CHEMICAL ENGINEERING
UNIVERSITY of WASHINGTON

SEMINAR

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Modular Biomaterials for Molecular Recognition and Immunomodulation

1-2 pm PST Monday June 21st, 2021
Zoom link is provided via email, or
contact dyss@uw.edu

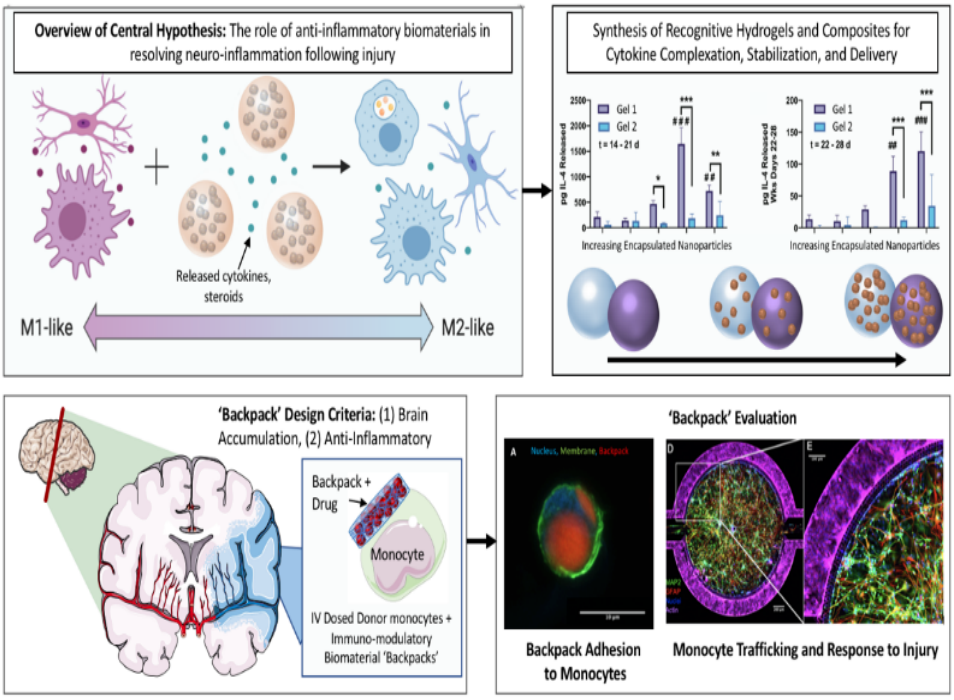
Bio

John R. Clegg is a postdoctoral fellow in Bioengineering at the John A. Paulson School of Engineering and Applied Sciences at Harvard University, affiliated with the Wyss Institute for Biologically Inspired Engineering. Working in the laboratory of Samir Mitragotri, John is investigating the ability of cellular backpacks to traffic to inflamed neurological tissue and attenuate secondary brain injuries. Prior to moving to Harvard, John was a Ph.D. student and NSF Fellow in Nicholas Peppas' lab at the University of Texas at Austin. While at UT, John investigated the role of hydrogels' molecular recognition properties on relevant drug delivery outcomes such as protein retention, sustained release, cellular targeting, cellular internalization, and toxicity. While at UT Austin, John also completed a Masters of Arts degree in STEM Education, with research on the implementation of a challenge based instruction model in undergraduate Biotransport. He has received a number of research and teaching awards, including the Livingston Award from UT Austin, their top teaching honor for a graduate student, and the Student Award for Outstanding PhD research from the Society for Biomaterials. In August 2021, John will start his independent career as an Assistant Professor of Biomedical Engineering at the University of Oklahoma.

Abstract

As a result of neurological diseases or traumas, patients can experience neuroinflammation, blood brain barrier disruption, and neurotoxicity. These inflammatory injuries are diffuse within the brain parenchyma, and thus require a therapeutic modality that [1] can be recruited to diffuse sites of inflammatory brain injury and [2] resolve the inflammation prior to cellular toxicity. In spite of growing clinical evidence for the role of immune processes (i.e. peripheral immune cell infiltration, inflammation) in neurological diseases and trauma, there are no FDA-approved therapeutics indicated for neuroprotection from these immune insults. Neuroprotective agents largely fail to demonstrate efficacy in clinical trials because they insufficiently reach and accumulate within the brain. Therefore, the central theme of my research is to use combinations of therapeutics, biomaterials, and cells to overcome biological barriers to brain drug delivery and protect neurons from immune insult.

The first portion of my talk will investigate how recognitive biomaterials or gels can be used to selectively complex, stabilize, and sustain the delivery of protein cargo. To establish this concept, I synthesized a library of multifunctional poly(methacrylate) hydrogels with similar crosslinking density. By binding libraries of proteins with different properties (molecular weight, isoelectric point) to these gels, I established predictive relationships between hydrogel composition (number of charge, hydrophobic moieties) and protein affinity / adsorption. I also demonstrated the utility of recognitive nanomaterials (i.e. multi-functional nanogels containing hydrophobic, charged, or peptide-based subunits) for sustaining the release kinetics of encapsulated cargoes and targeting cells. I will then discuss how gels and composites with 'molecular recognition' properties are useful for stabilizing immunomodulatory cytokines (IL-4, IL-10) and sustaining an anti-inflammatory brain microenvironment. I synthesized a library of hyaluronic acid-based hydrogels and hyaluronic acid-heparin hydrogel blends. Using an photopolymerized composite of heparin, hyaluronic acid, poly(ethylene glycol) crosslinker, and affinity nanomaterials (PLGA, nanogel, laponite nanoclay) I successfully delivered a therapeutic dose of IL-4 or IL-10 in vitro for up to 28 days. This duration is in stark contrast with the in vivo half-life of these delicate therapeutics (approx. 20 min).



I will conclude with a discussion of my most recent postdoctoral research, designing and evaluating cellular ‘backpacks’ for neuro-immunotherapy. Previous studies within the Mitragotri lab have demonstrated that adoptively transferred monocytes are recruited to sites of inflammatory injury and that cell-adhered drug delivering microparticles or ‘backpacks’ can effectively influence the phenotype of the adoptively transferred cell in vivo. With a team of collaborators from Massachusetts General Hospital and Harvard’s School of Engineering and Applied Sciences, I have developed a composite monocyte ‘backpack’ which adheres to primary monocytes (derived from human blood or mouse bone marrow) and delivers a combination of anti-inflammatory cytokines (IL-4) and small molecules (steroids). Using an ‘organ-on-chip’ model of the disrupted blood-brain-barrier following inflammatory injury, we have established that these primary monocytes can recognize sites of inflammation and invade the parenchyma locally. With growing clinical interest in cell-based therapeutics for a variety of diseases, we anticipate that these cellular ‘backpacks’ could be a useful platform technology for influencing the phenotype of injected cells hours to days after administration.