Structural Characterization and Targeting of Higher-Order Promoter G-Quadruplexes

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G-quadruplexes (G4s) are four-stranded nucleic acid secondary structures that can form in genomic regions of high guanine content. G4s are highly concentrated in the promoter regions of cancer-associated genes and can up- or down-regulate adjacent gene transcription. G4s are now actively pursued for their ability to selectively repress the transcription of many hard-to-target cancer proteins, such as c-Myc, k-Ras, and c-Kit. G4 targeting small molecules exhibit excellent in vitro and in vivo anticancer activity, however, none have progressed through clinical trials. We contend that this is the result of targeting the small, singular G4 domains that have been "convenient" to study by traditional structural biology methods, such as NMR and X-ray diffraction, that have similar topologies and few small druggable pockets. By utilizing an integrative structural biology approach (ISB), which combines small-angle X-ray scattering (SAXS), circular dichroism, molecular modeling, fold prediction, and footprinting, my lab has shown that multiple cancer gene promoters contain contiguous G4 motifs that adopt higher-order arrangements. The higher-order tertiary folds reveal quantitively better drug targeting sights relative to the traditional small G4s as determined by SiteMap analysis. We go on to show that models developed in our approach are useful as in silico targets for virtual drug discovery efforts with multiple examples of successful drug screening.

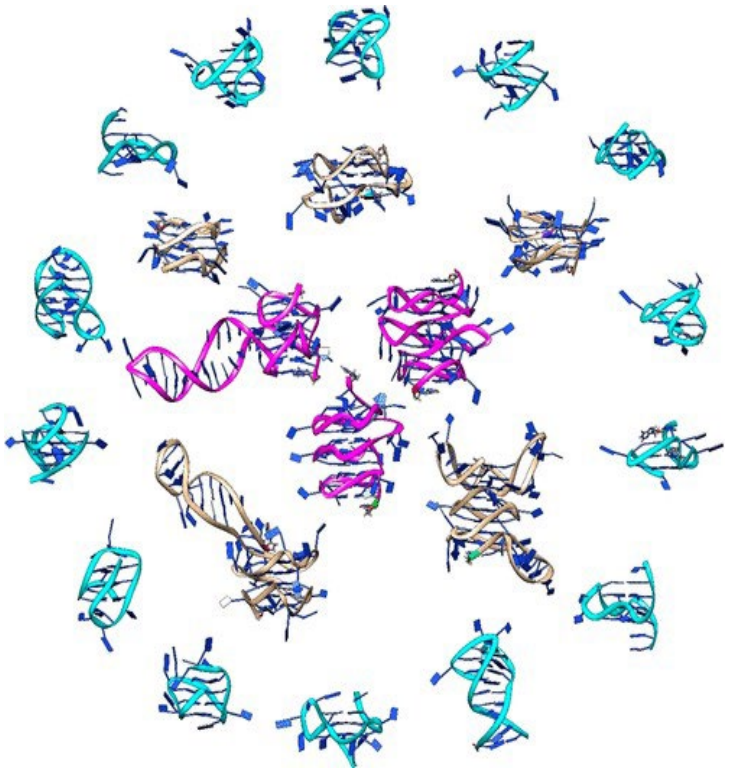

Figure 1