

Translational Applications of Dendrimers for Drug and Gene Delivery

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AIChE Dallas Section
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B.S.
B.S., Biochem Eng Emphasis
M.S.
Ph.D.
Certificates

THE LINDA AND BIPIN DOSHI DEPARTMENT OF CHEMICAL AND BIOCHEMICAL ENGINEERING FUND



Linda and Bipin Doshi

\$10M naming gift

The largest individual contribution
to an academic program in the
university's history

MISSOURI
S&T

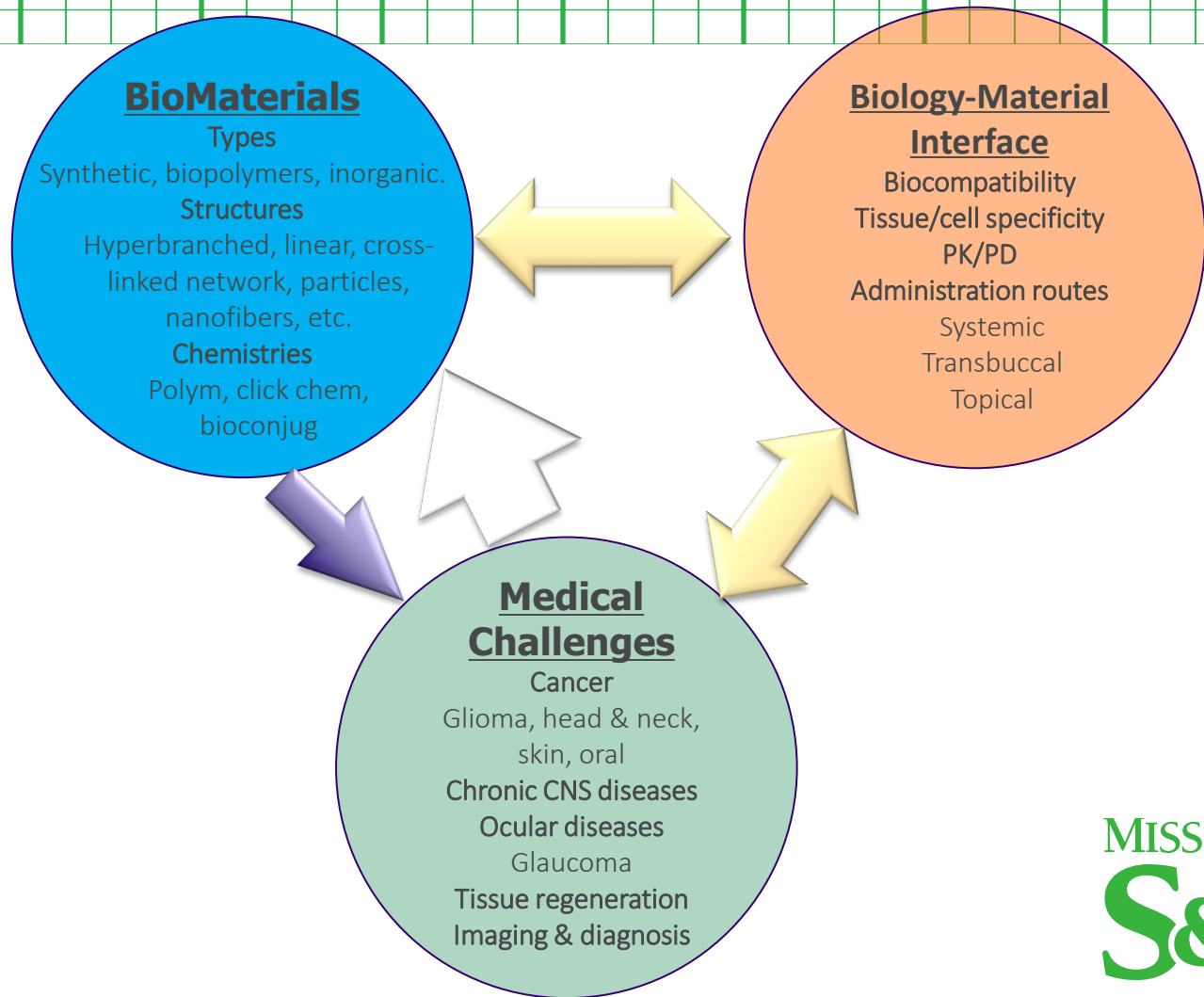
Two junior faculty positions

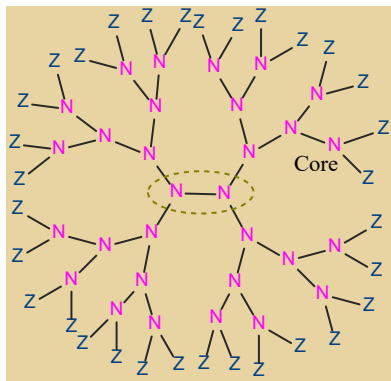
- > Bioengineering (position 1)
 - Drug and gene delivery, biomaterials, nanomedicine, tissue engineering
- > Carbon management (position 2)
 - Carbon capture, carbon storage, carbon conversion

Research overview & career motivation

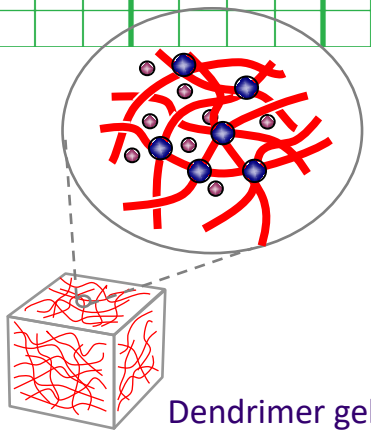
Develop enabling delivery systems to

- improve therapeutic index & drug properties
- achieve controlled release ,
- enable non-invasive alternative administration and improve patient compliance
- foster translational and convergence research and education

