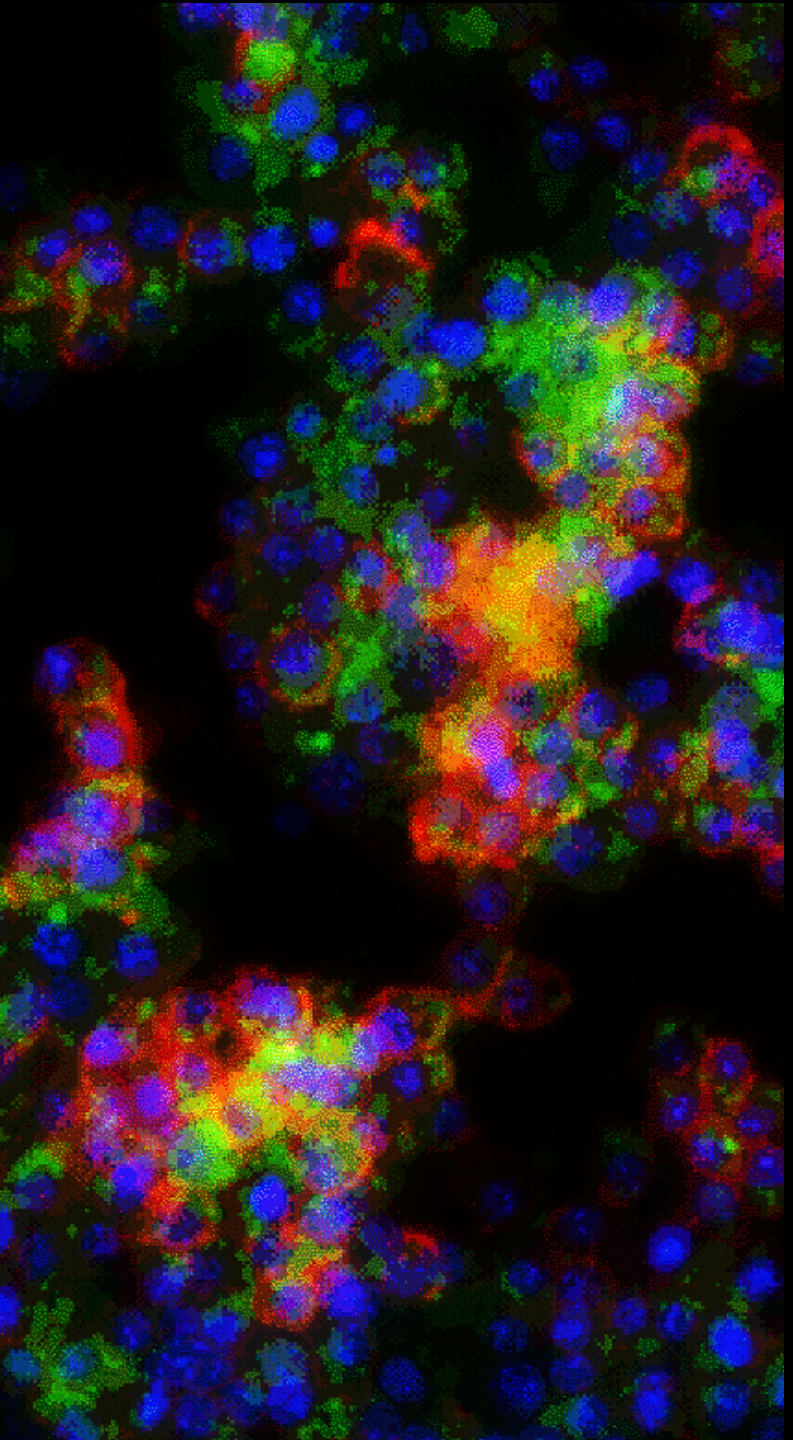

The University of Texas at Austin

Harvard John A. Paulson School of Engineering and Applied Sciences

Multi-Responsive Nanogels for Biosensing, Drug Delivery, and Regenerative Medicine

John R. Clegg[1,2]

[1] John A. Paulson School of Engineering and Applied Sciences,

[2] Wyss Institute for Biologically Inspired Engineering,

Harvard University, Cambridge, MA, USA

Wyss Institute for Biologically Inspired Engineering

IBDR Institute for Biomaterials, Drug Delivery & Regenerative Medicine

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Introductions

Mike Lesiecki
Host

Luka Partners

Atilla Ozgur Cakmak
Assistant Professor
NACK Network

PennState

Postdoctoral Fellow in Biomedical Engineering at Harvard University

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and Applied Sciences

Introduction

- The purpose of this webinar is to introduce you to ***environmentally responsive hydrogels*** with particular focus on ***fabrication and application of nanoscale hydrogel networks, or nanogels.***

- We have shown that these nanogels can be fabricated ***by a number of methods.*** Here, we focus on one particular method, which uses ***free radical co-polymerization of functional methacrylates, followed by orthogonal modification.***

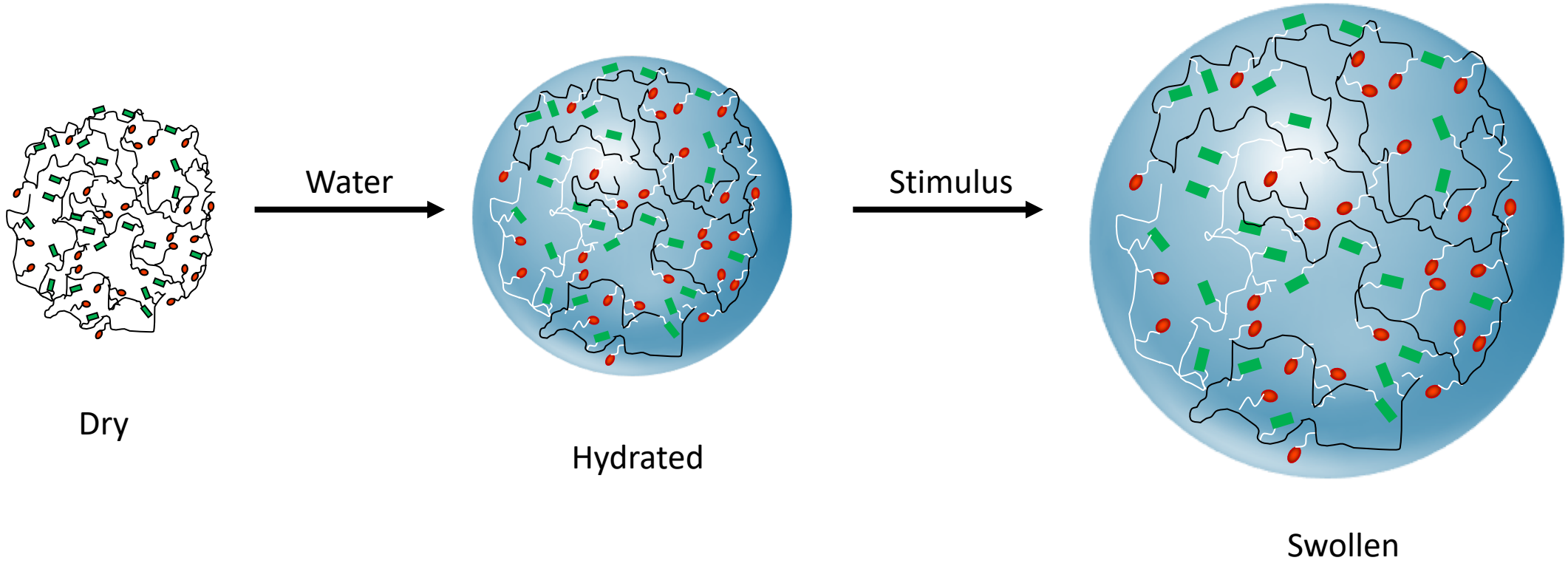
- I will first provide ***a high-level thermodynamic analysis of how crosslinked networks behave in a good solvent.*** This fundamental understanding is critical in order to apply nanogels in a practical sense.

- Then, I will discuss in detail one application of nanogels – ***cancer precision medicine***.

- Finally, I will conclude with an overview of how similar nanogel systems are being applied within ***biosensing, drug delivery, and regenerative medicine.***

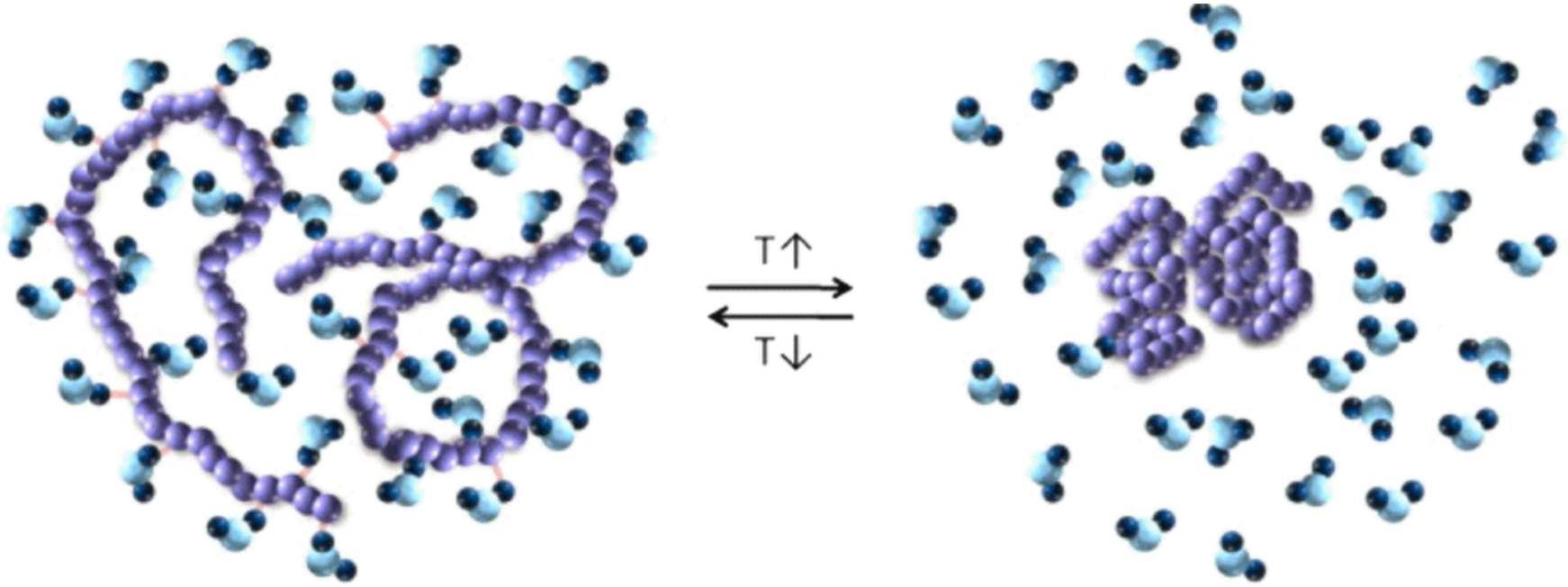
Thermodynamics of Gels: Swelling and Stimulus Response

$$\Delta G_{total} = \Delta G_{elastic} + \Delta G_{mixing} + \Delta G_{ionic}$$



Koetting MC, Peters JT, Steichen SD, Peppas NA. Stimulus-responsive hydrogels: Theory, modern advances, and applications. Materials Science and Engineering: R: Reports. 2015 Jul 1;93:1-49.

Thermodynamic Response to Environment: Molecular Level



Hydrated Coil

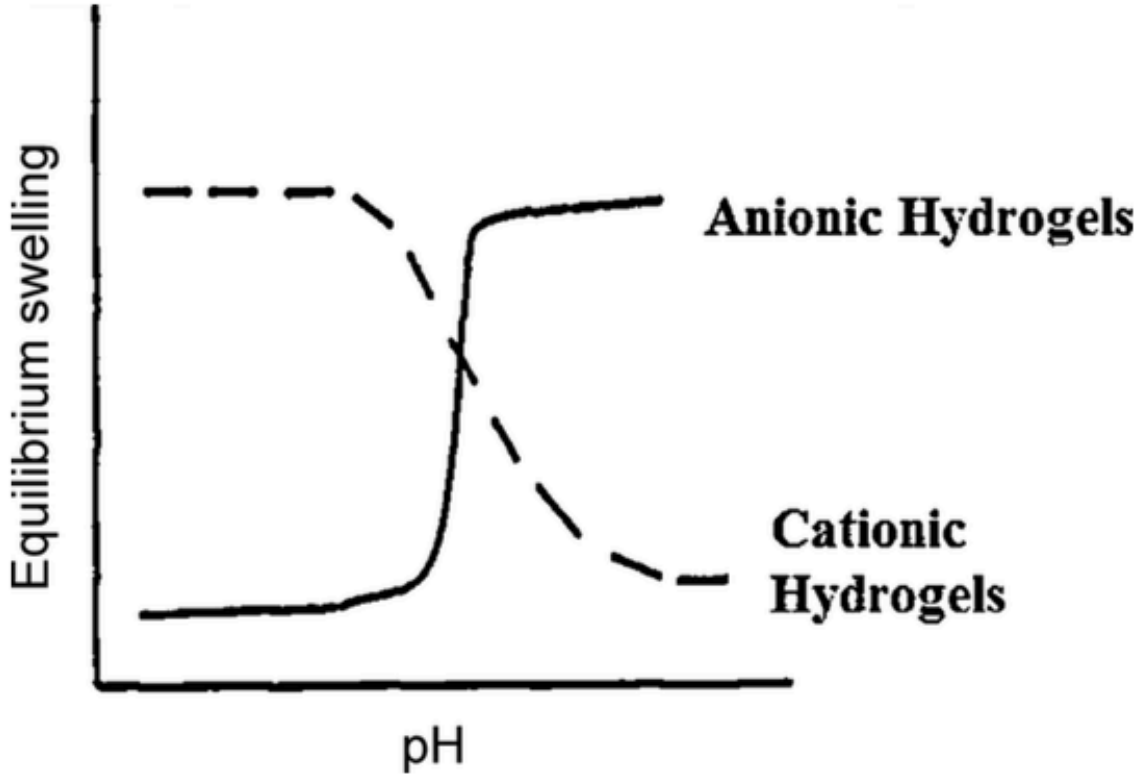
Collapsed Globule

Clegg, J.R., Wagner, A.M., Shin, S.R., Hassan, S., Khademhosseini, A. and Peppas, N.A., 2019. Modular fabrication of intelligent material-tissue interfaces for bioinspired and biomimetic devices. *Progress in Materials Science*, p.100589.

Biologically Relevant Example: pH Responsive Hydrogels

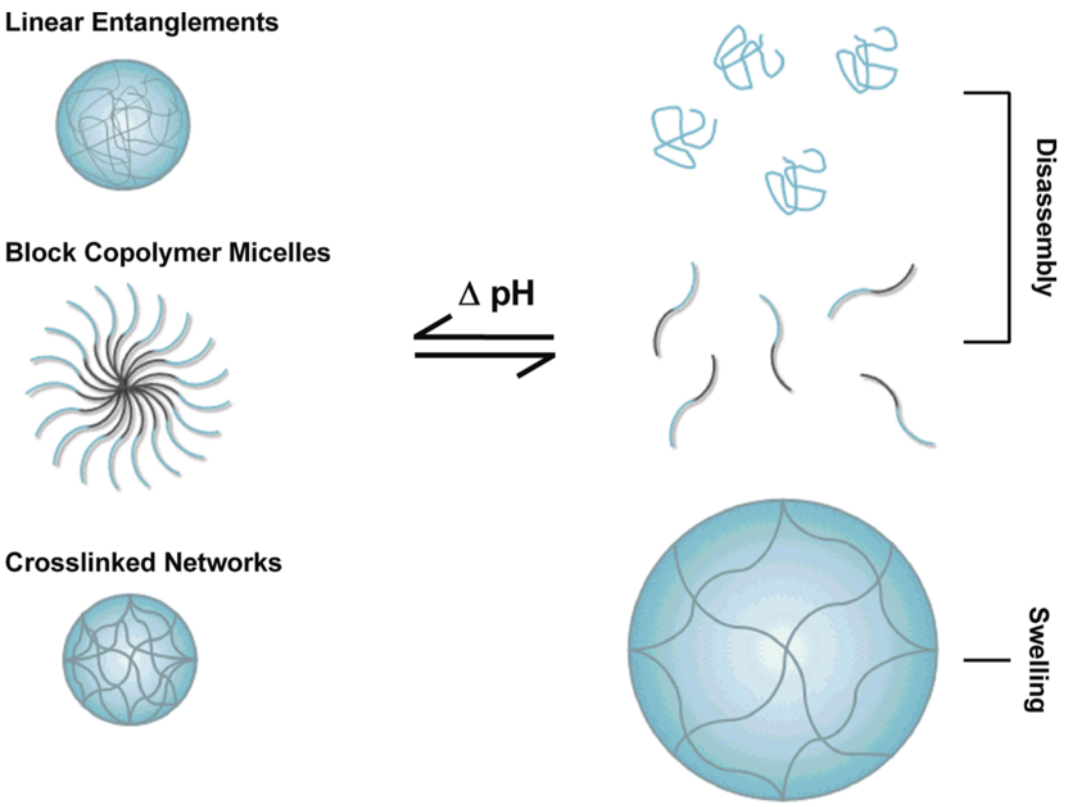
Location	pH
Blood	7.34–7.45
Stomach	1.0–3.0
Upper small intestine	4.8–8.2
Colon	7.0–7.5
Tumor, extracellular	7.2–6.5
Early endosome	6.0–6.5
Late endosome	4.5–5.0
Vagina	3.8–4.5
Inflamed tissue/wound	5.4–7.4

