Keith Johnston Research Group

Nanomaterials Chemistry/Colloid and Interface Science/Polymer Science

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Monoclonal antibody stability and subq delivery (covid19, cancer, autoimmune)

Morphology , protein-protein interactions, statistical mechanics and rheology, SAXS (Truskett, Lilly, Merck)

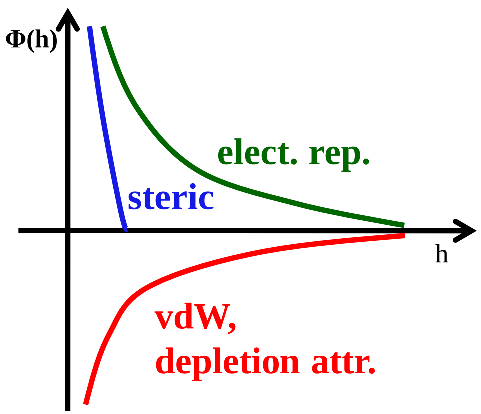
Polymer Nanocapsules and Polyelectrolyte Complexes for Controlled Release

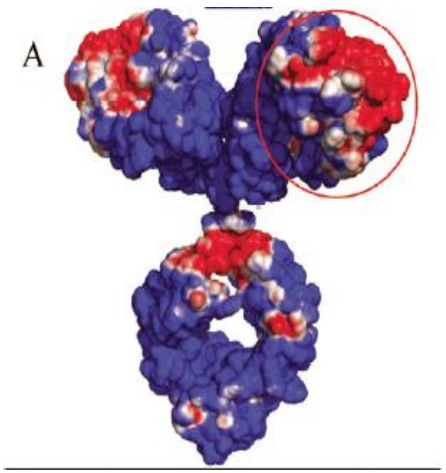
Stimuli responsive (with Pennell, Brown University)

Cancer imaging/drug delivery with polymersomes (with Truskett and Sokolov: UT MDA Cancer Center)

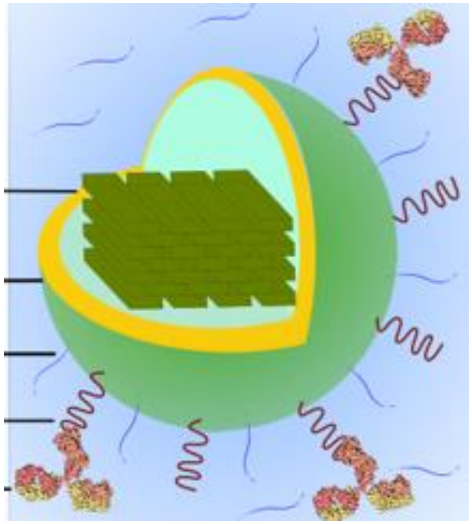
Nanoparticle Interactions at Fluid and Solid Interfaces

Solar powered water purification and moisture harvesting from air (nanostructured polymer gels with nanoparticles) (with Guihua Yu, MSE)

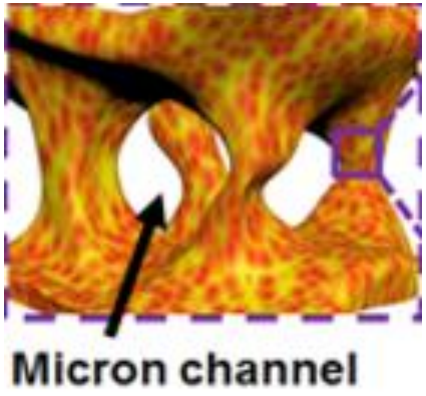




Monoclonal antibodies

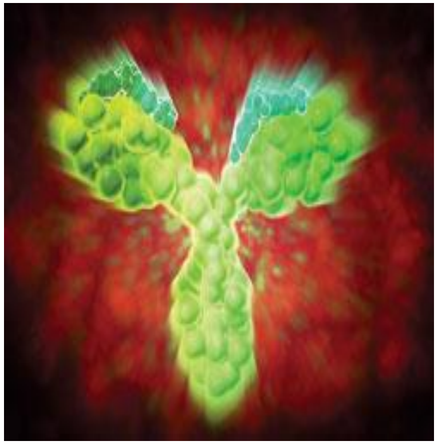


Imaging agents drugs in polymersomes



Solar water purification

Therapeutic Monoclonal Antibodies are the Leading Class of Biologics



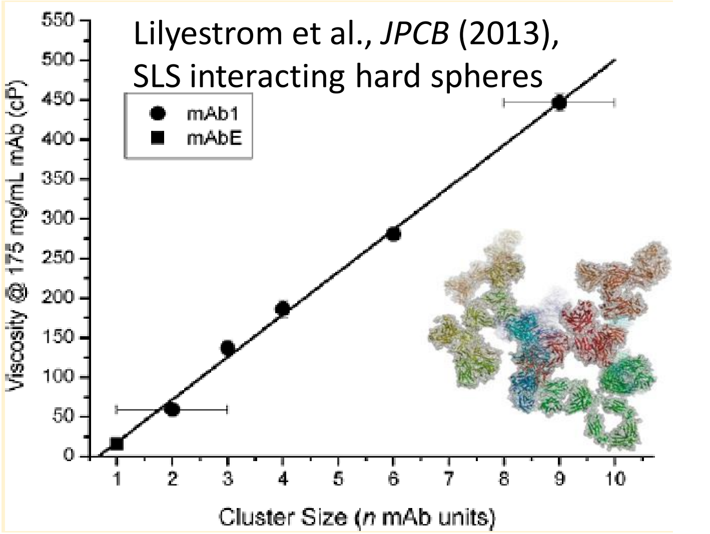
- 1/3rd of 900 Biologics in development are mAbs
- Covid19, other infectious diseases, cancer, inflammatory diseases, cardiovascular diseases
- At > 200 mg/ml for sub-cutaneous deliv. viscosity and stability are challenging

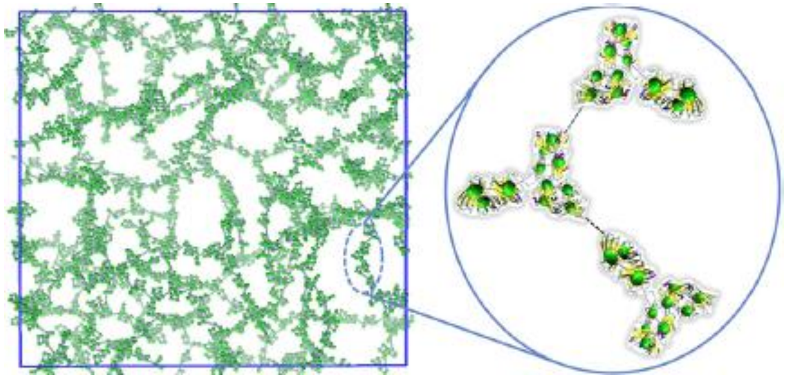
Attributes	I.V. Infusion	Subcutan. Injection
Typical volume (mL)	50 to 250 mL +	< 1.2 mL >200 mg/ml
Duration	1 to 2 hrs. for infusion	< 20 Sec
Location	Healthcare facility	Home / self-injection

Short ranged attraction increases formation of reversible oligomers that raise viscosity and lower stability

- Electrostatic PPI (charge-charge and charge-dipole, H bonds, dipole-dipole)
- Hydrophobic attraction
- Prediction of viscosity from B_{22}, k_d at low conc inaccurate

- SAXS and coarse grained MD simulation quantify local SR attraction to describe reversible oligomers