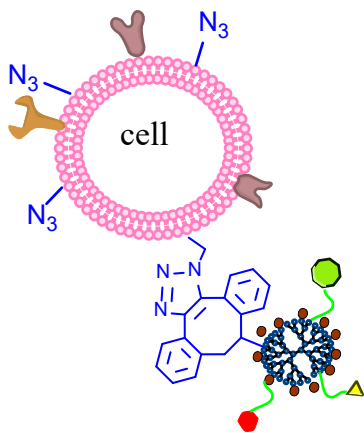




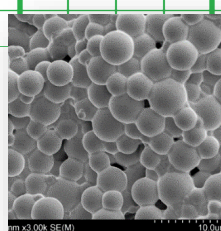
Dendrimer



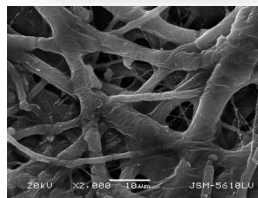
Dendrimer gel



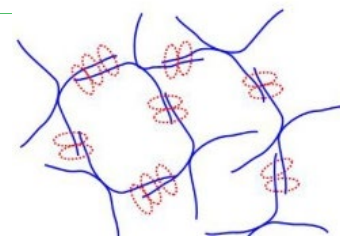
Cell-nanoparticle hybrids



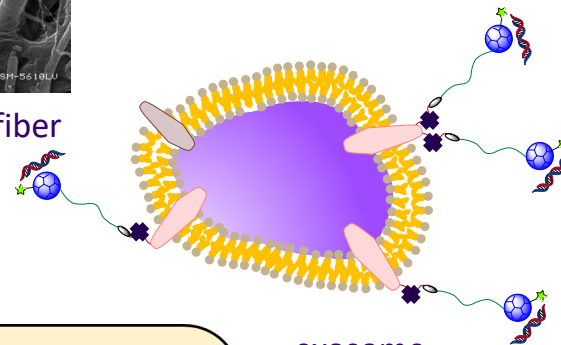
Dendrimer gel particles



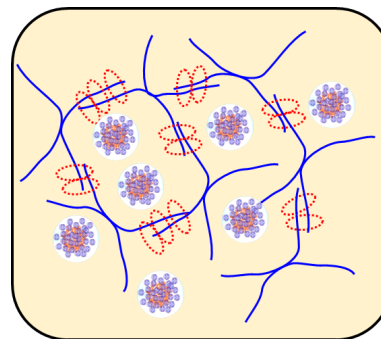
Dendrimer fiber



Supramolecular hydrogel



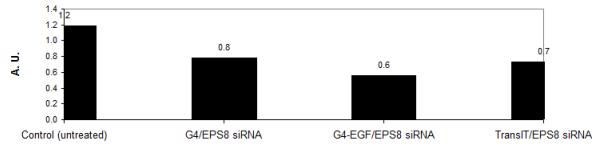
exosome



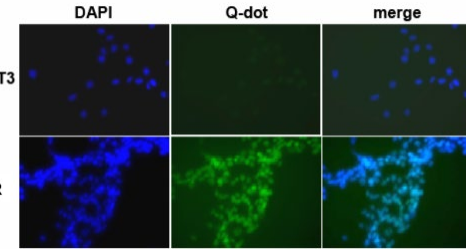
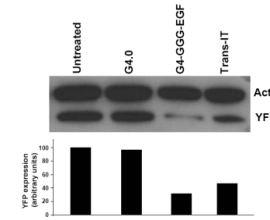
adenovirus



National Institute of Dental and Craniofacial Research

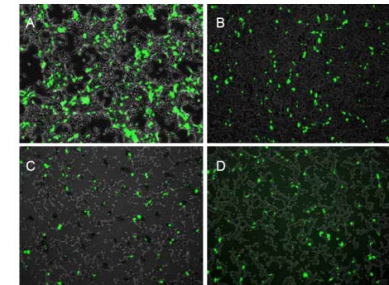
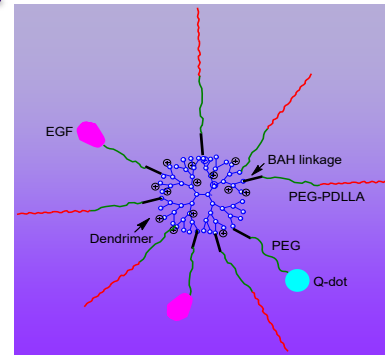


EPS8 knockdown for head and neck cancer



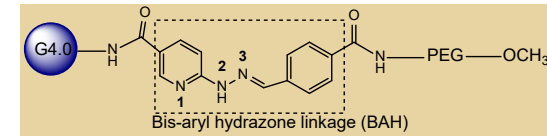
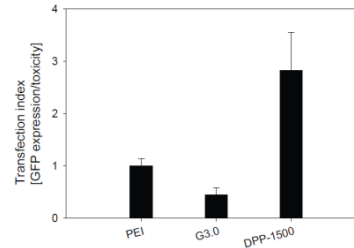
Oral Oncology 2010

- Targeted delivery
- Improved gene transfection
- Tumor imaging
- Improved biocompatibility



Fusogenic property for permeation through the plasma membrane

Acta Biomaterialia 2010



Biomacromolecules 2010

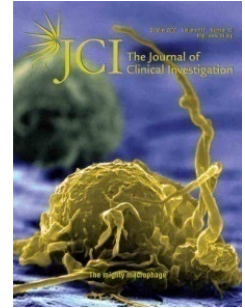


Philips Institute for Oral Health Research



Roles of Cholesteryl Ester Hydrolase (CEH)

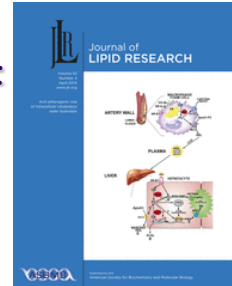
2007 - Macrophage-specific transgenic expression of CEH attenuates diet induced atherosclerosis and lesion necrosis in LDLR^{-/-} mice - increased RCT as the underlying mechanism. *JCI* 117:2983-2992



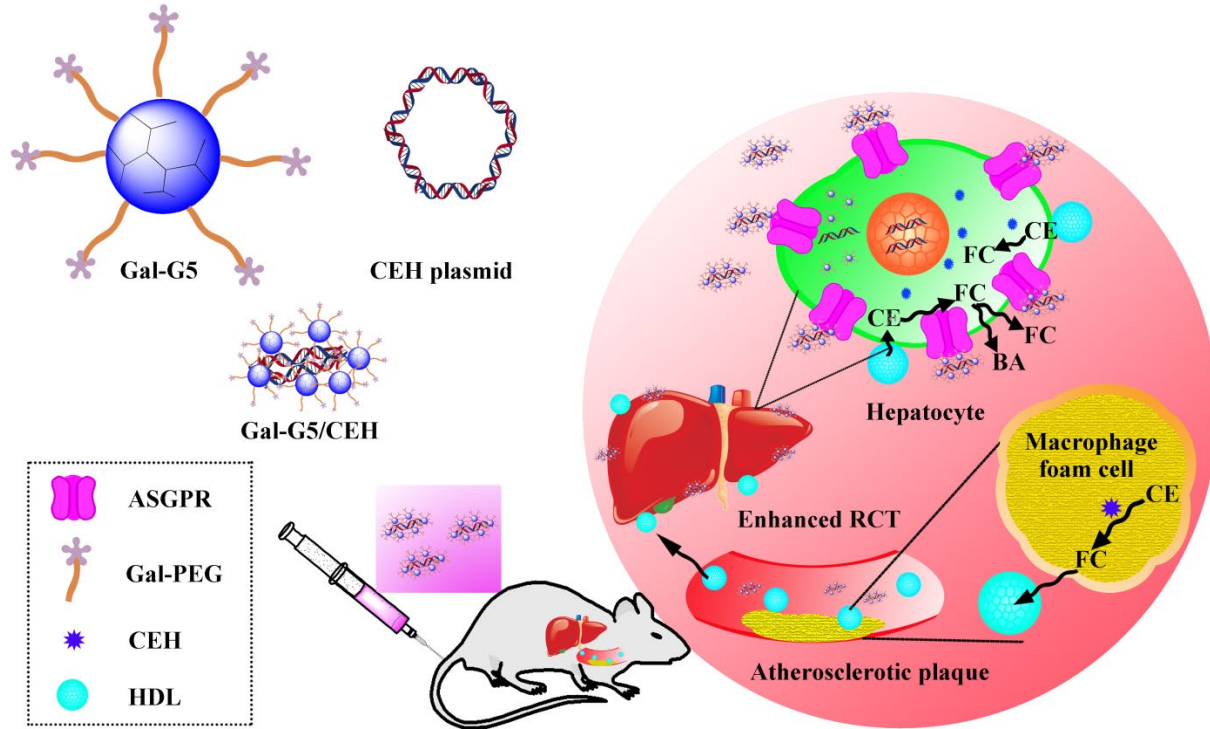
2010 - LXR agonist increase CEH promoter activity. *Vascular Pharmacology* 52:1-10

