Computational Screening and Design of G-quadruplex Ligands Targeting *c-MYC* in Breast Cancer

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G-quadruplexes (G4) are four-stranded nucleic acid secondary structures formed by guanine-rich sequences of DNA or RNA. It has been shown that G4 are involved in relevant biological functions of normal mammalian cells, but more importantly, in cancer cells. Several studies reported that G4 is prevalent in telomeres and promotor regions of several oncogenes like *c-MYC*, which has a key role in several cellular regulatory processes, cancer development and progression[1].

G4 formed in the promoter region of *c-MYC* may constitute an anticancer drug target by inhibiting the DNA transcription via the block of DNA polymerase and binding of transcription factors. Interestingly, G4 in the *c-MYC* promoter is reported to be unwounded by the helicase DHX36, a protein of the eukaryotic DEAH/RHA family that recognises specifically G4s and promotes the regulation of DNA transcription[1,2]. Therefore, we will take advantage of the identified biological relevance of G4, together with the recent published crystallographic structure of DHX36 helicase with the *c-MYC* G4, to develop an *in silico* approach to identify inhibitors of this DNAG4-helicase interaction, with the objective to promote an anti-proliferative activity and downregulation of this oncogene expression[2,3]. In this communication, we report a molecular docking workflow that considers different scoring functions coupled to a consensus analysis approach to identify the most promising indoloisoquinoline (IDQ) derivatives capable to bind to *c-MYC* G4. From an initial library of 1104 ligands, we were able to identify a small group of fragment substituents with a high prevalence in the compounds with higher binding affinities to the *c-MYC* G4. These results will guide the chemical synthesis of a small subset of IDQ derivatives, and consequent *in vitro* validation. The obtained results will then afterwards be used in subsequent *in silico* structure/activity studies to assure for the optimization of the most promising *c-MYC* G4-helicase interaction inhibitors.

Acknowledgements: FCT to projects PTDC/BIA-BFS/28419/2017 (B. L. Victor) UIDB/04046/2020−UIDP/04046/2020 (BioISI) and UIDP/04138/2020 (iMed).I. Aljnadi acknowledges Global Platform for Syrian Students and ULisboa for a PhD scholarship.

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