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| **Title** | **The fluid interplay of nucleic acid interaction networks** | |
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**Project description:**

The formation of non-canonical DNA structures at gene 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 the structural organization of selected genomic sites 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) the relative biomolecules distribution within different compartments which can cluster selected biomolecules in a limited space at high concentration. In this context, along with the intracellular space subdivision defined by membranes, it is emerging the relevance of membrane free -compartments, which are frequently generated by nucleicc acid-protein interactions that can drive liquid-liquid phase separation.

These issues make difficult ( and likely unreliable!) to properly evaluate the modulation of cellular pathways from the silencing of a single site.

From these assumptions, we are working to provide an in-deep comparison of the structural and functional roles of the nucleic acid supramolecular organization to dissect the consequences of the binding of proteins or small molecules on their architecture as well as on the transcriptional machinery.

These works integrate distinct competences on biopharmaceutics, biophysics and cellular biology to finally explore the pathways affected by structure-selective nucleic acid ligands and to unveil possible relationships between interconnected genomic pathways at structural, biological and functional level.

This approach will provide the biological rationale for the design of novel therapeutic strategies and targets with more favorable outcome for patients.

**Publications**:

- Ghezzo M and Sissi C (2023) Structural characterization of a cytosine-rich potential quadruplex forming sequence in the EGFR promoter, Journal of Thermal Analysis and Calorimetry, https://doi.org/10.1007/s10973-023-12060-0

- Ceschi S, Berselli M, Cozzaglio M, Giantin M, Toppo S, Spolaore B, Sissi C (2022) Vimentin binds to G-quadruplex repeats found at telomeres and gene promoters Nucleic Acid Res, 50(3):1370-1381

- Vesco G, Lamperti M, Salerno D, Marrano CA, Cassina V, Rigo R, Buglione E, Bondani M, Nicoletto G, Mantegazza F, Sissi C\*, Nardo L (2021) Double-stranded flanking ends affect the folding kinetics and conformational equilibrium of G-quadruplexes forming sequences within the promoter of KIT oncogene. Nucleic Acids Res, 49, 9724-9737

- Palumbo M, Sissi C (2022) Bench to bedside: The ambitious goal of transducing medicinal chemistry from the lab to the clinic, Bioorg Med Chem, 69, 128787

- Rigo, R., Palumbo, M. and Sissi, C. (2016) G-quadruplexes in human promoters: a challenge for therapeutic applications, BBA, bbagen.2016.12.024

**Collaborations/Network:**

Prof. J. Plavec, University of Lubiana; Prof. J. L. Mergny, Polytecnique Paris; 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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