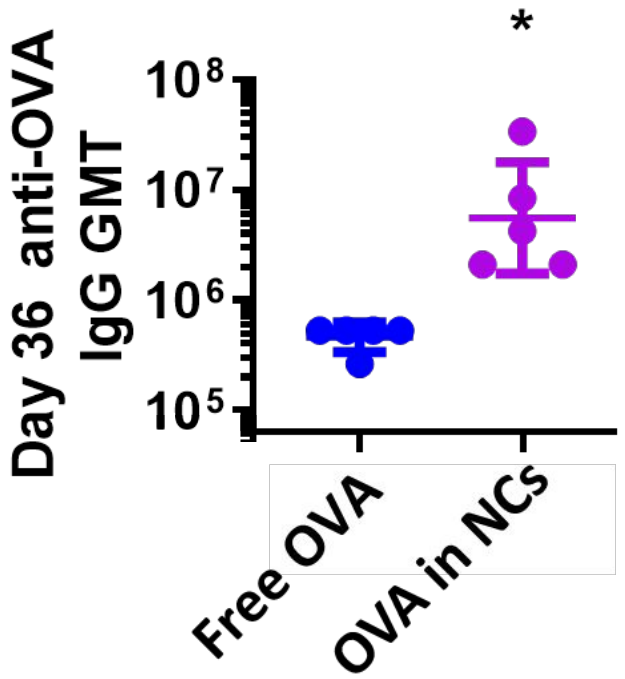


In press, Adv. Mat. Tech.

In vivo efficacy of NCs made by FNP with HIP

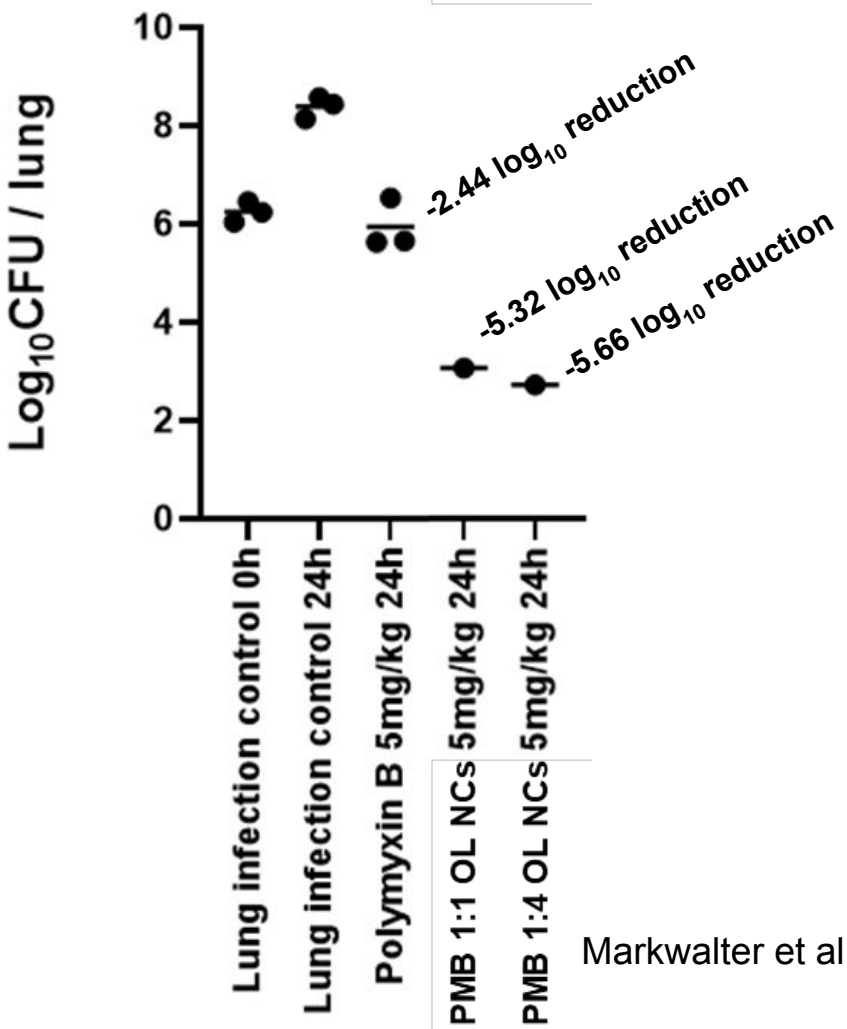
Ovalbumin (OVA): 43 kDa, pI = 5.2

- EE: 88% OVA loading: 29%
- NC formulation improved immunogenicity *in vivo* in a nasal vaccine mouse model



Ristroph et al., *Int. J. Pharm.* 2021

Efficacy of pulmonary delivered polymyxin B nanoparticles against *Ab* N16870.213 in mouse lung infection



Markwalter et al., *JCR* 2021

Acknowledgements and conclusions

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WuXi AppTec
MMV Medicines for Malaria Venture
optimeos life sciences inc.
KELLER CENTER
NSF
GRFP NSF GRADUATE RESEARCH FELLOWSHIP PROGRAM
SCHMIDT SCIENCE FELLOWS
PURDUE UNIVERSITY AGRICULTURAL & BIOLOGICAL ENGINEERING

- We are continuing to expand the Flash NanoPrecipitation platform to enable novel nanoformulations for enhanced delivery.

- This work will continue in the newly-formed Ristroph Lab at the Purdue University Department of Agricultural & Biological Engineering. www.ristrophlab.com