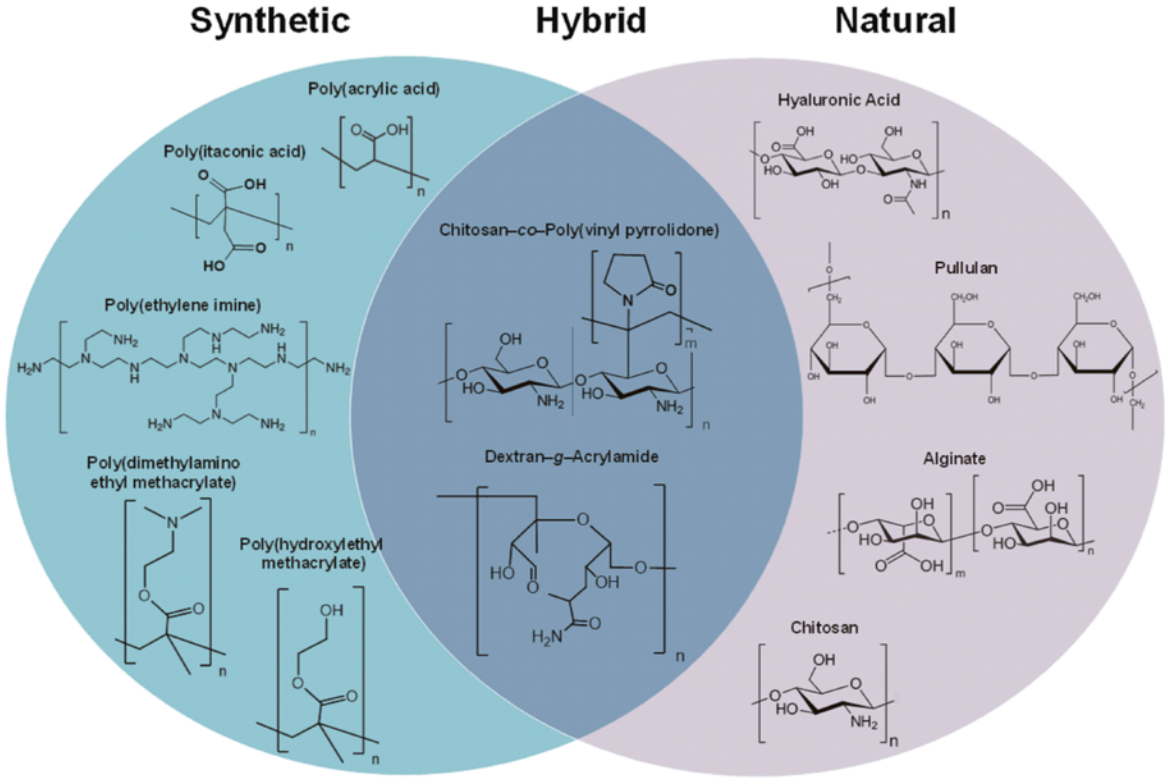
$$\frac{V_1}{4I}\left(\frac{v_{2,s}^2}{\bar{v}^2 M_r^2}\right)\left(\frac{10^{-\mathrm{p}Ka}}{10^{-\mathrm{pH}}+10^{-\mathrm{p}Ka}}\right)^2 = [\ln(1-v_{2,s})+v_{2,s}+\chi_1 v_{2,s}^2] + \left(\frac{V_1}{\bar{v}\bar{M}_c}\right)\left(1-\frac{2\bar{M}_c}{\bar{M}_n}\right)v_{2,r}\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3}-\left(\frac{v_{2,s}}{2v_{2,r}}\right)\right]$$



Koetting MC, Peters JT, Steichen SD, Peppas NA. Stimulus-responsive hydrogels: Theory, modern advances, and applications. Materials Science and Engineering: R: Reports. 2015 Jul 1;93:1-49.

Fabrication and Responsiveness of Ionizable Nanogels





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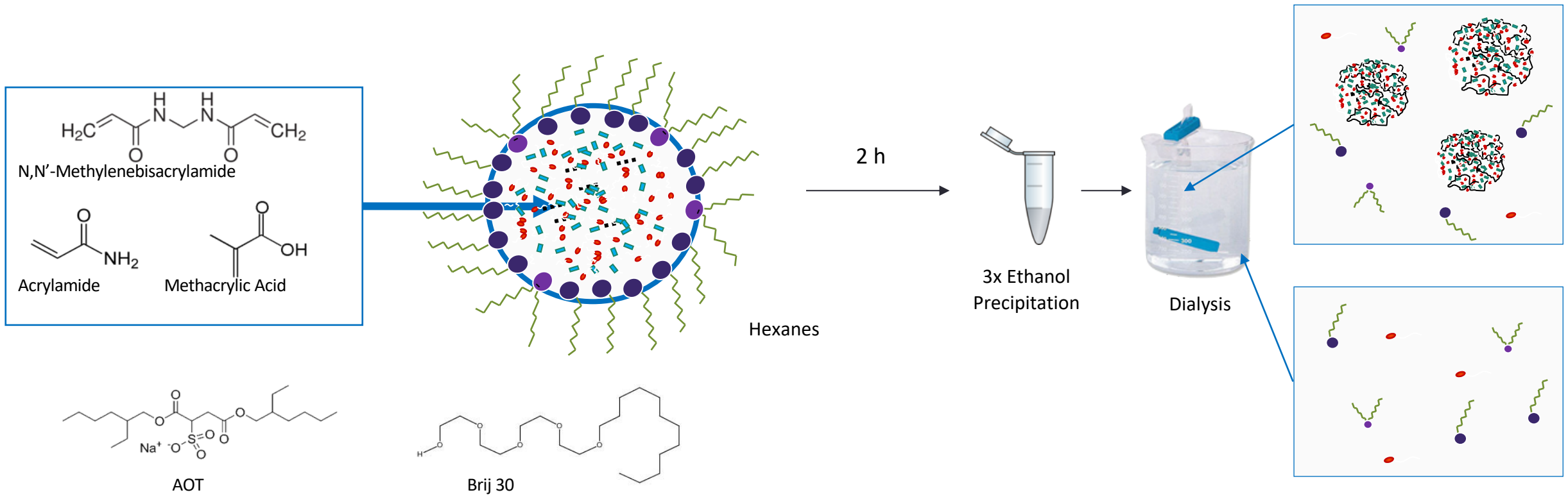
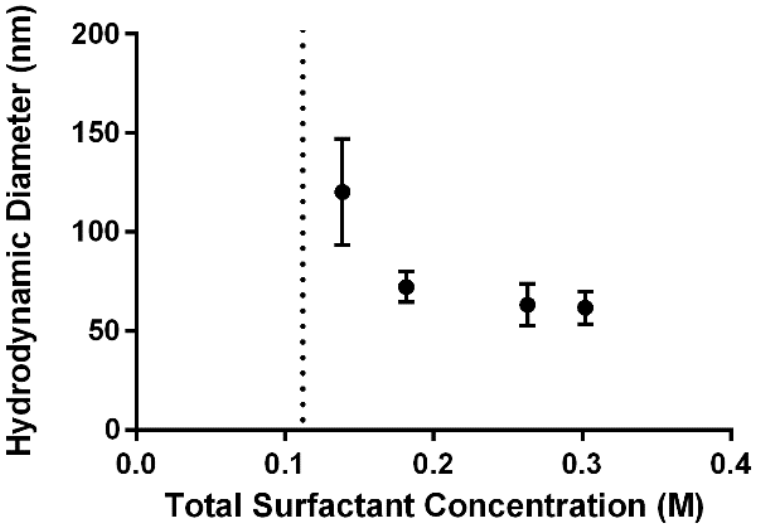
A Brief Question Break

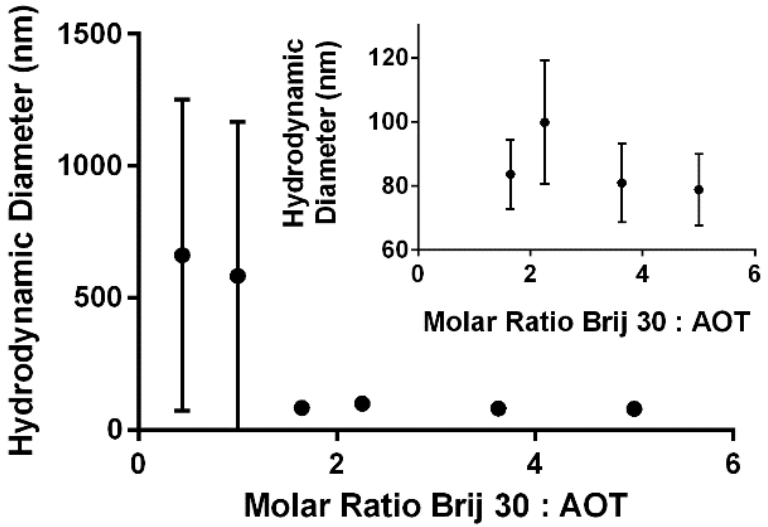
Synthesis of Intelligent Nanogels via Inverse Emulsion Polymerization

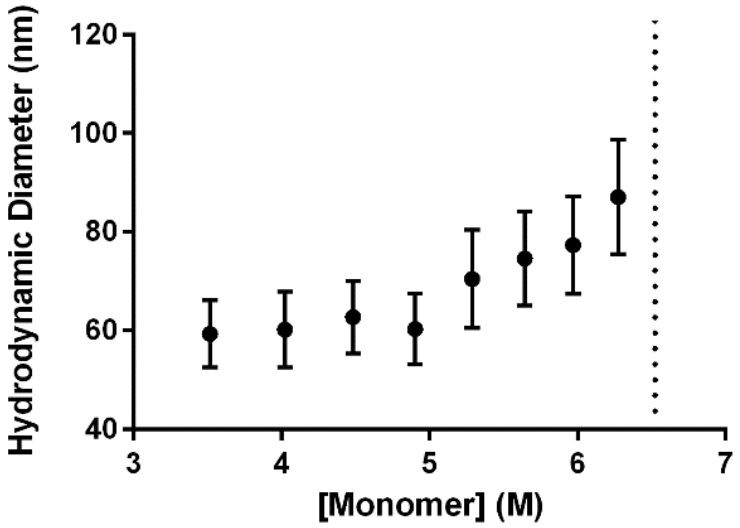


Zhong, Justin X., John R. Clegg, Eric W. Ander, and Nicholas A. Peppas. "Tunable poly (methacrylic acid-co-acrylamide) nanoparticles through inverse emulsion polymerization." *Journal of Biomedical Materials Research Part A* 106, no. 6 (2018): 1677-1686.

Tunability of Nanogel Diameter via Modulation of Emulsion Parameters



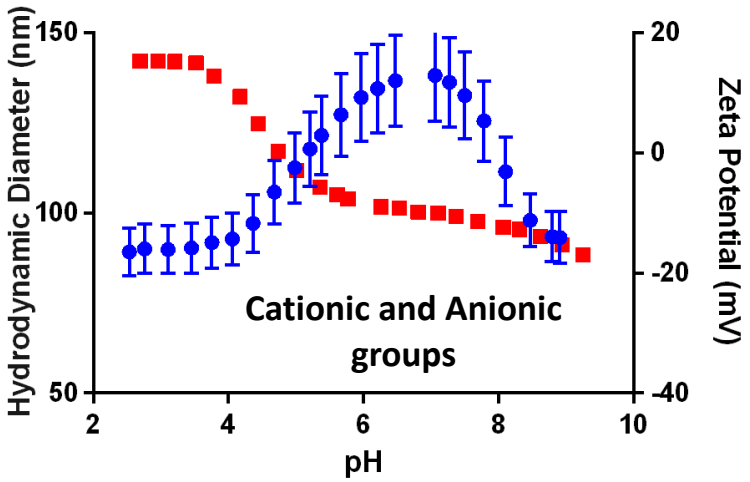


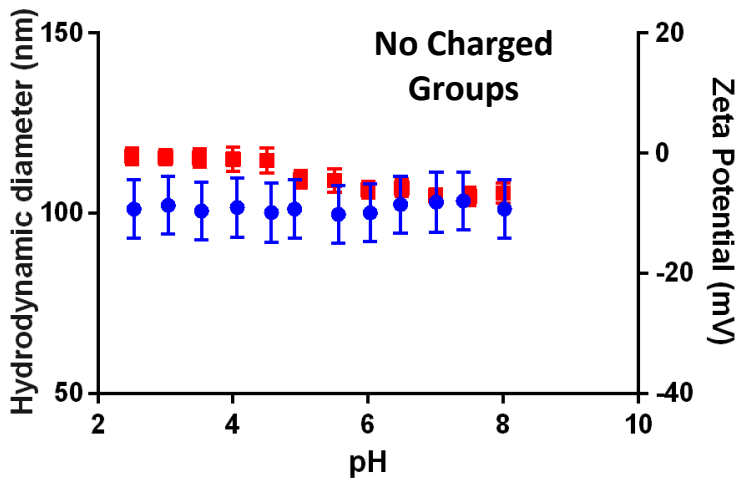


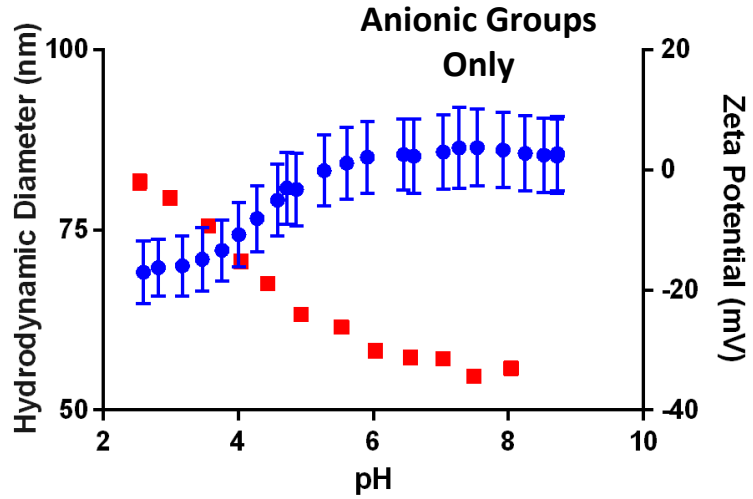
- ✓ Nanogel diameter is tunable through modulation of polymerization parameters
- ✓ Critical levels determined for successful nanogel formation

Zhong, Justin X., John R. Clegg, Eric W. Ander, and Nicholas A. Peppas. "Tunable poly (methacrylic acid-co-acrylamide) nanoparticles through inverse emulsion polymerization." *Journal of Biomedical Materials Research Part A* 106, no. 6 (2018): 1677-1686.

Response of Intelligent Nanogels to the pH Environment: Diameter and Surface Charge

