THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

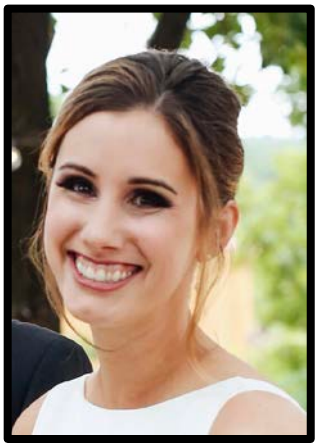
Rachel Sterling Lane

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

Tuesday, April 11, 2017, 12:00 p.m.
Room 109, Basic Research Center, OUHSC

Novel Glycosaminoglycan Design, Synthesis, and Use in Drug Delivery Models

COMMITTEE IN CHARGE: Paul L. DeAngelis, PhD, Chair, Franklin Hays, PhD, Kenneth Humphries, PhD, Guangpu Li, PhD, Ann Louise Olson, PhD, Scott Plafker, PhD



ABSTRACT: Glycosaminoglycans (GAGs) are amino-containing polysaccharides that include heparan sulfate/heparin, hyaluronan, and chondroitin sulfate/dermatan sulfate in mammals. In vivo, secretion of GAGs enable pathogenic bacteria to invade a host undetected and uninhibited by an immunogenic response. While this principal often enables bacteria to compromise health, it may also help fight disease. Modifying therapeutics with GAGs (e.g., GAG-drug conjugates or GAG delivery systems) can favorably alter their biochemical properties and pharmacokinetics. *We hypothesize that GAGs can treat disease either through direct modification of the polymer itself or by using GAGs to mediate drug delivery.*

To investigate the first part of our hypothesis, that GAG composition can improve therapeutic potential, we employed a novel C6-sulfonated UDP-glucose in the synthesis of hyaluronan and heparosan. Precise sulfation patterns in polymers confer unique biological activity but efficient, effective *in vitro* methods for intentional sulfate placement on polysaccharides are elusive. Our work is the first known attempt to gain control over sulfate placement by polymerizing GAGs with a sulfated UDP-sugar. These studies also led to the discovery of a novel polysaccharide and the development of new GAG chimeric constructs. To address the second aspect of our hypothesis, that GAGs are viable candidates for use in drug delivery, we tested the effectiveness of heparosan in several therapeutic transport systems. Heparosan (HEP) is a β1-4 glucuronic acid (GlcUA)–α1,4-N-acetylglucosamine (GlcNAc) polysaccharide, synthesized in the Golgi as the precursor to heparin or heparan sulfate. The non-immunogenic, bio-inert properties of heparosan make it a prime candidate for drug modification. Our efficacy studies in mouse models of human breast cancer suggest that heparosan-coated liposomes are a promising alternative for current, immunogenic liposome coatings. In addition to liposomes, we present evidence that HEP is also an appropriate platform for prodrug and micellar delivery systems. These translational studies will guide the design and development of next generation therapeutics.