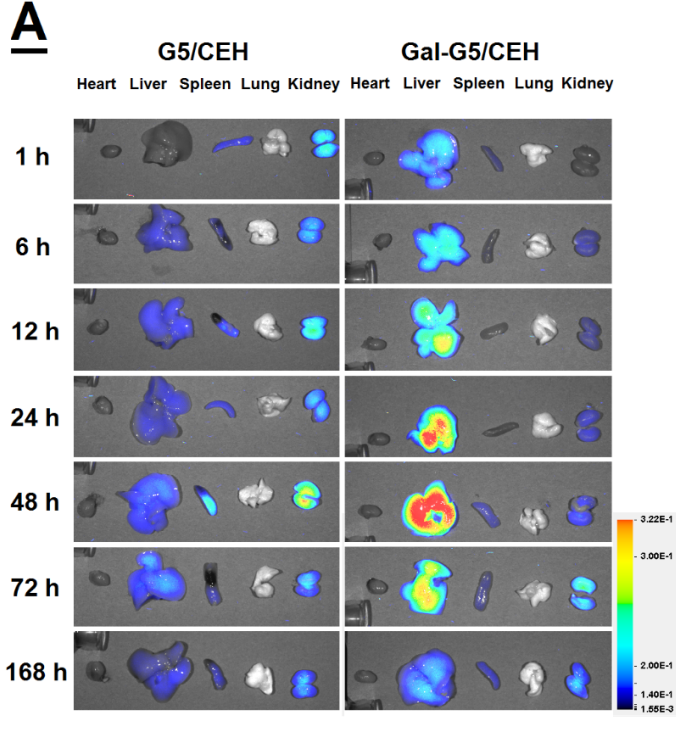
2011 - Decreased CEH in human atherosclerotic plaques. *Expert Review of Cardiovascular Therapy* 9:329-340

2014 - Liver-specific transgenic expression of CEH reduces atherosclerosis in LDLR^{-/-} mice. *JLR* 55:729-738

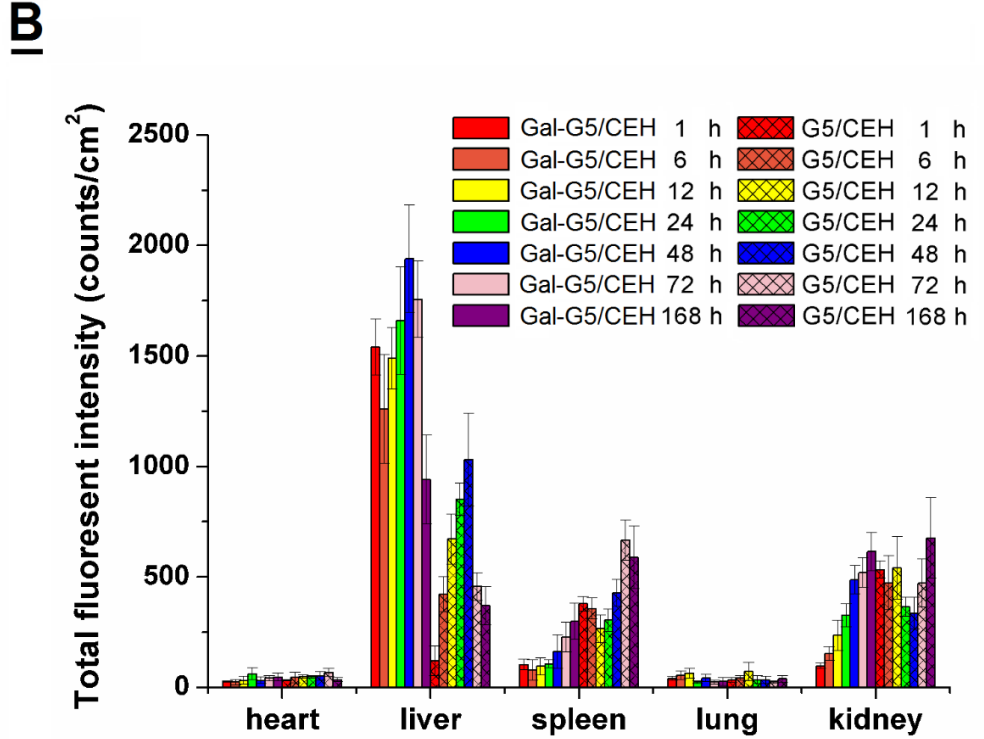


Galactose-functionalized dendrimers (Gal-G5) for CEH plasmid delivery

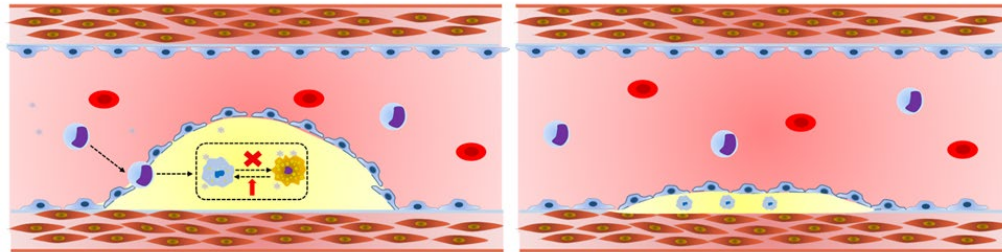
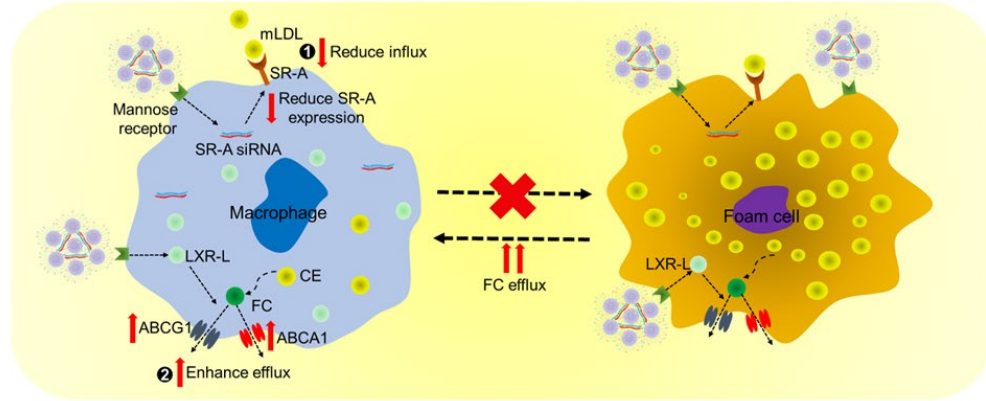
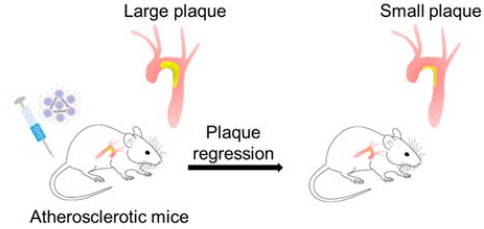
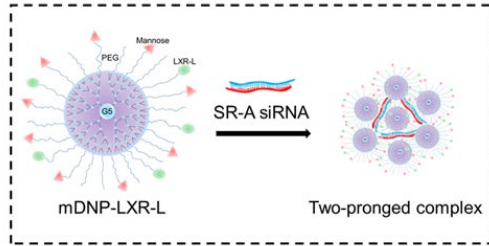




