Title	**Non-canonical nucleic acid structure: foldings, functions and small molecule targeting**
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Project description:
The formation of non-canonical DNA structures in promoters is a recently explored mechanism to control the activity of the transcriptional machinery. In particular, their stabilization by small molecules has been widely investigated to suppress oncogene expression but, at present, none reached the clinic. Starting from available data, we identified main points that are rationally connected to this poor outcome: 1) the description of promoter structural organization cannot safely derive from studies on an isolated DNA structural motif. Indeed, we start to collect solid evidences of functional interactions among different nucleic acid structural domains; 2) DNA accessibility (topological state, hystone deposition), DNA modifications (iper- or ipo- methylation, oxidation) and DNA-protein complexes (transcription factors) make the system a different target for a small molecule 3) only a limited knowledge of a potential crosstalk between oncogene pathways is available. This makes difficult to properly evaluate the modulation of cellular pathways deriving from the silencing of a single oncogene.
From these assumptions, we are working to provide an in-deep comparison of the structural and functional role of the supramolecular organization of oncogene promoters and to dissect the consequence of the binding of small molecules on their transcriptionally active architecture.
This work explore the affected pathways by integrating distinct competences on biopharmaceutics, biophysics and cellular biology G4 ligands and unveil possible relationships between interconnected oncogenic pathways at structural, biological and functional level. it will provide the biological rationale for the design of novel therapeutic strategies and targets with more favorable outcome for patients.
Publications:
Rigo, R., Palumbo, M. and Sissi, C.* (2016) G-quadruplexes in human promoters: a challenge for therapeutic applications, BBA, bbagen.2016.12.024
Da Ros, S., Zorzan, E., Giantin, M., Zorro Shahidian, L., Palumbo, M., Dacasto, M. and Sissi, C. (2014) Sequencing and G-quadruplex folding of the canine proto-oncogene KIT promoter region: might dog be used as a model for human disease?, PLoS One, 9, e103876
Bianco, S., Musetti, C., Krapcho, A. P., Palumbo, M. and Sissi, C. (2013) Ni2+ and Cu2+ complexes of a phenanthroline-based ligand bind to G-quadruplexes at non-overlapping sites, Chem Commun (Camb), 49, 8057
Collaborations/Network:
Prof. J. Plavec, University of Lubiana; Prof. J. Chaires, University of Louisville, USA; Prof. Alcaro, University of Catanzaro; Prof. Randazzo, University of Naple. Dr. N. Zaffaroni, Istituto Tumori Milano, Dr, M. De Vivo, IIT, Genova.
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