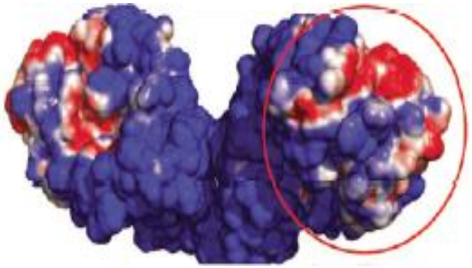


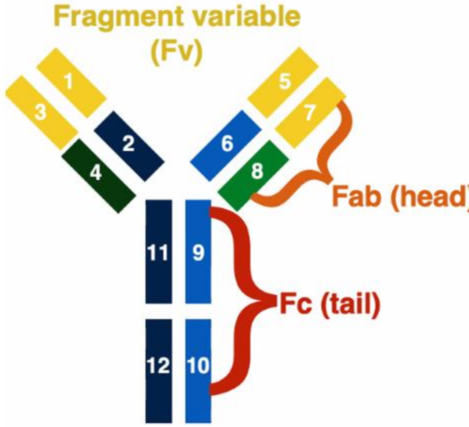


Buck, et al., *Mol Pharm* (2012)

- $\frac{\eta}{\eta_0} = 1 + 2.5\,\phi$ (Einstein)

Spherical particles



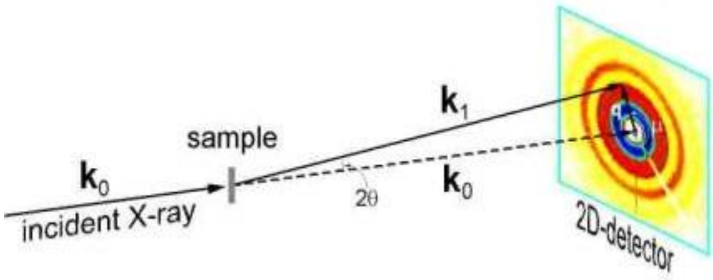


Site dpdt prot.-prot. interactions by SAXS

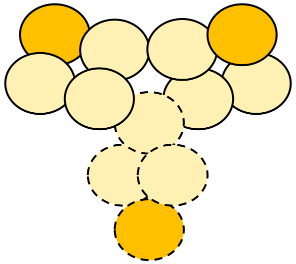
$$l_{Bragg} = \frac{2\pi}{q} \qquad q = \frac{4\pi}{\lambda}\sin(\theta)$$

$$I(q) = \varphi * (\Delta\rho)^2 * P(q) * S(q)$$

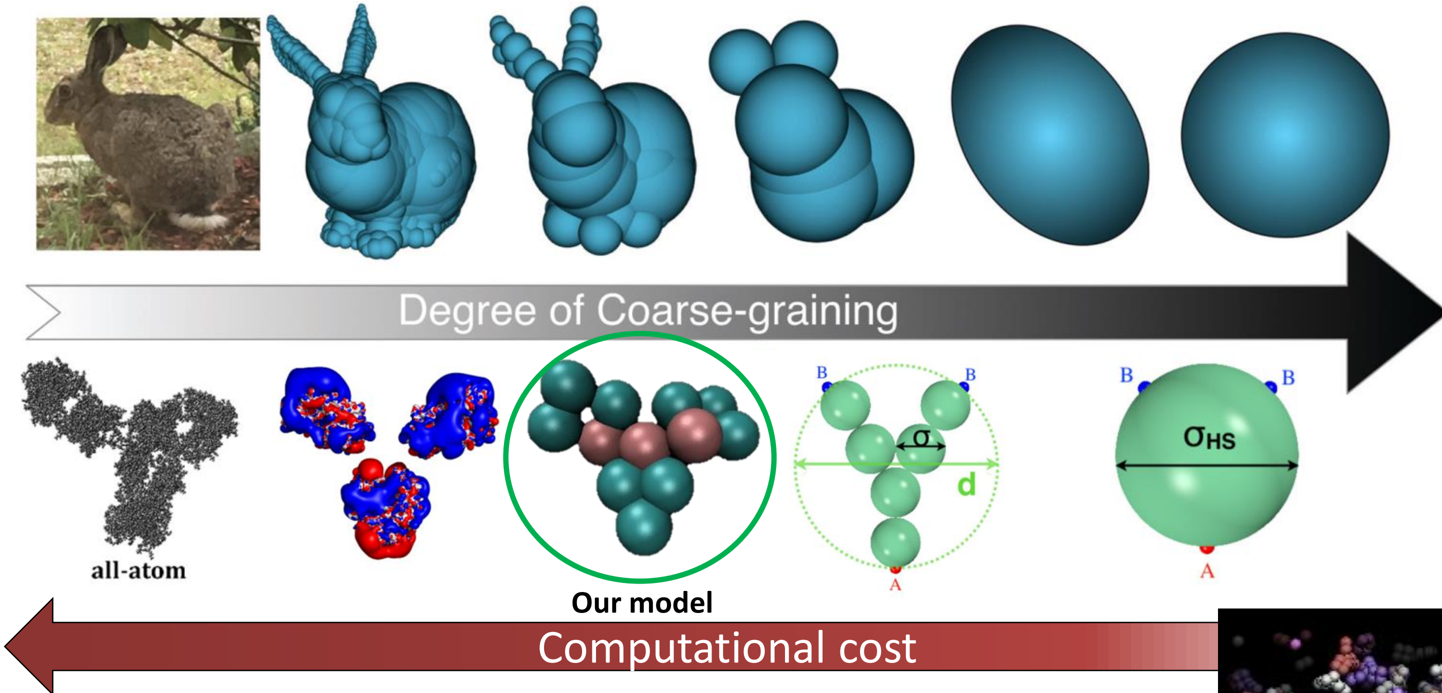
P(q): form factor at low conc.
S(q): structure factor
(interparticle interactions)

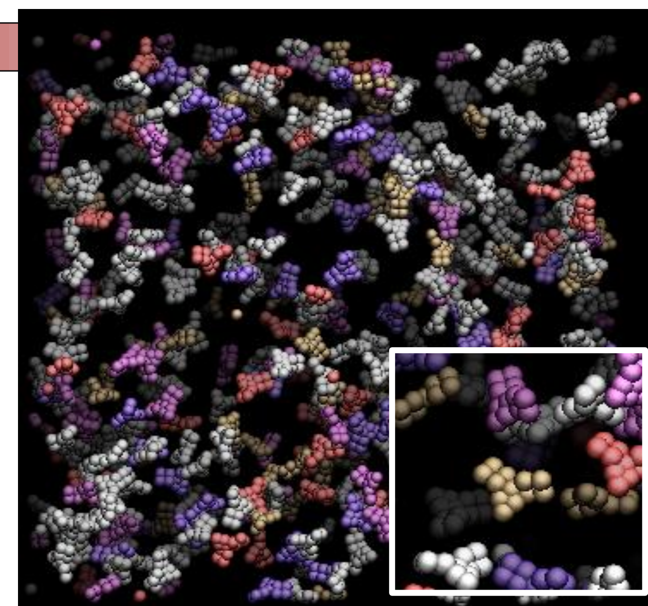


- Probe mAb solution structure at 5 to 100 nm length scale (10 nm mAbs)
- Coarse grained model: Add attractive sites to 12 bead models from form factor
- MD simulations of S(q) at high conc. to analyze SAXS data
  - determine real space properties, g(r) including clustering
  - Determine bead specific short-ranged attraction parameters
- Orange: specific bead attraction
- Yellow: VDW, Coulombic



Using coarse-grained models to study antibodies at high concentration to determine structure, clustering and viscosity



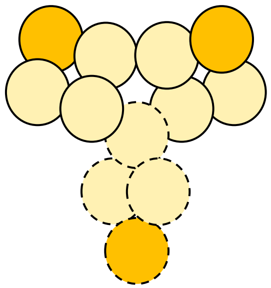


- 12-bead model preserves molecule shape and major domains
- > 200 mg/mL
- Relate strong attraction sites to structure and formulation

Stradner and Schurtenberger, *Soft Matter* (2019); Calero-Rubio, Roberts et al., *JPCB* (2016); Skar-Gislinge, Stradner et al., *Mol Pharm* (2019); Dear, Truskett, Johnston et al., *JPCB* (2019)