CEH: cholesteryl ester hydrolase plasmid



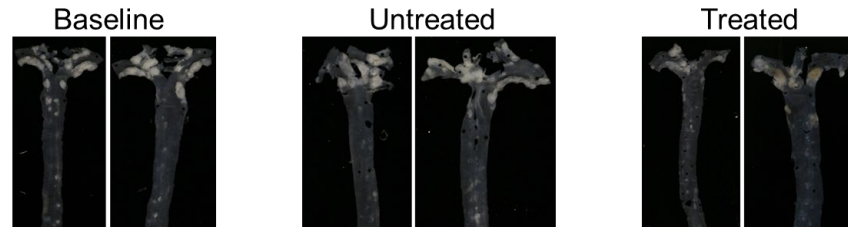
A two-pronged approach to combat atherosclerosis



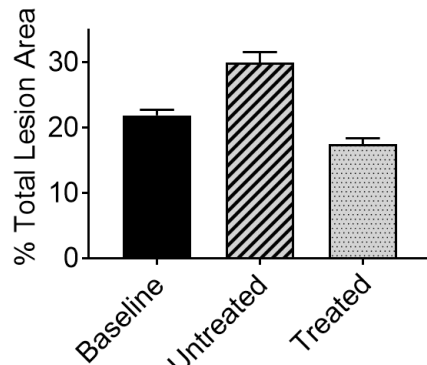
Plaque regression



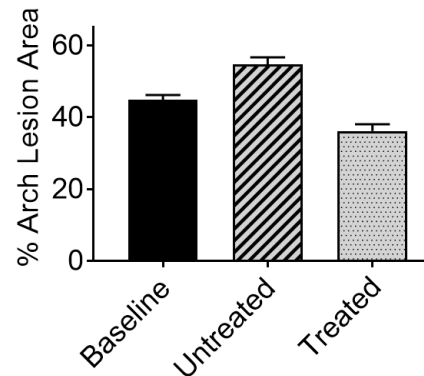
A



B



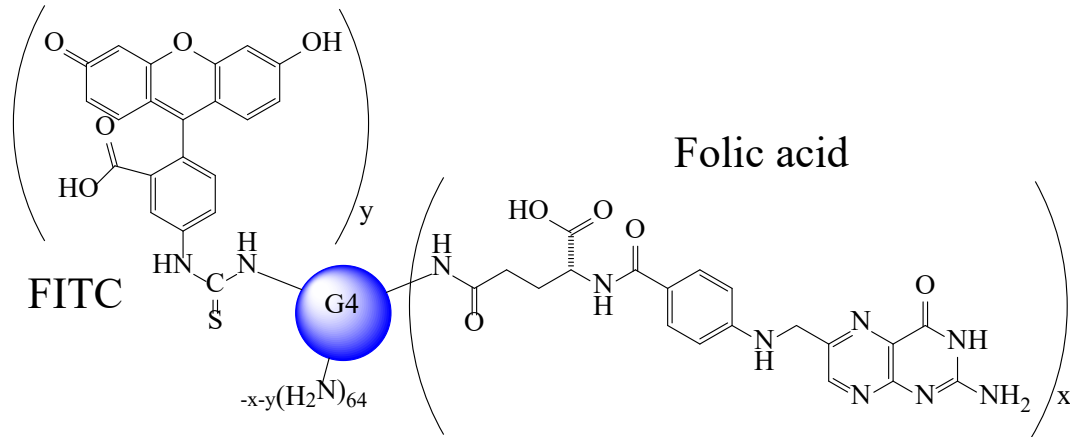
C

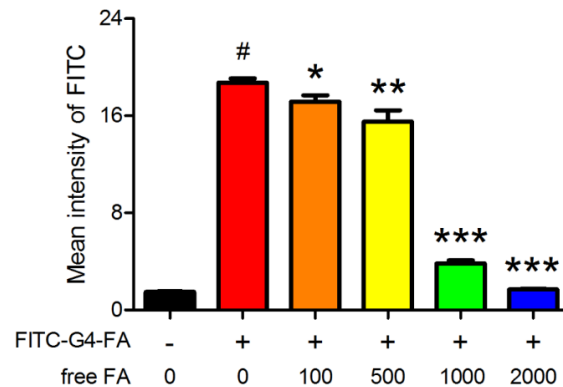
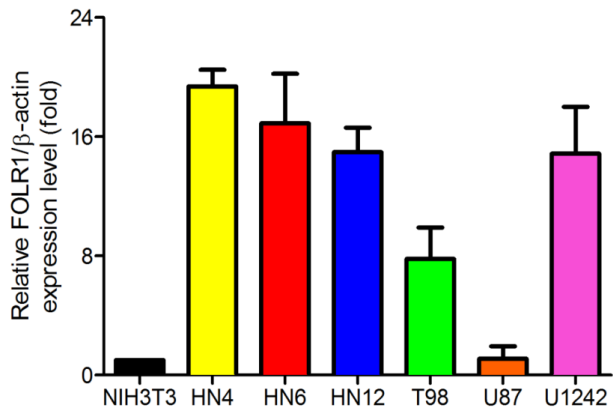
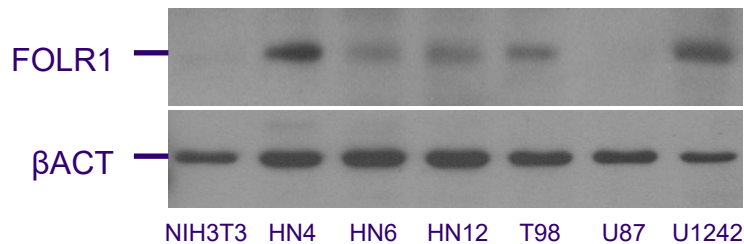


D

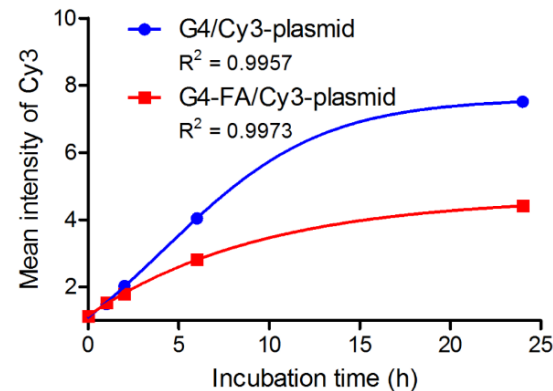
Groups Compared	Total Lesion Area	Arch Lesion Area
Baseline vs Untreated	21.9 ± 3.7 vs 29.9 ± 7.1, p<0.0001	44.8 ± 5.8 vs 54.6 ± 8.6, p=0.0007
Baseline vs Treated	21.9 ± 3.7 vs 17.4 ± 3.7, p=0.0382	44.8 ± 5.8 vs 36.2 ± 8.1, p=0.0026
Untreated vs Treated	29.9 ± 7.1 vs 17.4 ± 3.7, p<0.0001	54.6 ± 8.6 vs 36.2 ± 8.1, p<0.0001

Folic acid-functionalized dendrimers for siRNA delivery

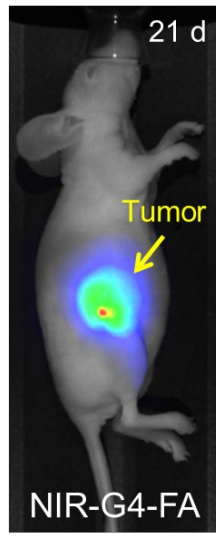
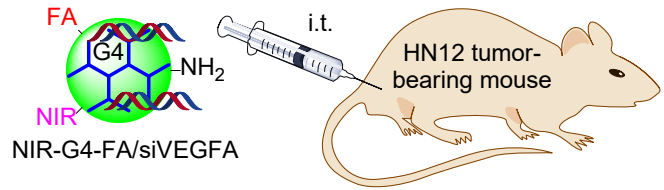




