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Addendum

1) Thank you for your suggestion. According to your advice, I have made the necessary changes in the thesis to enhance the coherency between the chapters. I have submitted a corrected thesis.

In Chapter 2, I identified a new G quadruplex (GQ) structure in the promoter region of the stemness marker gene REX1 and did a structural characterization of the GQ by employing selected small molecules. It also revealed the potential relevance of the GQ in regulating the REX1 gene, whose upregulation in metastatic condition is responsible for the acquisition of stemness characteristics by the cancer cells. While in Chapter 3, I have focused on studying the dynamic cooperative interaction of transcription factors with the reported GQ sequence in the promoter region of the proliferative marker gene c-MYC. And also the modulatory effect of Curcumin in altering DNA-protein interaction and downregulates c-MYC, which concomitantly suppresses the metastatic propensity of cancer cells. In Chapter 4, I have discussed the interaction and stabilizing effect of Itraconazole on c-MYC GQ which is the reason behind the downregulation of MYC gene in metastatic cells. Altogether, I have shown the importance of G quadruplex as a gene regulatory element and drug targetability potential of these crucial higher-ordered structures using different small molecules. Employment of TMPyP4 and BRACO-19 revealed the flexibility of a newly identified GQ between its folded and unfolded states. Employment of Curcumin revealed the efficient binding and stabilizing interaction of a natural bioactive compound with c-MYC GQ which focuses light on the development of targeted drugs utilizing the skeleton of Curcumin molecule. And in Chapter 4, I have discussed about the interaction of Itraconazole, an established anti-inflammatory drug molecule with c-MYC GQ, shedding light on the repurposing of these drugs as an anti-cancer agent in combination with a lower dose of chemotherapeutic drug cyclophosphamide.

Altogether, the information provided in the thesis about the interaction of multiple small molecules with the regulatory element G quadruplex in c-MYC and REX1 gene shall be of massive help in the future development of highly efficient anti-cancer drugs.

Thank you for your comment. Yes, Chapter 5 is unrelated to the main part of the thesis, but the explanation provided in this chapter is crucial for understanding the next chapter which is

related to my thesis. According to your suggestion, I have listed Chapter 5 and the second part of Chapter 6 as supplementary work and highlighted in pink.

In Chapter 6, I have discussed the vital role of GQ as a regulatory element in controlling the expression of the LINC00273 gene which when active transcribes into a long non-coding RNA. LINC00273 is a prometastatic gene, upregulation of which promotes cancer stemness and metastasis. In this chapter, I have discussed the employment of a small molecule M2 in targeting the GQ in the promoter region of this metastatic gene which leads to the downregulation of LINC00273 and further suppression of the metastatic potential of the cancer cells. Further, we have unraveled the mechanism of LINC00273 in controlling the expression of multiple oncogenes which is via miRNA sponging. This part of the chapter seems a little unrelated, which according to your advice, I have mentioned. But here also, in the miRNA sponging role of LINC00273, we found that the repetitive G-rich stretch within the LINC00273 transcript harbors complementary binding domains to the seeding sequence of multiple miRNAs compared to the upstream and downstream regions of the transcript, opening a new avenue in the research field on the functional importance of GQ in sponging activity which needs to be further explored.

2) Thank you for your suggestion. According to your advice, I have increased the resolution of the figures for a clearer view of the legends. As per your comment, I have numbered page number 54 in the corrected thesis copy.