The role of RecQ helicases in the interaction and resolution of G-quadruplexes

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G-quadruplexes (G4s) are involved in many cellular pathways, adding an additional layer of regulation complexity to the genome, by modulating transcription at promoters (including numerous oncogenes), replication, telomere homeostasis and genome stability. G4s have emerged as promising targets for anticancer drugs, but so far this strategy had only limited success. Among the specialized helicases that have evolved to unwind/modulate G4s, a particularly important role is played by the RecQ family, including RecQ1, BLM, WRN, RecQ4 and RecQ5: many of these enzymes are involved in genetic diseases and cancer development. Most of these helicases are involved in genetic diseases and cancer development.

Although there are multiple reports on the interactions between RecQ helicases and G4s, most analysis looked at one or two G4s, ignoring the wide diversity displayed by these structures, which include unimolecular, bimolecular and tetramolecular assemblies, parallel, antiparallel and mixed configurations, syn and anti conformations of the glycosidic bonds, short and long tailes and/or loops, etc.. Moreover, a single atomic structure for a G4:helicase complex is available in the Protein Data Bank; the paucity structural information prevents a full understanding of the underlying molecular determinants of G4 and helicases interaction.

There is thus the need of a more systematic biophysical and structural analysis to clarify the specificity and selectivity of each helicase towards different G4 topologies, and to better understand their distinct and/or overlapping roles in G4 metabolism. Biophysical, biochemical and structural studies on a variety of binary G4-RecQ helicase complexes will be complemented by *in vivo* analysis to look at the modulation of G4 structures in cells upon the impairment and/or modulation or mutation of the various human RecQ helicases.

The project is a close collaboration between the Structural Biology Laboratory at Elettra - Sincrotrone Trieste, that has a long-standing expertise in the study of helicase structures, and the Department of Pharmacy of the University of Naples Federico II, that has long been studying G4 structures froma a physical-chemistry and biophysical perspective.

Small molecules have been designed to bind and stabilise G4s, thus potentially affecting the growth of cancer cells at multiple levels, by modulating oncogene transcription, triggering apoptosis by stabilizing telomeric G4s, and possibly affecting DNA replication via the putative G4s present at origins of replication. However most of these ligands have shown to be not selective enough to be used as therapeutic agents.

A comprehensive biophysical, biochemical and structural study of G4: RecQ helicase interaction will provide a detailed understanding the molecular determinants of the G4s:helicases interactions, and will pave the way for novel anticancer approaches.