HN12 cells, 10 μ g/ml FITC-G4-FA conjugates, 2 h incubation



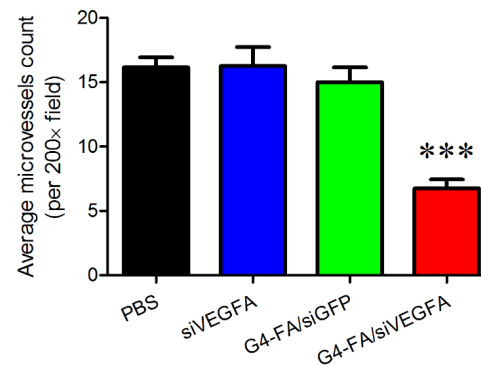
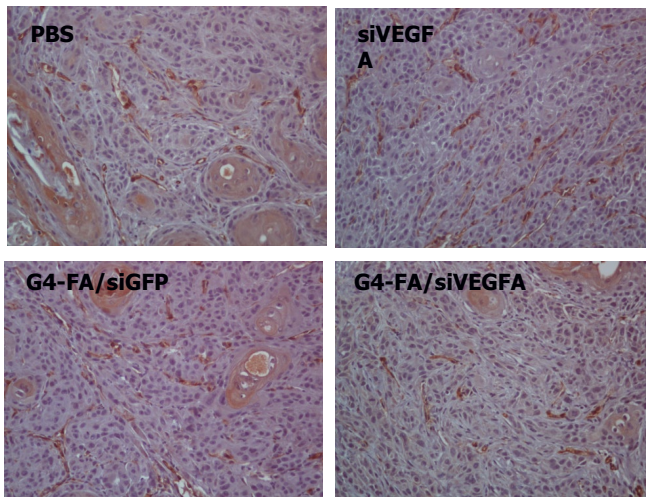
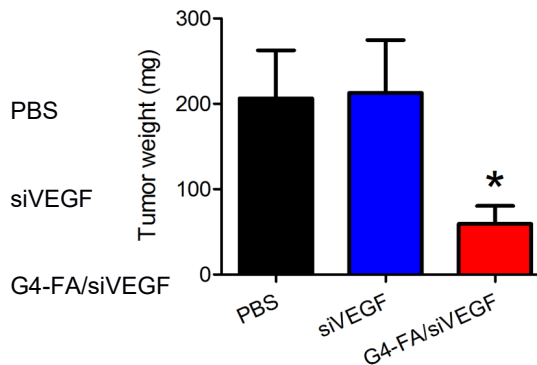
HN12 cells, G4-FA/Cy3 plasmid (5:1, wt/wt), free FA (0 or 500 μ g/ml)



35 µg of siVEGF/175 µg of dendrimer (n=6)

Acta Biomaterialia, 2017





Angiogenesis evaluation: CD31 staining

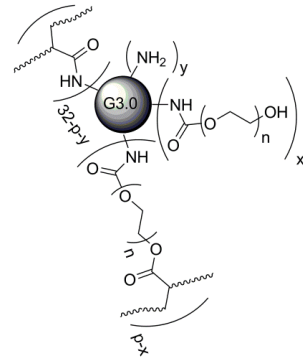
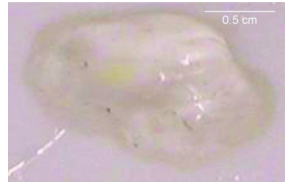
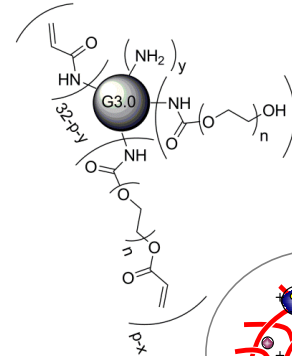
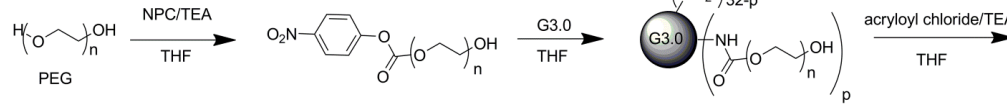
Cross-linking dendrimers: An innovative way to build higher order structures



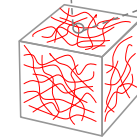
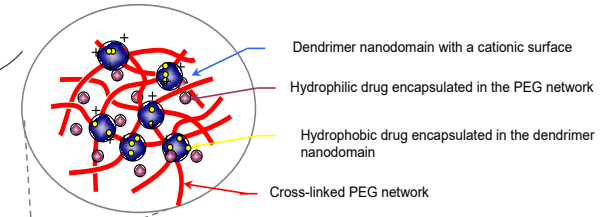
University
of Colorado
Denver



Department of
Ophthalmology



UV-curing
the eosin Y-based photoinitiating system



PEGylated dendrimer hydrogel



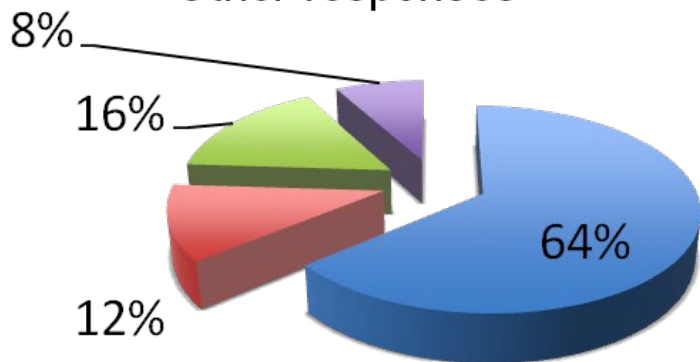
Biomacromolecules, 2010



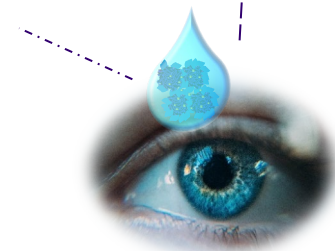
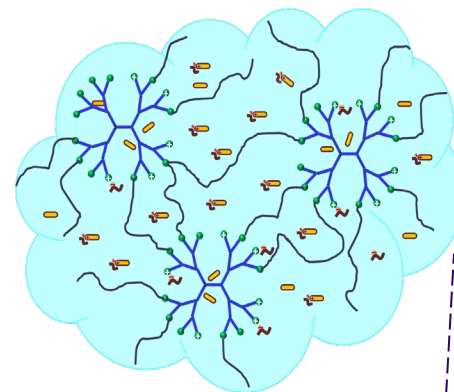
- Need

Patterns of Compliance

- Used as directed
- Missed occasional dose
- Missed up to 2 doses/week
- Other responses



- Our Solution



Developing safe, long-acting eye drop microgel formulations

MISSOURI
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A study shows over 70% surveyed patients prefer reduced dosing frequency.

