STUDY OF THE BIOLOGICAL FUNCTIONS OF CHEMICALLY MODIFIED GLYCOSAMINOGLYCAN DERIVATIVES AS POTENTIAL THERAPEUTIC AGENTS

by

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An Abstract of a Thesis Submitted to the Graduate

Faculty of Rensselaer Polytechnic Institute

in Partial Fulfillment of the

Requirements for the degree of

DOCTOR OF PHILOSOPHY

Major Subject: Chemistry

The original of the complete thesis is on file
In the Rensselaer Polytechnic Institute Library

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Troy, New York

November, 2010
(For Graduation December 2010)

ABSTRACT

Glycosaminoglycans belong to the family of glycans and are highly negatively charged polysaccharides composed of linear disaccharide repeating units, each including an *N*-substituted hexosamine and an either hexuronic acid or hexose. They are prevalent in all mammalian cells and function in many biological processes such as coagulation, cell proliferation, differentiation, communication and death. My doctoral project mainly focused on the study of biological functions of chemically modified glycosaminoglycans, including heparin, in order to find either new anticoagulants at lower cost or therapeutic agents to treat other heparin-related diseases.

Oversulfated chondroitin sulfate was firstly synthesized as a potential substitute of heparin in anticoagulant market due to its similar structure and sulfonation level with heparin. However, during 2007 to 2008, it was found that oversulfated chondroitin sulfate triggered anaphylactic responses and caused deaths. By studying the interaction of oversulfated chondroitin sulfate with plasma proteins of the coagulation cascade, kallakrein-kinin pathways, and complement process, I hypothesized the possible biochemical mechanism to explain the severe adverse effects caused by this compound. Also by investigating the commercial heparins prepared from 1941 to 2008 and the commercial low molecular weight heparins prepared by different methods, I conclude that with the exception of the tinted heparin lots during 2007 to 2008, quality control was adequate for commercial heparin preparation. Also I suggest a better quality control method combing both NMR and PAGE techniques and improving depolymerization process for the preparation low molecular weight heparins.

Moreover, I synthesized a series of derivatives by chemically modifying different functional groups of commercial heparin and tested their effects on pulmonary artery smooth muscle cell proliferation. Most of the derivatives showed antiproliferation properties on those cells smooth muscle, proving that they might be used as a drug to prevent pulmonary hypertension caused by overgrowing those cells in wounding healing processes. Similar inhibition properties were also noticed in lung tumor proliferation

both *in vitro* and *in vivo*, suggesting those compounds alternative options as candidate compounds for cancer treatment.

In conclusion, I synthesized series of chemically modified glycosaminoglycan derivatives and studied their biological functions during my doctoral research. The results have helped us understand more about the role heparin plays in both anticoagulant and autoimmune process; also they shed on the light of the development on potential therapeutic agents for other heparin-involved health issues such as hypertension and cancer.