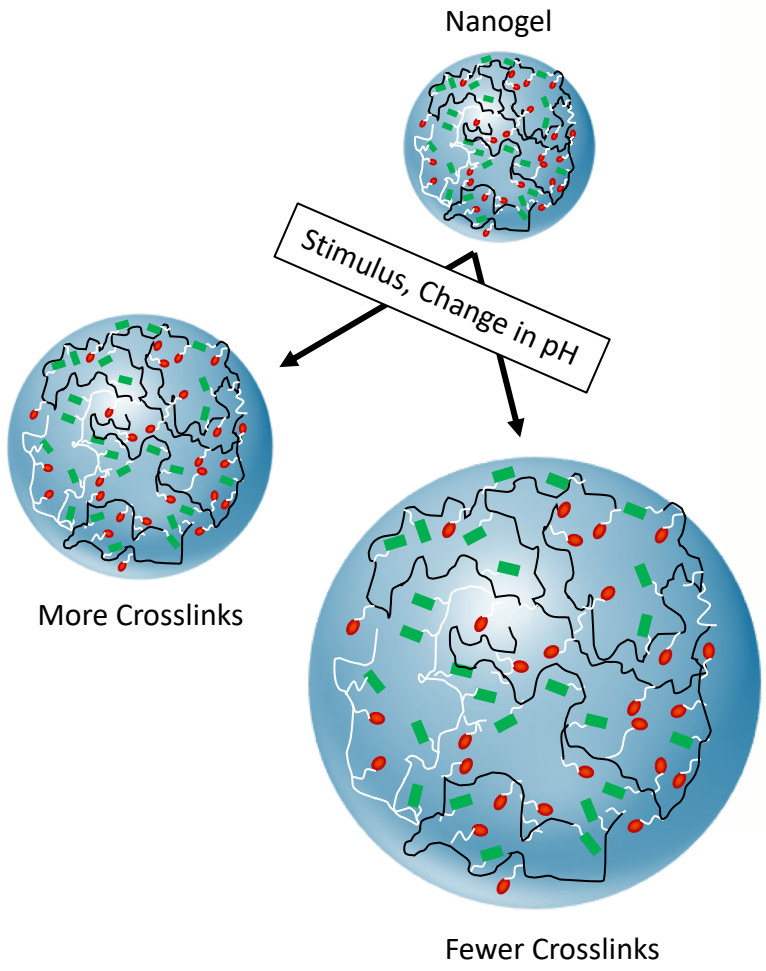


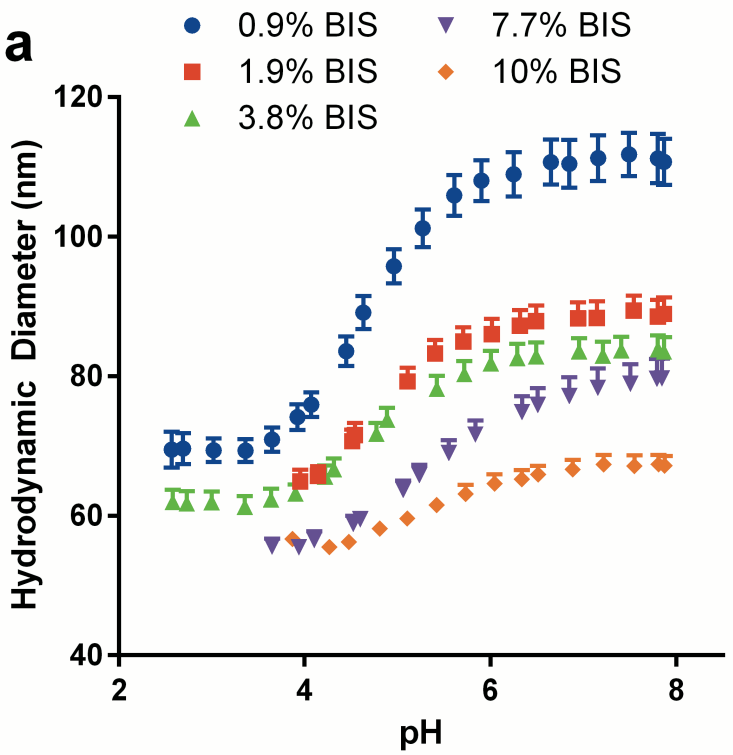


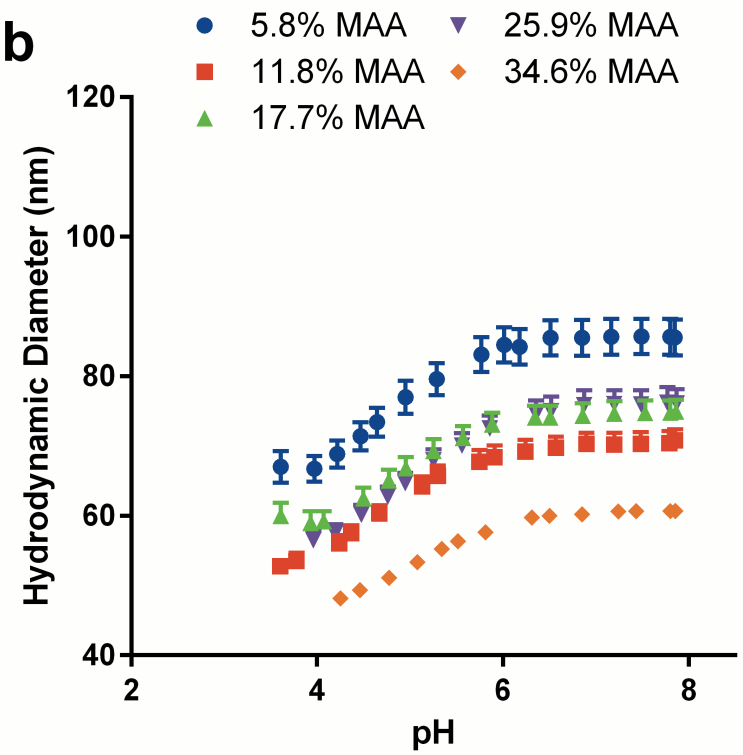


Zeta Potential, Hydrodynamic Diameter

Tunability of the Magnitude of pH Response: Change the Network Structure





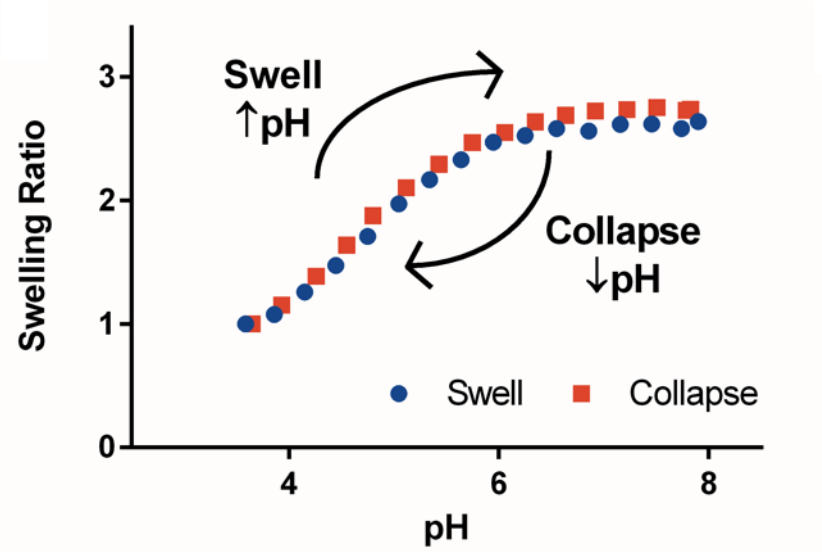


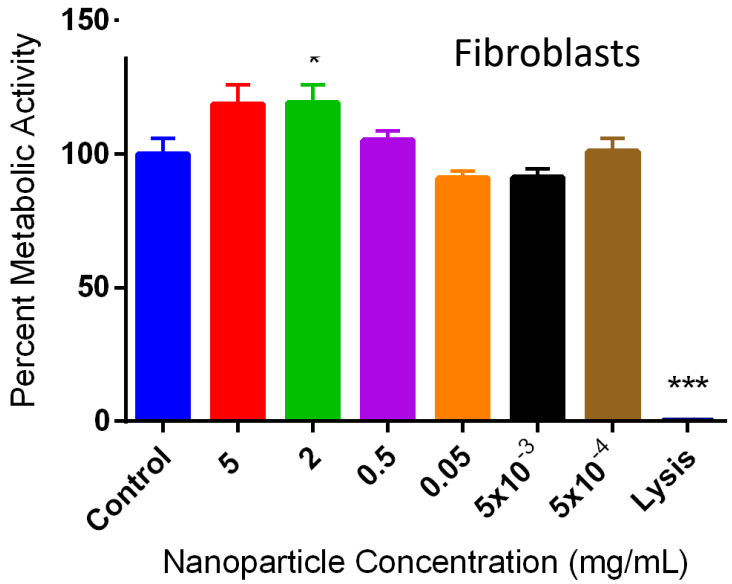
- ✓ Tunable via modulation of the monomer feed
- ✓ Range of environmental responsiveness observed

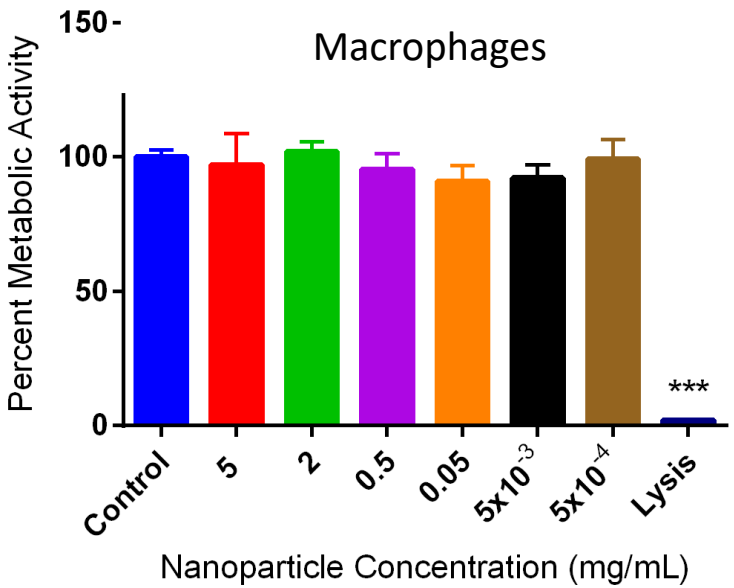
$n = 3$
$\bar{x} \pm \sigma$

Zhong, Justin X., John R. Clegg, Eric W. Ander, and Nicholas A. Peppas. "Tunable poly (methacrylic acid-co-acrylamide) nanoparticles through inverse emulsion polymerization." *Journal of Biomedical Materials Research Part A* 106, no. 6 (2018): 1677-1686.

Responsiveness and Cytocompatibility of P(AAm-co-MAA) Nanogels



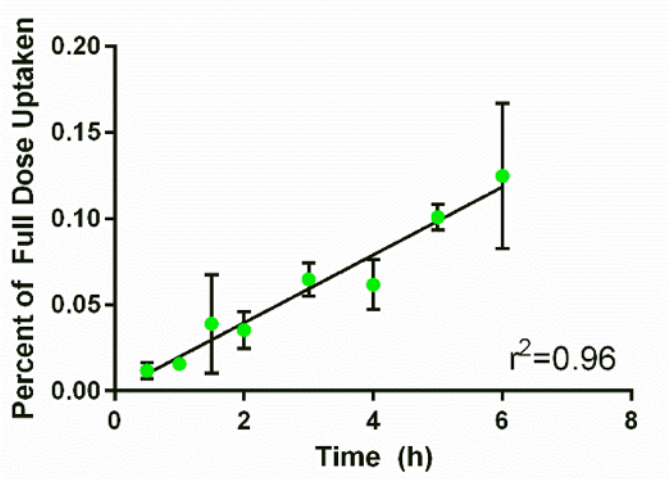


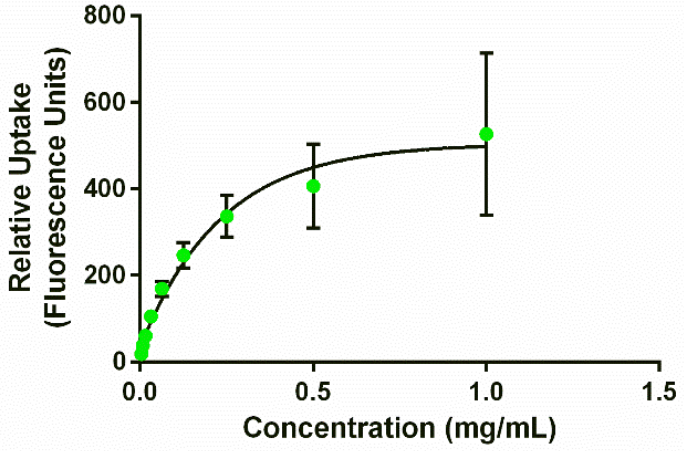


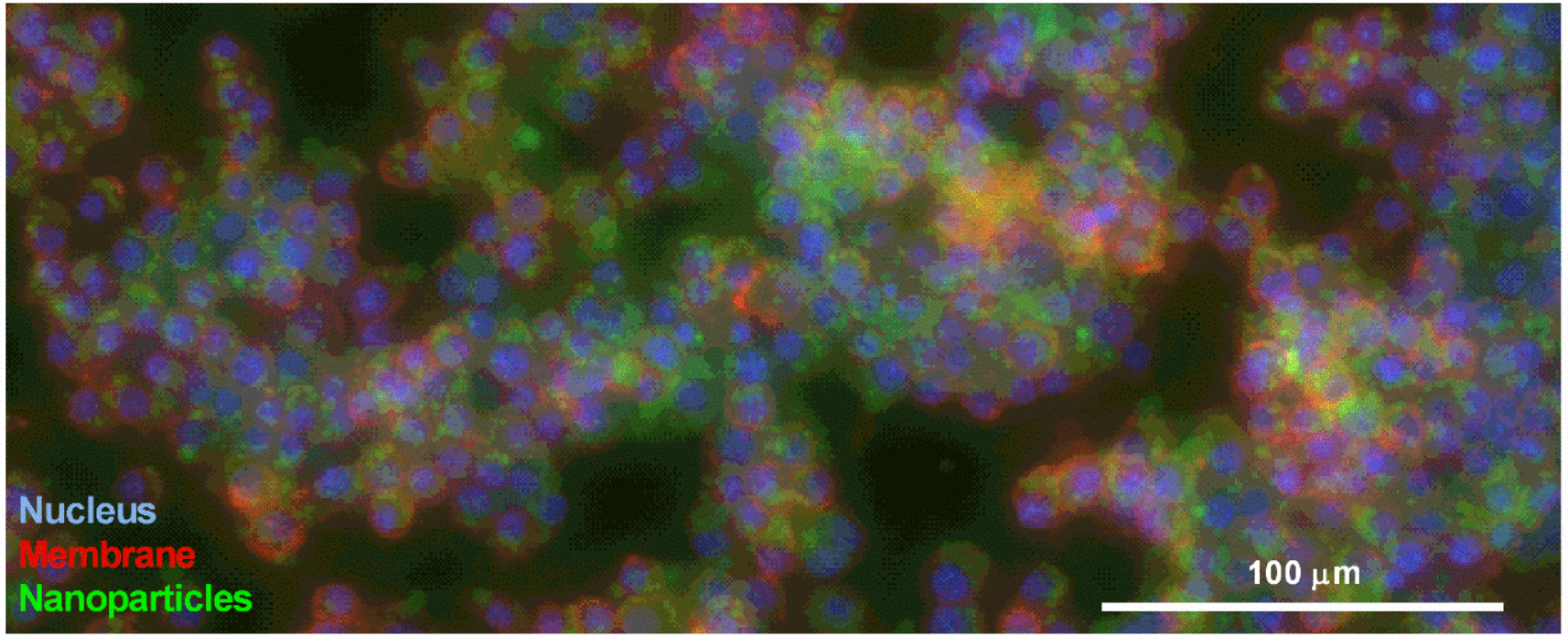
- ✓ Uniform, Spherical, Stable in Solution
- ✓ Reversible pH-responsive behavior
- ✓ Biocompatible

Zhong, Justin X., John R. Clegg, Eric W. Ander, and Nicholas A. Peppas. "Tunable poly (methacrylic acid-co-acrylamide) nanoparticles through inverse emulsion polymerization." *Journal of Biomedical Materials Research Part A* 106, no. 6 (2018): 1677-1686.

P(AAm-co-MAA) Nanogel Uptake by Murine Macrophages







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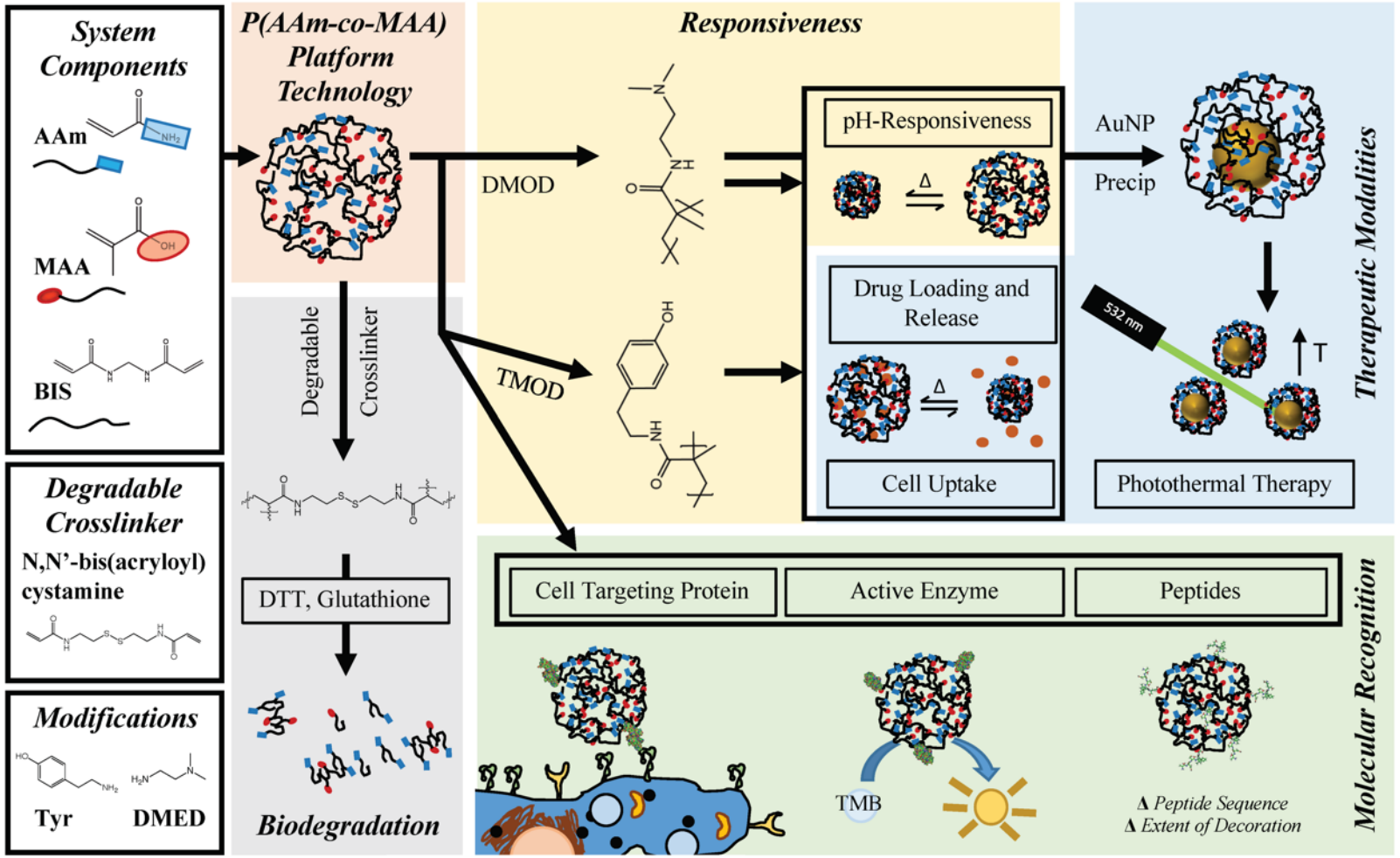
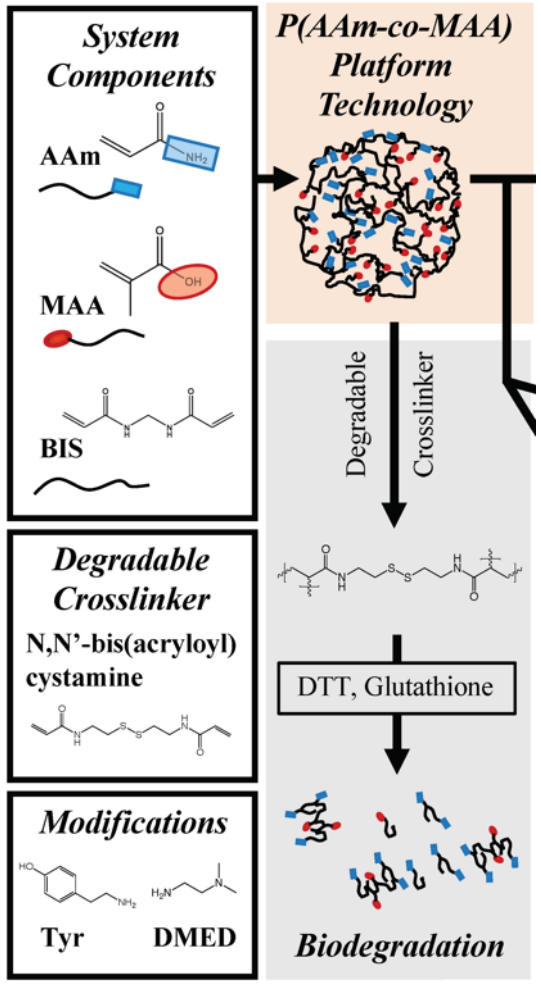
The Challenge of Cancer Precision Medicine