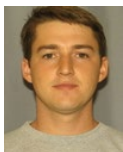


National Eye Institute

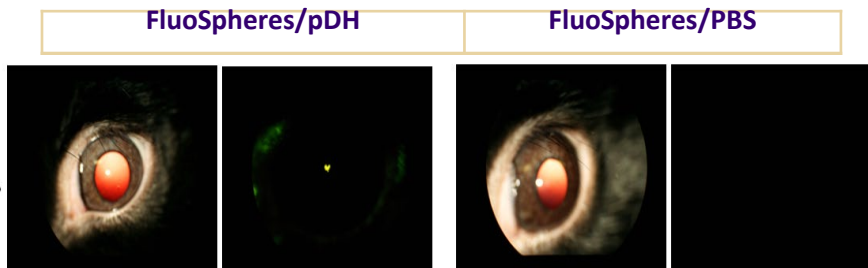
NATIONAL INSTITUTES OF HEALTH



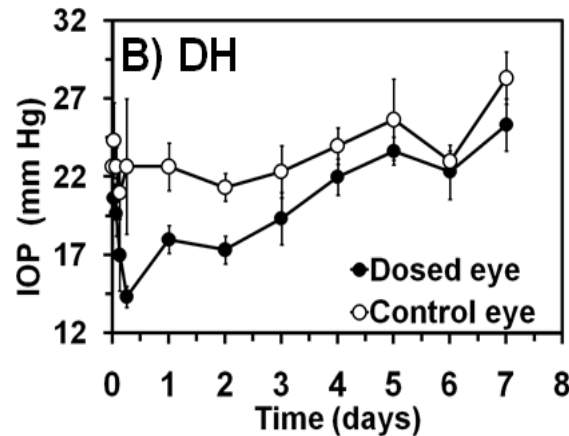
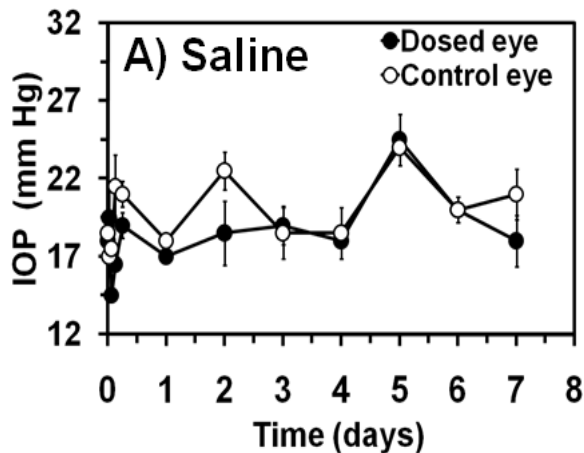
University of Colorado Denver



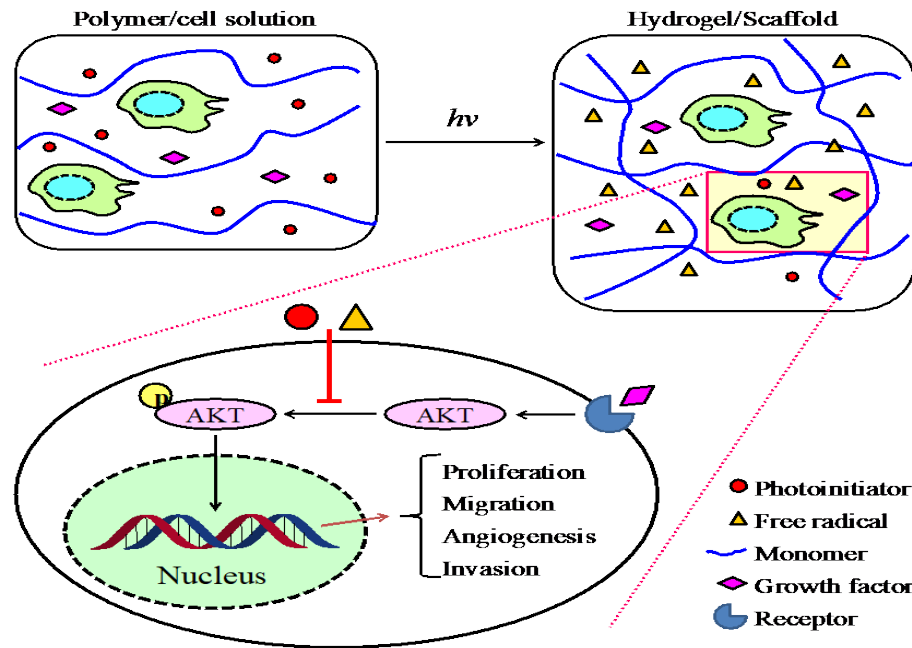
Day 7



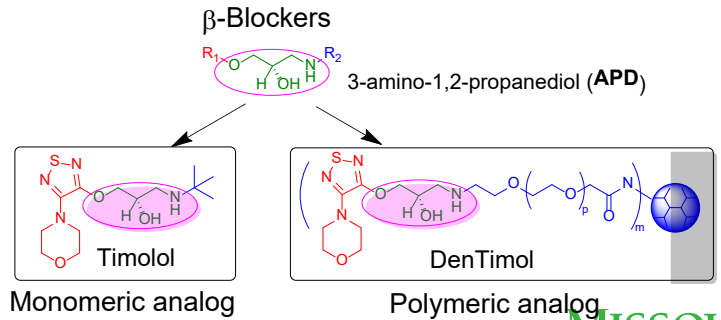
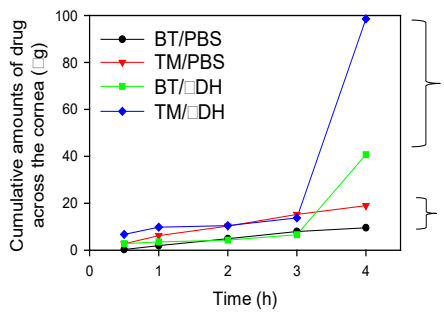
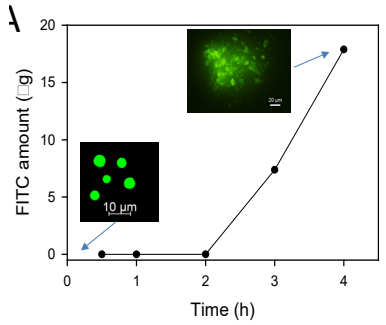
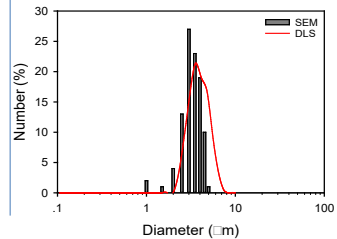
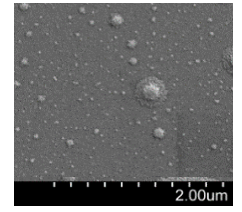
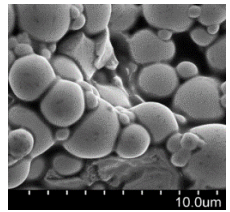
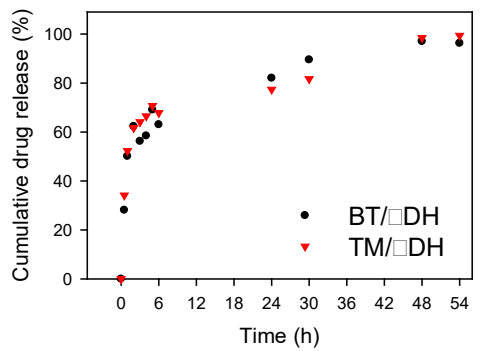
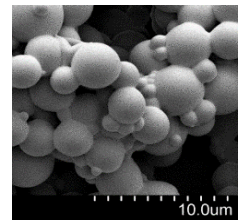
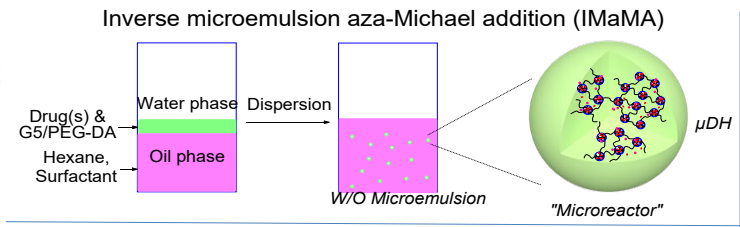
Dendrimer hydrogels for glaucoma

