SOUTH DAKOTA MINES

Nanoscience and Nanoengineering
Biomedical Engineering
South Dakota School of Mines and Technology
501 East St. Joseph Street, Rapid City, SD 57701

BioSNTR
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IMPACT SCIENCE

NANO-BME Seminar

Time: 4:00PM Thursday, April 21

Location: EP253 and https://sdsmt.zoom.us/j/94046899625

Innate Immunity: Friend or Foe in the Development of Therapeutic Biomaterials?

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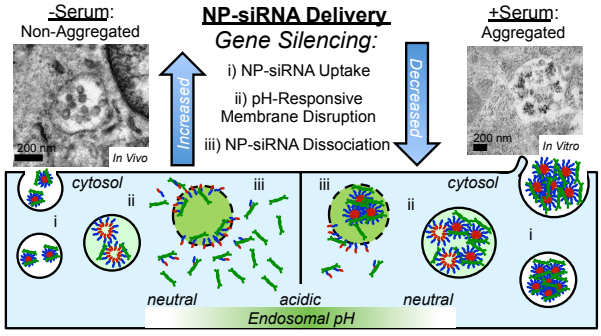
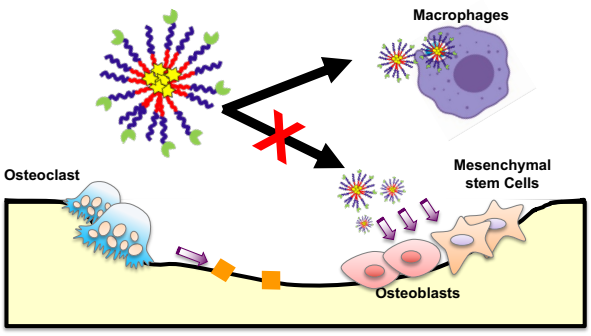
Abstract: There are huge challenges facing the therapeutics field due to significant drug delivery barriers. To this end, we are designing, synthesizing, and assessing 'smart', stimuli-responsive polymer delivery systems. We employ a controlled/living polymerization strategy known as RAFT (reversible-addition fragmentation chain transfer) to synthesize polymers with well-controlled molecular weight, polydispersities, flexible polymer chain end functionalities, and a multitude of architectures, all attributes enabling reproducible, effective, and targeted therapeutic delivery. My seminar will focus on two projects that highlight both the immense potential of our drug delivery system technologies and how leveraging greater understanding of biological interactions enable the development of more effective and innovative approaches.

Small interfering RNA (siRNA)-based therapies have significant therapeutic potential but are hampered by delivery barriers including drug instability and poor cell penetration and tissue/cell-specific delivery. To address these challenges, we have pioneered polymeric nanoparticles (NP) with cationic and pH-responsive characteristics to facilitate siRNA protection and cytoplasmic delivery after uptake. NP-siRNA delivery is shown to be highly effective in multiple therapeutic cell types *in vitro* and *in vivo*. However, NP-siRNA coincides with decreases in cellular metabolic activity and upregulation of immune stimulation pathways, resulting from NP-protein adsorption that diminishes the efficacy of siRNA delivery *in vitro* and leads to innate immune cell clearance upon introduction systemically. While local delivery *in vivo* is successful due to low protein concentrations, systemic delivery has greater patient acceptance. Thus, our recent focus is on development of novel anti-fouling NP modifications that also evade immune recognition even after

Innate Immunity Foe?



Innate Immunity Friend?



repeated exposures to avoid immunogenicity that is limiting continued use of PEGylation. While the goal is to limit protein adsorption, this achievement has been elusive to the Biomaterials field. Therefore, we have, in parallel, embraced immune cell uptake to stimulate fracture healing. Specifically, a bone-targeted poly(styrene-alt-maleic anhydride)-b-poly(styrene) nanoparticle (NP) delivery system for a Wnt/β-catenin agonist was developed. A peptide with high affinity for tartrate-resistant acid phosphatase (TRAP), a protein deposited by osteoclasts on bone resorptive surfaces, was introduced to the NP corona to achieve preferential delivery to fractured bone. Targeted NPs significantly improved fracture healing. Intriguingly, however, >90% of NPs are taken up by macrophages rather than cell types traditionally considered to be regenerative. Upon further investigation, NPs were shown to polarize macrophages to the regenerative M2 phenotype, which underpins improved fracture healing.

About the speaker: Danielle Benoit is the James P. Wilmot Distinguished Professor within the Department of Biomedical Engineering with appointments also in chemical engineering and the Center for Musculoskeletal Research. Her research specializes in the rational design of polymeric materials for regenerative medicine and drug delivery applications.