Tutor: Bruno PAGANO (PO - SSD CHIM/02)
Co-tutor: Mariateresa Giustiniano (PA - SSD CHIM/08)

Title: Multimeric G-quadruplex–forming DNA sequences: from characterization to the development of specific binders

In human cells, nucleic acids can assume a variety of non-canonical secondary structures that control important biological functions. One of these is the G-quadruplex (G4), which is a transient structure formed by guanine-rich DNA and RNA sequences. These sequences may adopt several conformations, thus making G4s highly polymorphic structures. Long G4-forming DNA sequences (referred to as multimeric G4s) are even more complex, as they may multimerize and give rise to higher-order structures where the different G4 units may interact with each other. In recent years, multimeric G4s have been shown to be key in protecting or disrupting the pathogenic cascade of various diseases, such as cancer and neuropathies. Such evidence made them a hot research topic and an attractive target for drug design. Therefore, the research topic of this PhD proposal is the investigation of the large-scale structure, conformation and stability properties of multimeric G4s by means of biophysical methodologies. This project also aims at the development of ligands specifically targeting multimeric G4s with high affinity and selectivity, as well as lower toxicity and increased functionality compared to the traditional DNA-targeting drugs. Such potential drugs will be developed by applying innovative green synthetic approaches such as visible light photoredox catalytic methodologies and/or multicomponent reactions (MCRs). The latter are particularly acknowledged for their high atom-economy, ease-of-performance along with the ability to explore a huge chemical space in terms of both complexity and diversity. On the other hand, the wide scope, the robustness and the chemo-selectivity offered by visible light photocatalysis would additionally enable a site selective late-stage manipulation of complex structures such as known bioactive ligands and natural compounds, thus speeding up the identification of hit/lead compounds and pharmacological tools. Furthermore, a combined use of biophysical and biological experiments will be employed to gain insights into the properties of the potential therapeutics developed.
The long-standing experience and competence of the tutors in the field of noncanonical DNA structures and in the development of their ligands, as well as the adequate funding obtained (AIRC grant id. 24590 to B.P., PRIN 2022 id. 2022SP38PS to B.P., and PRIN 2022 id. 202279575W to M.G.), will guarantee the PhD student a training path leading to a broad knowledge and a strong interdisciplinary set of skills.