“Smart Nanoparticles”

Stimuli Sensitive Hydrogel Particles

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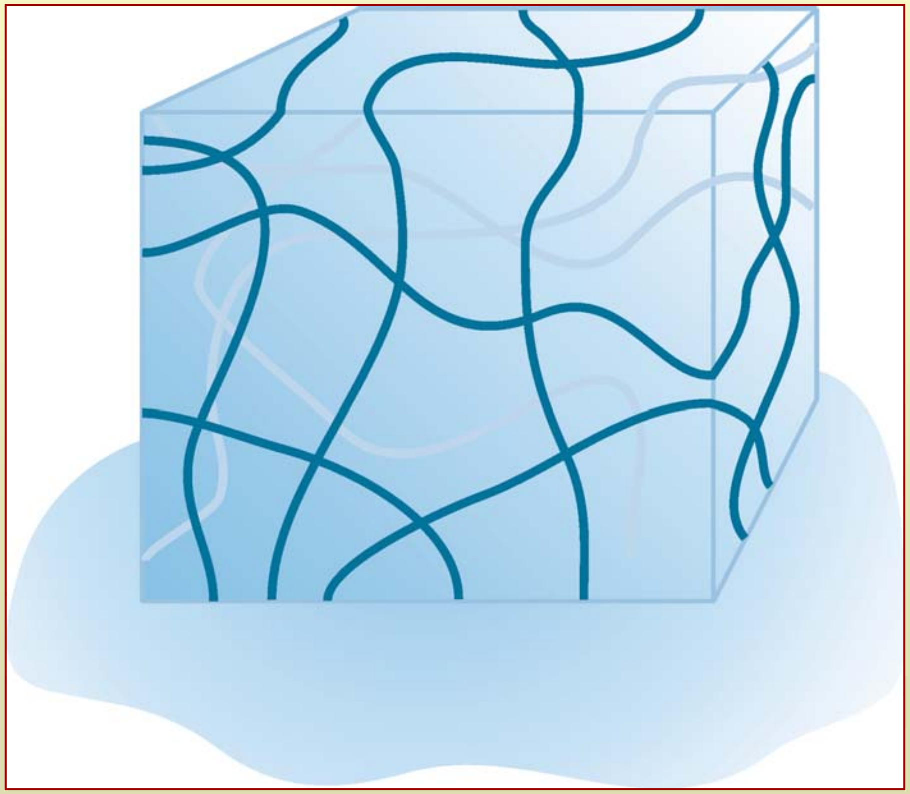
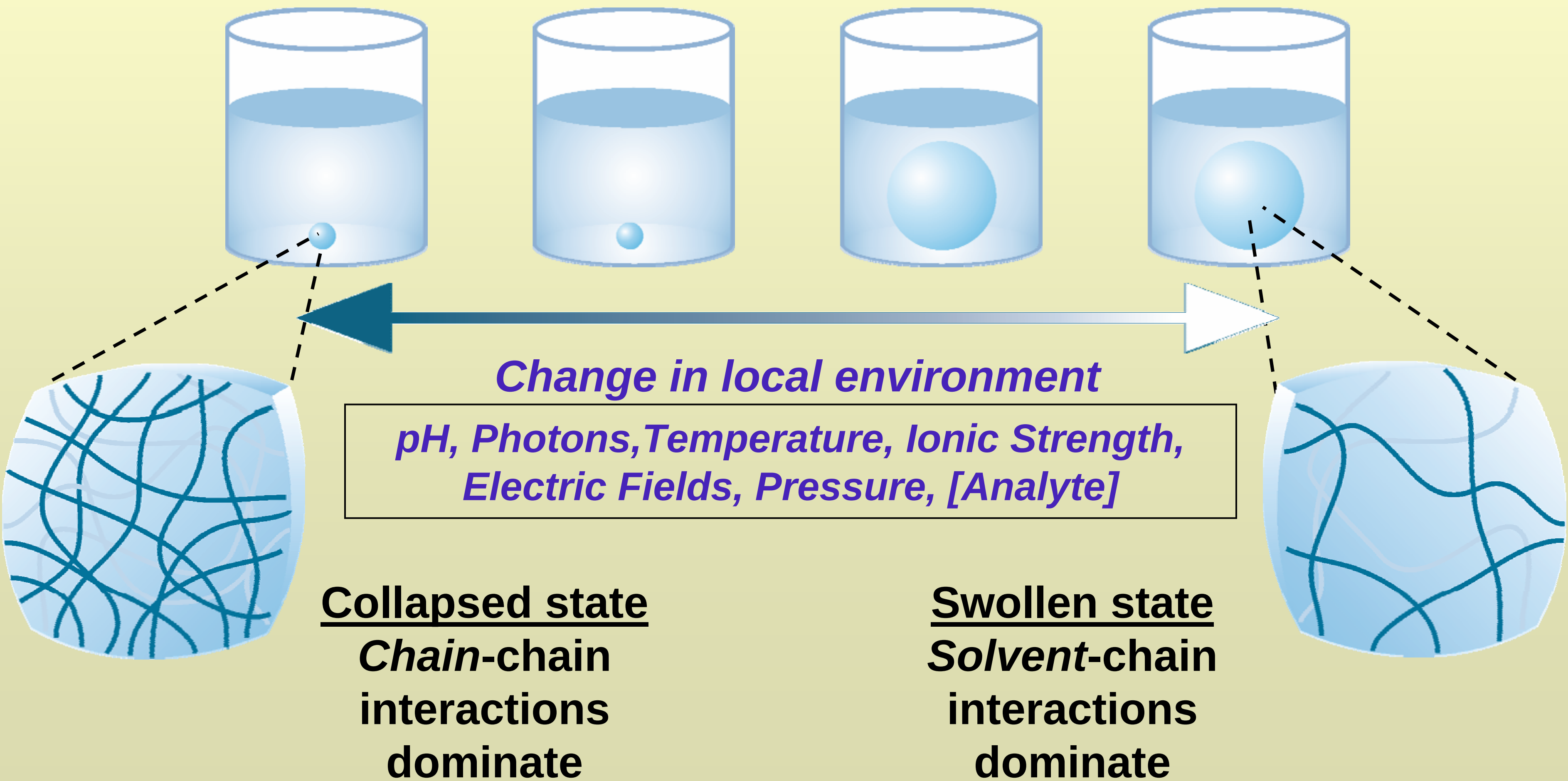
Hydrogels

Crosslinked water soluble polymers – a physically restricted, dimensionally-stable, polymer solution



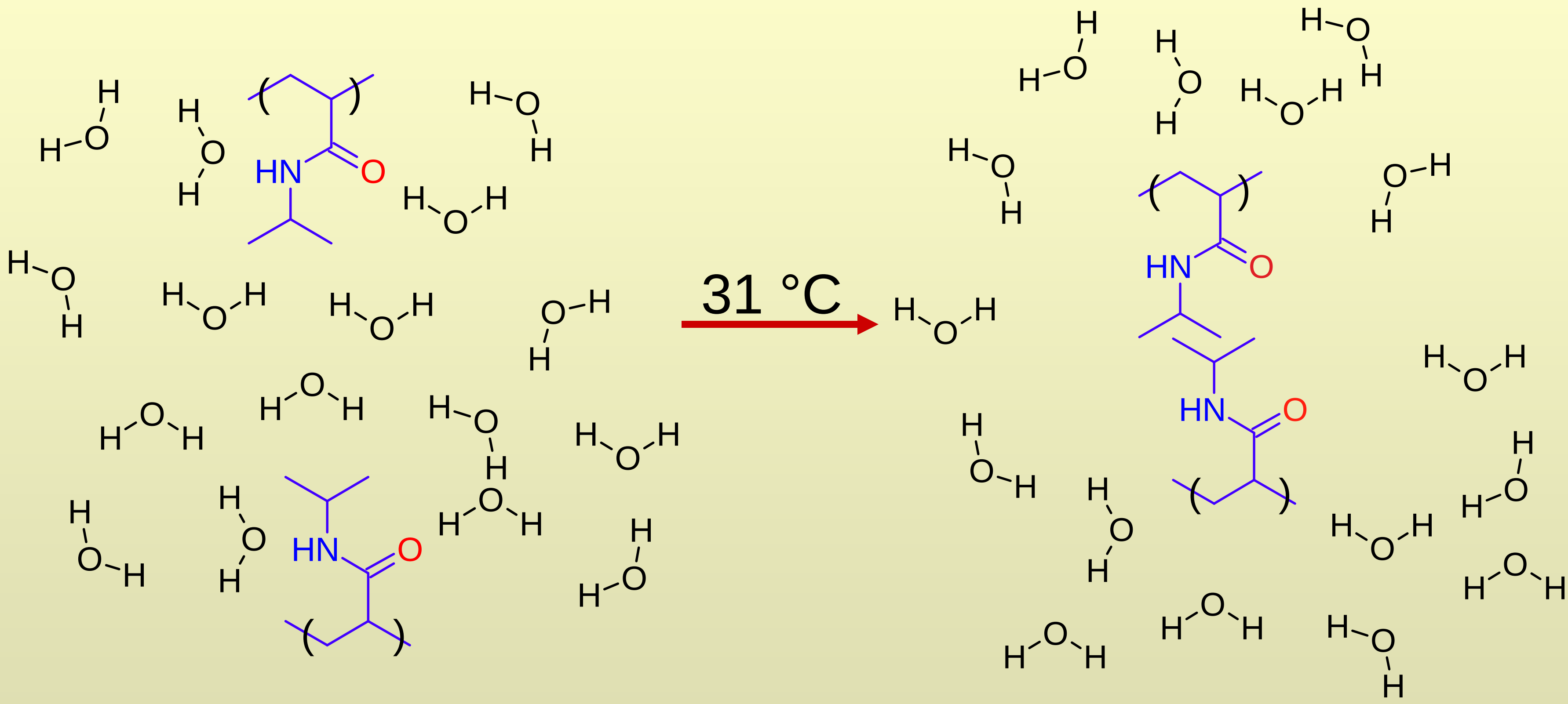
Responsive Hydrogels

Polymeric gels can be designed to undergo environmentally-initiated phase separation events (volume phase transition).



Typical Responsive Gel

poly(*N*-isopropylacrylamide) (*p*NIPAm) – Thermoresponsive Gel

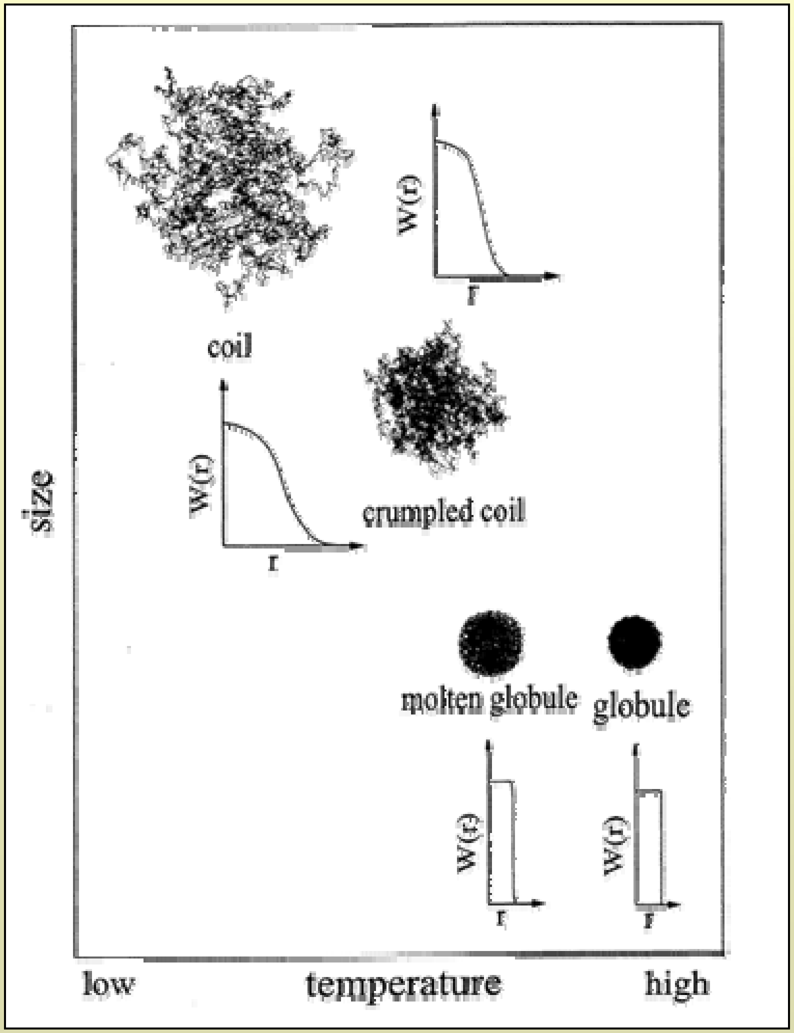


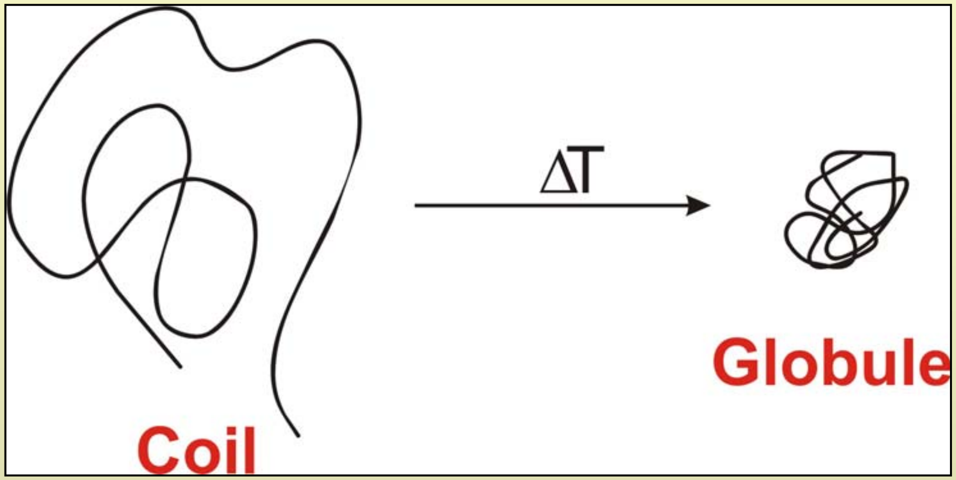
Swollen/Hydrophilic

Collapsed/Hydrophobic

Polymer Phase Separation

Phase separation of poly-*N*-isopropylacrylamide occurs *via* an entropically-driven coil to globule transition.



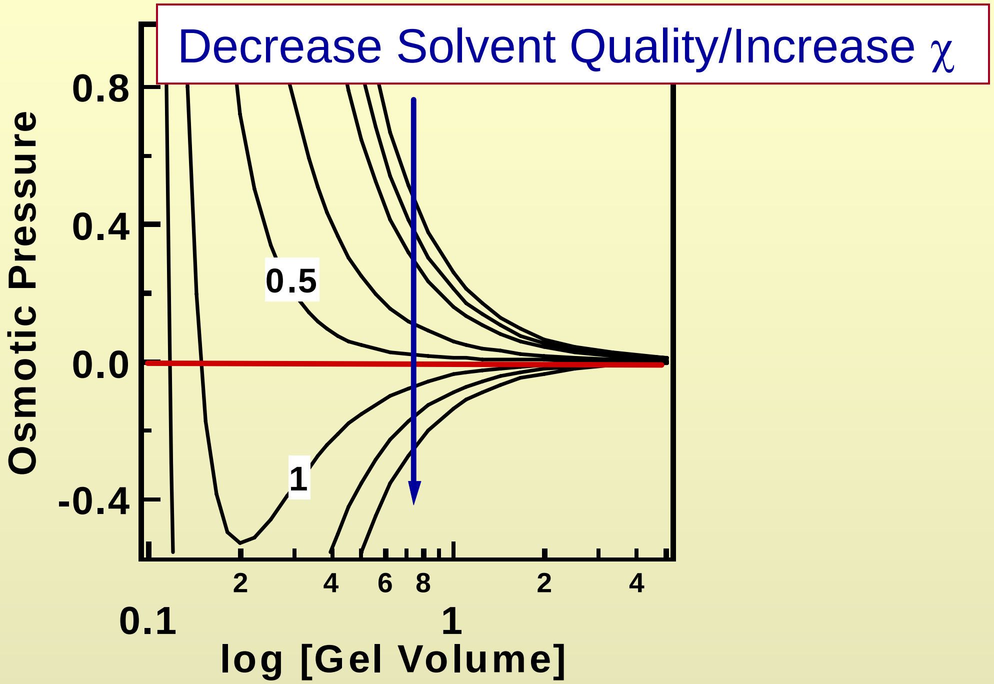


Xiaohui Wang; Xingping Qiu; Chi Wu
Macromolecules, **1998,** 31 (9), 2972 –2976.

Responsive Hydrogels

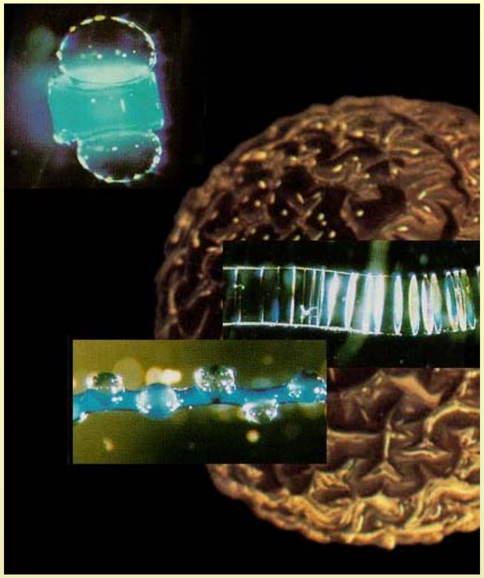
Volume phase transitions in simple gels can be modeled as a crosslinked polymer in a vdW fluid.