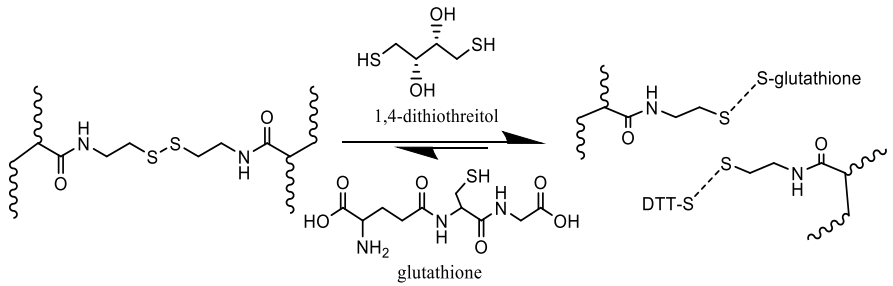
P(AAm-co-MAA) as a Modular Technology for Precision Medicine

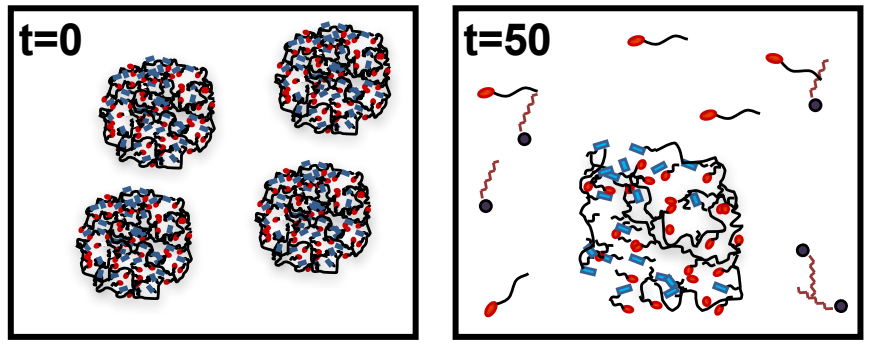


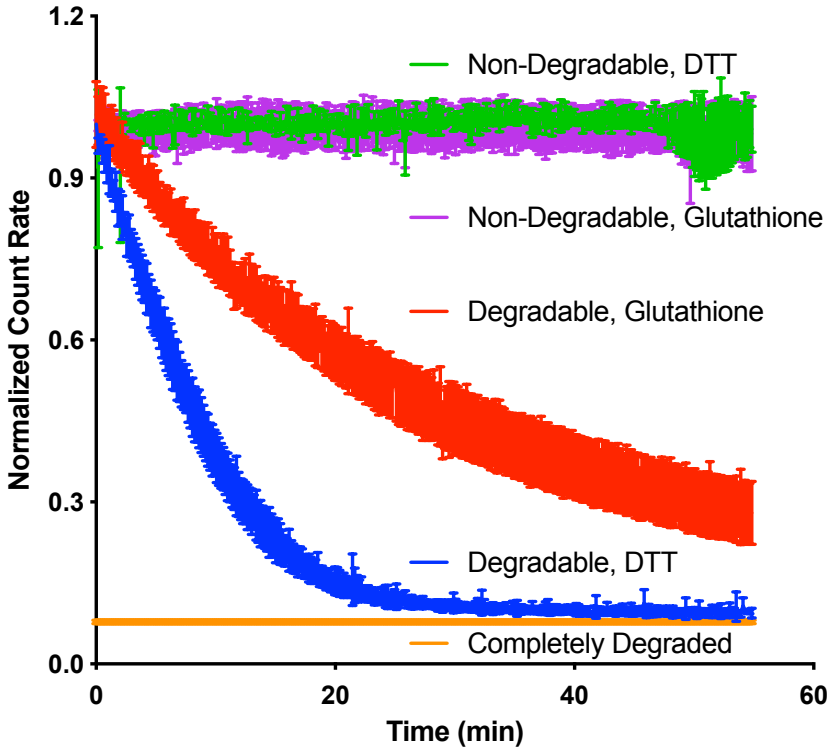
Clegg, J. R., Irani, A. S., Ander, E. W., Ludolph, C. M., Venkataraman, A. K., Zhong, J. X., & Peppas, N. A. (2019). Synthetic networks with tunable responsiveness, biodegradation, and molecular recognition for precision medicine applications. *Science advances*, *5*(9), eaax7946.

Biodegradation Kinetics and Analysis









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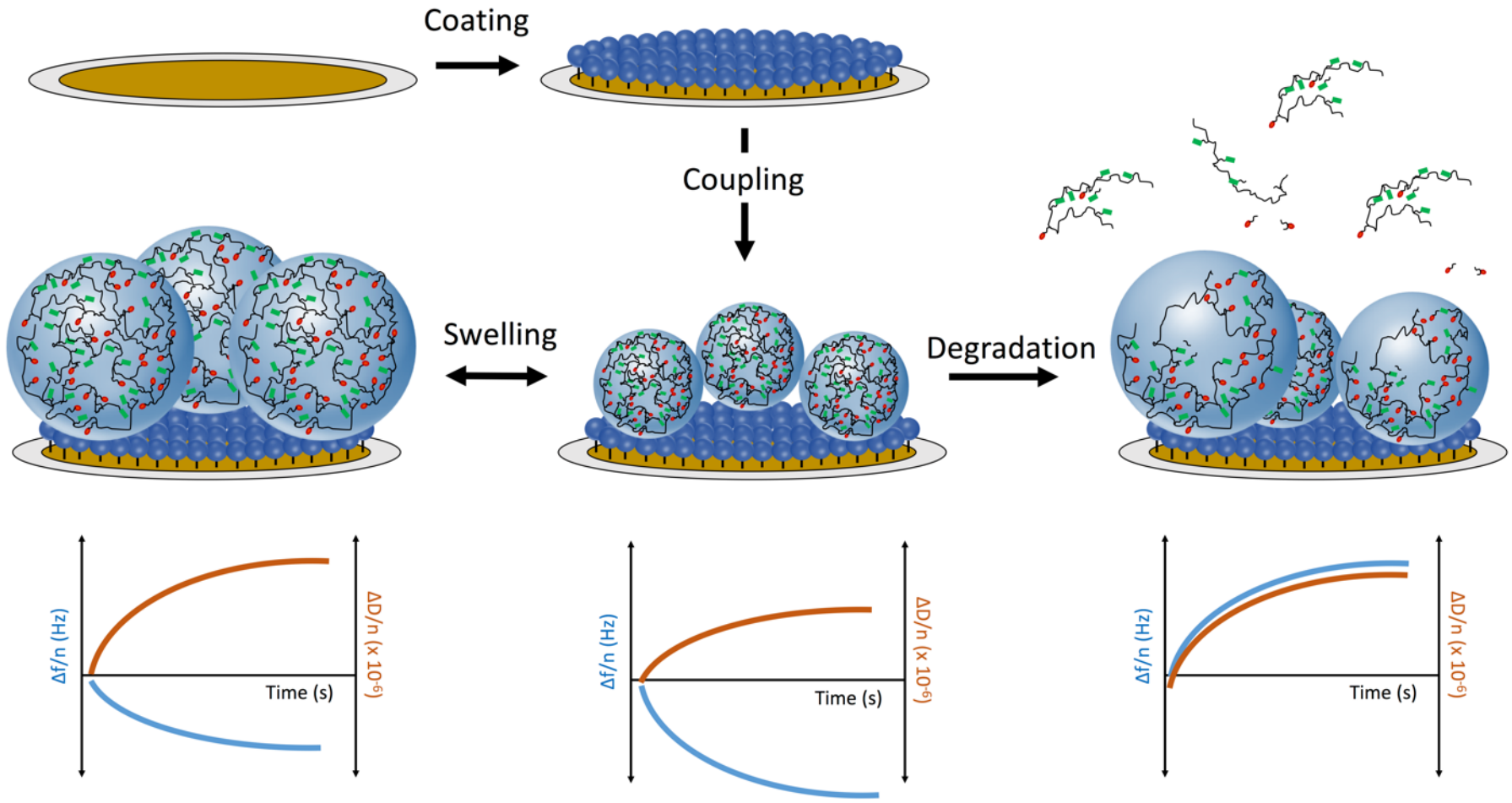
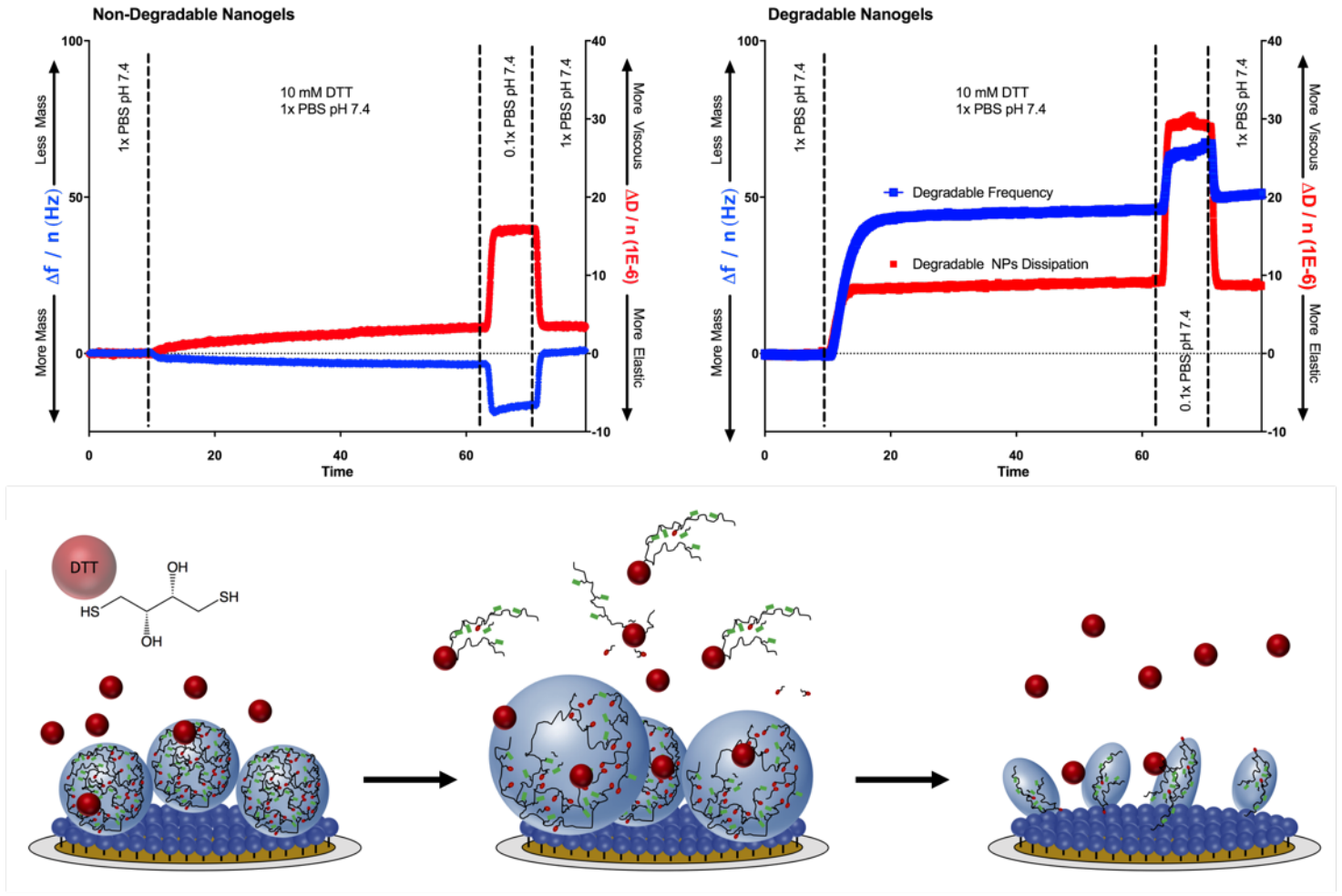
QCM-D Analysis of Nanogel Biodegradation



Clegg, JR., Ludolph, CM., Peppas, NA. (2019), QCM-D assay for quantifying the swelling, biodegradation, and protein adsorption of intelligent nanogels. *J Appl Polym Sci*, 48655.

QCM-D Analysis of Nanogel Biodegradation



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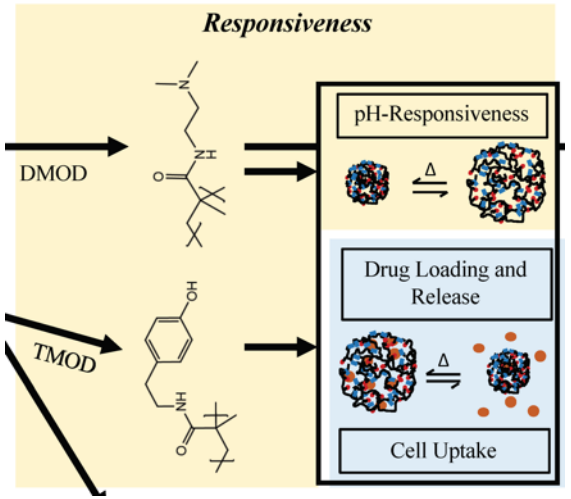
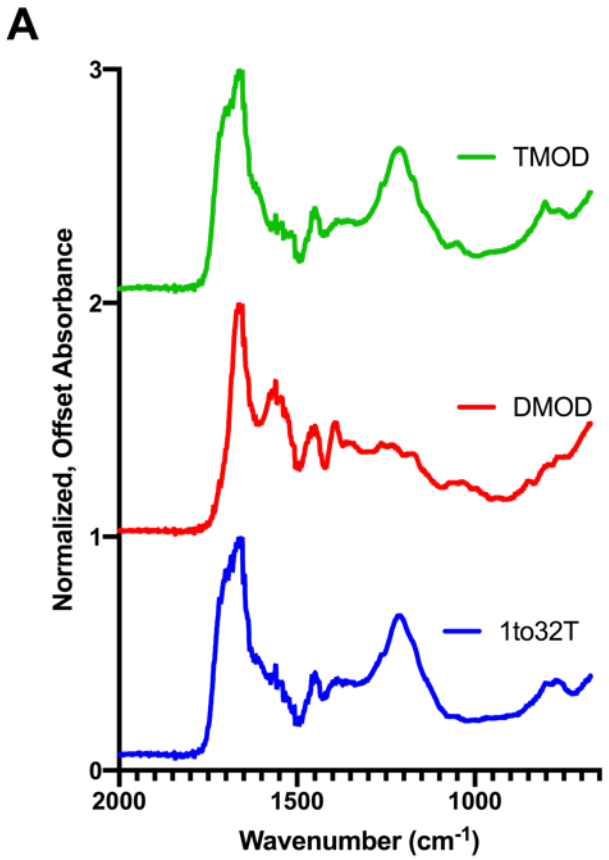
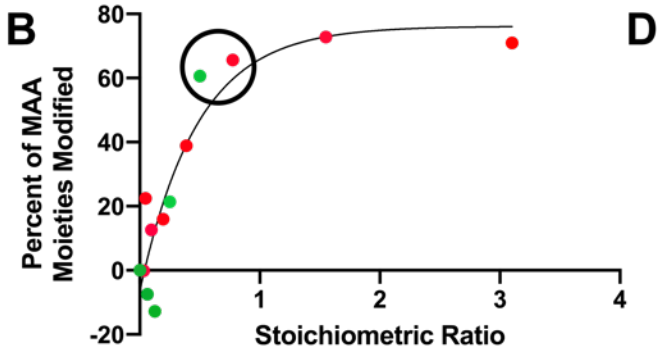
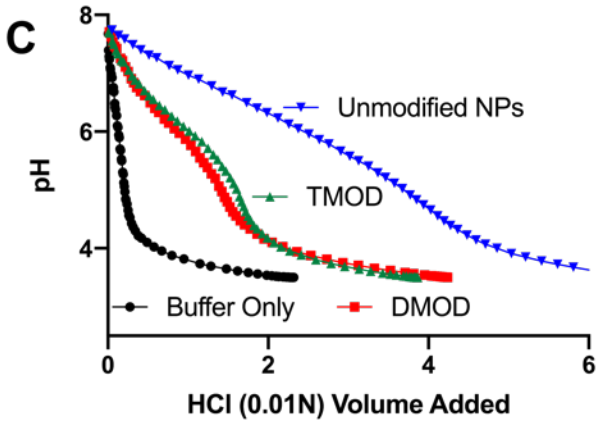
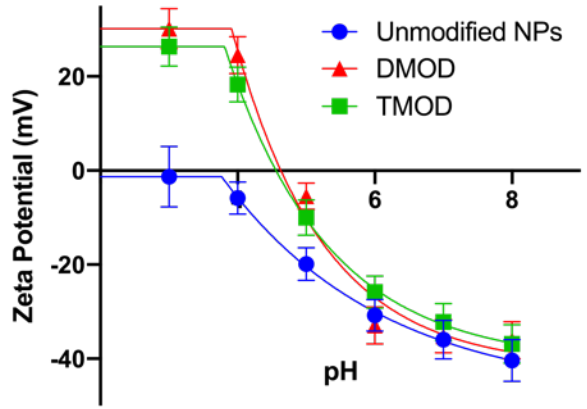
Synthesis and Characterization of Small Molecule-Modified NPs

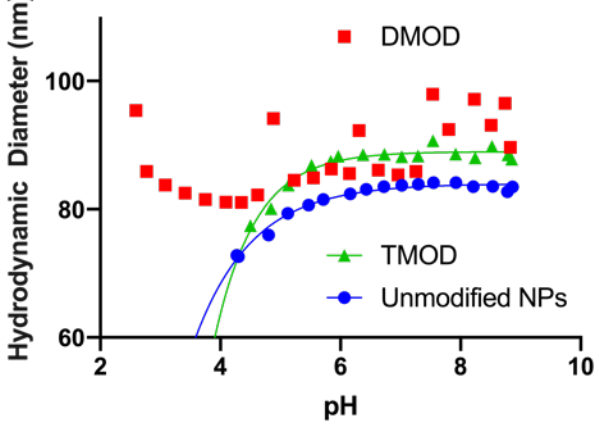








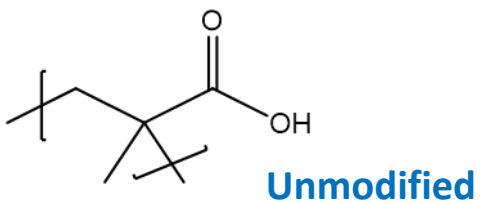




Wyss Institute for Biologically Inspired Engineering

Clegg, J. R., Irani, A. S., Ander, E. W., Ludolph, C. M., Venkataraman, A. K., Zhong, J. X., & Peppas, N. A. (2019). Synthetic networks with tunable responsiveness, biodegradation, and molecular recognition for precision medicine applications. *Science advances*, *5*(9), eaax7946.