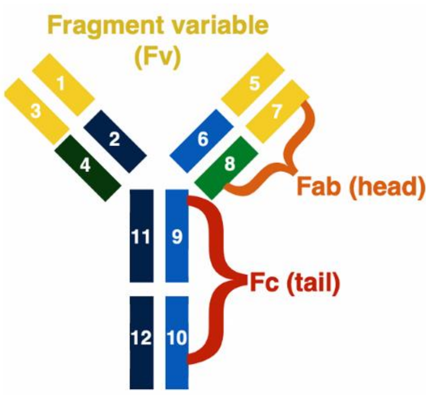
Objectives

- **Characterize protein interactions and cluster formation by SAXS experiments and coarse grained MD simulations at high conc.**



  - S(q) and g(r): 12 bead coarse grained model (bead specific short range attraction), implicit solvent
  - Effect of mAb structure, pH, ionic strength and cosolutes such as arginine

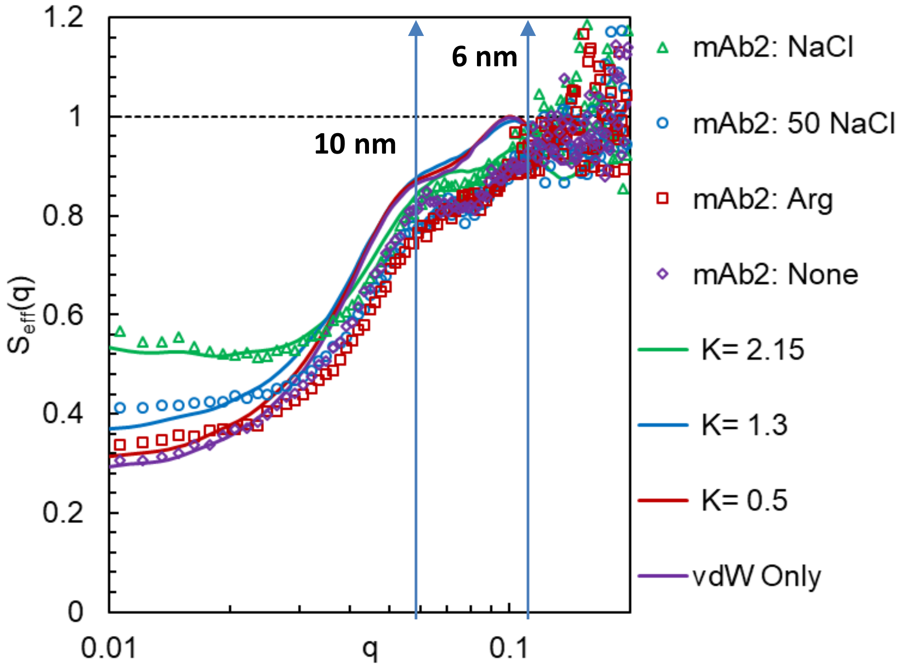
- **Relate cluster formation to bead specific protein-protein interactions**

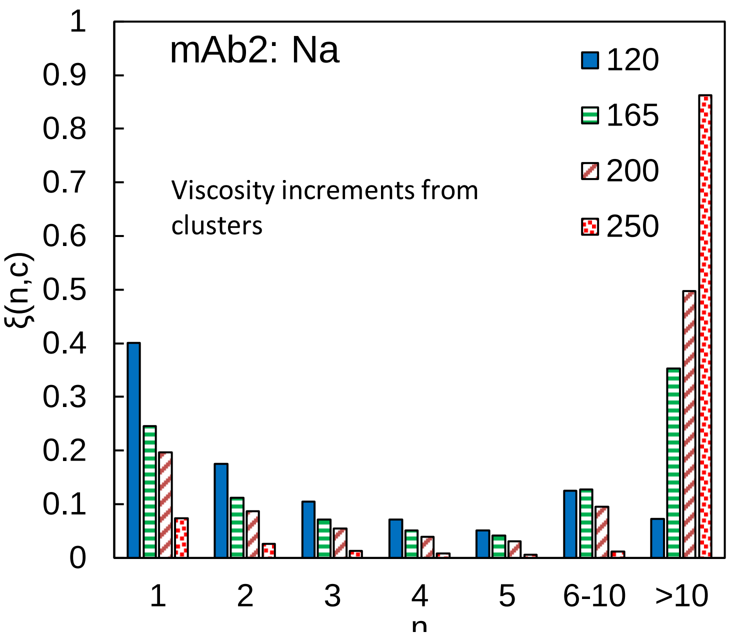


- **Determine viscosity from protein-protein interactions including effect of cluster size distribution**

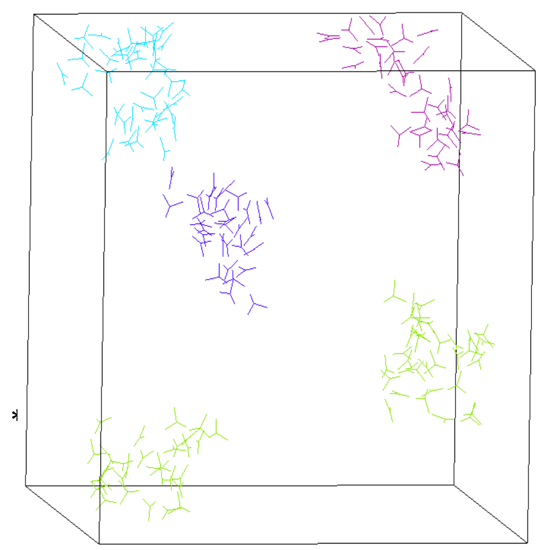
- **Potential application for discovery/developability, protein processing, storage, and drug delivery.**

Fab-Fab, Fab-Fc and Fc-Fc interactions: relate viscosity to cluster size distribution (120 mg/ml)





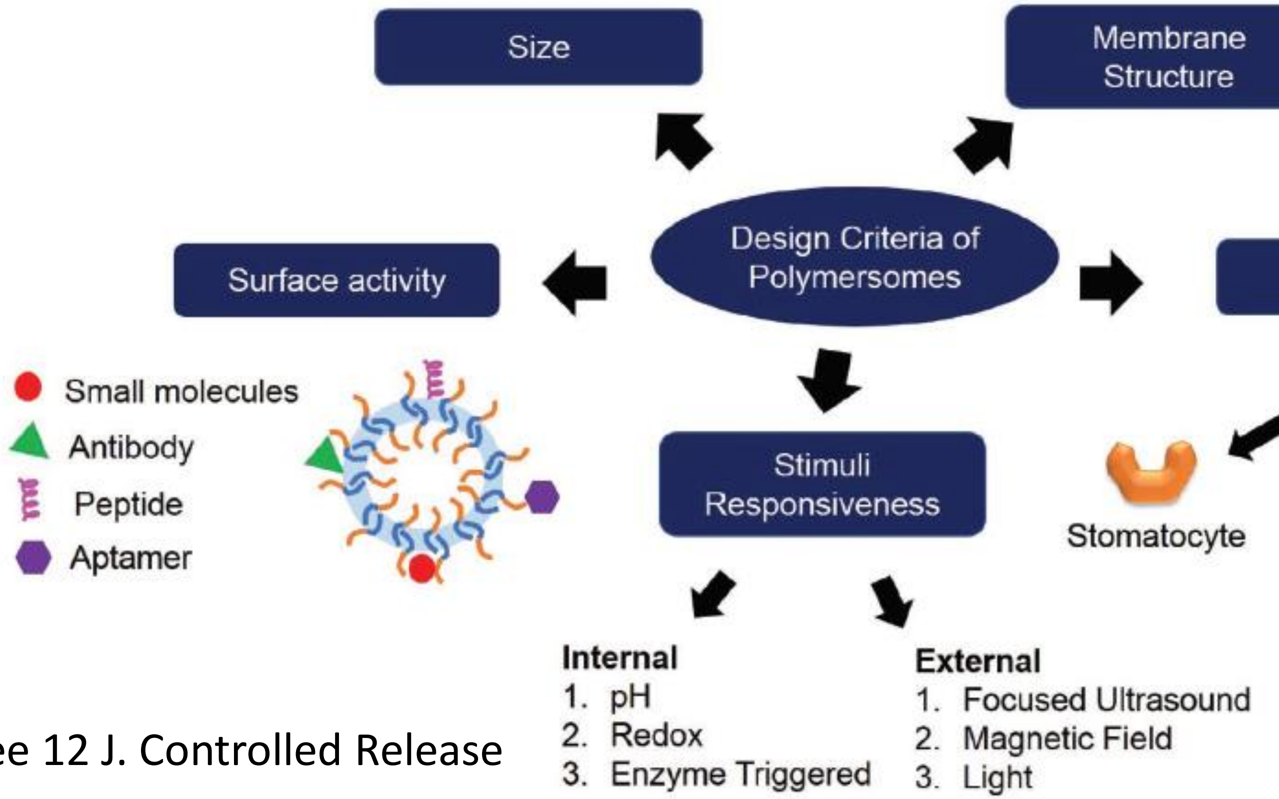
- Fit expt'l structure factor with MD simulations
  - determine cluster size distributions
  - understand protein stability and viscosity
- Examine various length scales
- Basis for modifying mAb sequence and formulation