A change in osmotic pressure on either side of the interface induces a solvation/desolvation response

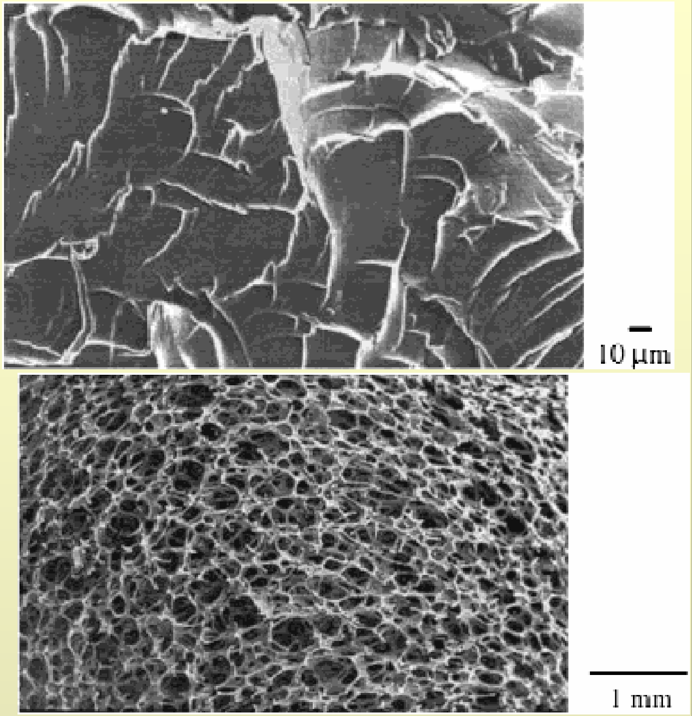


$$\frac{\pi}{k_B T} = \frac{\pi_{el} + \pi_M}{k_B T} = \frac{n_0}{N_x}\left[\frac{1}{2}\left(\frac{n}{n_0}\right) - \left(\frac{n}{n_0}\right)^{\frac{1}{3}}\right] - \frac{1}{v}\left[\ln(1 - nv) + nv + \chi n^2 v^2\right]$$

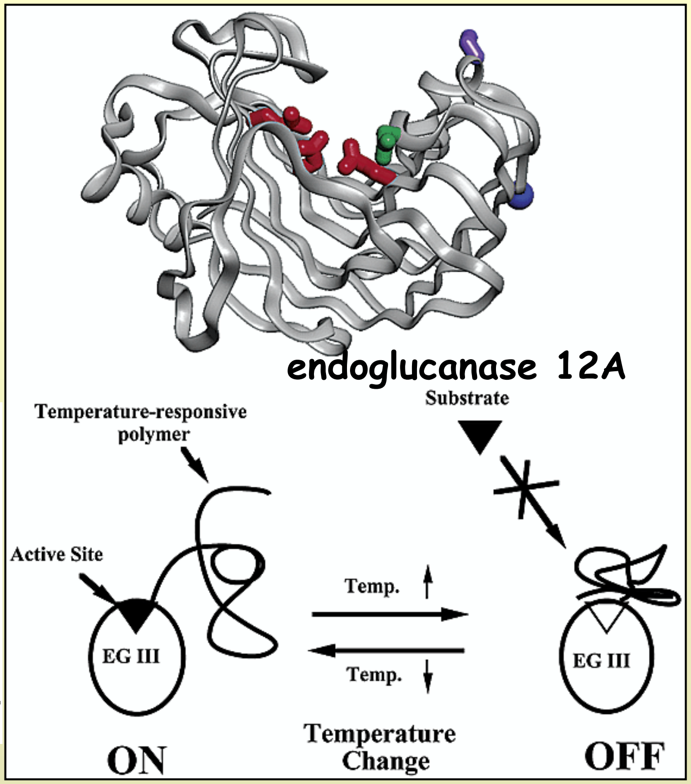
"Smart" Polymers



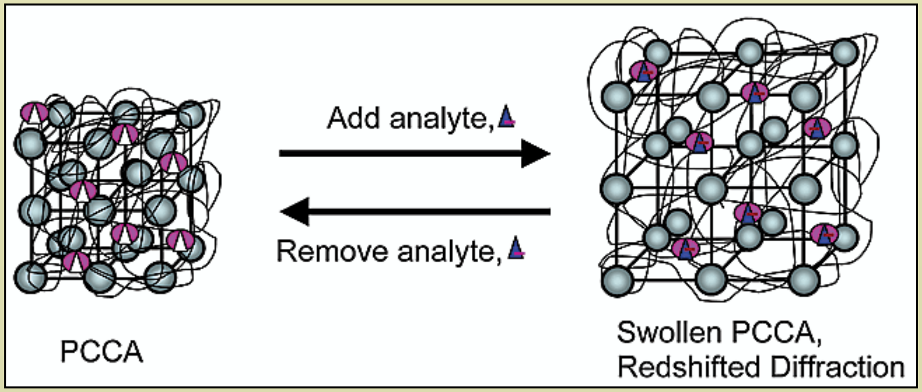
web.mit.edu/physics/tanaka/background/patterns.html



Chen, Park, and Park *J. Biomed. Mat. Res.* **1999**, *44(1)*, 53-62.

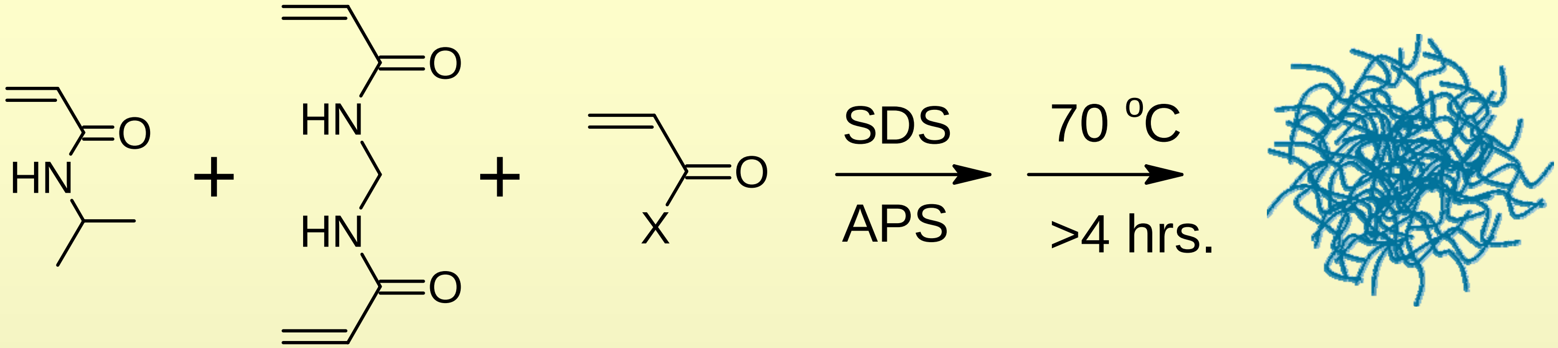


Shimoboji, Larenas, Fowler, Hoffman, and Stayton *Bioconj. Chem.* **2003**, *14(3)*, 517-525.

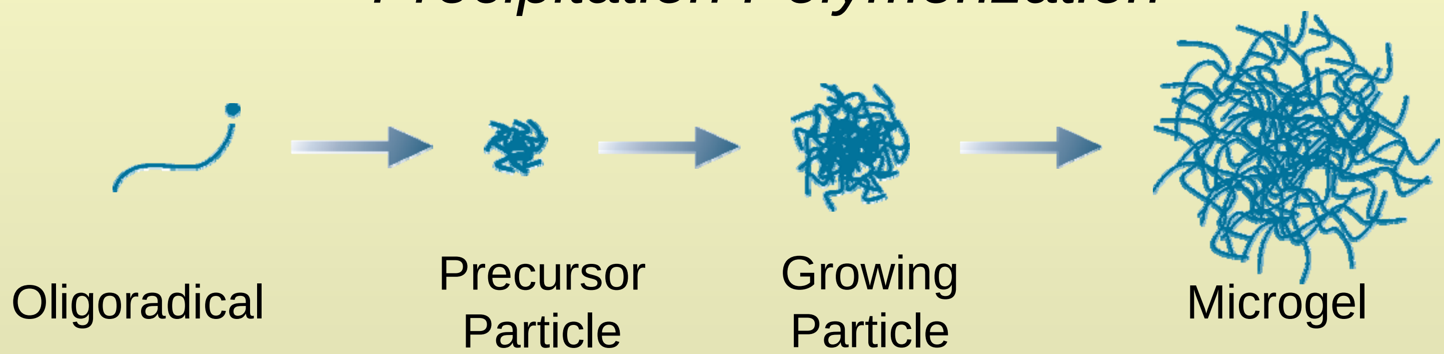


Asher, Sharma, Goponenko, and Ward *Anal. Chem.* **2003**, *75(7)*, 1676-1683.

pNIPAm Microgel/Nanogel Synthesis



Precipitation Polymerization



Controllable Parameters:

particle porosity/solvent content (crosslinker identity/conc.)

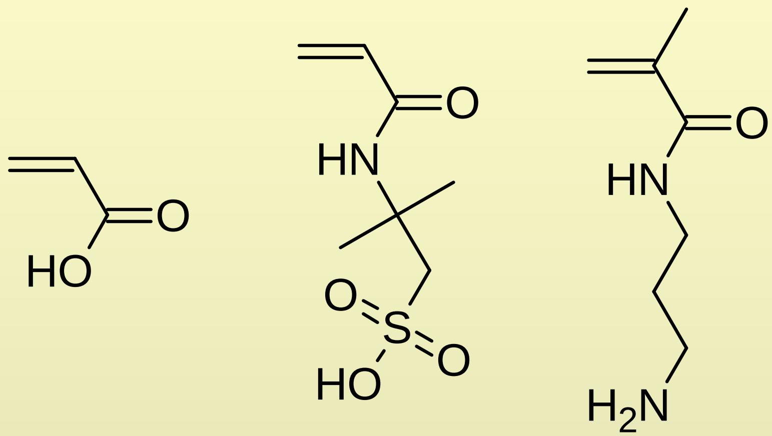
size – 50 nm to 5 μm (initiator, surfactant conc.)