Impact of Nanogel Modification on Responsive Release of Methylene Blue



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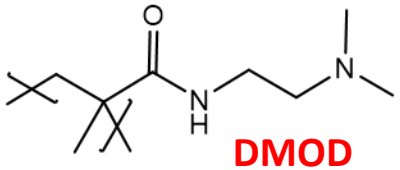

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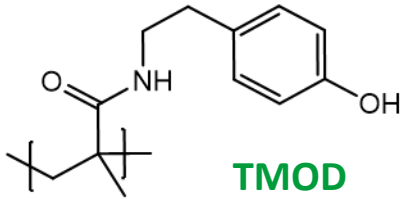

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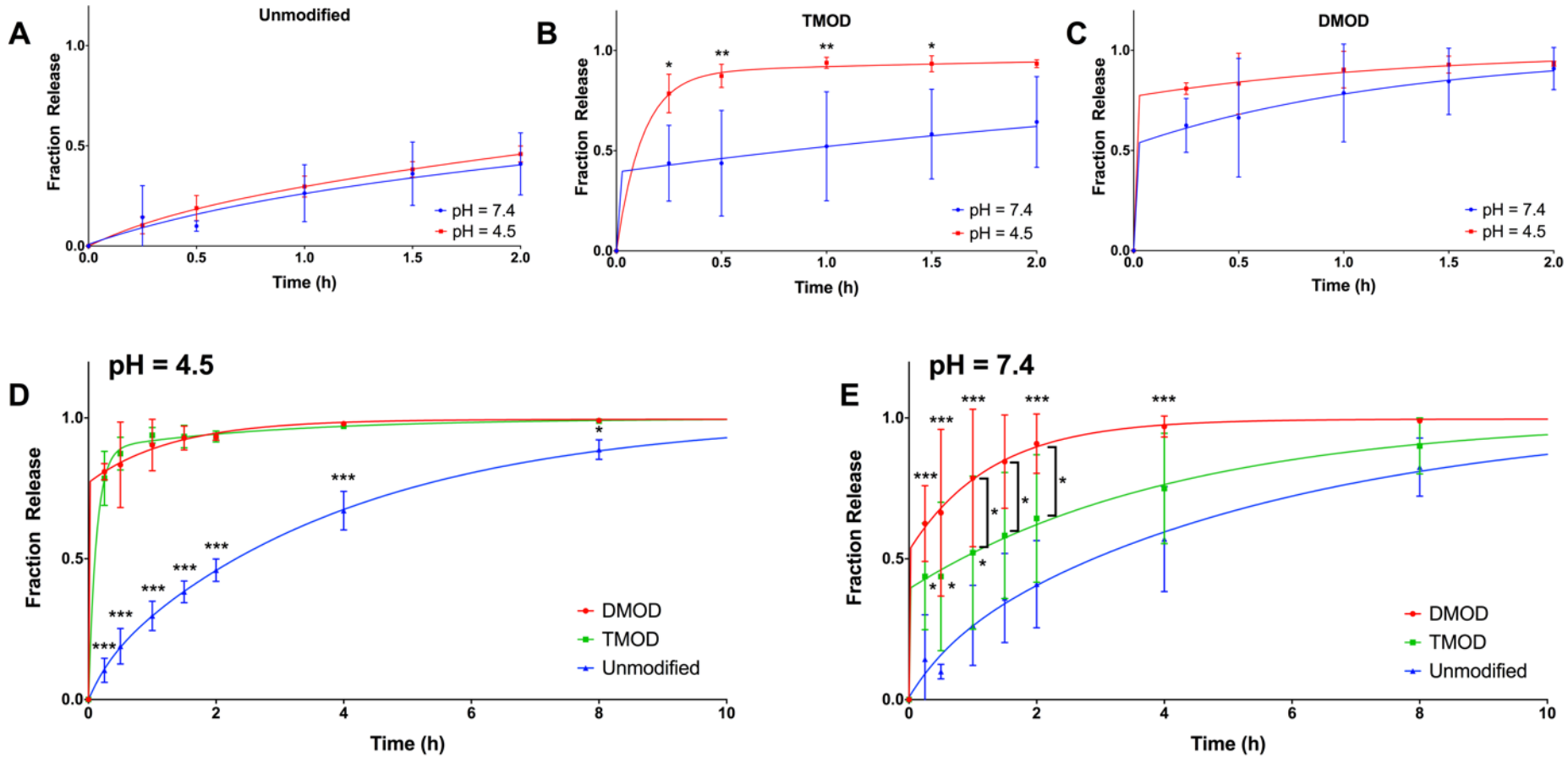

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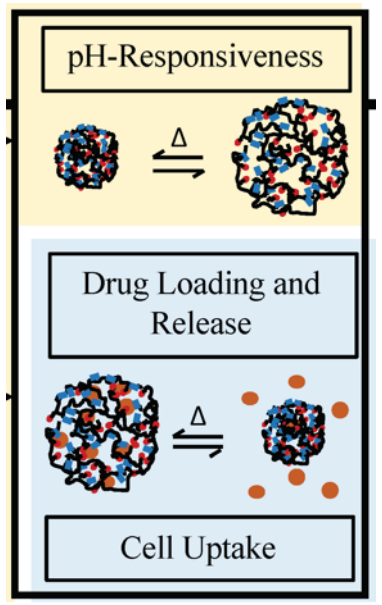
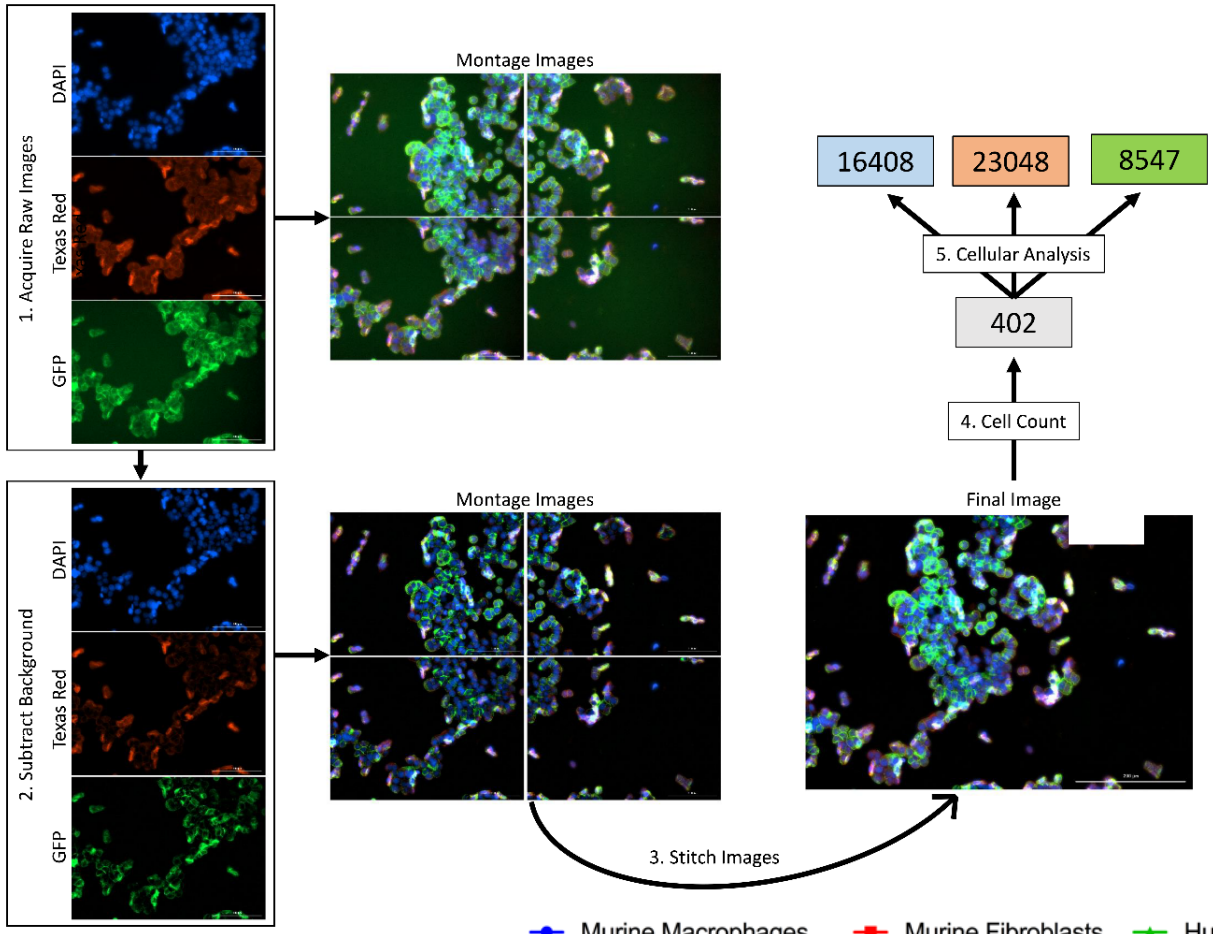
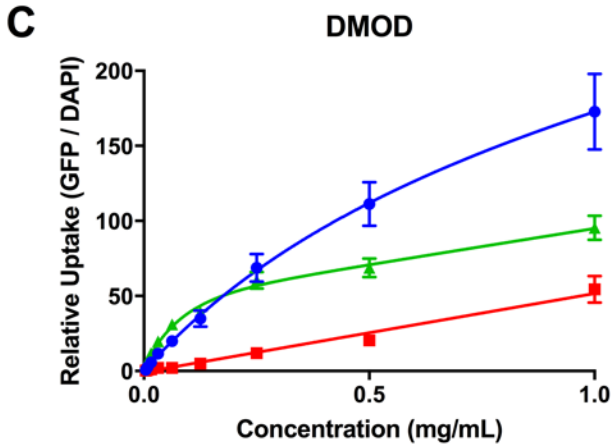
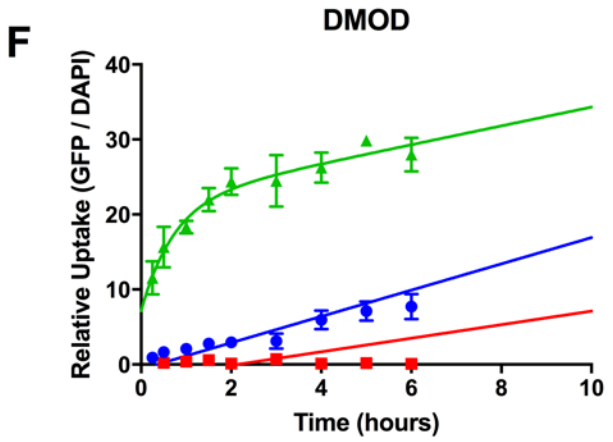
A High-Throughput Assay for Nanogel Uptake





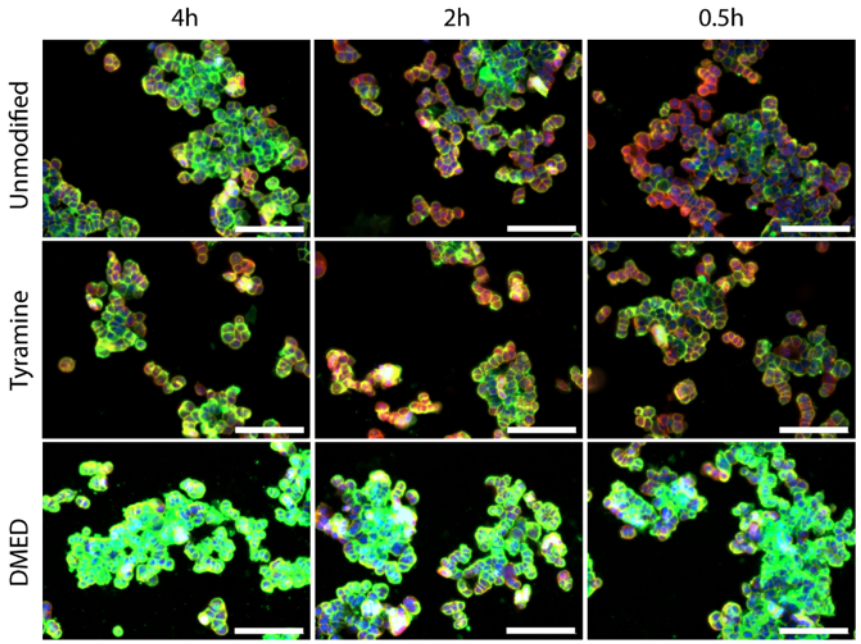




Murine Macrophages Murine Fibroblasts Human Colorectal Carcinoma

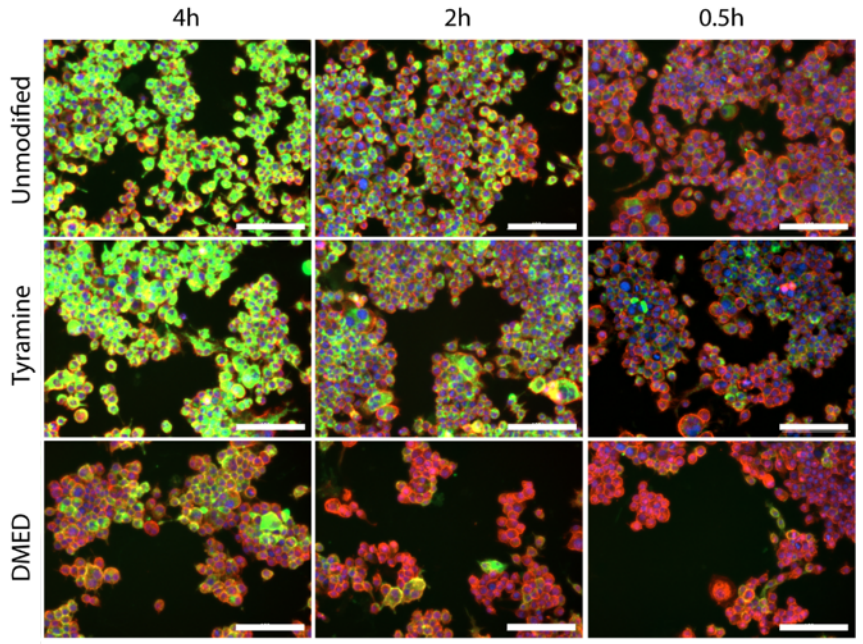
Clegg, J. R., Irani, A. S., Ander, E. W., Ludolph, C. M., Venkataraman, A. K., Zhong, J. X., & Peppas, N. A. (2019). Synthetic networks with tunable responsiveness, biodegradation, and molecular recognition for precision medicine applications. *Science advances*, *5*(9), eaax7946.

