CHEMICAL ENGINEERING

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Bioinspired Drug Delivery Strategies for Treating Bone Fractures and Spinal Cord Injuries

ABSTRACT: Tissue engineering holds tremendous promise for patients suffering from severe injuries and degenerative diseases. Potent, regenerative proteins can be delivered to stimulate the body's own repair mechanisms to heal damaged tissues. However, clinical application of protein delivery is hindered by the lack of effective, non-invasive delivery methods to provide the long-term protein presentation necessary to induce repair. Consequently, developing biomaterials that can provide local, sustained protein delivery within tissue injury sites is a crucial step in developing protein therapeutics for the clinic.

The primary goal of my work is to improve sustained protein delivery by exploiting natural affinities between therapeutic proteins and other biomolecules. At Georgia Tech, I fabricated injectable heparin microparticles (HMPs) for protein concentration and delivery [1-3]. Heparin, which is a naturally occurring polysaccharide, can reversibly bind bone morphogenetic protein-2 (BMP-2), a potent growth factor used clinically for bone repair. Since HMPs contain a higher heparin density than other heparin-based materials, they can bind ~1000 times more BMP-2. I demonstrated that HMPs could be easily injected into large bone defects in rat femurs to strongly localize BMP-2 and induce bone healing. The ability to dose-dependently control spatial and temporal release of BMP-2 *in vivo* using HMPs presents exciting opportunities for protein delivery. To fully investigate this, I developed a computational model of BMP-2 diffusion through tissue to systematically evaluate the effect of HMPs on BMP-2 release, revealing a tunable system to modulate protein delivery.

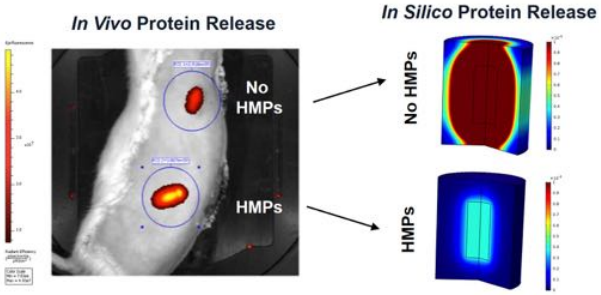

Figure 1. Improved local BMP-2 retention and decreased BMP-2 release in HMP-containing constructs implanted in rats and modelled computationally. (Hettiaratchi, et al. *Under Review).*

In my current work at the University of Toronto, I am building upon our understanding of heparin-protein interactions to engineer biomaterials that can provide precise protein delivery to other tissues. The Shoichet laboratory has developed an affinity-based protein release strategy in which proteins are expressed with Src homology 3 (SH3) domains that bind to specific peptide sequences [4, 5]. Incorporating these peptides into injectable biomaterials enables controlled protein release. While this strategy requires modification of proteins with SH3 domains, I plan to generate affinity release systems that avoid protein modifications by identifying natural binding partners for therapeutic proteins. I will use diffusion models and high throughput peptide screening methods, such as phage display, to create a library of peptides with defined, physiologically relevant affinities for proteins necessary for spinal cord repair. Since this new strategy relies on specific protein-peptide interactions, it will enable independently tunable delivery of multiple proteins from a single material.

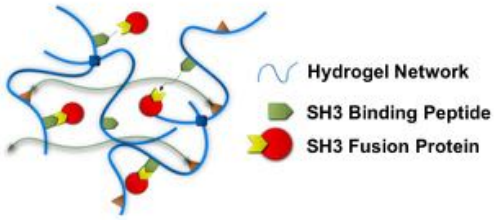

Figure 2. Affinity-based release using SH3 fusion proteins and binding peptides (Vulic, et al. 2015).

Biomaterials that can precisely deliver proteins can overcome challenges in tissue repair by effectively augmenting healing cascades in the body. Insight can be gained from both the "top down" biomimetic approach of using heparin's natural protein binding abilities and the "bottom up" modular approach of conferring affinity to a material through the addition of binding peptides. We anticipate that these platform technologies can also be broadly applied to protein delivery for brain, cardiac, and muscle regeneration in the future, and thus will be at the forefront of controlled release strategies bound for clinical application.

[1] Hettiaratchi, et al. *Biomaterials* 2014; [2] Zimmermann, et al. *Stem Cells Transl Med* 2016; [3] Hettiaratchi, et al. *Tissue Eng Part A* 2017; [4] Pakulska, et al. *J Control Release* 2013; [5] Pakulska, et al. *Science* 2016.

BIOGRAPHY: Marian Hettiaratchi is a post-doctoral fellow in Dr. Molly Shoichet┌s laboratory in the Department of Chemical Engineering and Applied Chemistry at the University of Toronto. She received her B.Sc. in chemical engineering in 2011 from the University of Calgary, and her Ph.D. in biomedical engineering in 2016 from the Georgia Institute of Technology and Emory University, working under the supervision of Dr. Todd McDevitt and Dr. Robert Guldberg. Her Ph.D. research focused on developing heparin-based microparticles for sustained protein delivery in bone regeneration applications. Her current research uses computational (in silico) and empirical (in vitro) strategies to enable precise, tunable protein release from injectable hydrogels for treating spinal cord injury. Marian is a recipient of several national and international research awards, including the Natural Science and Engineering Research Council (NSERC) of Canada Post-Graduate Scholarship and Philanthropic Educational Organization (PEO) Scholar Award.