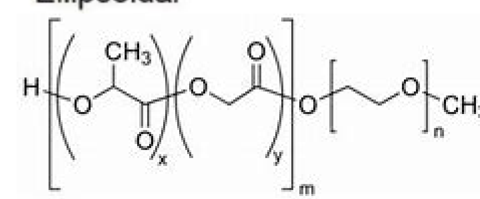
Dear, TT, KPJ et al., J. Phys. Chem. B. (19);

Chowdhury, KPJ, TT et al., Mol. Pharm. (20)

Drug delivery/imaging with polymersomes

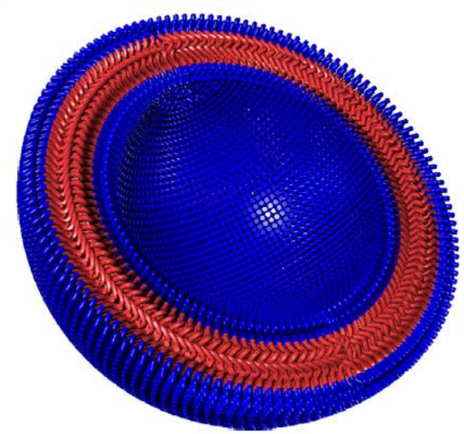


Lee 12 J. Controlled Release

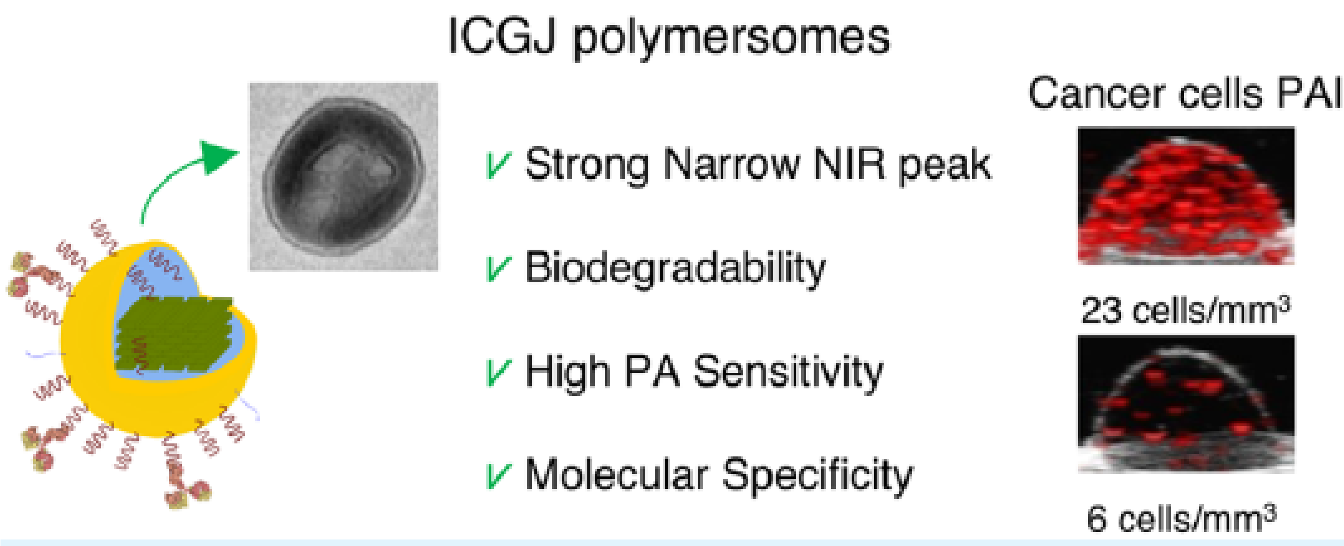


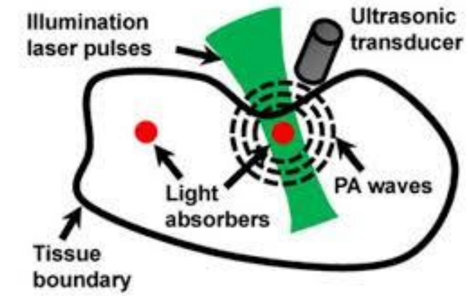
Platform technology with mAbs on surface to target cancer cells
Unlimited potential for cargoes: drugs, imaging agents

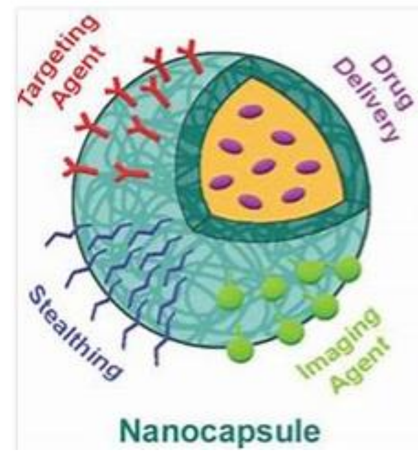
Educational value: polymer synthesis and self- assembly,
interfacial mechanisms and colloidal properties
integrated design hierarchy with UT MD Anderson for translation to animals



Design of polymersomes with colloid and polymer science: advance imaging and drug delivery







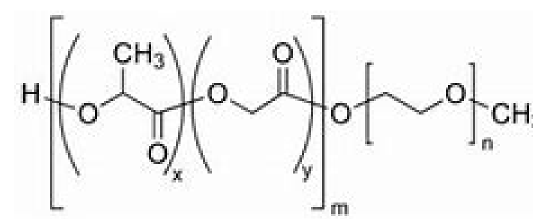
Objectives: Controlled size and loading of drugs and imaging agents