phase transition magnitude

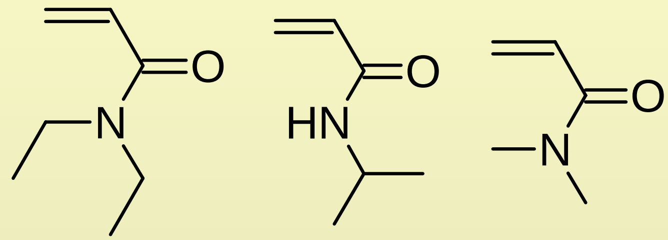
volume phase transition shape

Hydrogel Design

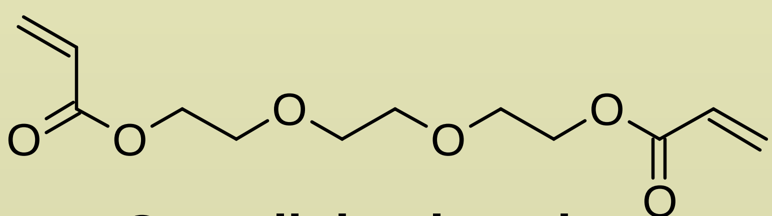
Particle design via copolymerization



pH sensitive/polyelectrolytes



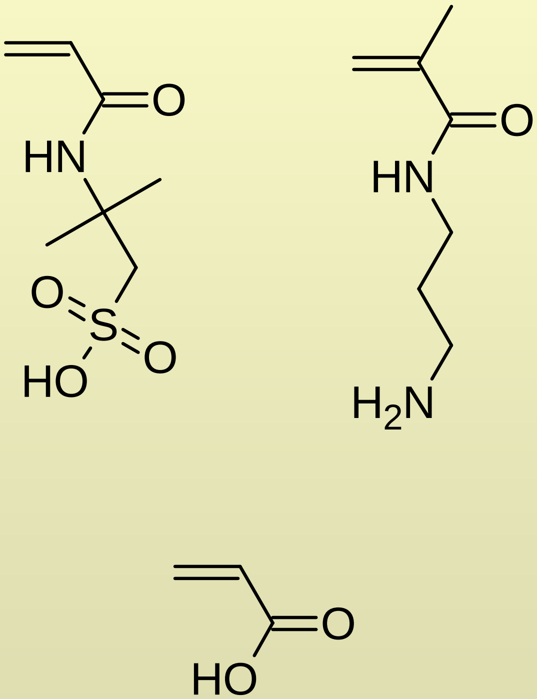
thermosensitive



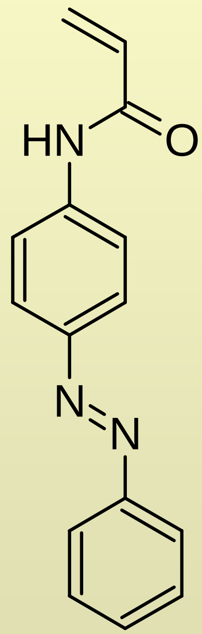
Crosslinker length

Hydrogel Design: Responsivity/Sensitivity

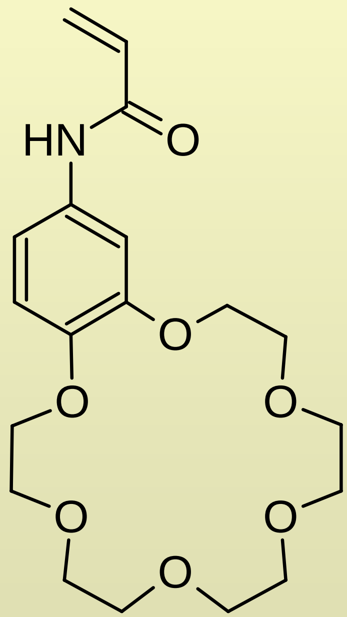
Electric Field



Light

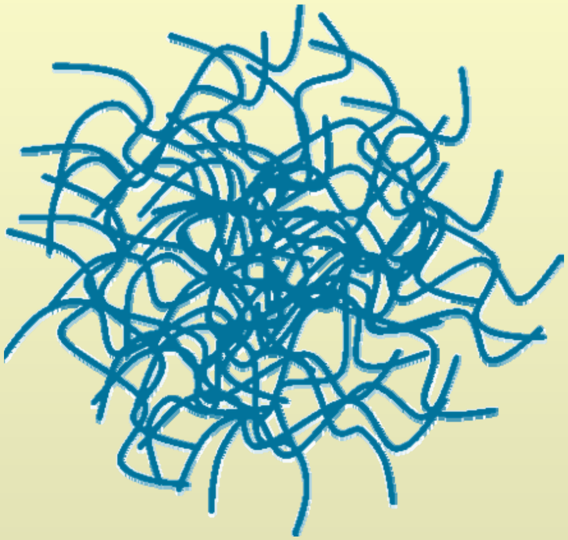


Metal Ions

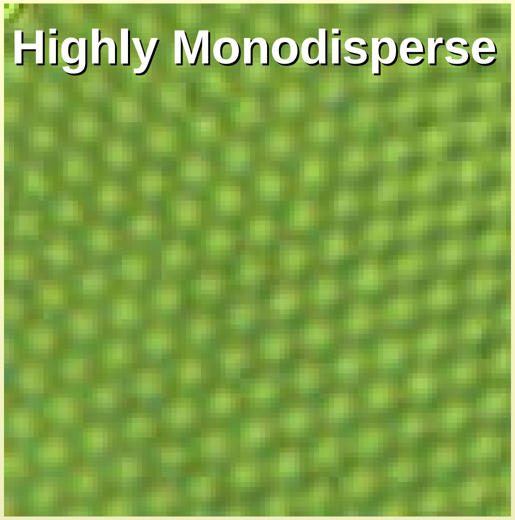


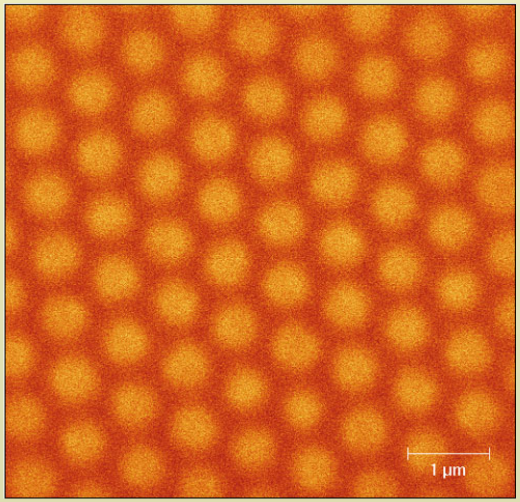
Hydrogel Particle Characteristics

Infinite Spherical Network

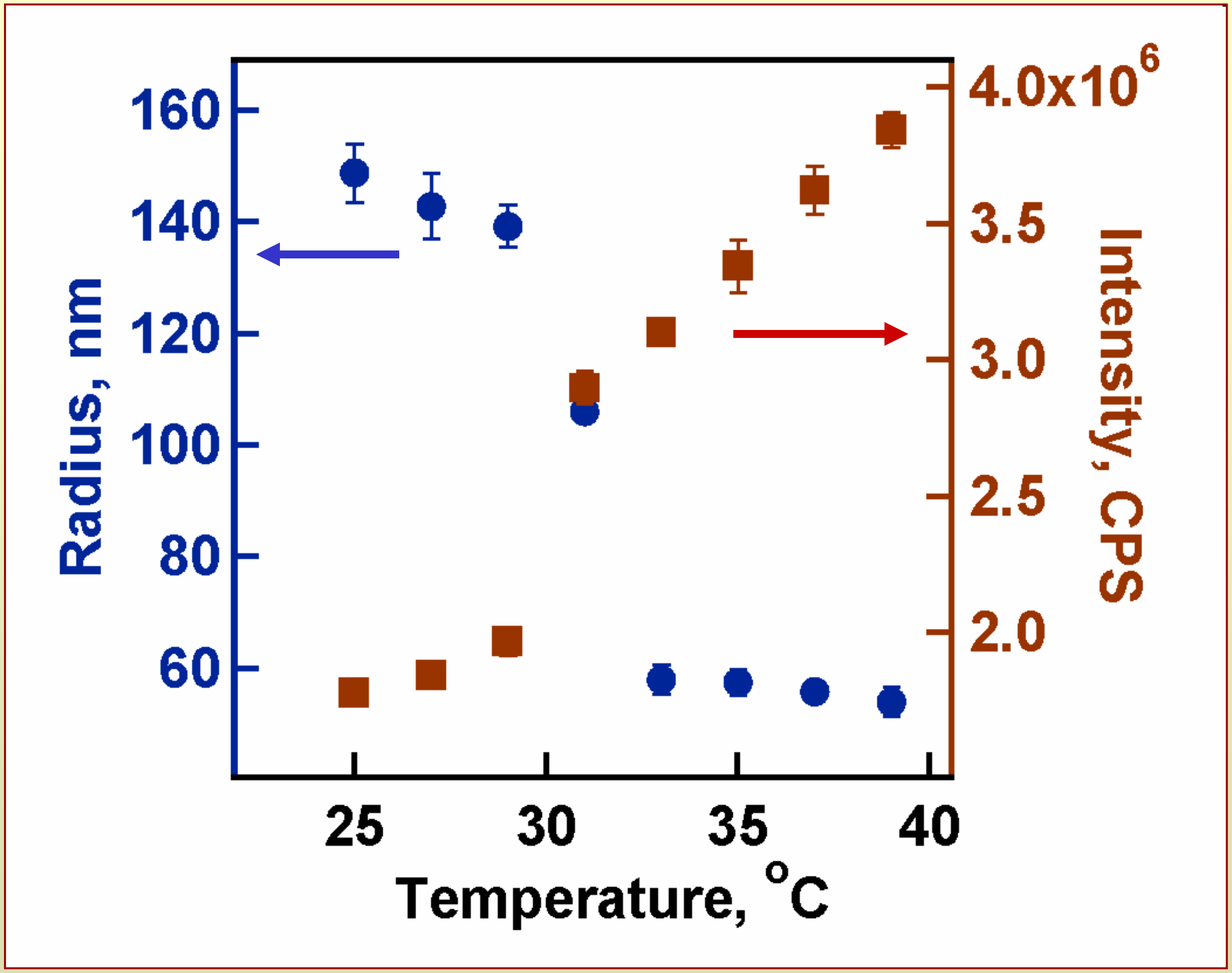


High water content (90-99% v/v)
a microgel is effectively *all surface area*





Volume Phase Transitions

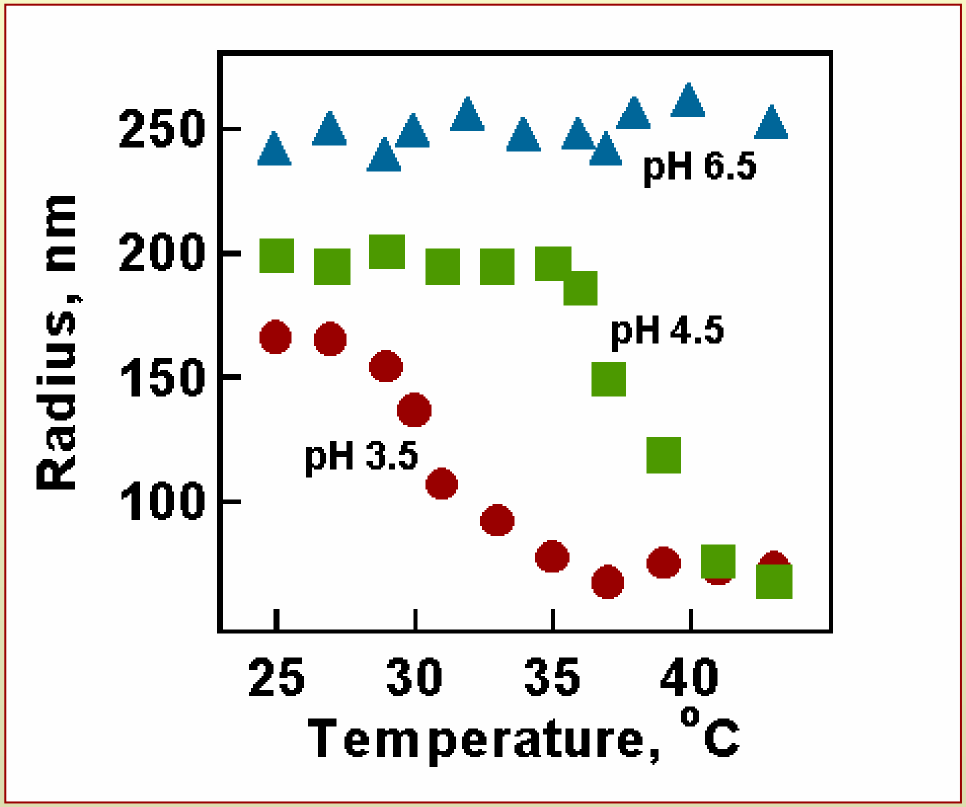


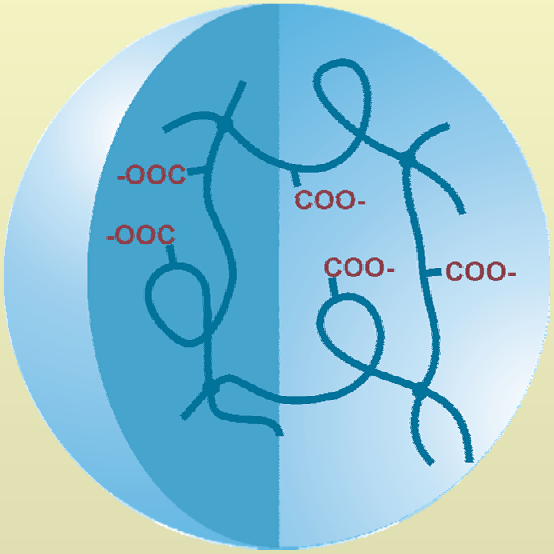
2 mol% crosslinked pNIPAm in water

Dynamic Light Scattering (Photon Correlation Spectroscopy)

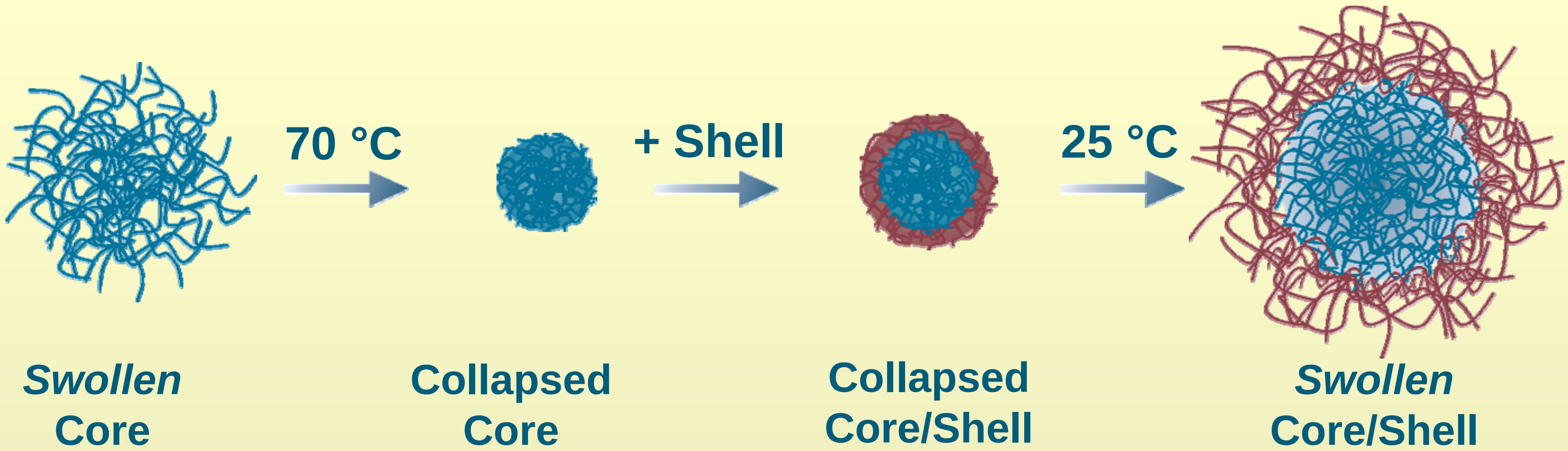
Multiresponsive Hydrogels

pNIPAm-*co*-Acrylic Acid – pH and temperature dependent





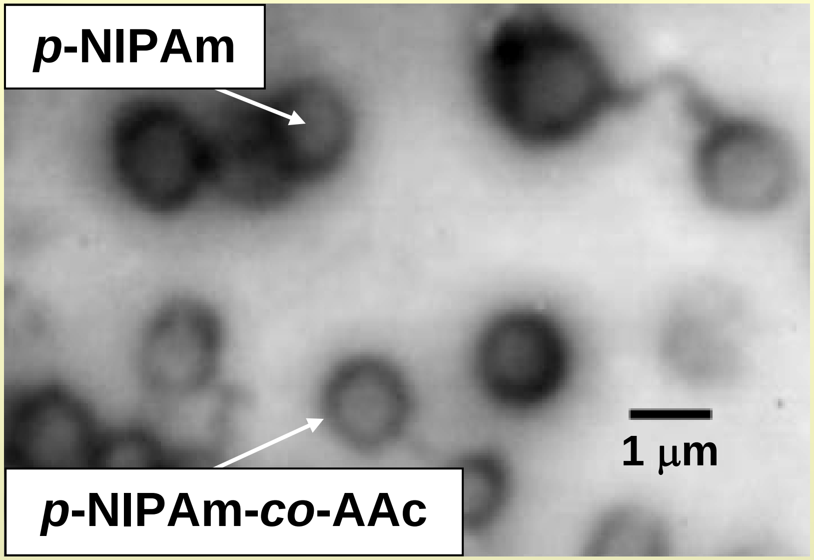
Core/Shell Synthesis

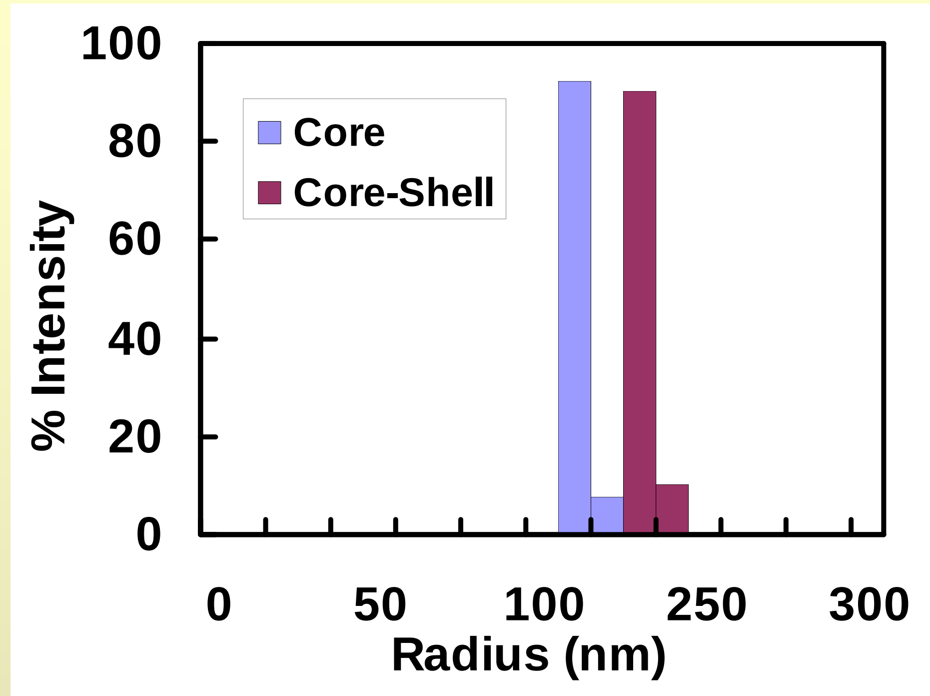


Collapsed core particles act as preexisting hydrophobic nuclei onto which growing polymer *(the shell)* adds.

Must control hetero-nucleation vs. homonucleation to achieve monodisperse populations.

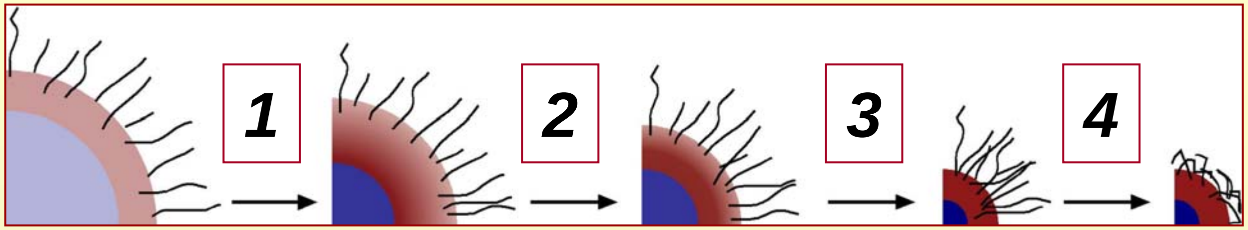
Core/Shell Particle Characterization





Light scattering data typically show an increase in particle size between core and core/shell with invariant polydispersity.

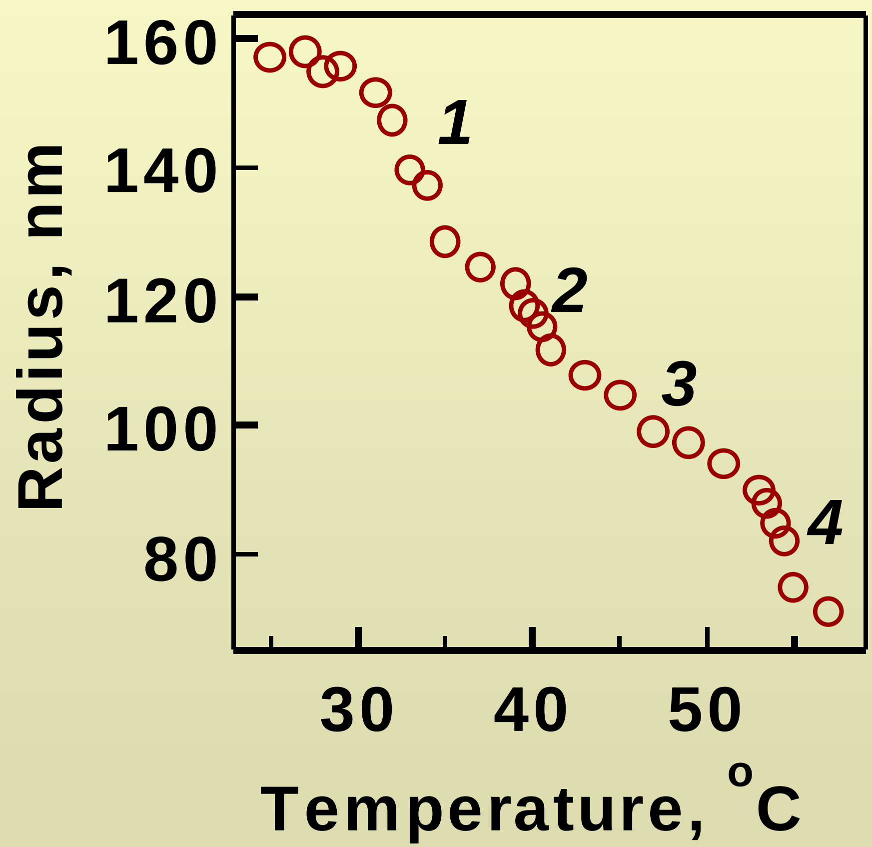
Multiresponsive Core-Shells



***p*-NIPAm Core**

***p*-NIPAm -*co*-AAc Shell**

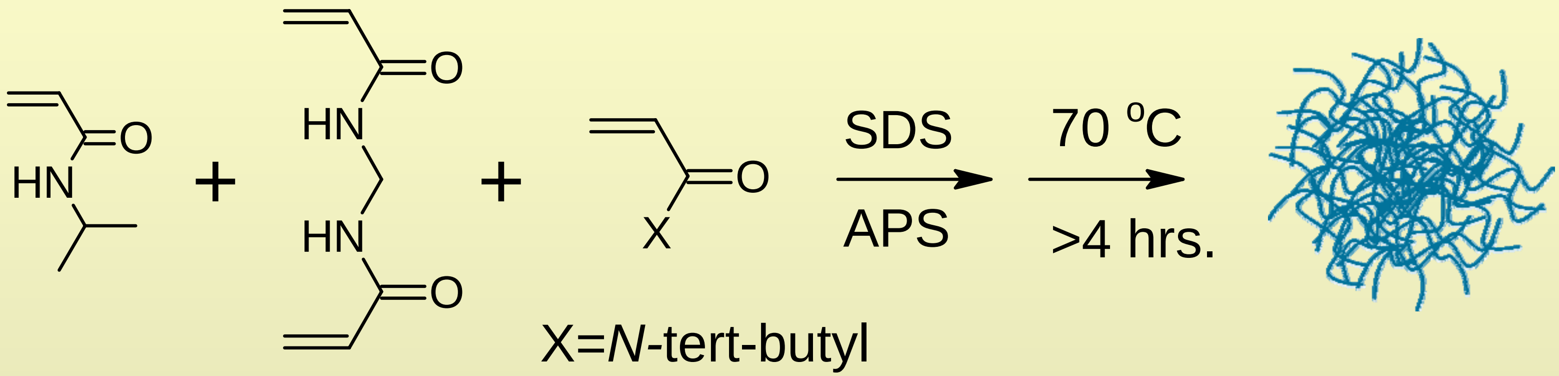
pH 6.5



Jones, C. D., Lyon, L. A. *Macromolecules*, **2000**, *33*, 8301-8306.

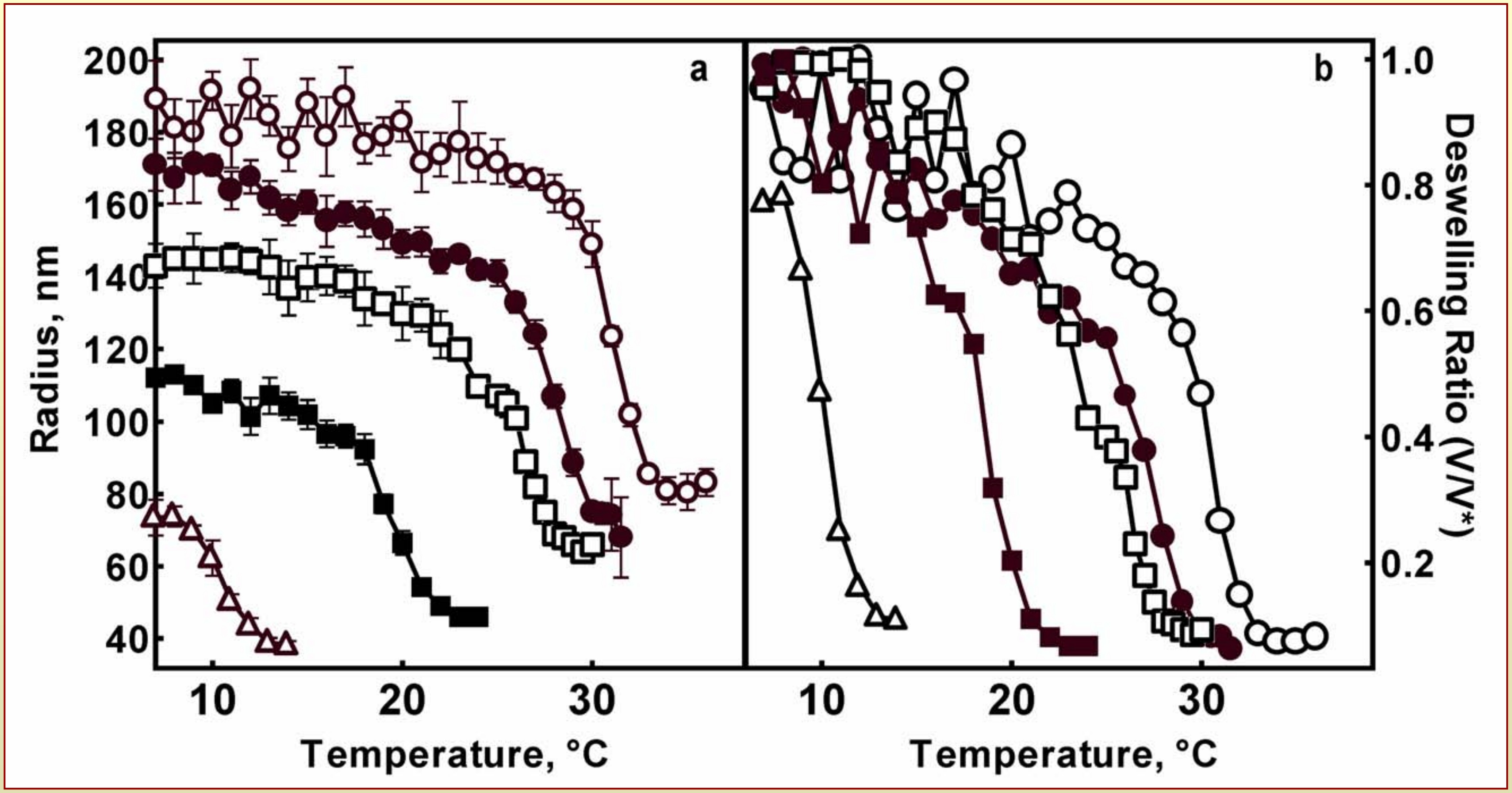
Phase Transition Tuning

Phase transition temperature determined by hydrophilic/hydrophobic balance.