High-Throughput Assay for Cell Internalization of Nanoparticles (Macrophages vs. Colon Cancer (400 µg/mL)

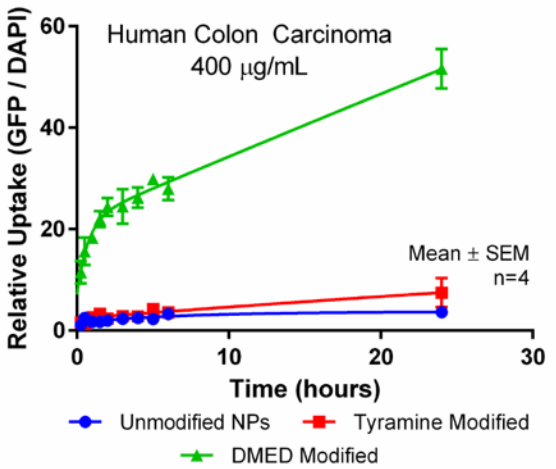


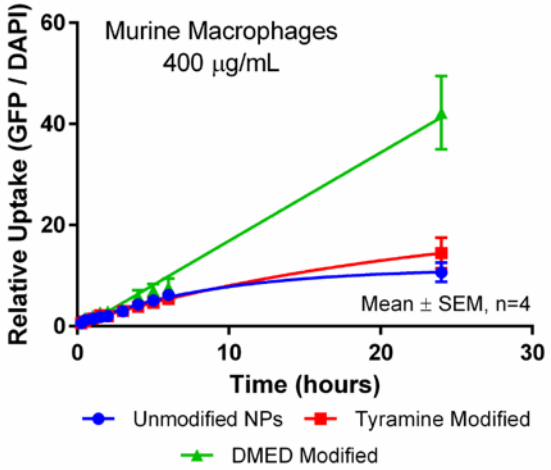
Colon Cancer Cells

Scale bar = 100 µ*m*



Macrophages





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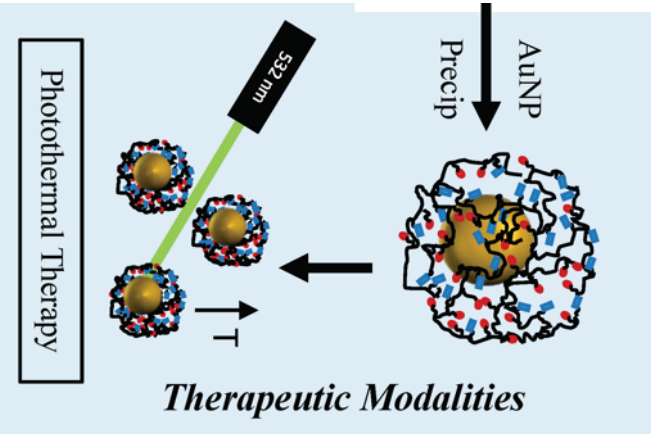
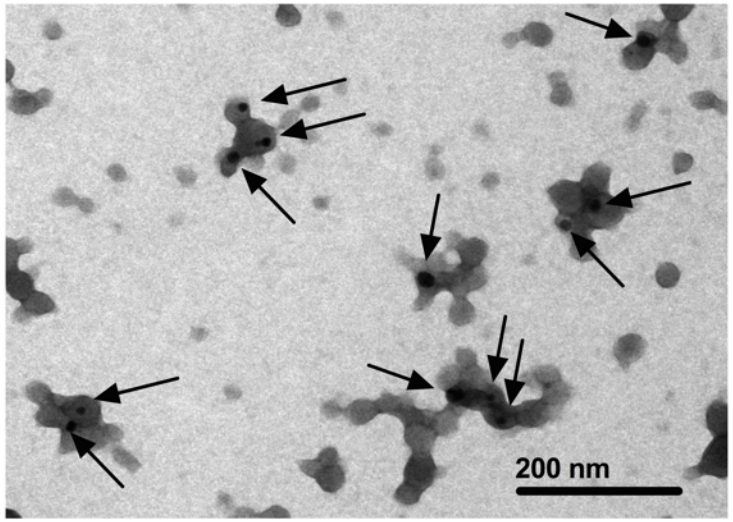
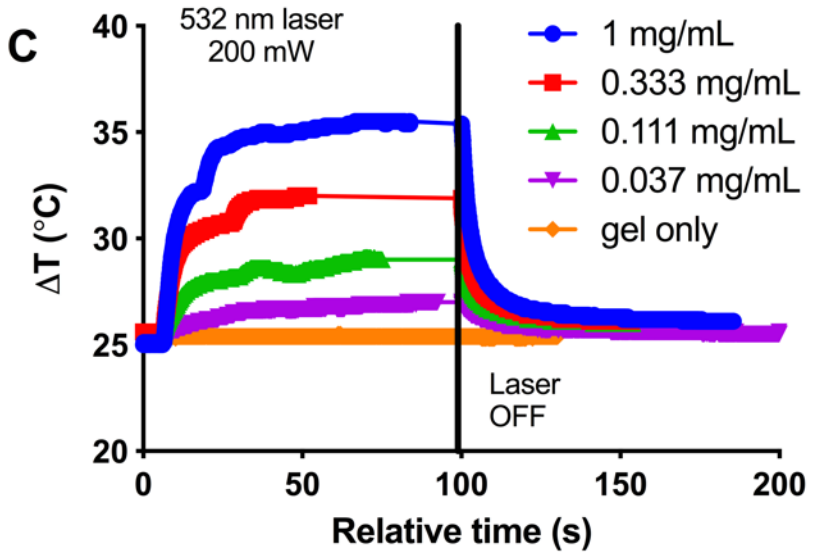
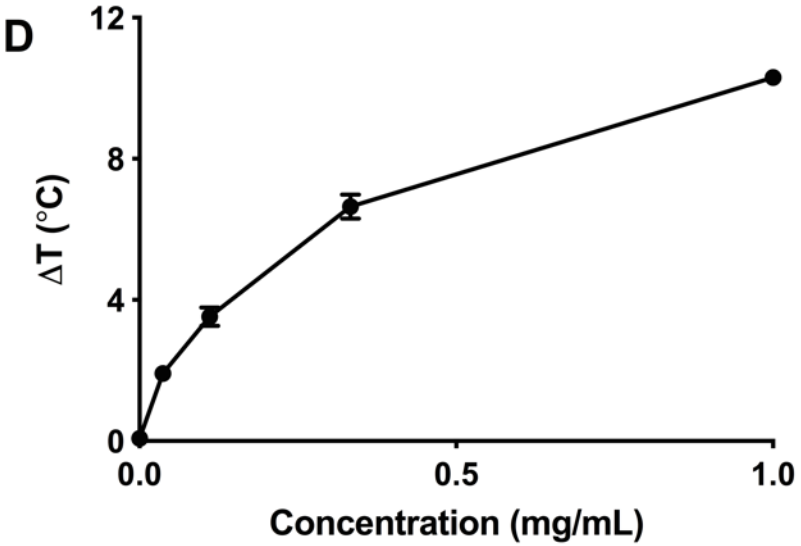
Photothermal Therapy: Composite DMOD Nanogels with Gold Nanoparticles









- ✓ Precipitation of gold nanoparticles due to the intrinsic reducing ability of N,N-dimethylethylenediamine
- ✓ AuNP absorb 532 nm laser and transduce to heat

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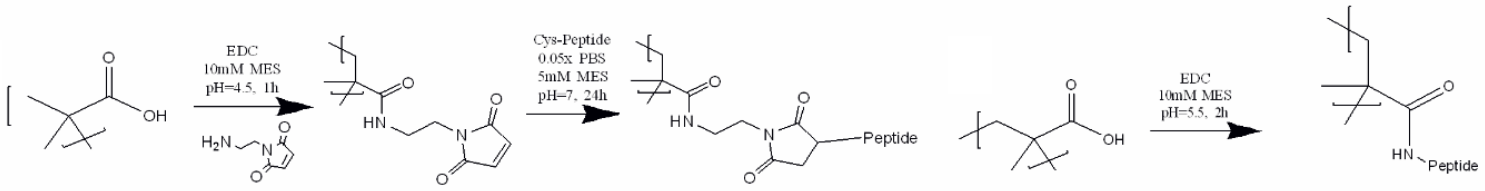
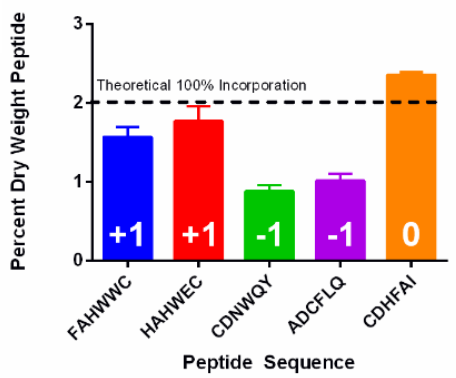
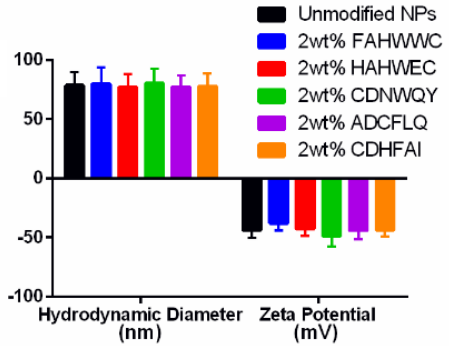
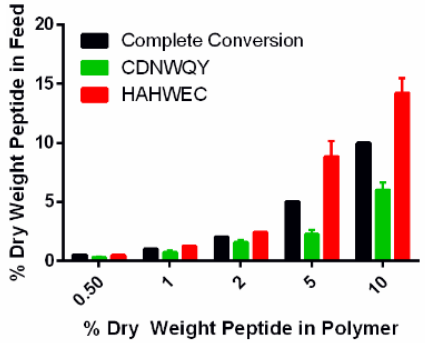
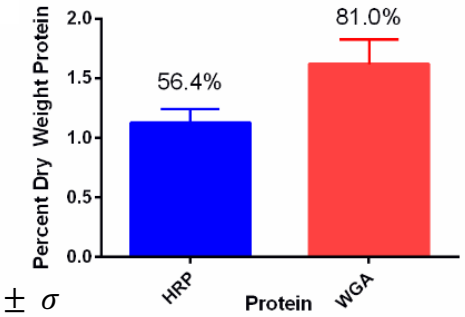
Nanogel Bioconjugation: Peptides and Proteins



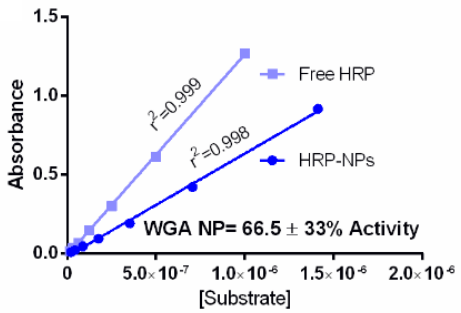


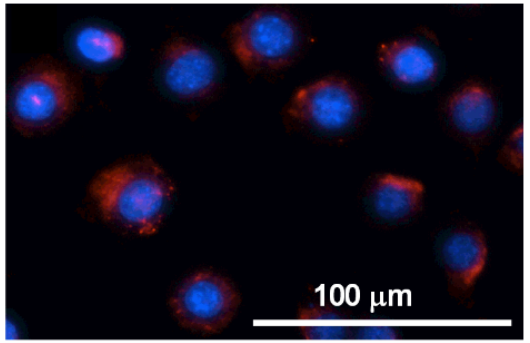






n = 3, $\bar{x} \pm \sigma$





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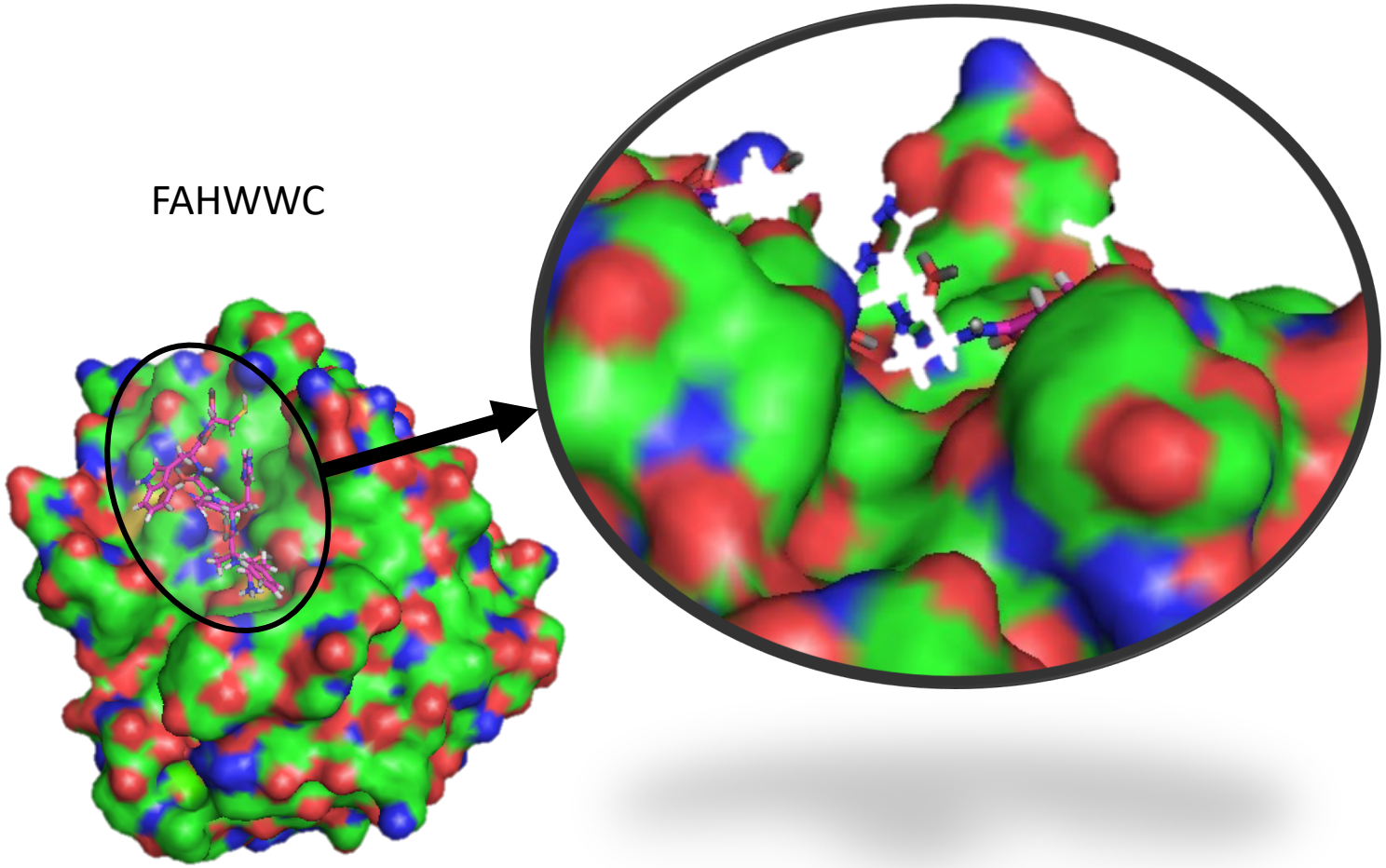
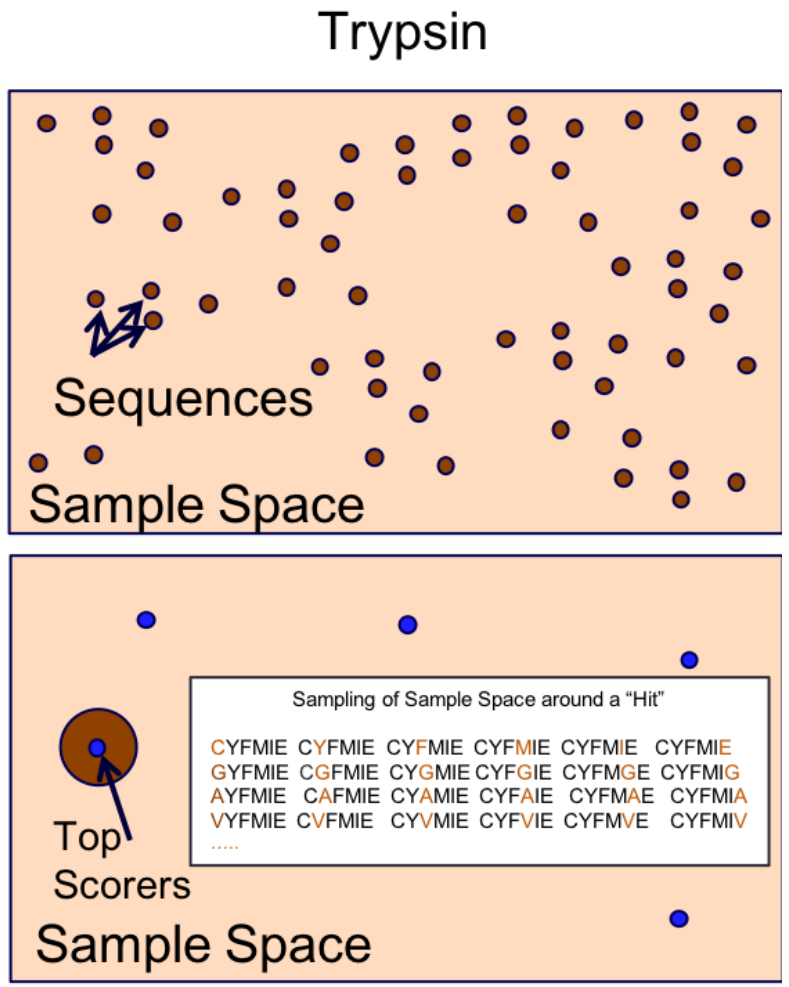
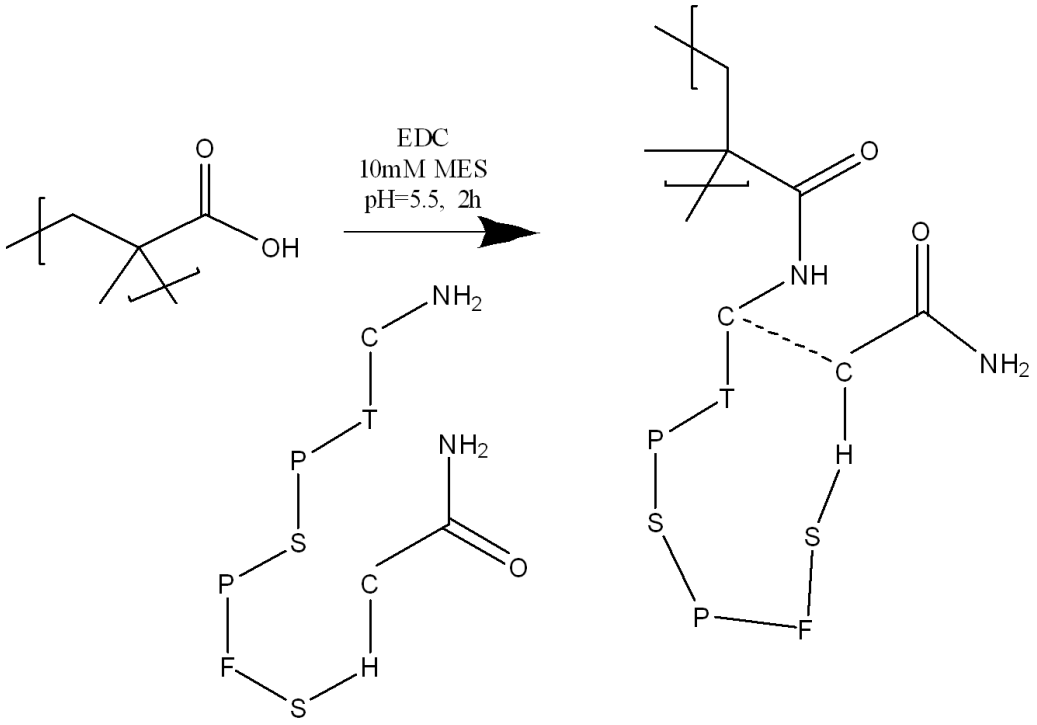
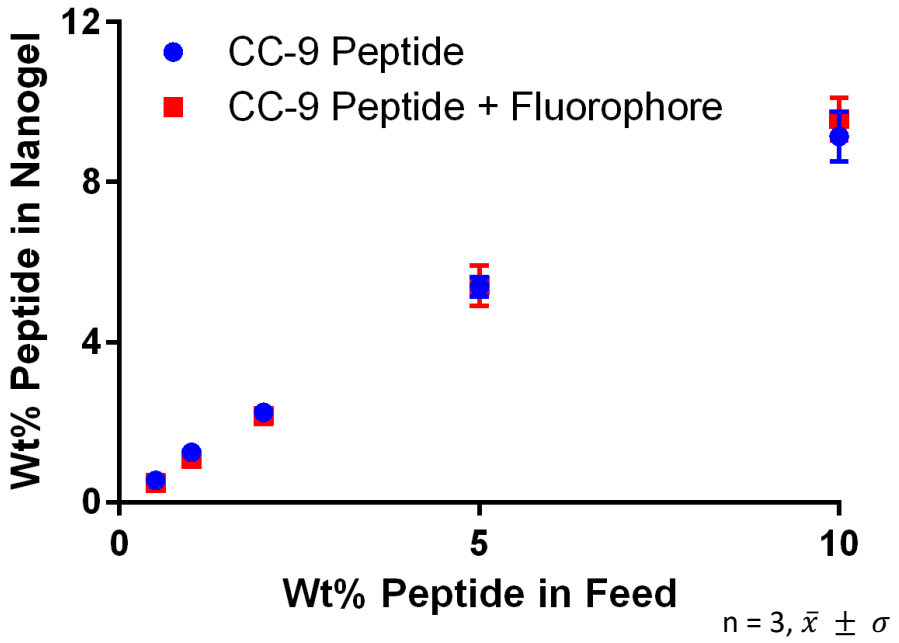
Methods for Peptide Identification – Molecular Docking