Nontoxic with FDA approved materials, stable for 24 hours, clearable,

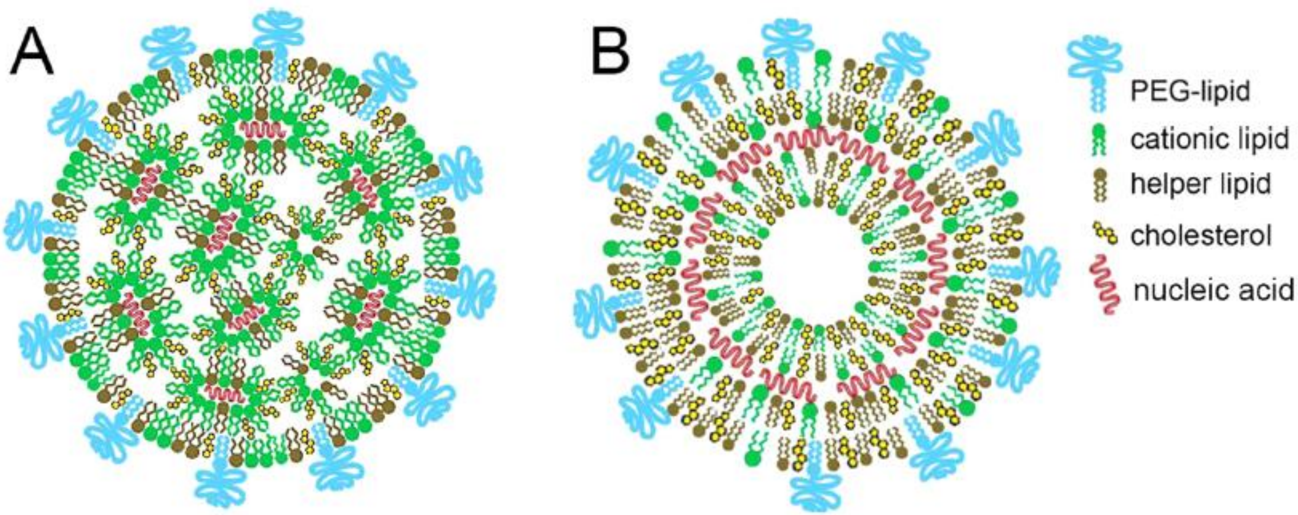
mAbs on surface for targeting of particular cancers: click chemistry of azides with alkynes

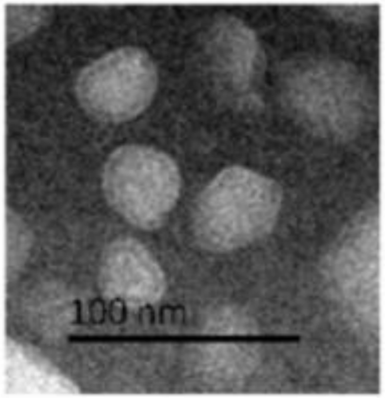
Cocktails of imaging agents and drugs at very high loadings

Changalvaie, Truskett, Sokolov, Johnston et al. (19) ACS Appl. Mat. Interfaces



Lipid nanoparticles mRNA vaccines for covid19





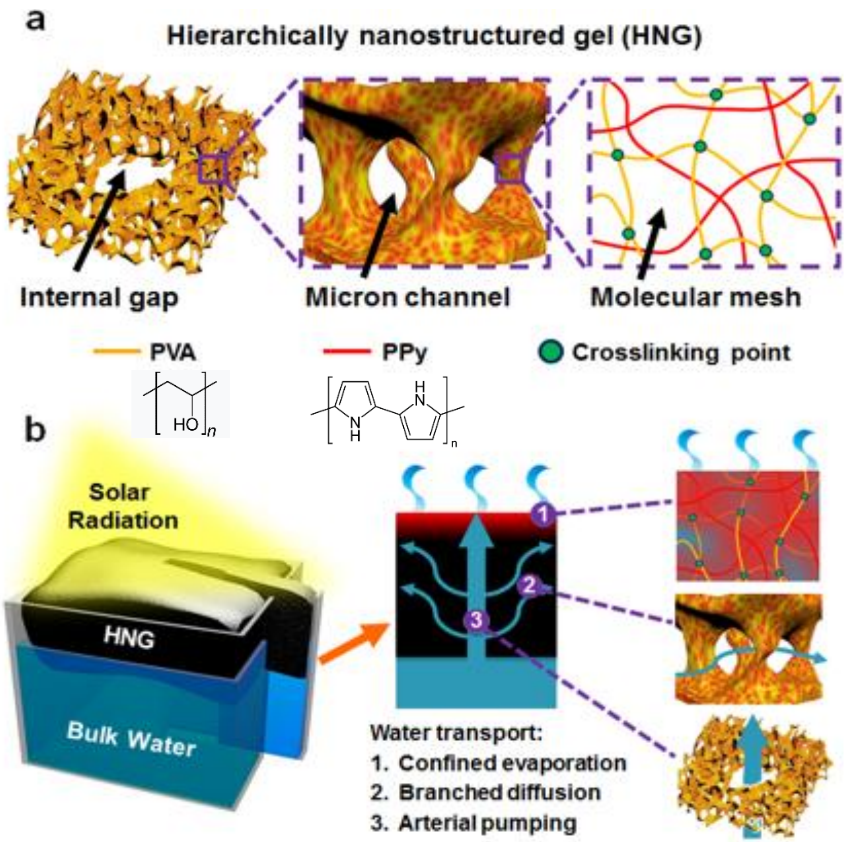
- Lipid NPs: self-assembled structures encapsulate, protect and deliver nucleic acids
- Electrostatic complexing of anionic nucleic acids and cationic lipids \
- Better insight into structural properties will enable designs to improve endosomal escape
  - SAXS and cryo TEM
- Formed by rapid microfluidic mixing

Huang et al. (21) J. Contr. Release, Patel et al. (20) Nature Com.

Hydrogel-enhanced Solar Vapor Generation

(Guihua Yu (MSE), Lynn Katz and Keith Johnston)

An efficient way of harvesting solar energy for purification of polluted or saline water.

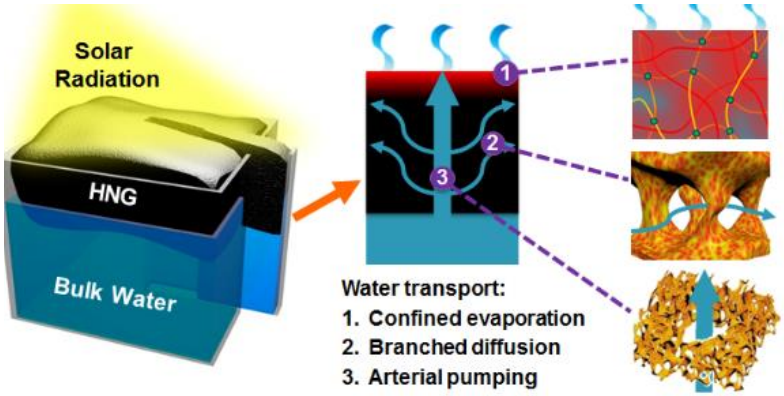


- Confined evaporation
  Solar heat used for evaporation can be localized by PVA gel at the water-air interface→reduce the energy loss of bulk water at the bottom
- Branched diffusion and arterial pumping
  Micron channels and internal gaps of PVA gel can generate capillary force to rapidly replenished molecule meshes from bulk water below.
- *Polymer gel network reduces energy demand of water evaporation: improve porosity*
- Anti-salt-fouling function

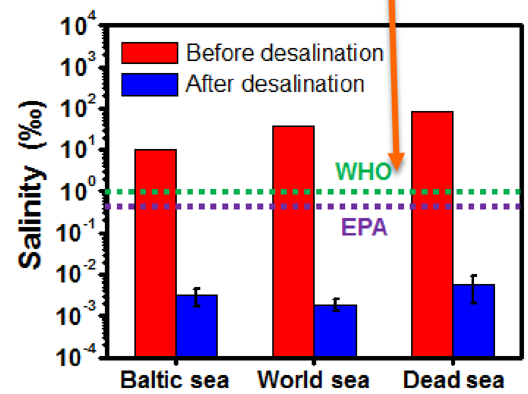
Yu Group, *Nature Nanotechnol.* 2018, 13, 489