Ratio of *N*-isopropyl to *N*-tert-butyl determines transition point.

Phase Transition Tuning

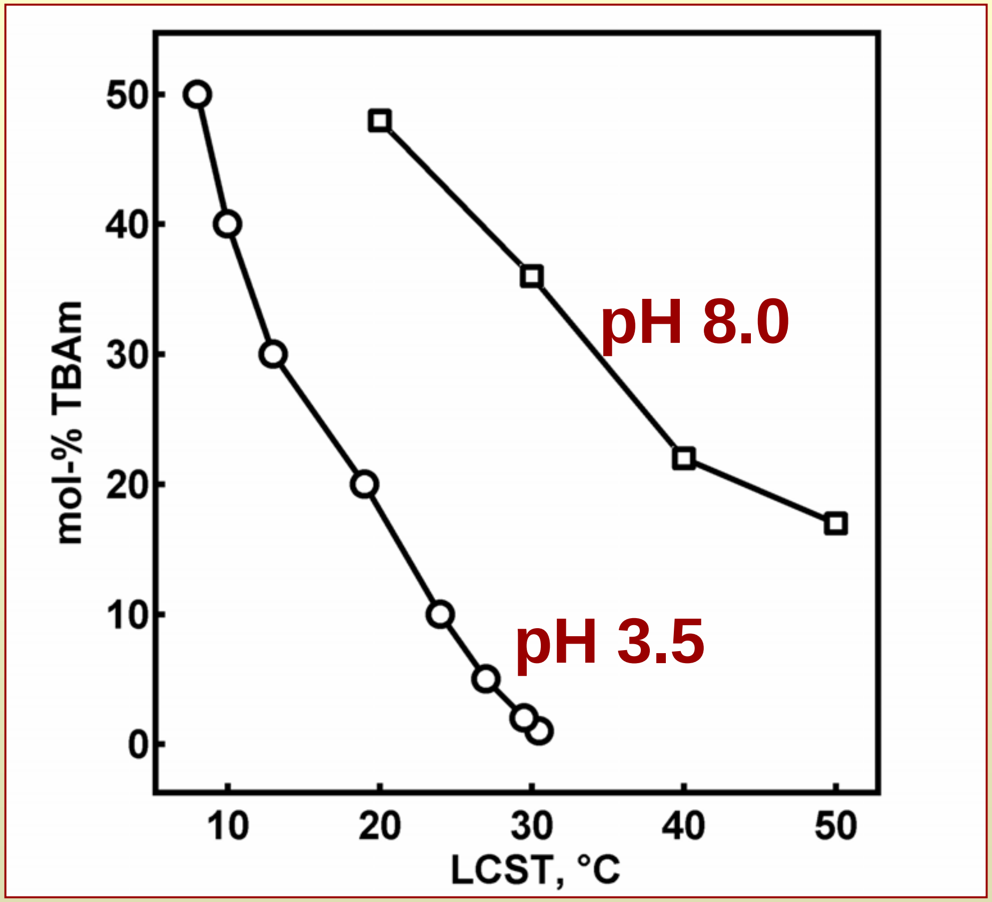


(○) 1 mol-%, (●) 5 mol-%, (□) 10 mol-%, (■) 20 mol-% and (△) 40 mol-% TBAm

Debord, J. D.; Lyon, L. A. *Langmuir*, **2003**, *19*, 7662-7664.

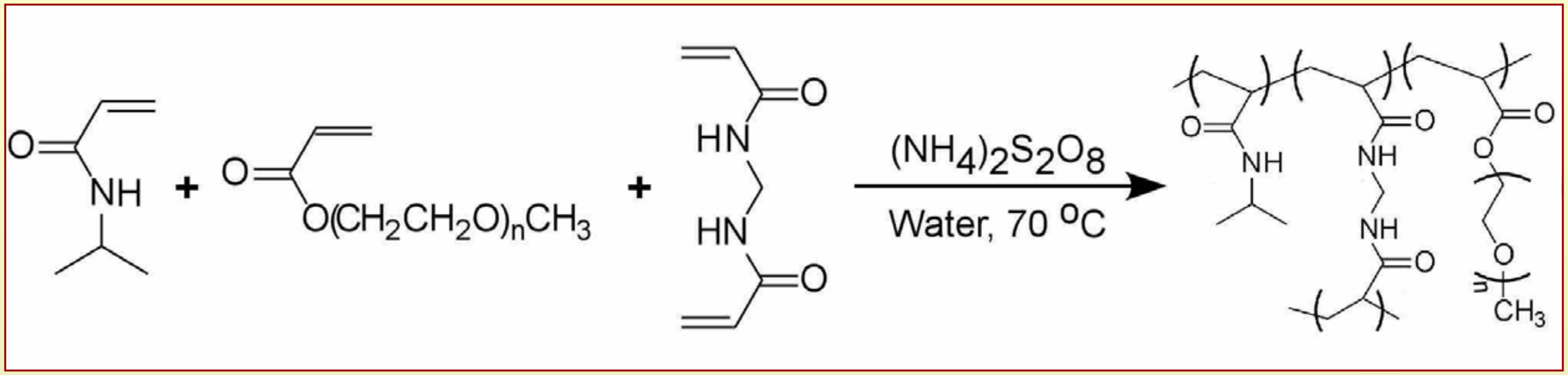
Phase Transition Tuning – pH and Hydrophobicity

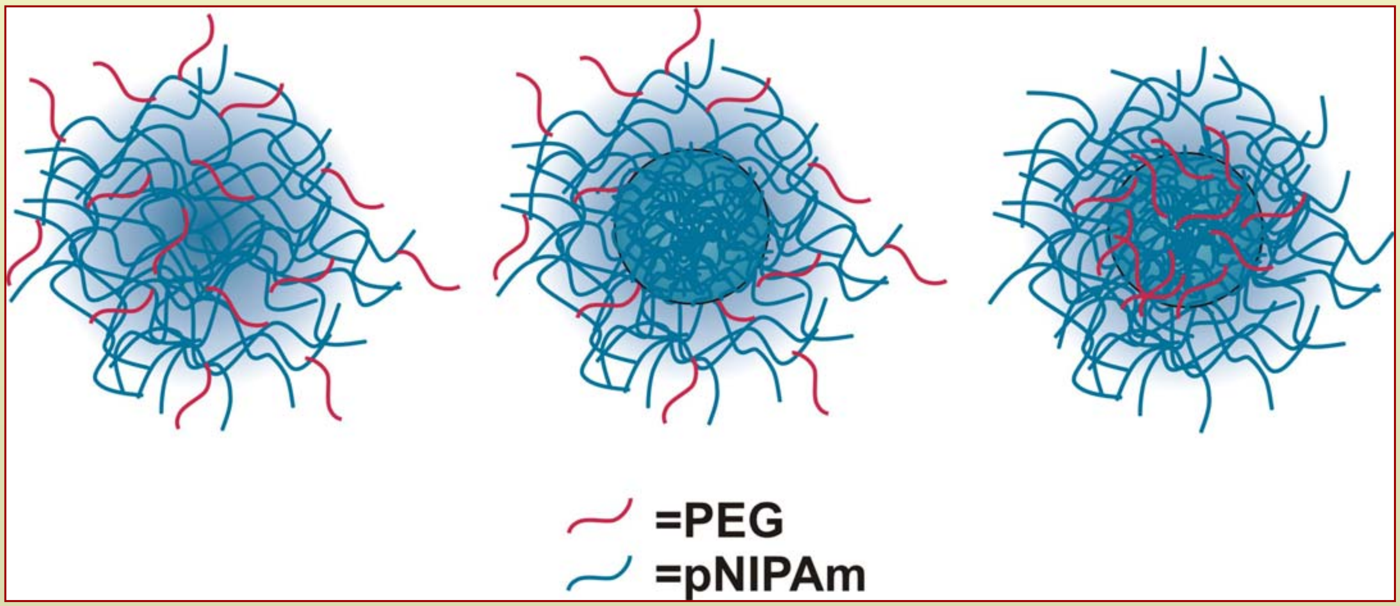
Poly(*N*-isopropyl acrylamide-*co*-*N*-tert-butyl acrylamide-*co*-acrylic acid) microgels – electrostatic repulsion mediates hydrophobic collapse.



Multi-Functional Nanogels

PEG-grafted "core" and core/shell particles

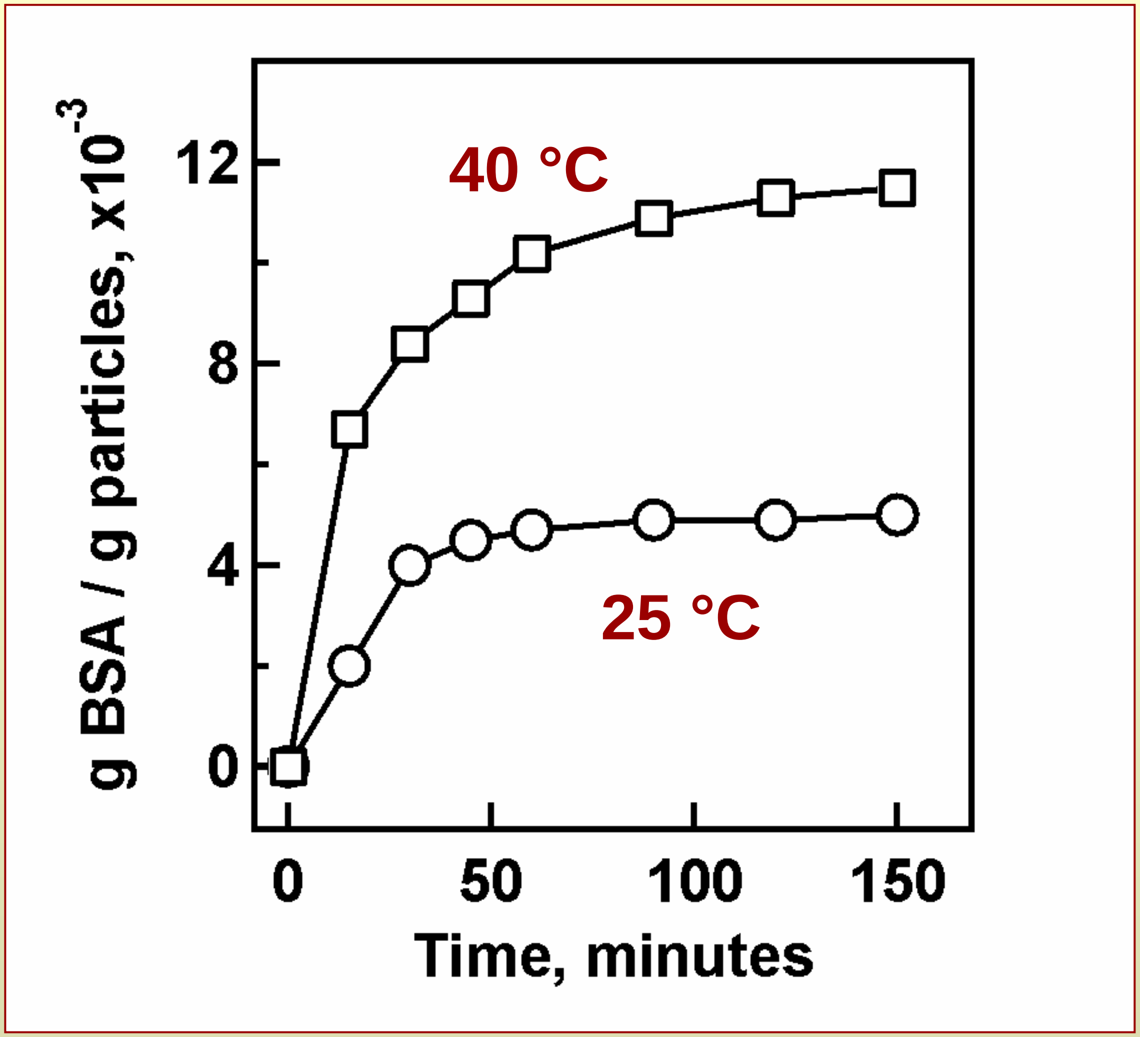




How does PEG-grafting impact protein adsorption?

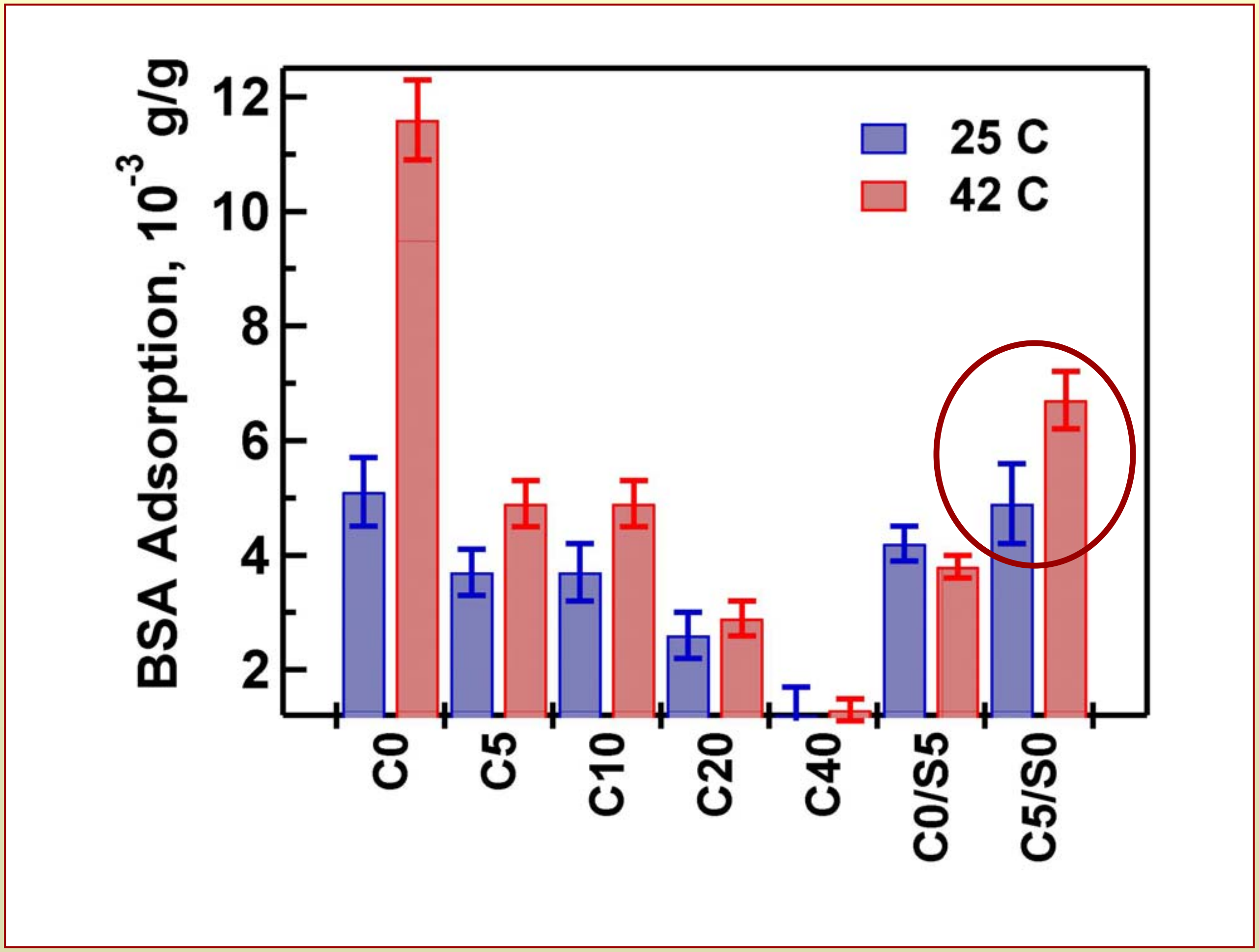
Multi-Functional Nanogels

“Bare” pNIPAm microgels (no PEG) display strong T-dependent protein adsorption. Below phase transition = hydrophilic; above phase transition = hydrophobic.



