

University of Naples Federico II Department of Pharmacy *Doctoral Course in Pharmaceutical Sciences XL Cycle*



EXPLORING THE ROLE OF NON-CANONICAL NUCLEIC ACID STRUCTURES IN THE DEVELOPMENT OF DISEASES

Tutor: Prof. Antonio Randazzo e Co-tutor: Prof.ssa Annapina Russo

DNA is recognized as a structurally dynamic molecule which is also able to adopt alternative secondary conformations such as cruciforms, hairpins, G-quadruplexes (G4s), triplexes, and i-motifs (iMs), mainly depending on the nucleotide sequence.

G4s fall among the most widely investigated non-canonical DNA secondary structures. They occur in guanine-rich sequences and consist of stacked layers of G-tetrads, planar arrangements of four guanines held together by eight Hoogsteen hydrogen bonds.

The complementary cytosine-rich strand of a G4-forming sequence can fold into an i-motif, a four-stranded DNA conformation held up by hemi-protonated cytosine-cytosine+ base pairs.

Both G4s and iMs are highly prevalent in biologically relevant genomic regions such as telomeres, oncogene promoters, and replication initiation sites, thus being potentially involved in a number of critical cellular processes including genomic stability, gene transcription, and DNA replication.

Firstly, with the aid of a multi-omics approach including transcriptomic, proteomic and metabolomic analyses, this research project aims at dissecting the implications of non-canonical nucleic acids in the development of different types of disorders such as metabolic, neurodegenerative, inflammatory, genetic diseases or cancer. This might allow to identify unprecedented pathogenetic mechanisms G4s and iMs could participate in.

This project is also intended to provide a more in-depth knowledge about the specific roles of G-quadruplexes and i-motifs in the cellular environment and this will be also performed by studying the effects, a biomolecular level, of treatments of specific cell-lines with ligand having high specificity for G4s and iMs.