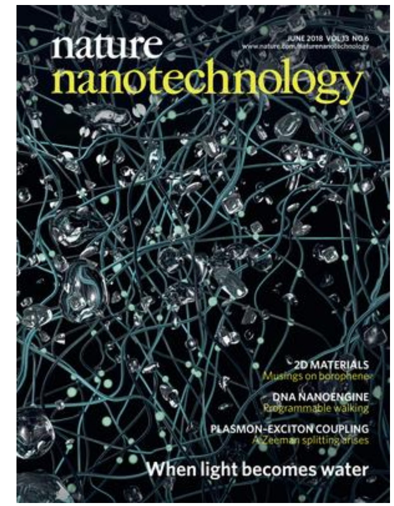
Solar Hydrogel: turning light to clean water

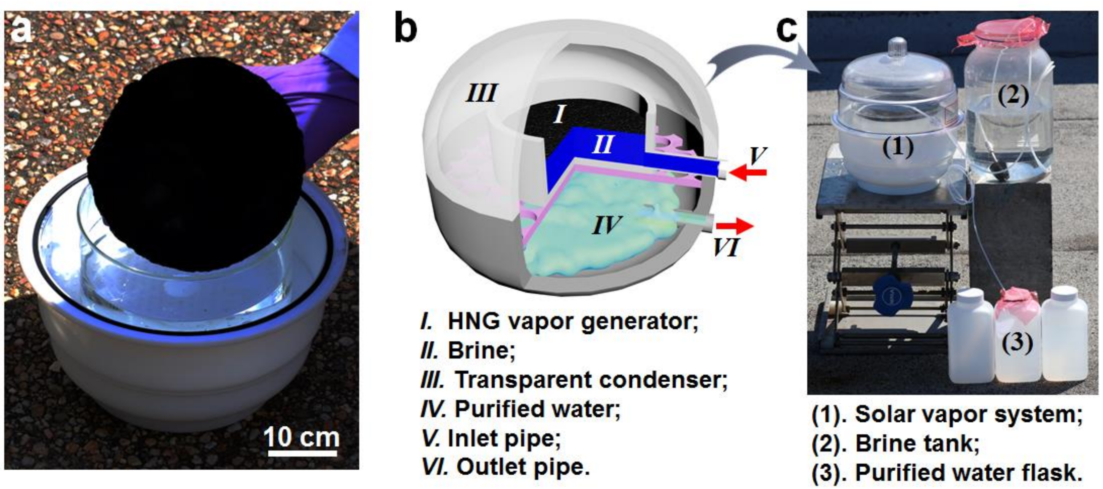
Solar water desalination



Salinity criterion of drinkable water







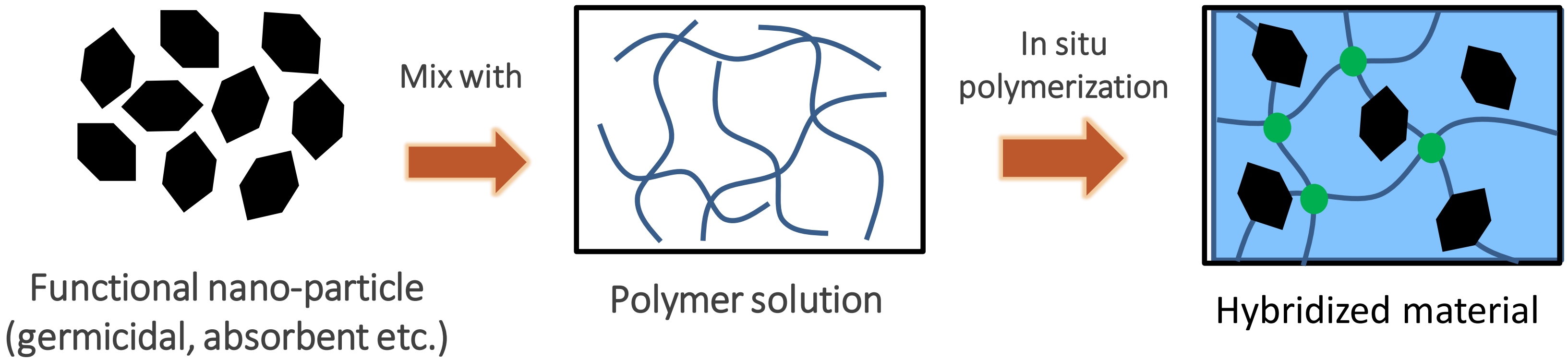
Efficient solar vapor generation achieved under natural sunlight.

Prototype seawater purification system demonstrated with a daily yield of ~23 L/m^2.

***Nature Nanotech**. 2018, 13, 489 (Featured in National Geographic, R&D Mag., Science News, Nature, over 100 channels)*

Regulate Water Properties via Polymer-NPs Interaction

Polymer network design of the Multi-functional solar evaporator



Solar Absorber Nanoparticles

- Dispersity in polymer network and control of porosity
- Solar energy conversion/confinement
- Surface area for high contact with intermediate water
- Protection against biofouling
- Surface charge/hydrophobicity
- Selectivity towards targets (heavy metals, catalytic functions for removal of VOCs, etc)

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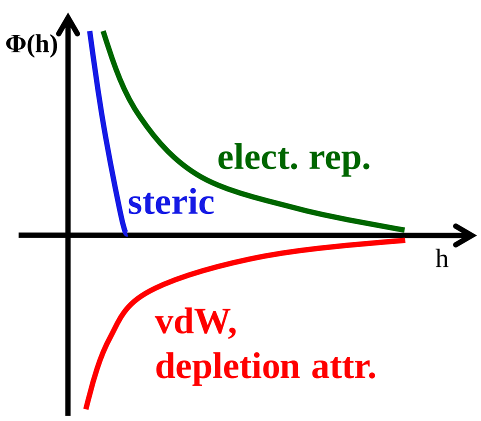
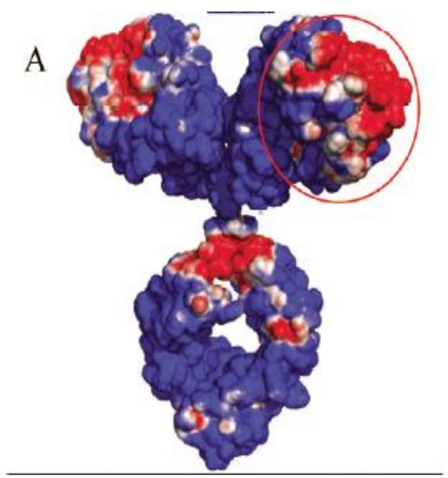
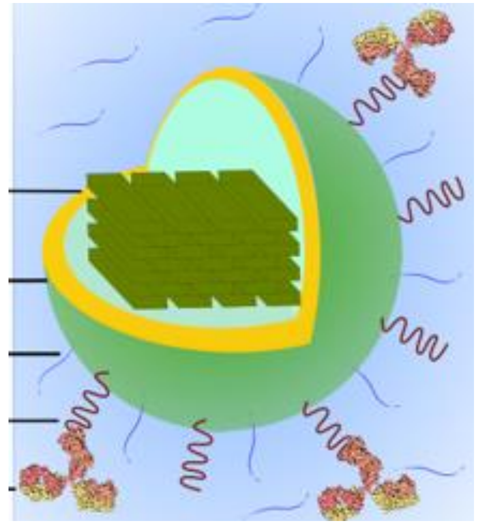
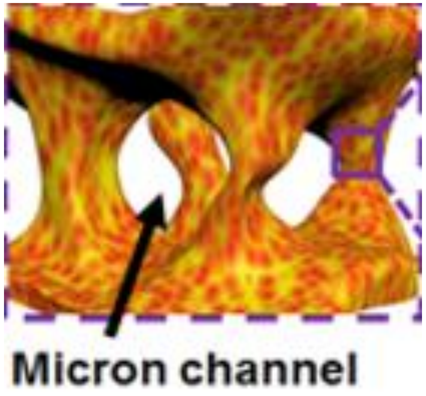