Multi-Functional Nanogels

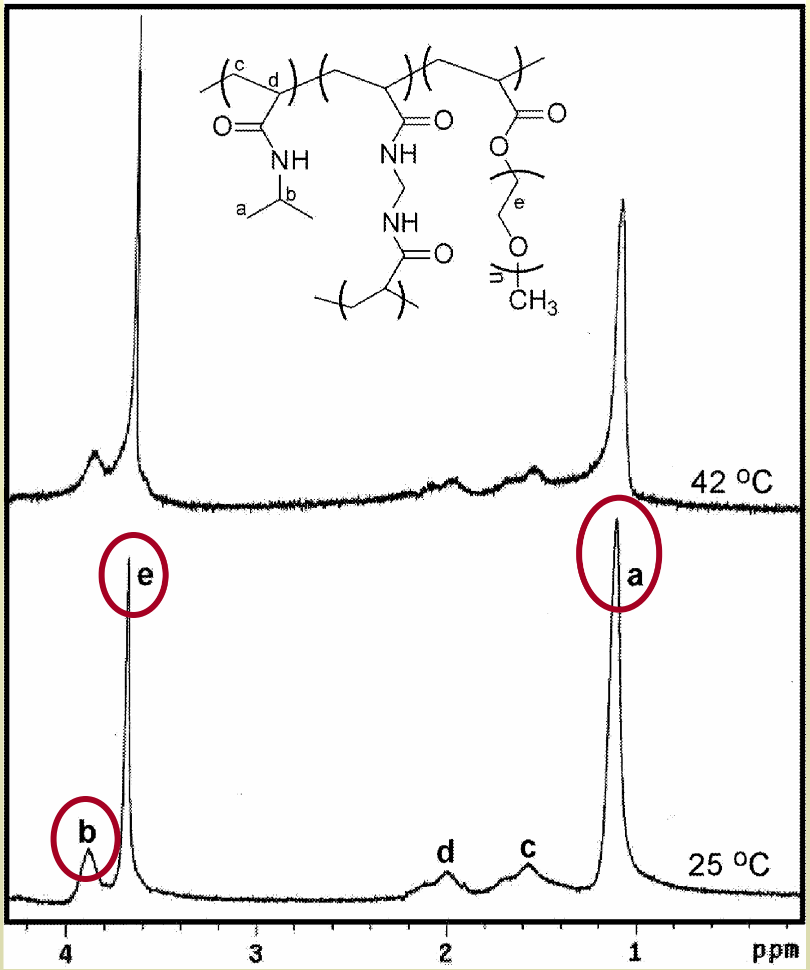
PEG-Modification renders collapsed particles *hydrophilic.*

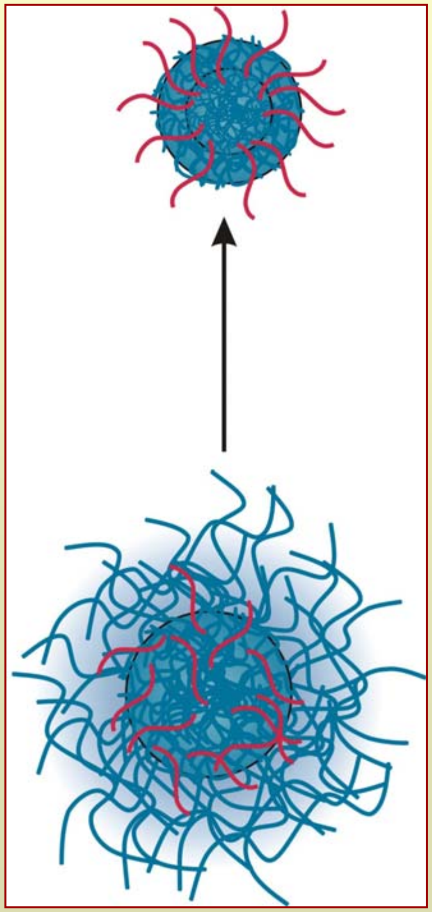


Gan, D.; Lyon, L. A. *Macromolecules*, **2002**, *35*, 9634-9639.

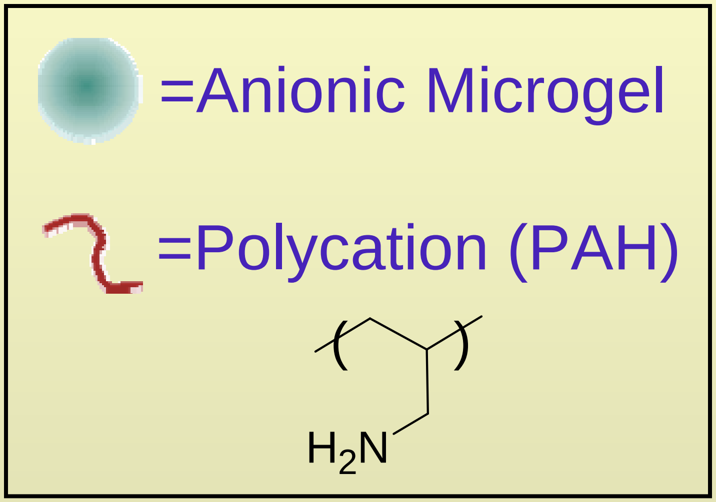
Multi-Functional Nanogels

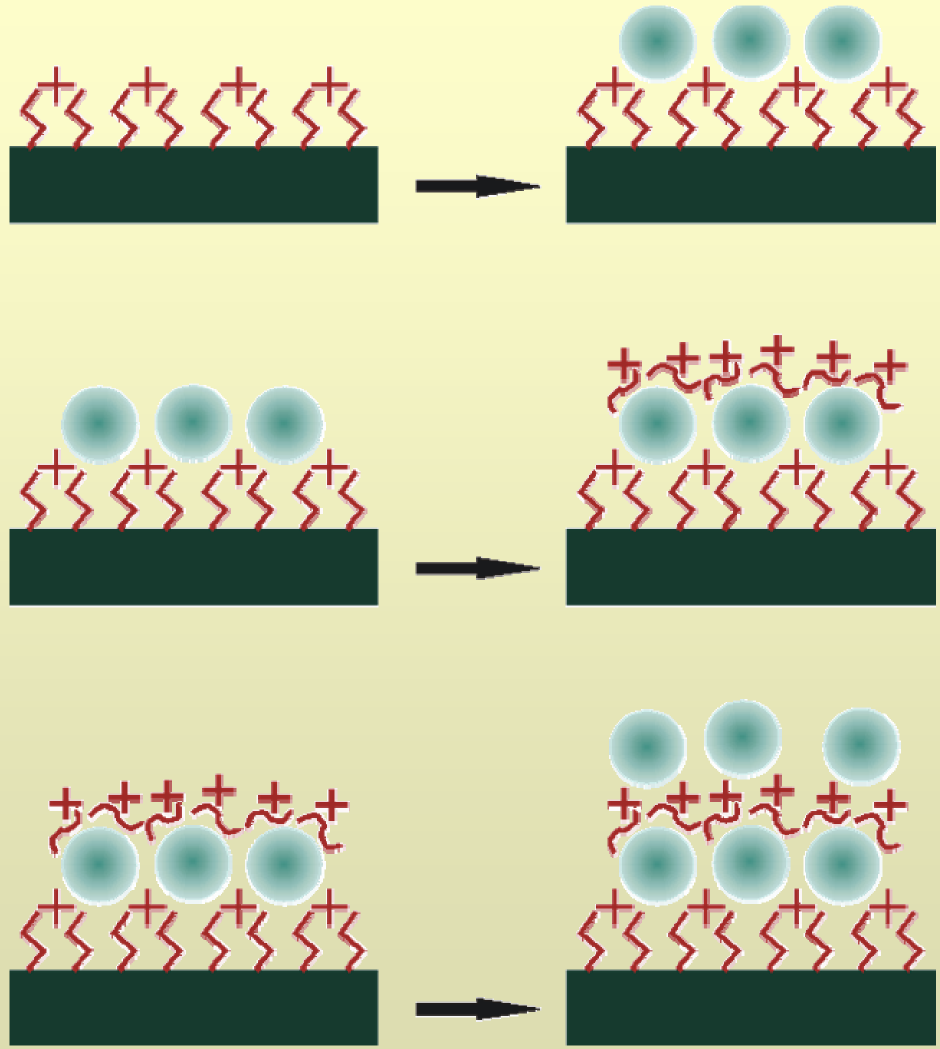
NMR Analysis indicates a relative change in polymer hydration – PEG “core” phase separates to shell surface.





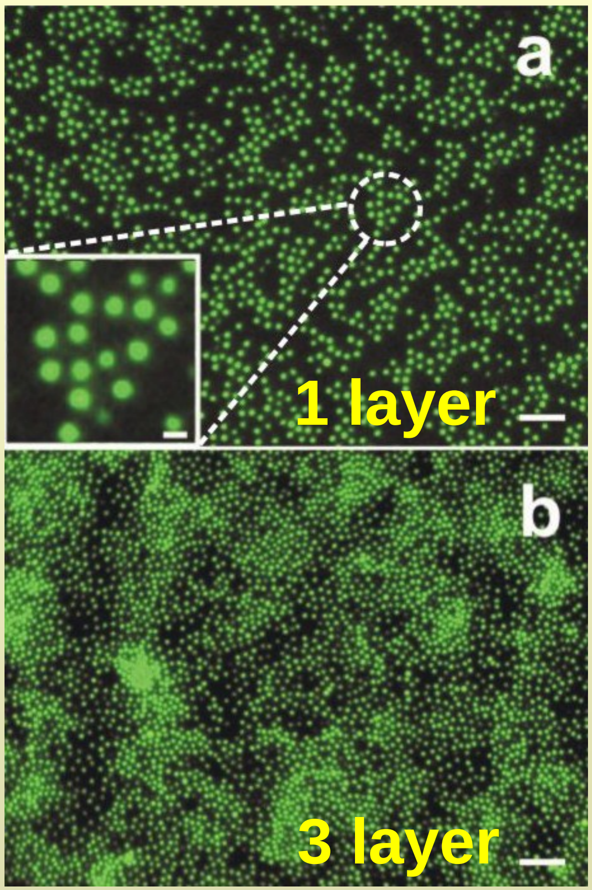
Polyelectrolyte/Microgel Multilayers



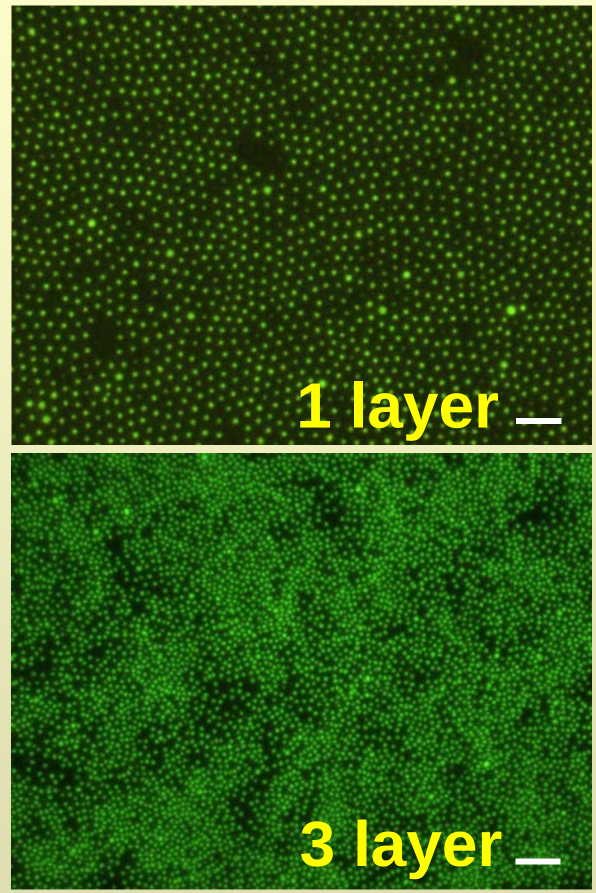


Microgel Film Formation

Passive Adsorption



Spin Coating



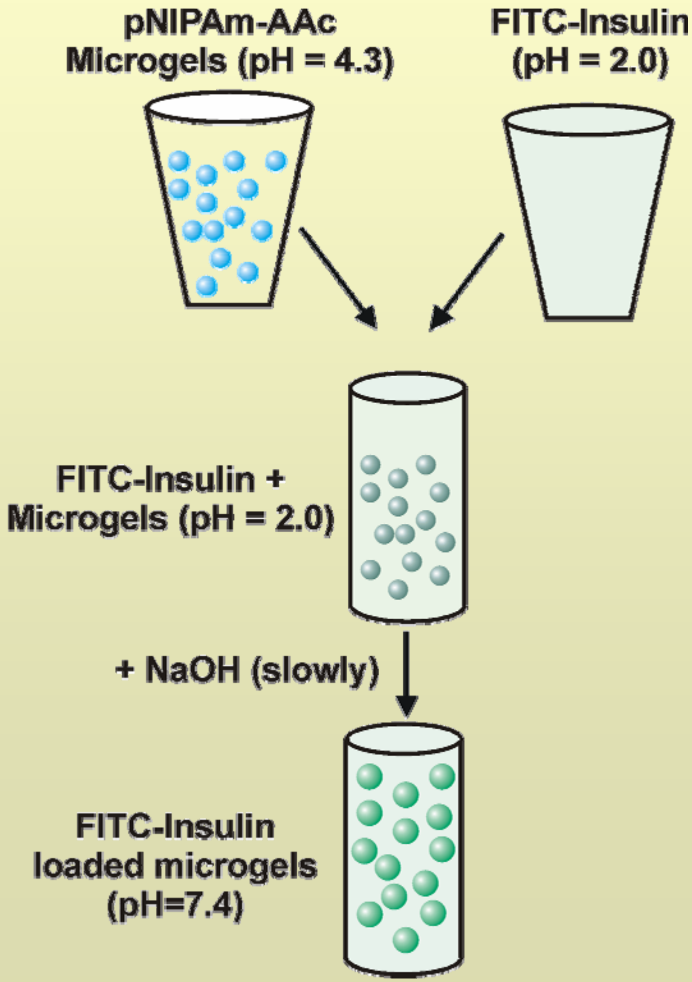
pNIPAm-AAc = polyanion

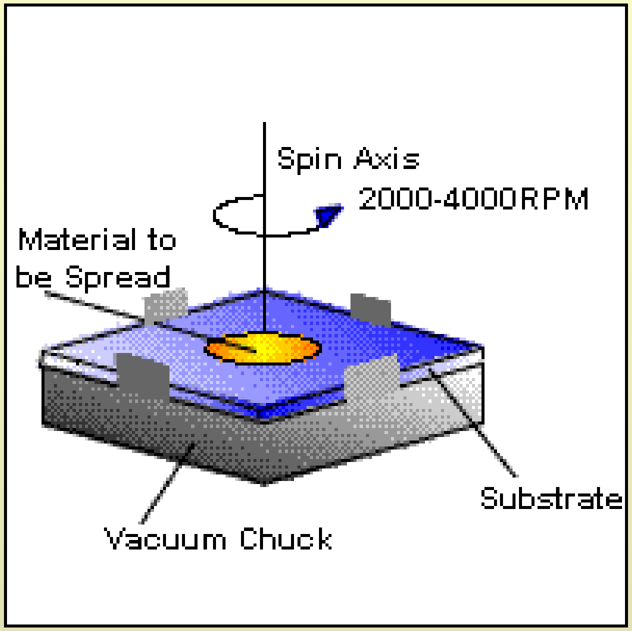
poly(allylamine)•HCl (PAH) = polycation

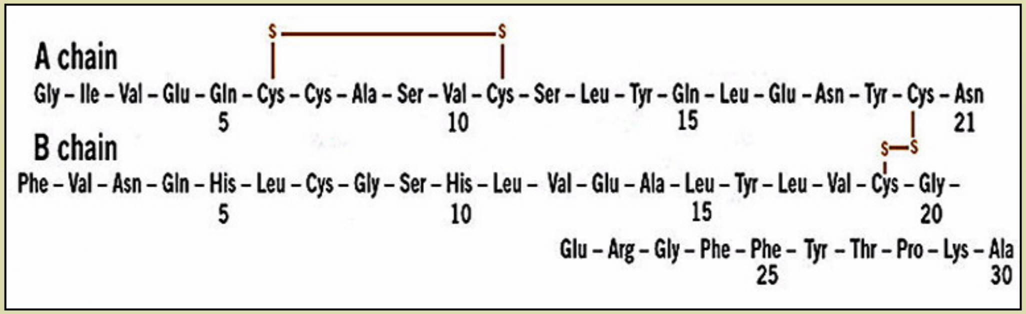
Serpe, M. J.; Jones, C. D.; Lyon, L. A. *Langmuir,* **2003,** *19*, 8759-8764.

Co-Deposition of Macromolecules

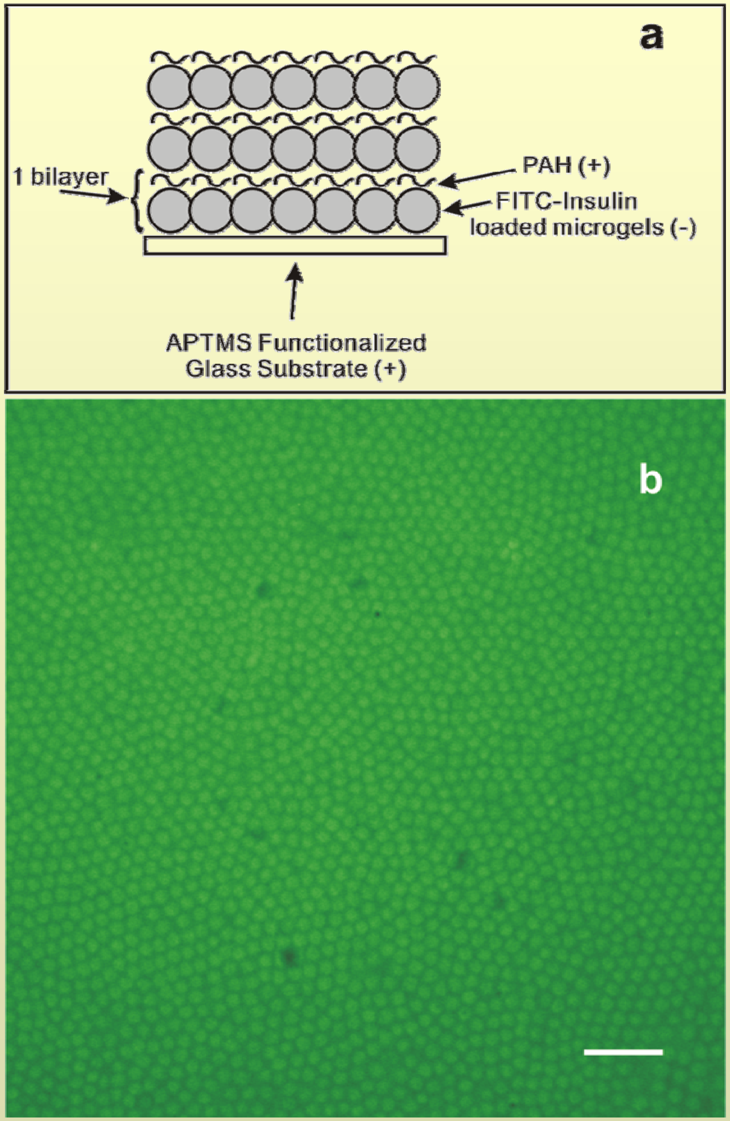
Insulin-impregnated films obtained via incubation of particle solution with peptide.