Covalent Coupling of Cell Targeting Peptides to P(AAm-co-MAA) Nanogels

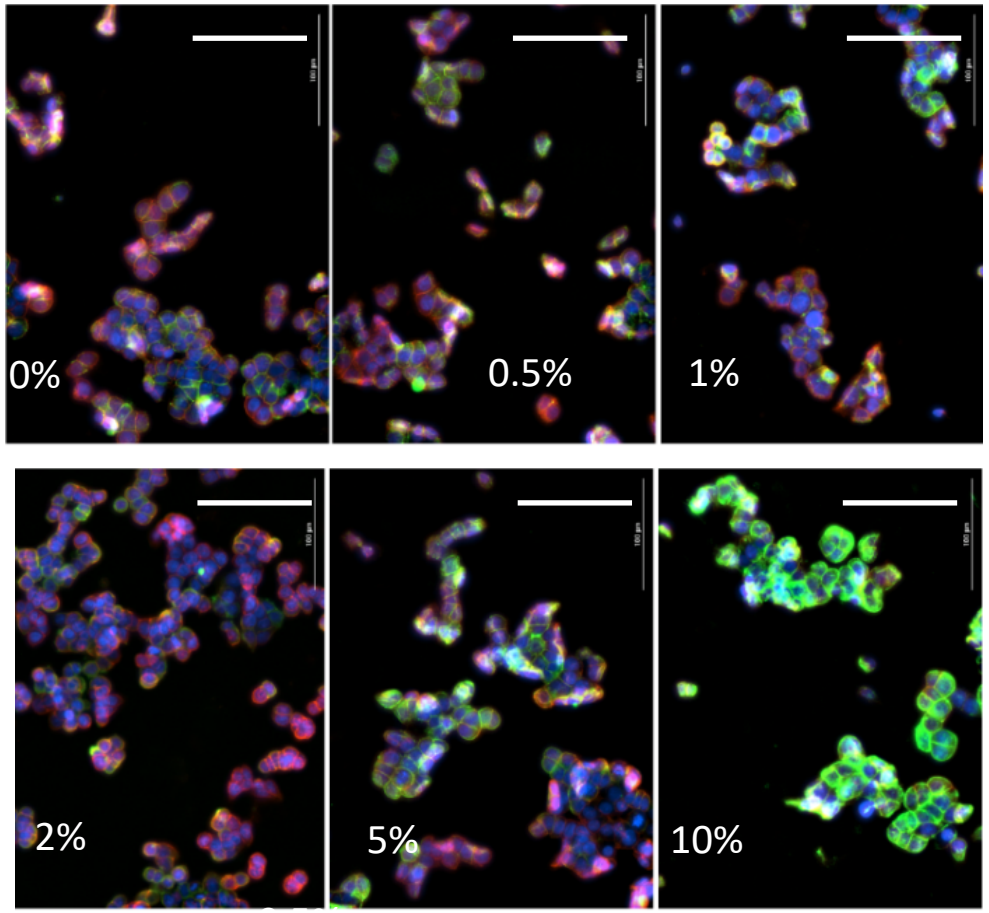


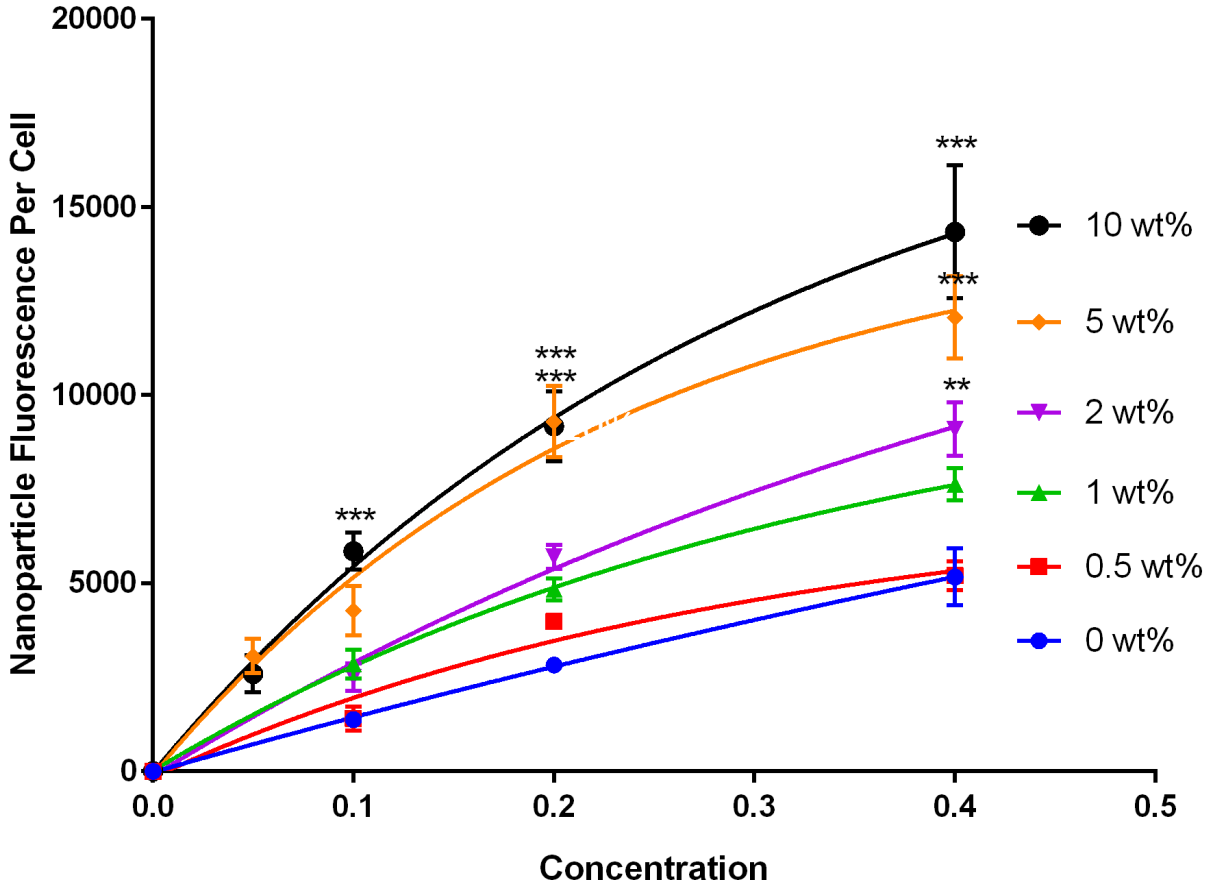


n = 3, $\bar{x} \pm \sigma$

Targeting of Colorectal Tumors with a Peptide-Polymer Nanoparticle Conjugate

Scale bar = 100 μm





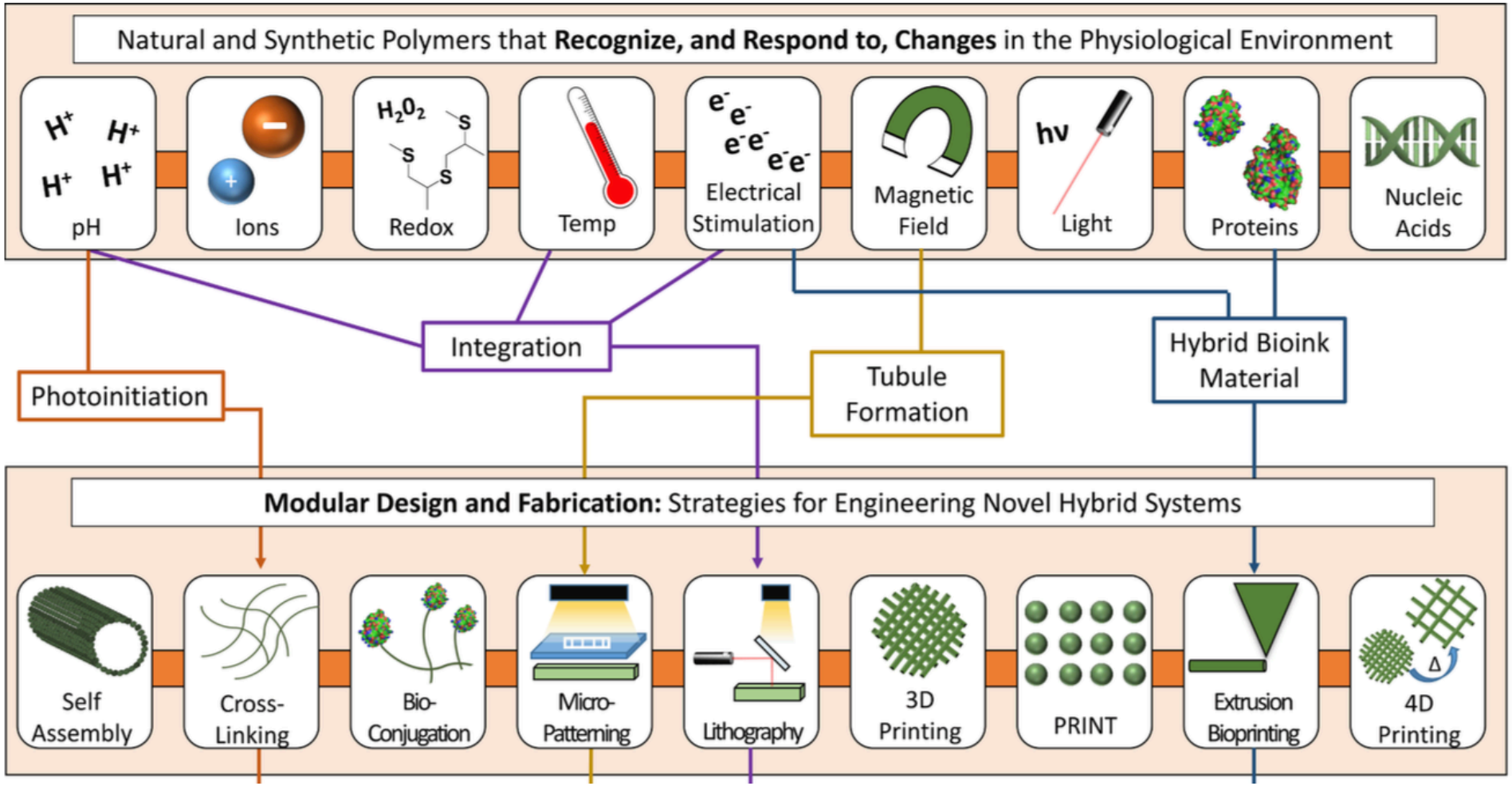
n = 4-8, $\bar{x} \pm \sigma$, *p<0.05, **p<0.01, ***p<0.001

Question Break

Summary

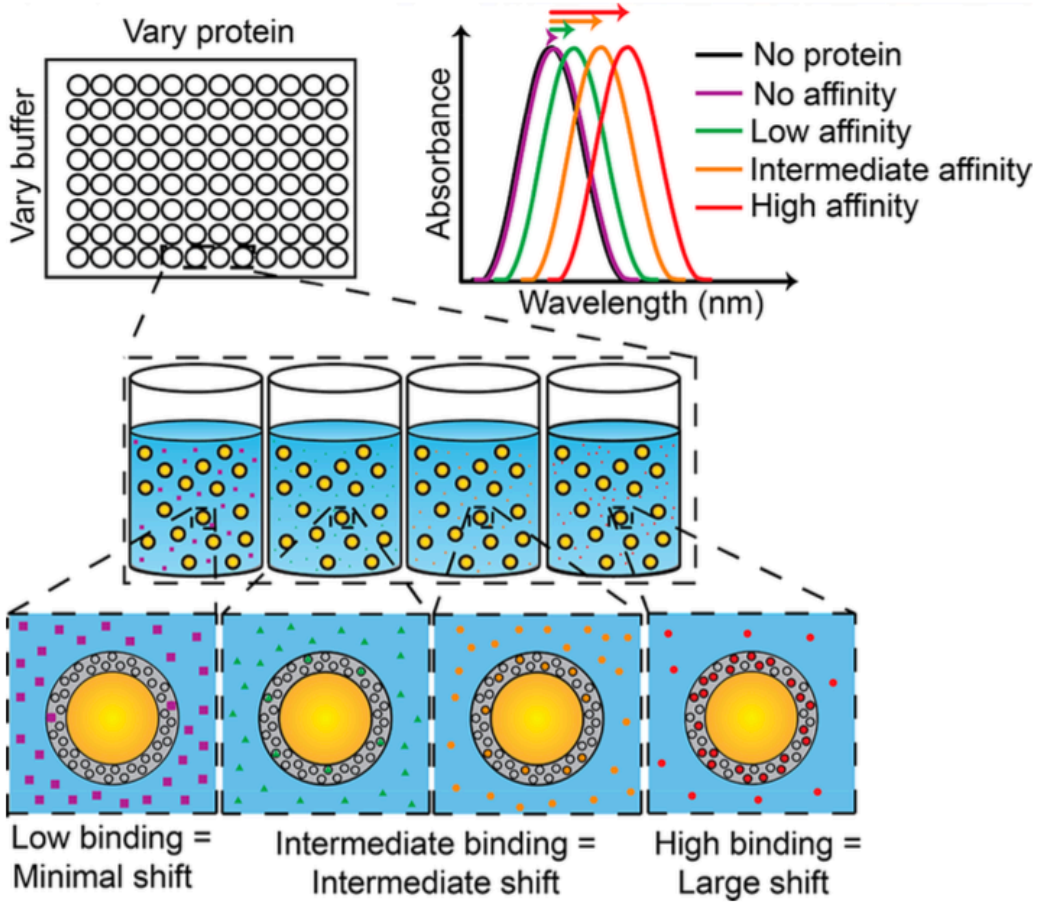
- We have invented a ***new P(MAA-co-AAm) nanogel*** platform.
- P(MAA-co-AAm) is modifiable through EDC-catalyzed crosslinking. We have demonstrated how modification with functional small molecules ***promoted pH-responsive therapeutic release, enhanced cell uptake, and facilitated photothermal therapy.***
- Peptide modification is ***readily tunable*** by modulating the mass fraction of free peptide in the modification medium
- ***CC-9 targeting peptide*** modification increases internalization by colon cancer cells by up to 310%
- Along the way, we developed new **QCM-D methods** for quantifying the biological behavior of nanogels, as well as a **high throughput assay for nanogel uptake by cells.** Both new methods will be useful to the nanomedicine field.

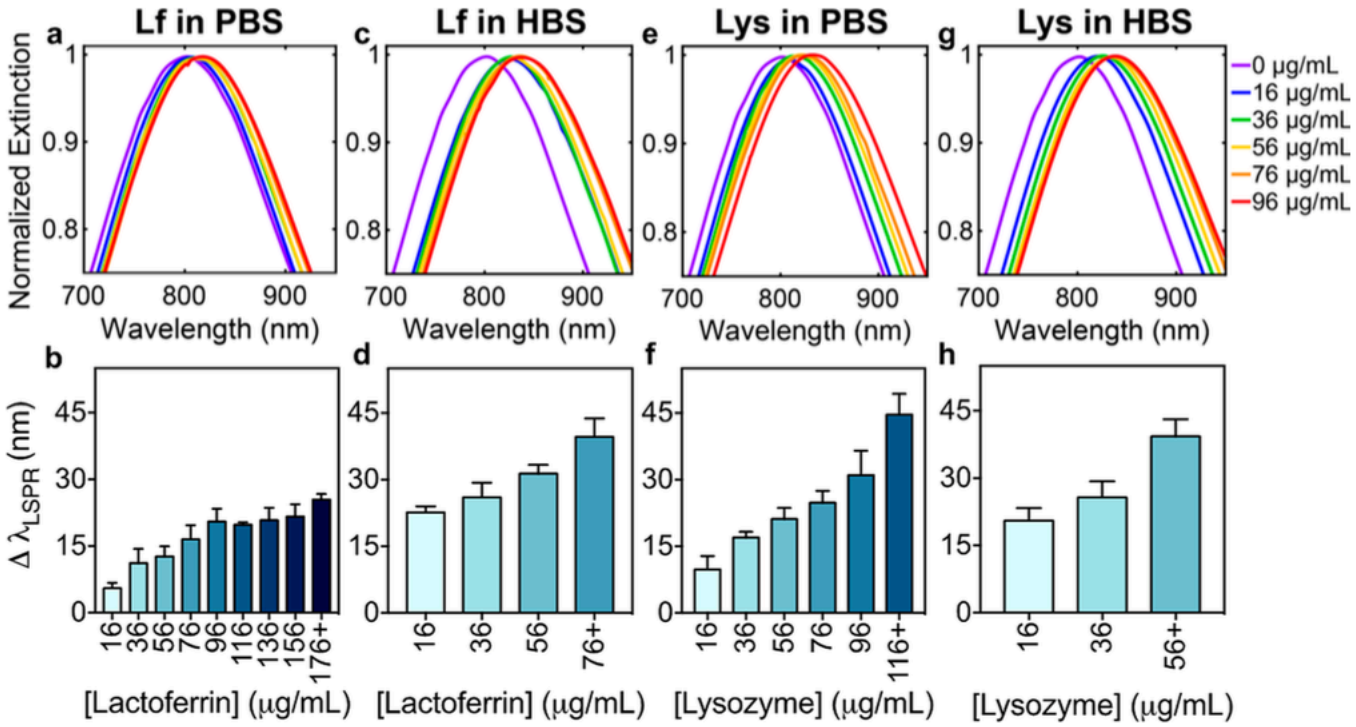
Design and Evaluation of Recognitive Biomaterials for Diverse Precision Medicine Applications



Clegg, J.R., Wagner, A.M., Shin, S.R., Hassan, S., Khademhosseini, A. and Peppas, N.A., 2019. Modular fabrication of intelligent material-tissue interfaces for bioinspired and biomimetic devices. *Progress in Materials Science*, p.100589.