Monoclonal antibodies

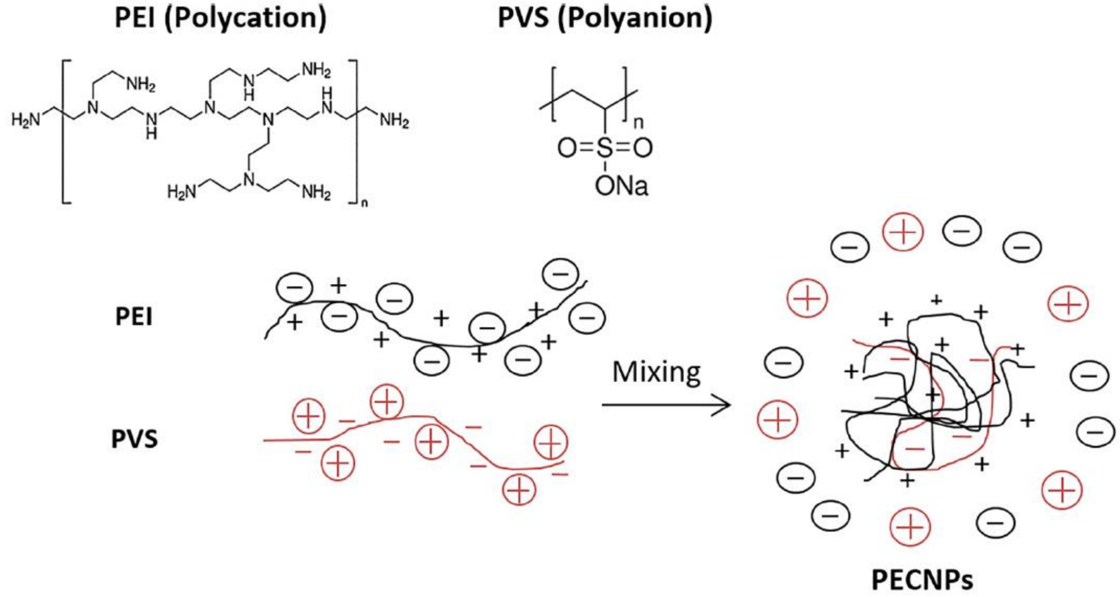


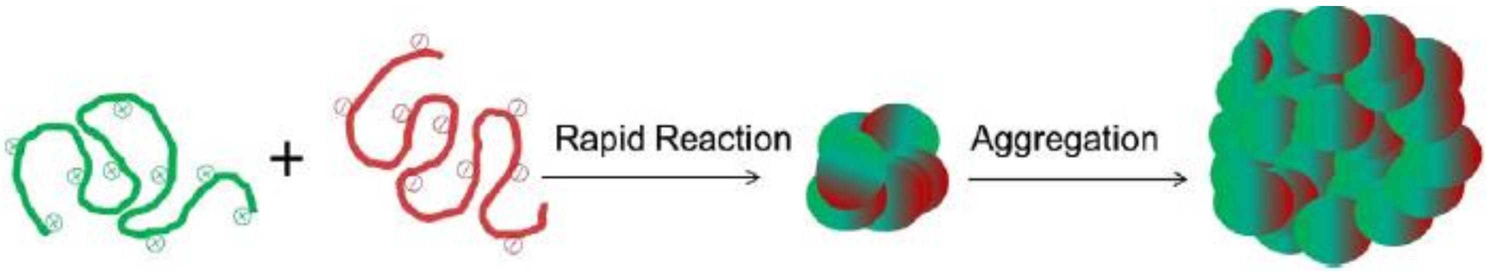
Imaging agents drugs in polymersomes

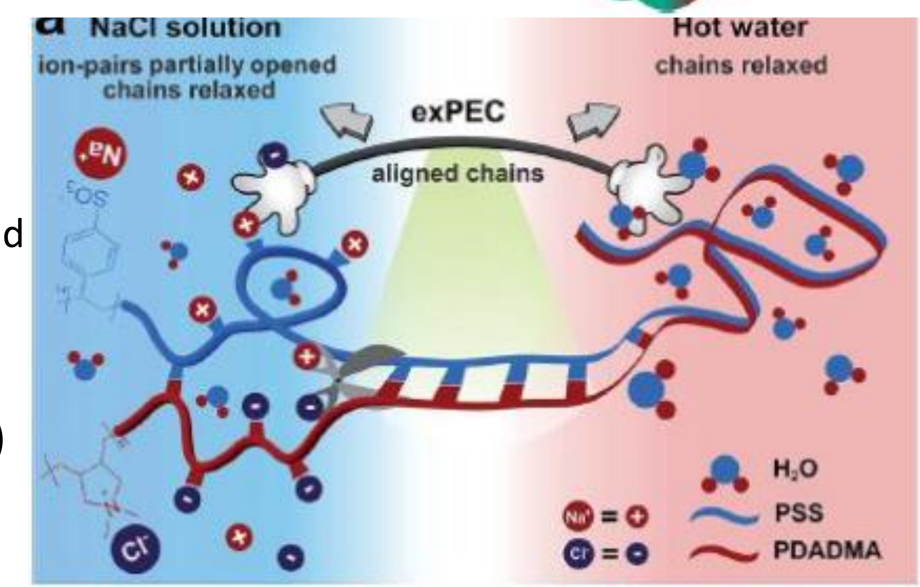


Solar water purification

Polyelectrolyte complexes for extended release







Objectives:
Control release low molecular weight molecules and ions and polymers from polyelectrolyte complexes

Wang, Schlenoff (14)

Ladder like (ordered) and scrambled egg packing domains (Das 17)

pH influences PEI as it will be more extended in charged state at lower pH

pH used to control size and stability of PEI-PVS PECs

Salt level during formation influences chain extension

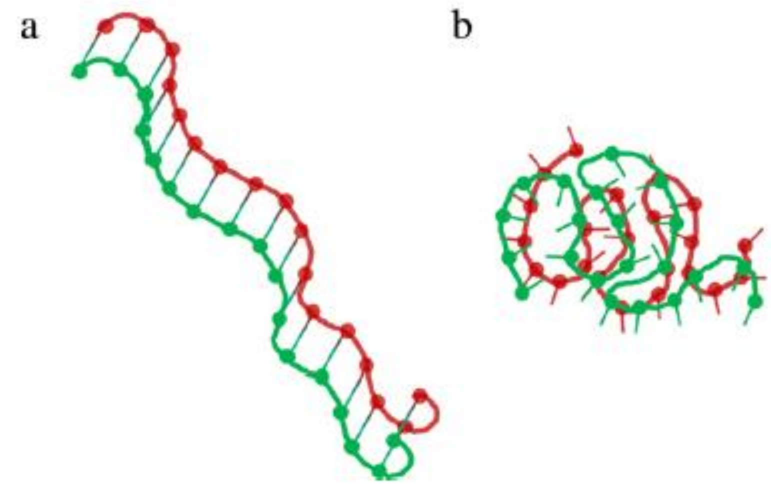


Fig. 7. Schematic of (a) 'ladder' model and (b) 'scrambled egg' model, the two types of polyelectrolyte complex structures.