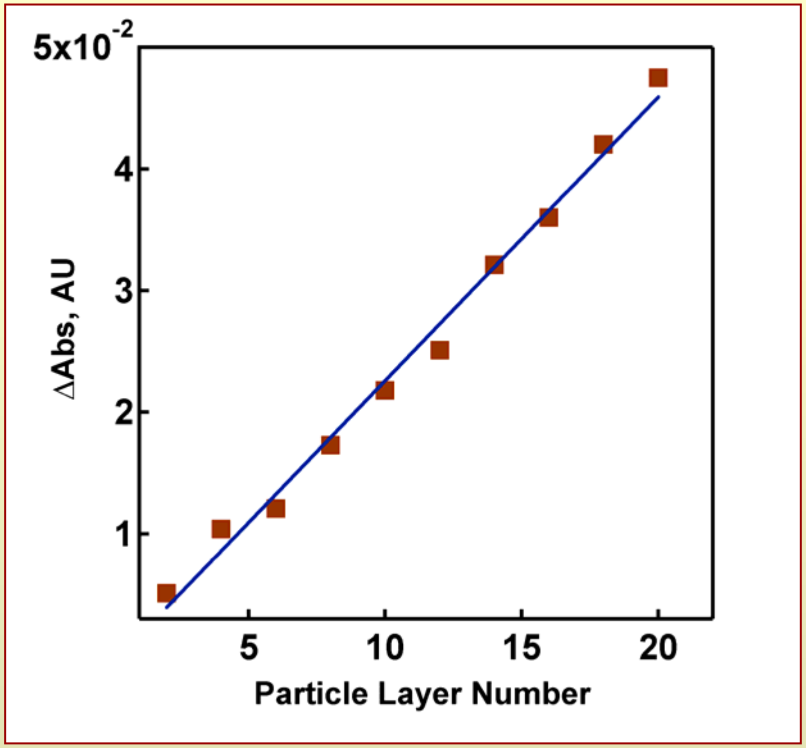






Labeled Insulin Incorporation

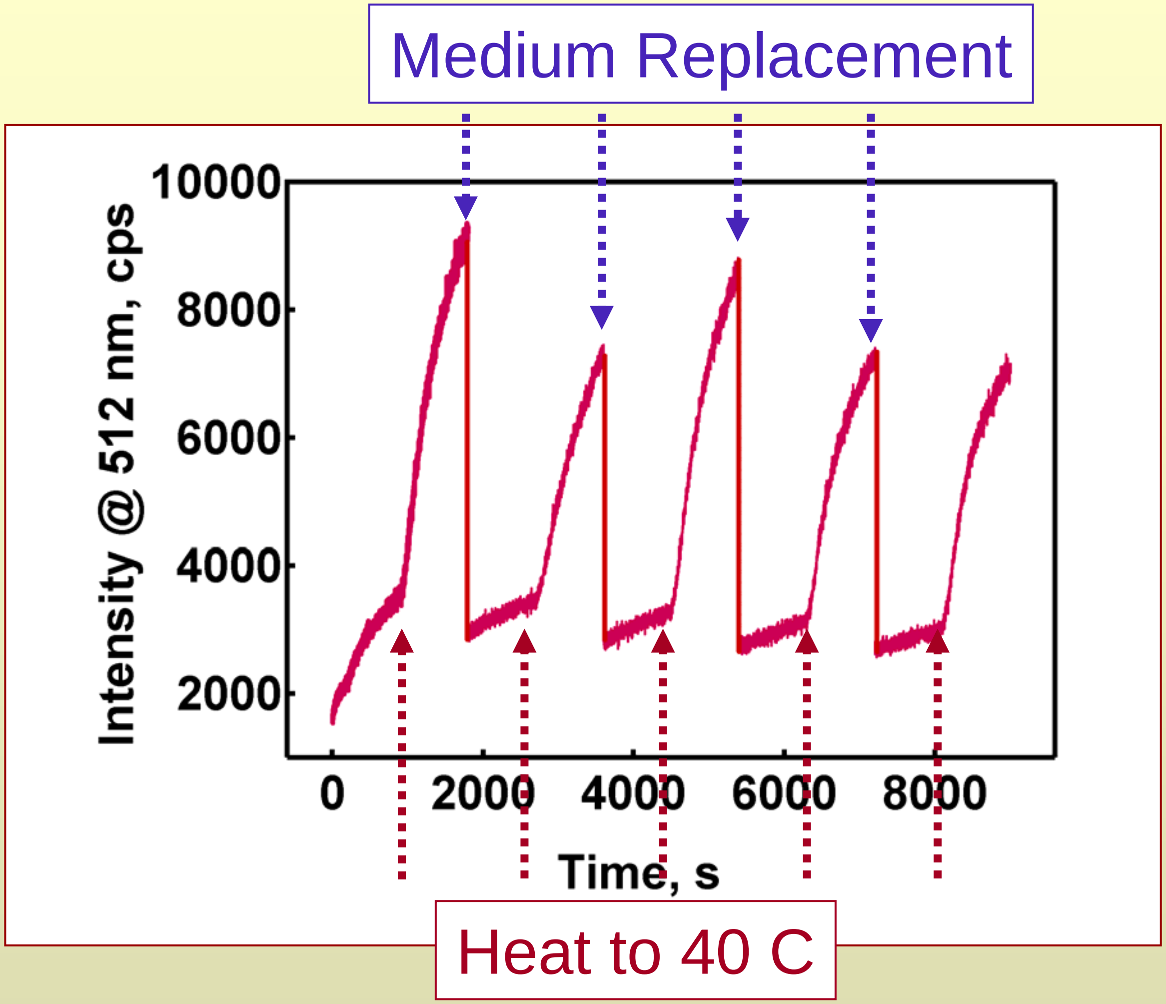


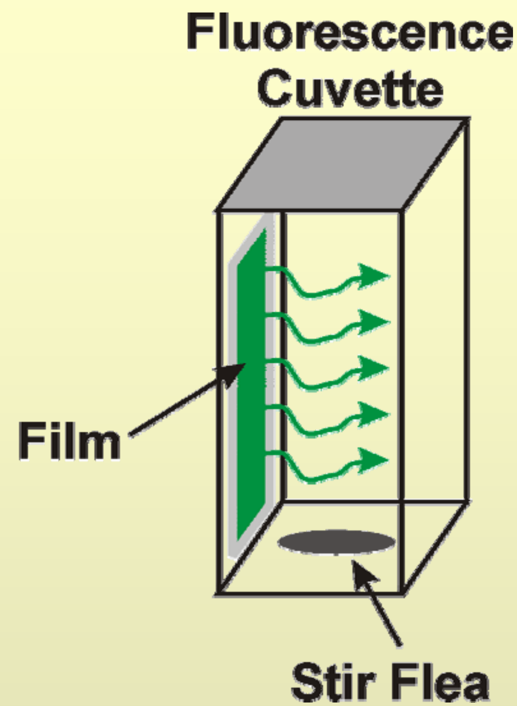


Linear increase in insulin content with particle layer number.

Nolan, C. M.; Serpe, M. J.; Lyon, L. A. *Biomacromolecules* **2004**, *in press.*

Pulsatile Insulin Release

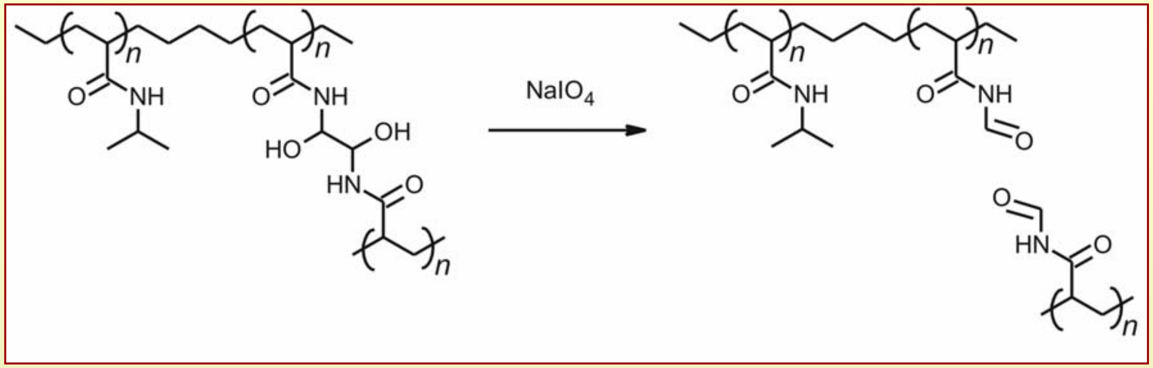




9-layer film in
0.02M PBS
pH=7.4

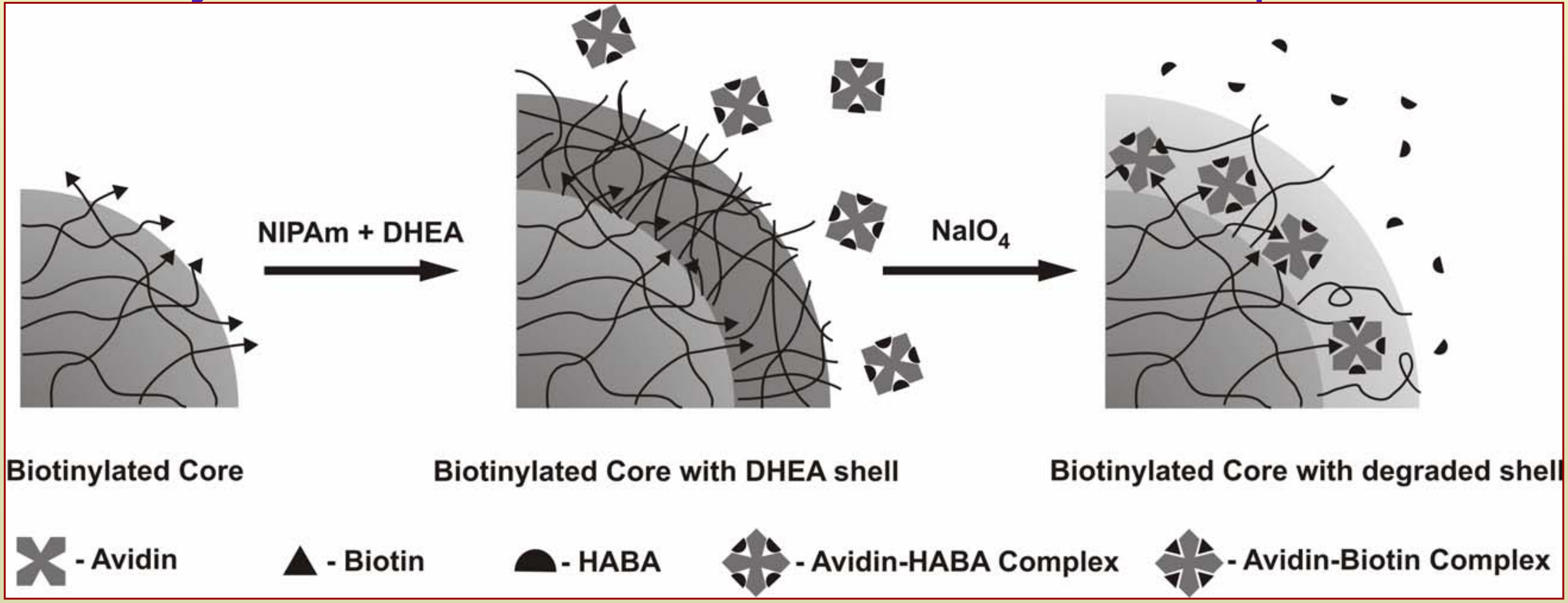
Fast, pulsatile insulin release during film deswelling.

Bio-Functional Nanogels with Designed Topology



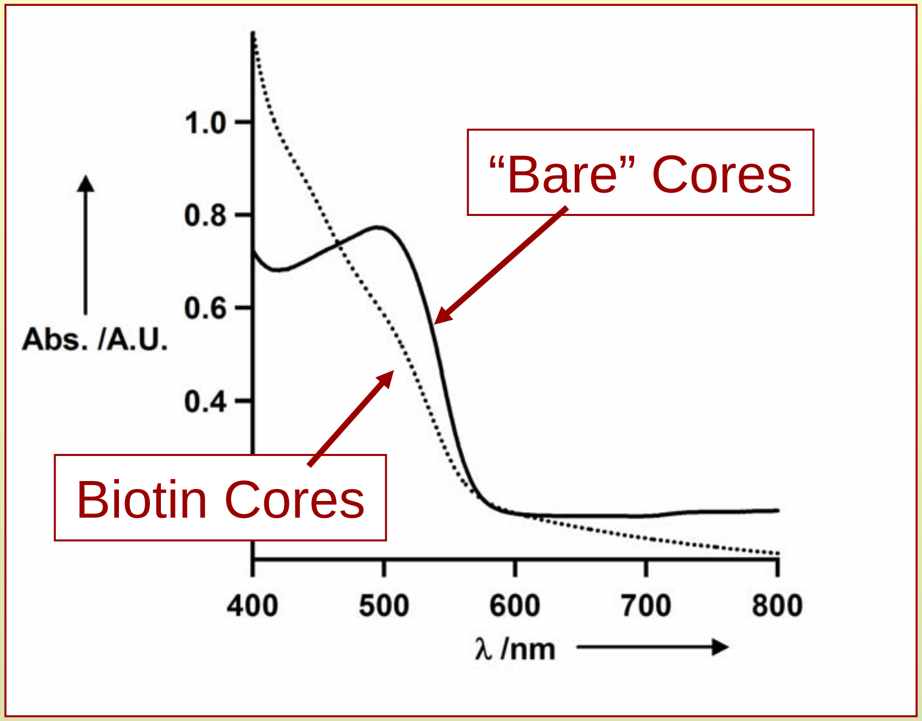
Cleavable diol crosslinks (DHEA)

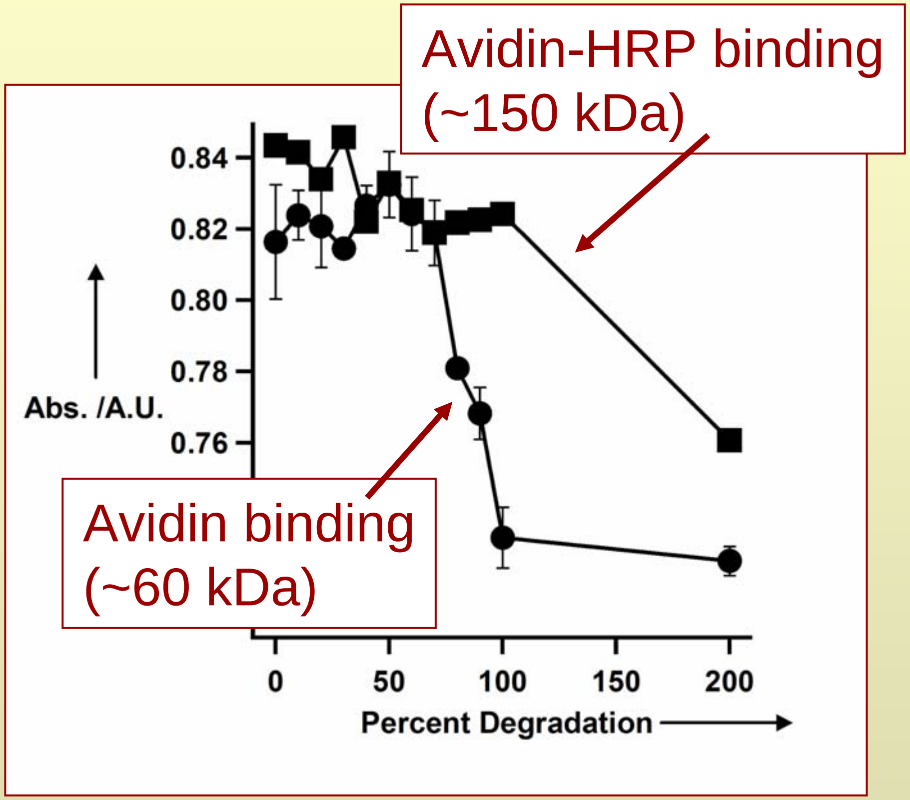
Biotinylated core beneath a shell with tunable pore size.



Bio-Functional Nanogels with Designed Topology

HABA assay for biotin-avidin binding



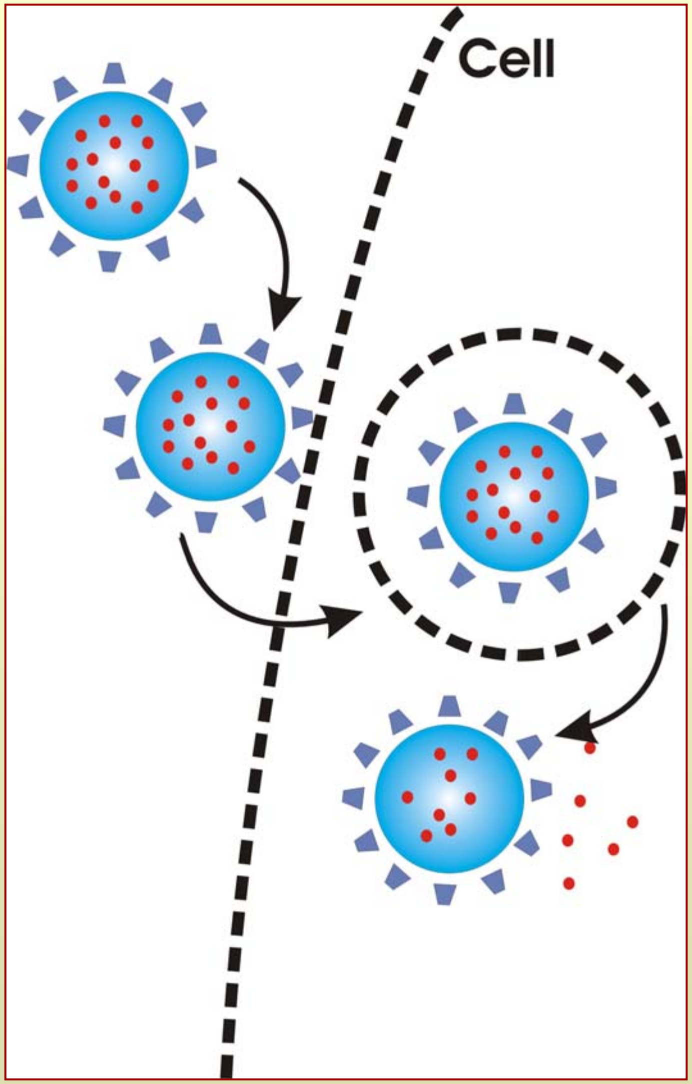


Partially degraded shell → MW dependent binding.

