Notice of the Final Oral Examination
for the Degree of Doctor of Philosophy

of

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MSc (Andhra University University, 2001)
BSc (Andhra University, 2004)

“Design, Synthesis, and Evaluation of Polycomb Reader
Protein Cbx7 Antagonists”

Department of Chemistry

Tuesday, September 5, 2017
9:30 A.M.
Elliott Building
Room 230

Supervisory Committee:
Dr. Fraser Hof, Department of Chemistry, University of Victoria (Supervisor)
Dr. Cornelia Bohne, Department of Chemistry, UVic (Member)
Dr. Lisa Rosenberg, Department of Chemistry, Uvic (Member)
Dr. Caroline Cameron, Department of Biochemistry and Microbiology, UVic (Outside Member)

External Examiner:
Dr. Dustin Maly, Department of Chemistry, University of Washington

Chair of Oral Examination:
Dr. Nigel Horspool, Department of Computer Science, UVic
Abstract

Writer, eraser, and reader proteins are three classes of proteins/enzymes that add, remove, and recognize PTMs on histone tails, respectively. The orchestrated action of these protein classes controls dynamic state of chromatin and influences gene expression. Dysregulation of these proteins are often associated with disease conditions. All three classes are targeted with small molecule inhibitors for various disease conditions. This is a promising area of research to develop therapeutics for various clinical conditions.

I worked on a methyllysine reader protein Cbx7, which belong to polycomb group of proteins. Cbx7 is a chromodomain containing protein and it uses its chromodomain to recognize methyllysine partners such as H3K27me3. Aberrant expression of Cbx7 is observed in several cancers including prostate, breast, colon, thyroid, etc. Hence targeting Cbx7 with potent and selective inhibitors would be beneficial for therapeutic intervention for Cbx7 associated diseases.

Here I report my work on design, synthesis, and evaluation of Cbx7 inhibitors. In my work, we identified several potent and selective inhibitors for Cbx7 and we published first-in-class antagonists for Cbx7. Few of these inhibitors were tested on cancer stem cell models. Further, I propose future work for targeting Cbx7 and other chromodomain containing proteins.