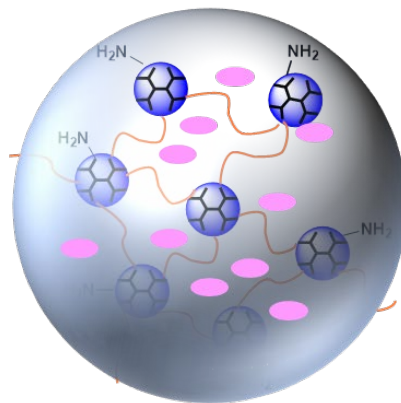
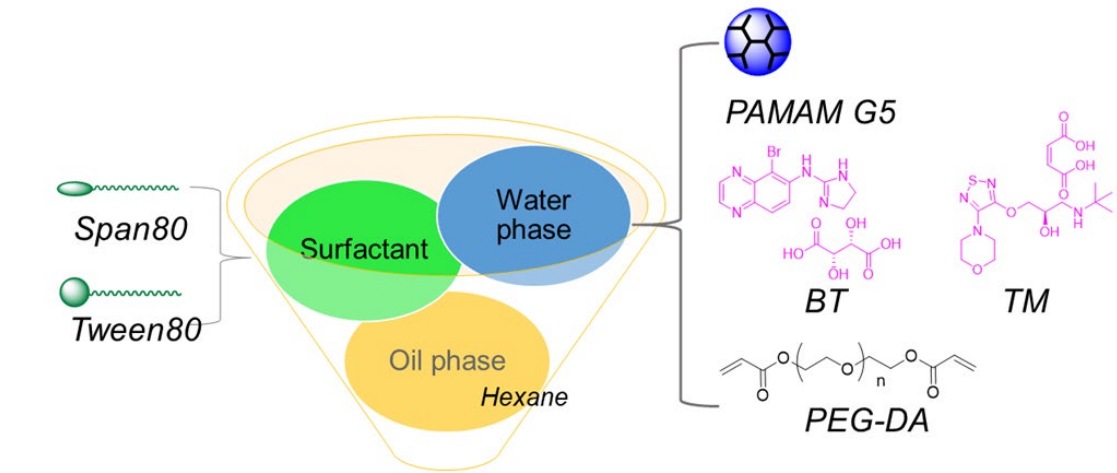


Administration: Topical
Dose: 0.7% brimonidine/3.5% timolol
Animal: Dutch belted rabbits

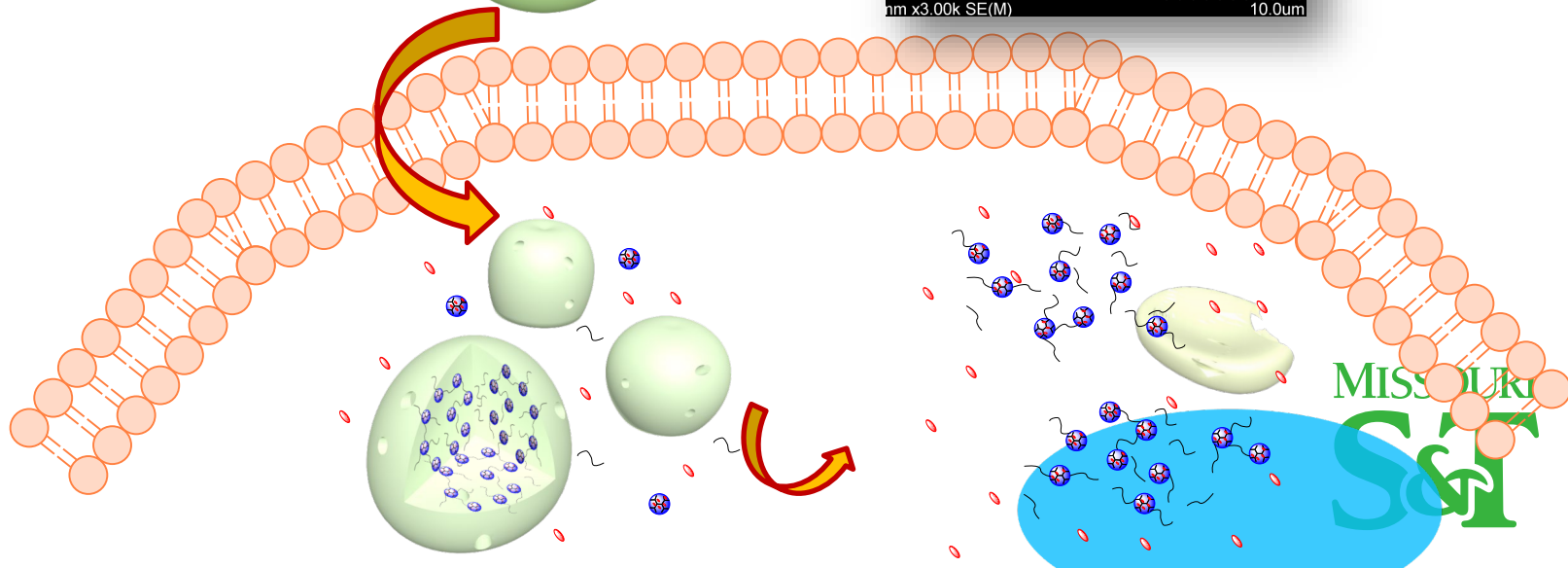
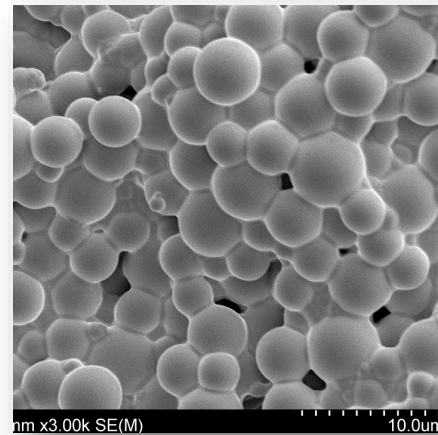
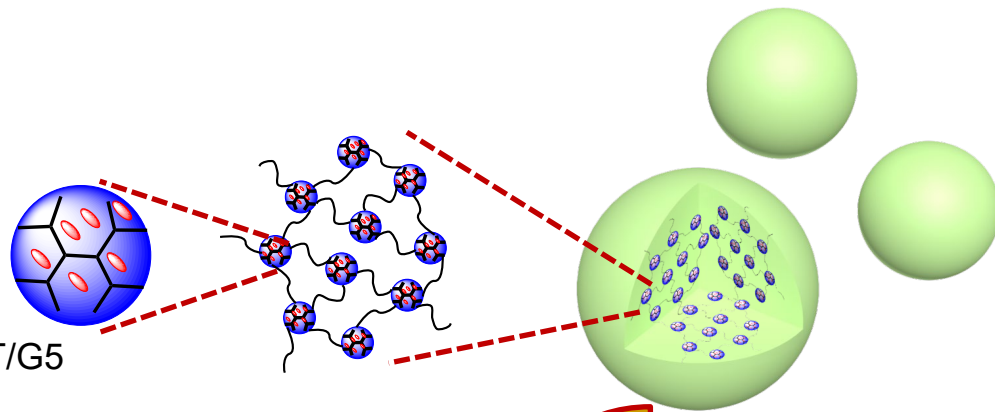