Towards a Smarter Nanogel

Drug/Gene/RNA delivery
Goals:

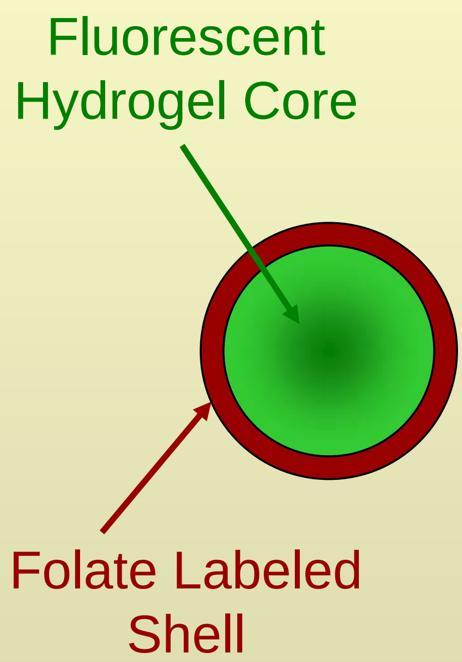
1. Long Circulation Time
2. Cell-Specific Targeting
3. Receptor Mediated Endocytosis
4. Endosomal Escape
5. Cytosolic or Nucleus-Localized Release

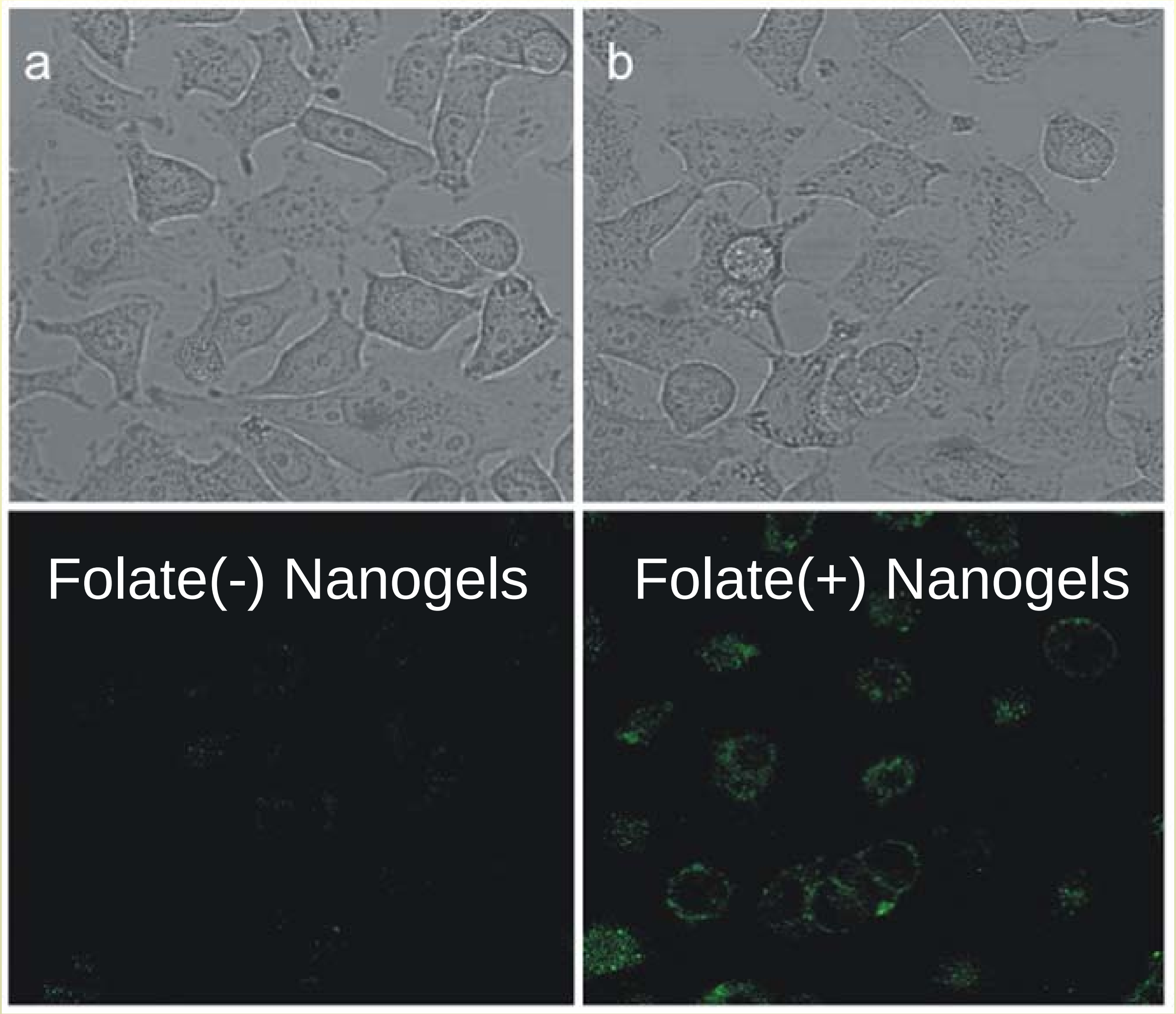


These steps comprise a state-dependent "program"

Cancer Targeting with Nanogels

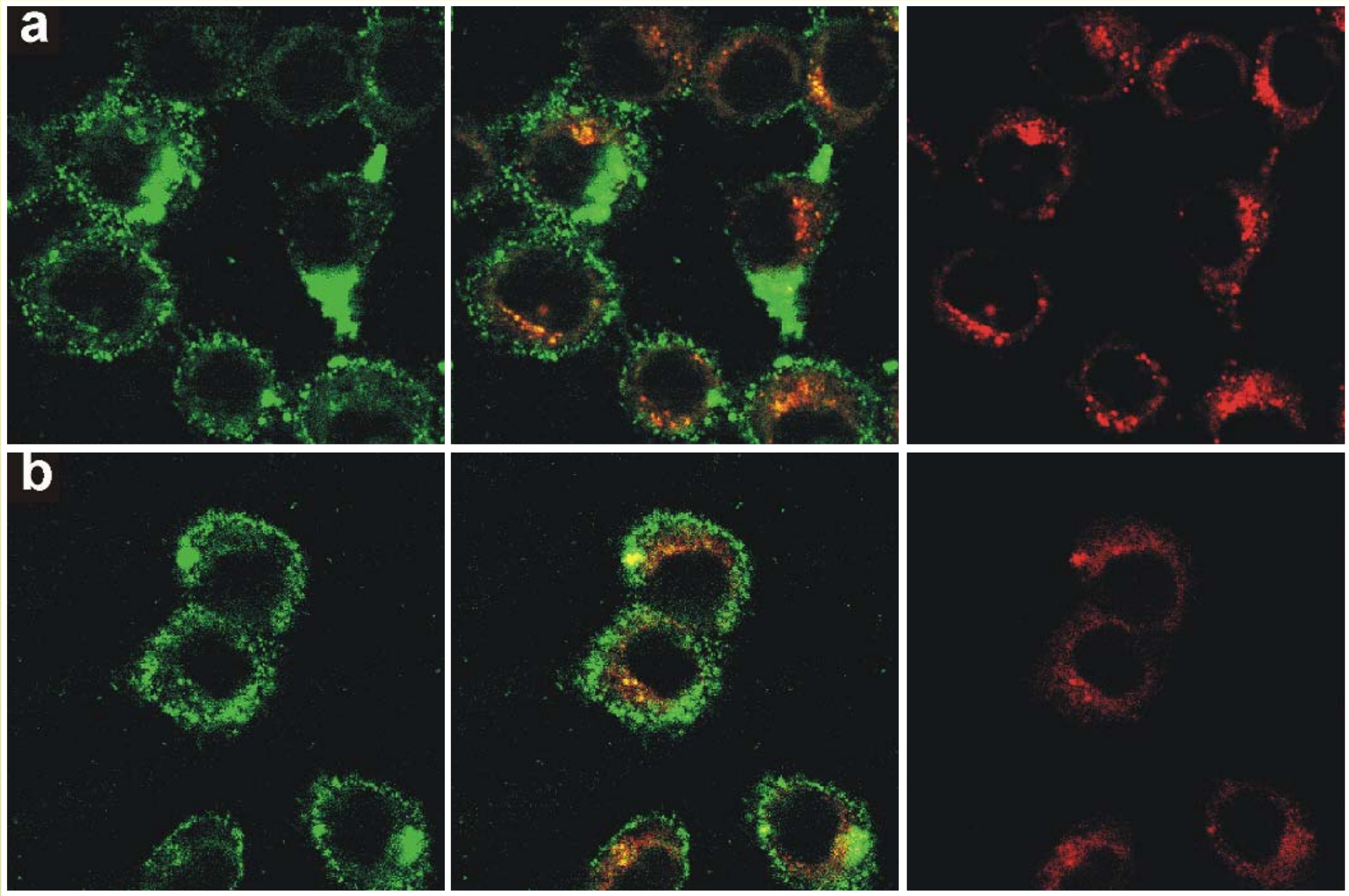
Folic acid - an effective ligand for targeting solid tumors.





Cancer Targeting with Nanogels

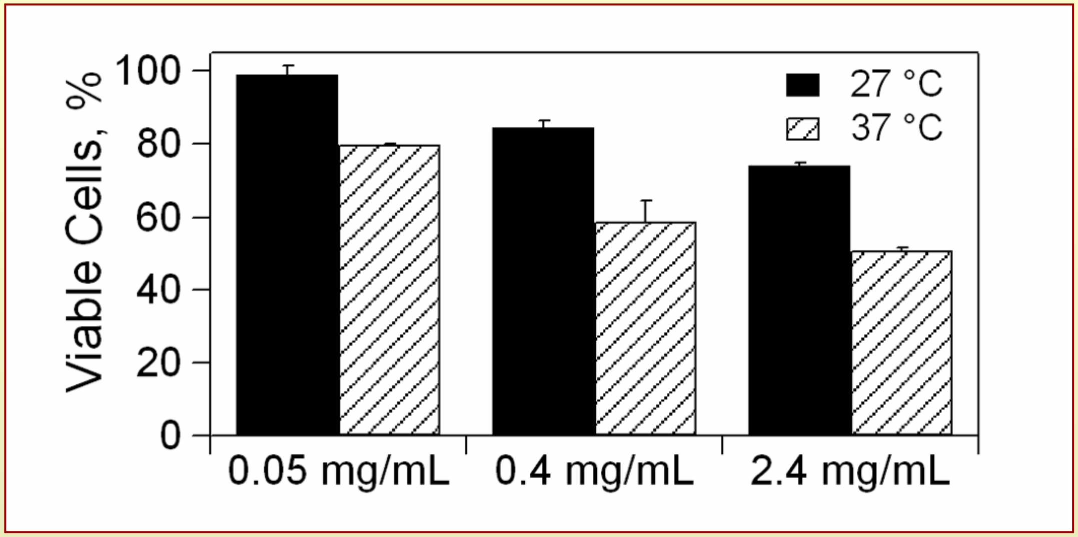
Dual staining (particle+lysotracker) illustrates endosomal escape.

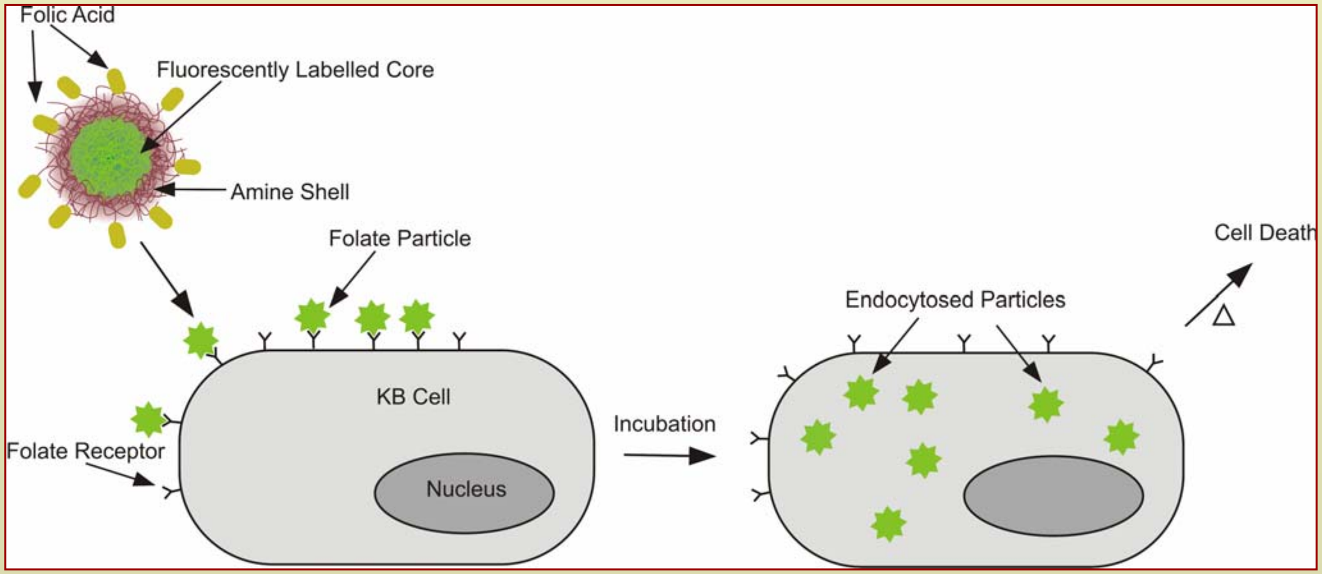


Nayak, S.; Lee, H.; Chmielewski, J.; Lyon, L. A., *submitted*.

