Nucleic acids are known for their ability to adopt diverse structural conformations, ranging from double-helical A-, B-, Z-DNA forms to noncanonical structures like triplex or quadruplex, a property that enables to fulfill a variety of functions. For example, the double helix of DNA provides the means of information storage for the whole of life, meanwhile, the primary function of the messenger RNA (mRNA) is to serve as a template for protein synthesis *via* translation. Among various noncanonical DNA structures, unquestionably G-quadruplex (G4) have recently attracted significant attention from across many disciplines as promising therapeutic targets, catalysts, and as the basis of functional materials. These structurally distinctive oligonucleotide sequences are built up from π-π stacked G-quartets stabilized by Hoogsteen hydrogen bonds and, cation coordination (Na^+, K^+). Importantly, G4s are found in the human genome and have been linked to key cellular processes such as transcription, replication, repair, and telomere maintenance. As a consequence, they became the target for small molecules which can help to control their biological function. To date, a plethora of small molecules based on different recognition processes have been reported to target G4 motifs, however, only a few of them have shown promising reversible binding mechanisms. In this context, light-responsive compounds are key components in the design of advanced phototherapeutics. Light is an ideal tool for the non-invasive manipulation of biological pathways as it can be controlled both in space and time with high selectivity, without providing chemical waste, making modulation of biological functions restricted only to the targeted sites decreasing, therefore off-target effects. In this case, a particularly important group of compounds are azobenzenes (ABs), well-known photochromic switches – that are compounds whose geometry can be reversibly changed under light exposure. The consequence of the geometry being changed is the difference in properties of isomers, which makes ABs an excellent photoresponsive molecular tool for remote manipulation.

Here, we propose an interdisciplinary effort to develop new **light-activated G4-binders** as advanced therapeutics. We will design and synthesize ABs and study their binding properties toward G4 structures both *in vitro* and in cancer cells. The novelty of this research project relies on the fact that it will be the first studies devoted to investigate **the ability of ABs to reversible modulate G4 functions in cellular systems**. In this project, we want to (I) use azobenzenes because they can be switched between ON-OFF G4 binding states, (II) check if the *in vitro* G4 data correlates with cell data in cytotoxic experiments (III) investigate whether the different cytotoxicity obtained for the two isomers correlates with their ability to interfere with DNA transactions, for instance through G4 stabilization (IV) and if our molecules interfere with DNA transactions, check whether we can selectively downregulate the expression of particular cancer genes (e.g. MYC, KRAS, etc). By doing so, we will be able to tune the expression of cancer-associated genes containing G4 motifs providing a proof-of-concept to inspire future **G4-based (photo)therapies.**

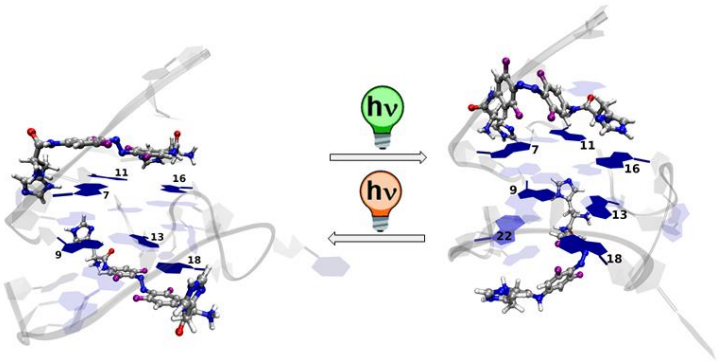

Figure 1. The light-induced *trans*-to-*cis* conversion of azobenzene derivative for example may lead to tune the interactive binding process/localization of the azobenzene in a light-controlled manner, which in turn may affect G4 stability.