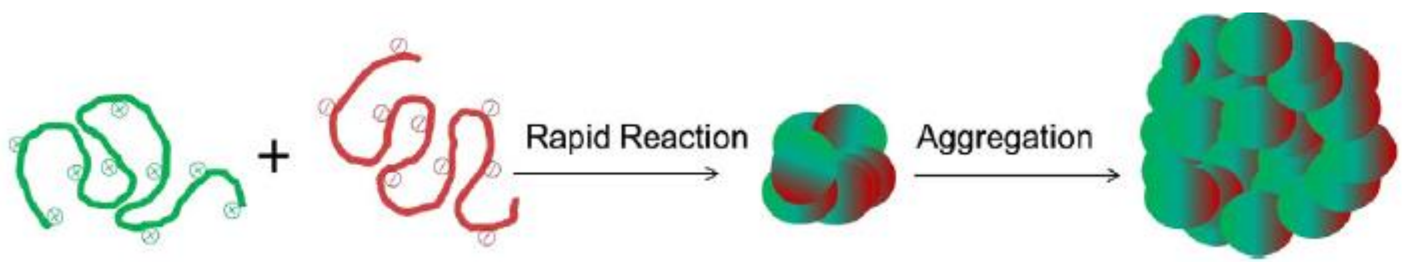
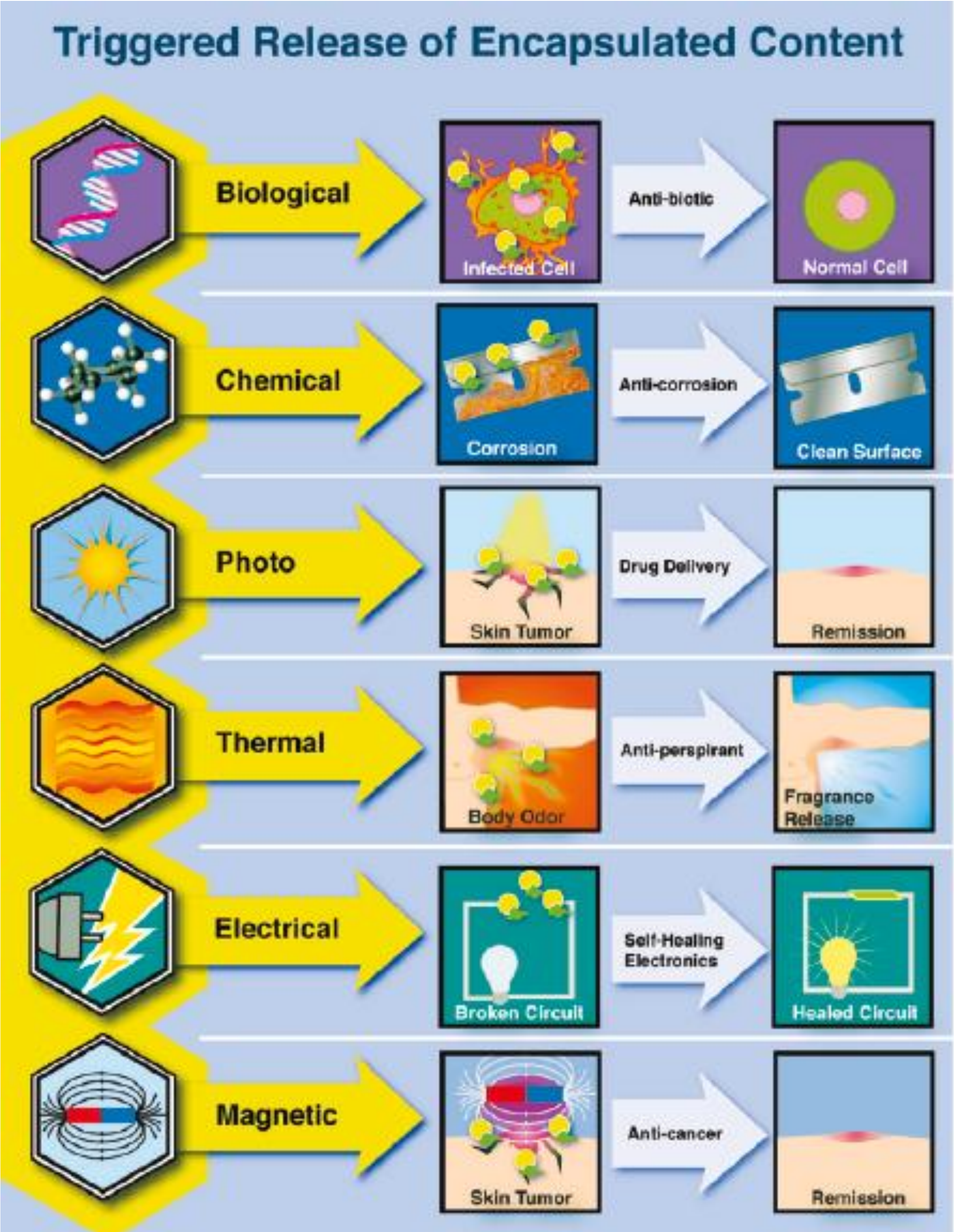


Fig. 1. Schematic depicting polyelectrolyte complex particle formation during mixing of polycations and polyanions followed by aggregation to form larger structures [38].

Charge on initial PEC will influence growth during aggregation stage



Ovarian, breast and other cancer imaging and therapy

Platform concept for with payloads and mAbs on surface

Deliver drugs at tumor sites

NIR heating to rupture capsules for delivery on site

Delivery of small molecules and polymers in chemical applications

Esser-Kahn, Moore et al. Macromolecules, 2011

Destination of PhD Students

Gupta	Virginia Tech.
Balbuena	Texas A + M
Meredith	Ga. Tech.
Yates	U. Rochester
Da Rocha	Virginia Tech.
Lee	U. S. California
Ziegler	U. Florida
Lu	Nat. Univ. Singapore
Elhag	Petroleum Inst. (Abu Dhabi)
Lee	Myongji Univ.
Esteban-Benavides	Univ. Mississippi

Shah	Pfizer
Chen	Abbott
Dickson	Exxon-Mobil
Smith	Exxon-Mobil
Overhoff	Schering-Plough
Engstrom	Bristol-Meyers-Squibb
Matteucci	Dow
Gupta	Exxon-Mobil
Tam	Bristol-Meyers-Squibb
Patel	Lam Research
Ma	Dupont
Miller	Medimmune
Slanac	Dupont
Murthy	Roche
Chen	Dow
Xue	Ecolab
Borwankar	Bristol-Meyers-Squibb
Worthen	Exponent
Hardin	Exponent
Hung	Bristol-Meyers-Squibb
Dear	Bristol-Meyers-Squibb
Forslund	Intel

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- 2. Guo, Y. H.; Dundas, C. M.; Zhou, X. Y.; Johnston, K. P.; Yu, G. H., Molecular Engineering of Hydrogels for Rapid Water Disinfection and Sustainable Solar Vapor Generation. *Adv. Mater.* **2021,** *33* (35), 8.
- 3. Da, C.; Chen, X.; Alzobaidi, S.; Johnston, K. P., Elastic and Ductile Interfaces for Highly Stable Foams with Grafted Anionic Silica Nanoparticles and an Anionic Surfactant in Concentrated Brine. *J. Colloid Interface Sci.* **2021,** *submitted*.
- 4. Chowdhury, A.; Guruprasad, G.; Chen, A. T.; Karouta, C. A.; Blanco, M. A.; Truskett, T. M.; Johnston, K. P., Protein-Protein Interactions, Clustering, and Rheology for Bovine IgG up to High Concentrations Characterized by Small Angle X-Ray Scattering and Molecular Dynamics Simulations. *Journal of Pharmaceutical Sciences* **2020,** *109* (1), 696-708.
- 5. Chowdhury, A.; Bollinger, J. A.; Dear, B. J.; Cheung, J. K.; Johnston, K. P.; Truskett, T. M., Coarse-Grained Molecular Dynamics Simulations for Understanding the Impact of Short-Range Anisotropic Attractions on Structure and Viscosity of Concentrated Monoclonal Antibody Solutions. *Mol. Pharm.* **2020,** *17* (5), 1748-1756.
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- 7. Dear, B. J.; Bollinger, J. A.; Chowdhury, A.; Hung, J. J.; Wilks, L. R.; Karouta, C. A.; Ramachandran, K.; Shay, T. Y.; Nieto, M. P.; Sharma, A.; Cheung, J. K.; Nykypanchuk, D.; Godfrin, P. D.; Johnston, K. P.; Truskett, T. M., X-ray Scattering and Coarse-Grained Simulations for Clustering and Interactions of Monoclonal Antibodies at High Concentrations. *J. Phys. Chem. B* **2019,** *123* (25), 5274-5290.
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