Cancer Targeting with Nanogels

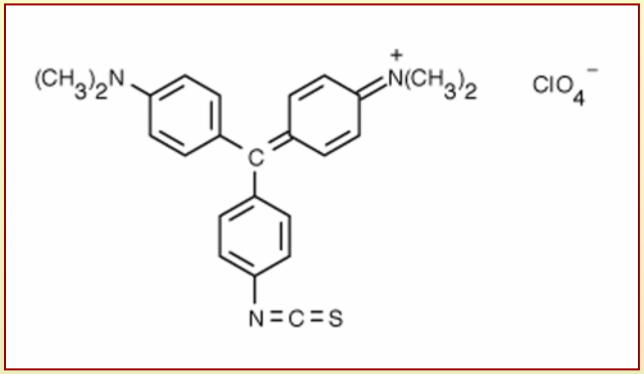
Thermal trigger induces cytotoxicity



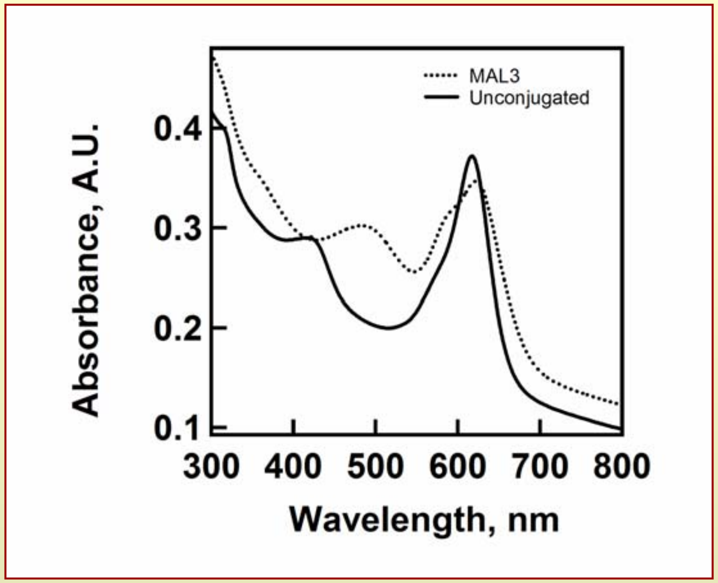


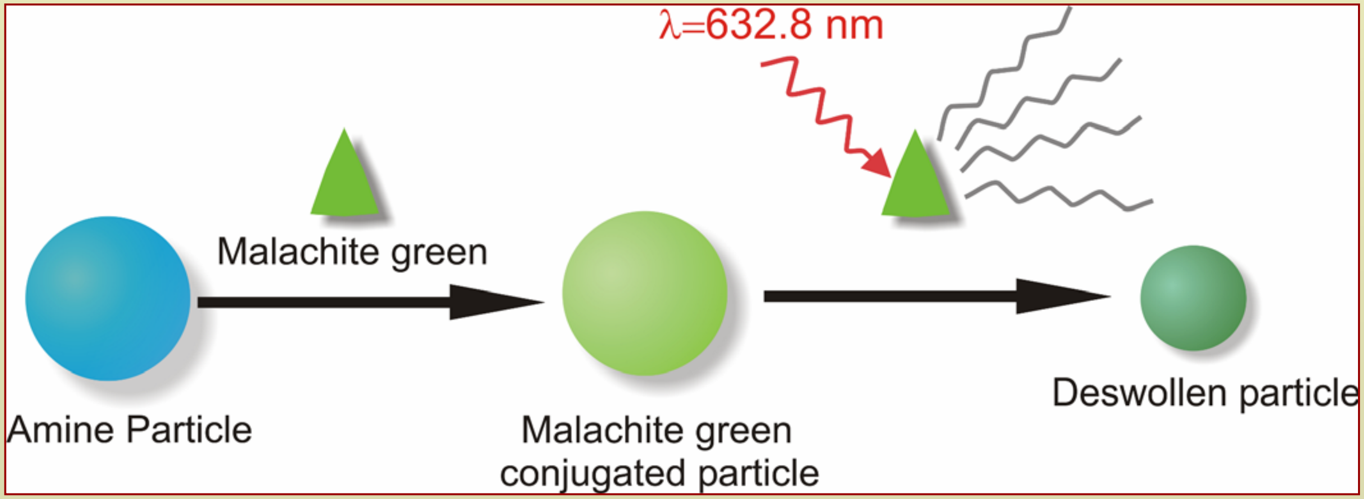
Other Stimuli: Photons

Photosensitive microgels via T-jump dyes

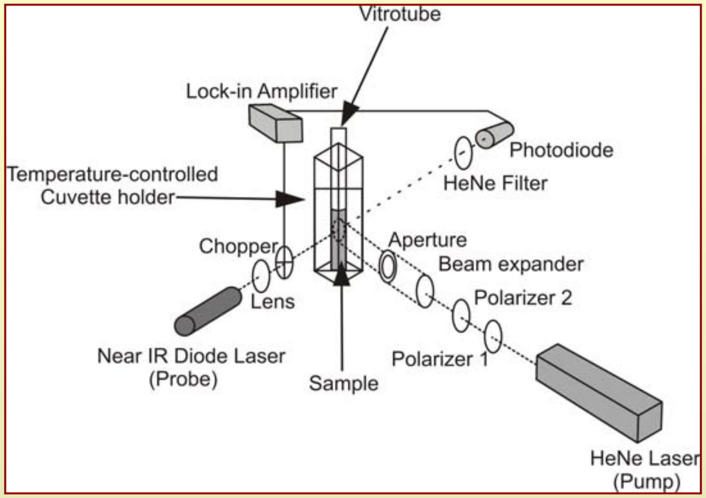


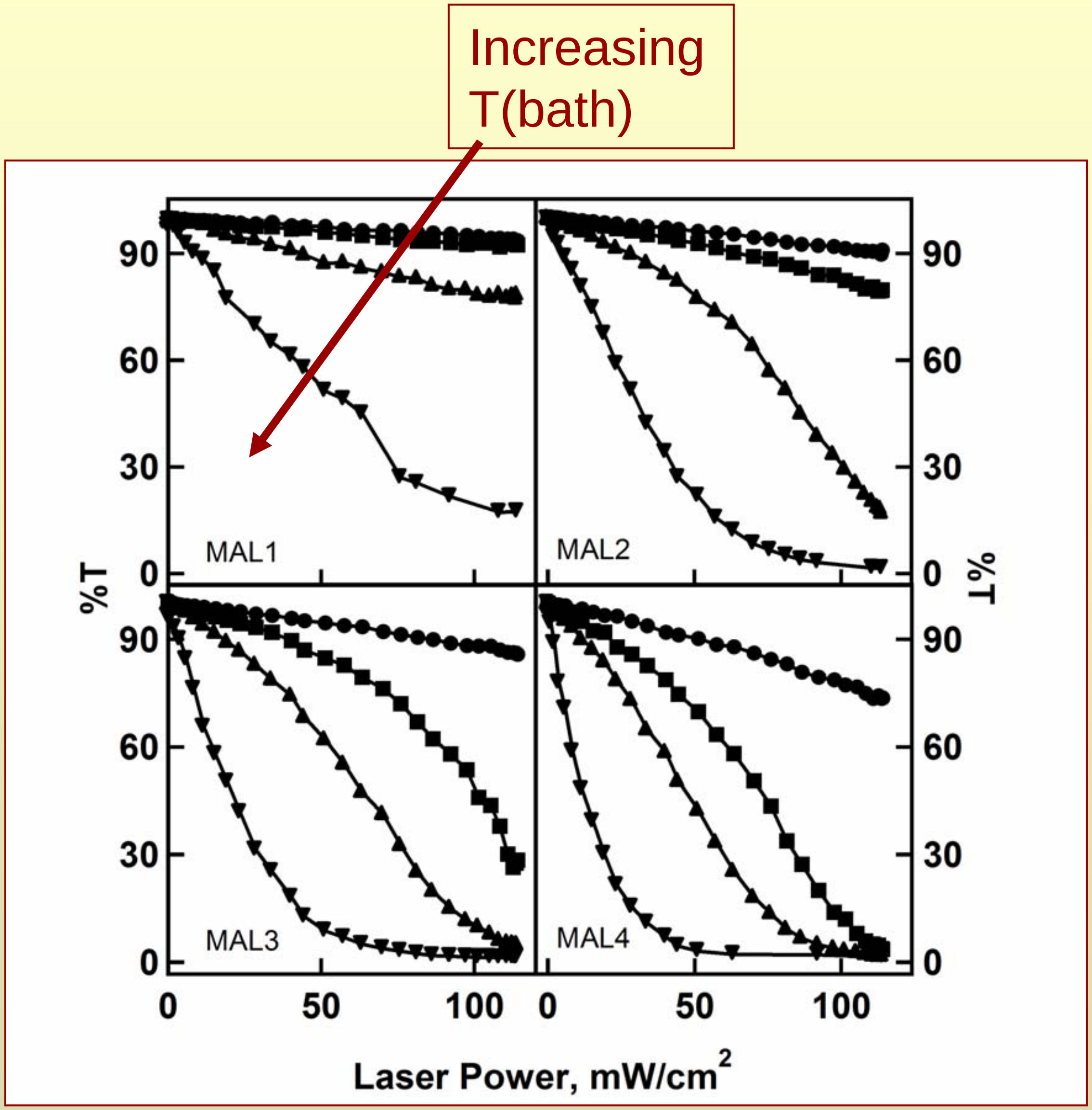
$\varepsilon = 150{,}000;\ \phi = 0$





Photosensitive Microgels

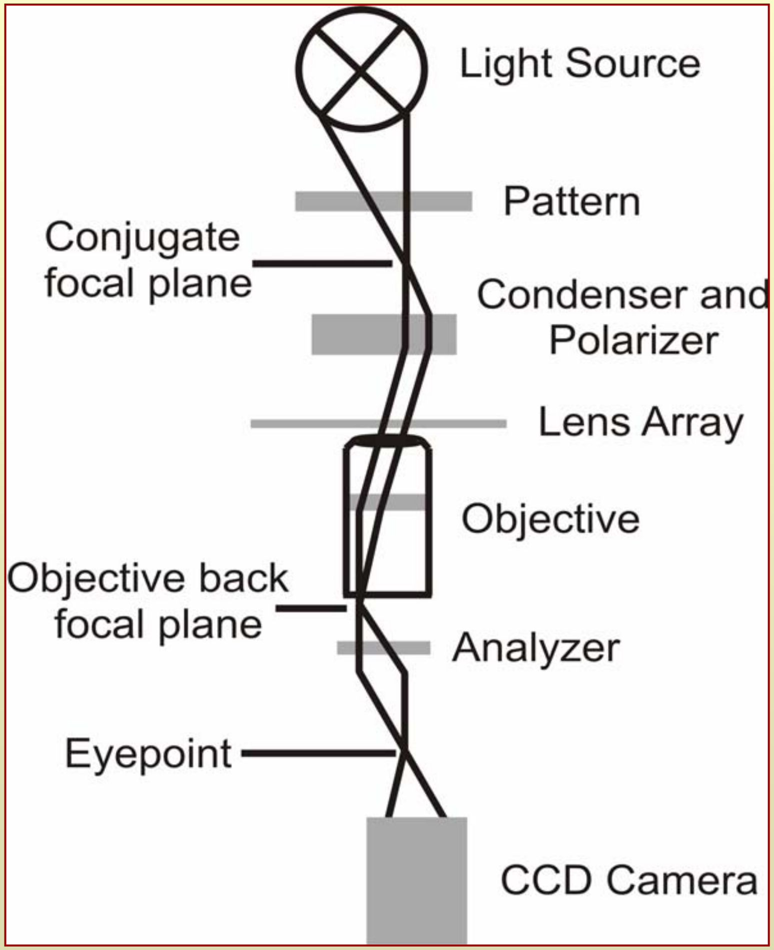


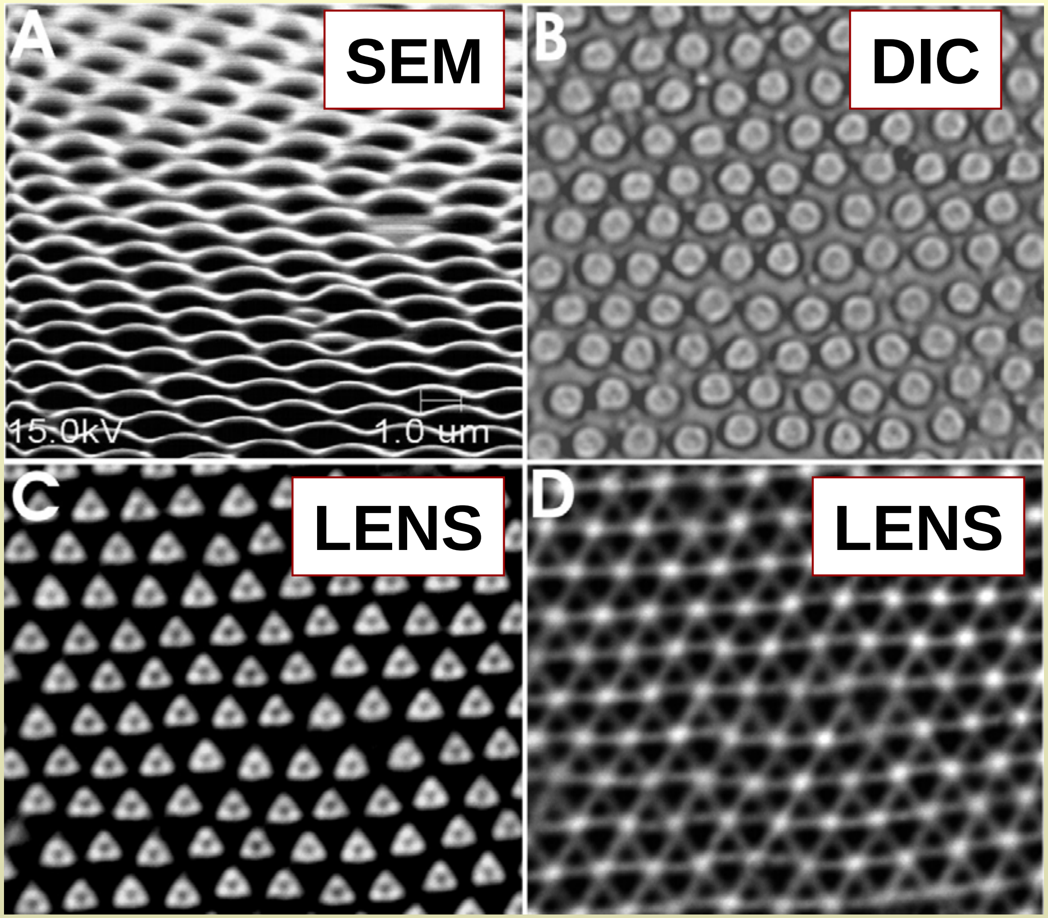


Increasing dye concentration = greater photoheating.

Hydrogel Micro-Optics

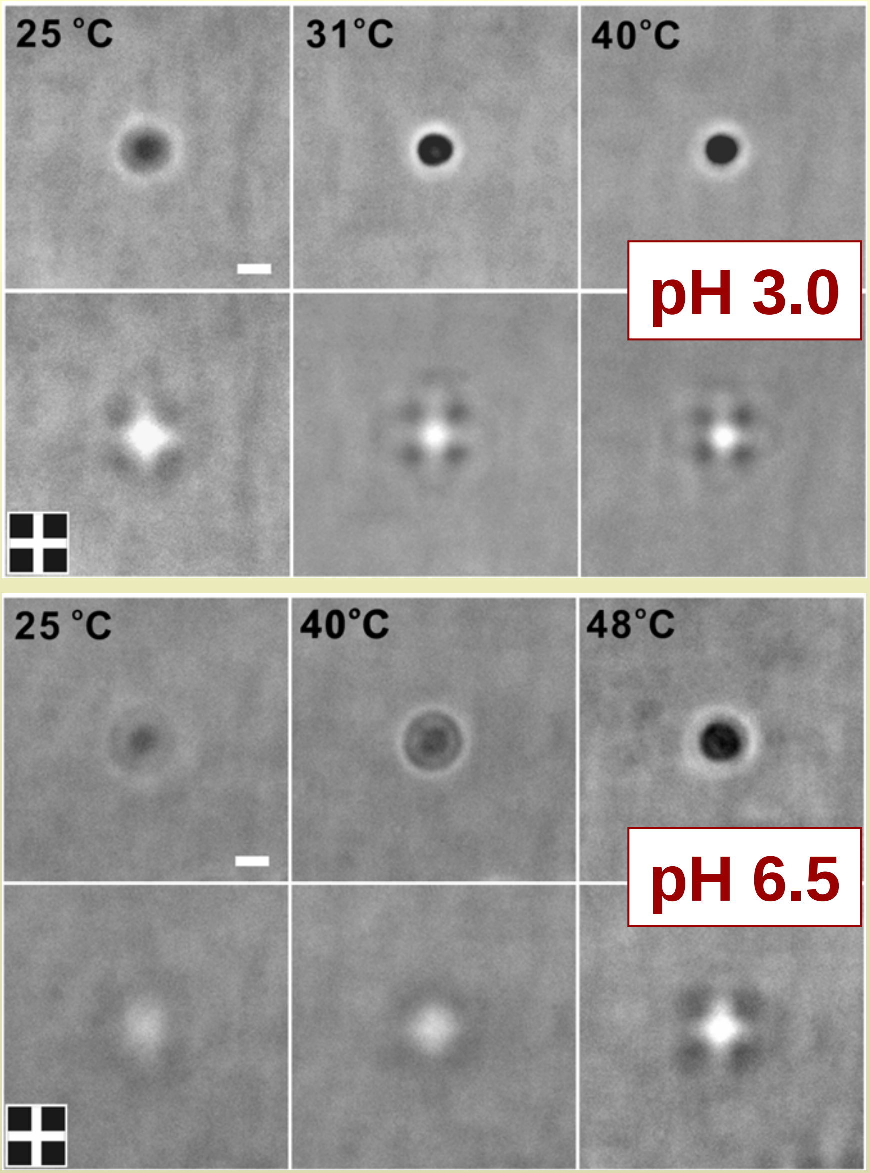
Substrate-supported microgels behave as microlenses.

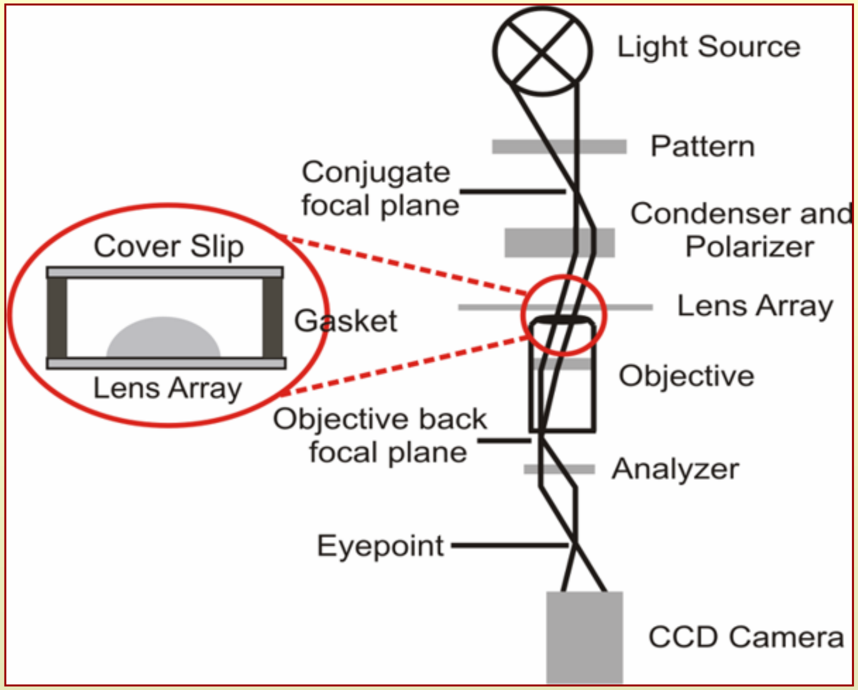




Serpe, M. J.; Kim, J.; Lyon, L. A. *Advanced Materials*, **2004,** *16*, 184-187.

Tunable Aqueous Microlenses

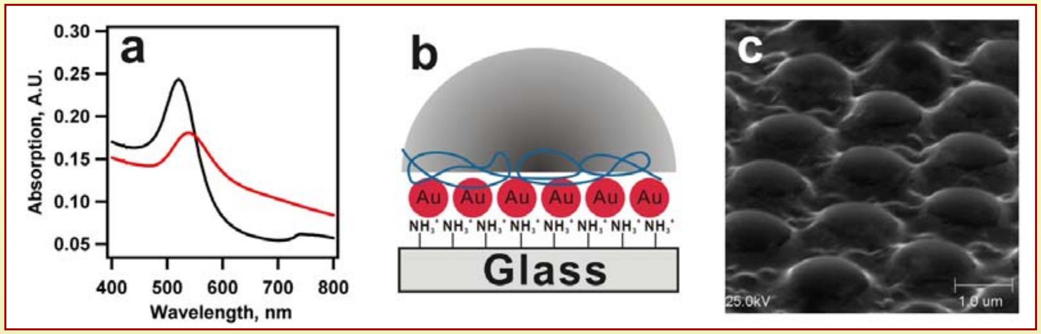


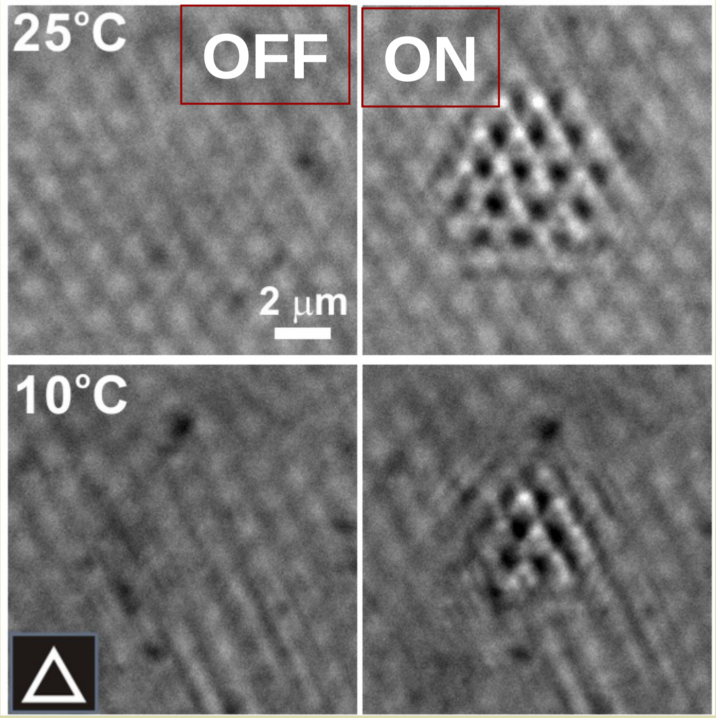


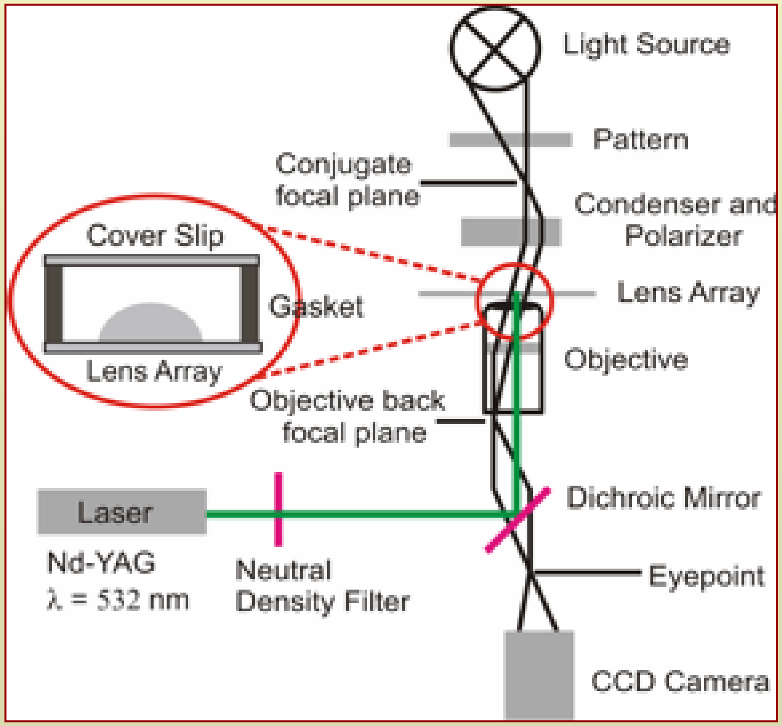
pNIPAm-*co*-AAc – temperature and pH tunable lensing.

Photoswitchable Microlenses

Laser heating of gold nanoparticles provides route to photoswitching







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