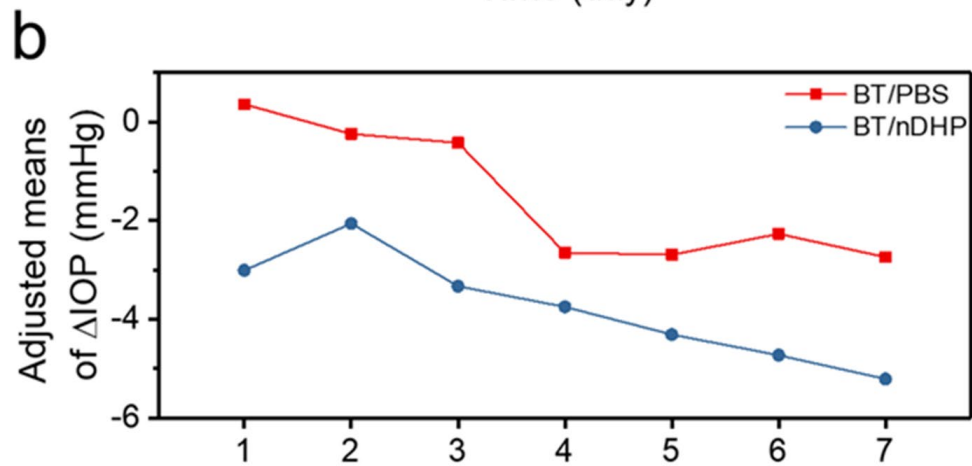
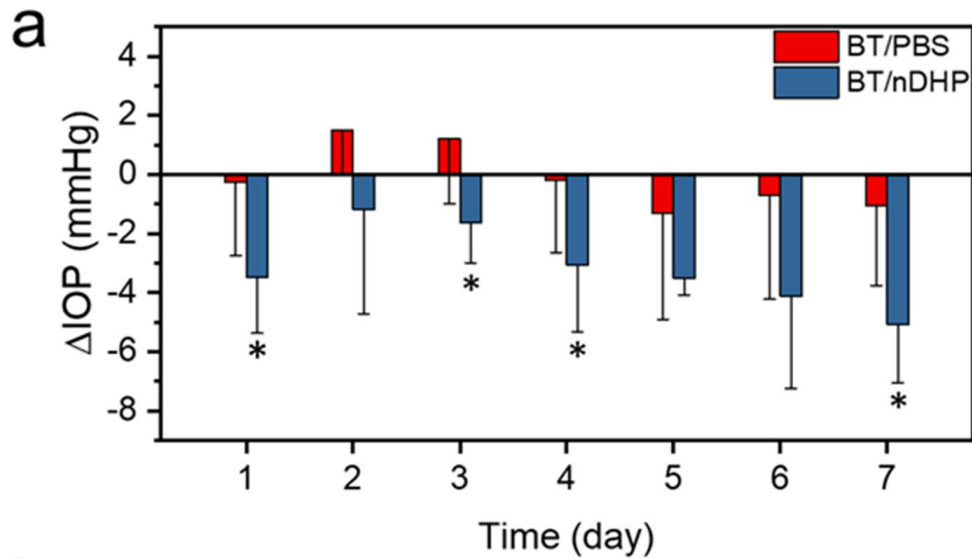
Dendrimer gel particles with expanded structural features for programmable drug delivery and release

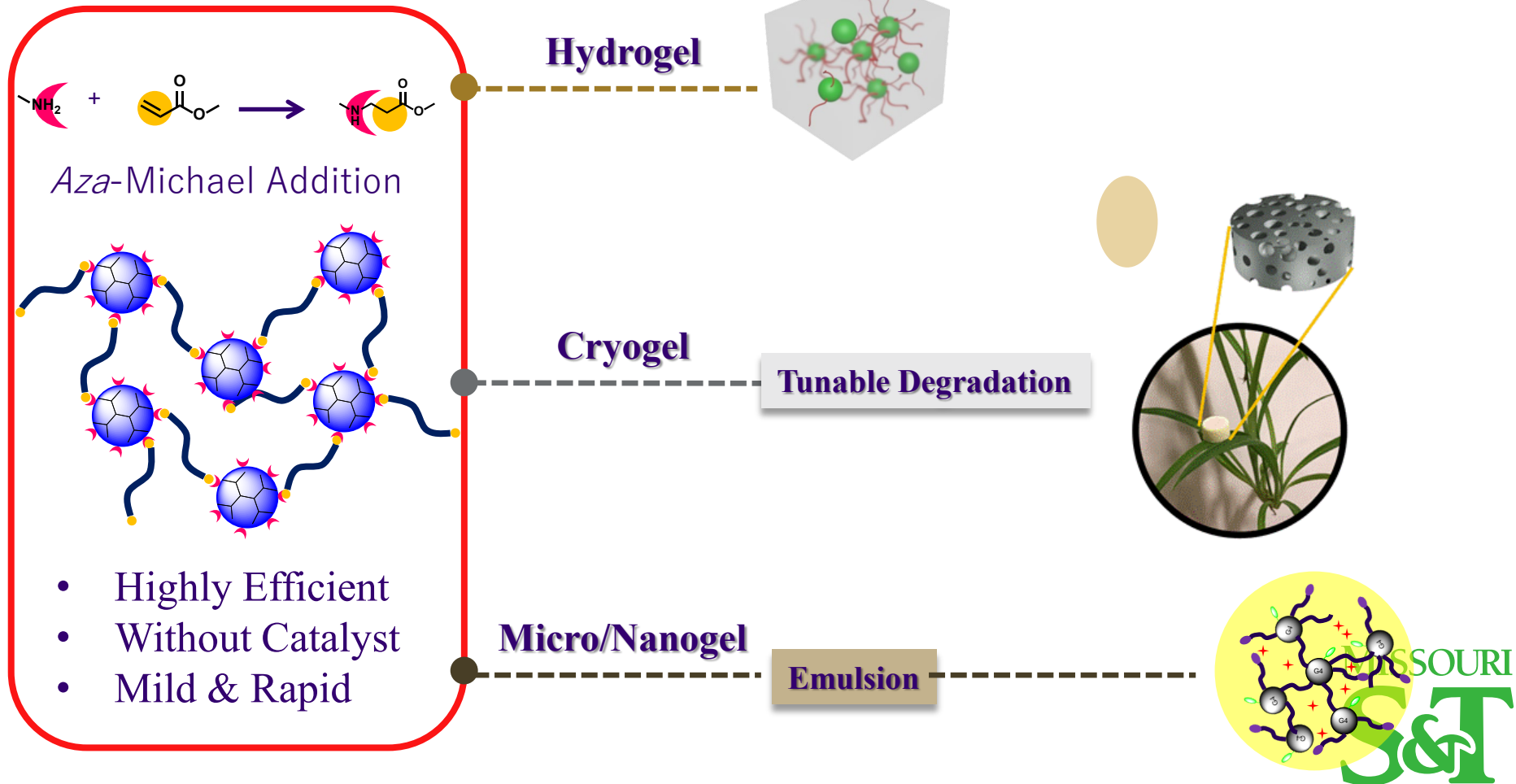




CPT/G5







Thank you!