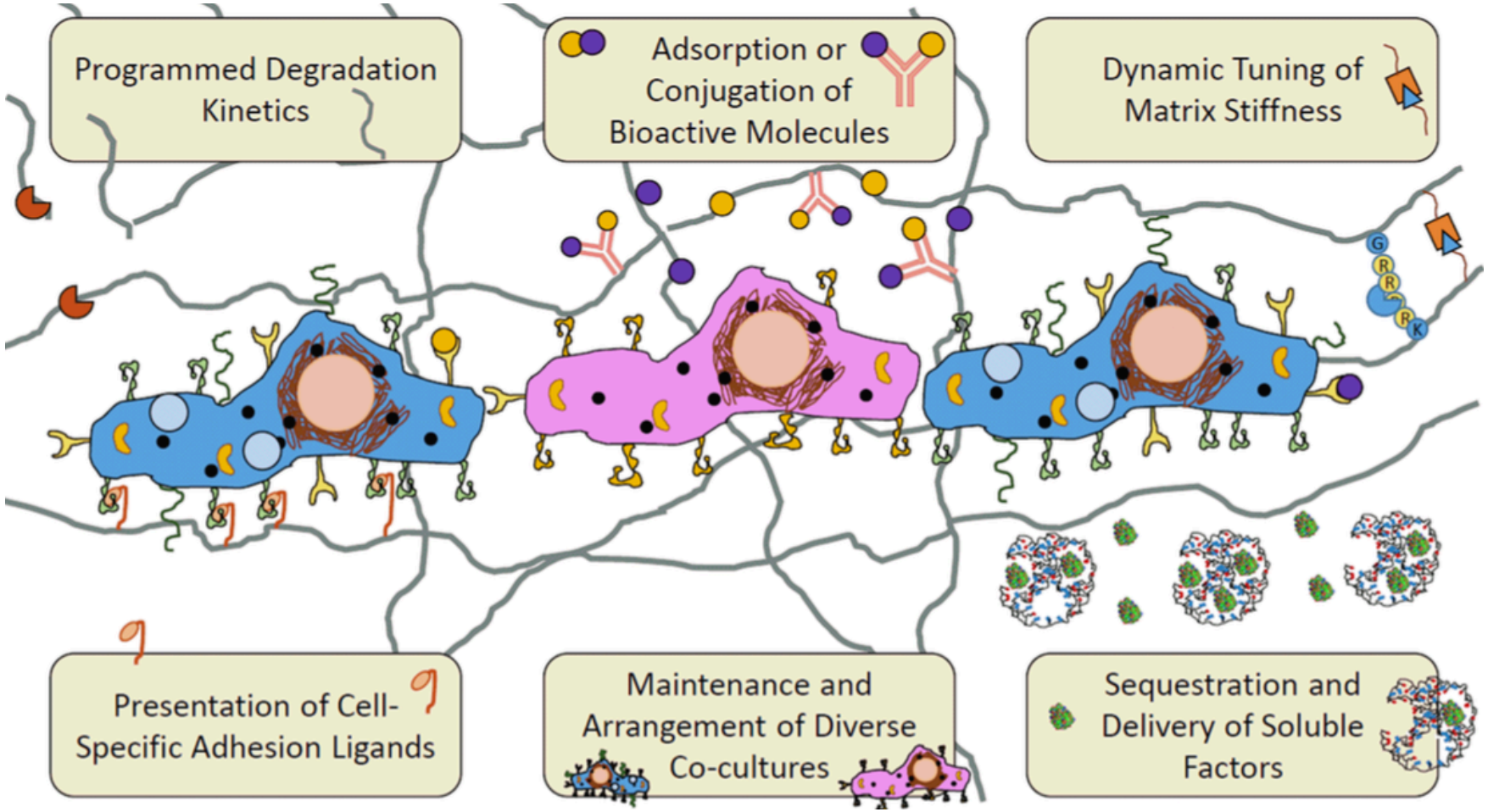
Polymeric Recognition Elements as Biosensors

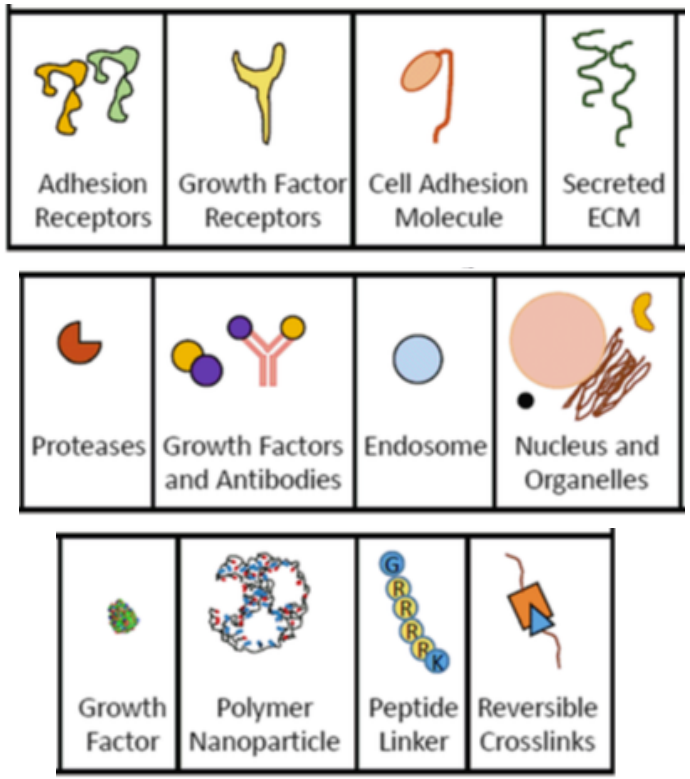




Culver, H.R., Wechsler, M.E. and Peppas, N.A., 2018. Label-free detection of tear biomarkers using hydrogel-coated gold nanoshells in a localized surface plasmon resonance-based biosensor. *ACS nano*, *12*(9), pp.9342-9354.

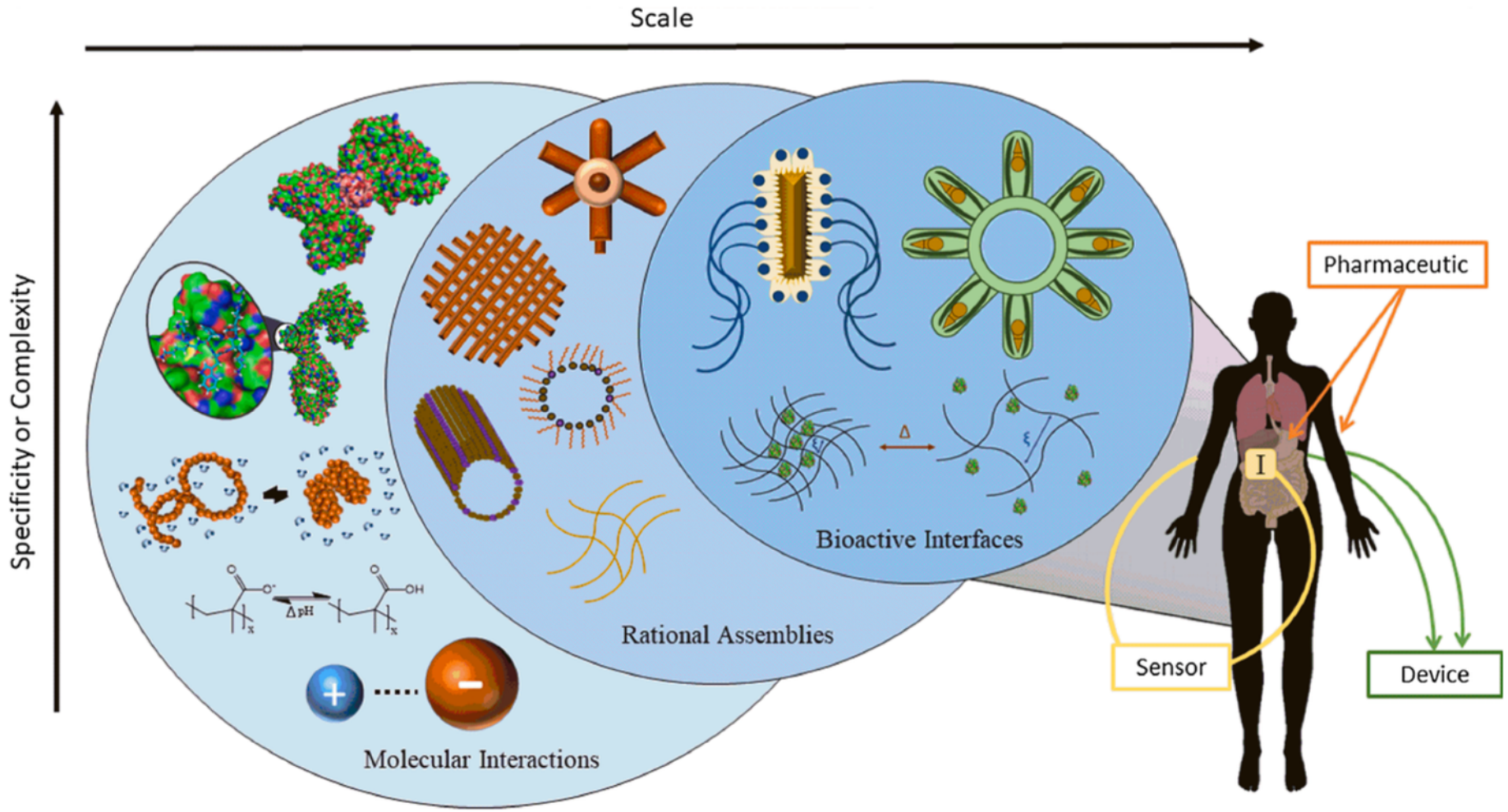
Modular Scaffolds for Tissue Regeneration





Clegg, J.R., Wechsler, M.E. and Peppas, N.A., 2017. Vision for functionally decorated and molecularly imprinted polymers in regenerative engineering. *Regenerative engineering and translational medicine*, *3*(3), pp.166-175.

Modular Fabrication of Bioinspired Materials: Soft Actuators



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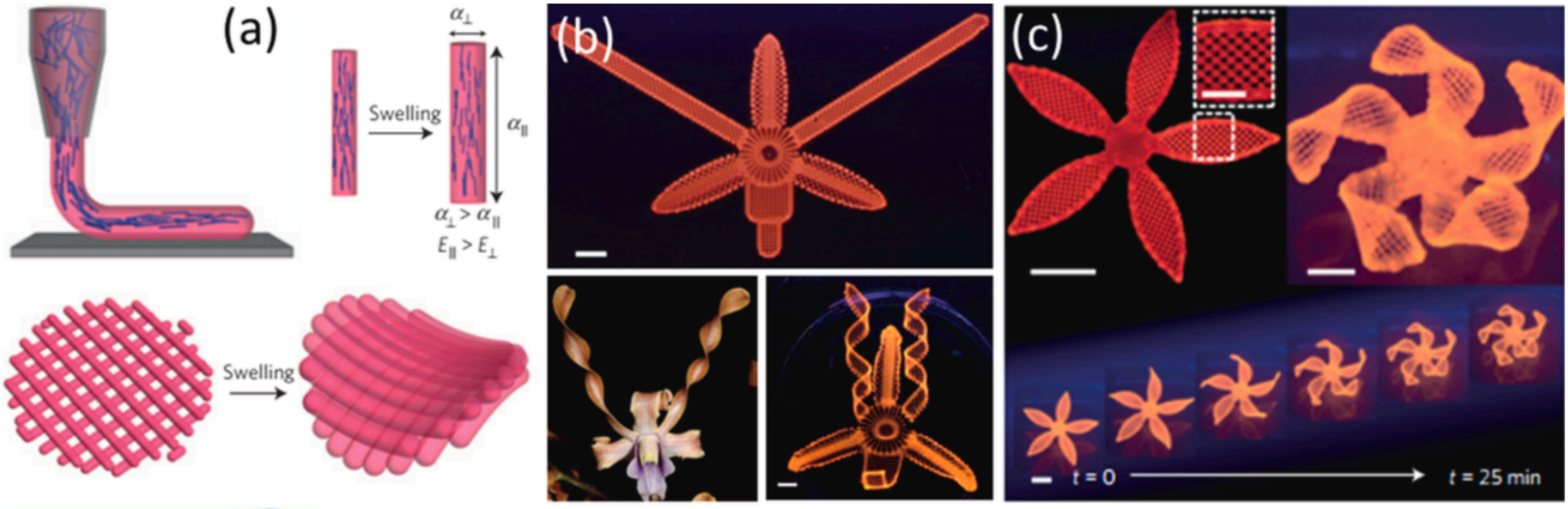
Bioinspired Soft Actuators: Bioprinting Smooth Muscle Cells



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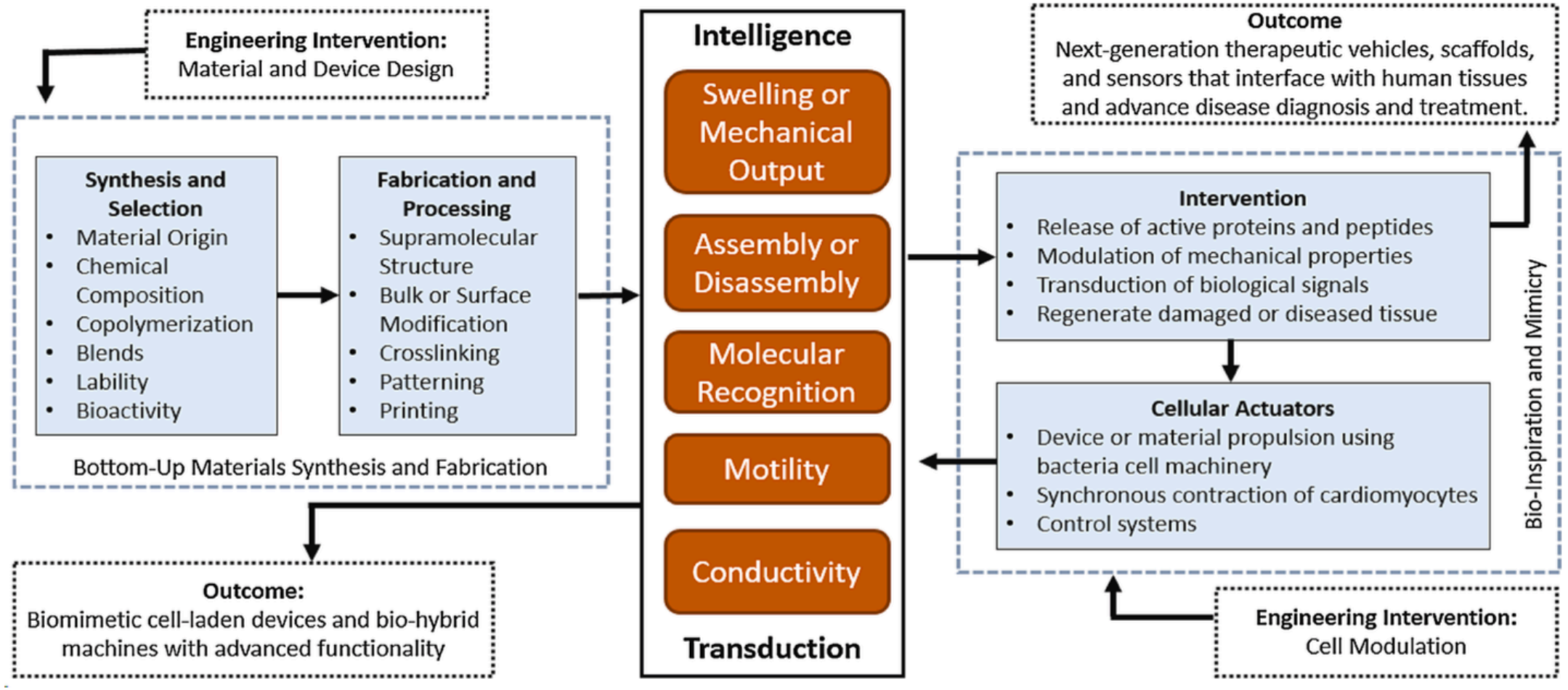
Summary and Conclusion



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Summary and Conclusion

- The thermodynamics of polymer-solvent and polymer-analyte interactions lead to **interesting and useful properties, which can be leveraged for medical applications.**

- Through rational design of intelligent or responsive materials, it is possible to apply new formulations within **drug delivery, biosensing, and tissue regeneration, amongst other applications.**

- I provided on detailed case study, on applying modular nanogels for **cancer precision medicine.** As you could see, through responsiveness to the environment and recognition of cell receptors, we achieved **cell targeting, tunable biodegradation, and a controlled release of therapeutic agents.**

- It is my hope that responsive materials, and constructs thereof **can address unmet healthcare needs in the future.**

Acknowledgements:

Email: jclegg@seas.harvard.edu
Twitter: @JohnRClegg

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Cockrell School of Engineering

UT Austin | Portugal
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